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Editorial

Evolutionary perspectives on the role of oxytocin in human social behavior, social cognition and psychopathology

The articles in this Special Edition summarize the latest research on oxytocin (OT), and often arginine vasopressin (AVP), in human parental behavior, other social behaviors, social cognition, social information processing in the brain, as well as developmental disorders and psychopathology. These articles aspire to not only review progress in these areas but to identify the limitations of what have been done and also to articulate high priority directions for future research. The relevance of the emerging evidence for understanding the psychobiology of mental illness is emphasized. To set the stage, here we discuss how OT in the central nervous system (CNS) might have mediated the critical advances in social behavior during the evolution of placental mammals.

Selection for avid and sustained maternal behavior was critical for the successful evolution of placental mammals. OT was selected from phylogenetically earlier nonapeptides to enable the unique features of placental mammalian reproduction: birth of neonates after in utero fetal development (parturition); delivery into the mouths of suckling infants of high quality nutrition produced within the mother's body by the larger process of lactation (milk ejection); and activation of maternal nurturing of newborns. In all mammalian species tested to date, OT appears to facilitate the postpartum initiation of maternal behavior (Pedersen, 2013). In sub-primate mammals, this involves, in concert with and dependent upon the reproductive hormone conditions that promote the onset of parturition, OT-initiated motivation to exhibit hard-wired, species-specific sets of offspring-directed care-taking behaviors. To restate this point in a more general way that is a central theme of this Special Issue: with the evolution of placental mammals, OT was selected to activate brain systems promoting maternal behavior, a sustained and prosocial motivational state. Other social attachments and social behaviors that were selected later during mammalian evolution appear to be at least partially based on OT (and AVP) neural systems that first emerged during the evolution of maternal behavior. Supporting this contention are the OT and AVP dependence of pair-bond formation in the monogamous prairie vole (Young and Wang, 2004) and marmosets (Smith et al., 2010), studies indicating OT regulation of social interactions in rhesus macaques (Chang et al., 2012; Parr et al., 2013; Ebitz et al., 2013; Winslow et al., 2003) and the rapidly accumulating number of reports of OT influences (mostly positive) on human trust, cooperation and social cognition (e.g., see Meyer-Lindenberg et al., 2011).

During early placental mammalian evolution, OT was also coopted to produce affective changes vital to the success of maternal behavior, e.g., reduced fear/anxiety (see Febo and Ferris; MacDonald and Feifel, both this volume; Neumann et al., 2000; Figueira et al., 2008), which enabled suppression of newborn-directed aggression during parturition (McCarthy, 1990; McCarthy et al., 1986) and regulation of intruder-directed aggression during lactation (Bosch et al., 2005; Consiglio and Lucion, 1996; Consiglio et al., 2005; Giovenardi et al., 1998; Lubin et al., 2003) AVP (also selected from earlier nonapeptides during the evolution of mammals) appears to play an important role in activating and sustaining maternal behavior (Bosch and Neumann, 2008; Pedersen et al., 1994) and regulating affective changes and increases in intruder aggression associated with the onset of maternal behavior (see Febo and Ferris, this volume). These points are relevant to another theme that is central to this Special Issue: from early on in placental mammalian evolution, OT and AVP were selected for important roles in emotion regulation necessary for successful social behavior.

The evolution of avid and sustained maternal behavior as well as other unique aspects of placental mammalian reproduction effectively eliminated long-standing barriers to development of larger and more complex brains and, eventually, higher intelligence. In utero development and maternal protection during maturation as well as a uniquely rich and reliable source of nutrition, i.e., milk, substantially increased the percentage of offspring that survived to reproduce. Therefore, numbers of offspring required for reproductive fitness decreased allowing each offspring to be larger and endowed with a bigger brain. In addition, maternal protection during the lactation period allowed further brain growth and development to occur before offspring had to fend for themselves. This also created a malleable period during which epigenetic influences from the mother, siblings and the environment influenced brain development in survival-enhancing ways (McGowan and Szyf, 2010; Champagne, 2012). Selection for mental abilities that increased the

effectiveness of maternal behavior, and later paternal behavior, in enhancing the survival of offspring to reproductive age may have also spurred on the evolution of more complex brains and greater intelligence.

In many rodent species (e.g., rats, mice), the strong, OT-dependent maternal motivation that is activated at parturition is directed towards newborns in general. Mothers in these species do not bond to individual offspring (Pedersen, 2013). OT appears to have been centrally involved in the next evolutionary leap in prosocial behavior in mammals; formation of selective attachments to specific individuals. The formation of selective bonds requires the ability to learn the identity of important conspecifics (e.g., offspring, mothers, mating partners). In sub-primate mammals, individual identification is based largely on learning the unique olfactory cues of others. Oxytocin was coopted during the evolution of selective social bond formation to facilitate acquisition of the memory of odor cues of other individuals. For example, OT release in the olfactory bulbs is necessary for ewes to encode the memory of the specific odors of their newborn lambs in the immediate postpartum period (Kendrick et al., 1997). The capacity to form selective, olfactory-based bonds may have emerged from the ability earlier in evolution to form transient memories of the odors of novel conspecifics. For example, rats and mice are able to remember the unique odor of a novel individual for approximately 1–2 h. Experiments with OT gene knockout mice or central administration of OT antagonists have demonstrated that formation of transient social memory is entirely OT dependent (Ferguson et al., 2000; Takayanagi et al., 2005). These findings indicate that OT has played a significant role in social cognition since early in mammalian evolution. Evidence for extensive involvement of OT in human social cognition is another major theme developed in many of the articles in this Special Issue.

During the evolution of primates, maternal and other social behaviors have become less dependent on specific sex hormones and olfactory cues. The neurobiological control of social interactions has evolved from hard-wired behavioral programs reflexively triggered by specific sensory cues to more flexible and complex processing and integrating of cues from multiple sensory modalities. These evolutionary changes in the psychobiology of social relationships in primates have certainly been facilitated by, and perhaps contributed to the selection for, expansion of non-olfactory regions of the cortex and advances in intelligence. OT still clearly plays a crucial role in primate maternal behaviors. Intracerebroventricular (ICV) infusion of OT in nulliparous rhesus macaques increases their interests in infants measured by looking, touching, maintaining proximity, and lip-smacking (Holman and Goy, 1995). Furthermore, peripheral administration of OT antagonist delivered to the limbic regions of the CNS substantially reduces nulliparous female macaque's interest in infant and sexual behavior (Boccia et al., 2007). Using non-human primates also permits unique investigations into the role of OT in mediating more complex social behaviors and social cognition than maternal behaviors and pair-bonding. Converging evidence from the studies examining the role OT in complex social cognition in non-human primates as well as in humans (Bartz et al., 2011) suggests that the effects of OT are critically gated by social contexts and intrinsic social orientations. For example, ICV administration of OT in male squirrel monkeys increases associative behaviors in low status males but increases sexual assertiveness in higher status males, upon exposures to female monkeys (Winslow and Insel, 1991). Furthermore, increasing OT levels in the CNS via OT inhalation in rhesus macaques promotes either other-regarding or self-regarding behaviors depending on social decision contexts (i.e., what the available options are concerning self and others) (Chang et al., 2012), while controlling for the state of social vigilance toward specific social stimuli (Parr et al., 2013; Ebitz et al., 2013). Taken together, these findings endorse the idea that OT interacts closely with the neural systems involved in social perception and decision-making. Chang and Platt (this issue) review selected studies of OT and social behavior in non-human primates, focusing on the interplay between social motivation and social vigilance for promoting social behaviors. The emergence of OT research in non-human primates (see Chang and Platt; Evans et al., this volume) provides a platform for investigating the neurobiology of central OT for shaping complex social cognition. Importantly, a non-human primate model can further help test the efficacy and safety of long-term OT-based therapies in the same subjects by systematically monitoring neurophysiological and other physiological and behavioral changes (see Chang and Platt, this volume).

In this volume, Febo and Ferris summarize their pioneering functional magnetic resonance imaging (fMRI) studies in awake rats, including nursing mothers, and Swain et al. provide a review including the latest fMRI studies of brain activation in human parents elicited by visual and auditory stimuli from infants. Both show the remarkably complex neural processing associated with parental behavior toward the lower end and the peak of mammalian evolution. Many brain areas activated by nursing stimuli in rat mothers and infant visual and auditory stimuli in human parents are analogous, specifically areas involved in sensory processing, mobilization of hard-wired, instinctive nurturing behaviors (referred to as reflexive/instrumental caring responses by Swain et al.), and emotion regulation. Febo and Ferris surmise from evidence that many of these brain areas contain high concentrations of OT receptors in rats and are activated by ICV administration of OT as well as that central OT release during parturition may produce the coordinated activation of these many brain areas during the onset of rat maternal behavior, a conclusion that is supported by extensive studies in sheep (Kendrick, 2000). In humans, Swain et al. point out that these areas are most prominently activated by stimuli from very young infants whose behavior is limited to communicating basic needs (e.g., hunger, cold, discomfort). However, the more interactive stimuli from older human infants activate higher cortical regions and cortico-limbic connections implicated in mentalization, empathy and Theory of Mind which may enable human parents to provide more attuned and sensitive responses to their infants' social cues that are critical for the development of secure attachment in their offspring. However, little is known about relationships between central OT systems and the brain activation pattern in human parents, in part because of the lack of reliable methods to locate OT receptors in the human and non-human primate

brain. However, Pedersen (this issue) summarizes a recent immunohistochemical study (Boccia et al., 2013) that has identified OT receptors in limbic and some cortical brain sites (unfortunately the study did not examine prefrontal and temporal cortices) that are activated in human parents by infant visual and auditory stimuli (the cover of this Special Issue illustrates OT receptor immunostaining in the human amygdala visualized in the Boccia et al., 2013 study).

To date, most studies of OT and parental behavior in humans have examined blood concentration relationships with parent–infant interactions. Apter-Levi et al. (this volume) summarize the considerable body of evidence, much of it from their own group, that OT levels in human parents and their children are inter-related and correspond to the degree of synchrony of their interactions. They then report the first evidence that parent AVP levels are related to stimulatory contact with their infant, joint attention to objects, and efforts to increase object salience following infant social gaze. These novel findings add further to the bio-behavior synchrony model of parent–infant interactions that has been developed by this group (Atzil et al., 2012). Kim et al. (in this Special Issue) report the first study to examine the relationships between OT levels and maternal responses during conditions that are stressful to their infants (a modified still-face procedure). They found that the duration of maternal gaze toward the distressed infant, a key index of sensitive parenting, is directly related to maternal release of OT. Elmadih et al. (this volume) employ the novel strategy of comparing OT levels between mothers who exhibit high sensitivity in their interactions with their infants and mothers with low sensitivity. Surprisingly, OT levels were significantly higher in low sensitivity mothers, a finding that contrasts with positive relationships between OT levels and sensitive parenting found in previous studies. Citing reports that higher OT levels are associated with stress in social relationships or disturbed parental relationships in childhood, Elmadih et al. hypothesize that low sensitivity mother may have greater stress responses to the demands of caring for their infants and/or experienced deficient parenting early in life. Elmadih et al. conclude that mothers' stress reactivity and attachment history are core variables that should be assessed in studies of OT relationships with parent–infant interactions.

Van IJzendoorn, Bakermans-Kranenburg and colleagues have pioneered fMRI studies of the effects of intranasal OT on responses to infant stimuli. In this issue, they (Voorhuis et al.) report a puzzling finding that intranasal OT administration in women increased activity in temporal and frontal cortical sites but at the same time decreased accurate interpretation of images of infant facial expressions. Their results contrast with findings that intranasal OT increases accuracy of emotion recognition when viewing images of adult faces (Domes et al., 2007; Guastella et al., 2010). The Van IJzendoorn and Bakermans-Kranenburg group previously found that OT administration to nulliparous women decreased amygdala activation and increased activity in emotion regulation sites in responses to infant crying or laughter (Riem et al., 2011, 2012). These effects were interpreted as evidence that OT improves responses to infant's emotional states by decreasing negative emotional arousal and increasing empathy for infant distress and the incentive salience of infant laughter. In light of the functional disconnect between OT effects on brain activity and infant face emotion recognition in the current Voorhuis et al. article, behavioral/emotional tests might be critical for interpretation of fMRI studies that look at OT-mediated modulations in hemodynamic activity.

Studies in which OT is administered by the intranasal route have enabled rapid advance in our understanding of OT regulation of human social behavior and social cognition as well as the psychotherapeutic potential of OT. Initial, indirect evidence that intranasal OT penetrates the CNS was provided by Born et al. (2002) when they demonstrated that intranasal AVP (only two amino acids different from OT) crosses the blood–brain-barrier. Evidence that OT administered by the intranasal route enters the CNS has more recently been reported in rats (Neumann et al., 2013) and monkeys (Chang et al., 2012). Early on, intranasal OT was reported to have a number of prosocial effects in human subjects including increasing interpersonal trust (Kosfeld et al., 2005; Baumgartner et al., 2008; Mikolajczak et al., 2010); cooperation (Andari et al., 2010) and eye contact (Andari et al., 2010; Guastella et al., 2008) as well as improving performance in domains of social cognition such as face emotion recognition, Theory of Mind, perception of the trustworthiness of faces, and empathy (Domes et al., 2007; Fischer-Shofty et al., 2010; Guastella et al., 2010; Hurlemann et al., 2010; Petrovic et al., 2008; Theodoridou et al., 2009). Kanat et al. (this volume) review and critique the burgeoning number of fMRI studies of intranasal OT effects on brain region and circuit responses to social stimuli. Most consistently, OT administration has affected social stimuli influences on the activity of the amygdala and associated regions of the temporal and prefrontal cortices as well as their connectivity. However, the specific regions affected and the directionality of effects are strongly influenced by differences in social stimuli, gender, reproductive state in women, and attachment style as well as variations in the oxytocin receptor gene.

This Special Issue includes several articles that provide important additions to our understanding of the complexity of OT effects on human social behavior and social cognition. Our understanding of the often contrasting effects of OT in different conditions and the wide range of variables that appear to influence those effects will require a great deal of future research. Evans et al. (this volume) take on the task of comparing the many reports of intranasal OT effects on human social behavior and social cognition. Initially they examine the controversy about whether OT administered by the intranasal route penetrates the CNS. The authors then view and critique the inconsistencies in the rapidly increasing literature on intranasal OT effects. The notion that OT is always “prosocial” is refuted. Striking gender differences in the effects of OT are emphasized. The authors discuss suggestions by some investigators that a general effect of OT such as anxiety reduction or enhancement of the salience of social stimuli might account for the wide range of social facilitating influences of OT that have been reported.

De Dreu and colleagues have published a series of groundbreaking studies demonstrating that OT has strikingly contrasting effects on attitudes and behavior directed toward simulated in-group and out-group members. They found that

intranasal OT increases positive attitudes and empathy only for in-group members, enhances agreement more with in-group members and promotes greater in-group cooperation when competing with an out-group. Ten Velden (this issue) summarizes their earlier work and reports the results of this group's latest study. In a simulated poker game situation, they found that subjects who received intranasal OT withdrew from betting more, even when they had a strong hand, if they were competing with an in-group member but not when competing with an out-group member. The body of work from De Dreu and colleagues powerfully demonstrates that OT effects on human social behavior are situation dependent and could exacerbate conflict between groups. Blandon-Gitlan et al. (this volume) report the fascinating finding that intranasal OT treatment eliminates same race bias in face recognition memory, a phenomenon that has been strongly validated in previous studies. In contrast to those receiving placebo, participants who received intranasal OT prior to initial viewing of face images of Black and White individuals subsequently exhibited no race difference in accurate identification of previously seen faces. The Blandon-Gitlan et al. report seems to conflict with the implication of De Dreu's studies that the prosocial effects of intranasal OT are exclusively in-group directed and emphasizes the importance of understanding and comparing the underlying psychobiology in situations in which OT amplifies or diminishes group differences.

The generally prosocial effects of OT in animal and human studies has generated considerable interest in examining OT as an etiological factor in and a potential treatment for developmental and psychiatric disorders in which social deficits are prominent. Anagnostou et al. (this volume) report the results of a small (15 subjects) preliminary 12-week randomized, placebo-controlled clinical trial of intranasal OT in high functioning children and adolescents with autism spectrum disorders (ASDs). A number of measures of social cognition and functioning as well as repetitive behaviors and anxiety improved in OT recipients over the treatment period. Gains in some measures persisted 3 months after discontinuation of intranasal OT treatment. No adverse events, OT-related side effects or clinically significant changes in laboratory tests occurred. In a recently published 6-week randomized, placebo-controlled pilot clinical trial in 19 adults with ASDs, Anagnostou et al. (2012) found that subjects receiving twice daily intranasal OT compared to placebo demonstrated improvements in empathic accuracy, lower order repetitive behaviors and quality of life. Francis et al. (this issue) review the remarkable evidence that, in developmental disorders with markedly different underlying genetic abnormalities and pathophysiology, OT function is significantly altered in ways that correspond to the social behavior anomalies exhibited by individuals with those disorders. Specifically, the marked social avoidance and anxiety in ASDs, the Prader–Willi Syndrome and the Fragile-X Syndrome are associated with impaired OT (and in some cases AVP) activity and/or release in patients or animal models of the disorders. In contrast, in individuals with Williams Syndrome who exhibit hypersociability, a positive correlation is found between OT levels and increased stranger approach and decreased adaptive social behavior. Francis et al. hypothesize that the distinct neurobiological abnormalities of these four disparate neurodevelopmental disorders may all lead to dysregulation of OT control of social behavior.

Virtually all psychiatric disorders are associated with some degree of impairment of social function although profound deficits are primarily associated with severe and persistent mental illnesses such as psychotic disorders. Numerous studies conducted in animal models of psychiatric disorders have found that OT may have therapeutic potential in a wide spectrum of disorders including anxiety, depression, psychosis and addiction (Macdonald and Feifel, 2013; Meyer-Lindenberg et al., 2011). These considerations as well as ample evidence that intranasal OT treatment exerts effects in the CNS have led a few investigators to conduct randomized clinical trials (RCTs) in some psychiatric disorders (as well as neurodevelopmental disorders—see Anagnostou et al., in this issue). Pedersen (this issue) emphasizes the diversity of OT therapeutic effects by reviewing relevant animal and human background studies and summarizing the very promising results of intranasal OT compared to placebo treatment in RCTs conducted in patients with schizophrenia and alcohol dependence. OT significantly reduced psychotic symptoms in patients with schizophrenia in all three published studies in which intranasal treatments were administered twice daily for 2, 3 or 8 weeks. Furthermore, in one study (Pedersen et al., 2011) OT improved performance in some social cognitive domains and, in another study (Feifel et al., 2012), OT improved performance in one neurocognitive domain, verbal learning. The latter findings are particularly exciting because social cognitive and neurocognitive deficits contribute substantially to social dysfunction which is a major cause of disability in schizophrenia (Fett et al., 2011) and does not respond to currently available antipsychotic medications (Bellack et al., 2004; Penn et al., 2009). Pedersen presents his recent preliminary evidence that intranasal OT is remarkably effective in blocking withdrawal in highly alcohol-dependent patients. He presents the rationale for testing intranasal OT efficacy in decreasing drinking in alcohol dependence. Pedersen poses and discusses numerous questions about our remarkable lack of information about OT systems in the human brain and heretofore unexamined OT mechanisms that may be important in the pathophysiology of psychotic disorders and addictions. Finally, Pedersen speculates that antipsychotic and withdrawal-blocking efficacy of OT may be linked to as yet unexplored OT mechanisms that were selected during the evolution of maternal and other social behaviors in placental mammals.

MacDonald and Feifel (this issue) explore the broad topic of OT as a pathophysiological factor as well as a potential treatment of anxiety disorders. These issues are particularly important because disabling levels of anxiety occur in many psychiatric illnesses. The authors begin with a discussion of the vague and inconsistent ways in which anxiety is referred to and conceptualized across disciplines followed by a review of preclinical studies of OT and anxiety. An evolution-based theoretical framework is then developed about the centrality of OT and other socially relevant neuropeptides and neurotransmitters in regulating the balance between fear, anxiety, avoidance and aggression-generating brain systems that have been selected to enhance self-preservation and anxiolytic,

approach, affiliation-generating systems that have been selected to increase social/reproductive success. MacDonald and Feifel continue with a highly comprehensive review of studies of intranasal OT effects on as well as the relationship of OT levels and OT receptor gene variants with anxiety measures, stress hormone levels and anxiety-generating brain region activity in normal subjects as well as individuals with anxiety disorders or anxiety phenotypes. This includes the authors' trend level findings that intranasal OT reduced anxiety in male subjects (but exacerbated anxiety in female subjects) in a small (N=13), preliminary 3-week RCT in patients with generalized anxiety disorder. While acknowledging that connections between brain regions play important roles in anxiety, the potential significance of OT activity in several brain areas in anxiety and anxiety disorders is thoroughly examined. The authors leave the reader with ten as yet unanswered questions to guide future work on OT and anxiety. Overall, a strong case is made to conduct clinical trials testing the efficacy of intranasal OT in anxiety disorders.

Soeken et al. (this issue) make the case that dysfunction of OT systems may contribute to postpartum depression and that OT may be an effective treatment in this disorder. The authors summarize current treatment options and discuss their limitations. Animal and human research is reviewed supporting the antidepressant efficacy of OT and the potential role of OT in depression especially in the postpartum period. Areas requiring further research are identified.

There is broad consensus among evolution theorists that higher primate and human intelligence is the product of selection for mental abilities that provide advantages in assessing complex and variable social situations and adjusting social behavior to enhance access to resources and mating opportunities (Barrett and Henzi, 2005; Moll and Tomasello, 2007; Pinker, 2010; Heyes, 2012) in often highly fluid social milieus. The primary function of the human brain and its advanced mental abilities, such as abstract thought and language, is viewed as enabling social success. The social brain concept of human intelligence thus far has had minimal impact in biological psychiatry and even less influence on CNS drug development by the pharmaceutical industry (Macdonald and Feifel, 2013; but see also Brüne, 2008). The extensive evidence cited in this and other articles in this Special Issue suggest that CNS OT systems are a key component of the human social brain. The rapidly accumulating evidence that central OT abnormalities are found in many psychiatric and developmental disorders and that OT treatment reduces the severity of symptoms in a wide range of disorders supports the view that malfunctions of the social brain contribute to many psychopathophysiological conditions (Brüne, 2008). Intranasal OT administration and other methods of examining brain OT systems may provide unique opportunities to test the significance of this central element of the social brain in psychiatric disorders. The high degree of tolerability and safety of intranasal OT administration adds to its feasibility and appeal as a means of probing the normal and psychiatrically-disabled human social brain.

At the request of the Editors, articles in this special volume have gone beyond reviewing and critiquing studies on OT in human social behavior and psychopathology by articulating novel and innovative concepts and illuminating uncharted territory that hopefully will inspire new directions in human and clinically-relevant animal research on OT and psychopathology. To this end, many of the authors point out the enormous gaps in our current understanding of OT systems in the human brain, propose novel hypotheses about the mechanisms of OT psychotherapeutic effects and discuss the possible etiology of those effects in heretofore unexplored roles for which OT may have been selected during the evolution of placental mammalian maternal and other social behaviors. As the Editors, we hope the papers appearing in this special issue will collectively generate new and fruitful discussions toward future research aimed at understanding and treating social deficits in psychopathological conditions.

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Research Report

Approaching the biology of human parental attachment: Brain imaging, oxytocin and coordinated assessments of mothers and fathers

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ABSTRACT

Brain networks that govern parental response to infant signals have been studied with imaging techniques over the last 15 years. The complex interaction of thoughts and behaviors required for sensitive parenting enables the formation of each individual's first social bonds and critically shapes development. This review concentrates on magnetic resonance imaging experiments which directly examine the brain systems involved in parental responses to infant cues. First, we introduce themes in the literature on parental brain circuits studied to date. Next, we present a thorough chronological review of state-of-the-art fMRI studies that probe the parental brain with a range of baby audio and visual stimuli. We also highlight the putative role of oxytocin and effects of psychopathology, as well as the most recent work on the paternal brain. Taken together, a new model emerges in which we propose that cortico-limbic networks interact to support parental brain responses to infants. These include circuitry for arousal/salience/motivation/reward, reflexive/instrumental caring, emotion response/regulation and integrative/complex cognitive processing. Maternal sensitivity and the quality of caregiving behavior are likely determined by the responsiveness of these circuits during early parent-infant experiences. The function of these circuits is modifiable by current and early-life experiences, hormonal and other factors. Severe deviation from the range of normal function in these systems is particularly associated with (maternal) mental illnesses – commonly, depression and

Abbreviations: MPOA, medial preoptic area; BNST, bed nucleus of the stria terminalis; dlPFC, dorsolateral prefrontal cortex; IPV-PTSD, interpersonal violence-related posttraumatic stress disorder; nACC, nucleus accumbens; ACC, anterior cingulate; IFG, inferior frontal gyrus; NAcc, nucleus accumbens; OFC, orbitofrontal cortex

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anxiety, but also schizophrenia and bipolar disorder. Finally, we discuss the limits and extent to which brain imaging may broaden our understanding of the parental brain given our current model. Developments in the understanding of the parental brain may have profound implications for long-term outcomes in families across risk, resilience and possible interventions.

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1. Introduction to the parental brain

Human mothers and fathers exhibit a repertoire of parental thoughts and activities that manifest interesting similarities and differences as part of an array the crosses cultures (Hrdy, 2000) and species across species (Clutton-Brock, 1991) with the common goal of caring for offspring. For humans, besides meeting the primal evolutionary needs for survival and continuation of our species, parenting involves interrelated biological, psychological, and behavioral caregiving mechanisms that contribute critically to the first environment the child experiences as a new family member.

The rich animal literature on parental brain (Bridges, 2008) strongly supports the notion that a coherent understanding of the physiology governing parenting in humans is also possible. Indeed, much of the research on the human parental brain involves attempts to look for human homologs of 'parental' brain circuits found in animals. This approach has initially been successful using audiovisual stimuli of babies during functional imaging – particularly with contrasts of own vs. unknown babies – to activate brain regions that recognize and respond to the special salience for the parent of their own baby's stimuli (Barrett and Fleming, 2011; Swain, 2011b; Swain et al., 2007).

In this review, we summarize the state-of-the art of human parental brain imaging in mothers and fathers. More specifically, we focus on the interpretation of brain-responses to baby-cry and baby visual stimuli respectively and consider attempts to integrate findings within the cognitive, affective, and social neurosciences. First, we selectively review the psychological and imaging evidence of relevant executive, emotion response/regulation and reward mechanisms that may be activated in the service of parental sensitivity. We then discuss these findings in the context of research on oxytocin, and review recent attempts to understand how parenting difficulties or even psychopathology may be understood as abnormalities or malfunctions of parental brain circuits. The importance of this mechanistic understanding of parenting is underscored by consideration of effects on offspring and possibilities to identify families at risk and optimize therapeutic interventions.

1.1. *Parental sensitivity and child attachment*

Ainsworth et al. (1978) first defined maternal sensitivity as a mother's ability to attend and respond to her child in ways that are contingent to the infant's needs. In the naturalistic context, sensitive maternal care behaviors show a great deal of variation between individual mothers, despite being relatively stable in the same mothers across time and contexts (Behrens et al., 2012; Jaffari-Bimmel et al., 2006; Wan et al., 2013). Maternal sensitivity represents a pattern of behavior which provides the infant with its primary social experience. This suggests that it is important for organizing and regulating the infant's emotional, social and cognitive systems and is consistent with accumulating evidence that maternal sensitivity predicts a range of social-emotional child outcomes – including the quality of their attachment relationships (Bakermans-Kranenburg et al., 2003; De Wolff and van Ijzendoorn, 1997), self-regulation (Eisenberg et al., 2001), social functioning (Kochanska, 2002; Van Zeijl et al., 2006), socio-emotional development (De Wolff and van Ijzendoorn, 1997), and cognitive and language competence (Bernier et al., 2010; Tamis-LeMonda et al., 2001). Furthermore, the absence of skills needed to respond sensitively to child signals has been linked to risk for maltreatment (Milner, 1993, 2003). Poor maternal sensitivity in infancy predicts later harsh parenting (Joosen et al., 2012) and attitudes towards punishment (Engfer and Gavranidou, 1987). Frightening and anomalous maternal behavior confers profound risk to the parent–infant attachment relationship (Schuengel et al., 1999) to subsequent child outcomes and future parenting of their own children.

The concept of parent–infant attachment represents a landmark of contemporary developmental psychology (Bowlby, 1969b, 1973). In fact, Bowlby formulated his attachment theory after studying associations between maternal deprivation and juvenile delinquency, postulating a universal human need to form close, affect-laden bonds, primarily between mother and infant. He strongly argued, from an evolutionary perspective, that attachment represents an innate biological system promoting proximity-seeking between an infant and a con-specific attachment figure. This proximity then increases the likelihood of survival to reproductive age.

Because of this powerful biological instinct for attachment, and in response to the patterns of attachment identified in the Ainsworth mother–infant studies (Ainsworth et al., 1978), Bowlby (1977) hypothesized that all human infants attach to their caregiver but that children manifest different patterns of attachment "security" depending on the quality of the care they receive. Indeed, a vast literature in the study of attachment over last several decades has established that infants of caregivers who are available, responsive and sensitive to their emotional and physical needs tend to manifest patterns of "secure attachment." Conversely, chaotic, unpredictable, rejecting or neglectful care in which non-contingent responses

to the child occur frequently, result in insecure or disorganized patterns of attachment evolves (Shaver et al., 1987).

Understanding the neurobiology of attachment–formation through parental sensitivity may help to formulate and ameliorate pervasive and complex social problems such as child abuse and neglect. However, little is known about the cognitive or neurobiological mechanisms which underpin healthy sensitivity, let alone poor sensitivity in mothers with mental illness. This may explain why promising interventions targeted at improving parenting through improved sensitivity have shown inconsistent findings and generally small effect sizes (Bakermans-Kranenburg et al., 2003; Wan et al., 2008c).

1.2. *Neurocognitive mechanisms underlying parental sensitivity*

For sensitive caregiver responses to infant cues, complex brain systems must manage an array of complex thoughts and behaviors contingent on feedback from the baby. These include recognition and acknowledgment of child signals, attribution of salience to child cues, maintenance of visual contact, expression of positive effect, appropriate mirroring and vocal quality, resourcefulness in handling child's distress or expanding the interaction, consistency of style, and display of an affective range that matches the infant's readiness to interact. Such behaviors are likely to be the result of complex neural networks involved in generating and organizing emotional responses (Kober et al., 2008) as well as in attention and executive function, reward and motivation, and sensorimotor circuits – a model well supported by the literature (Swain and Lorberbaum, 2008). We update this model below incorporating the newest work on fathers and the effects of mental illness on parenting capacity. Indeed, mental health problems may manifest as impairment in any of these networks and play a significant role in poor parenting. Identifying these may provide an opportunity to predict which parents are likely to have which type of parenting problems and facilitate targeting of interventions. Here, we highlight brain processes, mechanistically related to certain cortico-limbic circuits, and relevant for healthy parenting sensitivity.

1.2.1. *Executive function*

Executive functions, including attention control, working memory and flexible task-switching, are likely to be important to parental sensitivity. Deficits in attention set-shifting, spatial working memory and a sustained attention measure have been linked with poor maternal sensitivity to non-distress infant cues (Gonzalez et al., 2012). In closely related work, mothers with a classification of disorganized attachment responded more slowly to negative attachment words and the speed of response to such stimuli was correlated with disorganization, suggesting negative associations with attachment stimuli that may contribute to ongoing cognitive difficulties during mother–infant interactions (Atkinson et al., 2009). Greater attention bias to infant distress cues in late pregnancy has also been associated with better scores on a parental bonding questionnaire (Pearson et al., 2010), raising the question of how attention deficit disorder affects parenting – an issue yet to be studied. Attention bias to infant distress has also been compared between breastfeeding ($n = 27$) and formula feeding ($n = 24$) mothers of 3–6 month old infants and observed to be greater in breastfeeding mothers (Pearson et al., 2011). It is plausible that reduced attention bias towards emotional stimuli (specifically infant distress) is associated with low maternal sensitivity in some mothers. However, other mothers with low sensitivity may show a selectively exaggerated attention bias to infant distress which results in the mother becoming overwhelmed by the stimuli; this may be particularly relevant for mothers and fathers with schizophrenia or in those with little social supports in deprived circumstances. In depressed patients, evidence suggests a tendency to pay *more* attention to negative emotional stimuli (Elliott et al., 2011); an effect mediated by *enhanced* response in the ventral anterior cingulate, which may contribute to the maintenance of low mood.

1.2.2. *Emotion regulation*

Recognizing emotion in preverbal infants is more difficult than recognizing emotions in adults. In some parents, inability to recognize and distinguish the subtleties of infant emotion cues may underpin poor maternal sensitivity. Consistent with this, depression is associated with decreased discrimination of facial emotion (Anderson et al., 2011). Response to distressing signals from the infant also requires a mother to distinguish positive from negative emotions; indeed, studies suggest that a mother's sensitivity to distress may be a better predictor of child outcomes than her sensitivity to non-distress cues (Joosen et al., 2012; Leerkes, 2011; Leerkes et al., 2009; McElwain and Booth-Laforce, 2006). Thus, poor maternal care behavior could derive in part from reduced recognition, as well as reduced response to infant emotions generally, and/or specifically, to signals of infant distress. Conversely, some mothers may become overwhelmed by their infant's distress. Notably, enhanced responsiveness to negative emotions, (mediated by enhanced amygdala response), has been observed in non-parent depression (Arnone et al., 2012). In depressed mothers, studies suggest women may avoid or limit exposure to distressing infant stimuli (Field, 2010; Murray et al., 1996; Pearson et al., 2012). In anxiety and depression, modulating stress and emotional responsiveness is an important target for treatment and is associated with clinical improvement (Harmer et al., 2011). The importance of emotion regulation in the responses to baby stimuli is also consistent with the ideas of postpartum preoccupations discussed below (Section 1.2.4).

1.2.3. *Reward/motivation*

Extensive recent review of the animal literature (Numan and Woodside, 2010) suggests that response to infants forms a model motivational system employing dopamine and oxytocin-rich pathways such as the medial preoptic area (MPOA). Through such pathways, infant cues are thought to provide motivation for maternal care behavior. Reward processes include immediate hedonic responses ("liking") and approach motivation ("wanting") or learning (Berridge and Kringelbach, 2008). Frontostriatal brain regions are also critically implicated in reward, in particular the orbitofrontal cortex (OFC) (Rolls, 2004) and ventral striatum including

nucleus accumbens (NAcc) (Born et al., 2011). Although the OFC generally codes hedonic signals, the medial OFC is particularly important for computing reward value while the lateral OFC makes stronger contributions to reward learning. In mothers, the initial experience of pleasure and activity in these brain circuits when exposed to their own infant's cues may increase the salience of their infant's stimuli and promote greater attention and bond-formation to ensure continuous engagement in sensitive caregiving. Indeed, reward/motivation pathways have been shown to be active in response to baby-stimuli (discussed below). In mothers with low sensitivity, the motivational or incentive salience of emotional and/or infant cues may be diminished through deficits in this and also in other OT-opioid reward pathways (Curley, 2011). Thus, in rhesus monkeys, mothers with greater attachment to infants possess the G allele of the OPRM1 μ-opioid receptor and have higher oxytocin responses to lactation and pregnancy (Higham et al., 2011). Strikingly, activity of opioids at the μ-opioid receptor is also central to the processing of reward in the context of drug dependence (Herz, 1997; Simmons and Self, 2009), and social behaviors (Higham et al., 2011). Very few studies, however, have examined neural substrates of reward-related processes among mothers who display disrupted caregiving behavior.

1.2.4. *Parental thoughts – preoccupations/habits, empathy and positive thoughts*

Parents experience dynamic change in their thoughts and behaviors oriented toward their new infants. Immediately after a child's birth and during the first few months of the infant's life, parents are particularly drawn to their infants' vocalizations and physical attributes and focus their thoughts on the infants' physical and psychological needs (Bowlby, 1969a; Winnicott, 1956). Such intense mental focus and behaviors were first referred to as "*primary maternal preoccupation*" by Winnicott (1956) and seem also consistent with the activation of motivational-reward pathways by infant cues reflecting an important evolutionary mechanism through which infants promote long-term emotional ties with their parents (Atkinson et al., 2009; Feldman et al., 1999; Gonzalez et al., 2012; Leckman and Mayes, 1999).

Leckman et al. (1999) reported that all domains of parental preoccupation peaked right after childbirth and then began to decrease over the course of the first three to four postpartum months in mothers and fathers, albeit less intensely for fathers. Since newborns have very limited ways of communicating their needs, parents must constantly check the infants in order to identify and attend to those needs. The intensity of parental preoccupations decreases as parents gain more experience in parenting and infants become more responsive. However, excessively and persistently high levels of parental preoccupation, particularly anxious and intrusive thoughts and harm-avoidant behaviors can be associated with postpartum psychopathology such as postpartum obsessive compulsive disorders (OCD). In one sample, levels of parental preoccupations were related to postpartum anxiety at the first month postpartum (Feldman et al., 1999) and lower maternal sensitivity at 3–4 months postpartum (Kim et al., 2013). Abnormally low levels of parental preoccupation, e.g. in postpartum depression also pose difficulties in developing emotional bonds with the infant, and risk inadequate parenting (Feldman et al. 1999, 2009). Maternal schizophrenia also interferes with care giving behavior in ways that merit separate study and treatment (Abel et al., 2005; Wan et al., 2008a, 2008b, 2008c). For typically developing parents, the story for fathers will likely differ from mother. For example, unlike for mothers, paternal sensitivity was predicted by anxious as well as caregiving and positive thoughts (Kim et al., 2013). More nuanced assessments of mother and father thought, mood and behaviors are required to clarify how they are related over time and how they might inform the nascent study of paternal brain physiology (below).

Parental empathy, (appropriate perception, experience and response to another's emotion) may be especially relevant for preverbal infants. Deficits of empathy in disorders such as schizophrenia and autism have been associated with abnormalities in certain brain networks (Gallese et al., 2004; Iacoboni, 2009; Uddin et al., 2007). These systems overlap significantly with brain responses of parents to infant stimuli reviewed here i.e. cingulate and insular cortices (Bernhardt and Singer, 2012).

Experiencing pain personally and experiencing the pain of a loved one activate insula and anterior cingulate, with another's pain activating more anterior regions and own pain also recruiting brainstem, cerebellum, and sensorimotor cortex. Such decoupled, yet parallel representations of empathy in cortical structures like insula and anterior cingulate are postulated as necessary for our ability to mentalize, that is, understand the thoughts, beliefs, and intentions of others in relation to ourselves (Frith and Frith, 2003; Hein and Singer, 2008). Humans may utilize separate circuitry to "decouple" representations of external vs. internal information in order to understand physical properties and assess personal emotional values. In support of this, a brain network consistently activated during tasks that require mentalizing has emerged, including dorsomedial prefrontal cortex (DMPFC), medial prefrontal cortex (MPFC), precuneus/posterior cingulate cortex (PCC), temporoparietal junction (TPJ), and posterior superior temporal sulcus (pSTS) (Frith and Frith, 2006; Mitchell, 2009). Such a framework for understanding of the contribution of social ties to broad health issues (Eisenberger and Cole, 2012) promises to be very helpful in considering the importance of parent-infant dyads in health promotion.

By three to four months postpartum, infants are more socially interactive, and parents increasingly engage in reciprocal positive interactions. These positive interactions further help mothers to strengthen their attachment and heighten the experience of positive feelings toward their infants (Mercer, 1985). As they successfully feed, take care of, and build affectionate connections with their infants, mothers develop positive feelings and self-confidence about parenting (Benedek, 1954). Fathers may develop attachment to their infants more gradually (Anderson, 1996; Pruett, 1998). Positive feelings about their infants and parenting experience maybe critical in pathways engaging dopamine–oxytocin reward circuits described in animal models (MacDonald, 1992; Numan and Insel, 2003b; Shahrokh et al., 2010). Thus, interactions with the infant may enhance parental oxytocin and dopamine release and foster the maintenance of positive parental behaviors with associated attentiveness and sensitive caregiving – perhaps implicating

future therapeutic potential (Macdonald et al., 2013). In contrast, if interactions with the infant are negative and stressful, parents may experience less brain activation in reward-motivation pathways, find the relationship less satisfying, harbor fewer positive parental thoughts and be less willing to maintain it.

Such reward pathways maybe relevant very early in the postpartum, as mother's positive feelings towards her unborn fetus as well as her perception of her fetus have been associated with greater maternal sensitivity to the infant's signals and more affectionate vocalizations and touch (Keller et al., 2003; Keren et al., 2003). It may be interesting in the future to examine prepartum thoughts as relevant for postpartum behaviors. Idealization of the infant and positive thoughts about parenting may positively reinforce both quality of parenting and feelings of reward. On the other hand, worrying about the infant – such as health and other concerns – may be associated with lower parental sensitivity and higher intrusiveness. Indeed, negative feelings about parenting may be linked to the parents' difficulties in developing emotional bonds with their infants (Mercer, 1985; Nystrom and Ohrling, 2004) although the nature and direction of this link needs clarification.

The following sections review the current state of evidence from experiments designed to elucidate the brain basis of parental attachment by presenting infant stimuli – sometimes emotionally charged – during brain imaging. Such studies have incorporated psychological, behavioral and hormonal measures and a very few include parents with abnormalities in parenting or mental illness. The power and sensitivity of functional imaging deliver mechanistic understanding of abnormalities in brain associated with poor parenting and promise earlier detection of problems that may not be obvious from behavioral or self-report measures. In the future, brain-based understandings may allow refinement of tailored treatment approaches toward parenting and targeted augmentation of parenting resiliency (Rutter, 2013; Swain et al., 2012).

Tables 1 and 2 summarize experiments to date on human parents using baby sound and visual stimuli with brain fMRI.

1.3. *Human brain imaging methods*

The primary technique used to study the brain in this review is non-invasive blood-oxygen-dependent functional magnetic resonance imaging (fMRI). fMRI assays brain activity by indirectly measuring changes in regional blood oxygenation during different periods in which infant cues may be presented. The differences between a region's oxygenated and deoxygenated hemoglobin, between states of action vs. inaction for instance, provide characteristic magnetic signals localized to millimeters that are detected by scanners positioned around each subject's head. An important caveat throughout the interpretation of parenting fMRI studies, however, is that that brain activity measurements represent an integration of electrical brain activity that may be instantaneous yet the related blood flow change lags behind over seconds. Furthermore, experimental design captures brain activity over periods of a few seconds or 10's of seconds. On the one hand, short blocks or events may capture briefly held mental states, but miss bigger changes such as sustained emotion; while on the other hand longer blocks may capture more complex brain responses, but also average them out making subtle responses more difficult to detect. Brain activity during these blocks may then be measured and compared between periods of attending to stimuli of interest and control stimuli to generate maps of the brain indicating differences in brain activity that may be important for one set of perceptions and thoughts vs. another. With parents as subjects, infant cries and pictures have been stimuli and comparisons of brain activity measured during baby cry vs. control sound experience have been said to relate to the parental experience of a baby cry, and so the associated parenting thoughts and behaviors. Many of these studies make use of seed-based analyses with modest group sizes that will require replication in different populations to permit generalization of findings and all results could relate to activity that is excitatory or inhibitory. Future imaging with connectivity analyses also promise to define more than just response regions, but circuit behavior involving coordinated activity between distant brain areas (Sripada et al., 2013). The important limitation that response to baby cues may not be directly related to parental care is being addressed in studies that correlate responses to parental care described below.

2. Parental brain responses to infant stimuli

2.1. *What's in a baby-cry?*

In addition to communicating basic levels of discomfort, hunger, and pain (Soltis, 2004), baby cry also signals the need for physical proximity of caregivers leading to the dynamically interactive cry-care thoughts and behaviors that lead to attachment (Swain et al., 2004b), for which new parents appear to be primed (Bowlby, 1969b). Supportive studies have demonstrated that human mothers can recognize the cries of their own infants, and mothers and fathers activate brain in areas hypothesized to be involved in mammalian parenting behavior (Swain and Lorberbaum, 2008; Swain et al., 2007).

2.1.1. *Brain responses to auditory baby-stimuli: baby-cry – 1st 10 years*

Building on the thalamocingulate theory of maternal behavior in animals (MacLean, 1990), Lorberbaum et al. (1999) - in the first, though rather small study of its kind - predicted and found that baby cries selectively activate cingulate and thalamus in mothers in the early postpartum months exposed to an audio taped 30 s standard baby cry using fMRI. Informed by the animal literature, they expanded their hypotheses to include the basal forebrain's medial preoptic area and ventral bed nucleus of the stria terminalis and its rich reciprocal connections as being critical to parental behaviors (Lorberbaum et al., 2002). These include the descending connections which modulate more basic reflexive caring behaviors such as nursing, licking, grooming and carrying reflexes in rodent studies, and ascending connections such as the mesolimbic and mesocortical dopamine systems involved in more general motivation and flexible responses required to tend a crying infant or prepare for a threat. Even though these first studies involved cry stimuli

Table 1 – Human parent brain responses to infant stimuli.

Author, year	Parent group N	Age of infants	Paradigm, variable	Study design	Brain network			
					Arousal Salience	Reflex Care	Emotion Regulation	Cognition
	Baby-cry, Mothers							
Lorberbaum et al. (1999)	4	3 weeks to 3.5 years	Other vs. control	30 s Blocks	Y	Y	Y	Y
Lorberbaum et al. (2002)	10	1–2 months	Other vs. control	30 s Blocks	Y	Y	Y	Y
Seifritz et al. (2003)	10	<3 years	Other vs. control, +ve/−ve	6 s Events	Y	N	Y	Y
Swain et al. (2003, 2004a, 2006)	11–14	2–4 weeks and 3–4 months	Own vs. other, experience and thoughts	30 s Blocks	Y	Y	Y	Y
Swain et al. (2008)	12	2–4 weeks	Own vs. other, delivery	30 s Blocks	Y	Y	Y	Y
Kim et al. (2010a)	26	2–4 weeks	Own vs. control, early-life	30 s Blocks	Y	N	Y	Y
Kim et al. (2011)	20	2–4 weeks	Own vs. other, feeding	30 s Blocks	Y	Y	Y	Y
Laurent et al. (2011)	22	18 months	Own vs. other, HPA axis	21 s Blocks	N	Y	Y	Y
Venuti et al. (2012)	9 (of 18)	>4years	Hunger cry vs. noise, atypical cry from infants with autism	10 s Events	N	N	Y	Y
	Baby cry, fathers							
Seifritz et al. (2003)	10	<3 years	Other vs. control, +ve/−ve	6 s Events	Y	Y	Y	Y
Swain et al. (2003, 2004a)	9	2–4 weeks and 3–4 months	Own vs. other, experience and thoughts	21 s Blocks	Y	Y	Y	Y
Mascaro et al. (2013a)	36	1 or 2 years	Other baby-cry vs. control sound	5s events	Y	Y	Y	Y
De Pisapia et al. (2013)	9M+9F	1 year	Hunger cry; males vs. females	14 s Blocks	N	N	N	Y
	Baby cry, maternal-pathology							
Laurent and Ablow (2012)	22	18 months	Own vs. other, postpartum depression	21 s Blocks	Y	Y	Y	Y
Musser et al. (2012)	22	18 months	Own vs. other, maternal sensitivity	21 s Blocks	Y	Y	Y	Y
Landi et al. (2011)	54	2 months	Other vs. noise, high and low distress cry, substance abuse	2 s Events	Y	Y	Y	Y

Parental brain papers are comprehensively listed in chronological order and according to responses mothers, fathers and psychopathology – to baby cry with columns for parent group, time point (age of infant), experimental paradigm, and study design. Brain networks related to parenting featured in the article are also indicated. Empty boxes indicate lack of significance in the networks defined as
(i) Arousal/Salience=amygdala, ventral striatum,
(ii) Reflex Care=hypothalamus,
(iii) Emotion Regulation=mPFC, ACC, and
(iv) Cognition=dlPFC, insula, inferior frontal and orbitofrontal gyri, temporoparietal junction.

Glossary for Table: activations and deactivations, measured by functional magnetic resonance imaging, satisfied significance criteria of random effects analysis at $p<0.05$ or fixed effects analysis at $p<0.001$ at a minimum.

that did not originate from the parent's own infant, and the control sounds were emotionally negative (sounded like harsh static on the television), significant brain responses fit with existing knowledge about regulation of parenting behavior in animals (Numan and Insel, 2003a) and opened up the field.

Hypothesizing that parental gender and experience would also influence neural responses to baby sounds such as baby

Table 2 – Human parent brain responses to infant stimuli.

Author, year	Parent group N	Age of infants	Paradigm, variable	Study design	Brain network			
					Arousal Salience	Reflex Care	Emotion Regulation	Cognition
Mothers	*Baby Visuals*							
Swain et al. (2003, 2004a, 2004b, 2005, under review	9–14	2–4 weeks and 3–4 months	Own vs. other, experience and thoughts	30 s Blocks	Y	Y	Y	Y
Bartels and Zeki (2004)	19	9 months to 6 years	Own vs. other, comparison with romantic partner	15 s Blocks	Y	Y	Y	Y
Leibenluft et al. (2004)	7	5–12 years	Own vs. other	1.5 s Event	Y	Y	Y	Y
Ranote et al. (2004)	10	4–8 months	Own vs. other	20–40 s	Y	Y	N	N
Nitschke et al. (2004)	6	2–4 months	Own vs. other, affect	30 s Blocks	N	N	Y	Y
Strathearn et al. (2005, 2008, 2009)	28–30	3–18 months	Own vs. other, affect, OT	2 s Events	Y	Y	Y	Y
Noriuchi et al. (2008)	13	15–20 months	Own vs. other, distressed	32 s Video	Y	Y	Y	Y
Lenzi et al. (2009)	16	6–12 months	Own vs. other, joy/ distress	2 s Events	Y	Y	Y	Y
Atzil et al. (2011)	28	4–6 months	Own vs. other, parenting syn	2 min Video	Y	Y	Y	Y
Barrett et al. (2012)	22	3 months	Own vs. other, parenting	3 s Events	Y	Y	Y	Y
Riem et al. (2011, 2012)	21 (Non-mom)	N/A	Cry (2 days) vs. control	10 s Events	Y	Y	Y	Y
Atzil et al. (2012)	15	4–6 months	Own videos, synchrony, OT	2 min Video	Y	Y	Y	Y
Lahey et al. (2012)	35	4–6 years	Own vs. other, parenting	13 s Video	N	N	Y	Y
Fathers	*Baby visuals*							
Swain et al. (2003, 2004a, 2004b, 2005, under review)	9–14	2–4 weeks and 3–4 months	Own vs. other, experience and thoughts	30 s Blocks	Y	Y	Y	Y
Atzil et al. (2012)	15	4–6 months	Own videos, synchrony, OT	2 min Video	Y	Y	Y	Y
Kuo et al. (2012)	10	2–4 months	Own vs. other videos, Baby vs. Doll videos	15 s Video	Y	Y	Y	Y
Mascaro et al. (2013b)	70	1–2 years	Own vs. other images, measure T, father-behav	14 s Blocks, regional	Y	Y	Y	Y
Maternal psychopathology	*Baby visuals*							
Moses-Kolko et al. (2010)	30	12 weeks	Emotion faces, depression	4 s Blocks	Y	Y	Y	Y
Schechter et al. (2012)	20	12–42 months	Own > other, IPV-PTSD	40 s Video	Y	Y	Y	Y
Moser et al. (2013)	20	12–42 months	Own > other, IPV-PTSD	40 s Video	Y	Y	Y	Y
Laurent and Ablow (2013)	22	18 months	Own vs. other – depression	18 s Blocks	Y	Y	Y	Y

Parental brain papers are comprehensively listed in chronological order and according to responses mothers, fathers and psychopathology – to visual stimuli with columns for parent group, time point (age of infant), experimental paradigm, and study design. Brain networks related to parenting featured in the article are also indicated. Empty boxes indicate lack of significance in the networks defined as

(i) Arousal/Salience = amygdala, ventral striatum,
(ii) Reflex Care = hypothalamus,
(iii) Emotion Regulation = mPFC, ACC, and
(iv) Cognition = dlPFC, insula, inferior frontal and orbitofrontal gyri, temporoparietal junction.

Glossary for Table: activations and deactivations, measured by functional magnetic resonance imaging, satisfied significance criteria of random effects analysis at $p < 0.05$ or fixed effects analysis at $p < 0.001$ at a minimum.

cry and laughter, Seifritz et al. (2003) studied four groups: mothers and fathers of children under age 3, and non-parent males and females, with 10 subjects in each group. They used an event-related fMRI design, measuring brain responses to brief 6-s sounds. Over the entire sample, intensity-matched baby sounds of crying and laughing compared to "neutral" sounds (white noise pulsed at 5-Hz with an averaged frequency spectrum similar to the infant vocalizations) produced more brain activity in bilateral temporal regions. These regions might be important for hearing processes (Heshyl's gyrus and temporal poles), processing human vocalizations, and empathic emotion processing including emotional memory. They also reported that women as a group including, parents and non-parents (but not men), showed decreased activity in response to both baby cry and laughter in the subgenual anterior cingulate cortex. This finding is contrary to the other studies (Lorberbaum et al., 1999, 2002; Swain et al., 2005; Swain and Lorberbaum, 2008) and highlights how sample selection, choice of stimuli and precision of region of interest examined might affect findings. It is also the case that a 6 s vs. a 30 s stimulus time may have different meanings to new parents or that there may be non-linear or multiphasic responses within anterior cingulate similar to the well-recognized phasic responses seen in amygdala. Their within-group analyses reported that parents activated more to infant crying than laughing in the right amygdala, while non-parent response was greater for infant laughing than crying (Seifritz et al., 2003). Although there was no direct comparison between parents and non-parents, these within-group results suggest that being a parent might be associated with changes in amygdala function and represents the first attempts to include gender and experience-dependent aspects of human parenting.

Taking this approach further, Swain et al. (2003) have been gathering data on groups of new parents across a range of experience, temperament and parent–infant interaction styles using each parent's own baby cries and including comprehensive interviews and self-reports. In this design, parents underwent brain fMRI during 30 s blocks of infant cries generated by their own infant contrasted with a "standard" cry and control noises matched for pattern and intensity. In addition, they added a longitudinal component with scans and interviews at 2 time points: 2–4 weeks and 12–16 weeks postpartum to coincide with the transition to parenthood associated with peaks of parental preoccupation in the early postpartum (Leckman et al., 1999). They hypothesized that parental responses to own baby cries would include specific activations in thalamo-cortico-basal ganglia circuits believed to be involved in human ritualistic and obsessive–compulsive thoughts and behaviors (Baxter, 2003; Leckman et al., 2004). They also reasoned that emotional alarm, arousal and salience detection centers including amygdala, hippocampus and insula (Britton et al., 2006; LeDoux, 2003) would be particularly activated by own baby cry. The experimental block design was used in order to give parents a chance to reflect on their experience of parenting and, according to our hypothesis, become more preoccupied with their infants' well-being and safety. In a group of first-time mothers ($n=9$) at 2–4 weeks postpartum, regions that were relatively more active with own vs. unknown contrast included midbrain, basal ganglia, cingulate, amygdala and insula (Swain et al., 2003). This may reflect an increase in arousal, obsessive/anxiety circuits normally more active for new parents and persistently sensitive in some mental illnesses (Swain et al., 2007). Interview and self-report studies have reported that mothers are significantly more preoccupied than fathers, and this is consistent with relatively greater activation of amygdala and basal ganglia reported in mothers compared with fathers (Swain et al., 2004a, under review). In addition, grouping mothers and fathers together across experience and comparing activity at 2–4 weeks vs. 3–4 months postpartum for own baby cry showed that significant activity shifted from the amygdala and insula to medial prefrontal cortical and hypothalamic (including hormonal control) regions. This fits well with changes in parenting confidence/experience in healthy parents, as a mother learns to associate her infant cries with more flexible social behaviors and more mature attachment, there is greater regulatory cortical brain activity and less alarm and anxiety-related activity (amygdala and insula).

2.1.2. *Brain responses to auditory baby-stimuli: baby-cry – last 5 years*

Consistent with accumulating evidence of the importance of oxytocin (OT) in establishing and regulating parenting in humans (Galbally et al., 2011), neuroimaging in humans suggests brain circuits that respond to baby-stimuli are also associated with OT pathways. In one study, mothers experiencing vaginal vs. cesarean delivery – as a proxy for higher vs. lower OT – showed greater brain activity in response to own vs. other baby-cry at 2–4 weeks postpartum in emotion regulation and limbic regions, including the caudate, thalamus, hypothalamus, amygdala and pons (Swain et al., 2008). This fits with evidence for cesarean section being associated with increased risk of postpartum depression – a condition of aberrant emotion processing (Groenewold et al., 2012). At 3–4 months postpartum, the same mothers – all of whom remained healthy – no longer showed differing responses to own baby-cry (Swain, 2011a), suggesting that any potential early-postpartum abnormalities in oxytocin are reversible. However, the relationship between Cesarean section and PPD is strongly confounded by a range of factors including low maternal age, past depression and low social supports.

Recent studies have also used breastfeeding as a proxy for maternal OT levels Imaging studies using baby cry (Kim et al., 2011), find that breastfeeding vs. formula feeding is associated with greater activations to own baby cries vs. other baby cries in anterior and posterior cingulate, thalamus, midbrain, hypothalamus, septal regions, dorsal and ventral striatum, medial prefrontal cortex, right orbitofrontal/insula/temporal polar cortex region, and right lateral temporal cortex and fusiform gyrus. Additionally, when cry response was compared with the inter-stimulus rest periods, instead of the control sound (which some mothers judged to be aversive), the amygdala was active. Furthermore, and for the first time, Kim et al. (2011) reported a correlation of brain activity to own vs. unknown baby-cry with independently-rated behavioral measures of parenting in response (amygdala) and regulation (frontal cortex) regions, suggesting the importance of balanced responses for sensitive care giving. Such

studies have led to the suggestion that, combined with behavioral strategies, acute or prolonged OT treatment may offer a safe and accessible intervention for women at risk of postpartum depression although no randomized controlled trials have emerged.

Among nulliparous women, acute administration of oxytocin has been reported to decrease amygdala responses and increase insula and inferior frontal gyrus responses to potentially adverse stimuli i.e. infant cries (Riem et al., 2011). Similarly, acute testosterone was also found to increase insula response to infant cries (Bos et al., 2010) in nulliparous healthy women. Testosterone is metabolized to estradiol, which activates neural regions important for maternal motivation. Therefore, increasing oxytocin and testosterone availability in maternal brain may modulate the processing of distressing emotional information e.g. infant cries and facilitate more appropriate responses, especially in mothers with dysregulated responses to such stimuli (see above). By contrast, greater cortisol reactivity to stress has also been associated with reduced neural responses to own baby cries (vs. other baby cries) among primiparous mothers (Laurent et al., 2011). The reduced neural responses were detected in the regions important for emotion regulation (anterior cingulate cortex and medial PFC) and maternal motivation (limbic area and periaqueductal gray). Studies such as these implicitly address effects of early-life events on later parental brain function, translating to humans some aspects of well-established rodent and non-human primate models (Champagne, 2010; Kaffman and Meaney, 2007; Veenema, 2009) as well as long-term effects of early trauma on stress axis functioning in human studies (Lupien et al., 2009; McEwen, 2008). Thus, in mothers who report higher maternal care in their own experience of childhood, greater responses to infant cries may be seen in regulatory cortical regions, including emotion regulation areas of the middle and superior frontal gyri, whereas mothers reporting lower perceived maternal care may be more likely to show increased hippocampal activations (Kim et al., 2010b) This underlines the importance for parenting of coordinated responses of these cortical and subcortical regions, as well as the importance of early life experience in the functioning of these circuits.

Recent work has also examined whether variations in infant cries are associated with maternal neural response to the cries. One study exposed nulliparous women to two different (high and low) distress levels of infant cries (Montoya et al., 2012). Interestingly, women showed greater neural responses to low distress cries vs. high distress cries in the superior and middle temporal gyri. The findings suggest that, compared to high distress cries, it was harder for women to interpret the possible causes and meaning of the low distress cries. Another study exposed a group of men and women (a half of the total participants were parents) to cries of typically developing infants and cries of infants who later were diagnosed with autism spectrum disorder (ASD) (Venuti et al., 2012). Cries of the ASD children showed abnormal features including high frequencies, which elicited more negative feelings in healthy adults and women, not men, showed greater deactivations in dorsal medial PFC and posterior cingulate cortex in response to cries of healthy infants, indicating that women recruited more attention to process the sound information than men. However, such gender difference was not detected in response to cries of ASD infants – perhaps because of abnormalities in ASD-cries that are easier to detect. Alternatively, high distress or atypical cries may inhibit maternal brain responses in some women particularly if they are rendered more sensitive to negative valence stimuli, such as with depression (Groenewold et al., 2012).

Indeed, in the first study of baby cry in women who experienced a postpartum depression, mothers at 18 months postpartum showed reduced responses to own vs. other baby in regions that process reward stimuli and promote maternal motivation – nucleus accumbens, caudate and thalamus (Laurent and Ablow, 2012). More depressive symptoms were also associated with less activity in response to own vs. other baby cry in the OFC, dorsal ACC, and superior frontal gyrus – regions important for emotion information processing and regulation, including valence and salience. Similarly, mothers who used one or more teratogenic substances during pregnancy (e.g. tobacco and alcohol) showed decreased responses to low distress cries in prefrontal cortex, insula and amygdala (Landi et al., 2011). These reports may imply that maternal depression and addiction to substances are associated with disrupted mother-infant relationships and reduced neural activation to infants, including infant cries, although whether or how such associations are causal remains to be identified. Alternatively, abnormalities in reward pathways that contributed to the likelihood of substance use might also affect parenting independently of these substances. In any case, reduced activations in the PFC may considered a candidate biomarker associated for risk of harsh, neglectful or other forms of negative parenting among high risk women such as mothers with mental illness (Goodman et al., 2011; Molitor and Mayes, 2010) and represent a future potential therapeutic target.

Parenting styles in humans are likely to be transmitted across generations (Belsky et al., 2005; Champagne, 2010) which explains in part why the neural and behavioral variations of mothering are associated with a mothers' own parental care experiences. Quality of own parenting therefore acts as a specific early life environment that should perhaps be targeted for interventions for primiparous and multiparous mothers who report low quality of maternal care. Such new mothers exhibit both reduced brain density and activation to infant cries in frontal, orbital and temporal cortices compared to mothers who reported high quality maternal care (Kim et al., 2010b). Preliminary evidence also suggests that during the first few critical months postpartum, the same regions increase in size among healthy new mothers (Kim et al., 2010a) according to voxel based morphometry.

Parenting also influences the development of attachment style in children, which in turn affects the development of a child's social information processing. For example, insecurely attached nulliparous women displayed greater amygdala reactivity to infant cry sounds than securely attached counterparts (Riem et al., 2012), suggesting that infant cries represent more aversive stimuli for them. Amygdala responses to infant cry in new mothers have also been interpreted as a form of heightened sensitivity (Barrett and Fleming, 2011). It seems that amygdala responses may be associated with negative and

positive valence brain responses – perhaps relating to unmeasured factors in maternal experience.

2.2. *What's in a baby's face?*

Not only is facial recognition of one's infant and their emotional state critical to their survival, but evidence supports human preference for the exaggerated cute/infantile features of baby faces which appear to activate reward mechanisms within the caregiver and motivate/promote mothers to caregiving, bonding and attachment. In addition to activation of nucleus accumbens (NAcc) in response to baby schema (Glocker et al., 2009) and medial orbitofrontal cortex (OFC) response to infant faces relative to adults (Kringelbach et al., 2008), higher levels of infantile features are preferred (Parsons et al., 2011). Neuroimaging also suggests that the brain responds differentially to infant, relative to adult human and adult and infant animal faces, in non-parents, in regions including lateral premotor cortex, supplementary motor area, cingulate cortex, anterior insula and thalamus (Caria et al., 2012). Interestingly, activation in OFC and fusiform face area is disrupted when an alteration to the structure of an infant face (i.e. cleft lip) is perceived (Parsons et al., 2013). Once parenthood is established, data further indicate that greater specialization of the brain occurs with for example a right-sided lateralization in the prefrontal cortex (PFC) for emotional discrimination of infant relative to adult faces (Nishitani et al., 2011), perhaps as a result of attention processing (Thompson-Booth et al., 2014).

2.2.1. *Brain responses to visual baby stimuli – 1st 10 years*

Most early fMRI studies of parental responsiveness have very small samples and detail few characteristics of mothers or fathers making findings less reliable than some larger, newer studies. We shall outline the older literature first before considering more rigorous recent papers. One set of studies used photographs taken extremely early (i.e. 0–2 weeks postpartum), by the parents themselves. Using a block design, mothers and fathers 2–4 weeks postpartum saw 6 pictures continuously for 5 s each for blocks of 30 s (Swain et al., 2003, 2006) and own vs. other baby picture contrasts revealed activations in frontal and thalamo-cortical circuits. Correlations between activations to own vs. other contrast and parent–infant interactions also revealed significant activations in superior temporal lobe, OFC and ventral tegmental areas. These networks may be important for regulation of parental motivation and reward associated with baby-directed empathy, approach and caring behaviors, as well as social bonding.

To examine whether parental love may make use of the same reward circuits as other forms of love, Bartels and Zeki (2004) used photographs of own, familiar and unfamiliar infants (9 months to 3.5 years of age) as stimuli for parent brains. In 20 healthy mothers viewing still face photographs of their own child compared to age-matched photographs of other children, they reported increased activity in midbrain periaqueductal gray and substantia nigra regions, dorsal and ventral striatum, thalamus, left insula, ORC, sub-, pre-, and supra-genual anterior cingulate, and superior medial prefrontal cortex. There were also increases in cerebellum, left fusiform, and left occipital cortex, but decreases in the left amygdala. They also compared maternal brain responses of own vs. familiar child to contrasts of best friend vs. familiar friend to control for familiarity and positive affect and argued that responses were unique to the own child's stimuli. They proposed that parent–infant attachment was regulated by a "push–pull" mechanism involving selective activation of motivation and reward systems, with cortical regions suppressing critical social assessment and negative emotion systems (Bartels and Zeki, 2004); this they argued may be extended to orchestrate positive feelings and caring behaviors.

In another report, photograph stimuli of much older own vs. other children (5–12 years old) were used as stimuli and mothers were asked to focus on identity but not feelings during scanning (Leibenluft et al., 2004). Some social cognition regions which are important for empathy were significantly activated in this paradigm, including anterior paracingulate, posterior cingulate and superior temporal sulcus (Saxe, 2006). In another small fMRI experiment using visuals across familiarity, Nitschke et al. (2004) studied six healthy, primiparous mothers' at 2–4 months postpartum as they viewed smiling pictures of their own and unfamiliar infants. They reported OFC activations that correlated positively with pleasant mood ratings to infant pictures. In contrast, areas of visual cortex that also discriminated between own and unfamiliar infants were unrelated to mood ratings (Nitschke et al., 2004). Perhaps, activity in the OFC – which may vary across individuals – is involved with high order dimensions of maternal attachment. The implication that complex aspects of parenting could be quantified using fMRI of frontal areas to predict risks of mood problems in parents is appealing but requires further detailed work. Ranote et al. (2004) conducted a similar small experiment with the innovative, and perhaps more ecological video (silent) infant stimuli in 10 healthy mothers viewing alternating 40 s blocks of own neutral, and an unknown infant. They reported significant activation in "own" vs. "unknown" infant comparison in the left amygdala and temporal pole and interpreted involvement of circuitry regulating emotion and theory-of-mind (ability to attribute feelings and states of mind to others). This fits with fMRI experiments on biological motion, which activate similar temporal cortex regions (Morris et al., 2005).

Considering the contribution of the infant's affect to maternal brain function prompted a study, again using silent video clips of own vs. other infants in play or separation situations (Noriuchi et al., 2008). First, these authors confirmed increased activation associated with own baby pictures, in cortical orbitofrontal, anterior insula and precuneus areas, as well as subcortical regions including periaqueductal gray and putamen. These areas activate in arousal and reward learning. Second, they found strong and specific differential responses of mother's brain to her own-infant's distress in substantia nigra, caudate nucleus, thalamus, posterior and superior temporal sulcus, anterior cingulate, dorsal regions of OFC, right inferior frontal gyrus and dorsomedial prefrontal cortex – regions involved in emotion regulation and habitual behavioral response systems that are active in a range of normal and abnormal emotion-control states including obsessive–compulsive disorder (Swain et al., 2007). They also found correlations in OFC with

own baby-response and happiness as well as to their own distressed baby response in superior temporal regions. This is consistent with the emerging importance of these areas in social behaviors. Socially salient, personally tailored images and video-clips are now being combined with behavioral measures to understand better the functional architecture of parental brain. Taken together, fMRI experiments with parents, especially those using own vs. other/unknown baby visual stimuli commonly activate emotion/motivation-reward areas along with cortical regulation areas, thus laying the groundwork to test hypotheses about how such brain structures regulate parental thoughts and behaviors.

For example, empathy may be conceived as a key parenting thought process and studied in mothers observing and imitating faces of their own and someone else's child (Lenzi et al., 2009). In this study, regions believed to contain mirror neurons and connected limbic regions, including insula and amygdala respectively, were more active during emotional expressions from own child. Furthermore, the insula response correlated with the empathy-related measure of maternal reflective function. They also reported that baby joy expressions across identity evoked mostly right limbic and paralimbic areas important to emotional processing, whereas ambiguous expressions elicited responses in left-sided, high order cognitive and motor areas, logically reflecting associated cognitive effort and preparation to respond.

In addition to the capacity for complex empathic thoughts toward their infant, parents require motivation to undertake interactive behaviors and to derive reward from interacting with their infants. Integrating brain areas relevant for these actions with key hormones is likely to reinforce behaviors and provide for optimal parental sensitivity under a range of circumstances. Considering some of these complex factors, 28 healthy, first-time, singleton mother–infant dyads at 5–10 months postpartum were involved in one series of studies using visual infant facial cues of varying affect (smiling, neutral and crying) and scanning at 7–17 months postpartum. Notably, this is well past the ~3 month postpartum threshold for sophisticated social dyadic interactions (Strathearn et al., 2005, 2008). Dopamine-associated reward-processing regions were activated when mothers viewed their own vs. an unknown infant's face, including ventral tegmental area/substantia nigra, and striatum. In addition, there were frontal lobe responses in emotion processing (medial prefrontal, anterior cingulate, and insula cortex), cognition (dorsolateral prefrontal cortex), and motor/behavioral outputs (primary motor area). Furthermore, happy, but not neutral or sad own-infant faces, activated nigrostriatal brain regions interconnected by dopaminergic neurons, including substantia nigra and dorsal putamen. Finally, a region-of-interest analysis revealed that activation in these regions was related to positive infant affect (happy > neutral > sad) for each own-unknown infant-face contrast.

2.2.2. *Brain responses to visual baby stimuli – last 5 years*

In pursuit of the role of oxytocin in modulating the parental brain, Strathearn et al. (2009) studied a total of 30 first-time mothers using a variety of affect-laden baby picture stimuli in combination with the Adult Attachment Interview and peripheral plasma oxytocin responses to infant play. In response to their own infant's smiling and crying faces during fMRI, mothers with secure attachment showed greater activation of brain reward regions, including ventral striatum, and oxytocin-rich hypothalamic/pituitary regions. These results chime with effects of own parenting on fMRI activations to infant stimuli and suggesting that individual differences in maternal attachment experiences might also be crucial to measure in future imaging studies, and perhaps that they are linked with development and integration of dopaminergic and oxytocinergic neuroendocrine systems in striatum and hypothalamus.

In last few years, parental brain circuitry has been studied in the context of variables associated with parental illness (such as depression, anxiety, and substance misuse), and the work highlights regions-of-interest such as the amygdala, anterior cingulate cortex (ACC), PFC, insula and striatum. In a comparison of own-positive vs. unfamiliar-positive infant images, left amygdala response was reduced as a function of poorer concurrent maternal experience (measured by depression, anxiety, parental distress and attachment-related feelings about the infant) (Barrett et al., 2012). In a study employing similar task conditions, reduced dorsal (d) ACC activation to own-distress images was reported in depressed relative to non-depressed primiparous women (as measured by the Structured Clinical Interview for DSM-IV) (Laurent and Ablow, 2013). As a function of increased depressive symptomatology Center for Epidemiological Studies Depression (CESD) measure, reduced response was observed in the OFC and insula to own-joy faces and in left PFC and insula/striatum to own-joy vs. own-distress faces. Though infant stimuli were not included, brain response to negative emotional faces (fear and anger) in depressed vs. healthy postpartum women has been examined, yielding observations such as reduced dorsomedial (dm)PFC activation in depressed vs. healthy women to faces; a negative correlation between left amgydala and depression severity in depressed women; a positive correlation between right amygdala and absence of infant-related hostility in depressed women; and negative functional connectivity between left dmPFC and left amygdala in healthy, but not depressed women (Moses-Kolko et al., 2010). Finally, in a study examining substance users in the postpartum period relative to non-substance users, reduced activation to infant faces was reported in dorsolateral (dl)PFC, ventrolateral (vl)PFC, occipital regions, parahippocampus and amygdala (Landi et al., 2011). These studies suggest that maternal adversity and/or substance misuse may specifically be associated with reduced activation in reward and emotion circuits, with some indication that top-down connectivity between the PFC and limbic regions also may be compromised (Moses-Kolko et al., in press).

2.2.3. *Brain responses to mother–baby dyad movies*

Recent studies have employed mother–child dyadic vignettes as visual stimuli in the study of the parental brain. In one small but intriguing study, parental adversity, as defined by interpersonal violence-related posttraumatic stress disorder (IPV-PTSD), was examined. Motivated by findings demonstrating atypical caregiving in PTSD mothers following separation, vignettes of own vs. unfamiliar toddlers during play and following separation were presented to healthy mothers and those with IPV-PTSD (Schechter et al., 2012). IPV-PTSD mothers

vs. healthy mothers (11 vs. 9) reported greater stress to viewing separation vignettes, greater limbic and reduced fronto-cortical activity was observed in IPV-PTSD mothers relative to healthy mothers in separation vs. play conditions, with reports of stress to viewing separation linking to the neural findings. These results are consistent with those in depression indicating reduced fronto-cortical activity in response to own vs. other baby-cry (Laurent and Ablow, 2012). A follow-up study of the same subjects reported correlation between limbic brain activations in response to own-child video vignettes and dissociative symptoms (Moser et al., 2013), suggesting dissociative symptoms as a mechanism for reduced maternal sensitivity among mothers affected by IPV. More work with mothers affected by high-risk circumstances, such as IPV, depression and anxiety is needed to clarify and substantiate findings and begin to inform treatments.

So far, however, a few other studies have assessed parental brain response to mother–infant dyadic vignettes as a function of optimal vs. non-optimal parenting. Atzil et al. (2011) categorized participants with a synchronous, relative to intrusive, parenting style and asked them to view vignettes of their own infants; of themselves interacting with their infants and those of unfamiliar infants and dyads. In another study, when own vs. other infant vignettes were compared, maternal synchrony was associated with significantly increased activity of left NAcc, while maternal intrusiveness was linked to activity of right amygdala (Atzil et al., 2012). However, in this experiment, it is unclear whether this pattern of brain response was a function of synchronous mothers or the viewing of a synchronous mother–infant interaction. This group has also examined the role of oxytocin, reporting positive correlations between cross-sectional plasma oxytocin levels and activation in the left NAcc, left insula, left intraparietal lobule, left and right temporal cortices, left sgACC, and left NAcc and right amygdala in mothers, and a range of frontal cortical areas in fathers. More studies with rigorous identification of maternal caregiving quality and parenting style with brain imaging are required (Wan et al., 2014).

Accumulating research confirms what most people, and nearly all mothers know to be the case: infant stimuli occupy a privileged status for the adult human brain, which may be modeled as in Fig. 1. Auditory and visual signals from preverbal infants can enhance brain regions important to recognition, emotion and motivation (i), reflexive caring behaviors (ii), emotion regulation (iii), and empathy/theory of mind toward sensitive caregiving and attachment in order to increasing the likelihood that the vulnerable infant will survive into adulthood and successfully navigate the social world and find a mate.

The early study of parental brain employed a variety of baby audiovisual stimuli to elucidate a putative neurocircuitry for parenting. More recently, studies have added correlations with psychometrics of parenting, parental adversity (e.g. poor maternal experience, attachment, perinatal depression and PTSD) as well as indices of parenting quality (e.g. synchronicity and maternal sensitivity) and finally neuroendocrine measures (oxytocin).

In spite of this encouraging scenario, important problems with study design, gaps in the evidence-base and inconsistencies between studies mean many questions remain to be answered. First, we need better understanding of how the brain manages the presentation of static individual baby images relative to moving images involving the dyad. Does different responses to a vignette reflect something specific to the participant or to the vignette itself? Second, we have to understand how findings from neuroimaging studies examining perception of infant stimuli relate to the capacity for affective cognition of individual mothers and fathers. Future neuroimaging studies assessing parental affective cognition alongside behavioral measures of parenting may change our view of a dedicated parental circuitry. The findings from extant parental brain studies that have employed reverse inference in interpretation would be strengthened by studies that select more constrained and better described samples using more sophisticated paradigms. Third, imaging paradigms have explored the effects of only a few forms of parental adversity or mental illness. It is difficult to design a study which can selectively examine or isolate the effects of, for example, the severe chronic stress of poverty, young maternal age and early life trauma, and no studies have yet focused on resilience or the rescuing of adversity following intervention. We still know far too little about how or whether behavioral or neural correlates of maternal sensitivity/maternal responsiveness are modifiable. However we have reason to be cautiously optimistic given recent brain imaging studies of parents and the development of biomarkers for depression and its treatment (Harmer et al., 2011). Among possible medical treatments for low maternal sensitivity, oxytocin has been proposed. The following section examines points of intersection between the parental brain and oxytocin, and possible mechanisms that might inform studies which examine modulation of maternal responding in brain and behavioral paradigms through the use of oxytocin.

3. Parenting – connections between brain and oxytocin (OT)

The posterior pituitary neuropeptide hormone, oxytocin (OT), is a well-recognized component of a complex biobehavioral system crucial for the emergence of mother–infant bonding (Ross and Young, 2009). Research in rodents and other mammals has highlighted the importance of OT (on a background of changing levels of estrogen and progesterone during pregnancy and labor) to facilitate the onset and maintenance of maternal behavior (Champagne et al., 2001, 2003; Champagne, 2008; Insel and Young, 2001; Rosenblatt and Ceus, 1998). This was first suggested from studies that reported display of “full maternal behavior” in virgin female rats injected with OT (Pedersen and Prange, 1979). Conversely, inhibition of postpartum maternal behavior was affected in rats by injecting them with an OT-receptor antagonist (van Leengoed et al., 1987). Among high “licking and grooming” (i.e. maternal caregiving) female dams, significantly higher levels of OT receptors were also seen in brain regions implicated in the expression of maternal behavior across species, during pregnancy, at parturition and when nursing pups, such as the central nucleus of the

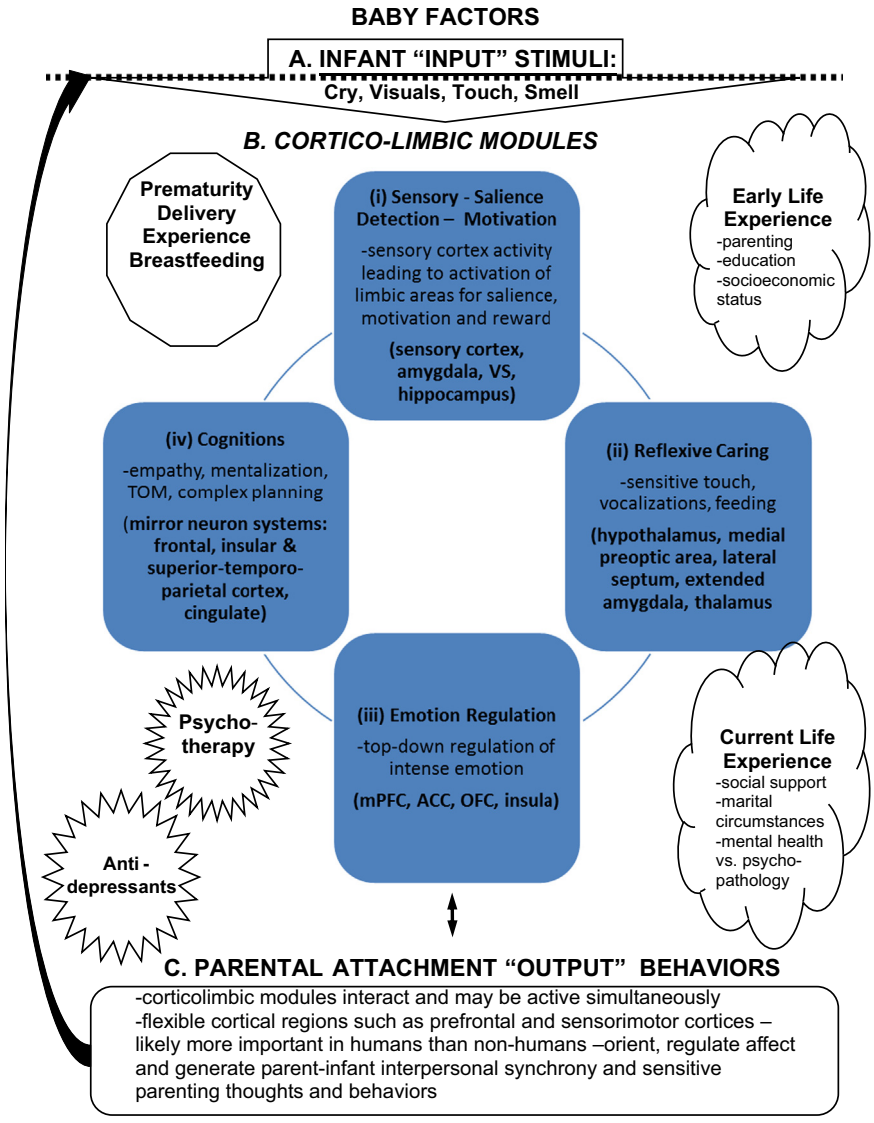

Fig. 1 – Human parental circuits. Brain regions expected to be important to human parenting. This is based on human and animal studies. Based on brain imaging of parents to this point, the following model is presented to stimulate discourse on the brain basis of parenting behaviors. First, key parenting sensory signals, including cry, visuals as well as touch and smell from baby (A) activate in parallel a set of cortico-limbic circuits (B) to (i) analyze the sensory input and update saliences toward motivation and reward and coordination of other modules for (ii) reflexive caring, (iii) emotion regulation, and (iv) complex cognitions, including mentalization, empathy and theory of mind. The output (C) of these modules forms the basis of parental sensitivity and influences child development. This inclusive and general model may be dissected in future studies involving different stimuli and specific measures of behavior and cognition.

amygdala and the paraventricular nucleus of the hypothalamus (Champagne et al., 2001). Following birth, the female offsprings of "low" licking and grooming mothers, who are cross- fostered and reared by "high" licking and grooming mothers, express a higher density of brain OT receptors than non-cross-fostered females, and similar levels to high licking and grooming mothers – suggesting that there is intergenerational transmission of the behavior sensitive to the rearing environment and likely dependent on epigenetic processes (Champagne, 2008).

Evidence for a similar "transition to maternity" affected by hormonal exposure during pregnancy and childbirth in human mothers is notably less robust, but also supports a role for OT during pregnancy. Mothers with a rising pattern of plasma OT reported higher maternal fetal attachment in the postpartum (Levine et al., 2007), and higher plasma OT levels during pregnancy and the first postpartum month were correlated with higher levels of maternal postpartum behaviors toward infants, such as gaze, vocalizations and positive affect in new mothers (Feldman et al., 2007). Maternal synchrony ("episodes when mother and infant coordinate their positive social engagement") is also reported to be positively correlated with maternal plasma OT level, while maternal intrusiveness ("inappropriate response from mother") is not

(Atzil et al., 2011). OT plasma levels have also been examined in relation to maternal own-attachment experience (Strathearn et al., 2009): higher levels of plasma OT were reported following mother–infant physical interaction among mothers reporting secure attachment patterns with their own mothers compared to those with insecure attachment patterns. Even among non-parents, plasma OT levels have been positively correlated with self-reported recall of parental care (maternal and paternal care) (Feldman et al., 2012; Gordon and Feldman, 2008).

The literature also points to a role for OT in the regulation of stress responses. Indeed, a well-established view has emerged that, in humans, OT is anxiolytic and reduces fear and stress (Ayers et al., 2011; Ishak et al., 2011). Studies imply that this role is influenced by an individual's previous experiences and difficulties in interpersonal relationships (Tabak et al., 2011): difficulties in relationships with primary partner (Taylor et al., 2006), or own infant (i.e. interactive stress) (Feldman et al., 2011), or romantic partner (Marazziti et al., 2006). These studies have all reported higher levels of cross-sectional plasma or urinary OT in relation to stress in social relationships. Some have concluded that OT appears to be an indicator of social affiliation, but it might also be a "signal" for the need to affiliate with others (Taylor et al., 2010).

Overall, a large and robust animal literature exists on OT's role in maternal care behavior and an accumulating, albeit weaker human literature associates plasma OT with a wide range of social and emotional stimuli; scenarios, ranging from romantic love, or marital distress to psychopathology. Interactions between central OT and dopamine systems have also been associated with individual differences in maternal behavior in rodents. For example, stable, individual differences in rat maternal licking/grooming of pups were abolished by OT receptor blockade mediated by the direct effect of OT on dopamine release within the mesocorticolimbic dopamine system (Shahrokh et al., 2010). While animal models of maternal behavior are compelling and have identified key regions in a putative mothering circuit, human behaviors are undertaken in a far more complex environment. As outlined above, processes such as cognitive flexibility, attention control, working memory, and the mother's ability to understand the intentions and emotions of her child (maternal mind-mindedness or empathy) are fundamental components of human mothering and highly dependent on PFC. Additionally, several studies mentioned already above (Atzil et al., 2011, 2012; Riem et al., 2011; Strathearn et al., 2009) have attempted to assess neural circuitry related to parenting in subcortical reward/limbic regions as a function of plasma oxytocin levels.

The clinical implications of these studies are yet to be fully explored. However, preliminary observations that expectant mothers at risk for postpartum depression have lower plasma OT during pregnancy (Skrundz et al., 2011) may suggest value in interventions which enhance availability of central OT during pregnancy and perinatally in order to reduce risk of postpartum depression. Perhaps certain administration regimes may be explored to overcome likely problems with the overlapping role of OT in uterine contraction during pregnancy and the risk therefore of inducing premature labor. Therapeutic uses of oxytocin are currently being investigated in other neuropsychiatric disorders associated with poor social cognition, including ASD, OCD and schizophrenia (e.g. Bartz et al., 2011; Macdonald and Feifel, 2013). However, in order to understand the potential effects of exogenous oxytocin administration in humans, several important lessons from decades of animal research bear consideration. First, oxytocin effects are moderated by robust, hard-wired neurobiological mechanisms; thus, centrally administered oxytocin increases aggression to same-sex intruders after mating in monogamous Prairie voles, but not in non-monogamous Montane voles (Winslow et al., 1993). Similarly, preexisting "primers" are necessary to induce oxytocin-facilitated social bonding in monogamous Prairie voles, and, depending on the study designs, these primers can be gonadal hormones (e.g. estrogen), mating behaviors, or prolonged preexposure to a former stranger (for an early review, (Insel, 1997)). In other words, exposure to oxytocin alone is not sufficient to create de-novo social bonding. It seems likely that oxytocin facilitates the development of social bonds only when acting in the appropriate environment.

These findings have several critical implications for humans. Oxytocin administration is likely to affect individuals according to their existing social cognition and attachment styles as well as their past experiences, much like with the monogamous Prairie vole and non-monogamous Montane vole. It is unlikely that acute or chronic exogenous oxytocin administration alone can reverse genetically and/or environmentally determined affiliation/attachment styles. Oxytocin administration is likely to affect individuals according to their existing social cognition and attachment styles as well as their past experiences, much like with the monogamous Prairie vole and non-monogamous Montane vole. So, although performance on tasks highlighting empathy (such as trust games) can be enhanced by acute OT administration and empathic interactions can similarly increase plasma OT levels and subsequent generosity in humans (Barraza and Zak, 2009), cultivating empathy in an "uncaring" individual is likely to be a more complex process; not least because its maintenance will surely rely on the accumulation of repeated positive experience. In support of this, oxytocin administration exerts no significant behavioral change in strangers who share no preexisting bonding relationship (Barraza et al., 2011; De Dreu, 2012b; Kosfeld et al., 2005; Zak et al., 2007) and a recent report finds that intranasal OT does not enhance approach/avoidance to social stimuli or exert a stronger effect on social vs. non-social stimuli in the context of processing emotional information but increases the salience of certain social stimuli and moderates salience of disgust stimuli (Theodoridou et al., 2013). Authors postulated that heightened responses to disgust may be particularly relevant for new mothers wishing to protect vulnerable young from contagion.

The positive effects of exogenous OT on social cognition may only be observed when the tasks demand a binding relationship in which reward contingencies are congruent between two players, where they form a partnership by becoming stake holders of common interest (Barraza et al., 2011; Kosfeld et al., 2005; Zak et al., 2007).Oxytocin administration also appears to increase polarized social behaviors in humans, e.g., in-group favoritism (De Dreu et al., 2011), by increasing within group cooperation and between group

competition (De Dreu, 2012a) and its administration may increase the emotional reactivity to perceived positive *and* negative cues in a social context (Olff et al., 2013). When social cues in the environment are interpreted as secure or positive ("me among us"), oxytocin may promote prosocial behaviors. In situations of higher threat or higher social stress, when the social cues are interpreted as insecure or negative ("me among them"), oxytocin may promote "anti-social" behaviors. This suggests that exogenous OT may serve to sharpen in/out group distinction (Colonnello et al., 2013).

Interestingly, it was found that OT levels in mothers, assayed from urine, were higher after interaction with children, no matter whether these were their own or unknown children (Bick and Dozier, 2010); also see Elmadih et al., 2014. In fact, OT levels appeared to be higher if the child was unknown compared to when the child was their own – perhaps serving an anxiolytic or anti-stress function in this particular experiment (Heinrichs et al., 2003). It may also fit with a role for OT in maternal protection and aggression towards intruders in several species including humans (Campbell, 2008; Neumann, 2008). Finally, in articles from this special issue, OT was measured and administered in respective experiments on mother behavior and non-mother responses to infant pictures. New mothers with low sensitivity showed *higher* plasma OT before and after playing with their infants compared to mothers with higher than average maternal sensitivity (Elmadih et al., 2014). These data suggest that OT is released as part of a stress response related to poor ability to cope with infant demands and may be moderating maternal stress in an attempt to promote care and bonding. This is complemented by the report that amygdala response to infant pictures among nulliparous women are enhanced by intranasal OT yet with more incorrect facial expression interpretation (Voorthuis et al., 2014) – again suggesting a role for OT in enhanced coping that may even interfere with nuanced responses to infant stimuli – although findings may be different among parents or with different OT administration protocols.

The complex literature on the effects in humans of externally administered hormone argue for further refinements in our understanding of how, and in what direction OT (measured in the plasma or elsewhere) is, or is not, causally associated with behavioral or emotional manifestations in people. When someone inhales OT, evidence points to its effects being determined by past experiences and present circumstances. For example, we observe that intranasal oxytocin may increase startle responses to stressful stimuli in humans (Grillon et al., 2013; Striepens et al., 2012) and that less anxiously attached, healthy men remember their mother as more caring and close after OT (vs. placebo), while more anxiously attached men remember their mother as less caring and close after OT (vs. placebo) (Bartz et al., 2010). Finally, healthy men with low emotion regulation abilities show higher cortisol stress responses (as expected), but also benefit more from intranasal OT; whereas those with high emotion regulating abilities do not (Quirin et al., 2011). This chimes well with early studies (Light et al., 2000) that reported increased plasma OT in mothers following a social stress task only when the mother held her baby before the task, but not if she did not.

3.1. *Controversies and limits to the OT literature in parenting*

The nature of the interaction between peripheral and central OT systems moment-to-moment remains elusive. Recent evidence in 41 non-psychiatric subjects concluded that there is no correlation between baseline CSF and plasma OT levels measured using sensitive radioimmunoassay (Kagerbauer et al., 2013). These authors rigorously appraise past literature using basal measurements of peripheral OT to reflect central effects of the hormone in humans, particularly in studies proposing links between plasma/salivary OT and human social behaviors. Such a critique of the evidence must caution future studies to acknowledge that OT occupies two physiologically distinct compartments (periphery and CSF) resulting in quite independent release patterns. This suggests that measuring plasma OT as a biomarker of a socio-emotional behavior assumed to be regulated by brain perhaps remains relevant only if a dynamic challenge paradigm is used with comparisons between distinct, well-characterized groups. Kagerbauer et al. (2013) acknowledge the relationship between gender, gonadal hormones and plasma OT; but they also point to a high quality study in pregnant women showing no correlation between plasma and CSF OT levels (Altemus et al., 2004).

Understanding how intranasal oxytocin affects human social behaviors clearly requires more thoughtful experimentation. These considerations do not foreclose the potential for exogenously/intranasally administered OT to reach brain and affect behavior relevant to parenting. Indeed, intranasal drug administration is increasingly favored as an effective means of delivering molecules rapidly to brain (Grassin-Delyle et al., 2012). But it is likely that effects are not only sex-specific, but task specific (some suggest that OT does not change the salience of social–emotional cues) and task-specific between sexes (Ditzen et al., 2012). Beyond pregnancy and infancy, we have little information on how the OT system functions in socio-emotional relationships during periods of rapid brain reorganization (e.g. puberty) vs. those of relative developmental stability and we know little in humans about brain OT-receptor distributions and densities and how they may be influenced by environmental effects and epigenetic regulation overtime and circumstance. To what extent central OT receptors are sensitive to epigenetic modification in humans and whether, like in the rodents from Champagne's (2008) work, they contribute to patterns of parental care that can be passed on (in a quasi-Lamarckian fashion) from generation to generation, are closely related questions. Other hormones and their receptor systems, including cortisol, estrogen, progesterone, endogenous opioids, are also important in the regulation of parenting and interact with OT (Gordon et al., 2011; Lahey et al., 2012; Nowak et al., 2011; Swain et al., 2011)

In summary, the complex links between OT and parental brain physiology in humans requires further, more detailed examination, taking into account key individual differences and maternal experiences past and present into account, in addition to other hormones, in order to appropriately interpret the inferences that can be drawn from studies using basal peripheral measures of the hormone alongside behavioral correlates.

4. Advances on the neurobiology of father brain

Studies of parent–infant interactions have historically targeted the mother–infant relationship. However, more recent research has demonstrated that fathering also plays a significant role for the child's cognitive, emotional and social development (Lamb, 2004; Ramchandani and Psychogiou, 2009). For example, literature examining parental behaviors suggests gender differences in expressed emotion during interactions with children (Volling et al., 2002). Specifically, maternal sensitivity is typically expressed by emotional warmth and support whereas paternal sensitivity frequently manifests as the provision of stimulating interactions (Grossmann et al., 2008). This gender difference is supported by a study of a time series analysis of 100 first-time mothers and fathers interacting with their 5-month-old firstborn child (Feldman, 2003). Mother–child play was characterized by face-to-face exchange and included patterns of mutual gazing, covocalization, and affectionate touch. In contrast, during play with fathers, a pattern of interactive arousal was identified that contained several quick peaks of high positive emotionality, including joint laughter and open exuberance.

Behavioral data with fathers have demonstrated important differences in typical father vs. mother–child interactions beginning in infancy (Crawley and Sherrod, 1984; Feldman, 2003). Fathers, for example, tend to exhibit increased physical interactions with their young children, often characterized as “rough and tumble” play (Carson et al., 1993). Furthermore, within father–child relationships, it is the quality of active, parent–child play interactions, and not sensitivity per se, that is related to positive social emotional outcomes in children such as interpersonal confidence and the development of positive peer relationships (MacDonald, 1987). These data suggest that there may be some shared brain mechanisms between mothers and fathers, and some differences. Recently, an interesting study with small groups showed that males respond differently to non-own hunger cries than mothers (De Pisapia et al., 2013). Studying 9 men and 9 women (half in each group non-parents), more activity was seen in the dorsal medial prefrontal and posterior cingulate areas of male brains regardless of parental status. Such sex differences were interpreted as relating to mind-wandering in men relative to women. Sex differences between mothers and fathers may relate to the establishment and maintenance of specific aspects of parent–infant relationship and warrant a further study. A theoretical basis for sex differences may be found in differential roles of mothers and fathers in the development of exploratory systems in the infant and young child according to activation relationship theory (Paquette, 2004). This theory includes two dimensions of fathering that underlie the father–child relationship: (1) *stimulation*, wherein fathers encourage the child's interaction with the outside world; and (2) *discipline* designed to provide children with limits that will maintain their safety (Paquette, 2004).

Such specialization of father–infant interactions is consistent with play studies showing more object-oriented or physical play associated with smiles compared with mother–infant interactions (Dickson et al., 1997; Feldman, 2003; Lamb, 1977; Yogman, 1981). Thus, unique contributions from father–child interactions (Boyce et al., 2006; Grossmann et al., 2002) to evolutionarily favorable sex-specific emotional expressions of the developing child may significantly constitute the mechanism through which sex differences in the expression of emotion (Vigil, 2009) cross generations.

The differential nature of father– vs. mother–child relationship suggests that the underlying neurobiology of fathering behaviors may be at least in part distinct. For example, in the model presented here (Fig. 1), paternal salience appraisal of infant stimuli may activate an emotional regulatory reaction in fathers that is stronger than that evoked for mothers. This kind of a response would underlie paternal capacity and motivation to effectively assess external contextual factors to determine whether situations are sufficiently safe to encourage the child's engagement and interactions with the broader social environment. In contrast, hormonal changes corresponding to the perinatal period may result in a stronger reflexive caring response for mothers. Finally, empathic/mentalizing cognitive responses to infant cues may be similar for mothers and fathers, as it supports all types of parenting responses and behaviors – at least after an initial period of adaptation of some months. This is not well studied but at least in keeping with the observation mother vs. father statistical equivalence of correct identification of own vs. other baby-cry (Swain et al., 2005).

Preliminary work on the brain physiology of parents is consistent with significantly overlapping neurobiological and behavioral parenting processes for mothers and fathers with some interesting differences. For example, using the fMRI methodology with a sample of coparent couples of 4–6-month old infants, Atzil et al. (2012) found greater activation in limbic areas in response to own-infant (vs. other infant) video clips for mothers (and not fathers) as well as correlations of these areas (e.g., NAcc, amygdala, and ventral ACC) with increases in plasma oxytocin (OT) levels. In contrast, *decreases* in plasma OT for fathers were correlated in own- vs. other-infant comparisons, primarily with cognitive areas, including areas that are responsible for regulating and organizing behavioral responses to emotionally salient stimuli (e.g., dorsolateral PFC, dorsal ACC, IPC, and precentral gyrus). Further, in fathers (and not mothers), increases in plasma arginine vasopressin (AVP) were correlated with activations of the inferior frontal gyrus (IFG) and insula suggesting an increased social-cognitive response to infant cues for fathers.

Using similar methodology with a sample of young infants (8–19 weeks), the brain responses of fathers to own vs. other infant videos (Kuo et al., 2012) were obtained. Whole brain analysis demonstrated increased activity in emotion regulation (iii) circuits, including bilateral inferior frontal gyrus, and the empathic/mentalizing (iv) module including supramarginal (parietal) gyrus and bilateral middle temporal gyrus among human fathers ($N = 10$) in response to own (vs. other) baby stimuli. In addition, on the contrast of baby (both own and other babies) vs. doll video contrasts, fathers exhibited increased activity in all modules (Fig. 1): Sensory/Salience (i), Reflexive Caring (ii), Emotion regulation (iii), and Empathic/Mentalizing (iv), including bilateral caudate, orbitofrontal cortex, superior frontal gyrus, and superior parietal lobe.

Activation of these systems plausibly supports a father's ability to attend to the infant and the surrounding environment and react as necessary to promote infant–environment interactions or to protect the infant from environmental dangers. Interestingly, greater responses to own (vs. other) baby stimuli in the PFC were associated with less paternal sensitivity. The findings may reflect the greater role of the OFC in interpretation of the unfamiliar infant cry among fathers.

Using infant photographs instead of video clips to stimulate father brains, Wittfoth-Schardt et al. (2012) found activations for own child in the left GP, the left hippocampus, the right mOFC (ii & iv, Fig. 1), as well as in the bilateral inferior frontal gyrus/anterior insula (iv) and activations for own child vs. other (unknown) child in the right GP, the left VTA (ii), the left mOFC, and the left inferior frontal gyrus(IFG)/anterior insula (iv). Additionally, OT administration reduced activation and functional connectivity of the left GP with reward- and attachment-related regions responsive to pictures of both own and unfamiliar child. Furthermore, in recent analyses of father brain activity, using an own vs. other child vs. adult picture task 1–2 years postpartum (Mascaro et al., 2013b), there was a main effect for child vs. adult pictures in the fusiform gyrus, dorsal medial prefrontal cortex, thalamocingulate and mesolimbic areas – fitting with arousal, reflexive caring and emotion regulation parental brain circuits (Fig. 1). VTA responses were associated with reduced testosterone levels, smaller testes volume as well as higher parental sensitivity. The findings support that fathers may gradually develop a strong attachment with their infants over the course of the first and second years, and the attachment building processes may be supported by neurobiological adaptations such as increased neural sensitivity to own infants and decreased testosterone levels. In response to 3–5 month-old infant cries, similar to the findings in mothers were reported for fathers 1–2 years postpartum (Mascaro et al., 2013a), including responses in bilateral IFG and GP. Furthermore, variations in androgen receptor gene were associated with activations in IFG and OFC – areas also involved in empathy and emotion regulation (iii & iv, Fig. 1). Anterior insula activity had a non-linear relationship with paternal caregiving, such that fathers with intermediate activation were most involved. These results suggest that restrictive attitudes may be associated with decreased empathy and emotion regulation in response to a child in distress, and that moderate anterior insula activity reflects an optimal level of arousal that supports engaged fathering.

Finally, the father brain structure is also being examined based on animal models (Kinsley and Lambert, 2008), and one neuroimaging report on gray matter volume increases in a number of brain regions of human mothers – including the striatum, thalamocingulate, and PFC from the first month (T1) to the fourth postpartum month (T2) (Kim et al., 2010a). For new fathers, gray matter changes may be associated with depression symptoms and paternal behaviors (Kim et al., submitted for publication). Ultimately, models that combine changes in structure and function may be required for comprehensive biological models of paternal behavior that may help identify biomarkers for risk, resilience and intervention.

In summary, brain imaging studies of the father brain over last few years have yielded functional and structural results that fit with a picture of paternal brain-behavior adaptations coordinated with relevant hormones after having a child in support of adaptive parenting. Future work will no doubt explore similarities and differences to the maternal brain.

5. Conclusions and future directions

By mapping parental brain responses to infant stimuli, non-invasive and highly sensitive functional magnetic resonance imaging (fMRI) has added greatly to our knowledge of the brain basis of parental sensitivity. Furthermore, it has been confirmed that the observed maternal behavior reflects a physiological composite of multiple behaviors, with discrete maternal brain activation likely to occur in relation to each aspect of this behavior. Such conceptualization presents the possibility of identifying distinct neuro-hormonal pathways to poor maternal sensitivity, and of using changes in brain activation in response to infant stimuli as potential biomarkers for the development and evaluation of new diagnostic and treatment strategies in at-risk parents.

Indeed, there are now many examples in which brain imaging can identify changes in neuronal activation that elude behavioral measures. For example amygdala activation and connectivity is significantly increased during subconscious processing of fearful faces (Pantazatos et al., 2012). fMRI might then provide insight into the neural basis of subconscious or "automatic" parental responses (Papousek and Papousek, 2002). Similarly, behavioral measures of emotional function can be relatively insensitive, whereas using affective cognition challenges, fMRI has allowed the identification of important biomarkers for psychopathology and for treatment response in depression such as the amygdala and ACC (Groenewold et al., 2012; Harmer et al., 2009, 2011). In this way, imaging data complements and enhances behavioral information. For example, observational measures of behavior can address questions about whether a parent at risk of poor maternal care (or poor maternal sensitivity) has biases in attention systems, but only imaging can address questions about how such a parent attributes salience or valence to emotional images of her own as compared to an unknown infant, and how they might differentially engage brain reward systems. A combination of brain imaging *plus* behavioral paradigms seems more likely to result in enhanced mechanistic specificity. Thus, if we find impaired performance in a parent behaviorally when he or she is under stress, then the imaging may be able to indicate if this is because of over-activity in limbic stress systems (e.g. enhanced amygdale and insula activation to stressful cues) and/or because prefrontal control systems are underactive, making executive performance more readily disrupted. Having more information about *which* neural mechanisms drive *which* behavioral outcome has important implications for designing more effective interventions – e.g. depending on the parent, interventions may focus on reducing stress responses, or improving executive performance, or both.

The interpretation of fMRI data on parents' brains responding to infant stimuli carries important caveats. These include consideration of timing, averaging of signals and the limitation of the paradigms themselves, which represent a

set of circumstances quite different from those actually experienced by a human parent in real-time with their own infant (Hari and Kujala, 2009; Schilbach et al., 2013). Lying in a magnet observing audiovisual stimuli is far from actual parenting and the field is working toward more ethologically accurate paradigms for use in brain imaging experiments of parental responsiveness.

In spite of these caveats and need for replication, fMRI studies of parental brain have revealed a set of cortico-limbic brain circuits that are activated in response to infant stimuli, and some of which track objectively measures parental sensitivity (Kim et al., 2011; Musser et al., 2012). Since parental behavior necessarily changes as infants grow and mature, so too do we have evidence that brain imaging activations change over time among healthy new mothers (Kim et al., 2010a) Plausible next research steps could include studies of the biological mechanisms required for specific aspects of parental brain adaptation. Such approaches to brain plasticity may be fruitful to understand the pathophysiology of parent-infant relational problems as well as potential opportunities for risk/resilience identification and brain-based intervention research. Intranasal oxytocin remains an interesting candidate to help augment parenting in future therapies.

Over the past decade, a number of clinical studies demonstrate the positive effect of intranasal OT (exogenous OT) on emotion recognition/social anxiety (e.g. (Guastella and MacLeod, 2012) and affiliative behavior between individuals (Riem et al., 2011), including fathers (Weisman et al., 2012). These suggest that OT administration may be indicated for vulnerable parents with poor maternal sensitivity, although caution is still required (Tabak et al., 2011). If fMRI can discriminate different patterns of brain activation between parents at opposite ends of a spectrum of high and low maternal sensitivity, it prepares the way for future efficient hypothesis testing of the effects of novel interventions in small numbers of normal volunteers. In other words, a distinct neural profile of "higher" sensitivity parents or parenting response means functional imaging may identify useful "biomarkers" for future interventions; for example, monitoring the effects of intranasal OT or non-drug interventions aimed at enhancing parental responsiveness on aspects of neural circuitry.

We would argue that fMRI utility derives from the proposal that specific fMRI activation patterns could act as objective biomarkers for treatment development and in risk identification. We would suggest that future work using fMRI in new parents should assess affective cognition and how it relates to parental care behaviors before and after interventions in order to determine underlying neural pathways for what is, and what is not "working" with respect to the parental care. Such a model is already being developed for the mood disorders, in which fMRI studies have consistently demonstrated that limbic hyperactivity in response to emotional faces offers promise as a biomarker for response to anti-depressant (Harmer et al., 2011; Victor et al., 2012). Similarly, abnormalities in response to rewarding stimuli are difficult to access in human behavioral studies, but numerous fMRI studies have mapped the different neural responses to different rewards. Brain imaging may be able to determine whether low sensitivity parents show reduced reward system responses to their infants – an extremely challenging task based on observed behaviors or self-report. In the same way, within-subject, placebo-controlled designs combined with the superior sensitivity of imaging are likely to be of particular value in answering whether acute oxytocin can modulate affective cognition and other neural responses to infants in low-sensitivity mothers.

Future fMRI investigation of parental sensitivity and its modulation should include examination of the relationship between deficits in key affective cognition pathways. Increasing amounts of money are likely to be spent on attempts to improve parenting or reduce the adverse effects of poor parenting. In our opinion, the success of such approaches will continue to be limited unless we understand in detail the neurobiology which underpins poor parental sensitivity. This means being able to distinguish differing pathways to, and components of, poor sensitivity. Brain imaging represents a highly efficient methodology to explore this in relatively small numbers compared to numbers needed even for pilot randomized control trials using exclusively behavioral outcomes. Significant differences in neural activation with intervention vs. placebo, (even if behavioral change is not recorded), would still support the value of comparing a *combination* of intervention *plus* behavioral vs. intervention alone in a future potential future randomized controlled trial.

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Research Report

Does oxytocin modulate variation in maternal caregiving in healthy new mothers?

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ABSTRACT

Background: Maternal sensitivity to infant cues and developmental needs may be pivotal for social and cognitive development. Animal and recent human studies emphasise a major role for Oxytocin (OT) in mediating sensitive caregiving but no study has examined the relationship between OT and extreme variation in human maternal sensitivity. *Methods*: From 105 expectant mothers, 80 underwent blind-rating of maternal sensitivity at 4–6 months postpartum through free-play interaction with their infants. At 7–9 months postpartum, 30 mothers at extremes of maternal sensitivity: 15 'sensitive mothers' (high sensitivity mothers – HSMs, mean=4.47; SD=0.74) and 15 'less sensitive mothers' (low sensitivity mothers – LSMs, mean=2.13; SD=0.52) underwent plasma OT measurements before and after 10 min infant play. *Results*: Baseline and post-interaction plasma OT was higher in LSMs than HSMs [$F(1, 26)=8.42$; $p=0.01$]. HSMs showed a trend towards significant reduction in plasma OT [$t(14)=2.01$; $p=0.06$] following play-interaction; no change was shown by LSMs [$t(13)=-0.14$; $p=0.89$]. Conclusion Higher baseline OT levels in healthy LSMs may imply greater stress responses to the demands of caring for an infant, or past deficiencies in own parenting relationship and act as a biomarker for poor parental sensitivity. OT may be acting to reduce stress and anxiety in LSMs consistent with studies of plasma OT and stress in women. By contrast, in HSMs, play interaction with their infants maybe relaxing as indicated by significant reduction in plasma OT from baseline. Ascertainment of mothers in well-defined sensitivity groups might facilitate examination of distinct coping strategies in parents and better understanding of variation in parental caregiving behaviour and its potential for modulation by OT.

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1. Introduction

Human infants are immature creatures depending wholly on their caregivers for survival. Maternal caregiving is a complex individualised behaviour (see Barrett and Fleming 2011), an essential element of which is being soothed at stressful times (Feldman et al., 2007). Recent animal (Champagne et al., 2001; Francis et al., 2000; Numan and Stolzenberg, 2009; Ross and Young, 2009) and human studies suggest that the nonapeptide oxytocin (OT) is essential to enhance social competence and to initiate and promote adequate maternal caregiving behaviour (Feldman et al., 2010a, b; Gordon et al., 2010; Lee et al., 2009; Numan and Woodside, 2010; Swain et al., 2008). Mothers who showed a rising pattern of plasma OT across pregnancy and the early postpartum also reported stronger maternal-fetal attachment (Levine et al., 2007). Similarly, higher plasma OT levels during pregnancy and at the first postpartum month were correlated with higher levels of maternal postpartum behaviours, such as gaze, vocalisations and positive affect in new mothers (Feldman et al., 2007). Maternal synchrony, defined as 'episodes when mother and infant coordinate their positive social engagement' (Atzil et al., 2011), was also found to be correlated with maternal plasma OT levels, while maternal intrusiveness, 'inappropriate response from mother', was not.

OT has also been examined in relation to the mother's own attachment experience. Higher levels of plasma OT have been reported following mother–infant physical interaction among mothers reporting secure attachment (with own parents) compared with those reporting insecure attachment (Strathearn et al., 2009). Even among non-parents, plasma OT levels have been positively correlated with self-reported recall of parental care (maternal and paternal care) (Feldman et al., 2012; Gordon et al., 2008). Similarly, among children, urinary OT in 4.5 year olds who were raised by their own parents showed a trend for higher levels compared with children raised in orphanages (Fries et al., 2005). Although most of the studies that link plasma OT to own parental experience involved a one-off plasma OT assessment (e.g. Fries et al., 2005; Gordon et al., 2008), post-infant challenge OT levels (rather than baseline levels) were found to be more relevant in reflecting the quality of experiences of being parented (Strathearn et al., 2009).

Recent evidence from studies in women generally (not pregnant or new mothers) suggests a role for OT in the regulation of stress related to interpersonal relationships (Tabak et al., 2011). Such studies report higher levels of plasma OT associated with stress in social relationships, including relationships with romantic partners (Feldman et al., 2011; Marazziti et al., 2006; Taylor et al., 2010), own mother (Taylor et al., 2006), or best friend (Taylor et al., 2006). This is consistent with the well-recognised anti-anxiety/anxiolytic and anti-stress effect of OT (Guzman et al., 2013; Numan and Woodside, 2010) and suggests OT maybe released in stressful situations in order to decrease or moderate stress responses (Marazziti et al., 2006).

To date, parenting studies that focus on OT in relation to maternal affiliative behaviour have not included rigorous examination of maternal sensitivity. In addition, only one study considered a mothers' social relationships, including relationships with their own parents in the context of examining maternal affiliative bond with own infants (Feldman et al., 2011). In the present study, we set out to examine (i) baseline and (ii) stimulated plasma OT responses in women occupying opposite ends of the spectrum of natural variations in maternal sensitivity; and (iii) to determine whether measurement of OT could distinguish between sensitivity groups. Finally, we explored the relationship between a mother's baseline and infant-challenge plasma OT levels, and her own parenting experience. Based on the studies which emphasise a positive relationship between OT and parenting, we hypothesised that: (1) higher sensitivity mothers (HSMs) would show significantly higher plasma OT levels at baseline and following interaction with their infants than lower sensitivity mothers (LSMs); (2) post-interaction plasma OT in each group of mothers (HSMs/LSMs) would be positively related to a favourable rating of the quality of her own parenting experience.

2. Results

Among the 30 mothers included in the current study: 15 were classified as 'sensitive' mothers (blind rated as 4–7 on the MACI sensitivity scale; mean=4.47; SD=0.74) and 15 mothers classified as 'less sensitive' mothers (blind rated as 1–3 on the MACI sensitivity scale; mean=2.13; SD=0.52). For description purposes, the two sub-groups are referred to here as 'high sensitivity mothers' (HSMs) and 'low sensitivity mothers' (LSMs), respectively.

2.1. *Assessing for confounders*

One outlier was excluded from analyses (scored >3 SD in all OT assessments). Household income was higher in HSMs compared with LSMs and accordingly was adjusted for in the subsequent analysis. The two groups did not differ in maternal age, marital status, maternal education (in years), parity, infant birthweight, infant gender, mode of delivery, mode of feeding, or postpartum stage (Table 1). No significant differences between high and low sensitivity mothers were found in anxiety scores (F (1, 27)=2.08, p=0.16) nor in depression scores (F (1, 27)=0.46, p=0.50).

No relationship was found between current breastfeeding status and maternal sensitivity F (1, 27)=0.17, p=0.68. Also, breastfeeding mothers did not significantly differ from other mothers in either baseline plasma OT measurement (mean=306.54 vs. 259.16, F (1, 27)=1.78, p=0.19) or post-interaction measurement (mean=275.17 vs. 254.61, F (1, 27)=0.30, p=0.59).

2.2. *Plasma oxytocin*

Three samples were collected from each participant (Table 2). A high level of OT individual stability was found in HSMs (r=0.79–0.96; p<0.01) and LSMs (r=0.92–0.99; p<0.01).

Repeated measure ANOVA showed no overall change in the mean level of OT from baseline to post-interaction

Table 1 – Comparing demographic and obstetric characteristics of mothers grouped by level of maternal sensitivity, excluding one outlier (high sensitivity mothers HSMs, N=15 and low sensitivity mothers LSMs, N=14).

Characteristic	HSMs (N=15)	LSMs (N=14)	t (27)	Chi-square test	p-value
Mean [SD]					
Maternal age (years)	30.40 [5.37]	27.64 [4.77]	−1.46		0.16
Average maternal education (years)	15.06 [2.82]	12.77 [2.76]	−1.94		0.06
Average annual household income (thousand pounds)	33.00 [4.61]	26.12 [4.13]	−2.11		0.04
Infant birthweight (kg)	3.44 [0.44]	3.20 [0.53]	−1.10		0.28
Postpartum stage (weeks)	35.93 [2.81]	34.64 [3.22]	1.32		0.20
Frequency (%)					
Married/cohabiting	13 (86.7)	11 (78.6)		0.56	0.65
Primiparous	6 (40.0)	8 (57.1)		1.65	0.21
Infant gender (female)	10 (66.7)	7 (50)		0.83	0.36
Mode of delivery (vaginal)	10 (66.7)	11 (78.6)		0.51	0.47
Mode of feeding (breast)	3 (20.0)	3 (20.0)		0.55*	0.64

* Fisher exact test.

Table 2 – Mean plasma OT levels (pg/ml) among the high (N=15) and low (N=14) sensitivity group of mothers.

Oxytocin sample	High sensitivity mothers (N=15) mean [SD]	Low sensitivity mothers (N=14) mean [SD]
OT1	235.09 [83.51]	301.87 [39.15]
OT2	223.67 [83.43]	303.27 [34.67]
OT3	210.01 [81.58]	301.56 [38.12]

Note: OT1: Oxytocin measured before mother–infant interaction, OT2 and OT3: Oxytocin measured after mother–infant interaction.

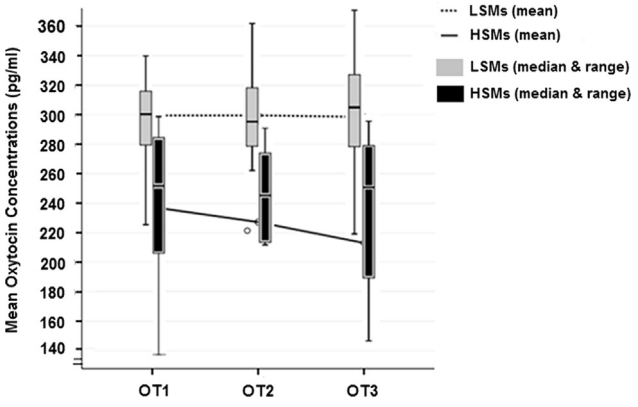

Fig. 1 – Means and box plots for plasma oxytocin measured before (OT1) and after mother–infant interaction (OT2 and OT3) among the high sensitivity mothers (HSMs, N=15) and low sensitivity mothers (LSMs, N=14), controlling for household income. Key: Dashed line represents the means of the three OT assessments among LSMs, and solid line represents means of the three assessments among the HSMs.

(within subject effect) Greenhouse-Geisser [F (1.37, 35.51)= 1.54; $p=0.23$]. Next, we examined between subject effects [F (1, 26)=8.42; $p=0.01$] and found significant difference in OT through the three assessment points when the two groups of sensitivity were compared (between subject effects). To confirm the direction of significance, this was examined further by paired t-tests; this showed a trend for a significant drop in OT levels among high sensitivity mothers; from OT_{pre} (OT1) (mean=235.09; SD=83.51) to OT_{post} ((OT2+OT3)/2) (mean=216.84; SD=79.18); t (14)=2.01; $p=0.06$ compared with no significant difference between the two time of measurements among low sensitivity mothers (mean OT_{pre}=301.87; SD=0.39.15, and OT_{post} mean=302. 15; SD=36.27, respectively); t (13)=−0.14; $p=0.89$, indicating the moderate change in response to interaction is confined to the HSMs (Fig. 1).

2.3. *Relationship between plasma OT and mothers' own parenting experience*

Controlling for household income, the two groups did not differ in own maternal care (transformed) [F (1, 26)=0.01; $p=0.93$], own paternal care (transformed) [F (1, 26)=0.41; $p=0.53$], own maternal overprotection [F (1, 26)=2.41; $p=0.13$], or own paternal overprotection [F (1, 26)=0.52; $p=0.48$].

OT_{pre} and the mean of OT2 and OT3 (OT_{post}) were considered to test the relationship with own parenting experience. Own maternal overprotection was positively correlated with both OT_{pre} and OT_{post} among LSMs ($r=0.62$; $p=0.02$; and $r=0.63$; $p=0.02$, respectively), such that the greater the overprotection they perceived from their mother in family of origin, the higher the baseline OT level and the less change in OT following child play challenge. However, similar relationship between OT_{pre} and OT_{post} levels and own maternal overprotection was not found among HSMs ($r=0.28$; $p=0.31$; and $r=0.07$; $p=0.79$, respectively) (Fig. 2/Table 3). Own maternal care, own paternal care, or own paternal overprotection were not correlated with plasma OT levels in any of the groups (all p's>0.22).

3. Discussion

We sought to examine how opposite extremes of the distribution in maternal sensitivity to infant cues are related to maternal plasma OT levels in a community sample of healthy new mothers. Contrary to our main hypotheses, we found that (1) HSMs have lower baseline plasma OT levels compared with LSMs and (2) following a play interaction with their infants, plasma OT levels showed a trend for a significant decrease in HSMs, whereas no significant change was seen in LSMs. We also found that greater levels of baseline and post-interaction plasma OT in LSMs were associated with less favourable reports of their own experience of being parented (i.e. higher own maternal overprotection).

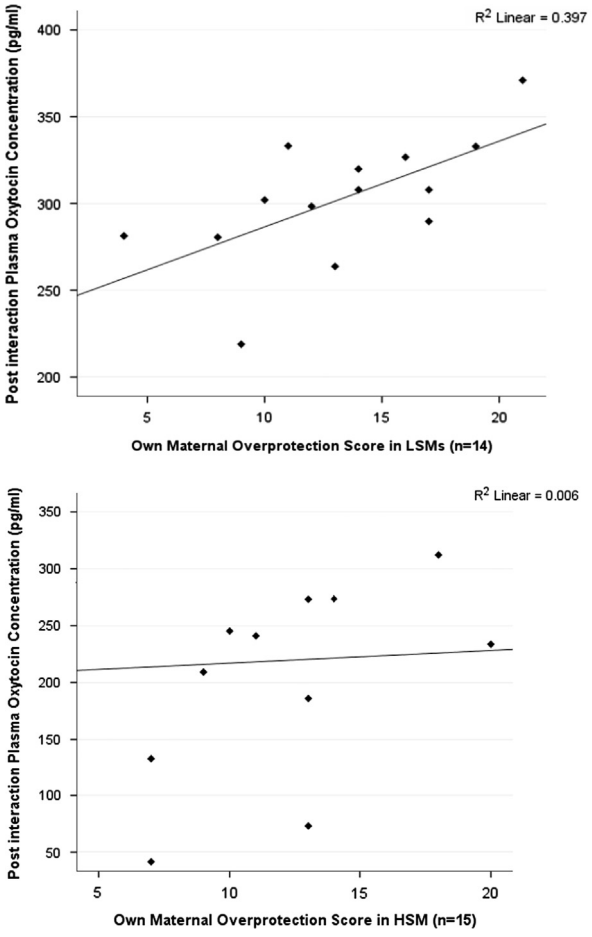

Fig. 2 – The relationship between post-interaction plasma oxytocin (OT_{post}) and own maternal overprotection among: (a) low sensitivity ($N=14$) and (b) high sensitivity mothers ($N=15$).

These findings contradict recent parenting studies reporting positive correlations between plasma OT levels and maternal (or paternal) behaviour (Atzil et al., 2011; Feldman et al., 2007; 2010a, b; Gordon et al., 2010). In the first study to explore the relationship between OT and different human attachment relationships, Feldman et al. (2011) recruited 71 mothers and 41 fathers and their 4–6-month-old infants. Plasma, salivary, and urinary OT levels of parents were assessed before and after play interaction with infants. Higher plasma and salivary OT levels were found amongst parents who showed 'high' affect synchrony towards infants as compared with 'low' synchrony parents, supporting previous findings by the same group that linked OT to more affectionate parenting behaviour (Feldman et al., 2007; Gordon et al., 2010).

However, our findings are consistent with studies that implicate OT in the regulation of interpersonal stress in women (Taylor et al., 2006, 2010) including mothers (Feldman et al., 2011). In the latter study, among mothers only, post-interaction urinary OT levels (which did not correlate with plasma or salivary OT) were positively associated with anxiety in romantic attachments (i.e. relationships with a partner), with self-reported parenting stress, and with interactive stress (i.e. proportion of time when infant shows negative reactivity whilst mother tries to re-engage her/him during interactive play). Urinary OT levels were also reported to show a negative trend with own parenting care. Their findings suggest a role for OT in stress regulation in mothers which is also similar to that reported by other studies in women (Taylor et al., 2006, 2010; Turner et al., 2002). Riem et al. (2011) conducted the first randomised controlled trial to examine the effect of intranasal OT on brain responses (using fMRI) among women (non-mother) (21 women received OT and 21 received placebo). They reported that reduced activation in regions of aversion (amygdala) was seen in response to infant cry in women who received OT compared to those who received placebo. This supports the role of OT in social stress alleviation.

In the current study, OT was assessed in mothers who were specifically chosen because they occupied opposite ends of the distribution of maternal sensitivity; therefore, these mothers may be more likely to have distinct affective and behavioural caregiving attributes (Thompson, 1997). By classifying mothers

Table 3 – Correlations between plasma OT and self-reported own parenting experience in mothers grouped by level of maternal sensitivity.

Own parenting experience domain	HSMs ($N=15$)		LSMs ($N=14$)	
	OT_{pre}	OT_{post}	OT_{pre}	OT_{post}
Maternal care[a]	−0.38	−0.21	−0.21	−0.07
Maternal overprotection	0.28	0.07	0.62*	0.63*
Paternal care[a]	−0.34	−0.34	−0.09	0.18
Paternal overprotection	−0.12	−0.06	0.16	0.03

* $p<0.05$.
[a] Transformed variable.

according to sensitivity behaviours, we may have 'tapped' into stress or anxiety coping strategies, at least in part modulated by OT (see Numan and Woodside, 2010). As far as we are aware, this is the first study to report such results in healthy mothers who have been carefully selected for high and low maternal sensitivity from within a healthy community sample.

OT appears to be an indicator of social affiliation (Feldman et al., 2007, 2010a, b), but it might also be a 'signal' for the need to affiliate with others (Tabak et al., 2011; Taylor et al., 2006, 2010). Animal literature suggests that OT has an 'openness' to early social experience, with higher OT receptors density found in relation to enriched, early perceived parenting environment (Champagne, 2008). The animal literature (Numan and Woodside, 2010) also elucidates how OT serves a dual role in maternal behaviour: It increases maternal motivation and it also decreases stress and anxiety. The latter effect may aid the mother in coping with difficult circumstances related to infant care. With respect to the human literature, different methods, which include postpartum stage of the mother–infant dyad and the ways in which mothers are classified, may differentially 'tap into' one or other of these separable aspects of OT involvement in maternal care giving behaviour.

3.1. *Elevated plasma OT in LSMs*

Elevated plasma OT levels were previously reported in relation to social relationship difficulties. In a study assessing stress in partnerships among 85 adults in stable relationships (62% women and 38% men), levels of plasma OT were significantly positively correlated with relationship distress in women (while plasma vasopressin correlated with relationship distress in men) (Taylor et al., 2010). In a further study by the same group, among 73 post menopausal women, plasma OT was negatively correlated with relationship with their own mother, or partner, and also marginally significantly correlated with relationship to best friend (Taylor et al., 2006). Similarly, Marazziti et al. (2006) reported a positive correlation between plasma OT levels and romantic relationship anxiety among 45 young subjects (33 women and 12 men). These findings suggest that plasma OT increases as a 'signal to affiliate with others as the pair-bond relationship is threatened'. OT might, therefore, act as a biomarker for a distressed pair-bond relationship (Taylor et al., 2010). In the current study, plasma OT among LSMs was positively correlated with negative recall of own maternal parenting experience, in particular, higher maternal overprotection which is a marker of difficulties in the relationship with their own mothers. We did not assess the quality of the 'relationship with partner' and so we cannot exclude a distressed pair-bond relationship as another explanation for the elevated plasma OT among the LSMs.

3.2. *Reductions in plasma OT in HSMs following infant play*

Our findings suggest that plasma OT levels are reduced in higher sensitivity mothers after playing with their infants but that low sensitivity mothers showed no change in plasma OT. A previous study has also demonstrated a reduction in plasma OT in women ($n=32$) after a laboratory-induced positive experience (viewing a comedy film), whereas no change was found after women viewed negative emotions (viewing a sad film) (Turner et al., 2002). Recently, Strathearn et al. (2012) reported a drop in maternal plasma OT when mothers showed higher levels of 'effortful control' during interaction with own infants, which is a prerequisite of sensitive mothering. In another recent study, urinary OT in mothers ($n=26$) was significantly higher following interaction with an unfamiliar child (2.5–4.5 years) as compared with own child (Bick and Dozier, 2010). The authors concluded that interaction with an unfamiliar child might constitute a more stressful situation that results in an increase in OT in order to modulate this stress.

It is possible that HSMs perceive their infant signals as a positive event (Turner et al., 2002), give appropriate attention and focus to these signals (Strathearn et al., 2012), and that their plasma OT levels accordingly reflects this and falls during play with infant. By contrast, LSMs may not perceive interaction with their infant as a positive event; they do not give proper attention and focus to their infant signals, and accordingly, their OT levels remain relatively elevated. This is consistent with Feldman et al. (2010a) who reported no difference in plasma OT levels among mothers rated as low in affectionate contact following interaction with their infants.

3.3. *Strength and limitations*

As far as we are aware, this is the first study to chart differences in plasma OT responses between mothers selected to represent higher and lower extremes of maternal sensitivity in a population of healthy new mothers. Its strengths include sampling healthy women from a community population and use of rigorous methodology for ascertaining maternal sensitivity scores. Both the final ($N=30$) and the original sample ($N=80$) provided for well-matched groups on key characteristics.

There remain some important limitations. First, while the sample from which we derived the high and low sensitivity groups was large enough to show a normal distribution of sensitivity and variability among HSMs and LSMs ($N=80$), it was still relatively small. Second, inferences about centrally functioning OT from plasma measurement must remain limited (Modahl et al., 1998) even if many previous studies do show modulation of peripheral plasma OT in relation to social affiliation (e.g. Gordon et al., 2008) or parenting brain responses (Strathearn et al., 2009). Third, the association we found between plasma OT and own maternal overprotection among HSMs does not imply a causal relationship, and there may be other, unidentified factors that could have accounted for this relationship. Fourth, own parenting experience was assessed by a self-report measure, although PBI has shown good psychometric properties and convergent validity over 20 years (Wilhelm et al., 2005). Finally, we were unable to examine for potential mediation effect that plasma OT might play between perceived parenting experiences and maternal sensitivity towards own infant. This is because selection of the sample was based on maternal sensitivity which is the outcome variable for mediation analyses.

Previous evidence suggested that in relation to plasma OT and stress, levels were elevated only in the context of stimuli which are social stressors i.e. social relationship difficulties.

However, we report evidence that a similar response occurs in new mothers with relatively reduced caregiving sensitivity. Although in the current study we did not find a correlation between OT levels and depression scores, but this is not necessarily inconsistent with our interpretation of the main findings since our sampling strategy meant that we excluded depressed mothers in the first phase and included only extremes in maternal sensitivity in the second phase.

Future studies replicating the present design might helpfully combine measurements of plasma OT with measures assessing other aspects of the stress response axis (e.g. cortisol). This might enable a more thorough evaluation of the role of OT in stress regulation (Neumann et al., 2000; Quirin et al., 2011). Plasma OT might usefully be employed as a biomarker in future studies exploring mechanisms of low parenting sensitivity and the effectiveness of interventions designed to improve parenting quality.

4. Experimental procedures

4.1. Participants

Women were recruited from 6 community antenatal clinics across the northwest region of England (Greater Manchester), as part of a larger longitudinal study examining natural variation in maternal sensitivity. Initially, 105 women, who were ethnically white British with no psychiatric illness, and scored below the threshold on depression screening (see below), were recruited during their last trimester of pregnancy (mean=33.90 weeks; SD=3.19). Following child birth, 80 women were then followed up and underwent evaluation of maternal sensitivity using videoed mother–infant interaction play at 4–6 months postpartum (mean=19.38 weeks; SD=2.47). Thirty mothers, representing extremes in the distribution of maternal sensitivity, were selected from this sample of 80. At 35 (mean) weeks postpartum (SD=3.26), we measured plasma OT levels before and after a mother–infant interaction. The majority of mothers (n=22, 73.3%) were on maternity leave. The study protocol was approved by the North West Research Ethics Committee: Ref: 10/H1013/69 and written consent was obtained from all women.

4.2. Measures

4.2.1. Manchester assessment of caregiver–infant interaction (MACI) (Wan et al., 2012, 2013)

This observational measure of caregiver–infant interaction evaluates global features of interaction from brief unstructured play in 7 (2 caregiver, 3 infant, 2 dyadic) scales. The current study focused on the 'caregiver sensitive responsiveness' scale (henceforth 'maternal sensitivity'), defined as the "the extent to which the infant's moment-to-moment behaviour and developmental needs are responded to and supported by the caregiver, appropriately and contingently". The MACI was developed for research purposes to provide relatively brief rating scales suitable for a wide age range in infancy, and which would provide measures of variance in the normal population and be sensitive in at-risk samples. Its scales were modified and refined from existing validated global scales of caregiver–infant interaction (Blazey et al., 2008; Murray et al., 1996). MACI has been validated for use in the 6–15 month-age range (Wan et al., 2012, 2013). The MACI-rated maternal sensitivity has demonstrated reliability and moderately high stability over 6 months (r=0.48; Wan et al., 2013).

The rating of 'sensitive responsiveness' varies from (1) 'minimally responsive/sensitive' to (7) 'very responsive/sensitive'. In the current study, high inter-rater agreement was demonstrated on maternal sensitivity (intraclass correlation: r=0.70; $p<0.001$, absolute agreement) based on independent blind ratings of 30% of interaction clips in the complete sample. Disagreements were resolved by both raters reviewing the clips to reach consensus.

4.2.2. The Edinburgh postnatal depression scale (EPDS) (Cox et al., 1987)

This 10-item self-report instrument is widely used to screen for depression in the postpartum and antenatal periods. Items are rated on a 4-point Likert scale and a cut-off score of 12 was used for screening positive. Using a cutoff point of 12, the EPDS shows sensitivity from 68% to 95% and a specificity of 78% to 96%, when compared to the diagnosis of major depression through psychiatric interview (Cox et al., 1987).

4.2.3. The Hospital anxiety and depression rating scale (HADS) (Zigmond and Snaith, 1983)

This 14-item questionnaire is a self-rating instrument to screen for anxiety and depression (7 items each). Items are rated on a 4-point Likert scale. Severity ratings correlate highly with clinical psychiatric assessments (r=0.70 depression and r=0.74 anxiety) (Zigmond and Snaith, 1983). The measure has high internal consistency and high test-retest reliability (Crawford et al., 2001). In this study a cut-off score of 12 was used for screening positive.

4.2.4. Parental bonding instrument (PBI) (Parker et al., 1979)

This self-report measure examines an adult's retrospective report of parents' caring behaviours (25 items for each parent) during the first 16 years of life, consisting of 'care' (12 items) and 'overprotection' (13 items). Items are rated on a 4-point Likert scale. The PBI possessed good internal consistency (Parker et al., 1979). Examination of test-retest reliability over 20 years supports the construct and convergent validity of the measure over an extended period of time which was found to be independent of mood effects (Wilhelm et al., 2005).

4.3. Procedure

4.3.1. Time 1 and 2: pregnancy and mother–infant interaction

At the third trimester of pregnancy (Time 1), women completed PBI, EPDS and HADS. Mothers were excluded if they scored both EPDS $\geq$ 12 and HADS-depression $>$ 11 at any time point in the study. At 4–6 month postpartum (Time 2), mothers were visited at home and asked to play with their infant on a floor mat as they normally do, with or without toys (as supplied), as they wished. The interactions were videotaped for 6 min and later rated, using the MACI caregiver sensitivity scale, independently by two trained researchers blind to study information.

4.3.2. *Time 3: oxytocin measurement*

Thirty mothers (15 HSMs and 15 LSMs) and their infants were invited to a clinical research facility for plasma OT measurement either during mothers' menstruation or on contraceptive pill free days. Blood samples were taken at the same time of day at 12:00–14:00 hours, an hour after the last nursing feed. Mothers were asked to refrain from caffeine and smoking for at least 2 h beforehand. Three 5 ml samples of blood were taken from antecubital veins through an intravenous cannula. The first sample (OT1) was taken 10 min after mother–infant separation, followed by reunion and a 10-minute mother–infant play interaction (as described earlier). The second and third samples were taken immediately post-interaction (OT2) and 5 min later (OT3).

4.3.3. *Oxytocin processing and assays*

All samples were processed as follows: samples were drawn into chilled vacutainer tubes containing lithium heparin injected with 200 ml of Trasylol (aprotinin) 500,000 KIU/ml blood. OT samples were kept ice-chilled until processed within 10 min. Samples were then centrifuged at 4 °C at 3500 rpm for 15 min. Five hundered microliters of supernatants were transferred to 2 micro tubes (aliquot 1 and 2) and stored at −80 °C until transferred on dry ice to the University lab for analysis. OT was analysed using: ab13305-Oxytocin ELISA (for protocol please refer to kithttp://www.abcam.com/oxytocin-elisa-kit-ab133050.html). Determination of OT was performed using the Max Binding Determination Competitive Assay protocol on Gen 5 software using Biotek Plate reader. Oxytocin analyses were performed by a laboratory scientist who was blind to all study information.

4.4. *Statistical analyses*

Demographic differences between the two groups of mothers were assessed through independent sample *t*-test or Chi-square test. Pearson correlations were used to examine correlations between plasma OT levels at the three assessment points as well as correlations with own parental experience. A repeated-measures analysis of variance (ANOVA) was employed to test for a significant change in plasma OT levels over time between groups (HSMs and LSMs). Analyses were performed using SPSS (version 19).

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Research Report

Intranasal oxytocin effects on social cognition: A critique

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Social cognition

ABSTRACT

The last decade has seen a large number of published findings supporting the hypothesis that intranasally delivered oxytocin (OT) can enhance the processing of social stimuli and regulate social emotion-related behaviors such as trust, memory, fidelity, and anxiety. The use of nasal spray for administering OT in behavioral research has become a standard method, but many questions still exist regarding its action. OT is a peptide that cannot cross the blood–brain barrier, and it has yet to be shown that it does indeed reach the brain when delivered intranasally. Given the evidence, it seems highly likely that OT does affect behavior when delivered as a nasal spray. These effects may be driven by at least three possible mechanisms. First, the intranasally delivered OT may diffuse directly into the CNS where it directly engages OT receptors. Second, the intranasally delivered OT may trigger increased central release via an indirect peripheral mechanism. And third, the indirect peripheral effects may directly lead to behavioral effects via some mechanism other than increased central release. Although intranasally delivered OT likely affects behavior, there are conflicting reports as to the exact nature of those behavioral changes: some studies suggest that OT effects are not always "pro-social" and others suggest effects on social behaviors are due to a more general anxiolytic effect. In this critique, we draw from work in healthy human populations and the animal literature to review the mechanistic aspects of intranasal OT delivery, and to discuss intranasal OT effects on social cognition and behavior. We conclude that future work should control carefully for anxiolytic and gender effects, which could underlie inconsistencies in the existing literature.

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1. Introduction

Oxytocin (OT) is a peptide that has numerous functions in the body, both peripherally as a hormone and centrally as a neurotransmitter, and OT-like peptides can be found in nearly all vertebrate species (Gimple and Farenholtz, 2001). Peripheral functions are wide in range. OT has a well-established role in reproductive function (Corona et al., 2012; Courtois et al., 2013)

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and in parturition and lactation in females (Carson et al., 2013; Gimple and Farenholtz, 2001). Synthetic OT has been used to assist in childbirth for decades. In addition, OT receptors are located in visceral organs such as kidneys and pancreas, as well as in the heart, fat cells, and adrenal glands (Gimple and Farenholtz, 2001), and OT has been found to be involved in the regulation of water balance, bone density, and appetite (Carson et al., 2013).

In contrast, it has been suggested that OT effects in the central nervous system (CNS) might be more specific, with OT playing an important role in modulating social behaviors and the processing of social stimuli. Whether these behavioral changes are modulated by OT in system-specific ways or due to more general effects are, however, unknown. The study of central effects of OT has been carried out in animal models and humans using different delivery methods: in animals both central and peripheral administration has been used, while in humans studies investigating the effects of exogenous OT typically use intranasal spray for delivery, with few exceptions (Hollander et al., 2003). How or if the OT enters the brain using this method is, however, still unknown. The purpose of this critique is twofold. We firstly discuss the potential mechanisms by which OT could enter the brain, and weigh the evidence from work in animals. Implications for human studies using intranasal OT are discussed. We then provide an overview of intranasal OT effects on social cognition in healthy humans, and explore whether OT is genuinely a neuropeptide with specifically "pro-social" effects. We incorporate findings published since other recent reviews on this topic (Bartz et al., 2011; Guastella et al., 2013; MacDonald et al., 2011), identify potential confounds that could underlie current inconsistencies in the literature, and provide suggestions as to how these could be resolved. In tying together both the mechanistic and behavioral aspects of intranasal OT delivery, we provide a summary several issues as a guide for future research.

2. Intranasal delivery: mechanisms

The OT peptide is composed of nine amino acids and is produced in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus in mammals. OT is released peripherally primarily from the neurohypophysis by exocytosis (Carson et al., 2013; Viero et al., 2010). Since OT is a relatively large, hydrophilic molecule, blood–brain penetration is too poor to cause any measurable effects on central systems (McEwen, 2004), so peripheral OT likely re-enters the brain in negligible amounts. Instead, OT is released directly in the CNS by OT neurons that project to numerous brain regions from the PVN, separate from those that go to the pituitary (Ross and Young, 2009; Veening et al., 2010).

OT receptors are widely distributed through many brain areas in rat, including the spinal cord, brainstem, hypothalamus, amygdala, and nucleus accumbens (Ross and Young, 2009). While localization of OT receptors has yet to be definitively mapped in primates and humans (Toloczko et al., 1997), efforts are being made to develop a radioligand that will bind with high specificity to human OT receptors (Smith et al., 2012). Distribution patterns of OT receptors across brain areas are highly species dependent (Insel and Shapiro, 1992; Young et al., 1996), and binding sites are up-regulated in specific areas in response to peripheral (such as pregnancy) or environmental (such as social cooperation) cues (Viero et al., 2010). Many OT neuron axonal projections run close to the ventricles, which may allow for release of OT into the ventricles for communication across numerous OT-receptive brain areas via the cerebrospinal fluid (CSF) (Veening et al., 2010). It has been proposed that this global communication process through CSF within the CNS is what may allow for the necessary simultaneous changes in the numerous neural mechanisms involved in rapid behavioral adaptation to environmental stimuli (Veening et al., 2010).

2.1. *CSF versus plasma*

The relationship between peripheral (plasma) and central (CSF) OT levels is complex. Studies in humans are typically restricted to peripheral OT assessments due to the risks associated with invasive CSF collection procedures (Carter, 2007; Challinor et al., 1994; Domes et al., 2010; Modahl et al., 1998; Parker et al., 2010). Studies that use measures in plasma to track changes in OT levels after nasal administration in humans have found significant increases in OT levels from baseline at 30 min (Gossen et al., 2012), 45 min (Domes et al., 2010), and over the course of 1 h (Burri et al., 2008). Furthermore, a number of human studies have reported correlations between peripheral levels of endogenous OT and behavior. High levels of plasma OT have been associated with trust and trustworthiness (Zak et al., 2005, 2007), positive physical contact with a partner (Grewen et al., 2005), and lower levels of anxiety in patients with depression (Scantamburlo et al., 2007). By contrast, low peripheral levels of OT have been found in patients with depression (Cyranowski et al., 2008), schizophrenia, (Goldman et al., 2008; Keri et al., 2009) and autism spectrum disorders (Green et al., 2001).

However, there are numerous animal studies that show no correlation between plasma and CSF levels of OT in response to a variety of manipulations, ranging from hormone administration to environmental cues (Amico et al., 1990; Rosenblum et al., 2002; Seckl and Lightman, 1987; Veening et al., 2010; Winslow et al., 2003). Winslow et al. (2003) reported significant differences in endogenous CSF OT levels between nursery and mother reared rhesus monkeys over a period of development, but no difference in plasma OT between the groups, and no correlation between CSF and plasma OT. Because OT cannot cross the blood–brain barrier (BBB), central and peripheral OT systems may be independently regulated, thus peripheral and central effects of OT are thought to be coordinated through its common release as a result of collateral axons in the pituitary and nucleus accumbens (Ross and Young, 2009). It may be that correlations cannot be detected due to temporal differences in responses between peripheral and central systems (Neumann et al., 2013). Bioavailability differs significantly in plasma versus CSF; OT is broken down within 2 min in plasma, while it lasts for up to a half an hour in CSF due to a lack of hydrolyzing enzymes (Jones and Robinson, 1982; Mens et al., 1983; Robinson et al., 1982; Robinson and Coombes, 1993; Veening et al., 2010; Viero et al., 2010).

Importantly, whether peripheral OT levels are indicative of central OT levels remains an open question. It is interesting that both CSF and plasma OT levels can be correlated with behavioral changes, but do not have a detectable correlation with each other. More work needs to be done to further investigate the nature of the relationship between peripheral and central levels.

2.2. *Intranasal delivery*

There is considerable uncertainty as to how intranasal OT might exert behavioral effects. Animal studies suggest that intranasal delivery can bypass the BBB via extracellular pathways in the epithelium, though more than one route is possible. Two potential pathways have been identified: a peripheral olfactory route connecting the nasal passages with the olfactory bulbs and rostral brain regions (e.g. anterior olfactory nucleus and frontal cortex), and a peripheral trigeminal system connecting the nasal passages with brainstem and spinal cord regions. Both routes provide rapid entry to the CNS (Thorne et al., 2004). Given that the behavioral effects of intranasal OT can appear shortly after delivery, these routes are likely candidates for a transport mechanism by which OT could enter the brain. Recent rodent work supports this suggestion (Neumann et al., 2013). After nasal administration of OT in rats and mice, it has been shown using microdialysis that OT levels increase in the dorsal hippocampus and amygdala of rats and mice, with peak levels occurring 30–60 min after administration. Corresponding changes were also observed in plasma. OT was found to be quite uniformly distributed within the brain extra cellular fluid (ECF) suggesting that effects were not due to locally released endogenous OT, particularly because there are no OT receptors in the dorsal hippocampus and no local OT pathways terminate in that area (Neumann et al., 2013). This is of note, since it has been speculated that very small volumes of the intranasally delivered drug might be sufficient to trigger release of endogenous OT as exogenous OT has been shown to have a positive-feedback effect on endogenous release in a dose-dependent fashion (Falke, 1989; Moos et al., 1984). However, the lowest dose of OT applied in this study was about 400 pg/ml. Estimates of the CSF level of OT in rats and monkeys following intranasal delivery is about 50 pg/ml (Neumann et al., 2013; Chang et al., 2012). Thus, estimates of CSF levels achieved by intranasal delivery are lower than the levels (400 pg/ml) that have been shown to lead to endogenous release and therefore it is not clear if the intranasally delivered OT can drive this mechanism.

Work with other peptides shows consistent findings. Neuropeptide S (NPS), another large, hydrophilic molecule, is detectable in the rat brain using fluorophore-conjugation techniques at 15 min after its intranasal delivery. It was also found that the neuronal populations targeted by intranasal administration were identical to those targeted by intracerebroventricular injection of NPS into the right lateral ventricle (Ionescu et al., 2012), suggesting that either delivery method would lead to similar results. Also, intranasal administration of radiolabeled 60-amino acid galanin-like peptide has been shown to cause transport of the peptide into the rat olfactory bulb, as well as other selected brain regions when combined with cyclodextrins for specific targeting (Nonaka et al., 2008).

Corresponding human data does not exist for OT, as clinical studies are limited to assessing only plasma levels after intranasal delivery (but see Born et al., 2002, for vasopressin assessment in CSF), though these studies consistently find correlations with increased plasma OT levels and changes in behavior (Challinor et al., 1994; Domes et al., 2010). OT behavioral studies often cite work showing that vasopressin, which is closely related to OT, reaches peak levels in CSF in 30-50 min when administered intranasally (Born et al., 2002). Limited data has shown increased levels of central OT after nasal administration, in two rhesus macaques (Chang et al., 2012). Future studies with a larger group of subjects are planned to determine whether intranasal administration of OT leads to reliable elevation of OT in the CSF and plasma compared to placebo.

While there is some suggestion that intranasal administration of OT increases CSF OT levels, the route of action is still unknown. It is not clear whether behavioral effects that follow peripheral administration of OT are driven by increased central concentrations of OT due to the OT entering the CNS, or to an indirect peripheral effect driving central production and release of OT. A third possibility is that peripheral effects of OT may drive indirect behavioral effects through unknown mechanisms. Further studies will be needed to determine the route and distribution of OT following intranasal delivery. There are at least two possible experimental approaches to track the intranasal route into the CNS. First, using a peripheral OT antagonist that does not cross the BBB in conjunction with intranasal OT administration would eliminate any peripheral actions (blocking peripheral OT receptors) that might confound interpretation of central effects. Second, radiolabelling or fluorophore-conjugated OT delivered in nonhuman primates would reveal the pattern of uptake and distribution, and show whether it is the exogenous OT that is acting directly in central locations, or whether it is triggering endogenous production and release without uptake into central areas.

Finally, it should be noted that individual differences in anatomy likely introduce variation in intranasal OT uptake. Nasal anatomy influences airflow, which influences the degree to which OT accesses the epithelium following nasal spray. Whether other constituents are included in the manufacture of the spray (e.g. uptake enhancers) is important, and dosage has also varied considerably between studies. The confounding effects of these factors could explain some of the inconsistencies in findings that are discussed in the next section. To minimize these effects, a protocol, which standardizes intranasal OT administration, has been proposed by Guastella et al. (2013).

3. Intranasal oxytocin: effects on social cognition

A possible “pro-social” role for OT was first suggested by work showing that OT could induce maternal behaviors in virgin female rats (Pedersen and Prange, 1979). Subsequent work showed that pulsatile release of OT influences pair bonding in the monogamous female prairie vole, in combination with olfactory signals (Williams et al., 1994). These findings, along

with the availability of OT nasal sprays, inspired researchers to search for corresponding effects in humans. The last decade or so has seen a large number of published findings demonstrating that OT can enhance the processing of social stimuli and regulate various social behaviors.

3.1. *Facial expressions*

OT has been shown to influence the recognition of emotional facial expressions in static (Di Simplicio et al., 2009; Guastella et al., 2010; Marsh et al., 2010) and dynamic (Fischer-Shofty et al., 2010; Lischke et al., 2012a) images of faces. In addition, studies have shown that OT affects probabilistic learning when participants have to learn to associate reward with happy, sad or angry faces: OT appears to counteract the natural aversion to selecting angry face stimuli while having no effects on other expressions (Evans et al., 2010). Other work has shown that OT can introduce a general positive bias in face judgment. OT administration increases ratings of trustworthiness and attractiveness of male and female targets in raters of both sexes (Theodoridou et al., 2009), and some researchers have found that OT enhances emotion recognition only for positive expressions (Marsh et al., 2010) and slows recognition of fearful ones (Di Simplicio et al., 2009), although conflicting results have been reported, with some studies reporting effects for fearful expressions only (Fischer-Shofty et al., 2010). Work by Lischke et al. (2012b) found that OT reduced the intensity at which all emotions could be recognized, with some evidence that this effect favors angry and fearful expressions. Several of these results are inconsistent with respect to which emotions are differentially processed following OT administration. This may be due to the small number of participants often used, and differences in the experimental approaches.

Studies of covert attention have shown that OT creates an attentional bias towards happy over angry faces, indicating that OT might shift early attentional processes towards positive social stimuli (Domes et al., 2013). Eye-tracking studies with male participants have shown that OT increases gaze time spent exploring the eye region compared with other parts of a face (Andari et al., 2010; Gamer et al., 2010; Guastella et al., 2008a), suggesting that improvements in facial emotion recognition might be due to an enhanced processing of the information-rich eye region. Three other studies, however, have not replicated this finding in female participants (Domes et al., 2010; Lischke et al., 2012a, 2012b).

In males, OT enhances the ability to infer the mental states of another person when only the eye regions are presented as a cue (Domes et al., 2007; Guastella et al., 2010). OT has been shown to decrease amygdala activation to fearful, angry and happy faces even when presented implicitly (Domes et al., 2007), suggesting that an OT-mediated reduction in amygdala activation might encourage the perception of social cues by making participants feel more at ease while viewing faces, since perception of any face stimulus activates the amygdala, particularly if its unfamiliar (Haxby et al., 2000) or involves direct eye contact (Kawashima et al., 1999). After intranasal OT, decreased activity in amygdala sub-regions associated with face processing seems to be associated with increases in sub-regions associated with gaze, supporting this suggestion; there is also evidence that OT can enhance amygdala activity for happy expressions, possibly reflecting a shift of processing toward positive social stimuli (Gamer et al., 2010). Whether these effects generalize to females is unclear; the issue of gender effects is discussed further below.

3.2. *Trust*

One of the most highly publicized effects of OT is its role in trust. Kosfeld et al. (2005) used a trust game involving real monetary stakes, where participants were asked to play the role of either investor or trustee. Investors who had been treated with OT made significantly more investments compared to investors treated with placebo. Importantly, no difference was seen in an identical 'risk' task where participants were playing against a computer rather than another human. OT has also been shown to affect trust adaptation: OT-treated individuals have been shown to persist in trusting behaviors even after repeated betrayal, and this has been linked to a modulation of amygdala activity (Baumgartner et al., 2008). Conscious and implicit distrust of faces is associated with amygdala activation (Winston et al., 2002) while amygdala lesions increase trust (Adolphs et al., 1998). Thus amygdala deactivation could explain why OT enhances stimulus processing and promotes trust behavior.

However, other findings contradict the notion that OT reliably promotes "pro-social" behavior (Bosch et al., 2005; Shamay-Tsoory et al., 2009). For example, findings by Shamay-Tsoory et al. (2009) seem to suggest that OT effects are not always positive in a trust context. Using a game of chance with financial stakes, it was found that OT increased self-report ratings of envy when another (fake) participant won more money, and increased ratings of gloating when the other participant lost more money. These results are presented as evidence for OT effects on a wide range of (not necessarily positive) social emotion-related behaviors. However, an alternative view is that OT reduces social inhibition, thus making participants more likely to admit to socially unacceptable emotions such as gloating.

3.3. *Memory*

OT also seems to promote recognition memory for social stimuli. OT administered before encoding of face stimuli improves the accuracy of familiarity made a day later, by lowering the false alarm rate and thereby improving the signal-to-noise ratio for discriminating new faces from old (Rimmele et al., 2009). Other studies have shown similar results, although Savaskan et al. (2008) found that OT improved recognition memory for neutral and angry, but not happy faces, whereas Guastella et al. (2008b) found that the effect was only present for happy faces. Despite this inconsistency, Rimmele et al. showed that OT does not improve recognition for non-social stimuli. It has been argued that this result parallels similar findings in mice, since OT-knockout mice seem to be impaired at detecting whether an intruder is novel or familiar, while non-social memory and olfactory function appear intact (Ferguson et al., 2002), and OT injected into the amygdala can reinstate normal performance (Ferguson et al., 2001). However, as noted by Insel and Fernald (2004), mouse social recognition paradigms differ

from person recognition in humans in that pheromonal recognition is a major factor.

3.4. Relationship status

There is intriguing evidence that OT might promote fidelity within monogamous human relationships and thus carry out a function similar to that observed in prairie voles. OT administration causes men in a monogamous relationship, but not single ones, to distance themselves from an attractive female experimenter, and to approach pictures of attractive women more slowly (Scheele et al., 2012). The early stages of romantic attachment have been linked to enhanced OT levels in plasma, the levels of which can predict whether the relationship is sustained 6 months later (Schneiderman et al., 2012). Physical intimacy and greater spousal support in a relationship has been linked to higher plasma OT levels (Grewen et al., 2005; Light et al., 2005), and it has been shown that a dose of intranasal OT delivered prior to a couple conflict discussion can increase positive communication and reduce conflict-related rises in salivary cortisol levels (Ditzen et al., 2009). Thus higher basal OT levels, and intranasal OT, seem to promote attachment to a partner and the resolution of conflicts, and OT causes males in a monogamous relationship to behave cautiously in the presence of another female, promoting monogamy. Interestingly, other studies have shown that plasma OT also increases with relationship distress in women (Taylor et al., 2006, 2010), and this is supported by work in prairie voles showing that long-term social isolation causes elevated plasma OT in females (Grippo et al., 2007). Elevated OT in this context has been interpreted as a signal to affiliate with others because the pair–bond relationship is threatened (Taylor et al., 2010). This issue requires further exploration, as does the gender-specificity. It would also be interesting to investigate whether relationship status affects response to OT within other social settings, such as trust.

3.5. Inconsistent gender effects

As discussed briefly above, both animal and human studies have reported inconsistent responses to OT between male and female subjects. Animal studies have suggested that the effects of OT might be modified by interactions with estrogen (McCarthy et al., 1996), and many human studies have opted to include male participants to simplify interpretation of results. Significant sex specific effects have been found for vasopressin (AVP). In men, intranasally administered AVP stimulates agonistic facial expressions and decreases perception of trust in response to pictures of same-sex strangers. In women, administration of the same peptide results in affiliative facial expressions and increased perception of friendliness (Thompson et al., 2006). Although limited data is available, studies point to powerful gender differences in OT effects as well. A recent study has investigated the role of exogenous OT in reaction to social stress in both genders (Kubzansky et al., 2012). Males given OT reported less distress to stress exposure, while females reported more distress and more anger. Moreover, neuroimaging work suggests divergent effects on amygdala activation. In males, OT tends to elicit decreased amygdala activity in response to emotional faces (Domes et al., 2007); in females, OT enhances reactivity to social and non-social threat, an effect which could be mediated by estrogen (Domes et al., 2010; Lischke et al., 2012b). More work is needed to investigate these gender differences; this is particularly relevant when considering OT in a therapeutic context.

3.6. Effects in clinical populations

Despite considerable interest in the "pro-social" effects of OT as a potential treatment option for schizophrenia and autism, it is important to note that OT does not always produce positive social effects in clinical populations. It has been shown that the "typical" responses to acute intranasal administration can be altered by individual variation in psychological profile or endocrine systems, and dose levels. OT can actually hinder trust and cooperation in participants with Borderline Personality Disorder (Bartz et al., 2010). A dose-dependent result in identifying emotional expressions in schizophrenic patients was found by Goldman et al. (2011), showing that emotion recognition actually decreased from baseline at a low dose of 10 IU, but then improved above baseline at 20 IU. Bales et al. (2013) also found dose-dependent effects on the development of pair-bonding in male voles; the direction of OT effects differed according to whether it was delivered acutely or chronically, demonstrating further that dosing regimen might be critical. The "pro-social" effects outlined above might not generalize to a chronic administration schedule.

3.7. Specificity of OT effects

A criticism of the work outlined above concerns the issue of specificity. The animal literature argues convincingly for OT effects to be specifically social in nature. Studies in humans have tended to work from the assumption that this is also the case, to the exclusion of considering alternative explanations for their findings. Churchland and Winkielman (2012) argue that OT effects might be better characterized in terms of more general mechanisms such as anxiety reduction, affiliative motivation, or social saliency. Indeed, it would be unusual for a hormone and neurotransmitter such as OT to affect processing and responses under very particular circumstances, especially when such circumstances are those which require the relatively abstract, 'higher order' operations of the social brain. Churchland and Winkielman instead suggest that the anxiolytic effects of OT can explain the majority of findings. These anxiolytic effects have been well demonstrated in mice (Mantella et al., 2003; Ring et al., 2006) and there is some evidence for similar effects in humans. Nursing mothers with higher OT plasma levels are more likely to describe positive mood states and reduced anxiety (Carter et al., 2001; Heinrichs et al., 2001) whereas abuse in childhood has been linked to lower OT concentrations in CSF and higher anxiety scores (Heim et al., 2009). Intranasal OT has been shown to decrease anxiety in a simulated public speaking test (de Oliveira et al., 2012; Heinrichs et al., 2003). The findings described above, which show that OT acts to promote affiliative social behaviors, could be due to a general reduction in anxiety. However, studies that have attempted

to assess mood and anxiety changes using brief self-report questionnaires after intranasal OT tend not to find any changes (Guastella et al., 2008b). This is confirmed by a systematic review of 38 randomised controlled trials of intranasal OT, which concluded that OT produces no detectable subjective changes in recipients (MacDonald et al., 2011).

Nevertheless, the notion that anxiolytic effects must be present to some degree is supported by the OT neuroimaging data, the majority of which concerns the amygdala, a key site in anxiety regulation. A study by Singer et al. (2008) investigated OT effects on empathy (using a paradigm where participants observe, and receive, painful stimulation of the hand), and "pro-social" behavior (using an economic exchange paradigm). The only observed effects were a reduction in amygdala activation in response to painful stimulation of self; "pro-social" behavior and empathy were unaffected, as was activity in brain regions implicated in empathy tasks of this type, such as insula.

In contrast, there are some lines of evidence suggesting that OT effects are indeed specific to social contexts and not anxiety-dependent. The use of non-social controls demonstrates specificity of effects, although it could be argued that some other variable (e.g. perceived complexity or importance) is not identical across conditions and thus responsible for the lack of effects (Kosfeld et al., 2005). It is hard to level such criticism at a study by Unkelbach et al. (2008), who found that OT speeds detection of positive words specifically associated with sexuality, bonding, and social relationships while having no effects on other positive and negative stimuli. Pupillometry studies have shown greater cognitive resource allocation to social stimuli under OT (Prehn et al., 2013). Hurlemann et al. (2010) used social (happy/angry faces) and non-social (colored dots) reinforcements in an associative learning task to show that OT improves learning in the social condition only. OT also improved self-reported emotional empathy intensity ratings for both positively and negatively valence pictures.

Perhaps the evolutionary importance of our social world justifies an argument for the effect of OT being socially specific. It is possible that a more general mechanism could explain the findings, but since the literature is so heavily biased towards social processing there is at present insufficient data. However, it is important to note that the anxiolytic effects of OT, which have been put forward as a possible explanatory mechanism (Churchland and Winkielman, 2012), are poorly specified in humans. Evidence of anxiolytic effects has been inferred from studies measuring basal levels of plasma OT (and thus offers no proof of a direct relationship, as well as being subject to the criticisms outlined above), and work showing an anxiolytic effect in a social context. Could it be that anxiolytic effects only emerge in a social setting, with anxiolysis actually resulting from a positive processing bias for social stimuli, generating an enhanced sense of social approval? In line with this suggestion, OT has been shown to potentiate the anxiolytic effect of social support during a stressful public speaking test (Heinrichs et al., 2003). It is clear that the anxiolytic effects of intranasal OT need to be better characterized, and all future studies should take more care in excluding anxiolytic effects as a confound. The literature would also benefit from a wider use of non-social control conditions, to assert specificity of effects with more confidence.

It is interesting to note that OT effects on the processing of social stimuli seem to be more robust than effects on social behaviors. In contrast to the work by Kosfeld et al. described above, some studies have shown that OT can actually decrease trust behaviors if the other party is portrayed as untrustworthy (Mikolajczak et al., 2010), is unknown (Declerck et al., 2010) or is a member of a social out-group (De Dreu et al., 2010). It could be that OT reliably increases the salience of social stimuli, but "pro-social" behaviors only emerge in the presence of context-dependent anxiolytic effects, or be dependent on other factors. Researchers should therefore be wary of assuming that OT enhances all aspects of social function. This is demonstrated by Hurlemann et al. (2010), who found that while OT increased self-reported emotional empathy in the Multifaceted Empathy Test, OT did not improve a participant's accuracy for inferring mental states. This finding supports the notion that OT makes social stimuli more salient, presumably at the level of the amygdala, but this enhancement does not necessarily translate to improved theory of mind. OT effects on higher-order social function seem to be complex and more work is certainly needed to determine the circumstances under which intranasal OT is "pro-social".

4. Conclusion

In conclusion, there are still many questions regarding the mechanisms by which intranasal delivery of OT enters the brain and the inconsistent behavioral effects reported in the literature. Future studies with larger subject groups should investigate whether intranasal administration of OT leads to reliable elevation of OT in the CSF and plasma and if peripheral and central OT levels are correlated. Furthermore, more studies will be needed to determine the route and distribution of OT following intranasal delivery. Despite the multitude of studies investigating the effects of OT on human behavior and social cognition, the inconsistent results leave open the debate between the notion that OT reliably promotes "pro-social" behavior or has anxiolytic effects. Moreover, some studies have pointed out powerful gender differences in OT effects, but most studies were conducted in males only, discounting gender effects. It seems that the small numbers of male participants typically employed, combined with differences in methods, tasks, and the stimulus sets used, could underlie these inconsistent findings. Future studies should investigate OT effects across genders and be designed to determine the degree to which possible general anxiolytic effects contribute to changes in response in socially specific challenges.

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Research Report

Intranasal oxytocin in the treatment of autism spectrum disorders: A review of literature and early safety and efficacy data in youth

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ABSTRACT

Background: There is a paucity of treatments targeting core symptom domains in Autism Spectrum Disorder (ASD). Several animal models and research in typically developing volunteers suggests that manipulation of the oxytocin system may have therapeutic potential for the treatment of social deficits. We review the literature for oxytocin and ASD and report on early dosing, safety and efficacy data of multi-dose oxytocin on aspects of social cognition/function, as well as repetitive behaviors and co-occurring anxiety within ASD. *Methods*: Fifteen children and adolescents with verbal IQs ≥ 70 were diagnosed with ASD using the ADOS and the ADI-R. They participated in a modified maximum tolerated dose study of intranasal oxytocin (Syntocinon). Data were modeled using repeated measures regression analysis controlling for week, dose, age, and sex. *Results*: Among 4 doses tested, the highest dose evaluated, 0.4 IU/kg/dose, was found to be well tolerated. No serious or severe adverse events were reported and adverse events reported/observed were mild to moderate. Over 12 weeks of treatment, several measures of social cognition/function, repetitive behaviors and anxiety showed sensitivity to change with some measures suggesting maintenance of effect 3 months past discontinuation of intranasal oxytocin. *Conclusions*: This pilot study suggests that daily administration of intranasal oxytocin at 0.4 IU/kg/dose in children and adolescents with ASD is safe and has therapeutic potential. Larger studies are warranted.

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1. Introduction

Autism Spectrum Disorder (ASD) refers to a group of neurodevelopmental disorders characterized by impairments in social communication, and repetitive behaviors and restricted interests (http://www.DSM5.org). The rates of ASD are on the rise with recent CDC numbers estimating the prevalence of the disorder at 1 in 88 children (CDC, 2008).

The social communication construct as it pertains to the ASD diagnosis has been debated extensively, even within versions of the DSM classification criteria, but there is agreement that it includes difficulties in social-emotional reciprocity, including difficulties in forming or maintaining peer relationships, deficits in nonverbal behaviors and in play skills. Restricted interests and repetitive behaviors are conceptualized to include repetitive motor behaviors such as arm flapping, rocking, bouncing, and spinning behaviors, as well as higher-level compulsive-like behaviors including rigid routines, ritualistic behaviors, and restrictive interests.

Despite the high burden of this disorder, there is no medication to date approved anywhere in the world for the treatment of social deficits or repetitive behaviors associated with ASD. A paucity of molecular targets available for the development of novel therapeutics related to the pathophysiology of ASD has been postulated to contribute to this gap. Specifically, drugs that were developed for other disorders with potentially overlapping phenotypes were tested in ASD, assuming that phenotypic spectra would be associated with neurobiologic spectra. The approach has been useful for the treatment of associated symptoms of ASD (e.g. atypical antipsychotics and irritability associated with ASD, McCracken et al., 2002), but has not produced a single agent shown to be effective for core symptoms. With the explosion of findings related to the biology of ASD and the biology of underlying core symptom domains associated with ASD, there is an opportunity for translational research to facilitate the development of novel therapeutics.

Oxytocin is a nine-amino-acid peptide (nonapeptide), which is synthesized primarily in the paraventricular and supraoptic nucleus of the hypothalamus, and released into the bloodstream by axon terminals in the posterior pituitary. Peripheral release of oxytocin facilitates uterine contractions during labor and milk letdown. Other peripheral targets of oxytocin include the kidneys and the pancreas. In addition to its peripheral role as a hormone, oxytocin is also widely distributed throughout the Central Nervous System (CNS) and functions as a neuromodulator. For example, oxytocin is released within the bed nucleus of the stria terminalis, the spinal cord, the anterior commissural nucleus, and the medial amygdala. Oxytocin fibers are evident in a variety of brain regions thought to be involved in social perception and cognition, as well as emotion regulation, including the amygdala and hippocampus and the ventral tegmental area of the midbrain (Gordon et al., 2011). Oxytocin receptors are also widely distributed in the CNS, although their distribution is highly species specific (e.g. Donaldson and Young, 2008). Oxytocin tract studies, at least in voles, would suggest that oxytocin release is not limited to the synaptic cleft, that dendritic release occurs and that it is independent of neuronal firing (Ludwig and Leng, 2006). The mechanisms by which central and peripheral release of oxytocin is coordinated remain poorly explained.

Central release of oxytocin and its closely related peptide, Arginine Vasopressin (AVP), are involved in aspects of social cognition and function including social recognition, social memory, affiliative behaviors, mother–infant and male–female pair-bond formation, separation distress, and other aspects of social attachment, as well as the regulation of stress response (Meyer-Lindenberg et al., 2011). Of note, oxytocin and AVP differ only by two amino acids, share evolutionary history, have overlapping functions, influence each other's pathways or receptors throughout development (Hirasawa et al., 2003; Landgraf and Neumann, 2004; Ragnauth et al., 2004) and as such they should be considered together in biobehavioral contexts.

In animal models, oxytocin has been shown to play critical roles in social processing, recognition, and bonding, and also to influence stereotyped behaviors such as exaggerated grooming (Carter, 1998; Insel et al., 1999; Winslow et al., 2003). In mammals, the Oxytocin Receptor (OXTR) is expressed at higher levels in early development (Shapiro Shapiro and Insel, 1989; Tribollet et al., 1989). Oxytocin knockout-mice have been shown to maintain olfaction and cognitive performance, but suffer deficits in social recognition that were recovered by intraventricular oxytocin (OXT), although not by AVP administration (Ferguson et al., 2000). OXTR knockout mice emit fewer ultrasonic vocalizations compared to the wild type, in response to social isolation, experience deficits in social discrimination, and demonstrate more aggressive behavior (Takayanagi et al., 2005). Similarly, AVPR1A knock-out mice have been reported to exhibit social memory deficits (Bielsky and Young, 2004), and the expression of the receptor gene in the lateral septum enhances social recognition (Bielsky et al., 2005). The pattern of AVPR1A receptor expression in the brain appears to be determined by variation in the length of a microsatellite in the promoter region of the gene (Hammock and Young, 2005).

1.1. *Human studies of neuropeptide hormones*

An explosion of studies has examined the effect of administering a single dose on OXT and social cognition in humans. This work has been reviewed elsewhere extensively (e.g. Macdonald and Feifel, 2013; Guastella and MacLeod, 2012; McCall and Singer, 2012; Kumsta and Heinrichs, 2013). Single dose studies in healthy volunteers have reported on increased trust (Kosfeld et al., 2005), empathic accuracy (Domes et al., 2006, Guastella et al., 2009), time spent looking at eyes (Guastella et al., 2008), and face identity recognition memory (Savaskan et al., 2008; Rimelle et al., 2009). Attenuation of amydgala activity has been documented with single dose of OXT vs. placebo (Kirsch et al., 2005; Zink and Meyer-Lindenberg, 2012; Domes et al., 2007). Such imaging studies suggest that manipulation of the oxytocin system may produce circuitry modification that is relevant to social deficits.

1.2. Oxytocin/Vasopressin and ASD

A number of researchers have hypothesized that OXT may be connected to autism given that repetitive behaviors and deficits in social interaction are core features of the disorder, and that this neuropeptide is involved in the regulation of social cognition and some repetitive behaviors. Abnormalities in the neural pathway for OXT could account for many features of autism including the early onset, predominance in males, genetic loading, and neuroanatomical abnormalities (Insel et al., 1999; Domes et al., 2007).

1.2.1. Oxytocin plasma levels and ASD

Individuals with ASD have been reported to have lower than average levels of blood OXT level in comparison to typically developing controls matched for age (Modahl et al., 1998; Andari et al., 2010), although not universally, depending on gender differences and assay methodology utilized (Miller et al., 2013). Higher levels of oxytocin precursor peptides have also been reported to be expressed in early ASD development with subsequent decrease with age (Green et al., 2001).

1.2.2. Oxytocin and vasopressin receptor genes (OXTR and AVPR1A) and ASD

Accumulating studies are reporting that single nucleotide polymorphisms of the OXTR gene are associated with ASD and related disorders (Wu et al., 2005; Jacob et al., 2007; Lerer et al., 2008; Yrigollen et al., 2008; Ebstein et al., 2012; Liu et al., 2010; Wermter et al., 2010). However, most SNPs reported are outside the protein coding regions and their functional significance remains unknown. There has been a recent report of a rare genetic variation of the OXTR gene within the protein coding region associated with ASD (Ma et al., 2013). A heterozygous deletion of the OXTR gene has also been reported in a patient with ASD and family history of OCD (Gregory et al., 2009). In addition to variations in coding sequence, there is some early data to suggest potential epigenetic modification related to the OXTR gene in ASD. Gregory et al. (2009) reported increased methylation of the OXTR gene promoter as compared to controls in two independent samples, including postmortem temporal cortex tissue from 8 ASD/control pairs.

1.2.3. Single dose OXT studies in ASD

There have been a growing number of OXT single dose studies in the last decade. Initially, an intravenous administration of oxytocin vs. placebo over a 4 h period (Hollander et al., 2003, 2007) facilitated the retention of social cognition in participants with ASD and produced significant reduction in repetitive behaviors – i.e., needing to know, repeating, ordering, needing to tell/ask, self-injury, and touching. Subsequent single dose studies have employed the intranasal formulation. Guastella et al. (2010) randomized 16 adolescents to a cross-over placebo-controlled study of a single dose of intranasal oxytocin and reported significant improvements in empathic accuracy as measured by the Reading-the-Mind-in-the-Eyes task (RMET) with minimal adverse effects. Andari et al. (2010) randomized 13 adults with ASD to a single dose of intranasal oxytocin and reported stronger interactions with a cooperative partner during a computerized ball game, increased trust, and time spent looking at eyes. However, single dose studies have limited ability to predict the therapeutic potential of administering intranasal oxytocin over a period of time and as such multi-dose studies are critical in evaluating the compound's long-term therapeutic potential (Macdonald and Feifel, 2013).

1.2.4. Early multi-dose studies of intranasal oxytocin in ASD

A small number of studies designed to evaluate the effect of multi-dose intranasal oxytocin on core symptom domains in ASD is available. In a single case report, Kosaka et al. (2012), reported on a 16 year old girl with ASD who received 8IU every day for 2 months. The authors reported that it was well tolerated and that improvements were noted both in social communication as well as irritability, based on clinician judgment and parent report on a standardized scale. Tachibana et al. (2013) reported on a case series of 8 male youth (ages 10–14 years) who received a total of 6 months exposure of oxytocin in the following manner: for the first 2 months they received 8 IU per dose twice a day followed by 2 months of 16 IU per dose twice a day, and finally 2 months of 24 IU per dose. Before each step, a 1–2 week period of placebo was administered. Improvements were noted in social and communication scores based on direct observation on a structured assessment, but not on parental reports of maladaptive behaviors. In addition, Dadds et al. (2013) evaluated a 5-day intervention with 38 male youths with ASD (ages 7–16 years). Boys were administered oxytocin (12 or 24 IU units depending on weight) or placebo during parent-child interaction training. No improvements were noted in emotion recognition, social skills and other behavioral domains compared to placebo, based on parent, clinician, or direct observation measures. Although the model of combining oxytocin with a social learning activity is of great interest, this study is limited by several factors including the use of an experimental psychosocial intervention with unknown effects as a 'monotherapy', as well as limited exposure (e.g. 5 days) to treatments targeting core skills deficits. Our group also recently published a pilot randomized trial of intranasal oxytocin vs. placebo in 19 adults with ASD (Anagnostou et al., 2012). Adults with ASD demonstrated improvements in empathic accuracy, lower order repetitive behaviors and quality of life on both self-report and experimental testing.

1.2.5. Rationale for intranasal administration

Oxytocin is metabolized in the gut by chymotrypsin and as such it cannot be administered orally. Despite its short half-life in the blood, the intravenous formulation has been found to produce behavioral effects (Hollander et al., 2003, 2007; Ring et al., 2006), but it is too invasive to administer. One alternative is intranasal oxytocin; it is thought to be absorbed through the highly permeable nasal mucosa and, in the case of the related peptide vasopressin, it has been shown to cross the blood brain barrier (Born et al., 2002), and produce rising CNS levels for at least 4 h after intranasal administration, mitigating concerns about the peripheral half-life of this compound. It is also easy to self-administer.

Given that oxytocin is involved in the regulation of social communication and some repetitive behaviors, and based on emerging pilot data, the authors received funding by the

Department of Defense to conduct a series of studies of intranasal oxytocin in children and adolescents with ASD. First, a modified Maximum-Tolerated-Dose (MTD) study was agreed upon in collaboration with Health Canada to identify a maximum dose for multi-dose studies in children up to a maximum of 24 IU/per dose adjusted for weight. The study also aimed at evaluating safety of multi-dose dosing in this age group and identifying measures sensitive to change to be used in a follow-up randomized controlled trial in this population. We report here the results of the MTD study.

2. Results

Fifteen children and adolescents (11 male; 4 females; mean age: 13.8 (2.4) years), with a diagnosis of high-functioning autism or Asperger's Disorder (ADOS:$_{Social+Communication}$:10.33 (3.21)); (ADI$_{social}$:19.87 (4.76)); (ADI$_{communication}$: 15.80 (3.67)); (ADI$_{repetitive}$ 5.80 (1.97)) were recruited into the 16 week study with twice daily dosing. Mean full scale IQ was 101.47 (22.60).

Of the 4 doses tested for 12 weeks duration (0.2, 0.26, 0.33 and 0.4 IU/kg/dose), the 0.4 IU/kg/dose was the maximum tolerated dose, as no serious adverse events (SAEs) or severe adverse events were noted at any dose level. Adverse events were mild to moderate, and either expected or typically associated with the disorder (Table 1). The WRAML revealed no adverse events related to memory (Verbal Recall $p=0.16$, Picture Memory Recognition $p=0.92$, Verbal recognition $p=0.6$). There were no clinically significant alterations in CBC, electrolytes, liver/renal function and osmolality, or electrocardiograms. There were no discontinuations due to adverse events (Fig. 1). One adolescent dropped out after the last dose (week 12) and was lost to follow-up for week 16 assessments, due to study burden and non-efficacy. Two participants dropped out before first dose was administered and were replaced in the MTD escalation scheme.

Table 1 – Safety (# events severity, if present in more than 10% of participants).

Neuropsychiatric disorders
Emotional lability (3 mild, 4 moderate)
Irritability (6 mild)
Headache (9 mild, 2 moderate)
Migraine (3 mild)
Gastrointestinal disorders
Abdominal discomfort (3 mild)
Nausea (1 mild, 1 moderate)
Infections and infestations
Upper respiratory Infections (5 mild, 2 moderate)
Metabolism and nutrition disorders
Decreased appetite (5 mild)
Skin and subcutaneous tissue disorders
Rash (3 mild)
Itchy nose (2 mild)
General disorders
Fatigue (4 mild, 1 moderate)
Respiratory, thoracic, and mediastinal disorders
Asthma attack (2 mild)
Tooth disorders
Tooth sensitivity/pain (1 mild, 1 moderate)
Serious adverse events 0

There was no effect of dose on measures of efficacy. However, with only 3 children per group, the study was not designed and not powered to examine efficacy with each dose range. Several measures were insensitive to change or not affected by oxytocin in our sample. These tasks included the DANVA, the Benton Facial Recognition Test, some subtests of the LFI battery, the Real and Apparent Test and the Second order Irony and Empathy tasks. For some, our participants experienced ceiling effects (e.g. DANVA) and for some the participants experienced floor effects (e.g. 2nd order irony and empathy tasks). Several other measures of social function, social cognition, repetitive behaviors and anxiety did show improvements across 12 weeks of treatment (Table 2). These include the ABC-SW scale, SRS, functional communication and social skills subtests of the BASC, general and separation anxiety subscales of the CASI, both repetitive behavior measures (CYBOCS and RBS-R), as well as measures of social recognition, empathic accuracy and theory of mind. Lastly, some of the measures of social cognition and function showed carry over effects 3 months after discontinuation of drug.

Ten of 15 participants were noted to be global responders based on Clinical global Impression CGI-I-Global at week 12 and 6/14 participants remained responders 3 months after the last dose was administered. In terms of the CGI-I-Social, 7/15 were classified as responders at week 12 and 6/14 remained responders at week 24.

3. Discussion

The study is contributing to accumulating literature to suggest potential efficacy and safety of multi-dose intranasal oxytocin in children and youth with ASD. Although this is not a conventional dose finding protocol, doses up to 0.4 IU/kg/dose, given twice a day over 12 weeks produced no severe or serious adverse events, and no metabolic or EKG abnormalities. Two thirds of the sample was classified as global responders, and almost half the sample was classified as responders in social function by the CGI at 12 weeks. Of particular interest, a large percent of week 12 responders maintained improvements 3 months after the end of the study, especially in the social domain.

A large number of measures were examined with respect to their sensitivity to change in this pilot study. The reader should note that this study was not a randomized controlled trial, the proper method to confidently answer questions of efficacy, and as such the results on outcome measures should be interpreted with caution. There is a lack of data on instruments that are sensitive to change with treatment, especially within the domain of social function. Our study was designed to determine instruments appropriate for follow-up in a larger randomized controlled trial. Within this context, improvements were noted in the social domain on both parent/caregiver report as well as direct assessments,

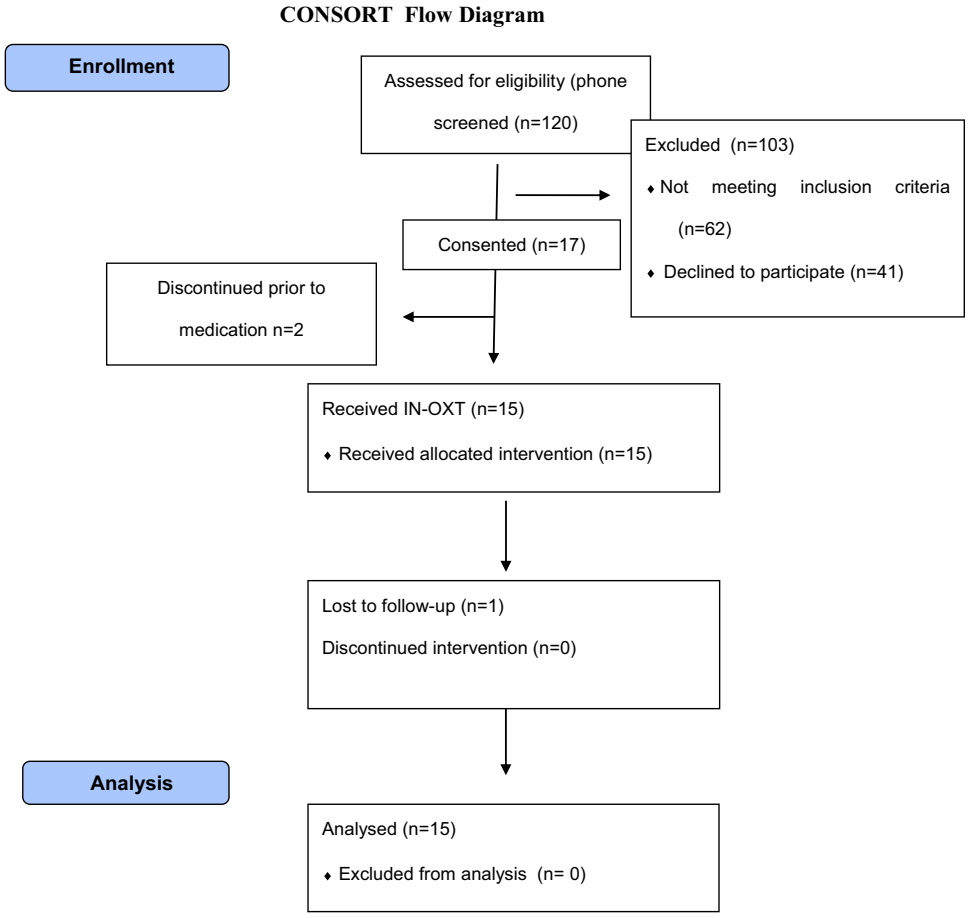

Fig. 1 – Consort flow diagram.

Table 2 – Estimates of 0–12 and 0–24 week change for the 14 outcomes of 35 with a statistically significant (unadjusted) effect.

Variable	0–12 week (95%CL)	*p* Value	0–24 week (95%CL)	*p* Value
Social function				
ABC_SW	3.00 (0.05;5.96)	0.05	2.91 (−1.98;7.80)	0.2
Srs_total_tscore	9.8 (3.8;15.8)	0.002	8.2 (−0.4;16.8)	0.06
Basc_social skills tscore	−2.84 (−5.31;−0.38)	0.03	−2.15 (−5.42; 1.13)	0.2
Basc_functional communication tscore	−4.10 (−6.23;−1.97)	0.0006	−4.19(−7.29;−1.10)	0.01
Social cognition				
RMET_hard items	−0.14 (−0.82;0.53)	0.7	−1.15 (−1.99;−0.31)	0.009
LFI_match_maker_ID	−10.9 (−19.3;−2.6)	0.01	−7.8 (−18.0;2.5)	0.1
LFI same different faces	−9.21(−15.26–3.15)	0.005	−7.4 (−15.5;0.6)	0.07
LFI same different houses	−10.73 (−18.5; −2.91)	0.009	−10.2(−20.3;−0.2)	0.05
Irony_Empathy_first order	−1.64 (−3.02; −0.27)	0.02	−2.31 (−4.08;−0.54)	0.01
Strange Stories Task	−1.36 (−2.72; 0.008)	0.05	−0.28 (−2.00;1.44)	0.7
Anxiety				
ASI – general anxiety tscore	11.0 (4.0;18.0)	0.004	6.5 (−2.5;15.6)	0.4
ASI – separation anxiety tscore	7.5 (0.2;14.8)	0.04	5.7 (−3.3;14.7)	0.2
Repetitive behaviors				
RBS-R total	17.3 (6.3; 28.3)	0.003	6.0 (−11.8;23.9)	0.5
CYBOCS	2.93 (0.95;4.91)	0.004	2.52 (0.11;4.93)	0.04

suggesting some consistency across measures using different measurement approaches.

Positive signals in the social domain were found on the ABC-SW, a measure of social withdrawal, the SRS total score, most likely a measure of global ASD severity, as well as the social skills and functional communication domains of the BASC. Of interest, gains noted by the SRS and the functional communication domain of the BASC were maintained 3

months post end of treatment, potentially suggesting a social learning effect. A similar pattern was noted in aspects of social perception/cognition. Improvements in face recognition, and theory of mind were noted at 12 weeks. Some persisted at 24 weeks and empathic accuracy improvements were most evident at 24 weeks, further supporting the hypothesis already in the literature that oxytocin may facilitate social learning. Of note, some non-specific improvements were noted in the "same-different" tasks of the LFI that were not specific to social stimuli and therefore cannot be interpreted as social recognition gains. Most likely such effects represent a nonspecific effect on attention and general, categorical learning. Anxiolytic effects were pronounced during treatment, but disappeared with discontinuation of treatment. Lastly improvements were noted in repetitive behavior over the 12 weeks with some maintenance of effect 3 months later.

3.1. *Limitations*

This is a small modified MTD study. As such, the sample size is too small to view both safety and efficacy data without caution. In addition, as the MTD design was modified in collaboration with regulatory agencies to not exceed the commonly used 24IU dose, it is not clear that doses higher than that would not confer benefit within acceptable safety parameters. Further, in the absence of placebo control, adverse events associated with oxytocin may be inflated. Lastly, given the sample size, interactions with concomitant medications (Table 3) could not be examined.

3.2. *Conclusions*

Accumulating data suggest that oxytocin manipulation may have therapeutic potential in ASD. Early single dose studies as well as case series and early multidose data support this hypothesis. Our data extends this data set, adds to the safety profile of the multidose intranasal oxytocin administration in children and youth, establishes maximum tolerated dosage within a range established by regulatory agencies and suggests several measures as potential candidates to be used in follow-up randomized controlled trials in this population, already funded.

Table 3 – Concomitant medications.

Medication (indication)	Frequency (out of 15)
Stimulants[a] (ADHD like symptoms)	6
Melatonin (insomnia)	4
Clonidine (insomnia)	1
Atomoxetine (ADHD like symptoms)	1
Sertraline (anxiety)	1
Risperidone (impulse control)	2

[a] Methylphenidate (Concerta:1); Lisdexamfetamine (Vyvance):1; Methylphenidate (Ritalin):1; Methylphenidate (Biphentin):2; Dextroamphetamine (Adderal):1.

4. Experimental procedures

This was a modified Maximum Tolerated Dose (MTD), open label trial of intranasal oxytocin in children and adolescents with ASD.

4.1. *Participants*

Children and adolescents, ages 10–17 inclusive, with a diagnosis of an ASD, and verbal IQ equal to or above 70, were enrolled in a 16 week study (12 weeks of medication exposure plus four weeks of follow-up off medication). Participants were recruited through the Holland Bloorview Kids Rehabilitation Hospital clinical database as well as presentations at local conferences and media. Diagnosis was established using a diagnostic interview to established DSM-IV criteria for an ASD, utilizing the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) and the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994) that were conducted by research reliable administrators. All eligibility assessments were completed prior to randomization into the study.

For inclusion in this study, participants had to have baseline severity score (Clinical Global Impression – Severity CGI-S) of ≥ 4 (moderately ill), be on stable pharmacological and or non-pharmacologic educational, behavioral, and/or dietary interventions ($>$ 3 months prior to screening), and have normal physical examination and laboratory test results. We excluded patients born prior to 35 weeks gestational age, patients with any primary psychiatric diagnosis other than autism at screening, those with current severe neurological disease, including, but not limited to, epilepsy/seizure disorder (except simple febrile seizures), severe movement disorder, tuberous sclerosis, fragile X, and any other known genetic syndromes, or known abnormal MRI/structural lesion of the brain, pregnant female patients, sexually active female patients on hormonal birth control and sexually active females who do not use two types of non-hormonal birth control, patients with a medical condition that might interfere with the conduct of the study, confound interpretation of the study results, or endanger their own well-being, those who are sensitive to Syntocinon or any components of its formulation, those with HIV, HBV, HCV, hemophilia, abnormal blood pressure, drug abuse (as per DSM criteria), immunity disorder or severe depression and those unable to tolerate venipuncture procedures for blood sampling. All patients or their legal guardians signed the institutionally approved informed consent/assent according to the Helsinki agreement and tri-council policy.

4.2. *Dose selection and MTD design*

A modified dose finding method was used to determine safety among four dose levels. In adults, the dose with most evidence is 24 IU/dose. This is the equivalent of 0.4 IU/kg for a 60 kg person. Therefore, the maximum dose to be tested in youth approved by Health Canada was 0.4 IU/kg/dose for a maximum of 24 IU/dose. This is different from a traditional MTD design where the upward titration does not typically

stop unless the participants experience serious adverse events. Half the dose (0.2 IU/kg/dose) was the minimum dose approved and 2 intermediate doses were also evaluated: 0.26 and 0.33 IU/kg/dose.

Dose-finding escalations were done in groups of three patients. The following dose escalation rules were applied:

1. Three patients were studied at the first dose level (0.2 IU/kg bid).
2. If none of these patients experienced Dose Limiting Toxicity (DLT), then the dose was escalated to the next higher level in the three subsequent patients.
3. If one of three patients had experienced DLT at the current dose, then up to three more patients were to be accrued at the same level. (a) If none of these three additional patients experienced DLT, then the dose were to be escalated in subsequent patients. (b) If one or more of these additional patients experienced DLT, then patient entry at that dose level would be stopped, the MTD exceeded and dose escalation would be stopped. Up to three more patients would be treated at the next lower dose. If zero out of three patients experience DLT at a dose of 0.4 IU/kg, an additional three patients were to be treated at that dose. Using this escalation scheme, the probability of escalating to the next level if the true proportion of adverse effects was 10%, 20%, 30%, 40%, or 50% was 91%, 71%, 49%, 31% and 17% respectively. Each participant only received one of the preset doses.

Twice a day dosing (morning and afternoon) was chosen given that CNS levels of vasopressin seem to rise for approximately 4 h post intranasal administration (Born et al., 2002), and in order to capture the most hours in which children and youth are most likely to be involved in social interactions.

4.3. *Definition of toxicity for MTD design*

Based on existing data, it was difficult to find a definition of toxicity for this compound. Although no standard toxicity studies have been published for IN-OXT in children, the Side Effect (SE) profile of IN-OXT in adults after decades of post marketing use has been very benign. Standard toxicity protocols are typically based on Serious Adverse Events (SAEs) to determine the Maximum Tolerated Dose (MTD). In our case, we decided to determine toxicity as the presence of SAEs or severe adverse effects that are deemed by the investigators to be likely or probably related to drug.

4.4. *Dosing schedule*

We selected morning and afternoon dosing to try to influence the greatest number of hours when youth are in settings with increased potential for social interaction (school, afterschool). Moreover, this regimen was associated with improvements in our adult pilot study (Anagnostou et al., 2012). Medication was administered by the parents before school and right after school. All patients received their child's first dose by the study physician to educate parents and themselves on proper administration and determine safety of first dose. Participants were advised to administer one spray every 30 s until they have reached the total number of sprays directed. They were told to sit upright, hold the bottle up right, insert the nozzle into one nostril and inhale gently through the nose while pushing down on the nozzle to activate the pump.

4.5. *Medications*

Oxytocin (Syntocinon, NOVARTIS, Switzerland) was administered in the form of IN-OXT.

4.6. *Safety assessments*

Participants were seen every two weeks during the 12-week study and then again at 16 weeks, 4 weeks after last exposure to drug, for Clinical Global Improvement (CGI-I) ratings, vital signs and adverse event monitoring. Adverse events were elicited using the SMURF (Greenhill et al., 2004) at every visit and the Wide Range Assessment of Memory and Learning (WRAML) (Sheslow and Adams, 2005) was done at baseline and end visits (weeks 12 and 24) to document any potential adverse events related to memory, based on early animal model concerns (Engelmann et al., 1996). Safety blood work and EKG were done every 4 weeks.

4.7. *Efficacy assessments*

As noted above, the aim of this study was to establish maximum tolerated dose and safety for IN-OXT in this age group in ASD. In addition, we piloted several outcome measures related to social cognition/function, repetitive behaviors and co-occurring anxiety to select those with documented sensitivity to change. These outcomes will be used in the follow-up randomized controlled trial in a larger sample with ASD and this study will also be funded by the Department of Defense.

4.7.1. *Social cognition measures*

All social cognition measures were administered at baseline and then week 12 and week 24.

Diagnostic Analysis of Nonverbal Accuracy (DANVA-2) (Baum and Nowicki, 1989). The DANVA-2, a measure of emotion recognition across multiple modalities with established reliability and validity for age 3–100, was administered to participants at baseline, week 12 and week 24.

Let's Face It! Skills Battery (or Victoria/Yale Face Processing Battery; VYFPB; Wolf et al., 2008) is a battery of computerized face processing tasks. The full battery consists of 11 separate computer-administered tests. It assesses 2 broad domains involving (1) the perception of facial identity and (2) the perception of facial expression, with good split-half reliabilities (>0.75).

Benton Face Recognition Task (BFRT) (Benton et al., 1994) is a standardized test frequently used to assess perceptual skill in developmentally delayed populations, with good reliability. It is appropriate for participants aged 6–74 and provides a standardized and objective procedure for assessing the capacity to identify and discriminate photographs of unfamiliar human faces.

The Revised Eyes Test (Baron-Cohen et al., 2001) assesses the ability to decipher mental states of others. Participants are presented with photographs of the eye-region of male and female actors accompanied by four descriptive words (e.g., "serious," "ashamed," "alarmed," or "bewildered") and must select the word that best describes what the actors are thinking or feeling. In addition to restricting stimulus presentation to the eye region, this test differs from others in that it assesses more complex emotional states (e.g., shame, bewilderment).

Strange Stories Task (Happé, 1994) assesses the ability to interpret nonliteral statements from stories read to the participant. Questions probe whether the child understands that (a) a nonliteral statement has been made and (b) the intent behind the statement (i.e., was the speaker was lying, being sarcastic, or joking?).

Real and Apparent Emotion task: (Dennis et al., 2000) evaluates children's understanding of real and deceptive emotion in short narratives. The task, typically mastered between the 6–8 years of age, represents an advanced assessment of theory of mind in that it requires judgments about socially expressed emotion in the context of belief.

Irony and Empathy Task (Dennis et al., 2001) measures children's understanding of first and second order intentionality associated with literal truth, ironic criticism, and deceptive praise. Six everyday situations depict a task (e.g. tidying a room, baking a cake), with two participants, a speaker who makes a comment about the task and hearer who did the task. The task has been well published in children with traumatic brain injury.

4.7.2. *Social function measures*

Aberrant Behavior Checklist (ABC) (Aman et al., 1985) The ABC is a symptom checklist for assessing problem behaviors (ages 6–54 years). The checklist consists of 58 items broken down into 5 subscales; only the Social Withdrawal subscale was used in this study. It was administered at baseline and weeks 12 and 24.

Social Responsiveness Scale (SRS) (Constantino, 2002) is a caregiver/educator rating scale of social behaviors specific to ASD. It is a sensitive and reliable assessment that is designed to aide diagnosis and measure treatment response with 4–18 years of age. The SRS measures social awareness, information processing, and social motivation and yields a quantitative score that has been useful in endophenotyping studies of ASD and was administered at every visit.

CGI-I-Social: The CGI-I is a well validated measure employing a 7-point scale of clinical global impression of improvement (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse) that the clinician fills out after considering all the available information on the subject including the parent history, the examination in clinic, reports from the school and other sources (Guy, 1976). In this case, the focus of the interview was on aspects of social function: approach, turn taking, peer relationships and was administered at every visit.

Behavioral Assessment System for Children-2 is used to evaluate the behavior and perceptions of children and young adults (ages 2–25 years). The BASC-2 is a revision of the Behavior Assessment System for Children (BASC) (Reynolds, 1992). We used the parent report scale with a focus on functional communication and social skills subscales.

4.7.3. *Repetitive behaviors*

Both measures were administered at every visit

- Child Yale-Brown Obsessive-Compulsive Scale (C-YBOCS) (Goodman et al., 1989, 65, modified by Scahill et al., 1997) The Yale-Brown Obsessive-Compulsive Scale is a clinician-rated questionnaire measuring the time spent, distress, interference, resistance, and control in relation to obsessions and compulsions based on a 5-point scale. The Compulsion subscale has been shown to be a reliable and valid scale in ASD, and in measuring change in treatment studies of autism, and we used the "adapted for PDD" version.
- Repetitive Behavior Scale-Revised (RBS-R) (Bodfish et al., 2000). The RBS-R is a parent-report measure developed to capture the breadth of repetitive behaviors that are specific to autism. It consists of 43-items that tap six repetitive behavior subtypes: Stereotyped, Self-injurious, Compulsive, Ritualistic, Sameness, and Restricted Interests.

4.7.4. *Anxiety measures*

Child and Adolescent Symptom Inventory (CASI) (Gadow and Sprafkin, 2009): The CASI is a clinician-reviewed, caregiver report form based on the DSM-IV used to assess comorbid psychiatric symptoms. The anxiety subscales were used.

Participants used a medication diary to mark down every time they took the medication. The diary was reviewed at every visit and the study clinician and the participant problem solved together in the case of missed doses to improve compliance.

4.8. *Statistical approach*

Data were analyzed using SAS 9.3 (ref 2002–2010 by SAS Institute Inc., Cary, NC, USA). We plotted all outcomes across time to visually assess any trends across dose. Data were modeled using repeated measures regression analysis controlling for week, dose, age, and sex. The changes from baseline to week 12 and baseline to week 24 and their 95% confidence limits were estimated from the model for each of the 35 outcomes variables examined. Eight of the outcomes were also available as raw scores– in all cases, the results were similar using either score and only *t*-scores are presented in the results.

Competing interests/Financial disclosures

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Authors' contributions

EA was the principal investigator for the study. She designed and ran the study, and prepared the manuscript. LS contributed to designing the study and manuscript preparation. JB contributed to the design of the study, supervised psychological assessments, and contributed to manuscript preparation. SJ contributed to designing the study, preparing the manuscript and is a site-PI on the subsequent RCT treatment trial. AD contributed to study design, data analysis and manuscript preparation. DM and SS were critical to running the study and contributed to manuscript preparation. All authors read and approved the final manuscript.

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Research Report

Maternal oxytocin response predicts mother-to-infant gaze

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ABSTRACT

The neuropeptide oxytocin is importantly implicated in the emergence and maintenance of maternal behavior that forms the basis of the mother–infant bond. However, no research has yet examined the specific association between maternal oxytocin and maternal gaze, a key modality through which the mother makes social contact and engages with her infant. Furthermore, prior oxytocin studies have assessed maternal engagement primarily during episodes free of infant distress, while maternal engagement during infant distress is considered to be uniquely relevant to the formation of secure mother–infant attachment. Two patterns of maternal gaze, maternal gaze toward and gaze shifts away from the infant, were micro-coded while 50 mothers interacted with their 7-month-old infants during a modified still-face procedure. Maternal oxytocin response was defined as a change from baseline in the mother's plasma oxytocin level following interaction with her infant. The mother's oxytocin response was positively associated with the duration of time her gaze was directed toward her infant, while negatively associated with the frequency with which her gaze shifted away from her infant. Importantly, mothers who showed low/average oxytocin response demonstrated a significant decrease in their infant gaze during periods of infant distress, while such change was not observed in mothers with high oxytocin response. The findings underscore the involvement of oxytocin in regulating the mother's responsive engagement with her infant, particularly in times when the infant's need for access to the mother is greatest.

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1. Introduction

While the neuropeptide oxytocin has been recognized for its functions in parturition and milk ejection for many decades, there exists now a substantial literature underscoring the role of oxytocin in regulating social behaviors (see reviews, Benarroch, 2013; Feldman, 2012; Meyer-Lindenberg et al., 2011). A sizable number of studies have implicated oxytocin in maternal care (Febo et al., 2005; Pedersen et al., 2006; Strathearn et al., 2009b), pair bonding (Ross et al., 2009; Schneiderman et al., 2012), interpersonal trust (Van IJzendoorn and Bakermans-Kranenburg, 2012), emotion recognition (Lischke et al., 2012; Perry et al., 2013), and empathy (Hurlemann et al., 2010; Rodrigues et al., 2009). Oxytocin has been characterized as a "hormone of affiliation" (Insel, 1992) and the oxytocinergic system has received attention as a key neural substrate of maternal caregiving, involved in the emergence and maintenance of maternal behaviors (Feldman, 2012; Strathearn, 2011). Many important advances in this regard have come from animal models (Francis et al., 2002; Keverne and Kendrick, 1992; Maestripieri et al., 2009; Pedersen et al., 2006; Williams et al., 2001), and they have been extended to human subjects over the past decade, revealing both parallel and divergent findings.

In humans, peripheral oxytocin levels are higher in pregnant and parturient women than non-pregnant women (Feldman et al., 2007; Gordon et al., 2008). Oxytocin levels show high intra-individual stability over the course of pregnancy (Feldman et al., 2007; Levine et al., 2007) and early motherhood (Gordon et al., 2010), suggesting that they may constitute a trait-like characteristic that underpins the expression of maternal behavior. Prospective and cross-sectional studies have demonstrated that maternal oxytocin levels are systematically associated with naturally occurring variations in maternal behavior, with high plasma oxytocin levels during pregnancy and postpartum predicting increased maternal behavior in the postpartum months (Atzil et al., 2011; Feldman et al., 2007; Gordon et al., 2010). Interaction with their young in the postpartum period further stimulates oxytocin response in mothers (Feldman et al., 2010a, 2010b), though significant inter-individual variations have been found (Strathearn et al., 2012), as with the baseline oxytocin levels. These natural variations in maternal oxytocin response have systematically predicted differences in the quality of maternal care provided by mothers (Feldman et al., 2010a, 2010b).

Quality provision of maternal care and formation of secure attachment bonds are of particular importance in the early postpartum months, given their long-term effects on the development of the offspring (Fonagy et al., 2007; Kochanska and Kim, 2013; Sroufe et al., 2005; Weinfield et al., 2004). It is well established that sensitive and responsive maternal behavior has direct bearings on the child's life-long capacity for social adaptation and stress regulation (Kochanska, 2001; Mayes, 2006; Mikulincer and Shaver, 2007; Schore, 2001). One important channel through which maternal sensitive responsiveness is communicated is mother-to-infant gaze. Gaze is a central modality through which mothers signal their availability, establish mutual engagement, and initiate regulation of infant arousal, particularly in times of infant distress (Beebe et al., 2010; Slee, 1984). Infants are highly sensitive to their mothers' gaze (Stern, 1974) and begin to join in mutual gaze with their mothers as early as 3 months of age, which serves as a basis for the mother–infant synchrony that subsequently emerges in other modalities (e.g., touch, vocalization, facial expression; Colonnesi et al., 2012; Feldman, 2007; Lavelli and Fogel, 2013; Tronick et al., 1980).

Despite its significance, the specific association between maternal gaze and maternal oxytocin has not yet been examined. Previous studies have measured maternal gaze, but only as part of a composite of maternal behaviors (also encompassing touch, vocalization, and affect; e.g., Atzil et al., 2011; Feldman et al., 2007, 2010b; Gordon et al., 2010). Furthermore, while attachment literature has underscored that maternal sensitivity to infant distress uniquely contributes to optimal socioemotional outcomes in the child (Leerkes et al., 2009; McElwain and Booth-LaForce, 2006), prior studies have examined maternal oxytocin only in relation to indices of maternal synchrony during episodes of positive affect and have not considered episodes of distress (Atzil et al., 2011; Feldman et al., 2010b, 2011).

In our previous functional magnetic resonance imaging (fMRI) study (Strathearn et al., 2009b), we demonstrated that mothers' peripheral oxytocin responses predicted their blood oxygenation level-dependent (BOLD) brain responses to their own infants' faces. The greater the mothers' oxytocin responses during interactions with their infants, the greater was their activation in regions known to be rich in oxytocin receptors (i.e., hypothalamic/pituitary region) when viewing their infants' faces in the scanner. In the present study, we extended our line of investigation to the mother's actual gaze behavior during real-time interaction with her infant. We sought to examine the relationship between maternal oxytocin response and mother-to-infant gaze during periods of infant non-distress as well as distress.

Mother–infant dyads were observed during 50-min semi-structured interaction sessions. Maternal oxytocin response was defined as any change in the mother's oxytocin level following interaction with her infant compared to baseline. Two patterns of maternal gaze, duration of maternal gaze toward and frequency of gaze shifts away from the infant, were coded during a well-validated interaction paradigm, a modified still-face procedure (MSFP; Koos and Gergely, 2001). The MSFP is a three-phase procedure, during which the mother interacts freely with the infant in phases 1 and 3, but is instructed to maintain a neutral 'still face' during phase 2, suddenly depriving the infant of maternal contingency and inducing stress in the infant (Koos and Gergely, 2001; Tronick et al., 1978; Fig. 1). The experimental manipulation reliably produces changes in the infant's level of distress: infants display clear signs of distress during phase 2, which have been shown to carry over to phase 3 (Haley and Stansbury, 2003; Mesman et al., 2009). The MSFP thereby offers an opportunity to examine the mother's behavior in the absence and presence of signals of infant distress. We hypothesized that maternal oxytocin response would be positively associated with maternal gaze toward the infant, and negatively associated with maternal gaze shifts away from the infant. We further predicted that this association would become more pronounced during periods of infant distress than non-distress, in phase 3 compared with phase 1 of the MSFP.

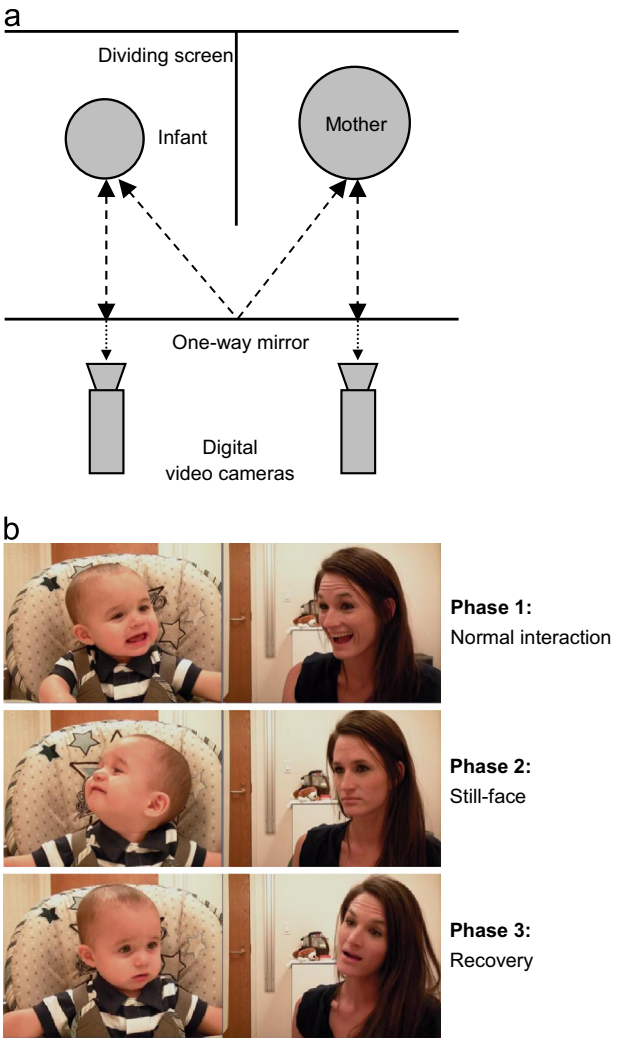

Fig. 1 – The modified still-face procedure (MSFP): (a) diagram of the experimental setting and (b) example still frames from all three phases.

Table 1 – Sociodemographic and behavioral characteristics of mothers and infants ($N=50$).

Characteristics	Value	Range
Baseline OT, pg/ml [a]		
Mean ± SD	1.75 ± .89	.50–4.80
OT response, pg/ml [b]		
Mean ± SD	−.06 ± .93	−3.70–3.15
Maternal age, years		
Mean ± SD	28.0 ± 4.6	19–41
Infant age, months		
Mean ± SD	6.4 ± 1.7	4–11
Infant sex, *n* (%)		
Male	21 (42.0)	
Female	29 (58.0)	
Marital status, *n* (%)		
Married	38 (76.0)	
Not married	12 (24.0)	
Maternal race, *n* (%)		
White	31 (62.0)	
Non-White	19 (38.0)	
Maternal education, *n* (%)		
College incomplete	11 (22.0)	
College/university degree	22 (44.0)	
Postgraduate degree	16 (32.0)	
Socioeconomic status [c]		
Mean ± SD	44.5 ± 15.4	15–66
Maternal IQ [d]		
Mean ± SD	110.2 ± 8.4	81–120
Maternal depression (BDI) [e]		
Mean ± SD	5.3 ± 4.8	0–19
Maternal personality pathology (PDQ) [f]		
Mean ± SD	19.4 ± 11.5	3–50
Maternal parenting stress (PSI)		
Child Domain, Mean ± SD	91.3 ± 14.1	64–121
Parent Domain, Mean ± SD	112.8 ± 23.6	66–157
Total Stress, Mean ± SD [g]	201.5 ± 34.5	109–264
Breastfeeding status [h], *n* (%)		
Not breastfeeding	13 (26.0)	
Still breastfeeding	28 (56.0)	
Daycare status [i], *n* (%)		
Less than 20 h per week	20 (40.0)	
More than 20 h per week	19 (38.0)	

Note. BDI = Beck Depression Inventory-II; PDQ = Personality Disorder Questionnaire−4+; PSI = Parenting Stress Index.

[a] Plasma oxytocin concentration was measured following a 20-min period of mother–infant separation (OT 1).

[b] Change in plasma oxytocin concentration between baseline (OT 1) and post mother–infant interaction (mean of OT 2 and OT 3).

[c] Socioeconomic status was estimated using Hollingshead (1975)'s Four-Factor Index of Social Status, and represents joint information with partner, when applicable.

[d] Maternal Full Scale IQ was estimated from the Wechsler Test of Adult Reading (WTAR).

[e] BDI-II score of ≤9 indicates minimal depression.

[f] PDQ-4+ total score of ≥50 is highly suggestive of DSM-IV personality disorder.

[g] PSI total stress score of <260 is considered in the normal range.

[h] Data were missing for 9 participants.

[i] Hours per week that someone other than the mother looked after the infant. Data were missing for 11 participants.

2. Results

2.1. *Participant characteristics and preliminary analyses*

Participant characteristics are shown in Table 1. Participants were a non-clinical sample of first-time mothers who were generally of middle to high socioeconomic status, three-quarters of whom held a college or postgraduate degree. All mothers scored below the clinical range for personality disorders, while four mothers scored in the mildly depressed range, one of whom also scored in the clinically significant range for parenting stress. However, these four mothers did not differ from the rest of the sample in oxytocin levels (*ps* > .65) or maternal gaze (*ps* > .20); neither did the exclusion of the four mothers significantly alter the results reported below. Maternal clinical characteristics are therefore not considered further. Maternal depression was unrelated to baseline oxytocin level ($r_{BDI\ \&\ baseline\ OT} = .01$, $p = .95$), oxytocin response (OTResp; $r_{BDI\ \&\ OTResp} = .09$, $p = .57$), maternal gaze variables ($r_{BDI\ \&\ gaze\ toward} = .08$, $p = .62$ and $r_{BDI\ \&\ gaze\ shift\ away} = .05$, $p = .77$), or infant affect variables ($r_{BDI\ \&\ positive\ affect} = -.08$, $p = .59$ and $r_{BDI\ \&\ negative\ affect} = -.04$, $p = .78$).

Breastfeeding status also did not correlate with oxytocin response ($r_{breastfeeding\ \&\ OTResp}=.15$, $p=.34$), or with maternal gaze variables ($r_{breastfeeding\ \&\ gaze\ toward}=.10$, $p=.54$ and $r_{breastfeeding\ \&\ gaze\ shift\ away}=-.17$, $p=.28$). Measures of menstrual cycle (i.e., estradiol and progesterone levels) were also not associated with OTResp ($r_{estradiol\ \&\ OTResp}=.07$, $p=.65$ and $r_{progesterone\ \&\ OTResp}=.06$, $p=.67$), or with maternal gaze variables ($r_{estradiol\ \&\ gaze\ toward}=-.01$, $p=.95$ and $r_{progesterone\ \&\ gaze\ toward}=.01$, $p=.93$; $r_{estradiol\ \&\ gaze\ shift\ away}=.18$, $p=.27$ and $r_{progesterone\ \&\ gaze\ shift\ away}=.13$, $p=.38$).

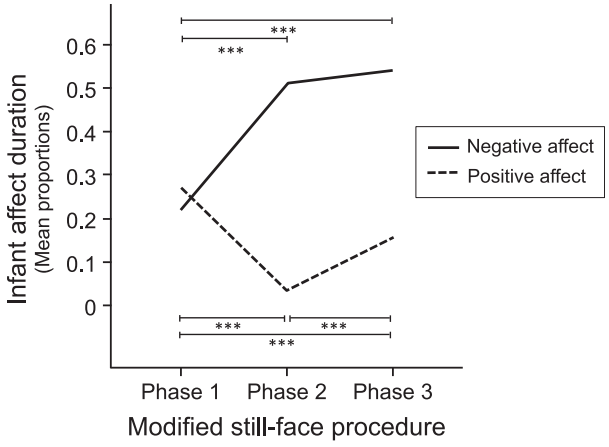

Fig. 2 – Duration of positive and negative affect displayed by infants across modified still-face procedure (MSFP) phases. The duration values on the y-axis were adjusted for the total length of the each respective phase of the MSFP and represent mean proportion values. Positive affect dropped and negative affect increased in the still-face segment (phase 2), while a rebound in positive affect and a carry-over of negative affect were seen during the recovery period (phase 3). ***$p<.001$.

2.2. *Infant affect during modified still-face procedure*

As expected, and consistent with previous research, significant changes were noted in infant affect across the three phases of the MSFP (positive affect, $F(2, 98)=33.78$, $p<.001$; negative affect, $F(2, 98)=35.24$, $p<.001$; Fig. 2). Compared to baseline (phase 1), infants displayed increased negative affect during still-face (phase 2) ($M_{phase\ 1}=.22$, $SD=.26$; $M_{phase\ 2}=.51$, $SD=.41$; $t_{phases\ 2-1}(49)=7.09$, $p<.001$), as well as decreased positive affect ($M_{phase\ 1}=.27$, $SD=.24$; $M_{phase\ 2}=.04$, $SD=.09$; $t_{phases\ 2-1}(49)=-7.83$, $p<.001$). While there was a rebound of positive affect during recovery (phase 3) ($M_{phase\ 3}=.16$, $SD=.23$; $t_{phases\ 3-2}(49)=4.08$, $p<.001$), negative affect carried over from phase 2 to phase 3 ($M_{phase\ 3}=.54$, $SD=.41$; $t_{phases\ 3-2}(49)=.86$, $p<.39$).

2.3. *Maternal gaze during modified still-face procedure*

Means and standard deviations of maternal gaze variables are shown in Table 2 for phases 1 and 3 of the MSFP. Duration of the mother's gaze toward the infant was significantly negatively correlated with the frequency of the mother's gaze shifts away from the infant ($r_{gaze\ toward\ \&\ gaze\ shift\ away}=-.79$, $p<.001$). Infant affect variables were not significantly associated with either of the maternal gaze variables ($r_{positive\ affect\ \&\ gaze\ toward}=-.09$, $p=.38$ and $r_{negative\ affect\ \&\ gaze\ toward}=.09$, $p=.38$; $r_{positive\ affect\ \&\ gaze\ shift\ away}=-.01$, $p=.91$ and $r_{negative\ affect\ \&\ gaze\ shift\ away}=.06$, $p=.56$), and did not significantly alter any of the observed main or interaction effects reported below when entered into the model.

Table 2 – Maternal gaze toward and away from infant during modified still-face procedure (MSFP) and results of mixed-effects regression analysis ($N=50$).

	Maternal gaze during modified still-face procedure [a]						Mixed-effects models of change over phase			
	Phase 1		Phase 3		Total [b]		Wald χ^2 ($df=3$) [c]	OTResp effect (95% CI) [d]	Phase effect (95% CI) [d]	OTResp x Phase [d] (95% CI)
	Mean	SD	Mean	SD	Mean	SD				
Gaze toward infant (duration)	.993	.018	.984	.043	.988	.028	13.52**	.003* (.0002 to .005)	−.005* (−.009 to −.0001)	.006* (.001 to .011)
Gaze shift away from infant (frequency)	.012	.009	.018	.024	.015	.015	16.14**	−.065* (−.126 to −.004)	.092** (.035 to .150)	−.036 (−.098 to .026)

[a] Numbers shown are duration and frequency values ($M\pm SD$) adjusted for the total length of time for which codable data were available in each respective phase of the MSFP. Untransformed values are reported here for illustrative purposes, while statistical tests were conducted using log-transformed variables.
[b] Total values represent data collapsed over the phases 1 and 3 of the MSFP.
[c] Wald χ^2 values are those obtained for the best-fitting mixed-effects models for the respective outcome variables, including a subject-level random intercept and a random coefficient for phase.
[d] Coefficients shown are beta weights (i.e., slopes) for the main and interaction effects of OTResp and phase.
* $p<.05$.
** $p<.01$.

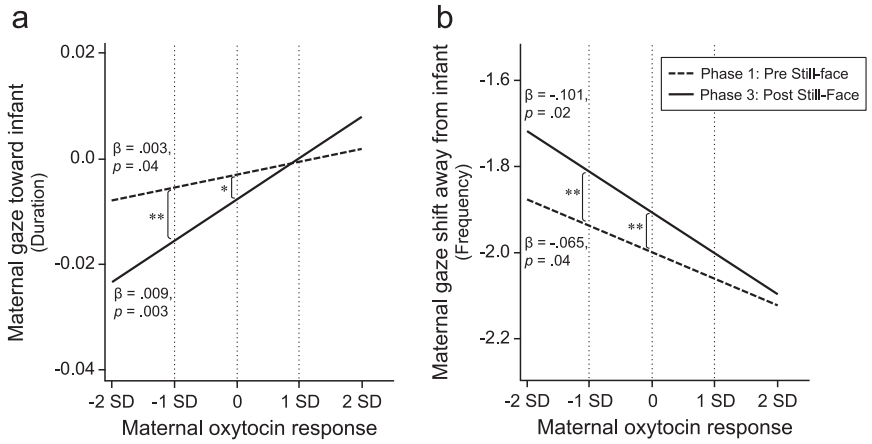

Fig. 3 – (a) Duration of maternal gaze toward infant and (b) frequency of maternal gaze shift away from infant as a function of maternal oxytocin response (OTResp; mean ± SD) and phase of the modified still-face procedure. The *y*-axes indicate log-transformed estimated marginal means. The statistical significance of the gaze differences between phases 1 and 3 is noted at low (i.e., −1 SD) and average (i.e., mean) levels of maternal oxytocin response.*$p < .05$, **$p < .01$

2.3.1. *Maternal gaze toward infant (duration)*

The optimal model included a subject-level random intercept (LR $\chi^2(1) = 5.86$, $p = .016$) and a random coefficient for phase (LR $\chi^2(2) = 38.55$, $p < .0001$), providing a significant fit (Table 2). Consistent with our hypothesis, a significant main effect of OTResp was found, with the duration of mother-to-infant gaze increasing as OTResp increased across participants. The main effect of phase was also significant, indicating that the duration of mother-to-infant gaze decreased in phase 3 as compared to phase 1. OTResp and phase interacted significantly. Decomposition of the interaction revealed that a simple effect of phase was significant at low (i.e., 1 standard deviation below the mean) and average levels of OTResp ($\beta_{\text{phase, at low OT}} = -.010$, 95% CI = −.017 to −.004, $z = -3.06$, $p = .002$ and $\beta_{\text{phase, at mean OT}} = -.005$, 95% CI = −.009 to −.0001, $z = -2.00$, $p = .045$, respectively), but not significant at high (i.e., 1 standard deviation above the mean) levels of OTResp ($\beta_{\text{phase, at high OT}} = .001$, 95% CI = −.006 to.007, $z = .24$, $p = .814$) (Fig. 3(a)). This indicated that mothers with high OTResp displayed gaze duration that was similar during phases 1 and 3, while maternal gaze duration was significantly reduced for mothers with low/average OTResp during phase 3.

2.3.2. *Maternal gaze shift away from infant (frequency)*

The optimal model was obtained with a random effects structure that included a subject-level random intercept (LR $\chi^2(1) = 26.75$, $p < .0001$) and a random coefficient for phase (LR $\chi^2(2) = 8.62$, $p = .013$; Table 2). As hypothesized, a significant main effect was found for OTResp, with mothers displaying less frequent gaze shifts away from their infants as OTResp increased (Fig. 3(b)). The main effect of phase was also significant, indicating that mothers' gaze shifts from infants increased in phase 3 compared to phase 1. OTResp and phase did not interact significantly.

3. Discussion

The present results are the first, to our knowledge, to document that measures of maternal peripheral oxytocin are systematically associated with individual variations in mother-to-infant gaze. As hypothesized, maternal peripheral oxytocin response was positively associated with the duration of mother-to-infant gaze, while negatively associated with the frequency with which maternal gaze was directed away from infants. Also consistent with our expectation, these associations were more pronounced under conditions of infant distress than non-distress. It is worth noting that mothers with low/average peripheral oxytocin responses demonstrated a significant decrease in their mother-to-infant gaze during periods of infant distress, while such change was not observed in mothers with high peripheral oxytocin responses.

The association documented here between maternal oxytocin and mother-to-infant gaze is consistent with and extends previous studies that have reported on the links between maternal oxytocin and other forms of synchronous maternal behavior (e.g., affectionate touch; Atzil et al., 2011; Feldman et al., 2010a, 2010b, 2011). In keeping with previous data from animal (Snowdon et al., 2010) and human research (Dawood et al., 1979; de Geest et al., 1985; Feldman et al., 2007; Levine et al., 2007), we found significant individual variations in mothers' peripheral oxytocin responses, spanning from those that demonstrate a decrease from baseline oxytocin level following interactions with infants to those demonstrating an increase. This variation, likely reflecting naturally occurring differences in mothers' oxytocinergic system functioning, was associated with two patterns of mother-to-infant gaze observed at a micro-behavioral level. Our present finding, in conjunction with the existing literature (Feldman et al., 2010a, 2011; Strathearn et al., 2009b, 2012), points to the role of oxytocin in regulating the mother's responsive engagement with the infant. It is of note that the strength of the observed association between oxytocin and maternal gaze increased during periods of infant distress. From the inception of attachment theory (Bowlby, 1969/1982), the biological function of mother–infant attachment has been thought to be one of ensuring the infant's access to the mother in times of distress (Goldberg et al., 1999; Mikulincer

and Shaver, 2003). Our data underscore the involvement of oxytocin in preparing mothers for such a function.

The significant difference reported here between mothers with high versus low/average oxytocin response is worthy of attention. A corollary to this can be seen in a series of reports on rodents demonstrating that rat mothers who exhibit low licking-and-grooming and arched-back nursing (LG–ABN), a rodent equivalent of neglectful mothering, showed a reduced density of oxytocin receptors in brain regions critical for the emergence of maternal behavior (i.e., the medial preoptic area, the lateral septum, the paraventricular nucleus of the hypothalamus; Champagne et al., 2001; Francis et al., 2000). These mothers' low LG–ABN behavior, in turn, was associated with decreased oxytocin receptor expression in similar brain regions in the offspring (Champagne et al., 2001, 2003b, 2006) who, like their mothers, subsequently displayed reduced levels of LG–ABN behavior with their offspring (Champagne et al., 2003a; Francis et al., 1999; Lovic et al., 2001). While we have not examined infant outcomes in the present study, Beebe et al. (2010)'s micro-analysis of the interaction between mothers and their 4-month-old infants provides particularly noteworthy information in this regard. Beebe et al. (2010) reported on a group of mothers whose behaviors strikingly parallel the behaviors of mothers who demonstrated reduced oxytocin responses in the present study. Mothers of infants who went on to develop profoundly insecure attachment at 12 months were characterized not by their global failure of attunement, but rather by a remarkably specific failure to attend to their infants' distress. Maternal disengagement from infant distress is seen as a critical precursor to the formation of disrupted attachment (Allen, 2013). Similarly, the reduced gaze directed to infant distress reported here in a subsample of our mothers, and those mothers' decreased oxytocin response as a possible biological marker for their impoverished gaze and mirroring response, may subsequently be linked to less-than-optimal outcomes in their infants, particularly in terms of affect dysregulation (Fonagy et al., 2011). Future research should examine the longitudinal links between maternal oxytocin, maternal gaze, and infant developmental outcomes.

Several limitations of the study should be recognized. First, we relied on peripheral measures of oxytocin, using a radioimmunoassay technique. While a degree of concordance has been reported between central and peripheral measures of oxytocin (Carter et al., 2007), peripheral oxytocin levels may not accurately reflect central oxytocin activity (Amico et al., 1990). This represents a limitation yet to be fully overcome in human oxytocin research, although we have previously demonstrated a correlation between peripheral oxytocin response and brain activation in the hypothalamic/pituitary region, where oxytocinergic neurons are concentrated (Strathearn et al., 2009b). Second, we did not track changes in maternal oxytocin or gaze direction as a function of changes in infant affect. We were therefore unable to examine how maternal oxytocin moderated the temporal process by which infant distress modifies and is, in turn, modified by maternal gaze. This would be a fruitful area for further investigation. Third, we considered oxytocin concentration during the initial mother–infant separation as 'baseline,' although we acknowledge that this baseline measurement may have been confounded by the stress experienced during the separation procedure. Finally, our sample consisted largely of mothers of middle to high socioeconomic status, which may limit the generalizability of our findings.

The present study provides the first evidence for the unique relationship between maternal oxytocin response and mother-to-infant gaze. We have found results consistent with our understanding that maternal oxytocin may be substantially implicated in the mother's responsive engagement with her infant, particularly at times when the infant's need for the mother is greatest. The data presented here may have important implications for intervention in conditions that challenge optimal mothering. Helping mothers maintain their engagement during moments of infant distress may be an important focus of intervention for mothers whose oxytocin response may be compromised, who suffer from postpartum depression, or who have struggled with maternal substance abuse or trauma. Breastfeeding, though it may not lead to long-term changes in baseline oxytocin levels, induces a short-term release of oxytocin in mothers, and may hence be beneficial for these mothers (Strathearn et al., 2009a). Finding pharmacological or therapeutic ways to enhance maternal oxytocin release may be another important focus of future intervention.

4. Experimental procedures

4.1. *Participants*

Participants were 50 first-time mothers aged 19–41 ($M = 28.0 \pm .7$) years, recruited through prenatal clinics and community advertisements as part of a larger study. Of 116 participants initially recruited during the third trimester of pregnancy, 61 met eligibility criteria, and 50 completed oxytocin sampling and MSFP at 7 months postpartum. Exclusion criterion included mothers with past or present alcohol or substance abuse, mothers who used cigarettes during pregnancy, and mothers who were on psychotropic medication at the time of the study. The institutional review board at Baylor College of Medicine approved the research protocol, and all participants provided written informed consent.

4.2. *Measures and procedure*

4.2.1. *Oxytocin sampling*

Mothers attended the study session with their infants 7 months postpartum. Mothers were instructed to abstain from caffeine and tobacco 2–3 h prior to the scheduled visit. During the visit, mother–infant dyads participated in a semi-structured mother–infant interaction procedure, which consisted of two periods of separation and an intervening period of mother–infant interaction. Four serial measurements of plasma oxytocin were obtained from the mothers during the procedure (Fig. 4).

4.2.1.1. Baseline. Upon an initial separation of mother and infant, an intravenous cannula was inserted into the mother's forearm and a blood sample was taken for estradiol and progesterone levels. Blood was drawn again 20 min later to determine the first baseline measurement of plasma oxytocin (OT 1).

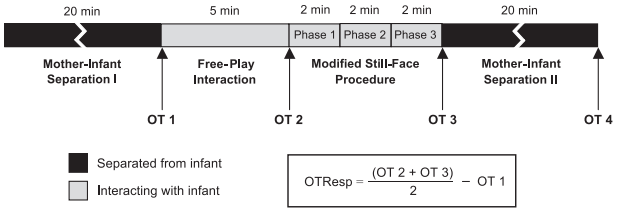

Fig. 4 – Mother–infant interaction procedure and oxytocin response (OTResp) calculation. Measurements of plasma oxytocin were obtained from mothers at four time points: (a) following the first period of mother–infant separation (OT 1), (b) following two periods of mother–infant interaction (OT 2 and OT 3), and (c) following the final period of mother–infant separation (OT 4).

4.2.1.2. *Post free-play*. Following an initial 20-min separation, mother and infant were reunited for a 5-min 'free-play' period, which included direct physical interaction between mother and infant on the floor with age-appropriate toys. The second blood sample was then drawn through the previously inserted cannula (OT 2).

4.2.1.3. *Post modified still-face procedure (MSFP)*. A 6-min MSFP was then conducted. The MSFP is a structured experimental paradigm whereby the mother interacts with her infant through three successive phases, including a still-face phase (see Section 4.2.2; Fig. 1). Mother and infant were able to see each other via a mirror and hear one another during the procedure, but were separated by a dividing screen and thus could not physically interact. A third blood sample was obtained following the MSFP (OT 3).

4.2.1.4. *Baseline (post)*. A second period of 20-min separation occurred between mother and infant, after which the final oxytocin blood sample (OT 4) was obtained.

4.2.2. *Modified still-face procedure (MSFP)*

The MSFP (Koos and Gergely, 2001) adhered to the standard still-face procedure (Tronick et al., 1978) with one exception: the mother and infant were seated beside one another (the mother in a chair and the infant in a high chair), separated by a divider and facing a one-way mirror (Fig. 1(a)). The purpose of the divider and one-way mirror was to prevent physical interaction and touch, but allow mother and infant to see each other reflected in the mirror.[1] On the opposing side of the one-way mirror were two cameras, generating a split-screen recording of the mother and infant. Interactions between mother and infant were videotaped during each of the three 2-min phases (Fig. 1(b)): (1) the baseline normal interaction phase (phase 1), (2) the still-face phase, during which the mother was asked to assume a neutral face (phase 2), and (3) the recovery phase, in which the mother resumed free interaction with the infant (phase 3). An intercom was used to communicate the start of each phase to the mother.

[1]The purpose of the modification of the still-face procedure was to test separate hypotheses regarding infant gaze preference (self vs. mother), which was not explored in this paper focusing on mother-to-infant gaze.

Trained raters, who had had no prior contact with study participants and were blind to the study hypotheses, coded the videotaped interactions. Coding of each behavior category was performed in 1-s time intervals during multiple viewings of videotapes (independently for each behavior). Tapes were viewed at normal speed during coding; however, they were often stopped or run in slow motion to confirm codes and accurately determine the beginning and end of episodes of maternal and infant behavior. Onset and offset times of behaviors were entered into a custom-built software, which generated frequency and duration data for each variable of interest. The median inter-rater reliability was $r_s = .86$ for 18 double-coded interactions (36%).

4.2.3. *Additional mother and infant characteristics*

Several characteristics of interest for mothers and infants were also examined. The Beck Depression Inventory-II (BDI-II; Beck et al., 1996), the Personality Disorder Questionnaire−4+ (PDQ-4+; Hyler et al., 1992), and the Parenting Stress Index (PSI; Abidin, 1995) were administered to assess symptoms of depression, personality disorders, and parenting stress in mothers. We also collected information regarding infants' breastfeeding and daycare status (i.e., if the mother was still breastfeeding or not, and the number of hours per week the infant was cared for by someone other than the mother). Details on the psychometric properties of all administered measures can be found in Shah et al. (2010).

4.3. *Blood collection and assay*

Blood samples were collected and processed by registered nurses from the General Clinical Research Center. Estradiol and oxytocin samples were placed in chilled heparinized tubes and kept on ice. These tubes were centrifuged to separate plasma within 2 h after collection, and the plasma was rapidly frozen and maintained at −80 °C. Before centrifuging, blood samples for progesterone were placed in a serum separator tube and allowed to clot at room temperature. A commercial laboratory determined plasma estradiol and serum progesterone concentrations using quantitative chemiluminescent immunoassay. Dr. Janet Amico's laboratory at the University of Pittsburgh received batches of oxytocin samples that were sent on dry ice by overnight courier. A sensitive and specific liquid-phase radioimmunoassay (RIA) of oxytocin in plasma was performed on acetone–ether extracted material, using previously published and validated methods in which oxytocin antiserum does not cross-react with arginine vasopressin or other oxytocin-like peptides (Amico et al., 1985). The lower limit of detection for this assay is .5 pg/ml and inter- and intra-assay coefficients of variation are each <10%. Although more labor-intensive than widely used alternate methods such as the enzyme immunoassay, RIA on extracted plasma has consistently produced valid and reliable results (McCullough et al., 2013).

4.4. *Variables*

4.4.1. *Maternal oxytocin response (OTResp)*

OTResp (Strathearn et al., 2012) was calculated by computing the change in oxytocin concentration between measurement

at baseline (OT 1) and measurement following mother–infant interactions (mean of OT 2 and OT 3; see Fig. 4). OT 2 and OT 3 were highly correlated with each other ($r_{s\ OT2\ \&\ OT3}=.61$, $p<.001$). OT 4 was omitted from further analyses as a carry-over effect was seen from the mother–infant interaction phases; OT 4 was associated with both OT 3 and OT 2 ($r_{s\ OT3\ \&\ OT4}=.41$, $p=.004$ and $r_{s\ OT2\ \&\ OT4}=.43$, $p=.002$), but not with baseline ($r_{s\ OT1\ \&\ OT4}=.15$, $p=.30$). Positive OTResp values indicated a relative increase in oxytocin during mother–infant interactions, while negative OTResp values indicated a relative decrease. For four mothers, a single missing oxytocin value was imputed using linear interpolation.

4.4.2. *Maternal gaze variables*

We coded maternal eye gaze toward and gaze shifts away from the infant during the two interactive phases (i.e., phases 1 and 3) of the MSFP. Maternal gaze toward infant was quantified by the total duration of time, in seconds, that the mother looked at her infant. Maternal gaze shifts away from infant were assessed by the total frequency with which the mother's gaze first fixated on the infant (i.e., remained stationary on the infant for a minimum of 1 s), then shifted away from the infant. MSFP phases were recorded for 2 min each with slight variations in timing due to mothers' compliance with procedure instructions and infant behavior. Thus, gaze duration and frequency values were adjusted for the total length of time in each phase of the MSFP.

4.4.3. *Infant affect variables*

Infant facial expressions and vocalizations were coded for positive and negative affect at 1-s intervals throughout the MSFP. Total duration of positive and negative affect was calculated for the three phases of the MSFP, adjusting for the total length of time in each respective phase.

4.5. *Statistical analysis*

All variables were inspected for normality via quantile–quantile plots of residuals against fitted values. Logarithmic transformations were performed on maternal gaze variables to optimize the approximation to normal distribution. Changes in infant positive and negative affect were examined in repeated-measures ANOVAs with MSFP phase as a within-subject factor, which were followed by post hoc mean comparisons. Maternal gaze variables were centered prior to being submitted to mixed-effects linear regression analysis. Model building was carried out as follows. (a) The initial model included the fixed main effects of OTResp and MSFP phase (phase 1 vs. phase 3). (b) Subject-level random intercept and slope were added to model systematic inter-individual variability. (c) Interaction terms were added sequentially and retained in the model if they improved model fit. (d) Infant affect variables were added as covariates to examine whether variability in infant affect altered the significance of the model fit or parameter estimates. The model was fitted by maximum likelihood estimation, and likelihood-ratio chi-square tests were used to assess the relative fit of nested models. All analyses were conducted using STATA/SE version 12.1 and SPSS version 21.

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Oxytocin and postpartum depression: Delivering on what's known and what's not

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ABSTRACT

The role of oxytocin in the treatment of postpartum depression has been a topic of growing interest. This subject carries important implications, given that postpartum depression can have detrimental effects on both the mother and her infant, with lifelong consequences for infant socioemotional and cognitive development. In recent years, oxytocin has received attention for its potential role in many neuropsychiatric conditions beyond its well-described functions in childbirth and lactation. In the present review, we present available data on the clinical characteristics and neuroendocrine foundations of postpartum depression. We outline current treatment modalities and their limitations, and proceed to evaluate the potential role of oxytocin in the treatment of postpartum depression. The aim of the present review is twofold: (a) to bring together evidence from animal and human research concerning the role of oxytocin in postpartum depression, and (b) to highlight areas that deserve further research in order to bring a fuller understanding of oxytocin's therapeutic potential.

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1. Introduction

Postpartum depression (PPD) is a debilitating disorder affecting at least one in seven American women annually (Gaynes et al., 2005). PPD impairs the mother's capacity for adaptation following childbirth, posing numerous challenges to the mother-infant relationship and the infant's subsequent development (Murray and Cooper, 1997). Despite the increased attention given to PPD over the past several decades, PPD is currently conceptualized and treated in much the same manner as

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non-postpartum depression, often leading to less than optimal treatment outcomes. In a separate but related line of research, a substantial interest has centered around oxytocin (OT), a neuropeptide hormone critically implicated in the transition to and adjustment during early motherhood. The past two decades have witnessed a surge of clinical trials evaluating OT's therapeutic potential in a wide range of psychiatric disorders, and increasing attention is now directed to PPD as another clinical syndrome for which OT may be of therapeutic benefit. In the present review, we draw upon available data from animal and human research to critically evaluate the potential role of OT in treating PPD. Our goal is to bring together relevant evidence that may elucidate the potential of OT as a therapeutic agent for PPD, while highlighting areas where further research is necessary.

2. Postpartum depression

2.1. *Definition and diagnosis*

PPD is defined as the presence of a major depressive episode following childbirth, although there remains controversy regarding the time criterion pertaining to its onset. The Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV utilized the specifier "with postpartum onset" to limit the diagnosis of PPD to depressive episodes manifesting within 4 weeks post delivery (American Psychiatric Association, 2000), while the newly released DSM-5 uses the specifier "with peripartum onset" to encompass depressive episodes present during pregnancy (American Psychiatric Association, 2013). In contrast to the DSM, the International Classification of Diseases (ICD)-10 classifies depression "as associated with the puerperium" if the onset is within 6 weeks postpartum (World Health Organization, 1992). In the face of a lack of consensus, two large-scale epidemiological studies have demonstrated that women's risk for psychiatric illness increased from childbirth to approximately 3 months postpartum; the risk increased up to 5 months postpartum specifically for depression (Kendell et al., 1987; Munk-Olsen et al., 2006). In consideration of the epidemiological findings and challenges in practical clinical applications, some experts have recommended that the time criterion be extended to 3 to 6 months postpartum (Elliott, 2000; Wisner et al., 2010).

As with non-postpartum depression, depressive symptoms must be present for more than 2 weeks to warrant the diagnosis of PPD. Common symptoms include depressed mood, loss of interest and energy, changes in sleep or eating patterns, diminished ability to think or concentrate, feelings of worthlessness, and recurrent suicidal ideations. While not currently a part of diagnostic criteria, anxiety is considered a prominent feature of PPD, present in approximately half of women diagnosed with PPD (Ross et al., 2003). In severe cases, PPD can be accompanied by psychotic features which may include delusions or command hallucinations to harm the infant (American Psychiatric Association, 2013).

2.2. *Prevalence and risk factors*

Prevalence estimates of PPD range widely from 5 to 25% (Gavin et al., 2005), primarily due to the variability in the criteria used, particularly the time criterion. However, findings from meta-analytic and systematic reviews converge to point to a more precise estimate of 10 to 15% (Gaynes et al., 2005; O'Hara and Swain, 1996), translating to approximately 600,000 women in the United States annually. This is distinguished from the postpartum blues, a mild and transient mood disturbance following childbirth, commonly experienced by up to 80% of postpartum women (Beck, 2006; Buttner et al., 2012). The risk of PPD increases with a history of prenatal depression, prenatal anxiety, or PPD (Beck, 2001; Robertson et al., 2004; Wisner and Wheeler, 1994). Stressors during pregnancy and the early postpartum, including perinatal complications, preterm birth, or infant health problems (Blom et al., 2010; Robertson et al., 2004; Sit and Wisner, 2009), also serve to increase the risk of PPD, as do poverty, low social support, and adolescent motherhood (Beck, 2001; O'Hara and Swain, 1996; Robertson et al., 2004; Troutman and Cutrona, 1990; Wang et al., 2011). PPD lasts for more than 7 months in over half of affected women (Sit and Wisner, 2009).

While studies have demonstrated a high heritability of depressive disorders (Sullivan et al., 2000), evidence is less conclusive concerning PPD (Corwin et al., 2010). The only published twin study of PPD is one by Treloar et al. (1999), who demonstrated that genetic factors accounted for 25% of variance in the onset of PPD in 838 Australian female twin pairs. Three family studies exist to date and suggest that the rate of PPD increases in female siblings of women with unipolar (Forty et al., 2006; Murphy-Eberenz et al., 2006) or bipolar depression (Payne et al., 2008). Although informative, these few studies have been criticized by some for methodological shortcomings (e.g., failure to distinguish between PPD and postpartum blues or to control for other psychiatric comorbidity; Corwin et al., 2010), particularly in light of the lack of association shown by other groups between a woman's familial history of depression and her development of PPD (Bloch et al., 2005; Dennis et al., 2004). Studies of genetic markers have also been underway and have highlighted the role of the polymorphisms of three candidate genes, the serotonin transporter, monoamine oxidase A, and catechol-O-methyltransferase genes (Doornbos et al., 2009; Sanjuan et al., 2008), although complex genetic and epigenetic interactions remain to be explored.

2.3. *Neuroendocrine considerations*

Elucidating the neuroendocrinology of PPD has been a challenge in the field due to normative and adaptive neuroendocrine changes that take place during pregnancy and postpartum. Gonadal steroid hormones have received attention, as levels of estradiol and progesterone drop drastically following parturition, often coinciding with the onset of postpartum blues or PPD symptoms. A noteworthy study by Bloch et al. (2000) found that the simulation of gonadal withdrawal precipitated depressive symptoms in euthymic women with a history of PPD, supporting the potential contribution of hypogonadism to the onset of PPD. However, the relationship between hypogonadism and PPD has been disputed by many others (Abou-Saleh et al., 1998; Harris et al., 1996; Klier et al., 2007; Zonana and Gorman, 2005). Currently, there is no consistent evidence that a decrease in absolute concentrations of gonadal hormones triggers PPD,

although available data suggest that PPD may manifest in women who are vulnerable to fluctuations in gonadal hormone levels (Workman et al., 2012).

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis has also garnered interest for its potential role in the etiology of PPD. The HPA system undergoes numerous changes during pregnancy and postpartum (Lightman et al., 2001; Tu et al., 2006). Adreno-corticotropic hormone levels increase during pregnancy, and cortisol reaches its peak at the end of pregnancy as the placental corticotropin-releasing hormone (CRH) levels rise, before dropping rapidly at parturition (Kammerer et al., 2006; Yim et al., 2009). There have been reports that women with PPD demonstrate more extreme changes in the activity of the HPA axis during pregnancy and postpartum (Jolley et al., 2007; Taylor et al., 2009), though directionality has been inconsistent, with increased (Lommatzsch et al., 2006; Okano and Nomura, 1992) or decreased cortisol levels being documented (Groer and Morgan, 2007; Jolley et al., 2007). Indeed, some have proposed that different subtypes of PPD may exist, underpinned by distinct genetic predispositions and differential regulation patterns (i.e., hypo- vs. hyper-regulation) of the HPA axis (Kammerer et al., 2006).

OT has received less interest than gonadal or stress hormones as a potential etiologic factor in PPD, although it has attracted attention for its involvement in breastfeeding difficulties often present in PPD (Stuebe et al., 2012). It is well known that OT is critically implicated in milk letdown (Pang and Hartmann, 2007). The documented association between breastfeeding difficulties and PPD (Dennis and McQueen, 2009; Taveras et al., 2003; Watkins et al., 2011) is worthy of attention (Skalkidou et al., 2010). To date, only one study (Stuebe et al., 2013) has examined OT as part of the link between lactation failure and PPD. In a group of mothers intending to breastfeed, the authors found that OT levels were inversely correlated with depressive symptoms in both the third trimester and at 8 weeks postpartum, corroborating and extending earlier findings by Skrundz et al. (2011). The authors also documented that OT release was reduced in depressed mothers during breastfeeding compared to non-depressed mothers, although no difference was found between the two groups in breastfeeding duration or intensity. Stress-attenuating effects of breastfeeding deserve consideration here (Heinrichs et al., 2001; Stuebe et al., 2012). Compared to their non-breastfeeding counterparts, breastfeeding women demonstrated attenuated HPA response to stressors (Altemus et al., 1995). Furthermore, cortisol levels decreased in breastfeeding women during lactation (Amico et al., 1994), while mood scores improved following lactation (Heinrichs et al., 2001). Animal models (Neumann, 2003) have suggested that disruptions of the OT system may be implicated in the observed relations between breastfeeding, stress regulation, and mood, which is of particular relevance to PPD given that all three components become disrupted in many affected women (Heinrichs et al., 2001; Stuebe et al., 2012).

3. Maternal caregiving in postpartum depression

PPD is well known to have deleterious effects on the development of the offspring. Reports show that children of depressed mothers are at risk for a wide range of cognitive, emotional, behavioral, and medical problems. Cognitively, they are likely to have lower IQ scores, attention problems, and special educational needs (Hay et al., 2001). Emotionally, they are susceptible to various forms of psychopathology including mood disorders, anxiety disorders, and substance use disorders (Apter-Levy et al., 2013; Murray et al., 2011; Schwartz et al., 1990). Behavioral problems are also prevalent, at times warranting the diagnoses of conduct disorder or oppositional defiant disorder (Alpern and Lyons-Ruth, 1993; Dawson et al., 2003). They are also often high utilizers of pediatric emergency services, while frequently missing outpatient pediatric visits (Flynn et al., 2004). Many of these adverse developmental outcomes have been associated with impaired maternal caregiving behavior in depression, even after controlling for the effects of demographic variables (Azak and Raeder, 2013; NICHD Early Child Care Research Network, 1999).

A large number of studies have highlighted that mothers with PPD are slow to read, decipher, and respond to their infants' signals (see reviews, Field, 2010; Tronick and Reck, 2009). While some depressed mothers are withdrawn, passive, and under-stimulating, others are intrusive, hostile, and over-stimulating (Lovejoy et al., 2000; Malphurs et al., 1996; Weikum et al., 2013). This provides infants with fewer and shorter moments of reciprocal engagement, joint attention, and shared affect (Feldman, 2007; Weinberg and Tronick, 1998). Infants are also given fewer opportunities to experience repair following moments of disrupted engagement (Jameson et al., 1997). Such disruptions in the early mother–infant relationship may serve as a precursor to insecure infant attachment (Mills-Koonce et al., 2008; Stern, 1995), which has longitudinally been linked to numerous adverse developmental outcomes (Sroufe et al., 2005), including the cognitive, emotional, and behavioral outcomes described above. One recent study (Laurent and Ablow, 2013) documented that maternal brain responses were altered in women with PPD. While viewing images of their own infants, mothers with PPD displayed blunted activity in brain regions known to be central for emotional responsiveness, empathy, and reward (e.g., anterior cingulate, orbitofrontal cortex, insula, and striatum).

Frequently, the impaired mother–infant relationship is further compromised by breastfeeding difficulties often experienced in women with PPD. While breastfeeding provides one of the earliest opportunities for the mother to establish an intimate bond with her infant, many depressed mothers report dissatisfaction with breastfeeding (Dennis and McQueen, 2007) and discontinue breastfeeding between 4 to 16 weeks postpartum (McLearn et al., 2006; Paulson et al., 2006).

4. Current treatment of postpartum depression

4.1. *Pharmacotherapy*

4.1.1. *Antidepressant medication*

PPD is currently treated in much the same manner as non-postpartum depression, with selective serotonin reuptake inhibitors (SSRIs) as the first-line of pharmacotherapy. As in non-postpartum depression (Cipriani et al., 2007), SSRIs

are efficacious in targeting depressive symptoms in PPD. A review of available randomized controlled clinical trials show that SSRIs improved mood in 43 to 88% of women with PPD (Appleby et al., 1997; Bloch et al., 2012; Misri et al., 2004; Sharp et al., 2010; Wisner et al., 2006; Yonkers et al., 2008), which are similar to rates reported for non-postpartum depression (Kirsch et al., 2008); 37 to 65% of treated women achieved remission of depressive symptoms (De Crescenzo et al., 2013). Despite the demonstrated efficacy, factors unique to pregnancy and the postpartum period complicate the antidepressant treatment of PPD (Ellfolk and Malm, 2010; Yonkers et al., 2009). Many healthcare providers are reluctant to engage patients in pharmacotherapy due to concerns about fetal or infant exposure to antidepressants, and three-quarters of women diagnosed with PPD are indeed left untreated (Bennett et al., 2004). Pregnant or postpartum women similarly show low acceptability of antidepressant medications (Chabrol et al., 2004), with available SSRI trials reflecting high drop-out rates (Appleby et al., 1997; Wisner et al., 2006; Yonkers et al., 2008). Medications may also be prescribed and used at sub-therapeutic doses (Bennett et al., 2004; Epperson et al., 2003), which may be a particular concern since women with PPD require higher doses of antidepressant agents for a longer duration to experience relief of symptoms (Dawes and Chowienczyk, 2001; Hendrick et al., 2000).

Data on the effects of antidepressant treatment on maternal functioning are limited. Only one group (Logsdon et al., 2009, 2011) has provided relevant data, demonstrating that antidepressants were effective in enhancing maternal role-gratification throughout the first postpartum year, but not maternal self-efficacy, overall maternal role functioning, or the quality of the mother–infant relationship. The literature on fetal or infant exposure to SSRIs is large and growing. As per a recently published report from the American Psychiatric Association (APA) and the American College of Obstetricians and Gynecologists (ACOG; Yonkers et al., 2009), the accumulated data are in support of small but significant associations between SSRI use during pregnancy and preterm delivery (i.e., <37 weeks gestation) as well as small-for-gestational-age birth weight (i.e., <10% of age-adjusted birth weight). Antidepressant use was generally not associated with major congenital malformations in the infant, although use during the third trimester was linked to transient poor neonatal outcomes (e.g., irritability, jitteriness).

4.1.2. *Hormonal therapy*

Estradiol therapy is a novel treatment that targets the flux of gonadal hormones that may render a subset of women vulnerable to depression in the postpartum period (Bloch et al., 2000; Moses-Kolko et al., 2009). Growing data suggest that estradiol therapy has promising antidepressant properties, with reported response and remission rates exceeding those of SSRIs. Within the first month of a double-blinded, placebo-controlled trial (Gregoire et al., 1996), women treated with estrogen patches showed greater and more rapid improvements in their depressive symptoms compared to those treated with placebo patches. Similar improvements were shown in another study (Ahokas et al., 2001), in which 83% of severely depressed women reached remission within 2 weeks of treatment with sublingual estradiol. Notably, decreases in women's depression scores were inversely correlated with increases in their serum estrogen levels, and available data suggest that estradiol therapy was well tolerated with low dropout rates. However, estradiol therapy may interfere with breastfeeding, a consideration important in the treatment of PPD (Fitelson et al., 2010; Moses-Kolko et al., 2009). Although early data suggested that synthetic progesterones may be therapeutic for PPD, this view has since been challenged and the use of progesterones is not recommended (Dennis et al., 2008). Currently, no data exist on the effects of hormonal therapy on maternal behavior.

4.2. *Psychological interventions*

Psychological interventions that have been empirically studied for the treatment of PPD include interpersonal psychotherapy (IPT; Grote et al., 2009; Mulcahy et al., 2010), cognitive behavioral therapy (CBT; Chabrol et al., 2002; Wiklund et al., 2010), psychodynamic therapy (Bloch et al., 2012; Cooper et al., 2003), and non-directive counseling (Milgrom et al., 2005; Murray et al., 2003). Several meta-analyses exist to date and suggest that psychological interventions are efficacious in reducing depressive symptoms (Cuijpers et al., 2008; Dennis and Hodnett, 2007; Lumley et al., 2004; Sockol et al., 2011) at rates similar to those of antidepressant medications (De Crescenzo et al., 2013; Sockol et al., 2011). No conclusive data exist to suggest the superiority of one psychotherapy modality to another in the treatment of PPD (Fitelson et al., 2010), although there is some evidence that IPT, which directly addresses interpersonal problems (e.g., role transitions, relational conflicts), may be more efficacious than CBT, which targets maladaptive depressogenic cognitions (Bledsoe and Grote, 2006; Sockol et al., 2011).

However, as with pharmacotherapy, a mere decrease in depressive symptoms is often not enough to enhance maternal functions (Forman et al., 2007; Murray et al., 2003). Psychological interventions without an explicit focus on the mother–infant relationship were effective in reducing maternal parenting stress, without benefiting maternal or infant behavior (Forman et al., 2007; O'Hara et al., 2000). Interventions that actively incorporated the mother–infant relationship as a focus generally yielded some improvement in this domain (Clark et al., 2003; O'Hara and McCabe, 2013; Poobalan et al., 2007). However, therapeutic gains were not sustained on longitudinal follow-ups and did not generalize to infants' cognitive or behavioral outcomes, with the exception of one study in which extensive and prolonged therapy was implemented (Cicchetti et al., 2000).

Current APA and AGOC guidelines recommend psychotherapy as the first-line of treatment for mild to moderate depression, although antidepressant medications are recommended in the presence of moderate to severe depressive symptoms, particularly in women with a history of recurrent depression (Kim et al., 2010; Yonkers et al., 2009). The acceptability of psychotherapy is reported to be high in postpartum women (Chabrol et al., 2004) and psychotherapy is often preferred to antidepressants in this population (Pearlstein et al., 2006; Turner et al., 2008).

5. Oxytocin: A novel therapeutic for postpartum depression?

As the preceding review suggests, currently available treatments of PPD are promising in reducing depressive symptoms, but are less effective in improving the mother–infant relationship. OT has emerged as a potentially viable treatment option in this context, given its role in regulating the onset and maintenance of maternal behavior, along with its antidepressant and anxiolytic properties.

OT is a nonapeptide synthesized in magnocellular neurons of the paraventricular (PVN) and supraoptic nuclei of the hypothalamus and released into the bloodstream from the neurohypophysis (Gimpl and Fahrenholz, 2001; Insel, 2010). OT receptors are located throughout the brain including regions known to be critical for the expression of maternal behaviors, such as the ventromedial nucleus of the hypothalamus, central nucleus of the amygdala, medial preoptic area (MPOA), bed nucleus of the stria terminalis (BNST), and ventral tegmental area (VTA). OT is also secreted in small amounts by numerous peripheral tissues such as the uterus, placenta, corpus luteum, testis, and heart (Gimpl and Fahrenholz, 2001). For many decades, OT was well recognized for its peripheral actions, including uterine contraction in parturition and milk ejection during lactation (Insel, 2010; Ross and Young, 2009), though it is now regarded a key neuroregulator implicated in social and stress-related disorders on one hand and maternal behavior on the other (Bartz and Hollander, 2006; Neumann and Landgraf, 2012). To assist in evaluating the potential of OT as a therapeutic agent for PPD, we examine available animal and human research on the role of OT in (a) anxiety- and depressive-like behavior and in (b) maternal functioning.

5.1. *Antidepressant and anxiolytic effects of oxytocin*

5.1.1. *Animal studies*

An antidepressant effect of OT was first reported by Arletti and Bertolini (1987), who demonstrated that acute and repeated intra-peritoneal injections of OT in mice reduced the immobility time in the forced swim test, a commonly used index of depressive behavior in animals. Similarly, subcutaneous OT infusions in rats reduced the escape failures in the learned helplessness test, another widely used animal model of depression (Nowakowska et al., 2002). Recently, these results were replicated following intracerebral administrations of OT (Ring et al., 2010), suggesting that central or peripheral administrations of OT may have antidepressant properties (Slattery and Neumann, 2010b). In rats, OT has also been shown to improve other features of depression (Neumann and Landgraf, 2012), including anhedonia (Liberzon et al., 1997), sexual dysfunction (Melis et al., 2007), and sleep disturbance (Lancel et al., 2003).

Anxiolytic and stress-attenuating effects of OT have also been well documented. Anxiogenic stimuli are understood to increase central OT release in the PVN of the hypothalamus (Nishioka et al., 1998), central nucleus of the amygdala (Ebner et al., 2005), and lateral septum (Ebner et al., 2000), which subsequently functions to dampen stress response by modulating the activity of the HPA axis (Engelmann et al., 2004; Neumann et al., 2000). OT knockout mice showed increased stress-induced fos expression in the medial amygdala and BNST, heightened CRH mRNA expression in the PVN, and elevated corticosterone release following exposure to stressors (Amico et al., 2008; Nomura et al., 2003). Furthermore, intracerebroventricular infusions of OT decreased the molecular and neuroendocrine responses of the HPA axis and attenuated anxiety-like behaviors in female rats, while administration of the OT receptor antagonist produced opposite results (Slattery and Neumann, 2010a; Windle et al., 2004).

While mechanisms of the antidepressant and anxiolytic effects of OT remain to be further elucidated, available evidence suggests that the effects may be produced in part by the interactions between the serotonergic, corticotropin-releasing factor (CRF), and OT systems (Neumann and Landgraf, 2012). OT release is understood to activate OT receptors in serotonergic neurons of the raphe nuclei to yield antidepressant and anxiolytic effects (Yoshida et al., 2009), whereas stimulation of serotonin release activates CRF and OT neurons in the hypothalamus (Javed et al., 1999), a mechanism that may underlie antidepressant properties of the SSRIs (Emiliano et al., 2007).

5.1.2. *Human studies*

OT-related dysfunctions have been examined in depressed patients, although results remain inconclusive. Some groups have shown that peripheral OT concentrations were lower in depressed patients, particularly female patients (Ozsoy et al., 2009), compared to controls (Frasch et al., 1995; Zetzsche et al., 1996). Another report showed that the severity of patients' depression and anxiety symptoms was inversely correlated with their plasma OT levels (Scantamburlo et al., 2007). However, other studies of plasma OT (Cyranowski et al., 2008; van Londen et al., 1997) and a few available studies of cerebrospinal fluid (CSF) OT (Demitrack and Gold, 1988; Pitts et al., 1995) failed to document reduced OT levels in depressed patients. Notably, these studies found a greater variability of OT concentrations in the patient group (Cyranowski et al., 2008; van Londen et al., 1997); in one study, a trend toward reduced OT was found only in a subgroup of patients (Pitts et al., 1995).

Endogenous OT released during breastfeeding (Chiodera et al., 1991) has been understood to underlie the attenuated HPA responsiveness and reduced anxiety behavior shown in lactating women (Heinrichs et al., 2001). However, exogenous OT administrations in humans have produced equivocal findings. Intranasal OT was reported to decrease stress responsiveness and anxiety in healthy men (Heinrichs et al., 2003), reduce levels of salivary cortisol during couple conflict in heterosexual couples (Ditzen et al., 2009), and attenuate fear-related amygdala reactivity in healthy males and patients with social anxiety (Kirsch et al., 2005; Labuschagne et al., 2010). However, these studies failed to document direct effect of intranasal OT on mood (Kirsch et al., 2005; Labuschagne et al., 2010). Furthermore, while the majority of the studies were conducted in men, intranasal OT was shown to enhance fear-related amygdala reactivity in healthy women (Domes et al., 2010; but see Rupp et al., 2012 for results in nulliparous women only), while producing null effects in healthy postpartum

women (Rupp et al., 2012). Notably, the only available study on PPD demonstrated that intranasal OT worsened self-reported mood ratings in this group of women (Mah et al., 2013). A study observing the use of OT to aid the progress of labor further showed that OT administration during labor did not reduce the incidence of PPD in first-time mothers (Hinshaw et al., 2008).

5.2. *Oxytocin and maternal behavior*

5.2.1. *Animal studies*

A large body of research supports the role of OT in the onset and maintenance of maternal behavior across species. Intracerebroventricular injections of OT induced a full range of maternal behavior in female virgin rats (Pedersen and Prange, 1979; Pedersen et al., 1982), whereas infusions of OT antagonist inhibited the emergence of maternal behavior in parturient rat dams (Pedersen et al., 1994; van Leengoed et al., 1987). Similar results were found in mice (McCarthy, 1990) and sheep (Kendrick et al., 1987; Keverne and Kendrick, 1992). These findings are in line with the report that lesions of the PVN, a main site of OT production in the brain, disrupted the onset of maternal behavior in rats (Insel and Harbaugh, 1989). Impaired maternal behavior was similarly found in female OT knockout mice (Ragnauth et al., 2005; Takayanagi et al., 2005) and postpartum mutant female mice with reduced OT neurons in the PVN (Li et al., 1999). Other prominent sites of OT receptors have also been examined in relation to the expression of maternal behavior. OT receptor density in the central nucleus of the amygdala and BNST was shown to be correlated with the quality of maternal care in rats (Francis et al., 2000); OT receptor binding density in the nucleus accumbens was similarly associated with the amount of time prairie voles spent crouching over pups (Olazabal and Young, 2006).

Another important line of research in this area concerns the modification of the OT system by early caregiving experiences (Champagne, 2008; Meaney, 2001). A series of experimental and cross-fostering studies demonstrated that female rats reared by low licking-and-grooming and arched-back nursing (LG-ABN) mothers showed a reduced density of OT receptors in brain regions critical for the expression of maternal behavior, including the MPOA, PVN, and lateral septum (Champagne et al., 2001, 2003b, 2006). Just like their mothers, the female rat pups were subsequently seen to display low levels of LG-ABN behavior with their offspring when they reached the postpartum period (Champagne et al., 2003a; Francis et al., 1999). Similarly, non-maternal rearing in rhesus monkeys was associated with reduced CSF OT levels across the first three years of life (Winslow et al., 2003).

Studies on OT-related maternal functions are continuing to expand. The current understanding is that OT circuits interact closely with dopaminergic circuits to regulate the expression of maternal behavior (Shahrokh et al., 2010; Strathearn, 2011). OT neurons in the PVN and MPOA of the hypothalamus project to the VTA and nucleus accumbens (Numan and Smith, 1984; Ross et al., 2009a), and the connections and signals between these regions increase with the quality of maternal behavior (Champagne et al., 2004; Shahrokh et al., 2010). The OT-dopamine interactions are thought to mediate the rewarding and reinforcing properties of the mother–infant interaction.

5.2.2. *Human studies*

Over the past decade, many important advances have been extended from animal models to humans, elucidating the central role of OT in human mothering. Peripheral OT levels in mothers have been consistently associated with naturally occurring variations in maternal behavior, with high OT levels during pregnancy and postpartum predicting enhanced maternal behavior (Atzil et al., 2011; Feldman et al., 2007; Gordon et al., 2010a, 2010b). Following the work of Meaney (2001) and Champagne (2008), research in this area has underscored the interindividual variability of OT-related functions in mothers. Interactions with infants stimulate OT release in mothers, but only in a subgroup of mothers who demonstrate secure attachment (Strathearn et al., 2009), display sensitivity to emotions and physical sensations (Strathearn et al., 2012), or exhibit synchronous and affectionate forms of mothering (Feldman et al., 2010a; Kim et al., 2014). Maternal OT increase during mother–infant interaction has further been correlated with the concurrently measured OT increase in the infant, supporting an intergenerational link between the OT functions of mother and infant in humans (Feldman et al., 2010b). Evidence continues to grow supporting the understanding that women's OT functions may be modified by their early caregiving experiences. Inverse associations have been reported between women's levels of CSF OT and the severity and duration of abuse and neglect to which they were exposed in childhood (Heim et al., 2009). Studies have further documented low plasma OT levels in individuals who reported receiving low levels of parental care (Feldman et al., 2011; Gordon et al., 2008).

Only a handful of studies have examined the role of OT in maternal brain responses. Strathearn et al. (2009) found that mesocorticolimbic dopaminergic reward regions (i.e., ventral striatum, medial prefrontal cortex) as well as the hypothalamic OT regions were activated when securely attached mothers viewed images of their own infants. Similar results were reported by Atzil et al. (2011), who demonstrated that mothers who displayed synchronous forms of mothering showed activation of the ventral striatum, a key reward region, while viewing video clips of their own infants. Notably, activations in these brain regions were correlated with the peripheral measures of OT in these mothers (Atzil et al., 2011; Strathearn et al., 2009). Brain responses of breastfeeding mothers have also attracted attention, given the role of breastfeeding in endogenous OT production (Chiodera et al., 1991). The only pertinent study to date is that by Kim et al. (2011), who found that breastfeeding mothers showed greater activation of the brain regions critical for the expression of maternal behavior, including the striatal reward region, in response to their own infants' cries.

Studies have recently begun to examine the role of exogenous OT administrations in maternal brain responses. Intranasal administrations of OT were shown to increase the incentive salience of an unknown infant's laughter in a group of women, as evidenced by the enhanced connectivity observed between the amygdala and emotion regulation regions (Riem et al., 2012). Conversely, in response to an

unknown infant's cry, intranasal OT decreased the women's negative emotional arousal, as reflected by reduced amygdala signals, while increasing activations in the empathy-related regions (Riem et al., 2011). It is important to note that intranasal OT further decreased the women's handgrip force in response to hearing infant's cry, although the effect was present only in women without early experiences of harsh parenting (Bakermans-Kranenburg et al., 2012).

5.3. *Oxytocin in the treatment of psychopathology*

In addition to its role in regulating the expression of maternal behavior as reviewed above, a large body of literature has implicated OT in a much broader range of social behaviors (Benarroch, 2013; Meyer-Lindenberg et al., 2011), including pair bonding (Ross et al., 2009b; Schneiderman et al., 2012), interpersonal trust (Kosfeld et al., 2005; Van IJzendoorn and Bakermans-Kranenburg, 2012), emotion recognition (Lischke et al., 2012; Perry et al., 2013), and empathy (Hurlemann et al., 2010; Rodrigues et al., 2009), to name a few. Due to its seemingly widespread prosocial effects, along with its antidepressant and anxiolytic properties, OT has gained widespread popularity over the past decade in the study of normative and psychiatric populations. A sizable number of trials have investigated its therapeutic potential in many psychiatric disorders, and many more trials are underway. To date, clinical trials in which OT has demonstrated therapeutic benefit over placebo include those of autism spectrum disorder (Anagnostou et al., 2012; Andari et al., 2010; Guastella et al., 2010), schizophrenia (Averbeck et al., 2012; Feifel et al., 2010; Modabbernia et al., 2013; Pedersen et al., 2011), social anxiety (Guastella et al., 2009; Labuschagne et al., 2010), and post-traumatic stress disorder (Yatzkar and Klein, 2009).

Despite the considerable excitement that these results have generated, a more complicated and nuanced picture emerges upon careful examination of the available data. Effects of OT reported in many social domains (e.g., social cognition, prosociality) are often inconsistent or, more precisely, are moderated by contextual and personal factors (Bartz et al., 2011b; Guastella and MacLeod, 2012; Macdonald and Macdonald, 2010). The context-dependent nature of the effects of OT is well demonstrated in a series of studies conducted on trust, in which exogenous administrations of OT increased participants' trust of individuals perceived as part of the in-group, but increased non-cooperation toward out-group members who were perceived as potential threats (De Dreu et al., 2010, 2012). The person-dependent nature of the effects of OT is well captured in a growing number of studies that demonstrate null effects of exogenous OT in individuals with adverse early caregiving experiences, whether assessed by reported severity of childhood abuse, neglect, or loss (Meinlschmidt and Heim, 2007), memories of parental love-withdrawal (Riem et al., 2013; van Ijzendoorn et al., 2011), or recollections of harsh parenting experiences (Bakermans-Kranenburg et al., 2012). Considering that the development of one's OT system may be critically modified by the quality of early caregiving one receives (Champagne, 2008; Meaney, 2001), it is possible that the OT system may have been altered at a more fundamental level, possibly at the level of receptors, in individuals with early adverse experiences. The resulting alterations in OT receptor density, affinity, or functions may underlie the decreased responsivity that is seen in these individuals upon exogenous administrations of OT (Bakermans-Kranenburg and van IJzendoorn, 2013).

This is of particular relevance in considering the use of OT in psychiatric patients, since early adverse experiences are rather common in this population. Not surprisingly, a review of data suggests that psychiatric patients have produced variable results in response to exogenous OT administrations, ranging from improvement (Guastella et al., 2010; Pedersen et al., 2011) to worsening of symptoms (Bartz et al., 2011a; Mah et al., 2013), along with some null findings (Epperson et al., 1996; Pitman et al., 1993). In some cases, exogenous administrations of OT have yielded opposing patterns of results for psychiatric and healthy groups (e.g., Bartz et al., 2011a; Pincus et al., 2010). This divergence is well reflected in the results of recent meta-analyses of available clinical trials, which demonstrated that, when taken together, exogenous OT administrations did not improve symptoms of psychiatric disorders with the exception of autism spectrum disorder, although weak to moderate beneficial effects were found for healthy controls (Bakermans-Kranenburg and van IJzendoorn, 2013). While meta-analytic results are discouraging, more research is necessary given that the number of clinical trials available for the meta-analyses were small for many psychiatric conditions.

5.4. *Can exogenous oxytocin benefit the treatment of postpartum depression?*

While data from animal models suggest that OT may have potential in the treatment of PPD, the future of exogenous OT in human psychiatric disorders remains unclear. To date, limited data exist on the antidepressant or anxiolytic effects of exogenous OT in women, and a small number of available studies have demonstrated null (Rupp et al., 2012) or negative results (Domes et al., 2010; Mah et al., 2013). The role of exogenous OT in human mothering has received more direct support (Riem et al., 2011, 2012), although growing evidence suggests that its effects are critically moderated by women's early caregiving experiences (Bakermans-Kranenburg et al., 2012). While we are cautiously optimistic about OT's therapeutic potential, we believe that there are many questions that remain to be answered. Here, we highlight some of these remaining questions for future research.

First, it would be of great importance to identify individual differences among PPD patients that may moderate the effects of exogenous OT. PPD patients are likely a heterogeneous group of individuals demonstrating a large variability in OT receptor function, endogenous OT production, and early caregiving experiences. As these factors are understood to alter one's responsivity to exogenous OT, careful investigation of these intraindividual characteristics and identification of relevant neurobiological and behavioral markers are of paramount interest. Given the pattern of results reviewed, it is possible that exogenous OT may yield beneficial effects only in a subgroup of PPD patients. Such results may not be apparent and may even be obscured in between-group designs, where effects are averaged across individuals and within-group

individual differences are overlooked (Guastella and MacLeod, 2012). We concur with others (e.g., Guastella and MacLeod, 2012) that the imperative next step in OT translational research is to develop cognitive, behavioral, and neurobiological markers that can index the degree to which patients may be responsive to exogenous administrations of OT.

Second, gender is an important consideration given the differences in the endogenous OT levels between men and women. Furthermore, gonadal hormones, estrogen in particular, are understood to be critically involved in the regulation of OT, whether endogenously produced or exogenously administered. It is in this regard that a relative dearth of clinical trials in women is particularly problematic. It is not yet clear to what degree the extant findings obtained in men can be generalized to women, and particularly to postpartum women who undergo significant hormonal changes. It is also unclear how, and to what extent, menstrual cycle and accompanying fluctuations in gonadal hormones moderate the effects of exogenously administered OT and contribute to divergent results (e.g., see Domes et al., 2010 vs. Rupp et al., 2012). It is important that future studies recruit female participants, and specifically postpartum women, to examine the effects of OT in this unique population.

Third, for therapeutic use of exogenous OT, it would be important to systematically address questions of dosage, timing, and side effects associated with long-term administration. All clinical trials to date have used low doses (18 to 40 IU) for a short span of time, with minimal reported side effects (MacDonald et al., 2011). Future research should examine the safety of high-dose long-term use of OT. It would be critical to understand how chronic exogenous administrations of OT may affect endogenous OT production as well as complex neuroendocrine functions in the postpartum period.

Fourth, it remains to be determined whether exogenous OT should be used as a stand-alone treatment or should better be integrated with other therapies. Most available clinical trials have excluded patients undergoing medication treatment, and there is currently limited data from which to draw conclusions about the safety and efficacy of OT as an augmentation agent (MacDonald et al., 2011). Furthermore, anxiolytic and prosocial effects of OT have led some to believe that exogenous OT administrations may help aid the process of psychotherapy. This would be a fruitful area for future investigation.

6. Conclusions

While OT initially appeared to offer much promise, the pattern of results that has thus far emerged is more nuanced and inconsistent than it appeared to be at first. The literature reviewed in preceding sections suggest that studies are beginning to shed light upon the complex context- and person-dependent nature of OT effects. We propose that future studies attend to individual variations that may be present among mothers with PPD, rather than looking for the uniform effect across all mothers. We underscore that focused studies that tease apart OT-related individual variations are necessary to fully evaluate the therapeutic potential of OT in the treatment of PPD.

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Research Report

Oxytocin and social cognition in rhesus macaques: Implications for understanding and treating human psychopathology

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Inhalation

ABSTRACT

Converging evidence from humans and non-human animals indicates that the neurohypophysial hormone oxytocin (OT) evolved to serve a specialized function in social behavior in mammals. Although OT-based therapies are currently being evaluated as remedies for social deficits in neuropsychiatric disorders, precisely how OT regulates complex social processes remains largely unknown. Here we describe how a non-human primate model can be used to understand the mechanisms by which OT regulates social cognition and thereby inform its clinical application in humans. We focus primarily on recent advances in our understanding of OT-mediated social cognition in rhesus macaques (*Macaca mulatta*), supplemented by discussion of recent work in humans, other primates, and rodents. Together, these studies endorse the hypothesis that OT promotes social exploration both by amplifying social motivation and by attenuating social vigilance.

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1. Introduction

Oxytocin (OT) is an evolutionarily conserved nonapeptide that mediates female sexual intercourse, parturition, lactation, as well as water regulation, and anxiolytic functions (Donaldson and Young, 2008). In highly social animals, these ancestral functions of OT have been co-opted to serve social functions, such as promoting maternal behavior (Champagne et al., 2001; Pedersen et al., 1982), fostering pair-bonding and affiliative behaviors (Cushing and Carter, 2000; Smith et al., 2010; Snowdon et al., 2010; Young and Wang, 2004), encouraging in-group bias (Dreu et al., 2010), reducing social vigilance

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(Ebitz et al., 2013; Heinrichs et al., 2003) and amplifying other-regarding behaviors (Barraza et al., 2011; Chang et al., 2012; Van IJzendoorn et al., 2011). Although there appears to be a large range of OT-mediated effects, one might argue that some functions of OT may be common to most, if not all, of OT-mediated social cognition. The anxiolytic, approach-promoting, and tolerance-enhancing roles of OT (Amico et al., 2004; Averbeck, 2010; Heinrichs et al., 2003; Kemp and Guastella, 2010; Neumann et al., 2000a; Riem et al., 2011; Ring et al., 2006; Uvnäs-Moberg et al., 1994; Waldherr and Neumann, 2007; Yoshida et al., 2009; Young, 2002) may serve as foundational substrates that promote social exploration and interaction while, typically, suppressing social avoidance.

A large number of studies have been conducted to probe the role of OT in regulating social behavior in both healthy and pathological states (Bartz et al., 2011; De Dreu, 2012; Guastella et al., 2012; Heinrichs and Domes, 2008; Insel, 2010; MacDonald and Feifel, 2013; Meyer-Lindenberg et al., 2011). Nevertheless, the neural mechanisms through which OT regulates social behavior and cognition—particularly in humans—remain poorly understood. Standard noninvasive neuroscientific techniques, such as functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS), used to study human brain and cognition are limited in their capacity to reveal the neuronal and circuit mechanisms that mediate the regulation of social behavior and cognition by OT. Conversely, rodent models permit exquisitely fine dissection of these neural pathways but lack the behavioral complexity of human social function.

Compared to other animals, primates, including humans, are unique in that they show remarkably complex social behavior in a society typically made up of many individuals. Adapting to increasing social complexity may have played a major role in primate brain evolution (Dunbar and Shultz, 2007). For example, across primate species, social complexity, as measured by group size, strongly predicts forebrain volume (after correcting for body size) (Dunbar, 1998). Although rodents offer the opportunity for exploitation of powerful molecular genetic techniques, their social behavior is not very similar to the social behavior of humans. While molecular genetic techniques are only beginning to be developed for use in non-human primates (Diester et al., 2011; Sasaki et al., 2009), their social behavior is much more similar to the social behavior of humans.

Here we argue that a rhesus macaque model (*Macaca mulatta*) can effectively bridge this gap. Rhesus macaques are Old World monkeys that live in large, hierarchical, and mixed-sex social groups, that last shared a common ancestor with humans some 25 million years ago (Smuts, 1987). Critically, rhesus macaques display basic aspects of complex social behaviors that are typically considered 'uniquely human' (Frith and Frith, 2007; Saxe, 2006). These include social imitation (Ferrari et al., 2006; Subiaul, 2004), prosocial behaviors (Chang et al., 2011; Masserman et al., 1964), as well as understanding others' perceptions (Flombaum and Santos, 2005; Santos et al., 2006). Mental capacities like these might be fundamental building blocks for empathy and theory of mind. Such similarities in social behaviors make rhesus macaques excellent models for studying neuropsychiatric conditions accompanied by complex social deficits, such as autism spectrum disorders (Watson and Platt, 2012). Although there are undoubtedly some differences between humans and rhesus monkeys (Byrne and Whiten, 1988), such as the strength of prosociality, rhesus macaques are outstanding models for studying the neural mechanisms underlying psychiatric disorders marked by social deficits. Due to their remarkably similar anatomy and physiology to humans, rhesus macaques have long served as the gold standard for electrophysiological, pharmacological, and lesion-based investigations into complex cognitive processes. In this review we highlight recent advances in understanding how OT influences social behavior in rhesus macaques, paving the way for future investigations into the neural mechanisms mediating these influences.

2. Inhaling OT increases its concentration in the brain

Numerous human studies have demonstrated that intranasally administered OT can modulate complex social cognition. One of the most exciting findings from recent OT studies is that the peptide appears to rescue some social deficits in individuals with psychopathological conditions (for a review, see: Insel, 2010; Meyer-Lindenberg et al., 2011). The clinical and basic science communities are currently working together to translate basic OT research into useful and safe OT therapies for social disorders (Miller, 2013). Nevertheless, whether or not intranasal administration of OT actually translocates the peptide into the central nervous system (CNS) remained unknown until recently. In humans, the closest demonstration was for arginine vasopressin (AVP), another neurohypophysial hormone with social functions closely related to OT and differing in only two amino acids. Intranasally administered AVP effectively increases CNS AVP concentration for a long duration (>80 min.) in a dose-dependent manner (Born et al., 2002). More recently, data from rhesus macaques demonstrated that aerosolized OT using a nebulizer system (Fig. 1A) effectively reaches the brain. Using a pediatric nebulizer, we recently showed that inhaled oronasal administration of OT increases its concentration in the cerebrospinal fluid (CSF), measured at 30 min post-delivery (Chang et al., 2012) (Fig. 1B). A recent microdialysis study in rats and mice has demonstrated that nasal administration of OT increases levels in the central nervous system (sampled from the amygdala and hippocampus), peaking 30–60 min from the time of nasal delivery (Neumann et al., 2013). Subsequent work in primates from another laboratory reported that the inhaled administration of aerosolized OT effectively elevates OT levels in the CSF in rhesus macaques, but the application of intranasal spray, which has been the standard method in studies in humans, does not (Modi et al., in press).

Anecdotally, monkeys readily accept and tolerate nebulization (e.g., training takes less than a week), a technique that is routinely used in babies and young children to administer drugs like albuterol to alleviate breathing difficulties, suggesting that this method may prove both effective and acceptable in young patients with neuropsychiatric disorders. This tolerability is particularly desired for an early OT intervention in young children or even infants. Further research will be

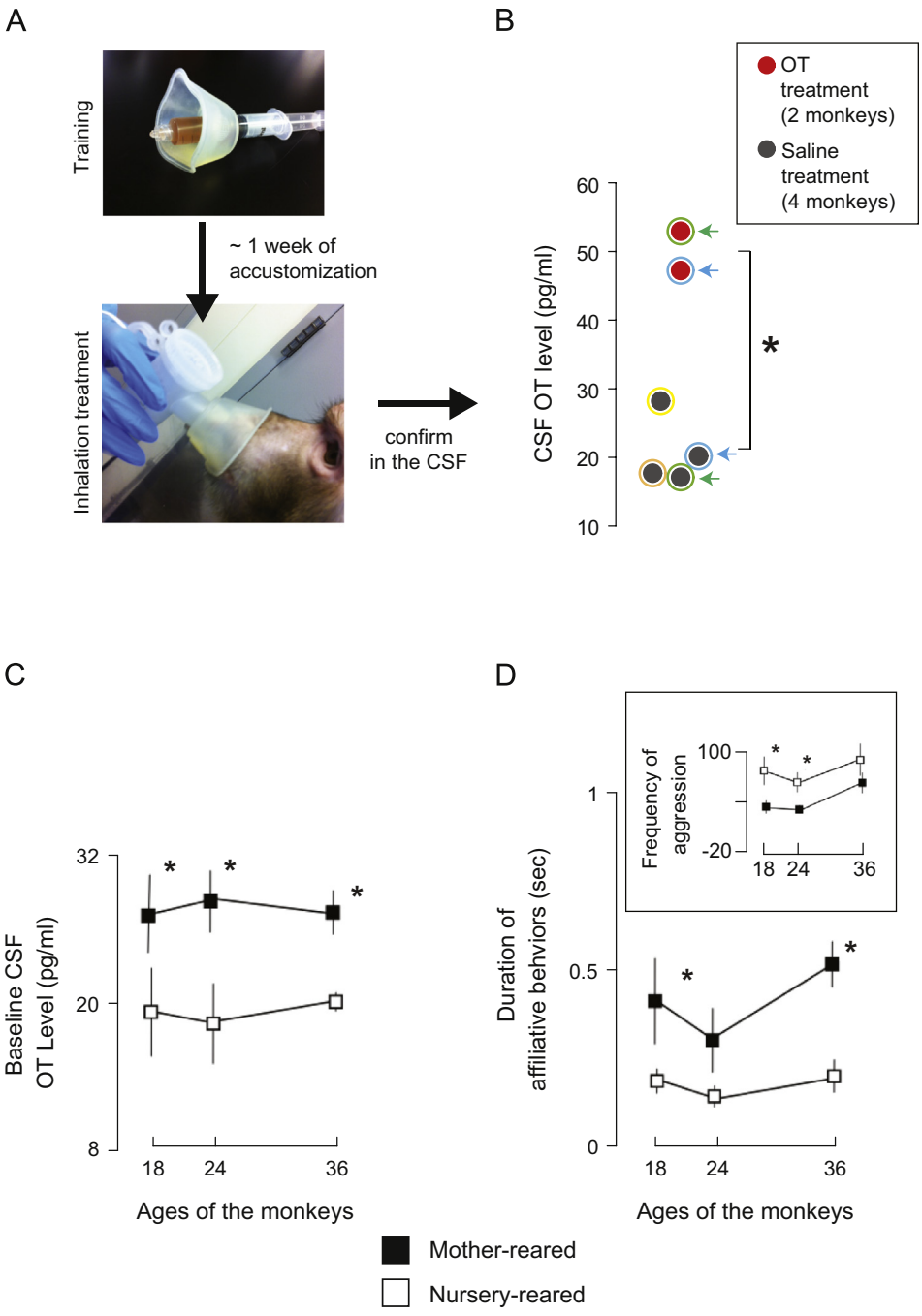

Fig. 1 – OT concentration in the cerebrospinal fluid (CSF) and social development in rhesus macaques. (A) A nebulizer-based inhalation setup using a nebulizer (PARI Baby Nebulizer) in rhesus macaques. Notice that both nose and mouth are covered with the inhalation mask. Top, a training phase in which juice rewards are delivered through the nebulizer mask (about a week). Bottom, a treatment phase in which aerosolized OT or saline solutions are delivered to the monkeys. (B) OT concentration in the CSF after inhaling 25 IU of OT (red) or saline (dark gray) in monkeys (5 min of nebulization at a 5 IU/min). The CSF samples were obtained from cervical punctures at 30 min post-delivery. Colored outlines on data points identify individual monkeys. Arrows with matching colors emphasize the CSF OT concentrations following saline (baseline) and OT inhalations within the same two monkeys. *, $P<0.05$, Welch two-sample *t* test. (C) Different levels of baseline CSF OT for mother-reared and nursery-reared male rhesus macaques across 18, 24, and 36 months of age. *, $P<0.05$, ANOVA. (D). Enhanced duration of affiliative behavioral engagements (e.g., allogrooming and reciprocal male mounting) in mother-reared compared to nursery-reared monkeys. The inset shows reduced frequency of aggressive behaviors toward conspecifics for mother-reared compared to nursery-reared monkeys. *, $P<0.05$, ANOVA. [B adapted from: Chang, S.W.C., Barter, J.W., Ebitz, R.B., Watson, K.K., Platt, M.L. (2012). Inhaled oxytocin amplifies both vicarious reinforcement and self reinforcement in rhesus macaques (*Macaca mulatta*). Proc. Natl. Acad. Sci. 109, 959–964, Copyright (2012) National Academy of Sciences, U.S.A.; C, D adapted from: Winslow, J.T., Noble, P.L., Lyons, C.K., Sterk, S.M., Insel, T.R. (2003). Rearing effects on cerebrospinal fluid oxytocin concentration and social buffering in rhesus monkeys. Neuropsychopharmacology 28, 910–918, Copyright (2003) Nature Publishing Group].

needed to confirm whether the enhanced efficacy of oronasal nebulization of OT translates to humans. The outcome of such investigations will have a critical impact on how OT is administered to individuals in clinical settings as well as how peripheral versus central effects of OT on social cognition are understood.

Although effective, non-invasive, and easy to administer, it is virtually impossible to determine the precise amount delivered to the brain using intranasal or inhaled administration. During the intranasal or inhalation process, some amount of OT is bound to be absorbed peripherally or simply leak out. This limitation of intranasal and inhalation delivery may limit the attractiveness of OT therapy if it requires a precise dose to be effective and safe. Future studies in animals should focus on estimating, as accurately and reliably as possible, the amount of OT delivered versus not delivered to the brain following intranasal or inhalation administration.

3. OT is critical for normal social development in rhesus macaques

Like humans (Hinde, 1974), the development of social behavior in infant rhesus monkeys depends critically on how they are raised. Infant monkeys raised away from their mothers later show a number of social deficits and stress-related abnormalities (Champoux et al., 1992; Harlow et al., 1965; Sackett, 1984; Suomi, 1991; Winslow et al., 2003). Based on the importance of OT in mother-infant relationships and bonding-related behaviors, such as mutual gaze, vocalizations, and affiliative touching (Feldman et al., 2007; Francis et al., 2000; Galbally et al., 2011; Pedersen, 1997; Riem et al., 2011; Strathearn et al., 2009), it seems likely that the peptide plays a crucial role in the early development of social behavior. Indeed, OT seems to shape the social behavior of both mothers and their infants. Evidence suggests that individual differences in maternal behaviors (e.g., attachment styles) are linked to oxytocinergic systems in reward-related brain regions, such as ventral striatum and amygdala (Francis et al., 2000; Strathearn et al., 2009). In rhesus macaques, baseline CSF OT levels, but not CSF AVP levels, are significantly reduced in males raised in a nursery compared to peers raised by their mothers (Winslow et al., 2003) (Fig. 1C), confirming a specialized role of OT in early social development. Furthermore, mother-reared monkeys display substantially more affiliative behaviors (e.g., allogrooming and reciprocal male mounting behaviors) (Fig. 1D) and less aggressive behaviors (Fig. 1D inset) toward other individuals, (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.) suggesting a link between CNS OT levels and affiliative social tendencies developed later in their lives (18–36 months of age) (Winslow et al., 2003). Similarly, human children who are neglected by their parents immediately after birth also show significantly reduced urinary OT levels later on (on average age of 4.5 years old) (Wismer-Fries et al., 2005). It remains to be determined whether urinary OT levels are directly associated with behaviors mediated by the central oxytonergic system. Overall, one needs to be cautious in interpreting these results since some variables other than early developmental style could be driving the changes in either central or peripheral OT levels. Furthermore, it is likely that the hypothalamic–pituitary–adrenal (HPA) system may contribute to the effects of different rearing conditions, resulting in changes in both social behavior and OT function. Nevertheless, OT levels (present either in the central or periphery system) are correlated with long-lasting social behaviors shaped from the very first encounters between infants and mothers. These findings strongly endorse the initiation of OT-based therapies as early as possible (using a tolerable nebulizer method) after detection of a neuropsychiatric disorder with social deficits, such as autism.

4. OT amplifies intrinsic social motivation in rhesus macaques

Much of our social interactions are driven by reinforcement, both direct rewards we receive ourselves and the reward we experience when good things happen to others (i.e., vicarious reinforcement (Bandura et al., 1963; Berber, 1962)). How might OT in the CNS shape both self and vicarious reinforcement during social decisions? We recently developed a social reward-allocation paradigm in rhesus macaques (Chang et al., 2011), in which an actor monkey makes a series of decisions to deliver juice rewards to himself, to a recipient monkey present in the room, to both simultaneously, or to no one. When given a choice between rewarding self and rewarding self and the other monkey together at no additional cost, actor monkeys prefer to deliver juice rewards to themselves only, displaying an antisocial preference (Chang et al., 2011). Moreover, not surprisingly, when given a choice between rewarding themselves only and the recipients only, the actor monkeys prefer to deliver juice almost exclusively to themselves (Chang et al., 2012, 2013a). On the other hand, when choosing between rewarding the other monkey and rewarding no one, the same actor monkeys prefer to deliver juice rewards to the recipient monkey, demonstrating an other-regarding preference that in humans would be considered prosocial (Chang et al., 2011, 2012, 2013a).

Oronasal nebulization of OT amplifies these self-regarding and other-regarding preferences in rhesus macaques (Chang et al., 2012). When choosing between allocating juice rewards to a recipient monkey and no one at all, exogenous OT enhances the baseline prosocial bias (Fig. 2A). Amplified prosocial preference is accompanied by an increase in gaze shifts to the recipient monkeys' face region following OT (Fig. 2B). Critically, the OT-treated actors do not increase such gaze shifts to the recipient monkeys when the juice rewards are delivered to the recipients by the experimenter (i.e., cued condition) (Chang et al., 2012). These OT-mediated gaze patterns during active decision-making suggest a link between reinforcing action and observation of the rewarding experience of the recipient monkeys. Such OT-mediated increases in attention to social stimuli like eyes and faces have been well documented in healthy humans as well as those with autism spectrum disorders (e.g., Andari et al., 2010; Guastella et al., 2008).

Furthermore, inhaled OT significantly increases reaction times when the actor monkeys choose between donating juice

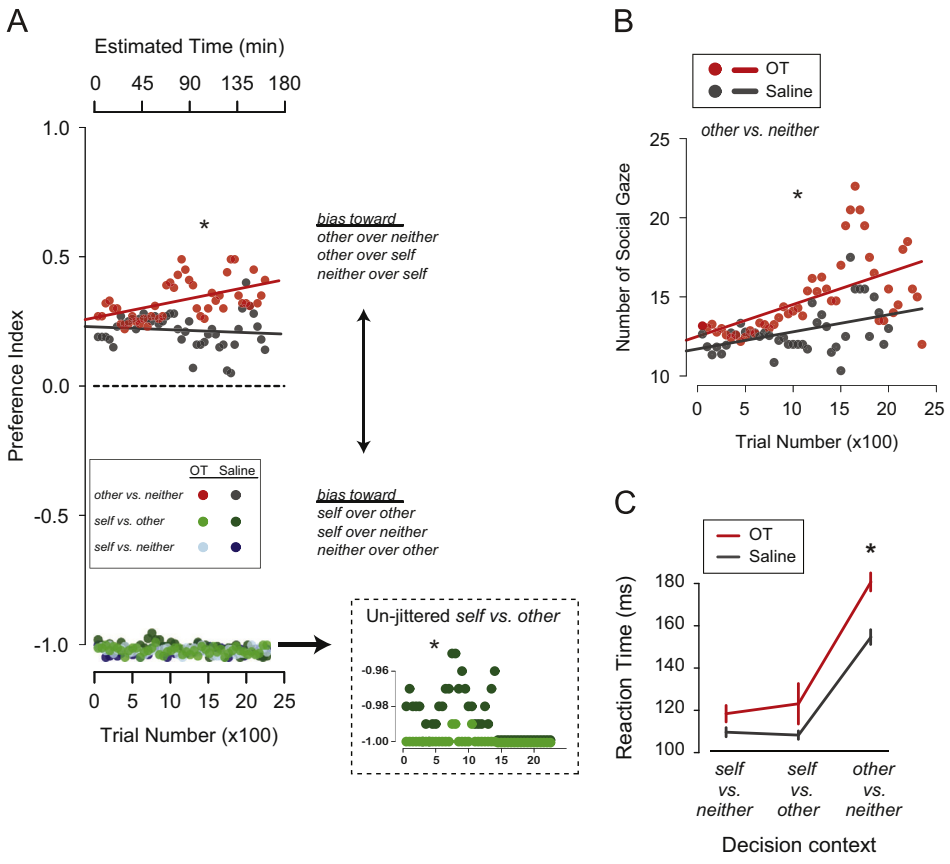

Fig. 2 – OT promotes social motivation in rhesus macaques. (A) Choice preference index following inhaled OT (red) or saline (gray) administration for rewards delivered to: *other* (recipient monkey) versus (vs.) *neither*, *self* (actor) vs. *other*, and *self* vs. *neither* in the social reward-allocation task. Data points from *self* vs. *other* and *self* vs. *neither* are jittered on the left plot for visibility. The inset shows unjittered data from *self* vs. *other* trials. *, $P<0.05$, Welch two-sample *t* test. (B) Number of gaze shifts made to the recipient monkey after reward delivery over the course of each session on *other* vs. *neither* trials. *, $P<0.05$, Welch two-sample *t* test. (C) OT selectively increases the decision deliberation time in the *other* vs. *neither* context (choosing to deliver juice rewards to other or no one) in which actor rhesus monkeys show a preference for delivering juice rewards to another monkey. *, $P<0.05$, Welch two-sample *t* test.
[A–C adapted from: Chang, S.W.C., Barter, J.W., Ebitz, R.B., Watson, K.K., Platt, M.L. (2012). Inhaled oxytocin amplifies both vicarious reinforcement and self reinforcement in rhesus macaques (*Macaca mulatta*). Proc. Natl. Acad. Sci. 109, 959–964, Copyright (2012) National Academy of Sciences, U.S.A.].

rewards to the recipient monkey and no one (Chang et al., 2012) (Fig. 2C), inviting the possibility that OT promotes prosocial choices by increasing internal deliberative processing in rhesus macaques. Such increased deliberation processes might be necessary for enhancing prosocial behaviors in highly despotic rhesus macaques, compared to humans who seem to spontaneously prefer, and thus show faster reactions times for, prosocial decisions (Rand et al., 2012). These results suggest that OT enhances vicariously reinforcing actions by possibly coupling reinforcement and social observation.

By contrast, when choosing between delivering juice rewards to themselves and to the recipients, inhaled OT amplifies the self-regarding preference (i.e., delivering juice to only themselves over only the recipients), essentially eliminating the small number of prosocial choices in this competitive context (Fig. 2A). Therefore, as in humans (Bartz et al., 2011), OT seems to elicit context-specific social behaviors in rhesus macaques. OT-mediated enhancement of social preferences in rhesus macaques is consistent with the effects of OT manipulation on prosocial choices in pair-bonding marmosets (*Callithrix penicillata*). In that study, treatment with an OT receptor antagonist effectively eliminated species-typical food sharing behavior between paired male and female marmosets (Smith et al., 2010). Taken together, these observations are consistent with the hypothesis that OT regulates the gain of pre-existing social preferences rather than changing their fundamental character.

5. OT relaxes social vigilance, thereby permitting social exploration in rhesus macaques

One way to promote social interactions is by modulating the social state of an animal in order to encourage social exploration. To investigate the role of OT in modulating the social state in rhesus macaques, our group has recently

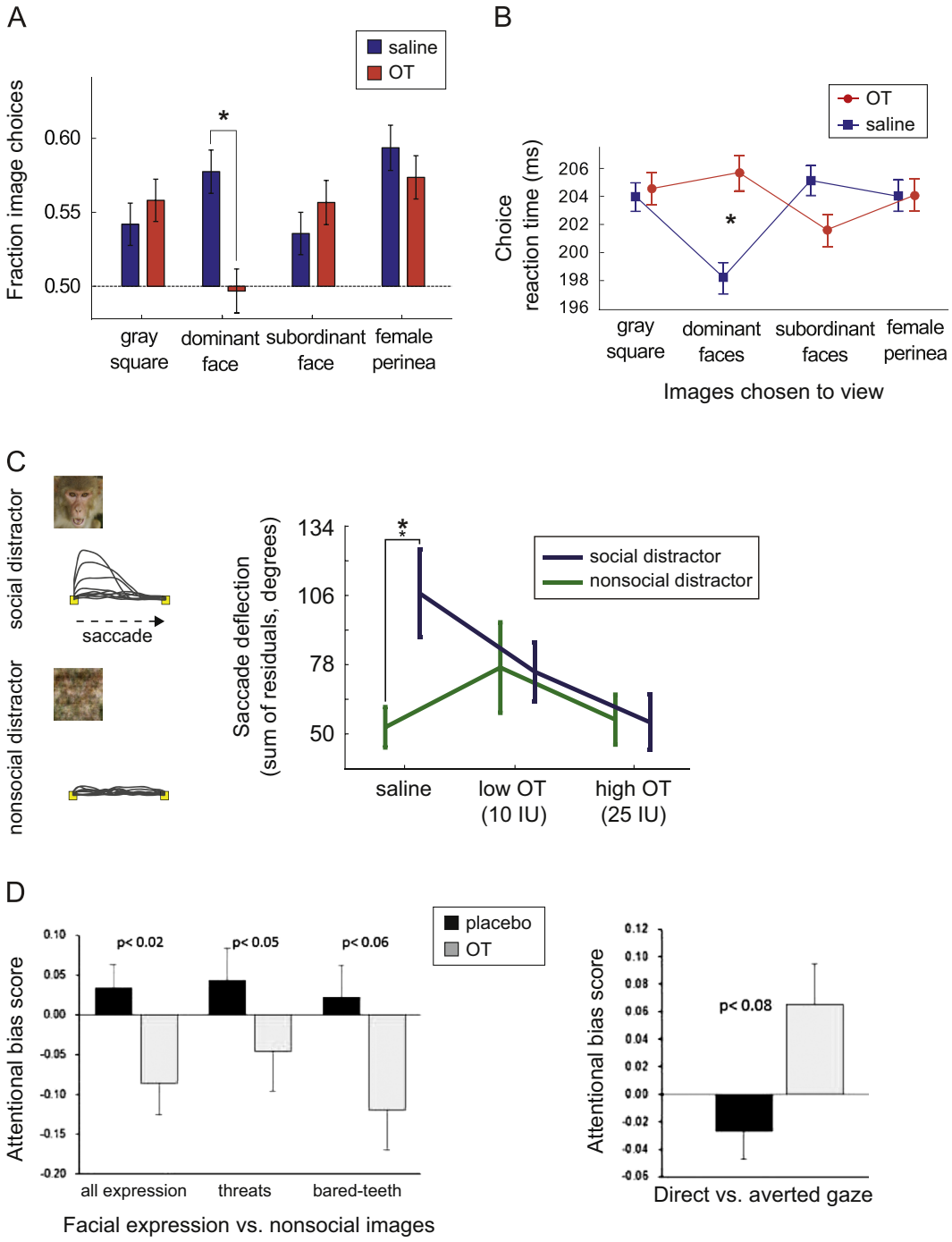

Fig. 3 – OT regulates social vigilance in rhesus macaques. (A) Inhaled OT selectively reduces monkeys' species-typical choices to view dominant face images in a task in which monkeys choose to view the images of dominant high status monkeys, subordinate low status monkeys, female perinea, or gray square (Deaner et al., 2005). *, $P<0.05$, Tukey LSD. (B) Accompanied by the reduction in monkeys' species-typical choices to view dominant face images (A), OT selectively eliminates typical reaction time facilitation of choosing to view dominant monkey faces. *, $P<0.05$, post hoc LSD. (C) Left, Examples of saccade residuals from trials with social distractors (upper) and nonsocial distractors (lower) presented at a neutral location relative to a target. Right, OT selectively reduces the typical saccade interferences (measured by the magnitude of deflections) to social distractors. *, $P<0.01$, Bonferroni-corrected post doc Tukey LSD. (D) Left, Attentional bias scores for facial expression stimuli categories after inhaled OT or placebo. Right, attentional bias scores for direct versus averted gaze trials after inhaled OT or placebo. OT reduces attention to emotional face stimuli (left), whereas it shows a trend of enhancing attention to facial stimuli with direct gaze (right). [A–C adapted from: Ebitz, R.B., Watson, K.K., Platt, M.L. (2013). Oxytocin blunts social vigilance in the rhesus macaque. Proc. Natl. Acad. Sci. 110, 11630–11635, Copyright (2013) National Academy of Sciences, U.S.A.; D adapted from: Parr, L.A., Modi, M., Siebert, E., Young, L.J. (2013). Intranasal oxytocin selectively attenuates rhesus monkeys' attention to negative facial expressions. Psychoneuroendocrinology 38, 1748–1756, Copyright (2013) Elsevier].

investigated social vigilance behavior in male monkeys following OT inhalation (Ebitz et al., 2013). When monkeys choose whether to acquire different types of visual information about the local social context (viewing different social images), OT selectively reduces species-typical tendencies to view the faces of dominant monkeys, a threatening but highly informative stimulus (Fig. 3A). Inhaled OT also eliminates the privileged processing for dominant faces over other images, effectively slowing monkeys down when making this particular decision (Fig. 3B). Moreover, OT substantially attenuates species-typical distraction by the peripheral flash of images of unfamiliar monkey faces, indexed by a reduction in gaze deflection towards them (Fig. 3C). These findings endorse the idea that OT helps regulate species-typical social vigilance. Reducing social vigilance state in turn could free up cognitive resources and promote social exploration (Ebitz et al., 2013).

Consistent with the role of OT in reducing social vigilance state, another recent study in rhesus macaques reported that inhaled OT selectively reduces attention to emotional facial expressions while enhancing attention to faces with direct gaze (Parr et al., 2013) (Fig. 3D), which is a threatening gesture in macaques. Moreover, OT delivered intranasally to squirrel monkeys (*Suimiri sciureus*) attenuates stress responses by lowering adrenocorticotropic hormone (ACTH) (i.e., corticotropin) levels following 90 min of social isolation (Parker et al., 2005). Such OT-mediated reduction in ACTH levels suggests that OT regulates social stress by acting through the hypothalamic–pituitary–adrenal (HPA) axis. Taken together, these findings suggest that OT may facilitate social interactions by lowering social vigilance and reducing social stress (Carter, 1998; Chang et al., 2013b; Ebitz et al., 2013; Neumann et al., 2000b; Uvnäs-Moberg et al., 1994).

Following intranasal OT (Syntocinon spray, Novartis), humans spend more time visually inspecting the eye region of faces compared to placebo (i.e., all inactive ingredients except for the peptide) (Gamer et al., 2010; Guastella et al., 2008). Moreover, intranasal OT improves test scores for the Reading the Mind in the Eyes Test (RMET) (Domes et al., 2007), which requires participants to infer mental states from photographs of eyes (Baron-Cohen et al., 2001). Intranasal OT also increases attention to the eyes in individuals with social deficits. Individuals with autism, for example, spend more time attending to the eye region of faces following intranasal OT compared to placebo (Andari et al., 2010). These results in humans may at first appear contradictory to the social vigilance results from rhesus monkeys (Ebitz et al., 2013; Parr et al., 2013). Although exogenous OT reduces social vigilance to social threats in rhesus macaques (Fig. 3A), it increases the amount of time rhesus spend looking at faces and eyes, as in humans (see Discussion in Ebitz et al., 2013). Moreover, when deciding whether or not to allocate juice rewards to another monkey present in the room, inhaled OT increases gaze to the face of the recipient monkey (Fig. 2B) (Chang et al., 2012). Based on these results, we conjecture that reduced vigilance might play a permissive role in social approach behavior, favoring increased attention to faces and eyes and subsequent enhancements in social cognition. Further studies will be necessary to test the idea that OT plays a permissive, rather than promotional, role in social behavior in rhesus macaques, and perhaps humans as well.

Increasing social exploration should have obvious consequences for forming and maintaining social bonds. Research in non-human primates as well as in humans (Bartz et al., 2011; De Dreu, 2012; Guastella et al., 2012; Heinrichs and Domes, 2008; Insel, 2010; MacDonald and Feifel, 2013; Meyer-Lindenberg et al., 2011) suggests that OT might be an important component of the neuroendocrinological regulation of social relationships. In non-human animals, social relationships can be studied by examining naturally-occurring social bonds (Brent et al., in press, 2013). A recent study in wild chimpanzees (*Pan troglodytes*) measured urinary OT levels after grooming bouts with different partners (Crockford et al., 2013). urinary OT levels after grooming behaviors predicted the strength of social bonds among the partners, and, surprisingly, this effect was not explained by genetic relatedness. Therefore, the action of OT in social processing seems to critically depend on the history of social interactions between two individuals. Future studies examining how prior social experience influences neural circuits regulated by OT should reveal important new insights into the neural basis of social relationships.

6. OT receptor distribution in the brain

Current knowledge regarding the distribution of OT receptors in the mammalian brain is derived primarily from rodents, though there have been some studies in humans and monkeys. In rats, some of the regions with high densities of OT receptor include the olfactory nucleus, hypothalamic regions, and the central amygdala (Tribollet and Barberis, 1996; Tribollet et al., 1992). Importantly, varying levels of OT receptors were detected across many functional subsystems, such as the limbic, basal ganglia, cortical, brainstem and the spinal cord (Tribollet et al., 1992). Autoradiographic studies have demonstrated that the distributions of OT receptors differ greatly between monogamous prairie voles (*Microtus ochrogaster*) and polygamous montane voles (*Microtus montanus*), in a manner consistent with differences in social bonding between these species (Insel and Shapiro, 1992; Young and Wang, 2004). Compared to montane voles, OT receptors in prairie voles are densely distributed in prelimbic areas, including a region analogous to the primate anterior cingulate gyrus, the nucleus accumbens, the bed nucleus of stria terminalis, and the lateral amygdala (Insel and Shapiro, 1992; Young et al., 1996). In human and non-human primates, immunoreactive studies have yielded mixed results with respect to finding OT receptors in the same areas as in rodents (Caffé et al., 1989; Jenkins et al., 1984; Sofroniew et al., 1981; Wang et al., 1997). Similar to findings in rats (Audigier and Barberis, 1985; Tribollet et al., 1992), OT immunoreactive cells were found in the hypothalamus, the bed nucleus of the stria terminalis, and the medial amygdala in common marmosets (*Callithrix jacchus*) (Wang et al., 1997), the new world primates that pair-bond similar to prairie voles. Nevertheless, studies in human and non-human primates have also found some notable differences in OT receptor distributions compared to rodents (Boccia et al., 2013; Caffé

et al., 1989; Jenkins et al., 1984; Loup et al., 1991). A recent immunohistochemical study in postmortem human brains localized OT receptors in the central and basolateral amygdala, medial preoptic area, hypothalamus, anterior cingulate cortex, and ventrolateral septum, among others (Boccia et al., 2013). In contrast to rat brains, the authors did not localize OT receptors in the hippocampus, supraoptic nucleus, and nucleus accumbens, among others, in their human brain tissues (Boccia et al., 2013). Clearly, resolving the distribution and binding affinities of OT receptors in human and non-human primate brains is a high priority and will require development of new ligands for OT receptors. Despite differences between species and these methodological limitations, it is interesting to note that some regions appear to express OT receptors across species, notably the amygdala. In the next section, we review current understanding of the role of the amygdala in OT-mediated social cognition.

7. Amygdala and context-specific OT-mediated modulations

The amygdala, which possesses an unusually high density of OT receptors (Francis et al., 2000; Insel and Shapiro, 1992; Young et al., 1996), may be a key site through which OT influences social behavior. The specialized functions of the amygdala in social cognition has been extensively reported in healthy humans and amygdala-damaged human patients (for a review, Adolphs, 2010). Experimental lesions to the amygdala in rhesus macaques lead to stereotyped social deficits, such as reduced aggression and increased submission (Amaral, 2002; Dicks et al., 1969; Kling, 1972; Kluver and Bucy, 1939; Meunier et al., 1999; Rosvold et al., 1954). Furthermore, neonatal bilateral amygdala lesions in rhesus macaques result in blunted affective expressions in adulthood toward both positive and negative stimuli (Bliss-Moreau et al., 2011). Moreover, neurons in the primate amygdala signal motivational values and is causally implicated in reward-guided learning (Baxter and Murray, 2002; Paton et al., 2006). These findings place the amygdala as an ideal anatomical substrate for the OT-mediated processing of motivation and vigilance state for guiding social behavior.

To date, most of the OT research examining the role of the amygdala in social cognition has focused on, broadly speaking, social state modulations. Human functional neuroimaging studies have shown that inhaling OT reduces BOLD (blood-oxygen-level dependent) activation in the amygdala when viewing or associating aversive social stimuli (Kirsch, 2005; Petrovic et al., 2008), during trust formation (Baumgartner et al., 2008), in response to pain (Singer et al., 2008), and in response to infant crying (Riem et al., 2011). Furthermore, OT inhalation reduces amygdala activation when viewing fearful faces but increases amygdala activation when viewing happy faces (Gamer et al., 2010). These findings suggest that OT modulates context-specific processing associated with both negative and positive valence in the amygdala, consistent with the encoding of both positive and negative motivational values by the primate amygdala neurons (Belova et al., 2007; Paton et al., 2006). For mediating fear-related responses, it has been verified in rats that oxytocinergic neurons regulate autonomic fear responses through a specialized circuit via the central amygdala (Huber, 2005; Viviani et al., 2011). This OT-mediated autonomic circuit might be also utilized for regulating social vigilance. Whether there are parallel oxytocinergic circuits for social motivational processing in the amygdala (e.g., in the basolateral subdivisions) remains unknown. Taken together, these findings suggest that OT may promote social exploration through modulations in socioemotional processing within the amygdala and its interconnected limbic circuitry.

Interestingly, one study on human participants found that the BOLD signals in the amygdala in women, unlike in men, actually increase when viewing fearful faces (Domes et al., 2010). One possible mechanism for this gender-specific effect of OT in amygdala activations is the interactions between oxytocin receptors and gonadal steroid hormones (Domes et al., 2010). It has been shown that estradiol promotes oxytocin receptor binding by increasing the oxytocin receptor concentrations, whereas progesterone inhibits oxytocin receptor by repressing its synthesis (Choleris et al., 2008; Gimpl et al., 2002; Nissenson et al., 1978). Interactions between OT and gonadal steroids have also been reported in monkeys as well. In male squirrel monkeys, ventricular injection of OT enhances sexual and aggressive behaviors toward a familiar female monkey in dominant males who have high testosterone levels, but enhances affiliative behaviors like touching and huddling in subordinate males who have low testosterone levels (Winslow and Insel, 1991). Such gender-specific effects of OT have been documented numerously in prairie voles (*Microtus ochrogaster*), and are verified to be centrally-mediated based on ventricular peptide manipulation experiments. For instance, the context-specific role of OT in pair-bonding and mate-guarding aggression is more critical to female voles, whereas the role of AVP in these two types of behaviors is more critical to male voles (Bales and Carter, 2003; Cushing and Carter, 2000; Insel and Hulihan, 1995; Winslow et al., 1993; Young and Wang, 2004). Further research is required to understand how and where in the brain OT system interacts with sex hormones to differentially influence social cognition in men and women. These interactions may govern the type of social states that is encouraged by OT in a context-specific fashion.

8. Caveats in developing OT therapy for social disorders

Without doubt, more research is necessary to fully and safely develop and implement OT treatment protocols for social deficits. In particular, determining the efficacy and safety of chronic OT treatment is a top priority because the majority of OT studies to date have focused on establishing the effects of acute OT on specific social functions. Unfortunately, chronic studies are practically difficult and sometimes ethically questionable in human subjects. For these reasons, we believe that non-human primates provide suitable models for monitoring the long-term safety and efficacy of repeated OT administration, both behaviorally and physiologically. Using non-human primates, researchers can administer OT at a regular interval (e.g., daily or weekly) in the same subjects over a long time period (e.g., months or years) to

estimate the efficacy and safety of repeated OT treatments in humans. It is also feasible to record neuronal activity or measure hemodynamic responses regularly over time in such studies in order to evaluate efficacy and safety at the neurophysiological level. Furthermore, it is also feasible to conduct other physiological measurements every month to assess inflammatory processes, including urine and blood analysis to measure cytokine and C-reactive protein levels.

Another line of future research should focus on the potential side effects of repeated exogenous OT exposure. In some cases, OT has been shown to evoke antisocial behaviors, such as envy (Shamay-Tsoory et al., 2009), negative outgroup bias (De Dreu et al., 2011), negative social perception in individuals with anxious attachment (Bartz et al., 2010), declined social interactions (Bales and Carter, 2003), as well as aggressive behaviors, such as mate-guarding aggression displayed by female voles toward other females (Bales and Carter, 2003). These important studies support the idea that the effects of OT depend critically on behavioral context (Bartz et al., 2011). Future studies thus need to determine the neurobiological mechanisms responsible for antisocial or aggressive behaviors elicited by OT. Neuronal recording studies in non-human primates designed to evoke their natural prosocial or antisocial behaviors following OT infusion will provide important insights into the underlying neural mechanisms, which can be refined by additional studies using molecular genetic techniques in rodents. It is also important to recognize the possibility that OT may acutely promote positive social behavior but may later promote negative social behaviors after repeated or long-term administration.

9. Concluding remarks

A rhesus macaque model of OT research has a clear translational value for understanding and treating neuropsychiatric disorders with social deficits. Most importantly, it can provide a unique opportunity for investigating how OT mediates human-like social cognition at both the neural circuit level and the level of the whole animal. The social behaviors of rhesus macaques are remarkably similar to those of humans (Maestripieri, 2007; Smuts, 1987). Arguably, most of the rudimentary forms of complex human cognition are present in these animals. Coupled with complex social behaviors, the amenability to single-unit recording and pharmacological perturbations permits scientists to directly examine the neural mechanisms mediating OT influences on social cognition. Furthermore, rhesus macaques are also tolerant to controlled experiments with an extremely high number of repeated trials (~1000 trials per day) allowing precise quantifications of behaviors as well as how these behaviors are related to underlying neuronal activity, which by nature is often highly variable. The efficacy of the nebulized inhalation method for delivering OT to the CNS in alert rhesus macaques prior to experimental tasks (Chang et al., 2012; Modi et al., in press) makes it easier to compare neurophysiological results from animal studies with behavioral or neuroimaging results obtained from both healthy people and those with neuropsychiatric disorders. Finally, non-human primates will be valuable for monitoring the efficacy and safety of repeated OT administrations continuously for months and even years at the behavioral as well as neuronal level in a controlled setting.

Author contributions

S.W.C.C and M.L.P. wrote the paper.

Conflict of interest

The authors declare that they have no competing financial interests.

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Research Report

Oxytocin and the social brain: Neural mechanisms and perspectives in human research

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ABSTRACT

The present paper summarizes functional imaging studies investigating the effects of intranasal oxytocin (OT) on brain responses to social stimuli. We aim to integrate previous research, point to unresolved issues and highlight perspectives for future studies. The studies so far have focused on identifying neural circuits underlying social information processing which are particularly sensitive to modulations by exogenous OT. Most consistently, stimulus-related responses of the amygdala and associated areas within the prefrontal and temporal cortices have been found to be modulated by OT administration. However, there are a number of unresolved issues related to the possible role of sex differences and hormonal status, genetic variability, and individual differences in socio-cognitive functioning. Future studies focusing on these open questions are expected to contribute to a more nuanced understanding of the role of the central OT system in humans and may provide the basis for novel treatment approaches for mental disorders characterized by social deficits.

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1. Introduction

1.1. *The role of oxytocin in human social cognition and behavior*

Within the last decade, the neuropeptide oxytocin (OT) has attracted increasing attention. Its importance for species-specific social functioning was first revealed by animal studies demonstrating that central OT receptor distribution critically determines several aspects of social behavior such as pair bonding and parental care (e.g. Insel and Young, 2001; Young and Wang, 2004).

In humans, most studies investigating the behavioral and neural effects of OT have used placebo-controlled intranasal application. The rationale for this approach is based on findings that neuropeptides are capable of reaching the central nervous system following intranasal administration (Born et al., 2002). An actual increase in central OT levels following intranasal OT administration was recently confirmed by microdialysis in relevant brain regions of rats and

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mice (Neumann et al., in press). Studies that have explored associations of peripheral OT levels with social stimulus processing are highly controversial regarding the validity of the assessment and interpretation with respect to CNS availability of the neuropeptide and need further investigation (Anderson, 2006; Horvat-Gordon et al., 2005; Landgraf and Neumann, 2004; Carter et al., 2007; for an overview, see Heinrichs et al., 2009).

To date, effects of OT on human social cognition and behavior have been summarized in several reviews and meta-analyses (e.g. Heinrichs and Domes, 2008; Heinrichs et al., 2009; Shahrestani et al., 2013; Striepens et al., 2011). The main body of empirical evidence so far suggests beneficial effects of intranasal OT on several aspects of social information processing and social behavior including eye gaze, facial emotion recognition, social reward processing and trust (for recent reviews, see Guastella and MacLeod, 2012; Meyer-Lindenberg et al., 2011; Shahrestani et al., 2013; Van IJzendoorn and Bakermans-Kranenburg, 2012). Together with results from animal studies, these findings point to the therapeutic potential of interventions in the central nervous OT system for the treatment of mental disorders characterized by social impairments like social anxiety, schizophrenia or autism spectrum disorders (for recent reviews, see Meyer-Lindenberg et al., 2011; Modi and Young, 2012; Striepens et al., 2011). Despite substantial evidence for beneficial effects of OT on social behavior, the neural mechanisms underlying these effects are still not well understood in humans.

1.2. *The oxytocin system in the human brain*

In rats, OT receptors are highly expressed in olfactory and hypothalamic regions, structures of the limbic system (e.g. amygdala), the thalamus, basal ganglia, as well as in the brain stem and spinal cord (for a review, see Gimpl and Fahrenholz, 2001). OT binding sites in humans, however, remain rather elusive. Preliminary results suggest that OT receptor distribution in the human brain differs substantially from other species with higher densities in dopaminergic neurons of the substantia nigra and the cholinergic nucleus basalis of Meynert (Loup et al., 1991). However, Gimpl and Fahrenholz (2001) point to the possibility that high levels of OT in one region might decrease local OT receptor expression to an extent that does not allow for detection by common methods like radioligand-based autoradiography. Thus, radioligands for in vivo PET studies in humans are still needed to provide a better understanding of OT receptor distribution in the human brain.

While mapping of OT receptors in the human brain is still in its infancy, functional brain imaging techniques allow for mapping of brain regions potentially mediating the effects of OT on human cognition and behavior. Some studies have explored OT effects on brain activation using EEG or MEG (Bick et al., 2013; Herzmann et al., in press; Hirosawa et al., 2012; Huffmeijer et al., 2013, 2012; Perry et al., 2010; Sheng et al., 2013). These methods have high temporal but rather low spatial resolution, which complicates localization of neural networks associated with the cognitive process under study, especially if the brain areas of interest are located subcortically. In comparison, spatial resolution is much higher in functional magnetic resonance imaging (fMRI), the most commonly used brain imaging tool in human OT research.

1.3. *Aims and structure of this article*

Here, we aim to provide a critical reflection on the current state of fMRI findings in OT research and highlight methodological challenges and open questions that should be addressed by future studies. We will start with a short review of selected fMRI studies integrating most of the previous evidence for effects of intranasal OT on neural correlates of social cognition and behavior (Table 1). In the majority of these studies, a single dose of OT was administered to healthy individuals following a randomized, placebo-controlled, experimental protocol. The cognitive functions under study included face perception and emotion processing (Domes et al., 2010a, 2007; Gamer et al., 2010; Kirsch et al., 2005; Lischke et al., 2012; Petrovic et al., 2008; Rupp et al., 2012), proxies of parental sensitivity and attachment (Riem et al., 2012, 2011; Rupp et al., 2013; Wittfoth-Schardt et al., 2012), as well as different aspects of social feedback processing (Baumgartner et al., 2008; Groppe et al., 2013; Rilling et al., 2012). So far, few studies have focused on potential effects of intranasal OT on brain responses in clinical samples characterized by social deficits such as social anxiety (Labuschagne et al., 2011, 2010), borderline personality disorder (Bertsch et al., in press), or autism spectrum disorders (Domes et al., 2013a, in press; Watanabe et al., in press).

2. Effects of OT on neural correlates of face perception and emotion processing

2.1. *The neural basis of social threat processing and anxiolytic effects of OT*

Results from both animal studies and human behavioral studies have consistently indicated anxiolytic effects of OT (e.g. Bale et al., 2001; Heinrichs et al., 2003; Huber et al., 2005; Viviani et al., 2011). An initial fMRI study therefore focused on OT effects on neural responses to threatening scenes and facial expressions (Kirsch et al., 2005). Compared to placebo, intranasal administration of OT dampened amygdala reactivity to negative social cues and reduced functional coupling of the amygdala with brainstem regions. These results correspond to recent findings from animal studies indicating that OT decreases behavioral fear responses by modulating amygdala signaling to brainstem regions (Knobloch et al., 2012; Viviani et al., 2011).

To gain a better understanding of potential anxiolytic OT effects in humans, a later fMRI study combined intranasal OT administration with a fear-conditioning paradigm in which neutral facial expressions were paired with electric shocks (Petrovic et al., 2008). After conditioning, participants were administered a single dose of OT and underwent fMRI scanning during which they viewed the same faces with shock electrodes applied. OT attenuated changes in affective stimulus ratings following fear conditioning and reduced neural responses to conditioned as compared to unconditioned stimuli in the amygdala, the medial temporal gyrus and the anterior cingulate cortex. These structures are discussed as part of a neural alarm

Table 1 – Effects of intranasal oxytocin administration on brain responses to positive and negative stimulus exposure in healthy men and women.

	Negative valence			Positive valence		
Sample	Stimuli	OT effects	References	Stimuli	OT effects	References
Male						
	Faces and scenes	↓ACC, **AMY**, CER, dlPFC, FG, ITL, MED, MTL, OFC, PAC, POC, PRC, THAL, vlPFC	Kirsch et al. (2005), Domes et al. (2007), Petrovic et al. (2008), Gamer et al. (2010), Striepens et al. (2012), Sauer et al. (2013)	Faces and scenes	↓**AMY**	Domes et al. (2007)
					↑**AMY**	Gamer et al. (2010)
		FC: **AMY**–BS, **AMY**–INS				
		↑INS	Striepens et al. (2012)			
	Social feedback	↓ACC, **AMY**, BS, CAU, INS, MB, POC	Baumgartner et al. (2008), Rilling et al. (2012)	Social feedback	↑**AMY**, CAU	Rilling et al. (2012)
		↑vlPFC, vmPFC	Rilling et al. (2012)			
		FC: INS-**AMY**, INS-IFG				
	Physical pain	↓**AMY**, MB, STRIA	Singer et al. (2008)			
		↑OFC	Singer et al. (2008)			
Female						
	Faces and scenes	↓**AMY**, dlPFC	Domes et al. (2010a, 2010b), Rupp et al. (2012)	Faces and scenes	↓SMA	Lischke et al. (2012)
		↑**AMY**, ATL, BS, CER, dlPFC, FG, HIPP, INS, MTL, POC, ROL, STG, vlPFC	Domes et al. (2010a, 2010b), Lischke et al. (2012)		↑CER, FG, HIPP, INS, MTG, ROL, STG	Domes et al. (2010a, 2010b)
	Social feedback	↓CUN, POC, PRC	Groppe et al. (2013)	Social feedback	↑VTA, MTL, OCC	Groppe et al. (2013)
		↑VTA	Groppe et al. (2013)			
	Infant crying	↓**AMY**	Riem et al. (2011)	Infant laughter	↓**AMY** FC: **AMY**–OCC	Riem et al. (2012)
		↑IFG, INS	Riem et al. (2011)		↑FC: **AMY**–ACC, **AMY**-ANG, **AMY**–HIPP, **AMY**–MTL, **AMY**–OFC, **AMY**–PREC	Riem et al. (2012)

↑=increased brain activity, ↓=decreased brain activity, ACC=anterior cingulate cortex, AMY=amygdala, ANG=angular gyrus, ATL=anterior temporal lobe, BS=brainstem, CAU=caudate nucleus, CER=cerebellum, CUN=cuneus, dlPFC=dorsolateral prefrontal cortex, FC=functional connectivity, FG=fusiform gyrus, HIPP=hippocampus, IFL=inferior frontal lobe, INS=insula, ITL=inferior temporal lobe, MB=midbrain, MTL=medial temporal lobe, MED=medulla, OCC=occipital cortex, OFC=orbitofrontal cortex, PAC=paracentral lobe, POC=postcentral lobe, PRC=precentral lobe, PREC=precuneus, ROL=rolandic operculum, SMA=supplementary motor area, STG=superior temporal gyrus, STRIA=striatum, THAL=thalamus, vlPFC=ventrolateral prefrontal cortex, vmPFC=ventromedial prefrontal cortex, and VTA=ventral tegmental area.

system in the context of threat processing (Liddell et al., 2005) suggesting mitigation of the conditioned fear response following OT administration. Taken together, the studies by Kirsch et al. (2005) and Petrovic et al. (2008) suggest that dampening effects of OT on neural reactivity to threat-related social stimuli might mediate its anxiolytic effects on human social behavior (Acheson et al., 2013; Heinrichs et al., 2003).

2.2. *Differential effects of OT on emotional valence processing and social attention*

OT effects within the amygdala, however, may not exclusively be driven by negative stimuli. Within a passive-viewing task, OT reduced amygdala responses to emotional faces irrespective of valence (Domes et al., 2007), a result which is at odds with the assumption that OT attenuates amygdala responses specifically for threatening cues. Instead, the dampening effects of OT on amygdala reactivity to emotional faces as found in our study may reflect a broader mechanism such as decreased vigilance or uncertainty towards social events.

Such inconsistencies could also be explained by differential interactions of emotion processing with visual attention processes. Accordingly, another study demonstrated that the amygdala mediates OT effects on both social attention and emotional valence processing in a healthy male sample

(Gamer et al., 2010). More specifically, OT increased the likelihood of reflexive saccades towards the eye regions of faces independent of the displayed emotional expression. This main effect was associated with an increase in posterior amygdala activity. Discrimination of different emotional expressions, on the other hand, was found to be associated with anterior amygdala activity: OT attenuated activity for fearful faces but increased activity for happy faces. A recent study employing the same experimental paradigm in female patients with borderline personality disorder showed that OT reduced patients' hypervigilance for threat cues and associated abnormal amygdala reactivity (Bertsch et al., in press). Taken together, these results illustrate that OT effects on visual attention should be taken into account when studying its effects on social stimulus processing in the amygdala.

2.3. *Effects of oxytocin on emotion processing in women*

In an initial study, a sample of healthy women received intranasal OT or a placebo before viewing emotional or neutral face stimuli in an MRI scanner (Domes et al., 2010a). Compared to placebo, OT increased reactivity to fearful facial expressions in brain areas involved in emotion processing, including the medial temporal lobe, amygdala, fusiform gyrus, superior temporal gyrus, and brainstem, but reduced activation in the prefrontal cortex. Increased amygdala reactivity to negative stimuli after OT treatment in healthy women was confirmed in studies using threat-related scenes (Lischke et al., 2012) and briefly presented facial expressions of anger (Bertsch et al., in press). The increased amygdala reactivity under OT found in women contrasts with earlier studies in men which consistently reported attenuated amygdala responses following OT treatment. This leads to the hypothesis that OT may exert opposing effects on amygdala reactivity in healthy men and women.

Moreover, effects of exogenous OT may differ depending on individuals' endogenous OT levels, which are known to be elevated in postpartum women (Drewett et al., 1982; Uvnäs-Moberg et al., 1990). This hypothesis is supported by a recent fMRI study showing differential effects of OT on amygdala activation in response to negative pictures in nulliparous and postpartum women (Rupp et al., 2012): nulliparous women had higher amygdala reactivity to negative stimuli than postpartum women under placebo; however, their amygdala reactivity was significantly reduced by a single dose of intranasal OT, thereby making their neural responses comparable to those observed in postpartum women. Thus, OT-induced attenuation of amygdala reactivity to arousing stimuli in women may reflect the neural basis for the stress-buffering effects of breastfeeding in postpartum women (Mezzacappa and Katkin, 2002; for a review, see Heinrichs et al., 2002) and known associations between breastfeeding, mother-infant-bonding, and maternal care (Bosch and Neumann, 2012; Feldman et al., 2010, 2007; for a recent review, see Galbally et al., 2011).

3. Effects of OT on brain responses to infant and sexual cues

Several fMRI experiments examined effects of OT on responsiveness to infant cues as a proxy of parental sensitivity and attachment. Healthy women were exposed to infant cry and laughter sounds (Riem et al., 2012, 2011) and infant pictures (Rupp et al., 2013) following intranasal OT treatment. Under placebo, exposure to infant crying elicited significant activation in the bilateral superior and middle temporal gyrus as well as the right amygdala (Riem et al., 2011). Intranasal OT reduced activation in the right amygdala but increased activation within the insula and the inferior frontal gyrus. During exposure to infant laughter, OT once again attenuated amygdala reactivity to emotional infant sounds, suggesting a mechanism that generalizes across positive and negative acoustic infant cues (Riem et al., 2012). OT also enhanced functional coupling of the amygdala with several brain regions associated with emotion processing and regulation, including the orbitofrontal cortex, anterior cingulate cortex, hippocampus, and middle temporal gyrus. The results suggest that OT might modulate fronto-cortical regulation of amygdala activation. In addition, decreased amygdala reactivity in postpartum women was also shown for the processing of infant and sexual pictures (Rupp et al., 2013). A recent study on OT-induced modulation of fathers' brain response to pictures of infants shows different results (Wittfoth-Schardt et al., 2012): intranasal OT administration decreased left globus pallidus (GP) reactivity to pictures of the father's own child, and reduced functional coupling of the left GP with the right GP, the left hippocampus and the left middle frontal gyrus, whereas amygdala activity appeared to be unaffected.

4. Modulation of neural activity by OT during social feedback processing

4.1. *Effects of OT on neural circuitry of trust and reciprocity*

In initial studies, OT was found to increase human trust behavior (Kosfeld et al., 2005), to maintain trust behavior following social betrayal, and to reduce neural responses associated with the experience of breached trust (Baumgartner et al., 2008). Specifically, feedback of social betrayal increased activation within the amygdala and caudate nucleus under normal conditions but not following OT administration (Baumgartner et al., 2008). Another study focused on reciprocal social cooperation in the context of a prisoner's dilemma game (Rilling et al., 2012). Participants played with a putative human partner or a computer partner who could either reciprocate or defect on their cooperation. Compared to placebo, intranasal OT increased reactivity of the left caudate nucleus and the left amygdala when participants' cooperative behavior was mirrored by a putative human partner as compared to a computer partner. Activation in both regions was highly correlated, suggesting that OT increased the reward value of experienced cooperation or enhanced the association of cooperative behavior with the

human partner. Together, these results support the hypothesis that OT shapes the processing of social cues in a prosocial direction by increasing the reward value of positive social cues while buffering against experiences of negative emotionality.

4.2. *Effects of OT on neural correlates of social reward and punishment processing*

A recent study directly tested whether OT influences the neural circuitry of social saliency and reward in the context of social feedback processing (Groppe et al., 2013). Female participants performed a social incentive delay task within the scanner in which they had to respond as quickly as possible to a cued target stimulus in order to receive social reward (happy facial expressions) or avoid social punishment (angry facial expressions). Under placebo, activation in the ventral tegmental area positively predicted correct responses in the social reward condition. OT increased activation in this area during anticipation of both rewarding and punishing social cues. This result is in line with the hypothesis that OT increases the motivational salience of social stimuli by modulating neural correlates of reward and punishment processing.

5. Studies targeting clinical conditions and individual differences

Several mental disorders with impairments in social information processing and social interaction are characterized by alterations in brain activation and connectivity. Such alterations have recently been reviewed for schizophrenia (Fitzsimmons et al., 2013), autism (Philip et al., 2012), and social anxiety (Freitas-Ferrari et al., 2010). While beneficial effects of OT on social cognition and behavior have been described for all of the above-mentioned neuropsychiatric disorders, recent meta-analytic results suggest that OT treatment may be specifically effective in autism spectrum disorders (Bakermans-Kranenburg and van IJzendoorn, 2013a). Overall, only few studies have explored the neural mechanisms that might mediate effects of intranasal OT on social cognition and behavior in clinical samples. Clearly, pre-existing differences in neural response patterns of clinical samples and healthy controls as well as individual drug medication need to be factored in when studying potential therapeutic effects of OT.

5.1. *OT-induced restoration of social cognition in autism*

Autism spectrum disorders (ASD) are characterized by several socio-cognitive impairments, including difficulties in recognizing faces or appropriately interpreting emotional cues of others. Previous evidence from behavioral studies suggests that OT exerts beneficial effects on social cognition and behavior in autism (Anagnostou et al., 2012; Andari et al., 2010; Guastella et al., 2010). Based on these findings, recent imaging studies focused on OT modulation of activity in the social brain in autism. A first study tested for OT effects on neural correlates of face processing in individuals with Asperger Syndrome (AS) and typically developed controls (Domes et al., 2013a). Intranasal OT administration induced preferential processing of faces within the amygdala in AS individuals which mirrored amygdala responses observed in neurotypical controls under placebo. In another study, OT improved emotion recognition performance and heightened amygdala reactivity to emotional facial features (eyes and mouths) in autistic individuals but not in typically developed controls (Domes et al., in press).

A recent study examined effects of intranasal OT on socio-communicational impairments in autism that stem from problems in interpreting nonverbal social cues (Watanabe et al., in press). When simultaneously-presented verbal and nonverbal information was in conflict, OT increased the number of judgments based on nonverbal as compared to verbal information. For judgments based on nonverbal information, OT enhanced activity in anterior cingulate and dorsal medial prefrontal cortex – regions that were previously found to display reduced activity in autistic individuals as compared to typically developed controls (Watanabe et al., 2012). Although a typically developed control sample was missing in the study of Watanabe et al. (in press), the increase in medial prefrontal cortex activity under OT may reflect hormone-induced normalization of neural responses in autistic individuals. In sum, preliminary evidence suggests that OT may be capable of restoring neural correlates of social cognition in autism.

5.2. *Normalizing effects of OT on neural hyperreactivity in social anxiety*

Socially anxious individuals typically show enhanced orienting towards socially threatening cues (Bar-Haim et al., 2007) and facilitated social threat conditioning (Pejic et al., 2013). These behavioral findings are mirrored in a neural hyperreactivity during social threat processing with a prominent role of the amygdala (Freitas-Ferrari et al., 2010; Pejic et al., 2013; Sladky et al., 2013). So far, two studies report modulating effects of OT on neural responses to emotional stimuli in social anxiety disorder (SAD) (Labuschagne et al., 2011, 2010): under placebo, individuals with clinical social anxiety as compared to healthy controls displayed a hyper-reactivity of the amygdala when processing facial expressions of fear and an increased activity in the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) when viewing sad faces. Administration of OT reduced this neural hyperreactivity in social anxiety, supporting the assumption that OT may reduce stress reactivity and exert anxiolytic effects by modulating activation in neural correlates of threat processing (Labuschagne et al., 2011, 2010).

5.3. *Influences of individual differences on reactivity to intranasal OT*

Evidence from several studies in healthy individuals suggests that OT effects may be generally moderated by individual levels of social functioning. For example, individuals with higher autistic traits indicative of poorer socio-cognitive functioning seem to show stronger beneficial effects of OT on empathic accuracy (Bartz et al., 2010). In female patients

with borderline personality disorder, OT was found to decrease interpersonal trust and social cooperation preferentially in individuals with anxious attachment style and high sensitivity towards social rejection (Bartz et al., 2011a). In autistic individuals, an OT-induced increase in amygdala reactivity was predictive of individual improvements in behavioral performance (Domes et al., in press), suggesting that individual differences in social functioning may generally account for differences in neural reactivity to intranasal OT within the social brain. Together, these findings illustrate the necessity of considering individual-related variables when studying effects of intranasal OT on behavioral and neural measures of socio-cognitive processing (compare Bartz et al., 2011b; Guastella and MacLeod, 2012; Kemp and Guastella, 2011).

6. Methodological considerations for fMRI studies with pharmacological OT protocol

Imaging OT effects on brain activity associated with social stimulus processing has revealed several neural substrates that may mediate its behavioral effects. Still, results from fMRI studies remain heterogeneous, and caution is warranted in theorizing about oxytocinergic modulation of neural transmission in humans. Functional MRI does not measure neural activity per se, but instead measures alterations of magnetic susceptibility in a brain area induced by temporary changes of cerebral metabolism associated with neural activation. This fact has some important implications.

6.1. *Choosing an appropriate experimental design*

First, the size of experimental effects on the measured BOLD response is generally low, and signal changes depend crucially on the experimental paradigm. Inconsistent results on OT effects in the human brain as revealed by functional imaging may therefore arise from differences in task characteristics. These may include task demands (e.g. cognitive load, implicit vs. explicit emotion processing), stimulus characteristics (e.g. stimulus size, emotional intensity), timing issues (e.g. blocked vs. event-related design) and appropriate contrasting to an adequate control condition. In addition, neural responses to intranasally-administered OT may depend on the dosage used in a particular study. The systematic exploration of dose–response characteristics of intranasal OT administration should therefore be considered an important next step in human OT research.

Especially if complex cognitive processes (such as trust) and their modulation by OT are under study, interactions with other cognitive processes are likely induced by an experimental task. As the amygdala was shown to display functional segregation, caution is warranted when interpreting OT effects in this brain region, as these can be mediated by different cognitive processes such as valence processing and attention orienting (see Gamer et al., 2010). In order to address potential confounding effects of OT on social attention, eye movements can be assessed as a physiological correlate of visual attention processes during MRI scanning (Domes et al., 2013b; Gamer et al., 2010; Guastella et al., 2008). However, OT research would generally benefit from a more thorough understanding of the neural networks that underlie fundamental cognitive processes that are assumed to be modulated by exogenous OT.

6.2. *Accounting for connectivity within social brain networks*

To date, it remains unclear whether modulation of socio-cognitive functions by OT is specifically or predominantly mediated by the amygdala. The studies so far simply suggest that paradigms which are sensitive to modulations of amygdala activity seem to be particularly sensitive to changes in central OT levels. Observed changes in amygdala responses following OT administration may therefore reflect local OT effects on other brain areas that exert modulatory influence on amygdala activation.

This assumption addresses a crucial limitation of classic functional imaging. Functional MRI usually aims at identifying brain areas involved in specific perceptual and cognitive processes. However, a purely localizing approach does not account for the existence of complex neural networks in which functions and performances arise from dynamic interactions between brain areas. Statistical tools for the analysis of connectivity measures allow for exploration of such regional interactions and usually focus either on modulations of functional vs. effective connectivity by an experimental stimulation (Friston, 1994).

Two recent studies explored OT-induced alterations in functional connectivity between brain regions using resting state fMRI in men and women (Riem et al., in press; Sripada et al., 2013). In men, OT increased resting-state connectivity of the amygdala with anterior cingulate and medial prefrontal cortex while reducing amygdala coupling with brainstem regions (Sripada et al., 2013). In women, resting state connectivity of the precuneus with the brainstem and the cerebellum was shifted in a positive direction following OT administration (Riem et al., in press). Together, preliminary evidence from resting state fMRI points to modulatory effects of OT on brain networks involved in social cognition and stress reduction.

Indeed, there is growing evidence for the assumption that OT effects on social cognition and behavior are mediated by transregional communication in the brain (for a recent review on OT effects on functional connectivity, see Bethlehem et al., 2013). For example, increased attention to the eye region of faces following OT administration has been reported by both behavioral and neuroimaging studies (Domes et al., 2013b; Gamer et al., 2010; Guastella et al., 2008). This increased eye gaze seems to be mediated by enhanced functional coupling of the posterior amygdala with the superior colliculus under OT (Gamer et al., 2010). OT was also found to increase functional coupling of the amygdala with prefrontal and temporal regions as well as the hippocampus during processing of infant laughter (Riem et al., 2012) suggesting enhancing effects of OT on the neural processing of positive stimulus valence (Iidaka et al., 2001; Whalen et al., 2013). In contrast, reduced functional coupling of the amygdala with brainstem regions for aversive social stimulation may reflect

protective effects of OT against negative emotionality and stress reactivity (Kirsch et al., 2005; Rilling et al., 2012).

It should be noted, however, that functional connectivity analyses describe statistical dependencies between the time-series of the measured BOLD response in different brain areas and therefore represent mere correlations. To address the question of causality within neural network communication and its modulation by OT, analysis of effective connectivity should be included in future research on OT effects on human brain functioning (Friston et al., 2003; Stephan et al., 2010).

7. Sexual dimorphisms in neural correlates of social cognition and implications for OT research

7.1. *Sex differences in social processing and sexually dimorphic effects of OT*

So far, results from fMRI studies exploring a modulation of social-stimulus related brain activity have suggested differential OT effects in men and women. These differences have mainly been observed in the context of amygdala responses. Studies in men have consistently reported attenuated amygdala responses following OT administration. In women, OT was found to increase amygdala reactivity to emotional cues in some studies (Domes et al., 2010a; Lischke et al., 2012) and to dampen amygdala activity in other studies (Riem et al., 2012, 2011; Rupp et al., 2012). The reasons for such differences may be manifold and no fMRI study has so far systematically addressed the question of differential effects of OT on brain activity in men and women within a single experimental protocol.

However, there is substantial evidence that men and women differ in terms of brain anatomy and neural processing. For example, women have larger volumes of the orbitofrontal cortex, the caudate and parts of the mirror-neuron system (Cheng et al., 2009; Filipek et al., 1994; Sowell et al., 2002); whereas size of the hypothalamus, angular gyrus, and amygdala is larger in men than in women (Goldstein et al., 2001). Notably, brain activity of men and women was found to differ on all domains of socio-cognitive functioning that show modulation by exogenous OT, e.g. emotion processing and regulation (Domes et al., 2010b; for recent reviews, see Stevens and Hamann, 2012; Whittle et al., 2011).

7.2. *Effects of gonadal hormones on social stimulus processing and potential interactions with OT*

These sex differences are likely mediated by the early influence of gonadal hormones on differentiation and morphology of the central nervous system (Ahmed et al., 2008; Schwarz and McCarthy, 2008; Sisk and Zehr, 2005) as well as their short-term modulation of neural transmission during rest and cognitive processing (Maki and Resnick, 2001). It is important to note that differences in gonadal hormone levels in men and women (especially estrogens) are not stable but change with age as well as across the female menstrual cycle. Menstrual cycle related changes were found to affect activity in brain networks underlying social stimulus processing (Derntl et al., 2008; Dreher et al., 2007; Marečková et al., 2012) and preliminary evidence suggests that brain morphology itself may change across the menstrual cycle and following oral contraceptive use (Ossewaarde et al., 2013; Pletzer et al., 2010).

Evidence from animal studies indicates that the OT system is strongly influenced by gonadal hormones (Champagne et al., 2001; De Kloet et al., 1986; Gabor et al., 2012; McCarthy, 1995; Tribollet et al., 1990). Although corresponding evidence for molecular cross-talk of steroid hormones with OT is lacking in humans, it seems likely that OT effects on human brain activity may interact with central actions of gonadal hormones. Studies investigating OT effects on brain activity in women therefore accounted for the menstrual cycle phase (Bertsch et al., in press; Domes et al., 2010a; Lischke et al., 2012; Rupp et al., 2012). To date, a systematic exploration of potential effects of hormonal changes associated with the female menstrual cycle on reactivity to intranasal OT administration is missing. Future studies addressing this issue may contribute to a better understanding of the amount of variance in OT effects that might be explained by gonadal hormones. In sum, there is pressing need of considering sex hormone influences and menstrual cycle associated hormonal changes in the study of central OT effects.

8. OT and neurogenetics

8.1. *Association studies on the oxytocin receptor gene*

Given the high variance in behavioral and neural effects observed after OT application in most studies, one promising approach aims at identifying variations in specific genes which contribute to individual differences in social behavior and social cognition, including vulnerability for neuropsychiatric or developmental disorders characterized by social deficits (Ebstein et al., 2010). Several studies investigated associations between the gene coding for the oxytocin receptor (*OXTR*) and individual differences in social behavior (for a review, see Kumsta and Heinrichs, 2013).

The neurobiology underlying such associations between *OXTR* variants and social behavior phenotypes is addressed by the imaging genetics approach which relates genetic variants to brain structure and function (Meyer-Lindenberg et al., 2011). Specifically, imaging genetics aims at identifying endophenotypes (or intermediate phenotypes) such as alterations in brain activity and morphometry that may bridge the gap between genotype and interpersonal variance in social behavior. Several neurogenetic studies showed that genetic variation of *OXTR* affects a limbic circuit involving the amygdala, the hypothalamus and the cingulate gyrus (e.g. Tost et al., 2011, 2010). Although preliminary data suggest that *OXTR* single nucleotide polymorphisms (SNPs) may affect social cognition and behavior by modulating anatomy and functioning of the social brain (Kumsta and Heinrichs, 2013; Meyer-Lindenberg and Tost, 2012), meta-analytic evidence for a direct impact of the two most frequently tested SNPs on human social behavior is missing (Bakermans-Kranenburg and van Ijzendoorn, 2013b).

8.2. *Epigenetic and dopaminergic influences on central OT signaling*

In addition to these structural changes, the importance of epigenetic mechanisms that regulate genetic function and expression without affecting DNA structure was recently reviewed (Kumsta et al., 2013). In particular, methylation of the *OXTR* promoter region is assumed to differentially influence activity in brain regions associated with social perception. Epigenetic states of genes are known to be modified by experiences, especially those occurring in sensitive periods early in life (e.g., traumatic experiences), forming the basis for a potential neurodevelopmental role of the OT system. More precisely, the influence of early adverse experiences on individual socio-emotional functioning may be mediated by epigenetically determined alterations of central oxytocin signaling (Kumsta et al., 2013).

Finally, two recent studies suggest that structural variations in genes regulating oxytocin and dopaminergic signaling in the brain may interact with exogenous OT administration (Sauer et al., 2013, 2012). It should be noted, that the demand for large sample sizes to ensure reliability of observed interactions between genetic factors and exogenous OT sets a severe restriction to such investigations. Still, future fMRI studies may benefit from a neuropharmacogenetic approach as it surely helps to clarify the amount of variance observed in measures of neuroanatomy and neural signaling that may be attributable to individual differences in genetic factors.

9. Conclusions and desiderata for future research

In the past eight years, more than two dozen experimental fMRI studies have been published regarding the effects of OT on regional brain activity during social information processing, with many more currently underway. The studies so far show some variability in regard to the experimental task and the populations studied; nevertheless, most of the published studies have reported modulations of amygdala reactivity in response to emotional as compared to neutral, or social compared to non-social, stimuli. The few fMRI studies in clinical samples suggest that this modulation depends on baseline socio-cognitive functioning of the population under study or differences in endogenous oxytocin signaling. In addition, some studies have provided evidence for OT-induced modulations of functional coupling between the amygdala and down-stream brain areas such as the brainstem, as well as areas implicated in the regulation of amygdala reactivity such as parts of the prefrontal cortex.

Presumably, differences between the studies summarized above stem from two major sources of variance: (i) differences between the populations under study (e.g. male vs. female and healthy vs. clinical samples) and (ii) differences in regard to the primary cognitive processes involved in a task. With regard to population characteristics, the issue of possible sex differences could be elucidated in future studies by directly comparing the effects of intranasal OT on male and female brain functions within the same study. These studies should further take variations of hormonal status over the female menstrual cycle into account. In addition, systematic use of structural and functional genetic information may contribute to explain individual variance in brain responses to exogenous OT. Differences in experimental design and the underlying cognitive processes addressed by a task add further variability to fMRI findings on OT effects in the human brain. This issue relates to the fact that complex social stimulus processing involves a number of basic cognitive processes (perception, attention, memory, etc.). Future imaging studies would benefit from a clear a priori definition of the basic cognitive processes under study and specifically tailored experimental tasks.

In addition, there is still a general lack of basic knowledge regarding the distribution of OT receptors and the molecular and cellular mechanisms of OT in the human brain. These issues are expected to be resolved as basic research into the genetic mechanisms of neuropeptides and receptor mapping moves forward. As previous approaches to explore effects of OT on brain connectivity were merely correlational, localizing the primary brain areas which are modulated by exogenous OT may benefit from advanced methods for analyzing effective connectivity using fMRI. Additionally, other neuroimaging techniques, such as source-localization with high-density EEG may be employed. Together, these methods will broaden our search from a single brain area to functionally integrated brain circuits underlying complex cognitive processes, such as the recognition of an emotion from a facial expression.

In sum, advances made in functional and structural imaging techniques and neurogenetics over the past years have revealed a yet-incomplete picture of the acute effects of OT on brain function. However, future studies focusing on some of the issues highlighted in the present paper will undoubtedly help to reveal the neural functions of OT in the context of social information processing and might pave the way to develop improved treatment strategies for mental disorders characterized by social dysfunction.

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Research Report

Oxytocin and vasopressin modulation of the neural correlates of motivation and emotion: results from functional MRI studies in awake rats

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ABSTRACT

Oxytocin and vasopressin modulate a range of species typical behavioral functions that include social recognition, maternal-infant attachment, and modulation of memory, offensive aggression, defensive fear reactions, and reward seeking. We have employed novel functional magnetic resonance mapping techniques in awake rats to explore the roles of these neuropeptides in the maternal and non-maternal brain. Results from the functional neuroimaging studies that are summarized here have directly and indirectly confirmed and supported previous findings. Oxytocin is released within the lactating rat brain during suckling stimulation and activates specific subcortical networks in the maternal brain. Both vasopressin and oxytocin modulate brain regions involved unconditioned fear, processing of social stimuli and the expression of agonistic behaviors. Across studies there are relatively consistent brain networks associated with internal motivational drives and emotional states that are modulated by oxytocin and vasopressin.

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1. Introduction

It is well established that the neuropeptides oxytocin (OT) and vasopressin (AVP) play major roles in what many consider to be vital behavioral functions (Carter et al., 2008). The range of functions encompasses a spectrum of emotional and motivational mechanisms that include social recognition, modulation of social memory, maternal-infant attachment, offensive aggression, defensive and fear reactions, and reward seeking behavior. Consistent with the range of neurobehavioral roles that have been discovered for oxytocin and AVP, the receptor distribution for these neuropeptides is observed to include various subcortical forebrain and midbrain areas of rats, which subserve

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the aforementioned behaviors. In non-human primates the expression of their receptors may include regions of the neocortex (Young et al., 1999). Among the challenges for studying these integrative brain functions using a systems-level approach is the limited amount of non-invasive methods that are available. Our group has used functional magnetic resonance mapping techniques to explore the modulatory roles of these neuropeptides in maternal and non-maternal brain networks. The present review offers a summary of these experiments in awake rats and puts forth several interpretations that could guide future fMRI studies in this area.

2. Functional magnetic resonance imaging of awake rats

Functional magnetic resonance methods developed by Ferris and colleagues have allowed fMRI studies in awake restrained rats (Ferris et al., 2005). There are obvious advantages to this experimental paradigm that is often overlooked by many in the neuroscience community. Most of the available fMRI studies in rodents are carried out while animals are under anesthesia. This is done despite the anticipation of studying neural circuits that underlie or drive distinct motivational and cognitive states. This, of course, is impossible when the awake state is suppressed by anesthetics. Experiments that employ the awake rat methods require acclimation to restraint and MR sound prior to experiments. We have been able to successfully implement these procedures in our studies. This requires the animals be placed under transient stress over the span of 5 days or so. Results from previous studies show promising outcomes in which animals show reductions in physiological and motor perturbations that may hinder the quality of the collected data (King et al., 2005). Moreover, the behavioral outcomes of restraint acclimation for fMRI do not appear to be permanent (Reed et al., 2013a, 2013b). Thus, the studies cited in the present review are all collected while rats are in the awake, unanesthetized state. Details of the experimental paradigms used, especially pre-processing strategies to screen for and to minimize the impact of motion artifact have been published (Ferris et al., 2008).

The non-invasive measurement of neural activity through the blood oxygenation level dependent (BOLD) signal is key to the enthusiasm in pursuing fMRI studies rodents and other species. To date, there are no neuroscience techniques that can supersede and replace this feature of fMRI. The BOLD signal arises from changes in tissue oxy-to-deoxyhemoglobin ratio and. Microvascular magnetic field gradients that are sensitive to changes in paramagnetic deoxy- and diamagnetic oxy-hemoglobin concentrations near brain areas of altered neuronal metabolism are a likely source of the BOLD fMRI signal. Changes in neuronal activity, and the accompanying compensatory adjustments in blood flow, in blood volume and in the cerebral consumption rates for oxygen, underlie the mapping of the measured BOLD signal changes. A variety of experimental paradigms have been developed over the years in order to examine brain function with fMRI. The premise in all of the paradigms is the external delivery of a sensory-driving stimulus, be it drug, autonomic, primary sensory, or a higher order complex stimulus.

Despite its advantages, it is important to keep in mind shortfalls of fMRI in awake rats. First, the quantitative assessment of excitatory/inhibitory neuronal firing as recorded using other invasive techniques is limited in fMRI. Second, restraint used for fMRI experiments precludes behavioral tests during fMRI scanning. There are always concerns about the effects of repeated exposure to transient, but significant, levels of stress. This is an important and ongoing area of study by our laboratories.

3. Affiliation: imaging oxytocin and maternal-offspring interactions

OT acts within the lactating brain to provide a major signaling mechanism that strengthens the mother-offspring bond early in life. Its synthesis mainly occurs in neurons of paraventricular (PVN) and supraoptic nucleus (SON) of hypothalamus. Suckling stimulates the release of OT into the bloodstream via the neurohypophyseal portal system and in the central nervous system of postpartum rats (Neumann et al., 1993b). Systemically, OT stimulates smooth muscle contraction, which is important for milk 'let-down' during nursing and for uterine contraction during parturition. OT release within the CNS during parturition initiates maternal behaviors and may act to coordinate emotion, social and cognitive networks necessary for maternal care. Many of the brain areas involved in maternal behavior in rat and other species of mammals express moderate-to-high levels of OT receptors (Tribollet et al., 1988a; Tribollet et al., 1988b; Vaccari et al., 1998; Veinante and Freund-Mercier, 1997; Yoshimura et al., 1993), suggesting a convergence of maternal and OT pathways. Brain regions include amygdala, dorsal hippocampus, hypothalamic paraventricular, ventromedial, and preoptic nuclei, lateral septum, olfactory structures, nucleus accumbens, substantia nigra (SN), ventral tegmental area (VTA), bed nucleus of stria terminalis (BNST), among others (See Fig. 1 and Table 1). Elevated OT receptor density in areas such as the preoptic area (mPOA) has been correlated with greater levels of pup licking and grooming in postpartum dams (Champagne et al., 2001; Francis et al., 2000). It is in these structures that OT may contribute to strengthening of mother-infant interactions. OT release in response to suckling has been measured using microdialysis in the substantia nigra, olfactory bulbs, mediobasal hypothalamus, BNST, MPOA and septum of parturient ewes (Levy et al., 1995), as well as in sites of origin, PVN and SON, of rat (Neumann et al., 1993a; Neumann et al., 1993b). Administration of an OT receptor antagonist locally within the latter two nuclei reduced OT release, suggesting that a positive feedback mechanism is involved (Neumann et al., 1994). Moreover, administration of an OT antagonist locally within the mPOA reduces arched back nursing in the rat (Bosch and Neumann, 2012).

In one of the first experiments investigating the putative functional neural circuits of lactating rat brain, we presented fMRI evidence that suckling-induced OT release into central neural sites increases the BOLD signal. This effect on the BOLD signal was reported for PVN, olfactory tubercle, anterior olfactory nucleus (AON), insular cortex, piriform cortex,

cortical amygdala, mPOA and prefrontal cortex. For several of the regions, suckling and central OT administration increased the BOLD signal in a strikingly similar pattern. The promising results were not unexpected if the technique were to reliably show lactation neural circuits, and the contribution of OT release into these sites. In addition, central administration of an OT receptor antagonist ($d(CH_2)_5$-[Tyr(Me)^2,Thr^4,Tyr-NH_2^9]-Ornithine Vasotocin) partly blocked the suckling-induced increase in the BOLD signal in cortical, midbrain and olfactory regions (Febo et al., 2005). OT antagonist blockade in olfactory regions suggests that OT release during nursing contributes to olfactory-related neural activity. The results of the above-cited study (Febo et al., 2005) illustrate a common theme present through several of the subsequent neuroimaging studies in rat. There is a close functional interaction between OT and AVP with olfactory function. This may be particularly important for enhancing the perception or facilitation of the registration of socially relevant stimuli into short- and long-term memory circuits of rats.

We have observed that neuranatomical substrates activated by central OT administration in the lactating rat closely paralleled that observed with suckling stimulation alone. OT given intracerebroventricularly (ICV) showed a dose-dependent BOLD activation of brain areas co-localized with OT receptors, or that are associated with OT-mediated behaviors (Table 1). Centrally administered OT activated areas associated with maternal, and other reproductive behaviors, e.g. the primary olfactory system, the ventral medial hypothalamus, mPOA and BNST. The 3D color model on the top of Fig. 1 depicts the brain areas in the rat that are reported to display a high density of OT receptor binding (De Kloet et al., 1985; Freund-Mercier et al., 1987; Tribollet et al., 1988c; van Leeuwen et al., 1985). As there are no reported differences in OT receptor binding sites between males and female rats (Barberis and Tribollet, 1996), this 3D model is representative of both sexes. These areas have been coalesced into a single volume (yellow), as shown in the lower 3D images for ICV administration. Areas in red are from composite images of BOLD signal changes collected in nine rats, each given OT ICV (1.0 ug). The localization of BOLD activation is clearly shown on the 2D axial sections of the MR atlas of rat. Blockade of OT receptors with a specific antagonist selectively reduced brain activity in many of these areas, evidence that endogenous OT has a role in the neurobiology of nursing. There were non-overlapping brain regions, namely the caudate-putamen, septum, and thalamus that might involve other neurotransmitter systems aside from OT.

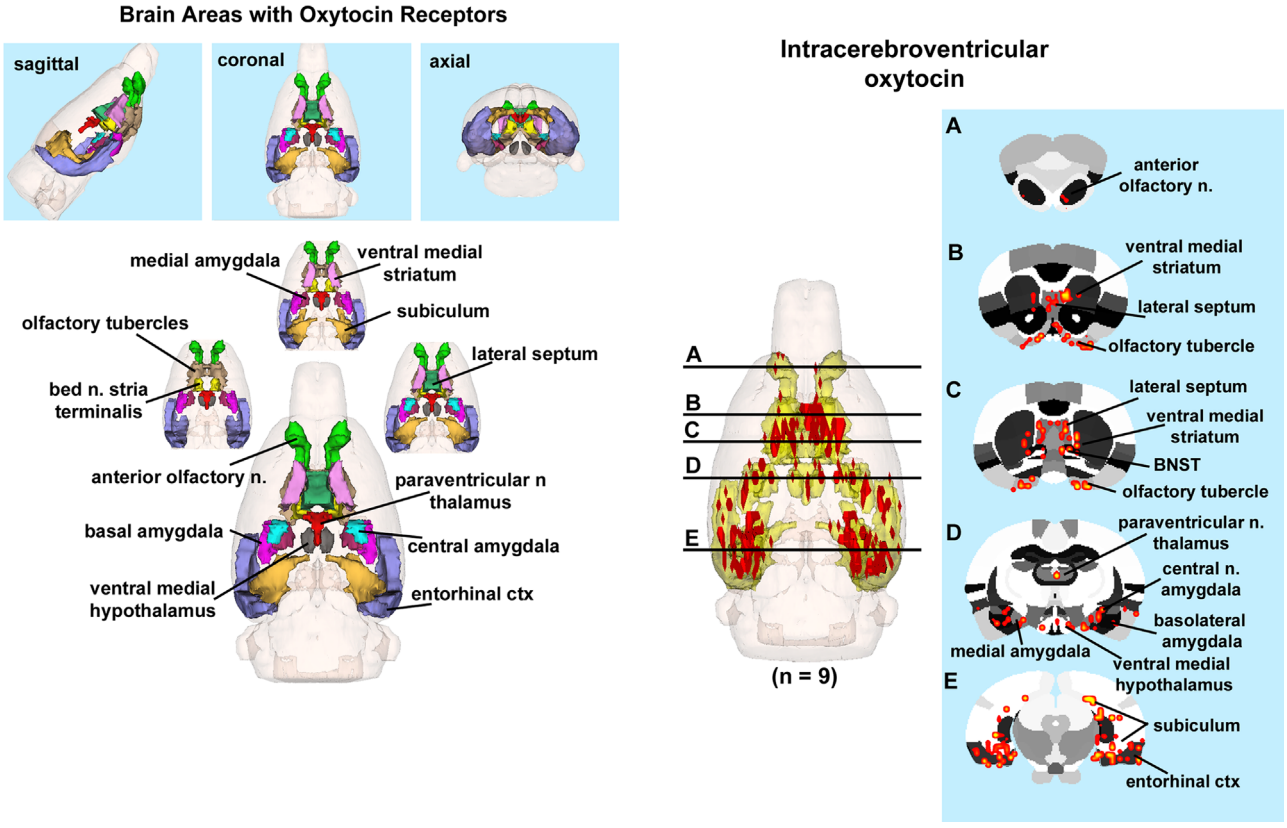

Fig. 1 – Neural circuitry of high density ot receptor binding sites. The 3D color model on the top depicts the brain areas in the rat with a high density of OT receptor. These areas are coalesced into a single volume (yellow) within a translucent shell of the brain, as shown in the lower 3D images for ICV. Areas colored red are the localization of activated voxels representing the composite average of nine rat brain fMRI scans. Once fully registered, and segmented, the statistical responses for each animal are averaged on a voxel-by-voxel basis. The averaged voxels that are significantly different from baseline, and exceed a 2.0% threshold, are show in their appropriate spatial location. The 2D images appearing to the right of each 3D image show the location of interpolated voxels of positive BOLD activation registered onto coronal sections of the segmented rat atlas. The approximate location of these brain slices are depicted by the black lines shown in the 3D ICV image.

Table 1 – Brain activation with intraventricular oxytocin.

Positive BOLD—volume of activation (voxel numbers)

Region of interest	1.0 ug med	0.1 ug med	0.01 ug med	vehicle med	P value
Retrosplenial cortex	101	42	49	53	0.001
Subiculum hippocampus	94	43	48	46	0.001
Substantia nigra reticularis	28	10	9	9	0.001
Substantia nigra compacta	8	3	4	5	0.001
Medial preoptic area	20	8	7	7	0.001
Olfactory tubercles	73	20	56	55	0.001
Medial dorsal thalamus	10	6	4	4	0.001
Dorsal medial hypothalamus	7	2	1	1	0.002
Orbital cortex	23	5	6	6	0.003
CA1 dorsal hippocampus	46	14	26	20	0.003
Ventral tegmental area	17	4	6	5	0.004
Piriform cortex	96	52	67	47	0.006
Dorsal lateral striatum	37	20	11	12	0.007
Ventral medial hypothalamus	14	6	7	10	0.008
Glomerular layer	8	2	0	0	0.01
Anterior cingulate cortex	64	27	42	42	0.01
Outer plexiform layer	13	2	0	0	0.01
Lateral preoptic area	12	4	3	3	0.013
Lateral septal nucleus	42	16	24	23	0.021
Ventral medial striatum	21	5	4	4	0.022
Granular cell layer	5	2	0	0	0.028
Basal amygdala	14	7	2	2	0.031
Medial amygdala	16	5	7	5	0.033
Ventral lateral striatum	16	6	10	10	0.039
Dorsal medial striatum	42	11	17	17	0.04
Insular cortex	17	6	19	18	0.041
CA1 ventral hippocampus	31	14	9	9	0.042
Bed nucleus stria terminalis	10	7	4	2	0.047
Parietal cortex	29	10	23	13	0.05

Shown is a truncated list from 152 brain areas and their median (med), number of voxels activated at 30 min post ICV injection of OT in doses of 1.0, 0.1 and 0.01 ug or vehicle. The brain areas are rank order for their significance. The voxel numbers for each treatment were analyzed using a Newman–Keuls multiple comparisons test statistic. *P* values are presented on the far right column. The yellow highlight denotes brain areas with high OT receptor binding and association with OT mediated behaviors.

As noted above, there are numerous studies showing that the main olfactory system, indeed the olfactory bulb itself, is critical for processing and remembering odors that relevant for social recognition (Sanchez-Andrade and Kendrick, 2009). Volatile chemical signals from the environment interact with odorant receptors on the olfactory epithelium. In the rat, there are approximately 1200 genes coding for odorant receptors (Quignon et al., 2005). These olfactory sensory neurons project to mitral cells in the glomerular layer of the olfactory bulb. Olfactory information is processed at the level of olfactory bulbs and conveyed to the olfactory cortex and amygdala. Natural maternal behavior in rats and mice (Fleming and Rosenblatt, 1974; Gandelman et al., 1971), maternal recognition of offspring in ewe (Baldwin and Shillito, 1974) and social recognition in male rats (Dantzer et al., 1990), require the olfactory bulbs. OT plays a significant role in each. During parturition and vaginal-cervical stimulation, OT levels increase in the olfactory bulbs (Kendrick et al., 1988a; Kendrick et al., 1988b; Larrazolo-Lopez et al., 2008). Blocking OT receptors in the olfactory bulbs immediately after parturition delays maternal behavior in rats (Yu et al., 1996). Conversely, OT injections into the olfactory bulbs induces maternal behavior in virgin rats (Yu et al., 1996). The memory preservation of social recognition of juvenile female conspecifics is reduced with injection of OT receptor antagonist into the olfactory bulb (Larrazolo-Lopez et al., 2008), while OT infused in the olfactory bulbs of male rats preserves the memory of prior social interactions (Dluzen et al., 1998). Indeed, the olfactory bulb, and its downstream connections to cortical amygdala, medial amygdala, BNST and medial preoptic areas, are all integrated in social recognition and all are sensitive to OT neurotransmission.

4. Aggression: imaging vasopressin and intruder aggression

4.1. *AVP V1a modulation of maternal neural correlates of aggression*

AVP varies from its cousin nonapeptide OT by way of substitution of the amino acids Phe for Ile in the 3rd position, and Arg for Leu in the 8th position (Gimpl and Fahrenholz, 2001).

It is implicated in the regulation of numerous social and behavioral processes such as aggression, social bonding, and maternal behavior (Goodson and Bass, 2001). Within the mammalian central nervous system, the synaptic actions of AVP are mediated to a large degree by the V_{1a} receptor subtype (Tribollet et al., 1988a), which is found throughout the rodent brain (Ostrowski et al., 1994), and the V_{1b} receptor subtype. AVP is important for the modulation of aggressive behaviors in males and females. Ferris and Potegal, (1988) demonstrated that microinjection of a V_{1a} receptor antagonist in the anterior hypothalamus reduced resident male hamster aggression toward a male intruder. Similarly, a microinjection of AVP into the lateral ventricle causes an increased BOLD signal in regions of the brain involved in aggression and that are known to contain V_{1a} receptors (Ferris et al., 2008). In microtine rodents, AVP also has been observed to promote offensive aggression, as well as partner preference (Winslow et al., 1993). Both the aggressive and affiliative responses may be mediated by V_{1a} receptors in this species of rodent (Lim et al., 2004; Young, 1999). AVP is also important in maternal behavior, as chronic AVP treatment in lactating rats increases maternal care (Bosch and Neumann, 2008), and V_{1a} antagonists impair maternal memory (Nephew and Bridges, 2008) and reduce nursing and pup retrieval (Pedersen et al., 1994).

One specific type of maternal behavior is maternal aggression, which is a robust form of aggression most evident within the first two weeks of lactation (Erskine et al., 1978). This aggressive response can be eliminated by bilateral olfactory bulbectomy (Kolunie and Stern, 1995); however, deprivation of auditory and visual inputs has no effect on maternal aggression (Kolunie et al., 1994), indicating that olfaction, but not auditory or visual stimulation, is essential for maternal aggression. Several brain regions have been associated with maternal aggression, including regions of the limbic system such as the amygdala, nucleus accumbens and BNST (Nephew et al., 2009; Numan and Numan, 1996). The hypothalamus is also associated with the onset of maternal behavior, particularly the VMH (Bridges and Mann, 1994). Lesions to the VMH advance the onset of maternal behavior in primigravid rats (Mann and Babb, 2004), suggesting that this region may be inhibitory toward maternal behavior. Interestingly, anxiogenic state may influence how OT and AVP modulate maternal aggression. Low anxiety behavior (LAB) dams reportedly show lower basal levels of attacks towards a nest intruder than high anxiety behavior (HAB) dams (Bosch and Neumann, 2012). Stimulating OT receptors in LAB dams increases the number of attacks, whereas blocking OT receptors decreases maternal aggression in HAB dams (Bosch and Neumann, 2012). Similarly, blocking vasopressin V_{1a} receptors also increases maternal aggression in LAB dams and reduces it in HAB dams (Bosch and Neumann, 2010). The similar outcomes of these two peptides might be the result of 'cross-talk' via their receptors.

Cortical regions involved in maternal aggression are less well understood. Conscious lactating female rats were injected ICV with either a V_{1a} antagonist or saline, and presented with a novel male intruder in the presence of her pups. Brain activation was measured using BOLD fMRI to determine the role of V_{1a} receptors on maternal brain activation during presentation of a novel male intruder. It was shown that central blockade of V_{1a} receptors modulated BOLD signal responses in primiparous dams (Caffrey et al., 2010). The differential BOLD responses were not generalized across the maternal rat brain, but were site specific. V_{1a} receptor antagonist enhanced the volume of BOLD activation in the AON, and reduced it in the cortical amygdala and VMH. Greater percentage increases in BOLD signal were observed across several brain areas in response to V_{1a} antagonist treatment, including the AON, gustatory cortex, infralimbic area, substantia innominata (which expresses V_{1a} receptors), and the somatosensory cortex. An unexpected finding of the study was that V_{1a} receptor blockade significantly enhanced BOLD signal in somatosensory areas during intruder presentation. The greater BOLD signal response occurred in both primary and supplemental areas, but was not generalized to the entire cortical mantle. The heightened BOLD response observed in this region of the cortex was not observed in primary or secondary motor cortical areas, or in parietal or temporal cortices. Thus, somatosensory modulation by V_{1a} receptors appears to be selective for this cortical region. The only region that showed a lower percentage change in BOLD with V1a receptor blockade was the VMH. The results indicated that V_{1a} receptors modulate neural processing in specific neural circuits recruited during a timeframe corresponding to the initial phases of maternal aggressive motivation. The V_{1a} sensitive circuits include structures which are involved in sensory processing, the control of visceral responses, and emotional memory. One interesting feature of the brain areas that were modulated by V_{1a} receptors in our imaging studies is that some of these share connectivity with the orbital prefrontal cortex in rats (Ongur and Price, 2000). Gustatory, infralimbic, olfactory, somatosensory and amygdalar networks are processed through this limbic cortical structure that plays an important role in sensory and visceromotor associations (Gabbott et al., 2005; Ongur and Price, 2000; Vertes, 2004). Although V_{1a} receptors in rat are not localized in the various cortical regions, the observed enhancement might be achieved through indirect subcortical actions of this receptor antagonist. It remains to be determined whether or not this is the case. Activation of the somatosensory cortex and its modulation by V_{1a} receptors is interesting in light of the fact that AVP receptors have not been detected in this brain region, and that a somatosensory stimulus was not presented to dams. Thalamic sensory relay nuclei were unaffected by antagonist treatment, and do not contain V_{1a} receptors. However, the substantia innominata, which has been shown to contain an understudied population of V_{1a} receptors (Ostrowski et al., 1994), sends major cholinergic projections to the cortical mantle, in particular the somatosensory and prefrontal cortices. Lesions of these cholinergic projections differ dramatically from sensory cortical ablations, and alter emotional reactivity in rats (Knox et al., 2008; Wozniak et al., 1989). Indeed, it is possible that V_{1a} receptors in this basal forebrain area, and its interaction with the somatosensory cortex, may control aspects of behavioral reactivity, and perception of internal autonomic/visceral states. Due to the transient nature of the BOLD changes in the substantia innominata, it is postulated that this nucleus may mediate the immediate response to the male intruder, perhaps mapping maternal autonomic bodily reactions to possible aggression towards pups (Caffrey et al., 2010). Though the above

interpretations appear plausible in light of previous literature and our reported data, they remain highly speculative at the moment.

4.2. *Male aggression: role of AVP V_{1a} neurotransmission*

With regards to the actions of AVP on aggression in rat and in other rodent models, it appears to partly mediate its effect via interactions with serotonin (5-HT) at the synaptic level. There is a body of literature reporting that blockade of V_{1a} receptors in a variety of animal models suppresses aggression (Ferris, 2005). Consequently, drugs that target, and block, the V_{1a} receptors are being developed as potential therapeutics for the treatment of impulsivity and violence. Recently, a new class of non-peptidic compounds targeting the human V_{1a} receptor was developed using a monocyclic beta lactam platform (Guillon et al., 2006). One of these potential drugs, SRX251, was tested for serenic activity in the hamster (Ferris et al., 2006). It was shown that oral administration of SRX251 caused a dose-dependent decrease in several measures of aggressive behavior, without affecting motor activity, olfactory communication, and sexual motivation.

Precisely how and where 5-HT and AVP interact to affect the organization, and expression, of aggressive behavior is unclear. Normal aggressive behaviors, and aggression characterized by impulsivity and violence, are envisioned to be organized and controlled by a distributed neural circuit. These include subsets of interconnected neurons conveying sensory and motor information to and from sites of integration (Ferris et al., 2008). With functional magnetic resonance imaging (fMRI) it has been possible to identify the neural circuitry involved in aggressive motivation using an experimental paradigm that drives an agonistic state just prior to the onset of attack. As part of the ethogram of aggression, resident male rats housed with a female cage will piloerect along the dorsal midline when in the presence of a male intruder. The piloerection is unique to offensive aggression, and is not seen in other behaviors signaling an impending attack (Blanchard and Blanchard, 1977). Using a novel aggression model adapted to the neuroimaging conditions, we discovered that even though a resident male is confined to a restraining device for an imaging session, placing an intruder into the vivarium with its cage mate induces piloerection. Our results identified distributed putative neural circuits associated with the genesis of attack behavior and their differential modulation but AVP and 5-HT acting compounds.

Enhanced 5HT neurotransmission is associated with a reduction in aggressive responding via interaction with 5-HT_{1a} and 5-HT_{1b} receptors (Simon et al., 1998; Grimes and Melloni, 2005). Oral fluoxetine suppressed aggression and diminished BOLD activation across the putative neural circuit of aggressive motivation (Ferris et al., 2008). Conversely, AVP neurotransmission promotes aggression by interacting with V_{1a} receptors. Oral SRX251, a V_{1a} receptors antagonist, suppressed aggression and produced a general reduction in BOLD activation in the neural circuitry of aggression similar to that seen with fluoxetine (Ferris et al., 2008). The observation that fluoxetine and SRX251 are similar in their fMRI profile during suppression of aggressive motivation was anticipated. There is evidence that the stimulation of aggression by AVP is regulated by 5-HT. The hypothalamus, the primary site of AVPergic facilitation of aggression, has a high density of 5-HT_{1a} and 5-HT_{1b} binding sites and receives a dense innervation of 5-HT fibers and terminals (Delville et al., 2000; Ferris et al., 1997; Grimes and Melloni, 2002; Ricci et al., 2006). Hypothalamic AVP neurons implicated in the control of aggression appear to be preferentially innervated by 5-HT (Ferris et al., 1991). Fluoxetine blocks resident-intruder aggression that is facilitated by the microinjection of AVP in the hypothalamus (Delville et al., 1996; Ferris, 1996; Ferris et al., 1997). Fluoxetine elevates 5-HT and reduces AVP levels in hypothalamic tissue in hamsters (Ferris, 1996) and rats (Altemus et al., 1992). Serotonin can also block the activity of AVP following its release in the hypothalamus as evidenced by the dose-dependent reduction of aggression with injections combining AVP and 5-HT_{1a} receptor agonists. Enhanced aggression caused by activation of V_{1a} receptors in the hypothalamus is suppressed by the simultaneous activation of 5-HT_{1a} receptors in the same site (Ferris et al., 1997). Personality disordered subjects with a history of fighting and assault show a negative correlation for prolactin release in response to D-fenfluramine challenge, indication of a hyposensitive 5-HT system (Coccaro et al., 1998). These same subjects show a positive correlation between CSF levels of vasopressin and aggression (Coccaro et al., 1998). Thus, in humans a hyposensitive 5-HT system may result in enhanced CNS levels of AVP, with a consequent facilitation of aggressive behavior.

While fluoxetine and SRX251 have similar effects on the putative neural circuitry of aggressive motivation, a markedly different fMRI signature was observed with each compound when treated males were challenged with sexual motivating stimuli (Ferris et al., 2008). With V_{1a} receptor blockade there was activation of the SN, VTA, and their afferent projections to the forebrain limbic cortex, as well as the dorsal and ventral striatum. Measures of sexual activity in the home environment were unaffected by SRX251 treatment. Treatment with fluoxetine, on the other hand, resulted in a diminished BOLD activation in response to sexual motivating stimuli. It also caused inhibition of sexual behavior in the home environment. These opposite effects point to a difference in drug specificity, and underscore the serenic properties of SRX251, specifically its ability to block aggression without affecting other appetitive behaviors.

5. Anxiety: imaging oxytocin and vasopressin in unconditioned fear

5.1. *OT and unconditioned fear in the lactating rat brain*

Attending and responding effectively to environmental dangers is important during the postpartum period. Lactating rats show aggression to conspecific males and are generally less fearful than virgin rats. Central release of OT and AVP during lactation may contribute to heightened maternal aggression and nest defense, and lower fearfulness (Bale et al., 2001; Blume et al., 2008; Bosch and Neumann, 2008; Francis et al., 2000; Windle et al., 1997a; Windle et al., 1997b). In the case of OT, it is released in the PVN and supraoptic nucleus during lactation (Neumann et al., 1993b) and nest

defense (Bosch et al., 2005), respectively. Blocking OT receptors reduces lactation-related behaviors (Bosch and Neumann, 2008; Pedersen and Boccia, 2003), increases anxiety related behavior in an elevated plus maze (Bosch and Neumann, 2008), and affects maternal offensive and defensive behaviors (Bosch et al., 2005). The actions of OT on aggression and fear are perhaps exerted through PVN and central amygdala (Bosch et al., 2005; Heinrichs et al., 2008); however, it is quite possible that a wider circuitry including other limbic and forebrain sites contributes to OT's role in fear reactivity during the postpartum period.

We investigated the effect of centrally administered OT on BOLD activation in response to an unconditioned fear stimulus in dams. Trimethylthiazoline (TMT), a chemical extract of fox feces, has been shown to evoke fear-associated freezing behavior (Wallace and Rosen, 2001), and it also has been observed to elevate plasma levels of corticosterone (Chen et al., 2009; Febo et al., 2009; Morrow et al., 2000). TMT-associated increase in corticosterone in lactating rats is enhanced when pups are in the nest (Deschamps et al., 2003). The physiological and behavioral signs of stress and fear in response to TMT are distinguishable from responses to novel acrid odors (Morrow et al., 2000; Staples et al., 2008), and considered innate since laboratory rodents have no prior exposure to predator odors.

Our fMRI findings showed that OT treatment modulates BOLD signal increases and decreases in response to TMT in lactating rats. OT enhanced TMT-induced positive BOLD signal changes in the anterior cingulate, a brain region involved in emotional expression and fear conditioning. While the BNST, which was previously shown to be responsive to TMT (Day et al., 2004), and also constitute part of the neural circuitry mediating behavioral responses to this predator scent (Fendt et al., 2003; Fendt et al., 2005), also showed greater BOLD signal as compared to vehicle controls. The latter basal forebrain region is interesting in light of the fact that it also modulates VTA dopamine neuron activity (Georges and Aston-Jones, 2001; Georges and Aston-Jones, 2002), thus providing a neurobiological interface between distinct motivation and emotional states. Interestingly, a wider array of structures showed negative BOLD signal changes in response to TMT following OT administration. The anterior olfactory nucleus, which serves as an initial relay site for olfactory-processing, showed primarily signal decreases. This was observed in the prelimbic prefrontal cortex, orbital cortex, mammillary bodies, secondary motor cortex and the gustatory cortex (Febo et al., 2009). The pattern of reduced brain activity (negative BOLD) underscores the importance of OT in regulating fear and anxiogenic responses during the lactation period. Moreover, the pattern varies from findings in male rats (see below). It is tempting to speculate on whether this represents an underlying physiological mechanism where activity in the anterior cingulate during exposure to an innate fear stimulus occurs in parallel with a lack of neuronal activity or inhibition in other adjacent limbic cortical regions controlling approach behavior and autonomic responses. Negative BOLD has, however, less support from the literature on its role in neuronal processing than positive BOLD (Logothetis, 2003). Although somewhat controversial, there are indications that negative BOLD correlates with reductions in synaptic activity (Shmuel et al., 2006).

Our results for OT and fear are in agreement with a previous study looking at the BOLD response to OT administration in lactating rats (Febo et al., 2005). ICV OT administration was observed to activate the anterior cingulate, parietal cortex, somatosensory, temporal cortices, dorsal striatum, preoptic area and ventral tegmental area. The actions of OT administration on BOLD responses within these regions may hold importance to emotional reactivity, particularly to innate fear reactions. For instance, the anterior cingulate is involved in the initiation of goal directed behaviors (Devinsky et al., 1995), as well as the emotional control of visceral, skeletal, and endocrine functions (Vogt et al., 1992).

OT receptor binding sites, and its receptor-encoding mRNA, have been detected in the BNST, lateral septum, posterior cortical amygdala, anterior olfactory nucleus, piriform cortex, main olfactory bulbs, central amygdala, subiculum, and dispersed cortical regions (Veinante and Freund-Mercier, 1997; Yoshimura et al., 1993). The observed TMT-induced BOLD responses were in partial agreement with areas of the rat brain expressing OT receptors. The BNST is particularly interesting. This region is part of the extended amygdala and not only participates in modulating stress and fear responses, but also expresses both OT and V_{1a} receptors. We observed a greater volume of activation in this area with OT pretreatment, which suggests a greater neuronal activity in response to TMT. Recent report shows that TMT exposure elevates extracellular norepinephrine levels in the BNST (Fendt et al., 2005). Blocking norepinephrine receptors with clonidine results in less time spent freezing in response to TMT (Fendt et al., 2005). Although electrolytic lesions of the lateral amygdala block conditioned fear, but not innate fear (Wallace and Rosen, 2001), the opposite has been shown for the BNST (Fendt et al., 2003). This suggests an essential role of the BNST in unconditioned fear response (Fendt et al., 2003). It might be interesting to examine the interactions between noradrenergic inputs and OT inputs to this region. It should be noted that the BNST also is important in behavioral and endocrine responses to contextual fear stimuli (Sullivan et al., 2004). Therefore, the BNST may be an important brain area where OT exerts its effect on TMT-induced freezing in lactating rats. Although there is no evidence showing OT receptors in the anterior cingulate, this region shares synaptic communication with the septum and amygdala, which might indirectly have regulated TMT-induced BOLD activation. Indeed, previous reports indicate that the anterior cingulate cortex plays a role in memory of emotional and fear-inducing events (Malin and McGaugh, 2006; Malin et al., 2007).

5.2. *OT and AVP modulation of unconditioned fear in the male rat brain*

Brain regions that are associated with unconditioned fear partly overlap with receptors for the neuropeptides OT and AVP. Therefore, it is important to consider the role of these neuromodulators as potential pharmaceutical targets for treatment of generalized anxiety disorders. The central distribution of OT and AVP suggest that they play a role in modulating olfactory processing, social behavior, as well as cognitive, emotion-related, and goal-directed behavioral functions (Huber et al., 2005; Ostrowski et al., 1994; Szot

et al., 1994; Tribollet et al., 1988a; Tribollet et al., 1988b; Veinante and Freund-Mercier, 1997). There is growing evidence that OT-mediated effects result in anxiolysis, while AVP actions through the V_{1a} receptor promote aggression and heightened anxiety (Appenrodt et al., 1998; Knobloch et al., 2012; Murgatroyd et al., 2004; Waldherr and Neumann, 2007). Not only do these neuropeptides control anxiety, but also their presence in amygdala and hippocampus suggests a prominent role in cognitive mechanisms, such as conditioned fear learning processes (De Wied et al., 1975; de Wied et al., 1984; Vawter et al., 1997). Based on their location within the components of the olfactory system, such as AON and the olfactory tubercles, as well as central amygdala and BNST, these peptides may control olfactory perception and the association between smell, social recognition and emotionality (Ferris, 2008).

We used functional MRI to investigate the role of OT and V_{1a} receptors in modulating odor-evoked brain activity in the awake male rat (Reed et al., 2013a, 2013b). A novel repulsive odor for the rats, butyric acid (BA), and unknown chemical constituents present in cat fur were chosen in order to examine unconditioned fear and anxiety responses. The results indicated that BA-induced BOLD signal increases were significantly greater than with cat fur. This presented challenges to the final interpretations of the data since the fear-eliciting chemicals in cat fur are unclear. BA activated several olfactory system structures and areas of the brain involved in the neural processing of smell. Cat fur odor caused modest activation in limbic structures compared to BA. We observed a significant effect of cat fur in anterior thalamic nucleus, BNST, ventral CA3, cortical amygdala, lateral amygdala, medial amygdala, olfactory tubercle, posterior amygdala, PAG, posterior hypothalamus, dorsomedial, dorsolateral and ventromedial regions of the striatum, nucleus accumbens core, subiculum, and ventral tegmental area (Reed et al., 2013a, 2013b). In spite of the shortfalls, an important finding was that OT and V_{1a} receptors differentially modulated BA- and cat fur-induced BOLD signal responses in several brain areas. BA-induced BOLD signal changes were curtailed in the cortical amygdala by the OT receptor antagonist (d$(CH_2)_5$-[Tyr$(Me)^2$,Thr^4,Tyr-NH_2^9]Ornithine vasotocin). V_{1a} receptor blockade using [β-Mercapto-β,β-cyclopentamethylenepropionyl^1,O-me-Tyr^2,Arg^8]-Vasopressin reduced cat fur-induced BOLD signal changes in the amygdala, hippocampus and PAG. OT blockade had no effect on the response to cat fur in these regions. In the central amygdala both OT and V_{1a} antagonists curtailed the BOLD response to cat fur.

The findings suggested that OT-mediated neurotransmission is important in responding to a novel odor such as BA. V_{1a}-mediated neurotransmission appeared more closely associated with cat fur induced BOLD activation across several brain regions. This could indicate a closer association between V_{1a} receptors and unconditioned fear than shown by OT receptors. However, the results only partly support this notion, and require improvements in the experimental model. The incorporation of conditioned fear stimuli, which holds significance to generalized anxiety and posttraumatic stress states, should provide the needed improvements.

It is noteworthy that we initially expected regions such as the ventral BNST, amygdala, ventral hippocampus, lateral septum, would distinguish the effects of cat odor from BA. Using c-fos immunolabeling, Staples et al. (2008) identified regions of rat brain that responded selectively to cat and TMT over no odor and formalin odor. They reported selective cat-induced activation of c-fos labeling in VTA, striatum (dorsal and ventral), basal and medial amygdaloid nuclei, subareas of AON, medial prefrontal cortex, anterior and ventromedial hypothalamic nuclei, BNST and dorsal premammilary nucleus (Staples et al., 2008). TMT had only modest effects on cellular activation, increasing activity in the cortical amygdala (anterior portion), piriform and ventral orbital cortices. Rosen et al. (2005) reported increased mRNA expression of *egr-1* in the hypothalamic paraventricular nucleus (PVN) of rats following exposure to a cat (Rosen et al., 2005). This is interesting since this region contains OT and V_{1a} receptors that control the central release of their corresponding neuropeptides via magnocellular neurons (Knobloch et al., 2012). Several lesion studies have provided evidence of a role for the ventral hippocampus and BNST in unlearned fear reactivity. Inactivation of the ventral BNST or blockade of norepinephrine α_2 receptors reduces freezing in response to TMT (Fendt et al., 2003; Fendt et al., 2005). Similar effects are observed with lateral septum inactivation (Endres and Fendt, 2008). These areas express V_{1a} receptor mRNA (Veinante and Freund-Mercier, 1997). In the case of the ventral hippocampus, lesions to this site result in significantly more time spent in the open arms of an elevated plus maze (Kjelstrup et al., 2002). The ventral hippocampus also shows significant V_{1a} receptor mRNA expression (Ostrowski et al., 1994). We observed significant effects of V_{1a} blockade on cat but not BA induced BOLD activation (Reed et al., 2013a, 2013b), which is consistent with some of the aforementioned studies.

In sum, investigating the neural circuitry of unconditioned fear and the modulatory role of OT and AVP may be improved by the development of alternative models for eliciting signs of fear that may be measurable from the rats. Something along the lines of what Ferris and colleagues reported for the resident-intruder model mentioned in the preceding section (Ferris et al., 2008). The use of olfactory-mediated fear is complicated by the ambiguous outcomes of TMT (is it stress responsiveness or true innate anxiety/fear circuits) and the lack of detail on the chemical components of cat fur and feces that may trigger fear and defense reactions in rats. Moreover, the use of centrally administered neuropeptides should be improved by the administration of orally active agents as well as using state of the art genetic tools to remotely drive activation of selective OT and AVP neurons in hypothalamic nuclei. Our first studies, however, indicate that OT and AVP may modulate fear and/or stress both centrally and during the initial processing stages in the olfactory system. This outcome is again consistent with the distribution of their corresponding receptors within olfactory and limbic structures (Fig. 1).

6. Potential role of V_{1a} receptors in social neural processing in autism spectrum disorders

Original studies of AVP linked this peptide neuromodulator to learning and memory functions (De Wied et al., 1975; De Wied et al., 1993; Vawter et al., 1997). Although this was a large focus of classical studies it has subsided somewhat, but there is an

important neuroanatomical and neurophysiological association between OT and AVP V_{1a}/V_{1b} receptor expression in the hippocampus and amygdala. Therefore, diseases in which the functional activities of these peptides are dysregulated could lead to impairments not only associated with anxiety, mood, violence, but also can potentially underlie memory/learning impairments. The neurophysiology underlying this possibility is studied very scarcely. One such area involving complex deficits including social deficits, emotional and cognitive disturbances, is autism spectrum disorders (ASD).

A pilot study to examine the possible role of V_{1a} receptors was carried out in a well-studied animal model of ASD (Felix-Ortiz and Febo, 2012). ASD's, which includes autism, Asperger's syndrome, and pervasive developmental disorder not otherwise specified (PD-NOS), are characterized by deficits in verbal and non-verbal communication, reduced social interactions, and restricted range of interests and motor stereotypies. Genome-wide screening has identified numerous gene mutations that might underlie ASD (Abrahams and Geschwind, 2008). Among the candidate genes for ASD are those encoding the V_{1a} receptor (Kim et al., 2002), and the OT receptor (Abrahams and Geschwind, 2008), which are known to modulate social behaviors in rodent models (Bielsky et al., 2004; Israel et al., 2008).

Genes encoding the V_{1a} receptor have been linked to ASD (Kim et al., 2002). The role of AVP in modulating the neural response to a social stimulus was assessed in adult rats exposed prenatally to valproic acid (VPA). VPA is a mood stabilizer and anticonvulsant, given during pregnancy to women suffering from epilepsy. Fetal exposure at embryonic day E20-E24 can produce neural tube defects and ASD-like deficits. In rats, teratologic effects similar to those reported in humans are observed when exposure occurs between E9.5-12.5 (Arndt et al., 2005; Miyazaki et al., 2005; Rodier et al., 1996; Stodgell et al., 2006). Reports indicate that VPA treated rats show early signs of developmental abnormalities (Markram et al., 2008; Rodier et al., 1996; Schneider et al., 2001; Schneider and Przewlocki, 2005) and these are consistent with motor and cognitive behavioral features partially resembling ASD. Neurobiological changes have also been reported and (Arndt et al., 2005; Ingram et al., 2000; Rinaldi et al., 2008; Rodier et al., 1996), which parallels postmortem pathological findings in autistics. Recent evidence indicates that neonatal VPA exposure can influence AVP immunolabeling in several regions of the rodent brain such as the anterior hypothalamic area and mediodorsal thalamus, and influences olfactory-based social behavior in rodents (Murray et al., 2011). We tested whether prenatally exposed rats show abnormal neurophysiological responses to social and non-social (visual) stimuli (Felix-Ortiz and Febo, 2012).

The experiments were designed to track the developmental progress of various social behaviors from the early postnatal period to adulthood. It was anticipated that gestational VPA would dramatically alter the way the specific brain regions of the rat respond to a social stimulus. Our neuroimaging data provided evidence of a lasting effect of prenatal VPA on social neural processing (Felix-Ortiz and Febo, 2012). VPA-exposed rats show significantly greater BOLD signal responses to a stimulus juvenile rat than saline control animals. Even though the observed behavioral changes suggested a deficit, the differences in neural responses to a social stimulus in VPA compared to controls were of greater magnitude. Differences were observed in cortical and subcortical limbic regions, including temporal, secondary motor and entorhinal cortices, basal region of the amygdala, medial genticulate, posterior hypothalamus and mammillary nuclei, and the substantia nigra pars reticulata. We also provided a primary sensory stimulus to study three brain regions of the visual pathway to examine whether differences in social neural processing could be attributable to changes in primary sensory processing, albeit through a specific sensory system. Interestingly, we observed that the greater activation found with the social stimulus was not observed with the visual stimulus. Instead, the visual cortex of VPA rats showed a lower percentage BOLD signal responses that perhaps occurs as a result of lower neural activity in this region. The effects of VPA on primary sensory systems were thus distinct from subcortical and higher order cortical processing of a socially salient stimulus.

In order to examine whether VPA-induced effects on social neural processing is associated with altered functionality activity through the V_{1a} receptor, we included subgroups of animals that received an ICV injection of a V_{1a} antagonist. A reduction in BOLD activity in these regions was observed with V_{1a} blockade. The antagonist on its own had no effect on the pattern of brain activation shown in control animals. The effect of the antagonist was not found to affect primary sensory processing (visual). Therefore, the actions of the antagonist could be interpreted as occurring in conjunction with VPA-induced deficits in higher order processing, but not primary visual processing.

The role of V_{1a} receptors in modulating socially-relevant neural circuits was influenced by prenatal VPA exposure. This is consistent with the role of the V_{1a} receptor subtype in social behaviors, and might point to V_{1a} receptors as a substrate affected by prenatal VPA treatment. Thus, in a teratologic model recapitulating severe ASD-like disturbances in rodents, we find a pattern of social responding that is partly rescued by V_{1a} blockade. These results are encouraging and support recent clinical trials examining the efficacy and safety of a selective and orally active AVP antagonist (RG7314) in individuals with autism spectrum disorders (http://clinicaltrials.gov/show/NCT01793441) (Nightingale, 2012). According to our data obtained in a rat model of VPA-associated social deficits, blocking V_{1a} receptors may potentially be effective at ameliorating the social and anxiogenic deficits observed in autistic individuals. However, more animal imaging studies are needed to examine specific mechanisms of action. Further data using neurochemical techniques are needed to confirm whether AVP, or V_{1a} receptors, or both, are affected. The role of V_{1a} receptors, and also OT receptors, in the regulation of emotion, cognition and social behavior merits further investigation, within the context of the neurobiology of ASD. Our results show a greater BOLD response to a social stimulus in the VPA rat. The V_{1a} receptor antagonist blocks this. Therefore, the greater 'sensitivity' to social stimuli could in part be mediated by excitatory AVP neurotransmission.

7. Conclusions

Over the past decade or so, we have taken a novel and non-invasive approach to studying the varied roles of OT and AVP

in modulating maternal, aggression, fear and social brain networks. The initial results are promising and call for furthering creative ways to examine vital emotional and motivation states. Our neuroimaging findings skim the surface of the underlying cellular and molecular mechanisms and really provide what might be considered as 'integrated network states'. That is, maps of how the brain under the tested conditions, initiates an effectively patterned response involving not just one region, but multiple disparate regions across the brain. The integration of the multiple (otherwise unassociated) brain regions in these states is perhaps an area that deserves deeper consideration. A resetting or synchronization of population firing across distributed brain regions may underlie the observed putative network states under the influence of the triggering sensory stimuli selected for each study. fMRI in such a case is ideally suited for reliably examining the patterned neural responses in rats.

We find that across the integrated network states (which involve many regions that have been associated indirectly, or casually, to cognitive, emotional and motivational mechanisms), OT and AVP exhibit modulatory functions. The observation of these modulatory functions indirectly link these neuropeptides to the brain networks and may be a rationale for targeting these substrates when the 'network states' fail, as in psychiatric illnesses. Under normal conditions, we observe that OT is released within the lactating rat brain during suckling stimulation and therefore activates particular networks of regions in the maternal brain (Febo et al., 2005). AVP and OT play major roles in modulating brain regions involved emotional states (Reed et al., 2013a, 2013b) and agonistic behaviors (Ferris et al., 2008). Across several of these studies, there are relatively consistent networks of brain regions that arise within the context of their role in internal motivational and emotional states that are modulated by OT and AVP and their receptors. Most of these are summarized in Table 1 and Fig. 1. The brain regions include as center points nuclei in the basal forebrain, amygdalar nuclei, midbrain regions and also include subregions of the cortex that were not previously associated with aggression, maternal care, and unconditioned fear. The results also point to possible differences according to reproductive status. Although this was not directly examined in the above-cited studies, there are clear differences between the studies in male rodents versus those including lactating rats. This warrants further investigation (Carter, 2007), as it might be important from a drug discovery and treatment development standpoint.

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Research Report

Oxytocin and vasopressin support distinct configurations of social synchrony

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ABSTRACT

Social synchrony – the coordination of behavior between interacting partners during social contact – is learned within the parent-infant bond and appears in a unique form in mothers and fathers. In this study, we examined hormonal effects of OT and AVP on maternal and paternal behavioral patterns and detail the processes of parent-infant social synchrony as they combine with hormonal activity. Participants included 119 mothers and fathers (not couples) and their 4–6 month-old infants. Baseline OT and AVP were collected from parents and a 10-minute face-to-face interaction with the infant was filmed. Interactions were micro-coded for parent-child contact, social signals, and social- versus-object focused play. Proportions and lag-sequential patterns of social behaviors were computed. Mothers provided more affectionate contact, while fathers provided more stimulatory contact. Parents with high OT levels displayed significantly more affectionate contact compared to parents with low OT and constructed the interaction towards readiness for social engagement by increasing social salience in response to infant social gaze. In contrast, parents with high AVP engaged in stimulatory contact and tended to increase object-salience when infants showed bids for social engagement. OT levels were independently predicted by the amount of affectionate contact and the durations of gaze synchrony, whereas AVP levels were predicted by stimulatory contact, joint attention to objects, and the parent increasing object salience following infant social gaze. Results further specify how synchronous bio-behavioral processes with mother and father support the human infant's entry into the family unit and prepare the child for joining the larger social world.

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1. Introduction

The nature of the affiliative bond between infants and their parents is crucial for understanding human relationships and the developmental psychopathologies that result from its malfunction (Douglas, 2010). Across mammalian species, the transition to parenthood involves a major neuro-hormonal reorganization that is essential for the provision of adequate caregiving and the formation of the parent-infant bond (Curley and Keverne, 2005). Thus, pregnancy and child-birth occur in the context of marked changes in maternal and paternal brain areas implicated in motivation, nurturance, and attention (Atzil et al., 2011; Kinsley and Amory-Meyer, 2011; Mosek-Eilon et al., 2013; Swain et al., 2007). Mothers' and fathers' brains undergo changes and become sensitive to their infants' cues (Kim et al., 2010), and similar changes are

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observed in hormonal systems (Feldman, 2012). These neurohormonal changes support the expression of the species-typical behavioral repertoire in mothers and fathers that prompt the parent-infant affiliative attachment (Feldman et al., 2007). A basic concept in the understanding of this affiliative bond is that of *bio-behavioral synchrony* (Feldman, 2007, 2012; Feldman et al., 2012). Human studies have shown that parent-infant social synchrony – the coordination of parental behavior with the infant's social signals – describes a distinct and stable behavior constellation that is uniquely expressed in mothers and fathers (Feldman, 2007, 2012; Feldman et al., 2012). The human maternal behavioral repertoire is largely based on eye contact with the infant, "motherese" vocalizations, affectionate touch, and the appropriate and synchronous adaptation of these behaviors to infant responsiveness (Feldman and Eidelman, 2004, 2007). The human paternal constellation, on the other hand, involves redirection of infant attention to the environment, stimulatory contact, and joint attention in the exploration of objects (Feldman et al., 2013; Feldman et al., 2013; Parke, 1996), although mothers and fathers both employ the "maternal" and "paternal" repertoire during social play. These behaviors parallel those described in the classical animal literature, mainly in rodents, that link maternal behavior to motivational and affective neural systems (Champagne et al., 2008).

There is currently much support for the notion that human attachment develops within the matrix of biological attunement and close behavioral synchrony (Atzil et al., 2013; Feldman, 2012; Feldman et al., 2011, 2012). An important area of research in the neurobiology of attachment has been the hormonal system, in particular the posterior hypophysial peptides oxytocin (OT) and vasopressin (AVP). Accumulating evidence has shown in both animals and humans that these hormones are indispensable elements in the developing formation of relationships, affecting individual differences in parenting behavior, social recognition, and affiliative behaviors (for review, Feldman, 2012; Ishak et al., 2011; Skuse and Gallagher, 2011). Studies in rodents (prairie voles) indicate that variations in maternal behavior based on distinct patterns of mothering correlate with a specific bio-behavioral profile and greater OT receptor densities in both mother and child (Olazábal and Young, 2006). In humans, OT levels in parent and child are inter-related and depend on the degree of interactive synchrony (Feldman et al., 2010a, 2011), including gaze synchrony and the matching of affective expression. Mothers who engaged in more synchronous interactions showed more coherent activations of the amygdala and nucleus accumbens (NAcc) to their infant's stimuli, and these activations correlated with maternal plasma OT (Atzil et al., 2011). Parallel to research in mice pointing to associations between mothers' and fathers' physiological and behavioral responses in the context of infant cues (Franssen et al., 2011), we found correlations between OT levels in human mothers, fathers, and infants (Feldman et al., 2013) as well as synchrony between mothers' and fathers' brain response to their own infant's stimuli (Atzil et al., 2012).

In contrast to OT, very little is known about the effects of AVP on human parenting. In rodents, AVP has been associated with male bonding and defensive and territorial behavior in rodents (Bielsky et al., 2005), and recent research has shown that AVP promotes social recognition in both animals, especially rodents, (Caldwell et al., 2008), and human males (Guastella et al., 2010). Regions characterized as part of the AVP circuitry are implicated in socio-cognitive processes in both humans and rodents (Goodson and Thompson, 2010). This AVP-brain associations may represent elevated AVP-dependent vigilance, which supports the father's ability to read the intention of others in order to defend mother and young (Atzil et al., 2012; Thompson et al., 2006). In contrast, in women, AVP was found to support the mother's ability to befriend with others. Thus, AVP may prompt differential social strategies in social contexts in women and men (Thompson et al., 2006).

OT effects on human social functioning, however, are not uniform and depend on the individual's attachment history and social skills (Bartz and Hollander, 2006; Weisman et al., 2013b). The influence of OT on social emotion processing in humans appears to depend, at least in part, on gender (Gamer et al., 2010), and OT significantly increased activations in brain areas involved with emotion encoding and empathy in females and not in males (Decety, 2010). This may imply that OT influences prompts different parental behaviors in mothers and fathers. Interestingly, in mothers, but not in fathers, plasma OT correlated with limbic activations (Zink et al., 2011). It thus appears that maternal instinctual care may originate from a limbic OT-sensitive motivational circuit, while fathering is acquired by experience, influenced by social-cognitive processes and AVP.

Brain activity–OT correlations provide additional support to the notion that mothering is guided by greater motivational-emotional focus whereas fathering by a more socio-cognitive executive focus. We found that plasma OT levels may reflect enhanced maternal but not paternal brain activity in limbic-emotional brain areas. In contrast, father OT correlated with higher activations in socio-cognitive circuits, whereas AVP was linked with fathers' amygdala activations (Atzil et al., 2012). It has further been reported that when fathers received exogenous OT, their infants' showed a comparative increased levels of salivary OT and both partners engaged in greater toy exploration (Weisman et al., 2012). Furthermore, infant OT response correlated with the behavioral repertoire typical of the father–infant bond, including paternal stimulation and joint object exploration (Feldman et al., 2010b). Similarly, Naber et al. (2010), showed that OT administration increased fathers' stimulatory and exploratory play with their toddlers.

The aforementioned synchronous bio-behavioral processes allow the human infant to enter the social world of the family unit and to prepare for joining the larger social group. The *bio-behavioral synchrony* conceptual model (Feldman, 2012; Feldman et al., 2012) postulates that the formation of human attachment includes a finely-tuned adaptation of the parent and infant's neural function. Still, there are some major gaps in the literature that require attention. The vast majority of studies have focused on maternal behavior and there is a relative lack of studies on fathers. Furthermore, most studies have not differentiated between the effects of the two "bonding" hormones, OT and AVP, on patterns of parental–infant bonding. Research on AVP is predominantly male oriented as AVP has been mostly

studied in the context of autism and aggression. There is a paucity of AVP research in humans, with no prior study testing the links between AVP and parenting behavior. Finally, there is a lack of understanding of how OT and AVP differentially structure the behavioral repertoire involved in social interactive processes.

As such, the goals of the present study were to compare the hormonal effects of OT and AVP on both maternal and paternal parenting behaviors and to detail the processes of parent-infant interaction as they synchronize with hormonal activity.

Our major hypothesis was that both OT and AVP levels would be associated with the social behaviors that form the basis of parental care. We also hypothesized that hormonal levels would correlate with the specific ways parents synchronize and structure social interaction with their offspring and that this would differ between OT and AVP. Finally, based on research showing that OT administration increases peripheral AVP (Weisman et al., 2013a), suggesting interrelatedness between the two hormones, we expected correlations between maternal and paternal OT and AVP.

119 parents (not couples) and their 4–6 month-old infants participated in the study. Parental plasma OT and AVP levels were measured. Parent infant interaction was coded systematically from video recordings focusing on Affectionate and Stimulatory Contact, Joint Attention, and Gaze Synchrony. In addition behavioral sequences of the parent's reaction to the infant's gaze, parent increase social or object salience were assessed.

2. Statistical analysis

In the first section, ANOVAs examined differences between maternal and paternal OT and AVP. Next, three MANOVAs examined differences between mothers and fathers in: (a) touch behavior; (b) synchrony variables, and (c) lag-sequential patterns. In the second section, similar three MANOVAs were computed twice: once for parents with high versus low OT and once for parents with high versus low AVP. In the third section, Pearson's correlations tested interrelationships between hormones and behavior. Finally, two hierarchical regression models were computed predicting parents' OT and AVP from touch behavior, synchrony variables, and lag-sequential patterns.

3. Results

3.1. *Differences in OT, AVP, and social behavior between mothers and fathers*

As a first step, we examined whether plasma OT and AVP levels differ between mothers and father. No differences were found in baseline OT and AVP, confirming our previous findings (Atzil et al., 2012; Feldman et al., 2010a, 2011). Levels of OT for mothers were 388.05 (SD=205.95) and for fathers 391.18 (SD=159.72), F (1, 118) =.010, NS. Levels of AVP for mothers were 223.29 (SD=85.93) and for fathers 201.37 (SD=86.37), F (1, 118)=1.855, NS. OT and AVP were each divided into high and low groups based on the median split (OT median=332.8 pM, AVP median=200.2 pM). Consistent with our hypothesis, parents' OT and AVP were inter-related, r=.21, p=.024.

Three MANOVAS examined differences between mothers and fathers in (a) proportions of touch patterns (*affectionate touch*, *stimulatory touch*), (b) synchrony variables (*social gaze synchrony*, *joint attention*,), and (c) lag-sequential patterns (*Infant gaze at parent–parent increase social salience*: *Infant gaze at parent–parent increase object salience*: *Infant gaze at parent–parent affectionate touch*, and *Infant gaze at parent–parent stimulatory touch*).

MANOVA for proportions of touch showed an overall effect for parent gender; Wilks' F (2, 116)=35.24, p<.000, Effect Size (ES)=.37. Mothers provided significantly more affectionate touch than fathers, Univariate F (1, 116)=19.80, p<.000, ES=.145, while fathers exhibited substantially more stimulatory touch, F (1116)=47.78, p<.000, ES=.29.

MANOVA for the synchrony variables showed no effect of parent gender, Wilks' F (2, 116)=1.02, p=.38, NS. Similarly, MANOVA for lag-sequential patterns showed no parent gender effect, Wilks' F (4, 114) =.49, p=.73, NS. These findings suggest that while mothers and fathers provide different types of touch, the sequential organization of their social behavior during play with their infant does not differ.

3.2. *Differences in social behavior between parents of high and low OT and AVP*

Next, similar three MANOVAs examined differences between parents high and low in OT, and, following, the same three MANOVAs tested those high and low in AVP.

Table 1 – Social Behavior in parents with high and low oxytocin.

Social Behavior	High OT		Low OT		F
	Mean	SEM	Mean	SEM	
Affectionate contact	56.82	2.6	42.93	3.07	11.86**
Stimulatory contact	27.88	1.77	28.38	1.52	.05
Gaze synchrony	6.75	.85	5.35	.76	1.51
Joint attention	3.51	.33	4.37	.4	2.72
Increasing social salience	1.14	.16	.73	.11	4.447*
Increasing object salience	.46	.11	.37	.09	.42

* p<.05.
** p<.01.

3.2.1. *High and low oxytocin*

Means and SD for all variables according to parental OT appear in Tables 1 and 2.

Parental touch – MANOVA revealed a significant effect for OT in parental touch; F (2, 116)=5.94, p=.003. ES=.093. Univariate tests showed that parents with high OT provided

Table 2 – Social behavior in parents with high and low vasopressin.

Social Behavior	High AVP		Low AVP		F
	Mean	SEM	Mean	SEM	
Affectionate contact	53.28	3.06	46.41	2.85	2.7
Stimulatory contact	30.5	1.53	25.77	1.7	4.3*
Gaze synchrony	6.02	.83	6.97	.79	.002
Joint attention	3.5	.33	4.37	.4	2.72
Increasing social salience	.96	.16	.92	.11	.03
Increasing object salience	.56	.12	.27	.57	4.45*

Differences between parents' high and low OT levels in means and SEM of social measures in child–parent interaction.
* $p<.05$.

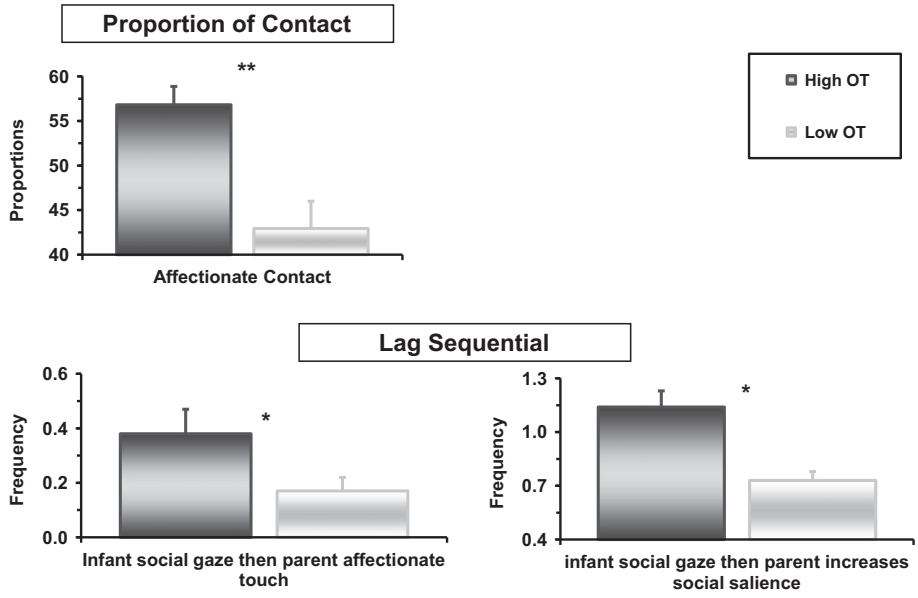

Fig. 1 – Parent–child contact and sequential patterns in parents with high and low oxytocin footer: *$p<.05$, **$p<.01$.

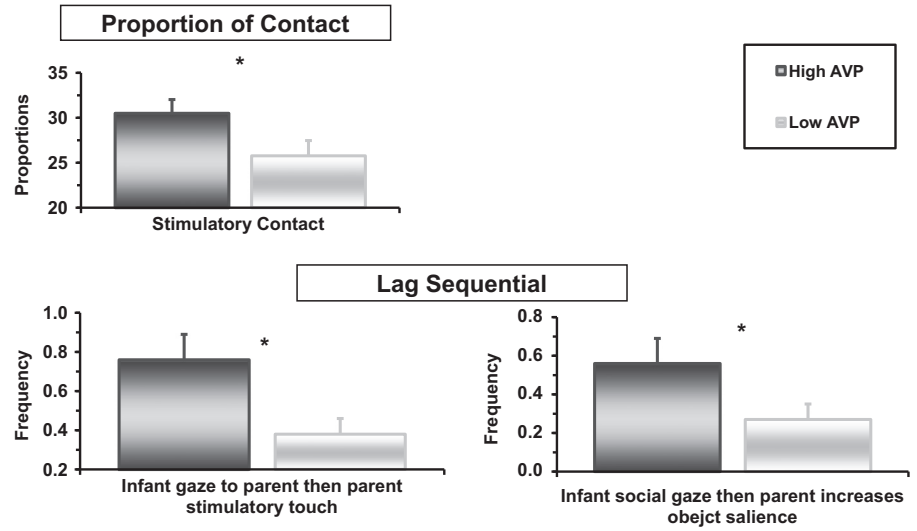

Fig. 2 – Parent–child contact and sequential patterns in parents with high and low oxytocin footer: *$p<.05$.

Table 3 – Correlations of hormones and social behavior.

Social Behavior	OT	AVP	Affectionate contact	Stimulatory contact	Gaze synchrony	Joint attention	Increasing social salience	Increasing object salience
Increasing object salience	.06	.192*	−.094	.001	−.159*	.03	~.15	1
Increasing social salience	.191*	02	.004	−.045	−.008	−.084	1	
Joint attention	−.04	15	−.15**	18*	.03	1		
Gaze synchrony	.11	−.004	.074	.04	1			
Stimulatory contact	−.02	.19*	−.163*	1				
Affectionate contact	.303*	.15	1					
AVP	−.04	1						
OT	1							

* $p<.05$.
** $p=.051$.

substantially more affectionate touch to their infants, F (1116)=11.86, $p=.001$, ES=.092, and no differences emerged in stimulatory touch (Fig. 1).

Synchrony variables – no overall difference was found for OT.

Sequential patterns – MANOVA revealed a significant OT effect for sequential patterns; F (2, 116)=2.685, $p=.042$, ES=.082. Univariate tests showed that interactions of parents with high OT included higher frequencies of the sequence: infant social gaze then parent affectionate touch, F (1116)=4.43, $p=.037$, ES=.037, and infant social gaze then parent increase social salience, F (1,116)= 3.81, $p=.05$, ES=.033 (Fig. 1).

3.2.2. *High and low vasopressin*

Parental touch – MANOVA indicated significant main effect for AVP, F (2, 116)=4.29, $p=.016$. ES=.069. Univariate tests showed that parents with high OT provided more stimulatory touch, F (1116)=4.29, $p=.04$, ES=.035, and no differences were found for affectionate touch (Fig. 2).

Synchrony variables – no overall effects were found for AVP.

Sequential patterns – MANOVA revealed a significant AVP effect for sequential patterns; F (2, 116)=2.372, $p=.05$. ES=.078. Univariate tests showed that parents with high AVP tended to respond to infant social bids with increasing object salience and stimulatory touch. Differences were for: infant social gaze then parent stimulatory touch, F (1,116)=5.73, $p=.018$, ES=.048, and infant social gaze then parent increase object salience, F (1,116)= 3.88, $p=.05$, ES=.033 (Fig. 2).

3.3. *Correlations between OT, AVP, and parental social behavior and synchronous sequential patterns*

Pearson's correlations (Table 3) indicate that parental OT was associated with greater affectionate contact and greater frequency of the sequence *infant social gaze-parent increasing social salience*. Parents' AVP correlated with more stimulatory contact and longer durations of joint attention. Stimulatory contact correlated with joint attention, and gaze synchrony with less parental increasing object salience following infant social gaze.

3.4. *Predicting parental OT and AVP*

Finally, two regression equations were computed predicting parents' OT and AVP from social behavior. Predictors were entered in seven theoretically-determined steps. Parent-gender was entered in the first step to partial out gender affect. Following, the two touch patterns, two synchrony variables, and two lag-sequential patterns were entered (Table 4). Both models were significant explaining 20% and 31% of the variability in OT and AVP respectively.

OT levels were independently predicted by the amount of affectionate contact, and the durations of gaze synchrony. AVP levels were uniquely predicted by the parent's stimulatory contact, the duration of parent-infant joint attention to object, and the parent responding to infant social gaze by increasing object salience.

4. Discussion

This study provides further evidence for the essential role of the pituitary hormones in parenting and for the complex and intricate relationship between the OT and AVP systems and both mothering and fathering. To our knowledge, this is the first study to examine plasma AVP in human mothers and fathers in comparison to plasma OT and parenting behavior. We found that each hormone is associated with both maternal and paternal behavior but in distinct, sometimes overlapping ways. It may thus be concluded that each hormone promotes a cascade of specific sequential behaviors which form the basic elements of parenting. Specifically, our central hypothesis – that hormonal levels would correlate with the ways in which parents structure social interactions with their offspring and that these correlations would differ for OT and AVP – was, in the main, supported by the findings.

Not surprisingly, our behavioral observations showed how affectionate contact was more characteristic of mothers, while fathers showed more stimulatory contact. This is consistent with studies in both rodents and humans (Szyf et al., 2007; Feldman et al., 2010b). It thus appears that paternal bonding and maternal bonding differ in their basic

Table 4 – Predicting parent oxytocin (OT) and vasopressin (AVP).

Social Behavior	Parental OT			Parental AVP		
	Beta	R^2 change	F change	Beta	R^2 change	F change
Parent gender	−.07	.00	.43	.09	.02	1.85
Affectionate contact	.36**	.12	16.39***	.07	.00	.96
Stimulatory contact	.15	.02	2.57	.52***	.21	22.92***
Gaze synchrony	.22*	.05	5.81*	.09	.00	.87
Joint attention	.04	.00	.005	.20*	.04	5.79**
Increasing social salience	.03	.00	.31	.07	.00	1.39
Increasing object salience	.08	.00	.98	.19*	.03	3.41*
R^2 total=	.20, F (7, 110)=3.81, $p<.001$			.31 F (7, 110)=7.13, $p<.001$		

* $p<.05$.
** $p<.001$.
*** $p<.0001$.

behavioral structure. Importantly, irrespective of gender, high levels of OT correlated with affectionate contact, response to infant gaze, and behaviors of high social salience. In contrast, high AVP levels correlated with joint attention to inanimate objects and to behaviors with more object salience. Furthermore, specific behaviors were shown to predict hormonal levels. Affectionate warm contact and duration of gaze synchrony predicted OT levels, emphasizing that the parent's ability to react to their infants synchronously related to OT. Predictors of AVP, on the other hand, were more related to stimulatory contact, durations of joint attention, and the parent responding to infant social gaze by increasing object salience in both mothers and fathers. These findings are supportive of those reported in previous research both in bi-parental rodents (e.g. Woller et al., 2012; Veenema, 2012) and humans (e.g. Feldman et al., 2012; Atzil et al., 2012; Gordon et al., 2010b, 2011; Skuse and Gallagher, 2011). The major novel aspects of this study, however, are the findings that OT and AVP effects are important for both fathers and mothers and to the way they sequentially segment parental behavior to direct infants to the social context or to features of the environment.

Fatherhood in itself can bring about hormonal changes in the father, particularly when fathers become increasingly involved in parenting. In the context of evolving cultural and social values that underscore father involvement in childcare (Lamb, 2010), understanding these processes in the context of the *bio-behavioral synchrony* conceptual model becomes increasingly relevant (Feldman, 2012; Feldman et al., 2012). Our results are consistent with perspectives that suggest a common neuroendocrine pathway in the development of fathering and mothering in nonhuman primate's biparental species and men (Wynne-Edwards, 2001). Whereas in the past, maternal sensitivity has been stressed as vital for infant development, sensitivity of both spouses is becoming recognized as critical for optimal growth and longitudinal studies specify the unique contributions of sensitive mothering and fathering to child social development (Feldman and Masalha, 2010; Feldman et al., 2013). Our study provides a biological justification for stressing both maternal and paternal sensitive responsiveness and show that the link between OT and AVP with the unique constellations of parenting behavior appears in both maternal and paternal play.

Research supports the important role of AVP in parenting. In humans, the lowest levels of maternal sensitivity were found among mothers who had a combination of high levels of early adversity and a variant of AVPR1A gene (Bisceglia et al., 2012). Fathers who had histories of adversity also showed hyper excretion of AVP that was related to differential activation of the amygdala, which in itself has shown to be a marker for parental attunement to the infant's emotional state (Seifritz et al., 2003). Similarly, AVP was found to be a component of prairie vole paternal care (Ross et al., 2009) and in rats, males with a higher density of V1aRs in the lateral septum are more likely to provide paternal behavior. Furthermore, AVP has the capacity to bind not only to AVP receptors but also to the OXTR, indicating that it has the potential to modulate the activity of various receptor subtypes (Kinsley and Amory-Meyer, 2011). Similar co-activation of the OT and AVP systems has recently been shown in our lab, with the administration of OT reliably increasing salivary AVP levels across the first hour after administration (Weisman et al., 2013a). However, apart from an earlier study by our group which showed a correlation between social cognitive circuits in fathers and serum AVP, the current study is the first to show a relationship between AVP and fathering in humans.

Oxytocin has been repeatedly implicated in the expression of human maternal behavior with higher OT associated with sensitive and adaptive maternal care (Feldman et al., 2010; Gordon et al., 2010a, b; Levine et al., 2007), and the current results are consistent with these studies. Our findings extend previous research by showing how OT is associated with some of the more complex elements of human parenting. In a previous study we tested differences between OT and prolactin in fathers and there is an interesting similarity in the relative contribution of OT and AVP to the OT/PRL effects on paternal behavior (Gordon et al., 2010c). Thus both AVP and PRL were associated with a specific aspect of paternal behavior not covered by OT: PRL with father facilitation of the child's exploratory behavior and OT with the father–infant affect Synchrony. In this context, AVP seems to be more associated with the cognitive-stimulatory aspects of the interaction.

It appears that early parent-child relationships take place in the context of a network of bio-behavioral experiences that shape children's affiliative biology and social behavior across

multiple attachments (Feldman et al., 2013). Future research will naturally expand our understanding of this network. It is becoming increasingly evident that complex behaviors are rarely influenced by a single locus of main effect and are subject to the influence of multiple neurohormonal systems and environmental conditions (Petronis, 2010). Possible areas for future research are the dopamine (DA) and serotonergic (5HT) system. Evidence is emerging implicating dopamine-OT interactions in the modulation of neural circuits that influence affiliative behaviors in rats (Shahrokh et al., 2010). In humans, receptor binding sites of OT and of DA tend to coexist in several brain regions that are central for the expression of parental care (Skuse and Gallagher, 2011). There is also considerable evidence for the relations between OT and the serotonin system. Animals exposed to elevated serotonin during early development have reduced OT expression and loss of OT-containing cells in the paraventricular nucleus in adulthood. This reduction is associated with reduced maternal bonding and socially explorative behaviors found in rats (McNamara et al., 2008). As such, a more comprehensive assessment of affiliative hormones within the context of multiple hormonal systems may shed further light on the neuroendocrine foundation of maternal and paternal care.

4.1. *Limitations*

The major limitation of the study is that it is cross sectional and thus cause–effect relationships cannot be inferred. As such, it is unclear whether the hormonal changes result from the behavioral changes or vice versa and prospective follow up studies are required to address this issue. In addition, a single study can only include a limited number of hormones. It is clear that OT and AVP do not act in a vacuum and are only part of multiple hormones and neurotransmitters which act in as a network to support parental care. As such, any linear model must necessarily be limited in its ability to explain complex human behavior such as parenting. Nonetheless, we believe that this study provides information that may lead to further programmatic hypothesis-driven research and ultimately to a better understanding of the issues involved in human bonding and parenting. Such understanding may, in turn, lead to the development of therapies to help young mothers and fathers provide the carefully-synchronous parenting their infant requires for his or her physiological, social, and emotional growth.

5. Experimental procedures

5.1. *Participants*

Participants were 119 parents and their infants, including 71 mothers and 48 fathers (not couples) and their 4–6 month-old infants ($M=167.4$ days, $SD=12.3$). Parents were of middle-class SES, healthy, and with at least 12 years of education. Mothers' age was, $M=28.9$, $SD=5.22$ years, and education, $M=15.17$, $SD=2.47$ years, and 81.3% were breastfeeding. Fathers' age was, $M=29.3$, $SD=4.26$ years and education, $M=15.53$, $SD=2.71$ years. Infants were born at term (birthweight: $M=3319.4$ gr. $SD=452.1$), mainly (96.3%) by vaginal delivery, received an Apgar score of 9.40 ($SD=1.56$), and 55% were firstborns. Infants were healthy since birth, parents were screened for depression and anxiety, and all parents reported sharing childcare responsibilities. The study was approved by the Institutional Review Board and all parents signed an informed consent.

5.2. *Procedure*

Parents and infants arrived at the lab during the early afternoon (1–4 PM) and following an acquainting period plasma samples were collected. Following, parent and child entered an observation room with an infant-seat mounted on a table and were filmed from an adjoined room by two cameras that were integrated into single frame using a split-screen generator. Parents were asked to engage in a fifteen-minute interaction that would include any type of touch they typically use. Parents were then interviewed and completed self-report measures.

5.3. *Hormone collection and analysis*

Blood was drawn from the antecubital-vein of the parents into 9 mL chilled vacutainer tubes containing lithium-heparin that were supplemented with 400 KIU of Trasylol (Bayer, Leverkusen, Germany) per 1 mL blood. Samples were kept ice-chilled for up to 2 h before centrifuged at 4 °C at 1000 g for 15 min. Supernatants were collected and stored at −70 °C until assayed. Parents were asked to refrain from food intake 30-minutes before blood draw. Maternal blood was drawn at least 30 min after nursing and 30 min before nursing. Previous studies (Feldman et al., 2007, 2010b, Gordon et al., 2010a) showed no differences between plasma OT levels in breastfeeding and non-breastfeeding mothers when OT is not measured around breastfeeding. Determinations of hormones were performed using a commercial oxytocin and vasopressin enzyme-linked-immunosorbent-assay (ELISA) kit (Assay Design, Ann Arbor, Michigan) as described in ours and others' research on plasma oxytocin and vasopressin (Carter et al., 2007; Feldman et al., 2007, 2010, 2011; Weisman et al., 2013a). Measurements were performed in duplicate and the concentrations of samples were calculated by MATLAB-7 according to relevant standard curves. The intra-assay and inter-assay coefficients for oxytocin were less than 7% and 15.8%, respectively. The intra-assay and inter-assay coefficients for Vasopressin were less than 3.9% and 16.9%, respectively.

5.4. *Coding of parent-infant interaction*

Interactions were micro-coded on a computerized system in. 01-second frame using our well-validated micro-coding scheme (Atzil et al., 2012; Feldman and Eidelman, 2004, 2007; Feldman et al., 2011; Feldman et al., 2010b), which has shown associations with multiple parental hormones and patterns of brain activations. Four categories of parent and infant's behavior were: Gaze, Affect, Vocalization, and Touch, each containing a set of mutually-exclusive codes. Codes included: *Gaze*: social gaze to partner, gaze to object (parent or child looking at object other than the focus of the partner's gaze), joint attention (parent and child looking at same object), gaze aversion. *Affect*: parent – positive, neutral,

negative-withdrawn, negative-angry; infant- positive neutral, fuss-cry. *Vocalizations*: parent – "motherese" high-pitched vocalizations, adult speech, none; infant – positive vocalizations, fuss-cry, none. *Touch:* parent: affectionate, cradle, functional, stimulatory, proprioceptive, parent stands child on his/her knees and moves infant around, touch with object, and none; infant: intentional, accidental, none. Inter-rater reliability was computed for 15 interactions and reliability *kappa*s averaged .84 (range=.76–.93).

The following variables were used in the current study as sum proportions:

Affectionate contact – was the sum proportions of parent affectionate touch and cradle. *Stimulatory contact* – was the sum proportions of stimulatory, proprioceptive, child on knees, and touch-with-object.

The following "synchrony" variables were used as conditional probabilities that index the co-occurrence of social behavior bin parent and infant and were computed as mean durations.

Joint attention – parent and child are attending to the same object. *Gaze synchrony* – parent and child are simultaneously engaged in social gaze (parent gaze at infant while infant gaze at parent).

The following variables were computed by lag-sequential analysis and index the frequencies in which a specific parent behavior follows the infant's social gaze to the parent as the behavior that signals infant initiation of social bid (i.e., infant gaze to parent then parent in behavior Y). *Infant gaze at parent–parent increase social salience* – number of times parent responds by social gaze, "motherese" vocalization, or positive affect to infant social gaze. *Infant gaze at parent–parent increase object salience*- number of times parent responds by gaze at object or joint attention to infant social gaze. *Infant gaze at parent–parent affectionate touch* – number of times parent responds by affectionate touch to infant social gaze. *Infant social gaze – parent stimulatory touch* – number of times parents responds by stimulatory touch to infant social gaze.

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Research Report

Oxytocin and vasopressin systems in genetic syndromes and neurodevelopmental disorders

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ABSTRACT

Oxytocin (OT) and arginine vasopressin (AVP) are two small, related neuropeptide hormones found in many mammalian species, including humans. Dysregulation of these neuropeptides have been associated with changes in behavior, especially social interactions. We review how the OT and AVP systems have been investigated in Autism Spectrum Disorder (ASD), Prader–Willi Syndrome (PWS), Williams Syndrome (WS) and Fragile X syndrome (FXS). All of these neurodevelopmental disorders (NDD) are marked by social deficits. While PWS, WS and FXS have identified genetic mutations, ASD stems from multiple genes with complex interactions. Animal models of NDD are invaluable for studying the role and relatedness of OT and AVP in the developing brain. We present data from a FXS mouse model affecting the fragile X mental retardation 1 (Fmr1) gene, resulting in decreased OT and AVP staining cells in some brain regions. Reviewing the research about OT and AVP in these NDD suggests that altered OT pathways may be downstream from different etiological factors and perturbations in development. This has implications for ongoing studies of the therapeutic application of OT in NDD.

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1. Introduction to OT and AVP neuropeptide hormones

Oxytocin (OT) and arginine vasopressin (AVP) are small mammalian neuropeptides nine amino acids in length, which differ by only two amino acids. OT is produced primarily in hypothalamic nuclei, including the supraoptic (SON) and paraventricular nuclei (PVN). AVP is also synthesized in the PVN and SON. In males, additional brain regions including the amygdala and the bed nucleus of the stria terminalis (BNST) also produce AVP. OT and AVP of hypothalamic origins are transported from the SON and PVN to the mammalian posterior pituitary by neurosecretion where they are released into the blood stream and act as hormones on target tissues. In addition, both OT and AVP are capable of moving throughout the central nervous system via diffusion in the cerebral spinal fluid (CSF; Neumann and Landgraf, 2012). The peptide-producing OT gene (OXT) is homologous with its evolutionarily related gene, vasopressin (AVP). The human OXT and AVP genes linked on chromosome 20p13 are separated by only 12 kilobases of DNA, and are positioned in opposite transcriptional orientations. Both

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have specific receptors, but their close evolutionary relationship permits cross-talk and interacting molecular systems. These neuropeptide hormones have receptors in various brain regions and throughout the body, including areas that are important for regulating social behavior and reactivity to stressors.

In both, the human and mouse genomes OT and AVP neuropeptide genes are located adjacently on the same chromosome. Often the blood levels of both hormones are highly correlated (Dai et al., 2012), suggesting a coordinated release. The receptors for both neuropeptides are localized in specific areas of the nervous system, especially in the brainstem. These brain regions influence social and adaptive behaviors, as well as regulate the hypothalamic–pituitary–adrenal axis (HPA) and autonomic nervous systems (Lim et al., 2005, 2004). Because OT and AVP are closely related and have the ability to act on the other's receptors, it has been proposed that they evolved to interact and sometimes have opposing physiological effects. For example, both hormones have been shown to affect the control of the autonomic nervous system, with OT having primarily parasympathetic actions and AVP serving as a central and peripheral regulatory component of the sympathetic nervous system and HPA axis (Kenkel et al., 2012; Sawchenko and Swanson, 1985). However, at high levels the neuropeptides can be partial agonists for their homologous receptors, which may result in AVP and OT pathways interacting (Chini et al., 1996).

Of particular importance in neurodevelopmental disorders (NDD) is the fact that OT and AVP can modulate social and repetitive behavior and other manifestations of anxiety and state regulation (Carter, 2007). Animal research has generally associated OT release or exposure with positive sociality, reduced anxiety, and lower levels of reactivity to stressors (Carter, 1998; Neumann and Landgraf, 2012). AVP influences anxiety, the regulation of HPA and stress responses. In general, central AVP is described as anxiogenic (Landgraf and Wigger, 2003). However, there is also evidence in rats that the effects of AVP are brain region specific and dose-dependent. For example, AVP may be anxiolytic if given in low doses (Appenrodt et al., 1998).

Mouse knockout (KO) studies of the OT receptor (OXTR) or OT regulators have found decreased social memory or recognition (Ferguson et al., 2000; Jin et al., 2007; Takayanagi et al., 2005). *Oxtr* KO mice also displayed decreased cognitive flexibility and a resistance to change of a learned pattern of behavior that is comparable to restricted/repetitive interests (Sala et al., 2011). Both social deficits and behavioral rigidity were ameliorated by OT administration (Sala et al., 2011). The finding that OT continues to have effects in *Oxtr* KO mice supports the hypothesis that OT can influence behavior through other receptors, especially the AVP receptors (e.g. AVPR1A and/or AVPR1B). Given the influence of these neuropeptides on brain regions affecting both social and repetitive behaviors, modulation of OT and AVP pathways are being explored as treatment targets for disorders, including Fragile X syndrome (FXS) and Autism Spectrum Disorders (ASD).

This and other research has set the stage for a series of recent studies on the effects of exogenous OT treatments in humans (Ebstein et al., 2012; Macdonald and Feifel, 2013). For example, intranasal OT (IN-OT) administration in healthy human males increased prosocial behaviors and trust, especially as measured by experimental economic games (Baumgartner et al., 2008; Kirsch, 2005; Kosfeld et al., 2005). IN-OT may also increase gaze towards the eye region of the face (Guastella et al., 2008), and has been associated with improved facial memory (Rimmele et al., 2009), enhanced salience of social cues (Shamay-Tsoory et al., 2009), and improved performance on the reading the mind in the eyes (RMET) task (Domes et al., 2007).

As previously reviewed, OT has been found to have anxiolytic effects improving social interactions, reducing fear, and improving the ability of healthy volunteers to interpret subtle social cues (Macdonald and Macdonald, 2010). In addition, OT dysfunction has been associated with neuropsychiatric disorders such as autism in human studies (Domes et al., 2007; Ishak et al., 2011; Winslow and Insel, 2004). By 2010 there were over 20 OT administration studies, which included ASD, schizophrenia, postpartum depression, post-traumatic stress disorder (PTSD), and irritable bowel syndrome (Macdonald and Macdonald, 2010). There have been a growing number of studies investigating the ability of IN-OT to treat a range of neurobehavioral disorders due to the associations between IN-OT and alterations in social decision-making, processing of social stimuli, certain social behaviors such as eye contact, and social memory.

2. Autism spectrum disorders

In 1943, Leo Kanner described a male patient with repetitive behaviors—"stereotyped movements [and]…repetitions carried out in exactly the same way in which they had been performed originally" and difficulties with social communication—"he always seemed to be parroting what he had heard said to him at one time or another…Words to him had a specifically literal, inflexible meaning. He seemed unable to generalize, to transfer an expression to another similar object or situation" (Kanner, 1943). This group of symptoms, later extended and described in detail, is currently known as ASD. As described in the DSM-5 (American Psychiatric Association, 2013), ASD is characterized by persistent deficits in social communication and social interaction across multiple contexts, and the diagnosis requires the presence of restricted, repetitive patterns of behaviors, interests, or activities. ASD is a heritable (Bailey et al., 1995) and highly heterogeneous disorder, caused by familial genetic risks in addition to possible gene-environment interactions during early development (Chaste and Leboyer, 2012). Individuals with ASD often suffer with anxiety disorders, irritability or aggression, and come to clinical attention due to their difficulties at home and school related to their communication deficits and restricted interests. Unfortunately there are currently no approved medications to treat the social deficits or restricted, repetitive behaviors (RRB) that are the core symptoms of ASD. There is some evidence in animal and human studies that OT improves the core symptoms of ASD.

2.1. Intranasal and intravenous OT studies in ASD

Currently medications for ASD concentrate on alleviating certain symptoms, but not the core features of ASD. Risperidone and aripiprazole may be used for irritability, whereas guanfacine and clonidine are used off label for aggression, and selective serotonin reuptake inhibitors (SSRI; i.e. escitalopram, fluoxetine, and sertraline) are used to treat anxiety (Jaselskis et al., 1992; McCracken et al., 2002; Owley et al., 2010). Recently, OT has been investigated as a target the treatment for ASD core symptoms, social deficits and RRB. Defined by DSM-5, restricted, repetitive patterns of behavior include stereotyped or repetitive motor movements, insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior. Highly restricted, fixated interests that are abnormal in intensity or focus, and hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment are also RRB.

Several studies, using intravenous OT or IN-OT, in patients with ASD have been conducted (Table 1). It has been shown that nonapeptides, like AVP, can be measured in CSF after intranasal administration (Born et al., 2002). Ease of giving intranasal drugs makes it preferred for most ASD studies, although more research needs to be conducted on how IN-OT reaches the brain and how it regulates receptors and neural pathways with different or chronic dosing strategies. Several studies have measured OT responses to single dose challenges in ASD (Andari et al., 2010; Guastella et al., 2010), while few have examined longer term treatment effects (Anagnostou et al., 2012). With varying administration and duration study protocols, studies have often focused on symptom subdomains or defined social tasks including: RRB (Hollander et al., 2003), emotion recognition (Dadds et al., in press; Guastella et al., 2010), affective speech comprehension (Hollander et al., 2007), and facial recognition (Domes et al., 2013).

Single dose studies, or challenges, have been utilized to study the acute and immediate effects of OT. An initial study in ASD examined the effects of a four-hour continuous dose of intravenous OT (Hollander et al., 2003). After one hour of infusion there was a decrease in RRB (repeating and touching). After four hours, 13 patients (86.7%) versus six control subjects (40%) had decreases in RRB. This study demonstrated that administration of OT led to a decrease in a core ASD symptom, RRB. More recently, a double-blind, randomized, placebo controlled study of IN-OT in 16 males with ASD (ages 12–19 years old) showed that a single IN-OT dose could improve the ability to recognize emotion, particularly in easy queries (Guastella et al., 2010). It is unclear whether emotion recognition performance goes back to baseline or pre-OT exposure after a single dose or if there are long-term learning effects.

Andari et al. (2010) also performed a single dose IN-OT study in 13 individuals with ASD and in age-matched controls to study the effect on social deficits. They researched the effects of IN-OT on trust and preference using a social ball tossing game (for greater detail of this task please see supplementary section of Andari et al., 2010). This group also assessed the visual scanning of faces under the influence of IN-OT. They found that patients given IN-OT had a significant preference for the "good player" (the computer player who tossed the ball back to the individual) that was similar to the control subjects also performing the task. This preference was further supported by the patients' reporting of trust, towards the "good player" after OT administration. Andari and colleagues also found that after IN-OT, patients increased eye gazing time on the socially informative region of the face. While single dose studies are valuable, evaluating long term effects of OT are essential to determine if OT has a therapeutic potential in ASD (Macdonald and Feifel, 2013).

Recently a five-day OT administration study was conducted during parent–child interaction training (Dadds et al., in press). Individuals with high functioning ASD received 12 or 24 IU (depending on the weight of the patient) IN placebo or IN-OT. The OT or placebo was administered once daily and RRB, emotion recognition, social interaction skills, and general behavioral adjustment were assessed. While improvements over time were detected in both OT and placebo, there were no differences observed between the two groups. Several proposed possible explanations for these null findings were: (1) emotion recognition was measured pre-post changes following multiple exposures versus while the patient was under the influence; (2) lower-order RRB respond to OT (Hollander et al., 2003), while higher-order RRB do not (Anagnostou et al., 2012); (3) increased eye gaze frequency is usually measured with artificial or computerized faces, while they had "real-life" interactions; (4) the OT receptor system disruptions in some patients with ASD may respond differently than in other ASD patients; and (5) differences between the studies regarding age and diagnostic characteristics of the sample. Studies pairing OT with a therapeutic activity or social training are highly needed, although design and outcome measures across studies will need to be similar in order to better interpret and compare results in ASD participants.

Investigating adults with ASD, Anagnostou et al. (2012) studied the safety and therapeutic effects of IN-OT with respect to two core symptom domains: social cognition and functioning, and RRB. They performed a randomized, double-blind, placebo-controlled parallel trial of IN-OT versus placebo. This was the first study to employ a treatment trial of daily administration of IN-OT in ASD. Overall, the IN-OT was well tolerated when given daily and no serious adverse effects were reported. This pilot study suggested therapeutic potential with daily administration of IN-OT in this population of adults with ASD. This six-week study noted improvements in social cognition, quality of life, RRB, and some measures of emotional well-being with IN-OT, in essence, improvement in the core domains of ASD. It may be important to note that reports of individual differences in the response to IN-OT are increasingly observed, although sample sizes in studies will need to be larger to explore individual response variation.

2.2. OT/AVP plasma levels in ASD

The inability to directly access the brain's oxytocinergic pathways has constrained human research. Therefore, peripheral OT levels have been used as proxies for OT levels in the brain. A widely used measurement is plasma OT, although urine and salivary OT levels have also been explored in some studies. A range of studies have observed

Table 1 – A summary of OT human trials in ASD.

Article	Design	Sample	Dose	Assessments, measurments and/or tasks	Outcome
Hollander et al. (2003)	Randomized double-blind, placebo-controlled crossover design	15 Adults with Asperger Syndrome or Autism (14 males) Mean Age=32.9 years (range 19.4–55.6 years)	Initial vial of 10 μ/mL combined with a 1L bag of normal saline given at a scheduled increased rate of infusion (4 continuous hours)	Repetitive Behaviors: Evaluated using an in-lab method that assessed six restricted, repetitive behaviors (RRB) at baseline, 60, 120, 180, and 240 minutes	Observed a significant reduction in repetitive behaviors over time versus placebo session; 86.7% of the participants during the OT session had reduction in RRB, while 40% of the subjects had a reduction in RRB during the placebo session (non-significant)
Andari et al. (2010)	Randomized double-blind, placebo-controlled within-subjects design	13 Adults with Asperger Syndrome or High Functioning Autism (11 males)	24 IU IN-OT	Cyberball Game (social interaction task)	Adults with Asperger Syndrome or High Functioning Autism exhibited stronger interactions in a simulated ball game (similar to healthy adults), and gazed at eyes longer on a face task with IN-OT
		Mean Age=26 years (range 17–39 years)		Free viewing of pictures of faces	
		13 Age-matched, healthy adults tested in a single visit (11 men)			
		Mean Age=26 years (range 18–40 years)			
Guastella et al. (2010)	Randomized double-blind, placebo-controlled crossover design	16 Young males with Asperger Syndrome or Autism	18 IU (ages 12–15 years) or 24 IU (ages 16–19 years) IN-OT	Reading the Mind in the Eyes Task (RMET)	Significant improvement in RMET compared to placebo Significant improvement in identifying emotions of easier items on the test
		Mean Age=14.88 years (SD=2.42 years)			
Anagnostou et al. (2012)	Randomized double-blind, placebo-controlled, parallel design trial of IN-OT vs. placebo	19 Adults with ASD (16 males)	24 IU IN-OT	Social Function/ Cognition: Clinical Global Impression, DANVA (primary measures); RMET, Social Responsiveness Scale (secondary measures)	Primary Outcome Measures: A non-significant decrease in lower-order RRB; 30% of the IN-OT group rated as improved by CGI, while 11% of the placebo participants improved (non-significant)
		Mean Age=33.20 years (SD=13.3 years)		Repetitive Behaviors: RBS-R (primary measure); Yale Brown Obsessive	Secondary Outcome Measures: A significant improvement in

Table 1 (*continued*)

Article	Design	Sample	Dose	Assessments, measurments and/or tasks	Outcome
				Compulsive Scale (secondary measure)	social cognition as measured by RMET and in quality of life as measured by WHOQOL
				Quality of Life: WHO Quality of Life Questionnaire (WHOQOL; secondary measure)	
Dadds et al. (in press)	Randomized double-blind, control trial over five days	38 Young males with ASD and a high level of commonly comorbid disorders	12 IU (<40 kg) or 24 IU (>40 kg) IN-OT	Social Interaction: Social Skills rating Scale, Video micro-coding and global coding of observations	No improvement in social interaction, emotion recognition, or general behavioral adjustment
	During the five days, the participants and their families underwent parent-child interaction training, which included Mindreading program and video feedback (based on Video Interactive Guidance)	OT Mean Age=11.79 years (SD=2.82 years) Placebo Mean Age=10.74 years (SD=2.38 years)		Repetitive Behaviors: Social Reciprocity Scale, Micro-analysis of observation videos Emotion Recognition: UNSW Facial Emotion Task Generalized Effects/ Diagnostic Status: OSU, Childhood Autism Ratings Scale, DISCAP-ASD	

associations between peripheral OT/AVP levels and social stimuli (Kenkel et al., 2012; Schneiderman et al., 2012; Schradin et al., 2013; Seltzer et al., 2010; Wismer Fries et al., 2005; Zhong et al., 2012).

As early as 1996, it was suggested by a number of researchers, including Waterhouse et al. that dysfunction in the OT and AVP systems might contribute to the atypical social behaviors in ASD. Two years later by studying the OT plasma levels from 29 ASD and 30 age-matched typical control children, Modahl et al. (1998) reported low levels of plasma OT in the children with ASD. In another study, which utilized Wing's topology, children were classified as “aloof”, “active but odd” and “overly formal” (Leekam et al., 1997). The lowest OT levels were found in the "aloof" subgroup. This suggested that the most severe socially-aloof symptoms were associated with more OT dysfunction.

Building on these results with the same study sample, Green et al. (2001) conducted another OT study and examined the forms of the OT peptide found in affected and unaffected children. Their results showed that there was an increase in OT-X, the precursor for OT, as well as an increase in the ratio of OT-X/OT associated with the reduction in OT observed in the patients with ASD. During the normal production of OT, the extended form (OT-X) is cleaved by enzymatic activity to yield the active peptide OT. There was also a positive correlation between OT-X and checklist items associated with ASD including stereotypies; OT-X correlated negatively with an item describing abnormalities in comfort giving within the ASD group. Consequently, changes in OT processing, specifically a failure to completely process the prohormone OT-X, might lead to a deficiency in OT, thus exacerbating some of the symptoms of ASD, such as features of social deficits. To our knowledge this study has not been replicated. Furthermore, other studies often in older patients have failed to report an OT deficiency (Jansen et al., 2006; Miller et al., 2013). Future studies may benefit from the measurement of OT-X in addition to plasma OT given the diverse methods employed for assaying OT, and the finding that the failure to process this prohormone can lead to a deficiency of OT.

Recently, connections between peripheral OT/AVP levels and ASD were investigated (Miller et al., 2013). Miller et al. measured OT and AVP plasma levels in 75 boys and girls (40 high-functioning ASD, 35 typically developing) aged 8–18 years. Miller et al. not only reported associations between the plasma levels and ASD behaviors, but sex differences as well. Higher levels of OT were observed in all

girls, and all boys had significantly higher levels of AVP. The higher OT levels were associated with greater anxiety in all girls, and with better pragmatic language in all subjects. Gender differences were also noted within the ASD sample. A positive association between AVP levels and RRB was reported in ASD girls, although a non-significant association with RRB was found in boys with ASD. Because of the limited number of girls affected by ASD, few other studies have sampled a large enough sample size of girls to investigate gender differences in OT plasma levels or response to exogenous administration.

Some studies have examined OT levels in addition to other hormones and blood biomarkers. In a study of adults with ASD, basal OT levels and heart rate were elevated in the ASD group compared to healthy controls. These adults with ASD showed normal cortisol responses to a public speaking task, but no change in norepinephrine, epinephrine, OT or AVP (Jansen et al., 2006). Recently, Hammock et al. (2012) analyzed correlations between the biomarkers of plasma OT and whole-blood serotonin (5-HT) levels in children and adolescents diagnosed with ASD and not on medications. Animal studies have shown that OT and 5-HT influence each other's release (Bagdy and Kalogeras, 1993; Jorgensen et al., 2003; Yoshida et al., 2009) and there have been many reports of hyperserotonemia within a subgroup of individuals with ASD (Abramson et al., 1989; Chugani et al., 1999; Kuperman et al., 1985; Leboyer et al., 1999; Leventhal et al., 1990; Schain and Freedman, 1961). OT and 5-HT were negatively correlated with each other in the Hammock et al. (2012) study. Whole blood 5-HT was found to be negatively correlated with age, having lower levels in adolescence than in childhood. This OT/5-HT relationship was especially prominent in children younger than 11 years old. Age may be an important covariate, because some studies do not find OT deficiencies or have reported higher than expected OT levels in their ASD samples (Jansen et al., 2006; Miller et al., 2013). OT like 5-HT may change after puberty according to recent data (Hammock et al., 2012).

Interest in parental bonding has led to the study of OT levels in parents of typical children, and more recently parents of children with ASD. An association between peripheral OT and parental care, both maternal and paternal, was reported by Feldman et al. (2012). When comparing parents and non-parents, parents were found to have higher levels of OT. Higher plasma OT levels were also associated with longer durations of gaze synchrony and reporting of greater parental care during the parent's childhood, while lower plasma OT corresponded to less parental touch. Subsequently, Xu et al. (2013) published a study comparing the OT and AVP plasma levels of mothers with and without ASD children in a Han population. They found that the mothers of ASD children had significantly lower plasma OT/AVP compared to the control mothers, as well as, a significant correlation between the plasma levels of the neuropeptides and the child's autistic behavior scores.

Over the last few years studies measuring peripheral OT have increased. As discussed in McCullough et al. (2013) and Szeto et al. (2011), the methodologies can lead to vastly different results (increased values, decreased values or values differing by an order of magnitude). For example, Modahl et al. (1998) performed plasma extractions and then radioimmunoassays (RIA) whereas Miller et al. (2013) utilized an enzyme immunoassay (EIA) with different plasma preparation methods. Additionally, there is also specific lab generated RIA versus commercial EIA and RIA kits. When manufacturer instructions are followed, values obtained have a similar order of magnitude, but it has been noted that some of these kits may also be detecting closely related metabolites. Note that studies often prepared samples differently with varying plasma processing/extraction methods and use of different assay techniques. Future research will need to determine if differences observed in the resultant OT levels of ASD studies reflect differences in the study populations (i.e. age) and/or the methods for assaying OT. ASD is a very heterogeneous disorder and OT level differences may be specific to clinical and etiological subgroups within the broader ASD population. In addition, there is variability of OT plasma levels across typical and healthy populations. The inherent U-shaped distribution (Zhong et al., 2012) observed in normative populations may also add to variability seen in OT measurements in ASD studies.

2.3. *OT and AVP animal and genetic studies in ASD*

The search for genes and biological risk factors contributing to ASD and its core symptoms has resulted in a range of human and animal model studies. Recently, several researchers have examined how the OT system is altered in various animal model or influences social and repetitive behaviors. For example, the BTBR T+tf/J (BTBR) mice have low social interactions, decreased vocalization in social settings and increased levels of repetitive self-grooming, behavioral phenotypes similar to the core symptoms of ASD. Comparing BTBR to the standard inbred highly sociable mouse, C57BL/6J (B6), Silverman et al. (2010) found elevated OT in the PVN, plasma corticosterone (in the trunk), and glucocorticoid receptor (GR) mRNA in CA of the hippocampus in the BTBR. Measurements of the other neurochemicals (CRF in PVN, GR mRNA in CA2 and PVN) showed no differences between the strains.

Another model, the BALB/cJ, has low sociability across development (Brodkin, 2007). A substrain of the BALB/cJ, the BALB/cByJ mouse, was also characterized as a good ASD model (Brodkin, 2007; Moy et al., 2007). These mice displayed low sociability with intact olfaction, locomotor activity and relatively high levels of anxiety. Similarly, the C58/J mouse is another ASD mouse model described in 2010 by Ryan et al. (2010). These mice show low sociability and deficits in social communication. Most striking, however, is their abnormal RRB including increased rates of pivoting, back flipping, upright scrabbling and “jack-hammer” jumping. All the traits are found in both the males and females of the C58/J strain. Recently, the reactions of the BALB/cByJ and C58/J strains to OT administration were compared (Teng et al., 2013).

Teng et al. (2013) did not only note the different reactions to OT administration between BALB/cByJ and C58/J, they also studied whether acute versus subchronic administration had differing outcomes (see paper for drug and experimental timeline). Both strains were administered OT peripherally via intraperitoneal administration. Acute administration in

BALB/cByJ showed no change in sociability, and RRB were not assessed in this timeline. However, in the subchronic regimen BALB/cByJ mice displayed a significant increase in social behaviors. Subchronic OT administration in the C58/J model also induced prosocial effects. In male mice these effects appeared two weeks post treatment, but the prosocial effects were evident in female mice sooner. Regarding RRB, Teng et al. observed a decrease in repetitive behaviors with increased self-grooming after an acute single dose of OT, in the C58/J mice. Most notably these studies have provided insight into how the genetic heterogeneity observed in humans may account for the wide variety and degree of behaviors seen in ASD. Additionally, the Teng et al. study highlighted how treatments can be dependent on both genotype and dose regimen. It is striking that all three mouse models of ASD have alterations in the OT system or respond to OT administration. This suggests that OT may be affected downstream in strains of mice that have different etiological factors influencing social and repetitive behaviors.

As the animal models have shown, the genetic heterogeneity of individuals with ASD could also account for the complexity of the disorder's genetic etiology. In a recent review (Ebstein et al., 2009), genetic polymorphisms of receptor and pathway regulators of OT and AVP, such as AVPR1a, OXTR, neurophysin I and II, and CD38 were discussed. In this review, Ebstein and colleagues presented preliminary data regarding their findings about CD38, a transmembrane glycoprotein involved in OT secretion and associated with OT plasma levels. The group genotyped 12 tag single nucleotide polymorphisms (SNPs) across CD38 in 170 ASD trios. IQ and social skills via Vineland Adaptive Behavior Scales (VABS) were assessed in the sample. They found a significant association between CD38 SNPs and categorical ASD measures, assessed by the Autism Diagnostic Interview – Revised (ADI-R; Lord et al., 1994) and Autism Diagnostic Observation Schedule – Generic (ADOS-G; Lord et al., 2000). Significance was also observed between VABS scores and four CD38 SNPs, haplotypes and VABS, and CD38 mRNA levels and VABS. Two studies in 2010 further supported a role for CD38 in ASD. Lerer and colleagues (2010) noted a reduced expression of *CD38* in the lymphoblastoid cells of patients with ASD as compared to "unaffected" parents. Then Munesue et al. (2010), observed a CD38 SNP in association with high functioning ASD in some populations. In 2012, several CD38 studies were completed that looked at the association of CD38 and ASD. In particular, Sauer et al. (2012) researched the common CD38 variant, rs3796863, in healthy young men. This SNP stood out in the ASD association studies performed by Lerer et al. (2010) and Munesue et al. (2010). Data were attained in a double-blind placebo-controlled crossover design using IN-OT. The subjects performed two tasks following administration of OT or placebo: (1) a face matching task, and (2) a gaze processing task. They found that the men with the ASD risk allele had significantly slower reaction times (RT) during the face matching task and that it was specific to social versus non-social stimuli. IN-OT reduced RT in the risk group. Gaze processing did not yield any significant results. Functional MRI data also were attained as the subjects performed the tasks. Sauer et al. (2012) hypothesized decreased activity in the amygdala and fusiform brain regions of the risk allele group given the results of previous studies (Jemel et al., 2006; Schultz, 2005). Unexpectedly, they saw increased activation in the fusiform brain regions. This led them to conclude that while more research needs to be done to confirm their findings, the link between CD38, the processing of social information and ASD was further solidified.

Other researchers have looked directly at the OXTR gene, to find possible genetic links between OT and ASD. Wu et al. (2005) genotyped four SNPs across OXTR in 195 Chinese Han ASD trios. With Family Based Association Testing (FBAT), they revealed significant associations between ASD and two OXTR SNPs (rs2254298, rs53576). When the markers were combined to create haplotypes, significant associations were found for all markers and especially in haplotypes containing rs53576. Following up the Wu et al. study, Jacob et al. (2007) researched rs53576 and rs2254298 in a Caucasian sample with strictly defined autism. They genotyped the OXTR SNPs in 57 autism trios. In this sample a significant association was observed between diagnosis and rs2254298. While the G allele was more frequent than the A allele, of note was the overtransmission of the G allele to the autistic Caucasian probands versus overtransmission of the A allele in the Chinese Han sample. Additional studies by Yrigollen et al. (2008) and Campbell et al. (2011) continued to build an association between the OT system and ASD. Yrigollen and colleagues hypothesized that genes associated with affiliative, social, and/or bonding behaviors would also be associated with ASD and several of its symptoms. Therefore, they studied 177 ASD probands from 151 families and they found the statistical strength was in the OXTR results. Different OXTR SNPs were significantly associated with stereotyped behaviors, communication skills, the multivariate ADI phenotype and multi-measurement variable overall diagnosis. Also, there was a significant SNP in the OXT/AVP region associated with stereotyped behaviors. In 2011, Campbell and colleagues, utilizing a repository sample of 2333 individuals with ASD in 1238 pedigrees, analyzed 25 markers across OXTR and detected associations. Although these SNPs had previously been associated with ASD diagnosis in studies, they also looked at associations with subphenotype measurements of social impairments in ASD and found associations with their selected three SNPs and ADOS, ADI-R and SRS measurement. While the results of the studies indicate a need for further research, these genetic studies have laid the foundation linking OT, social tasks, and more broadly ASD.

3. Prader–Willi syndrome and OT

Prader–Willi syndrome (PWS) is a complex disorder with multisystem effects and a distinct behavioral phenotype. It occurs in approximately 1/10,000–1/30,000 births, and is initially characterized by severe infantile hypotonia and difficulty feeding, although later in infancy and into adolescence individuals with PWS often eat excessively and develop morbid obesity. Other characteristics of PWS include hypogonadism, short stature, small hands and feet and strabismus. The cognitive phenotype is marked by delayed motor and language development, and behavioral difficulties including compulsive behavior, stubbornness and temper tantrums (Bittel et al., 2007b; Cassidy et al., 2011). The many

behavioral and psychiatric manifestations of PWS are evident in early childhood, and are characterized by hyperactivity, impulsivity, temper tantrums, emotional lability, anxiety and repetitive behavior (Borghgraef et al., 1990; Gross-Tsur et al., 2001; Whitman and Accardo, 1987). Often this phenotype is suggestive of ASD as well as attention deficit hyperactivity disorder (ADHD; Cassidy et al., 2012). Face processing is also altered in individuals with PWS, as they have difficulty reading facial expressions (Whittington and Holland, 2011).

The cause of PWS is the lack of expression of specific paternal genes located on chromosome 15q11.2-q13. Many of the genes expressed in this region come from the father, as those from the mother are normally inactivated. Consequently, either a lack of expression or absence of the paternal copy of the genes in this region leads to no expression (Saitoh et al., 1997). This may occur through microdeletions in the paternal chromosome, no copy of the paternal chromosome paired with two copies of the maternal chromosome—uniparental disomy (UPD), or imprinting defects due to epigenetic causes (Cassidy et al., 2012). The genes expressed in this region have been studied at length to develop models of PWS and to delineate their roles in the different aspects of the PWS phenotype. Such studies are complicated by differences in the behavioral phenotype between individuals with deletions and those with UPD, as those with UPD have a less severe phenotype (Bittel et al., 2007a) and higher verbal IQ scores (Dimitropoulos et al., 2000).

While the deletion of no one individual gene has been found to cause PWS, research has shown that the lack of expression of multiple genes may be central to the syndrome's expression. Specifically, five polypeptide coding genes, namely *MKRN3*, *MAGEL2*, *MAGED1*, *NECDIN* and *SNURF-SNRPRN*, have been shown to be centrally involved in PWS. Animal models lacking one of these genes have been developed for *Magel2* (Boccaccio et al., 1999), *Maged1* (Dombret et al., 2012), *Necdin* (Lavi-Itzkovitz et al., 2012; Muscatelli et al., 2000) and *Snurf* (Tsai et al., 1999), although none of these individual gene disruption models completely recapitulates the PWS phenotype.

Another line of approach to elucidate the physiological underpinnings of PWS has been to examine the OT system in individuals with PWS as well as in animal models. There is a deficit of OT producing neurons in the PVN of persons with PWS (Swaab et al., 1995), as well as lower levels of OT in CSF (Martin et al., 1998). IN-OT administration increases trust in others and decreases disruptive behavior in individuals with PWS (Tauber et al., 2011). In addition, administration of OT has also been shown to rescue behavior in a *Maged1* deletion model of PWS in which there is a decrease in hypothalamic OT (Dombret et al., 2012). Although rescue was not attempted in the *Necdin* model, this mutant also shows a reduction in OT-producing neurons in the hypothalamus (Muscatelli et al., 2000). Consequently, there appears to be disruption of the OT system in individuals with PWS, which is recapitulated in different animal models. However, the exact mechanism of OT dysregulation is unclear.

4. Williams syndrome and OT

Williams syndrome (WS) was first described over 50 years ago (Williams et al., 1961). The first reported cases were focused on infants with hypercalcemia, developmental delays, cardiac malformations and dysmorphic facial features (Morris, 1993). However, better characterization of this syndrome has elucidated a distinct behavioral phenotype marked by an increased social drive paired with social fearlessness, poor judgment, difficulty forming peer relationships and high anxiety levels (Jarvinen et al., 2013). The cause of this disorder has been determined to be a deletion of 25–30 genes in the q11.23 region of either maternal or paternal chromosome 7 that spans approximately 1.5 megabases (Ewart et al., 1993; Korenberg et al., 2000; Lowery et al., 1995; Schubert, 2009). *ELN*, the gene for elastin, was the first deleted gene identified and its absence is indicative of a diagnosis of WS. While *ELN* disruption affects connective tissue, particularly of the aorta (Lowery et al., 1995), other genes such as *LIMK1*, *CYLN2*, *GTF2I* and *GTF2IRD1* are involved in the behavioral phenotype of WS (Jarvinen-Pasley et al., 2008). The deletion of *Gtf2i* as well as *Gtf2ird1* has been shown to be involved in the social phenotype specifically (Proulx et al., 2010; Sakurai et al., 2011).

The social phenotype associated with WS is striking due to the hypersociability of the affected individuals, as well as the preference for novel social over non-social stimuli (Jarvinen-Pasley et al., 2008; Jarvinen-Pasley et al., 2010) and increased eye contact (Mervis et al., 2003). In addition, the speech of individuals with WS is marked by high levels of socially engaging language as compared to controls or individuals with other developmental disorders such as Down Syndrome (Jarvinen-Pasley et al., 2010; Jarvinen et al., 2013). However, this does not translate into the development of social relationships as individuals show difficulty with social adjustment (Gosch and Pankau, 1994, 1997) and social judgment (Einfeld et al., 1997; Gosch and Pankau, 1997). In addition, affected individuals show deficits in social understanding, as evidenced by difficulty identifying affect (Gagliardi et al., 2003; Plesa-Skwerer et al., 2006) or other's mental states (Jarvinen-Pasley et al., 2008).

The high sociability of individuals with WS positions this syndrome as a good mechanism through which to understand the biological underpinnings of social behavior. Mouse models of WS include GTF2I deficient mice which display increased social interaction with novel mice and diminished social habituation (Sakurai et al., 2011) and *Gtf2ird1* deletions, which also show increased sociability (Proulx et al., 2010). Recently, de novo duplications of regions of 7q11.23 have been shown to be associated with ASD, whereas deletions of the same region lead to WS (Sanders et al., 2011). Such opposite effects of gene expression leading to markedly contrasting phenotypes raises the issue of dosage effects, but it should be noted that both ASD and WS phenotypes include abnormal social relationships, although through different mechanisms. Whereas individuals with WS show prolonged face gaze, those with ASD display reduced face gaze (Riby and Hancock, 2009). In addition, although children with WS and ASD display high levels of anxiety, individuals with ASD have higher levels of RRB as well as greater rates of social phobia and separation anxiety (Cascio et al., 2012).

As deletions or increased expression of genes in the region defining WS can lead to the contrasting phenotypes of WS or ASD, respectively, the possibility of dysregulation of OT was examined by Dai et al. (2012). They show increased baseline

levels of OT in individuals with WS as compared to controls. Additionally, OT levels correlated positively with increased approach to strangers as well as decreased adaptive social behaviors. These results suggest that there may be a dose dependent effect of OT, as high levels may impair adaptive social behavior and may partly underlie the maladaptive social phenotype of WS.

5. Fragile X syndrome

Named for the fragile site observed at Xq27.3, Fragile X Syndrome (FXS) is the most common inherited form of intellectual disability and the most common known single gene mutation associated with ASD (O'Donnell and Warren, 2002). Prevalence estimates range from ~1 case in 1000 to 1 case in 4000 males and has settled at 1 case in 6000 worldwide for females (Brown, 1990; Morton et al., 1997; Turner et al., 1996; Webb, 2010). This rare genetic disorder is characterized by specific physical features, as well as cognitive and behavioral phenotypes (Berry-Kravis et al., 2002, 2011; McLennan et al., 2011). The physical features can include: a long narrow face with large protruding ears, connective tissue abnormalities (i.e. hyperextensive joints), macroorchidism, macrocephaly, obesity (especially in young males), loose skin over the hands, a high arched palate, a vertical plantar crease and flat feet (Moy et al., 2009; Schapiro et al., 1995). The behavioral and social characteristics of FXS include: hyperactivity, attention difficulties, mood lability, compulsive and perseverative behaviors, some aggressive outbursts, learning deficits, developmental delays (including delayed speech development), social shyness and gaze avoidance, sensory hypersensitivity and withdrawal from touch, stereotypic movements and behaviors (i.e. hand flapping and rocking), poor motor coordination and echolalia (Hagerman et al., 2009; Hall, 2009; Hall et al., 2009; Moy et al., 2009). Many of these behaviors are linked to the anxiety level of the individual, a meaningful link because physiological studies have noted increased sympathetic and decreased parasympathetic activity and poor coordination between the systems in children and adolescents with FXS (Hall et al., 2009).

Cognitive tests have indicated a specific pattern of strengths and weaknesses. FXS individuals exhibit deficits in visuo-spatial tasks, quantitative skills, short-term and working memory, expressive language skills, sequential processing and executive function (Berry-Kravis et al., 2002; Cornish et al., 1999; Freund and Reiss, 1991; Hall et al., 2012; Kwon et al., 2001; Maes et al., 1994). Relative strengths include receptive language skills, visual memory, acquisition of factual information, imitation skills and gestalt processing (Berry-Kravis et al., 2002). This population also has susceptibility to certain other neuropsychiatric disabilities including ASD, ADHD, anxiety disorders, and neurological disorders such as epilepsy (Hessl et al., 2001; Pretorius et al., 1998). While the genetic cause of FXS has been found, the neurological basis of FXS symptoms continues to be unknown. MRI studies have found that individuals with FXS have enlarged lateral ventricles and increased caudate nucleus volumes relative to control subjects (Reiss et al., 1995). Anatomical studies of post-mortem brains have revealed that dendritic spines of neocortical pyramidal neurons of FXS subjects are longer and thinner than those of matched controls, indicating perhaps the spines fail to mature normally in FXS patients (Hinton et al., 1991; Irwin et al., 2001; Rudelli et al., 1985; Wisniewski et al., 1991).

The majority of FXS patients have social anxiety and almost a third have symptoms that overlap with ASD (Hagerman et al., 2010). Published studies have reported the prevalence rate of FXS and autistic behaviors/ASD diagnosis to range from 25–47%, however sample sizes are often small (Hatton et al., 2006; Morton et al., 1997). Like FXS and ASD, autistic symptoms are more common in males than females. Individuals with both FXS and ASD often have poorer developmental outcomes, lower cognitive abilities, lower levels of adaptive behavior and more problem behaviors than FXS individuals with fewer autistic behaviors. Of the individuals with FXS and autistic behaviors, 15–40% of males and a few females meet the diagnostic criteria for ASD (Berry-Kravis et al., 2002). This group also tends to present with more severe communication deficits, stereotyped behaviors, and social anxiety versus social disinterest. Additionally, males present with more severe developmental delays than females. Overlapping behaviors between ASD and FXS, such as eye gaze avoidance (Hall et al., 2009), have led many scientists to study FXS as a way to understand and possibly target treatment for ASD. Some of the medical problems exhibited within this population include seizures (15–20% of male children, usually limited to childhood), gastroesophageal reflux, failure to thrive in early infancy, hypotonia, recurrent otitis media and sinusitis, vision problems, cardiac valve prolapse, sleep disorders, and orthopedic issues and dental malocclusions. In the few girls studied with FXS, these medical problems are more variable (Berry-Kravis et al., 2002).

Diagnosis is based on DNA analysis that identifies the number of CGG repeats in the fragile X mental retardation 1 (FMR1) gene at the Xq27.3 site (Turner et al., 1996). In most affected individuals, this genetic disorder is caused by a trinucleotide (CGG) repeat expansion in the 5' untranslated (promoter) region of the *FMR1* gene. *FMR1* encodes the fragile X mental retardation protein (FMRP); a 69kDa protein found in most adult and fetal tissues, high concentrations are noted in the brain and testes. The expression of FMRP in the brain seems to be experience dependent and is produced in the soma and near the synapse (Berry-Kravis et al., 2002, 2011). FMRP is essential to the shaping of dendritic spines (Davidovic et al., 2011). The protein and network of mRNA targets and interacting proteins contribute to several forms of synaptic plasticity involving learning and memory processes, notably induced by activation of type I metabotropic glutamate receptor (mGluR; Davidovic et al., 2011). Mice lacking FMRP have impaired long-term potentiations in somatosensory cortex (Li et al., 2002), visual cortex (Wilson and Cox, 2007), olfactory cortex (Larson et al., 2005), cingulate cortex, and amygdala (Zhao et al., 2005) and enhanced long-term depression in hippocampus (Huber et al., 2002). In synaptosomal preparations, stimulation of mGluR results in a FMRP-dependent increase in protein synthesis (Weiler et al., 1997, 2004). It is hypothesized that a decrease in *Fmr1* functionally affects the protein interaction network with direct consequences on signaling cascade and cellular metabolism

(Davidovic et al., 2011). There are two different *FMR1* mutations, full mutation and permutation (Goodrich-Hunsaker et al., 2011a, 2011b). Premutation, associated with Fragile X-associated tremor/ataxia syndrome (FXTAS; Wang et al., 2010), has a repeat length of 50–200 and does not usually cause mental deficits, but shyness, anxiety, and premature ovarian failure have been known to occur. Premutations do appear however to influence translation of *FMR1* mRNA (Feng et al., 1995). In many individuals with premutations, excess *FMR1* mRNA is produced, yet below normal FMRP is synthesized (Tassone et al., 2000a, 2000b) and may contribute to approximately 10% of male and 2–3% of female ASD cases (Wang et al., 2010). Upon female transmission the premutation can become a full mutation. FXS is caused by full mutation which is >200 trinucleotide repeats, and results in hypermethylation of the gene and transcriptional silencing (Tassone et al., 2000a). This creates an FMRP deficiency in the brain, which leads to FXS presentation (McLennan et al., 2011; Tassone et al., 2000a). Very rarely have other mutations in the *FMR1* gene involving deletions (Gedeon et al., 1992; Wohrle et al., 1992) or a point mutation (De Boulle et al., 1993) resulted in symptoms identical or even more severe than FXS.

5.1. *IN-OT as treatment for FXS*

Evidence has supported the investigation of OT as a treatment for FXS (Bartz and Hollander, 2006; Hall et al., 2012; Hollander et al., 2007). As described earlier OT, released endogenously or given exogenously, has been associated with positive social behaviors, reductions in anxiety, obsessiveness and stress reactivity, the central release of AVP and other peptides such as corticotropin-releasing factor, and may serve to counter the defensive behavioral strategies associated with stressful experiences (Carter, 2007). However, similar to ASD, available treatments for FXS focus on managing symptoms: stimulants are prescribed for attention deficit and hyperactivity; SSRI and antipsychotics treat aggression associated with anxiety; and carbamazepine are used for treatment of seizures (Hampson et al., 2011). Currently, there are no treatments on the market targeting the molecular abnormalities of FXS (Gurkan and Hagerman, 2012). Recent studies have begun to investigate IN-OT due to the autistic-like behaviors observed in FXS, and the social and anxiolytic effects of OT.

As of the time of publication, very few studies had been performed to research the effect of IN-OT on FXS, especially in humans. One such study was conducted by Hall et al. (2012). They set up a randomized double-blind placebo-controlled single-dose trial performed with intranasal administration of placebo, 24IU OT and 48 IU OT. Studying eight low functioning males between the ages of 13 and 28 years with FXS, they hypothesized that the prosocial and anxiolytic effects of OT would reduce, if not alleviate, socially inappropriate behaviors and social anxiety. The group collected eye gaze frequency, heart rate, respiratory sinus arrhythmia, heart rate variability (HRV) during two social challenges (10 min total in length), and salivary cortisol levels before and after the challenge, which was conducted 50 min after OT administration.

Confirmation of the hypothesis that OT would have beneficial consequences in FXS would be an increase in eye gaze frequency, a reduction in physiological arousal, and a decrease in salivary cortisol. The researchers observed a significant main effect with OT. As compared to placebo, 24IU OT led to a significant increase in eye gaze frequency. They found a significant decrease in salivary cortisol for the 48 IU dose as compared to placebo. No effects were observed in the physiological measurements (HR, HRV, and RSA), however, given the small sample and heterogeneous population additional research is needed. Based upon the data to date, Hall and colleagues hypothesized that in FXS administration of OT may dampen amygdala reactivity towards social stimuli that causes anxiety (Kirsch et al., 2005; Petrovic et al., 2008), decrease HPA axis activation, and increase social motivation (Witt and Insel, 1992; Witt et al., 1992).

5.2. *Animal models: a way to look at moderators of neurodevelopmental pathways and outcomes?*

Animal models have proven indispensable in the understanding of diseases and disorders, and in the development of pharmaceuticals used to treat them. The quality of an animal model is ascertained based on how well it can meet certain criteria of validity. Three of these criteria are construct, face and predictive validity (Bernardet and Crusio, 2006). How well the model's behavioral traits resemble the core traits of the disorder is face validity. Predictive validity is established when a drug reduces or improves symptoms in both the model and human. Construct validity is the "quality" of the model, its ability to accurately measure or represent what it claims to be measuring (Cronbach and Meehl, 1955). There are several FXS animal models, three in mice and a drosophila model that meet multiple criteria.

Two homologous genes to *Fmr1* in vertebrates are *Fxr1* (fragile X related gene) and *Fxr2*. The genes are highly homologous at the protein structure level and bind mRNA and bind to FMRP. Their proteins, FXR1P and FXR2P are both expressed in the brain and specifically in cell bodies, but they are also found in the dendrites near the synapse. Both *Fxr1* and *Fxr2* KO mice have been produced. FXR1P deficient ($Fxr1^{-/-}$) mice die within 24 h of birth, while heterozygous mice exhibit abnormal limb musculature. *Fxr2* KO have a normal lifespan, learning deficits similar to *Fmr1* KO, and circadian rhythm deficits (Berry-Kravis et al., 2011). The fruit fly model, a mutant lacking dFmr1 (also known as dFxr) protein, exhibits overextension of neurites during development of mushroom bodies (brain region linked with memory) and have a behavioral phenotype that includes circadian rhythm abnormalities and altered courtship behavior (Berry-Kravis et al., 2011; Gatto and Broadie, 2009).

One of the best characterized animal models of FXS was developed in 1994 by the Dutch-Belgian Fragile X Consortium. This mouse model, which lacks FMRP throughout its lifespan, corresponds to the molecular endpoint of the human disease. This mouse was created by inserting a neomycin cassette into exon 5 of the murine *Fmr1* gene. The insert disrupts the transcription of *Fmr1* mRNA causing an absence of FMRP. Even though the cause may not be identical, this mouse model exhibits behavioral similarities to FXS. *Fmr1* KO, in

comparison to the wild-type (WT) strain, are described as having lower than normal levels of initial social interactions (Mineur et al., 2006), fail to show a preference for social novelty, and display inappropriate social responses (Pietropaolo et al., 2011). In contrast, the OT and AVP knockout (OTKO or AVPKO) mice display high levels of social contact that does not diminish over time, but also fail to show indication of familiarity (Crawley et al., 2007).

While macroorchidism is observed in the *Fmr1* KO animals (Bakker et al., 1994) as well as in FXS patients, the behavioral patterns differ between the patients and the KO. By most accounts *Fmr1* KO mice appear to have relatively normal behavior, but research has shown that the behavioral and cognitive deficits of the KO are actually quite subtle and parallel FXS patients (Berry-Kravis et al., 2002; D'Hooge et al., 1997; Paradee et al., 1999; Peier et al., 2000). Among the behavioral phenotypes displayed in *Fmr1* KO are deficits in object recognition memory (including a failure to habituate to objects), and impairment of spatial memory (Mineur et al., 2002).

Several studies indicate that *Fmr1* KO mice are hyperactive and show indications of increased anxiety (Bakker et al., 1994; Mineur et al., 2002; Spencer et al., 2005) and sensory hyperresponsiveness, especially to auditory stimuli (Chen and Toth, 2001; Frankland et al., 2004; Nielsen et al., 2002). Loud tones may induce audiogenic seizures. *Fmr1* KO also exhibit abnormal social interactions, including a general reduction in social contact and a failure to show social recognition (Bernardet and Crusio, 2006; Mineur et al., 2006; Spencer et al., 2005; Yan et al., 2004). In some tasks there is variability in the results (i.e. complex visual and auditory discriminant tasks and activity level in an open field). The symptom variability among mouse models for FXS may be due to differences in genetic backgrounds. A similar hypothesis has been proposed to explain the variability observed in the symptoms of FXS patients. For example, in research by Pietropaolo et al. (2011), the validity of the *Fmr1* KO mouse on the B6 background was tested against WT and *Fmr1* KO on the FVB background. They found the *Fmr1* KO on the B6 background to be a good model for FXS and a suitable model for ASD (Pietropaolo et al., 2011; Yan et al., 2004).

These mice also have neuropathologic phenotypes that are similar to FXS patients including density of dendritic spines of pyramidal neurons in the visual and somatosensory cortices that are greater in adult *Fmr1* KO than WT. Some brain areas, in both mice *Fmr1* KO mice and FXS patients, have spines that appear similar to developing versus mature spines (Berry-Kravis et al., 2002). Absence of FMRP in both humans and mice results in improper development of dendritic spines on cortical pyramidal neurons (Comery et al., 1997; Irwin et al., 2000; Irwin et al., 2001; Irwin et al., 2002). The use of the *Fmr1* KO mouse has also provided some insight into the normal cellular function of FMRP. The subtle cognitive deficits of *Fmr1* KO mice present difficulties for preclinical testing of potential treatments, and highlight how complex the relationship between the mouse and human phenotypes are. One possibility is that the cognitive processes in which FMRP plays a vital role in humans are poorly developed in mice; thus mice lacking FMRP are not particularly disabled, at least compared to severely-affected patients. A second possibility is that other proteins can compensate for FMRP in the mouse but not in the human. Third, the behavioral paradigms thus far applied to the mouse model do not efficiently assay or correlate with the cognitive domains most affected in individuals with FXS.

5.3. *Examining OT in neurodevelopmental animal models: a way to examine early effects?*

Below we present preliminary data examining the OT and AVP systems in a mouse model in order to learn more about FXS pathway interactions during development. The methods used in this study are described in the text for Fig. 1. These preliminary results, based upon counts of immune-reactive cells, suggest a reduction in both OT-positive (Fig. 1) and AVP-positive (Fig. 2) cells in the PVN of *Fmr1* KO as compared to WT (Table 2). A trend, although not significant, towards lower OT-positive cells was also noted in the SON (Table 3). To analyze possible differences in the OXTR, the abundance of OXTR-immunoreactive cells were also measured in the hippocampus, retrosplenial granular and piriform cortices. None of these areas showed a significant difference in OXTR-immunoreactive cell density as compared to WT mice ($p > 0.05$). The PVN is an important component of the HPA axis, and reductions in OT-positive and AVP-positive cells of the PVN might be associated with deficits in the capacity to regulate emotional reactivity. Earlier work in voles has suggested that either OT or AVP may support a general tendency toward social contact (Cho et al., 1999). Thus, the absence of either OT or AVP in the presence of the other did not produce an "asocial" animal. However, selective social preferences, such as those necessary for pair bond formation, appear to require stimulation of both OT and AVP receptors. The importance of both OT and AVP to selective behaviors also may be supported by the fact that mice "knocked-out" for either OT or the OXTR no longer exhibited selective social memory (Young and Flanagan-Cato, 2012).

Although the preliminary data shown here for *Fmr1* KO mice need to be replicated in a larger sample and in other animal models, we include these findings as an example of possible approaches to examining the role of peptides including, OT and AVP, in molecularly characterized genetic syndromes. Work across these models also could provide additional insight regarding the role of OT and AVP in early development, especially in syndromes in which atypical trajectories in social development occur.

6. Conclusion and next steps

Each of the disorders described here (ASD, PWS, WS and FXS) is unique and each condition is characterized by atypical social behaviors, often with a tendency toward high levels of anxiety. Given the importance of OT and AVP to mammalian social behaviors and anxiety, the neuropeptides' investigative value in these syndromes is not unexpected. This review summarized the possible role of OT in these NDD (Table 4) through experiments conducted by others and ourselves.

Each of these early developmental disorders displays alterations in the OT system. These changes may impact behavior and emotional regulation through a variety of

molecular and neuroendocrine pathways. For example, our preliminary data suggests a decreased number of OT-positive and AVP-positive cells in the PVN of *Fmr1* KO mice, a mouse model for FXS. Individuals with PWS have shown lower levels of OT in CSF (Martin et al., 1998) and fewer OT producing cells in the PVN (Swaab et al., 1995). A subgroup of ASD affected children also appeared to have lower plasma OT levels (Modahl et al., 1998). In contrast WS, which is characterized by hypersociability, had a positive correlation between OT levels and increased stranger approach and decreased adaptive social behavior (Dai et al., 2012).

At present, the largest concentration of studies on the role of dysregulated OT pathways has been conducted in ASD. However, as new data are emerging it is striking that other disorders with phenotypes marked by abnormal social behavior, as well as anxiety (in some cases manifested by RRB) also appear to have abnormalities found within the OT system. For example, as in ASD, individuals with PWS have difficulty with social competence (Dimitropoulos et al., 2013), are aloof and avoid eye contact (Dimitropoulos et al., 2009). Furthermore, RRB is also evidenced in PWS (Greaves et al., 2006), although to a lesser

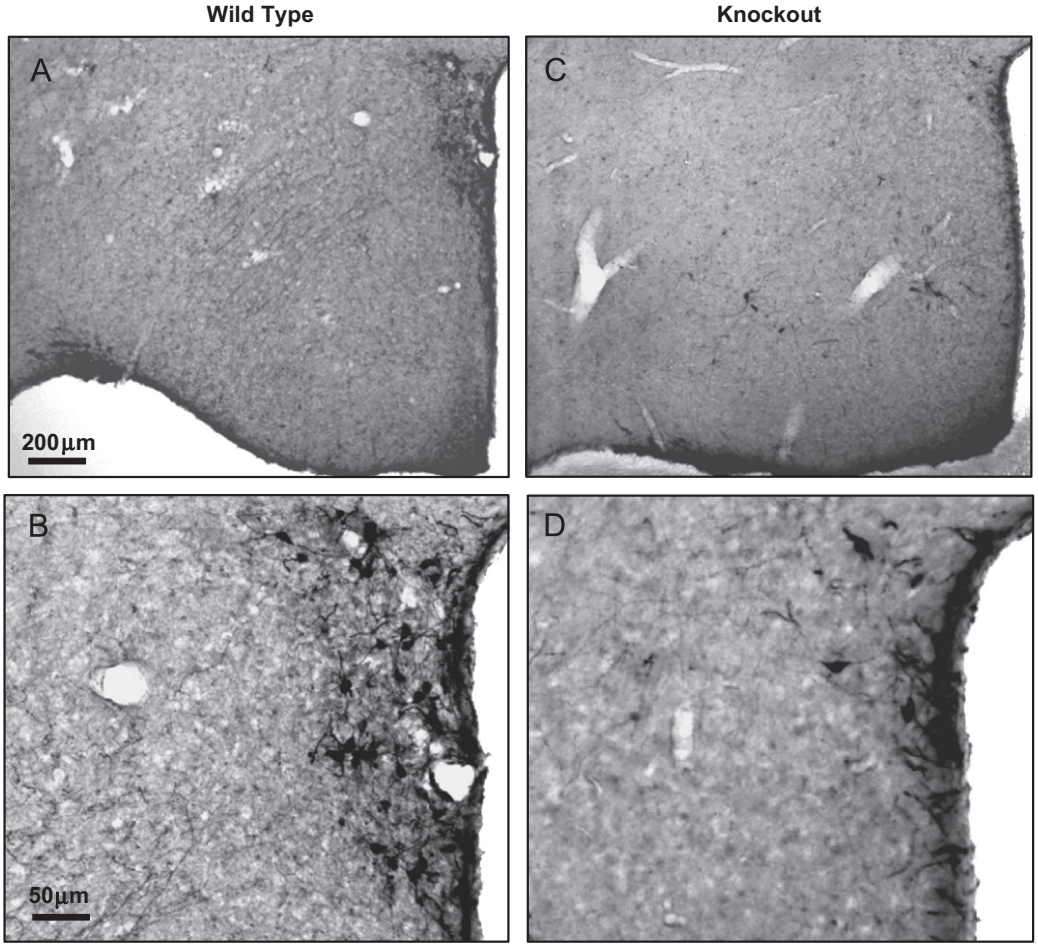

Fig. 1 – Expression of OT in the paraventricular nucleus (PVN), as measured by ICC, is reduced in *Fmr1* KO mice as compared to the wild-type (WT). Methods: The animal model was generated with WT and *Fmr1* KO mice from a colony founded with stock obtained from the Jackson Laboratory (Bar Harbor, ME, USA) that was backcrossed onto a B6 background >10 generations. Mice were genotyped using primers described previously (the Dutch-Belgian Fragile-X Consortium, 1994). Cells were stained using the immunocytochemical (ICC) staining procedures, following protocols described in early work on OT and AVP in voles (Yamamoto et al., 2004). All sections were double-stained for NeuN (a marker that stains cell nuclei only in neurons), which allowed precise localization of cytoarchitectonic boundaries. Stained sections were mounted on subbed slides and examined with OT and AVP antibodies (OT antibodies were generously provided by M. Morris and AVP antibodies were obtained from MP Biomedical #647171, formerly ICN; Solon, OH, USA). Slices of tissue for each animal were categorized as described in (Paxinos and Franklin, 2004) and carefully matched across subjects to allow comparable sections. Imaged slides were captured at 10×, then coded and scored by an experimentally blind scorer using Image J (NIH, Bethesda, MD) software. OT and AVP stained cells in the PVN of the hypothalamus regions were stained separately for OT and AVP ($N=6$–7 mice per group). Boxed sampling areas were: 125 × 125 μm^2 (PVN total staining density), 250 × 375 μm^2 (PVN fibers), 93.75 × 93.75 μm^2 for cell counts bilaterally in both the PVN and SON.

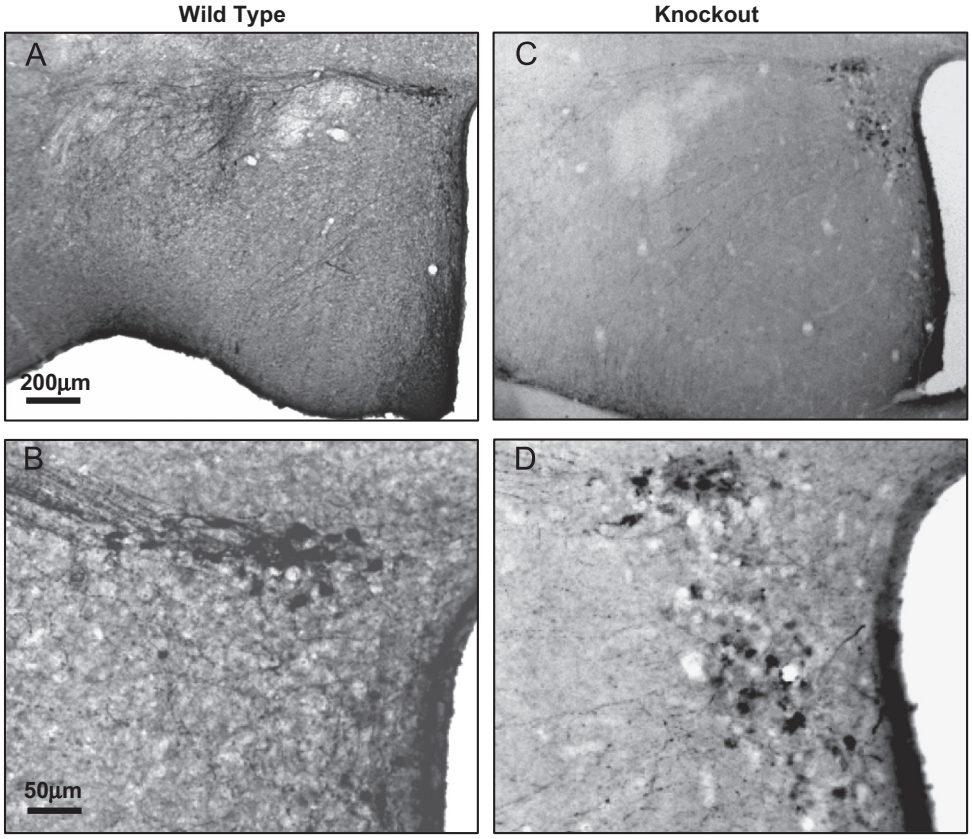

Fig. 2 – Expression of AVP in the paraventricular nucleus (PVN). In *Fmr1* KO mice, as compared to the wild-type (WT) AVP expression is reduced as measured by ICC.

Table 2 – Number of OT and AVP-positive cells in PVN of *Fmr1* KO versus WT mice.

	OT			AVP		
	WT	Knockout		WT	Knockout	
PVN	17[†]±2*	9±3	$p=0.047$	10±2	4±2	$p=0.05$

[†] Means number of positive cell/0.2 mm^2.
* Means ±SE (N=6–7/group).

Table 3 – Number of OT and AVP-positive cells in SON of *Fmr1* KO versus WT mice.

	OT			AVP		
	WT	Knockout		WT	Knockout	
SON	13[†]±2*	8±3	$p=0.254$	11±2	6±2	$p=0.107$

[†] Means number of positive cell/0.08 mm^2.
* Means ±SE (N=6–7/group).

degree than in ASD as measured by the Repetitive Behavior Scale-Revised (RBS-R; Flores et al., 2011). A subset of the genetic region associated with PWS is also associated with an increased risk for ASD, as maternally inherited duplications of the 15q11-13 region are associated with 1–3% of ASD cases (Bolton et al., 2001; Cook et al., 1997; Vorstman et al., 2006).

WS and ASD also share commonalities as both are marked by abnormal social phenotypes and anxiety. However, unlike PWS, individuals with WS show a phenotype that is markedly different from ASD. Although both groups are at risk for anxiety, individuals with ASD show higher levels of social phobia and separation anxiety, as well as higher rates of RRB. However, individuals with WS have higher scores on

Table 4 – A Summary of OT Affects on NDD.

Disorder	Neuropeptide system affected	References
Autism spectrum disorders	Atypical (↓↑ observed) levels of OT in blood (human) IN-OT ↑ social task performance and ↓ repetitive behaviors (human) To be studied: human neuropathology and animal models	Modahl et al. (1998) Andari et al. (2010) and Hollander et al. (2003) For a more extensive list of human trials see Table 1
Prader–Willi syndrome	↓ OT producing cells in the PVN (human) ↓ Level of OT in CSF (human) IN-OT ↑ trust and ↓ disruptive behaviors (human) ↓ Hypothalamic OT in *Maged1* deletion model (animal)	Swaab et al. (1995) Martin et al. (1998) Tauber et al. (2011) Dombret et al. (2012)
Williams syndrome	↑ OT levels (human) To be studied: human neuropathology and animal models	Dai et al. (2012)
Fragile X syndrome	↓ OT+ and AVP+ cells in the PVN (*Fmr1* KO mice) IN-OT ↑ eye gaze frequency (human) IN-OT ↓ salivary cortisol (human) To be studied: human neuropathology	See Tables 2 and 3, and Figs. 1 and 2 Hall et al. (2009) and Hall et al. (2012) Hall et al. (2012)

measures of generalized anxiety (Rodgers et al., 2012). WS is characterized by an increase in OT levels (Dai et al., 2012), as well as a deletion of the 7q11.23 region, as opposed to a de novo duplication which leads to ASD (Sanders et al., 2011). It is likely that features of ASD and WS are manifestations of gene dosage effects on similar behaviors. Studies of FXS and ASD mechanisms may also inform each other, as mutations in mGluR5 can contribute to the diagnosis of FXS or ASD, and mGluR5 antagonists have shown promise in alleviating ASD symptoms in mouse models (Silverman et al., 2012) as well as FXS pathology. Due to the rarity of these disorders and the complex animal models needed to study them, many of these experiments have small sample sizes. However, these studies remain significant and together provide a motivation and direction for future research in NDD, especially disorders with dysfunctional social behaviors as a symptom.

As summarized in this review, the dysregulation of the OT system in animals and humans is associated with marked deficits in social behavior as well as anxiety. This commonality across multiple NDD may indicate a shared OT pathway that is affected during development. The use of animal models, particularly those developed for FXS, WS and PWS will provide insight into such a pathway, as these disorders have well characterized genetics. In contrast, there are over a 103 disease genes and 44 genomic loci reported to be involved in ASD (Betancur, 2011). However, unlike ASD research, there is a lack of human data on the pathophysiology of FXS, WS and PWS, and pharmacological interventions. Ideally, scientists want to identify specific molecular pathways to target distinct syndromes and disorders for treatment. However, many effective medical treatments, such as drugs for hypertension, modulate common neurochemical or hormone pathways that are downstream from etiologically contributing factors. Combining the strengths of human and animal model studies across these NDD may provide important clues into the developmental role of OT. Additionally, as general mechanisms underlying social and emotional behaviors are specified, it may become possible to elucidate the complex neurophysiology of and create treatment targets for FXS, PWS, WS and ASD.

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Oxytocin differentially modulates compromise and competitive approach but not withdrawal to antagonists from own vs. rivaling other groups

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ABSTRACT

In humans, oxytocin promotes cognitive and motivational tendencies that benefit the groups on which humans depend for their survival and prosperity. Here we examined decision making in an incentivized two-player poker game with either an in-group or out-group antagonist. Sixty nine healthy males received 24 IU oxytocin or matching placebo, and played four rounds of a simplified poker game. On each round they received either low or high value cards to create differences in competitive strength, and then responded to a bet placed by their (simulated) (in-group or out-group) antagonist. Under placebo, participants withdrew and competed depending on their own (low vs. high) competitive strength, regardless of their antagonist's group membership. Under oxytocin, however, participants settled more and competed less with an in-group as compared to an out-group antagonist; withdrawal was unaffected by group membership. We conclude that oxytocin sensitizes humans to the group membership of their interaction partner, rendering them relatively more benevolent and less competitive towards those seen as belonging to their own group.

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1. Introduction

In their search for the neurobiological bases of social behavior, scientists across the behavioral and brain sciences turned their focus to oxytocin, an evolutionary ancient and structurally highly preserved neuropeptide (e.g., Bartz et al., 2010; Chang et al., 2012; Bos et al., 2012; Ross and Young, 2009; Striepens et al., 2012). Oxytocin is produced in the hypothalamus and released into the blood stream from axon terminals and into the brain from dendrites of hypothalamic neurons (Donaldson and Young, 2008; Ludwig and Leng, 2006). Functioning as both a neurotransmitter and hormone, oxytocin's targets are widespread and include the hippocampus and the amygdala (Kirsch et al., 2005). Oxytocin interacts with dopaminergic, reward processing circuits in the nucleus accumbens shell and in the ventral tegmental area (Skuse and Gallagher, 2008), and exerts anxiolytic effects via direct activation of oxytocin receptors expressed in serotonergic neurons of the raphe nuclei (Veenema et al., 2010; Yoshida et al., 2009).

1.1. Social bond formation and maintenance

Oxytocin is perhaps best known for its critical role in parturition and reproduction on the one hand, and social bond formation and maintenance on the other (e.g., Carter et al., 2008). First, male rodents engineered to lack (fore-brain)

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oxytocin receptors no longer discriminate between familiar and unfamiliar females, whereas normal rodents spent more time investigating unfamiliar female rodents vs. female rodents with whom they had shared a cage for several days (Macbeth et al., 2009; also see Ferguson et al., 2000, 2002). Along similar lines, participants who memorized pictures of faces under oxytocin performed better one day later on measures of familiarity, indicating that oxytocin makes a face in memory more familiar (Rimmele et al., 2009).

In addition to social bond formation, oxytocin also appears to stimulate empathic responding, which is important also to social bond maintenance. For example, in women exposed to infant crying, intranasal oxytocin modulates activity in the inferior frontal gyrus (Riem et al., 2011), fathers given oxytocin rather than placebo stimulate their toddler's exploration more and show less hostility (Naber et al., 2010), and in males exposed to biological motion (a point-light figure representing a walking human), intranasal oxytocin modulates neural circuitries involved in affective perspective taking (Keri and Benedek, 2009; Perry et al., 2010). Other studies showed that participants given oxytocin rather than placebo have increased sensitivity to other's fear (Fischer-Shofty et al., 2010), empathize more with people depicted in emotionally charged situations (Hurlemann et al., 2010; but see Singer et al., 2008), and more accurately infer emotions expressed by others (Domes et al., 2007). Indeed, both humans and non-human mammals show increased benevolence under oxytocin, including tendencies to benefit con-specifics (Chang et al., 2012), to trust others (Baumgartner et al., 2008; Kosfeld et al., 2005), to make fair offers in bargaining (Zak et al., 2007), and to benefit others at a personal cost (e.g., Morhenn et al., 2008).

1.2. *Indiscriminate benevolence vs. group-serving tendencies*

Whereas the heretofore reviewed work suggest that oxytocin promotes indiscriminate benevolence and generosity (e.g., Zak et al., 2007), a more accurate conclusion appears that oxytocin promotes group-serving tendencies (De Dreu, 2012; Goodson, 2013). For example, meerkats live in clans and their survival and prosperity depends on successful in-clan cooperation and coordination and defense to predators and roving competing clans (Drewe et al., 2009). In free-living meerkats, peripheral administration of oxytocin rather than placebo increased an array of cooperative behaviors directed at the own clan, including digging, associating with pups, and *time-on-guard* (Madden and Clutton-Brock, 2011). Other studies documented that oxytocin is key in triggering so-called *maternal defense*, which occurs when a breast-feeding mother is faced with an unfamiliar intruder and lashes out to protect and defend its pups (Bosch et al., 2005; Pedersen et al., 1982).

In humans, similar tendencies have been documented as well. First, the hypothalamic release of oxytocin is promoted by displays of trust and cooperation by others, especially familiar others like parents and intimate partners (e.g., Ditzen et al., 2007; Feldman et al., 2010; Gordon et al., 2010; Holt-Lunstad et al., 2008; Morhenn et al., 2008; Uvnas-Moberg, 1998; Zak et al., 2005). Second, when given oxytocin rather than placebo, humans display more positive attitudes and empathize only with members of their own group and not with those classified as rivaling out-group members (De Dreu et al., 2011, 2012b; Sheng et al., 2013). Third, individuals given oxytocin rather than placebo conform to opinions of in-group members more than to (identical) opinions voiced by out-group members (Stallen et al., 2012). Fourth, individuals given oxytocin self-sacrifice more, and contribute to their own group more than to the broader collective that includes both their own group and other groups (Israel et al., 2012). Finally, when their own group competes with an out-group, individuals given oxytocin prefer strong allies (De Dreu et al., 2012a; also see Kret and De Dreu, 2013) and display parochial altruism – a tendency to cooperate with the in-group and to compete against the out-group (De Dreu et al., 2010, 2012b; also see Choi and Bowles, 2007; Israel et al., 2012).

Taken together, it thus stands to reason that oxytocin does not promote indiscriminate pro-social tendencies. Instead, it appears that oxytocin promotes cognitive, motivational, and behavioral tendencies that are beneficial to the groups within which humans operate and upon which they depend for survival and prosperity (De Dreu, 2012; van Ijzendoorn and Bakermans-Kranenburg, 2012). Such tendencies include in-group love and, if necessary for in-group protection, out-group hate as well.

1.3. *Current study: decision making in competitive interactions*

The conclusion that oxytocin promotes group-serving tendencies rests on studies examining relatively cooperative situations where humans faced the choice to contribute to their group or not, to trust others or not, or to make (un)fair offers. However, in addition to these more benign situations, group life is marked also by conflict when, for example, individuals compete for status and scarce resources. Typically, such conflicts trigger a tendency towards (i) withdrawal and subordination, (ii) matching and compromise, or (iii) aggressive approach (De Dreu, 2010; Deutsch, 1973). Although individuals have an incentive to compete through aggressive approach, their overarching group fares better when conflict is mitigated through withdrawal and compromise (De Dreu, 2010). Accordingly, our conjecture that oxytocin promotes group-serving tendencies implies that in competitive interactions, oxytocin increases (i) costly withdrawal and/or settlement, and (ii) reduces aggressive approach, especially when (iii) antagonists are part of one's in-group rather than coming from rivaling out-groups.

We examined this possibility in an incentivized two-player poker game adapted from Ten Velden et al. (2012). Fig. 1 provides a schematic overview of the experimental procedures (see section 4 for further detail).

Participants received oxytocin or matching placebo, and were paired to a (simulated) antagonist from their own in-group, or from a rivaling out-group. In this simplified poker-game, participants are given chips with monetary value, and handed a card from a 52-card deck. Following an initial forced bet which starts the game, participants observe their antagonist's bet, to which they may respond by withdrawing from the game at a personal cost (i.e., "fold," where the bet is lost and the pot is handed to the opponent), by (ii) *compromising* (i.e., "call;" they match their antagonist's bet and the player

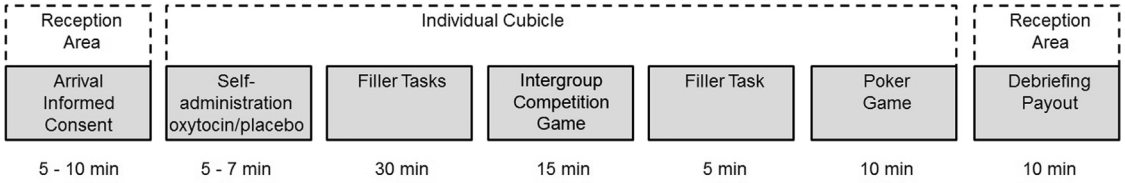

Fig. 1 – Time-line of the experiment; tasks taking place within individual cubicles were entirely computer-guided and participants worked alone at their own pace.

with the highest card wins the pot; in case of a draw, the pot is split between participant and antagonist), or (iii) *competing* (i.e., "raise," in which case the participant increases the size of the pot). Raising is considered an aggressive approach strategy with which more chips can be gained or lost (depending on the strength of the card) if the competitor calls the bet; chips can be gained if the competitor folds. In terms of our hypotheses, we expected individuals to fold and/or call more, and to raise less when confronted with an in-group (vs. out-group) antagonist, especially when given oxytocin rather than placebo. We manipulated Competitive Strength by providing participants twice with a high value card, and twice with a low value card (Section 4), to explore whether competitive strength modulates predicted effects of oxytocin on decision making.

2. Results

2.1. Manipulation checks

To verify the adequacy of the manipulation of the antagonist's group membership, we cross-tabulated responses to the question whether the antagonist was a member of one's own group, or of the other group (1=my team, 2=other team) with Antagonist's Group, Treatment, and Group × Treatment interaction. Responses only differed as a function of Antagonist Group, $\chi^2(1, 69)=68.108$, $p=0.0001$. Except for one mistake, the antagonist's group membership was accurately identified.

The competitive strength manipulation was verified after each decision, first, by asking participants to indicate on a slider whether their card was better (+60) to worse (−60) than their antagonist's card. Ratings were averaged across low value and high value cards, respectively, and submitted to a 2 (treatment) × 2(antagonist's group) × 2(high vs. low competitive strength) Mixed-Model ANOVA with competitive strength as within-subjects factor. Results showed only a main effect for competitive strength, $F(1, 65)=373.13$, $p=0.0001$, $\eta_p^2=0.852$, indicating that participants perceived themselves to be weaker than their antagonist when given a low value card ($M=-31.173$, $SD=13.488$, one-sample t-test, $t(69)=-20.605$, $p=0.001$), and stronger than their antagonist when given a high value card ($M=+18.185$, $SD=17.466$, one-sample t-test, $t(69)=8.194$, $p=0.001$). Second, we asked participants whether they felt they could win this round (1=not at all; to 5=very much). Ratings were averaged for low value and for high value cards, and submitted to a 2(treatment) × 2(antagonist's group) × 2(high vs. low competitive strength) Mixed-Model ANOVA with competitive strength within-subjects. Results revealed the expected main effect for competitive strength, $F(1, 65)=156.76$, $p=0.001$, $\eta_p^2=0.707$, and an unexpected competitive strength × treatment effect, $F(1, 65)=4.51$, $p=0.037$, $\eta_p^2=0.065$. Inspection of the means showed that in both treatment conditions, low value cards induced less perceived competitive strength than high value cards, but this effect was weaker among participants given oxytocin ($M=2.14$, $SD=0.72$ vs. $M=3.51$, $SD=0.92$) rather than placebo ($M=1.82$, $SD=0.78$ vs. $M=3.75$, $SD=0.73$). In all, however, we concluded that our manipulation of competitive strength was successful and as intended.

2.2. Decision making

Across decision rounds, participants were given twice a low, and twice a high value card. For each value, we counted how often participants decided to fold, call, or raise (each ranges between 0 and 2). Decisions were submitted to a 2(treatment) × 2(antagonist's group) × 3(decision: fold vs. call vs. raise) × 2 (competitive strength: low vs. high) Mixed Model ANOVA with the last two factors within-subjects. This revealed, first of all, a main effect for Decision, $F(2, 65)=38.109$, $p=0.001$, $\eta_p^2=0.543$, and a Decision × Competitive Strength interaction, $F(2, 65)=204.301$, $p=0.0001$, $\eta_p^2=0.864$. Fig. 2 shows that when given low value cards, participants more often decided to fold ($M=1.565$, $SD=0.606$), and less often to raise ($M=0.217$, $SD=0.449$), than when given high value cards ($M=0.014$, $SD=0.12$ for fold; $M=1.594$, $SD=0.577$ for raise). Decisions to call did not change as a function of competitive strength ($M=0.217$, $SD=0.449$ for low value; $M=0.391$, $SD=0.548$ for high value).

Treatment did not interact with Decision, $F(2, 65)=1.014$, $p=0.368$, $\eta_p^2=0.031$, indicating no overall preference change induced by oxytocin. However, as predicted, we did observe a significant Treatment × Decision × Antagonist's Group interaction, $F(2, 65)=4.045$, $p=0.022$, $\eta_p^2=0.112$. Follow-up analyses using the overall error term and associated degrees of freedom (Tatsuoka, 1988) indicated that whereas Decision and Antagonist's Group did not interact under placebo, $F(2, 65)=0.978$, $p=0.381$, $\eta_p^2=0.050$, they did under oxytocin, $F(2, 65)=3.848$, $p=0.026$, $\eta_p^2=0.214$. Fig. 3 (left panel) shows that when participants received placebo, their decision to fold, call, or raise did not depend on their antagonist's group membership. Fig. 3 (right panel) shows that when participants received oxytocin, however, they were more inclined to call when dealing with an in-group rather than out-group antagonist, $F(1, 66)=7.447$, $p=0.008$, $\eta_p^2=0.211$, and less inclined to raise when dealing with an in-group rather than out-group antagonist, $F(1, 66)=4.714$, $p=0.034$, $\eta_p^2=0.114$. These decision patterns did not differ for low vs. high value cards, in that the Treatment × Decision × Antagonist's Group × Competitive Strength interaction was not significant, $F(2, 64)=2.079$, $p=0.14$.

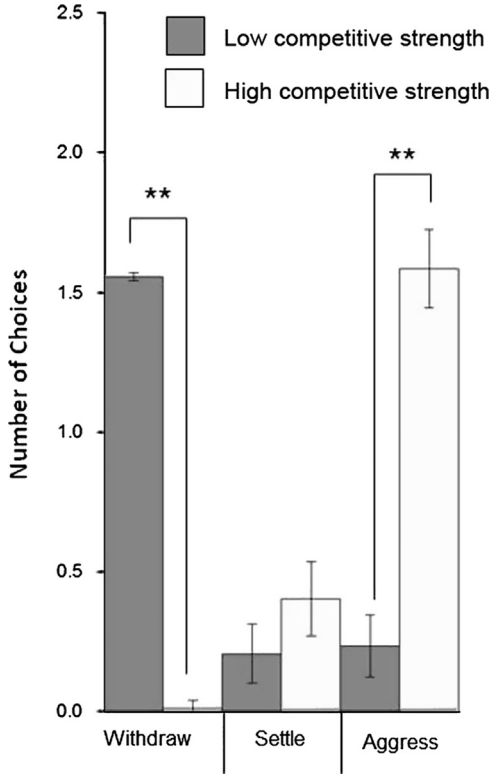

Fig. 2 – Decision Making depends on competitive strength such that individuals withdraw more and aggressively approach less under low competitive strength yet withdraw less and aggressively approach more under high competitive strength (range 0–2, displayed Means ±SE).

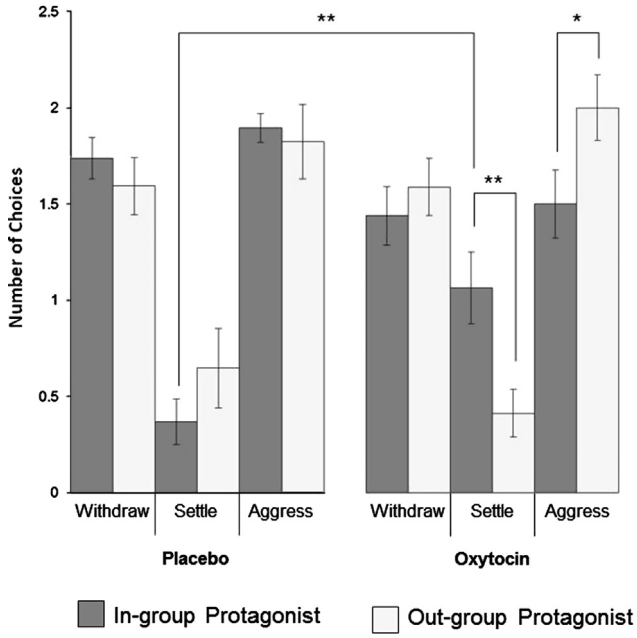

Fig. 3 – Decision Making as a function of Treatment and Antagonist's Group Membership range 0–4; displayed Means ±SE; Connectors indicate significant differences between means, with * $p<0.10$ and ** $p<0.05$ (N=69, two-tailed tests). Under placebo, antagonist's group membership has no effect on withdrawal, compromise, or aggressive approach. Under oxytocin, individuals compromise more and aggressively approach less in-group compared to out-group antagonists.

Another way of looking at this complex interaction among treatment, decision, and antagonist's group membership is by comparing oxytocin vs. placebo within each type of decision and for each antagonist. Treatment had no effect for costly withdrawal, regardless of whether the antagonist was in-group, $F(1, 66)=2.382$, $p=0.127$ or out-group, $F(1, 66)=0.088$, $p=0.767$. However, oxytocin compared to placebo led to more compromise when dealing with an in-group antagonist, $F(1, 66)=8.837$, $p=0.004$, $\eta_p^2=0.239$, and not when dealing with an out-group antagonist, $F(1, 66)=1.037$, $p=0.312$, $\eta_p^2=0.021$. Finally, oxytocin compared to placebo reduced competitive approach towards an in-group, $F(1, 66)=2.808$, $p=0.099$, $\eta_p^2=0.121$ (marginal), and non-significantly increased competitive approach towards an out-group, $F(1, 66)=0.606$, $p=0.441$, $\eta_p^2=0.012$. This corroborates earlier work showing that oxytocin compared to placebo increases benevolence towards in-group members and not, or to a much lesser extent, motivates competitiveness towards out-groups (De Dreu et al., 2010, 2011).

3. Conclusions and discussion

Results permit three conclusions. First, intranasal oxytocin does not increase indiscriminate benevolence in humans. This conclusion follows from the observation that in competitive interactions, humans given oxytocin reduce competitive approach only when their protagonist is an in-group member, and do not show an increased preference for settlement when protagonists are from a rivaling out-group. Second, and relatedly, intranasal oxytocin promotes cooperative conflict resolution in within but not between group competitions. This conclusion follows from the observation that, compared to placebo, oxytocin increased a preference for settlement with in-group protagonists, but not with out-group protagonists. Third, and finally, in competitive interactions, intranasal oxytocin does not influence preferences for withdrawal. This conclusion follows from the observation that regardless of competitive strength, and regardless of the protagonist's group membership, oxytocin exerted no influence whatsoever on the tendency to "fold" in the competitive poker-game studied here.

Results corroborate our conjecture that oxytocin plays a pivotal role in creating, maintaining, and promoting humans' bonds within the groups upon which they depend. Consistent with earlier studies on in-group favoritism (De Dreu et al., 2011; Sheng et al., 2013), social conformity (Stallen et al., 2012), and parochial altruism (De Dreu et al., 2010, 2012b), here we observed that oxytocin increases preferences for cooperative settlement and reduced preferences for competitive approach in interactions with in-group members, but not in interactions with out-group members.

The key finding that effects of oxytocin on competitive decision making are moderated by the antagonist's group membership subscribes to the general conclusion that, in humans, effects of oxytocin depend on both individual differences and personality characteristics, and on contextual

cues and situational constraints (Bartz et al., 2011). Scheele et al. (2012), for example, observed markedly different effects of oxytocin on interpersonal distance when participants were romantically engaged or not on the one hand, and the interaction target's sex. Other work observed effects of oxytocin to depend on early childhood experiences (Van IJzendoorn and Bakermans-Kranenburg, in press). Similar to the current findings, it thus appears that effects of oxytocin in humans are context-dependent, and that one key context involves (features of) the group setting within which the individual operates.

Our study involved healthy males engaging in a simple competition with a simulated protagonist. As such, current conclusions are limited, potentially, to males and may not generalize to female participants. There is some evidence that oxytocin up-regulates motivational attention to competition in males but not in females (Fischer-Shofty et al., in press). Future research should examine current hypotheses for both males and females. Second, competitive interaction was studied with a highly simplified poker game, in which participants made decisions without receiving feedback on the outcomes of these decisions. Accordingly, the current study contains no information about possible adaptation to the competitor's strategy, and about whether oxytocin increases flexible adaptation or not. There is some evidence that oxytocin, compared to placebo, promotes divergent thinking and flexible processing (De Dreu et al., in press), and it may thus be possible that humans given oxytocin more flexibly adapt to the outcomes of a competitive interaction, their opponent's strategy, and their combination. Herein lies another avenue for future research into the role of oxytocin in social behavior. Study limitations aside, our results inform an emerging debate about the fundamental mechanisms that account for the plethora of effects oxytocin seems to exert on social perception, social motivation, and social behavior. Three or more or less related accounts have been proposed. The first account rests on the well-documented anxiolytic effects of oxytocin. Oxytocin interacts with the hypothalamic-pituitary-adrenal axis to attenuate stress responses, and this has a pervasive influence throughout both the body and the brain (Neumann, 2008). Specifically, oxytocin reduces cortisol levels after exposure to stressors (Heinrichs et al., 2003), inhibits cardiovascular stress responses (Uvnas-Moberg, 1998), reduces the activation of the amygdala and attenuates its coupling to brainstem centers responsible for autonomic and behavioral components of fear (Kirsch et al., 2005; Petrovic et al., 2008). This, in turn, has been argued to allow the individual to consider alternatives to fight-or-flight – the typical autonomic response to (social) stressors – and permits pro-social approach (Lim and Young, 2006; Heinrichs et al., 2009; Taylor et al., 2000). This perspective fits the current finding that oxytocin increases a preference for settlement rather than aggressive approach with in-group competitors. However, it has difficulty accounting for the observation that oxytocin did not reduce aggressive approach towards out-group competitors, a finding that emerged in other work as well (De Dreu et al., 2010, 2011; Sheng et al., 2013; also see Declerck et al., 2010; Mikolajczak et al., 2010). A second possibility is that oxytocin increases attention to social cues and therefore it has widely varying effects on 'downstream' cognition and behavior, depending on the social context (Bartz et al., 2011; Shamay-Tsoory et al., 2009). In the current competitive context, this "social salience hypothesis" would imply that oxytocin may increase competitive approach when antagonists belong to a rivaling out-group, yet when they belong to the in-group interaction oxytocin increases cooperation and reduce competitive approach. However, whereas we indeed observed that oxytocin increases in-group cooperation (increased compromise; reduced competitive approach), it did not increase out-group competition (reduced compromise; increased competitive approach).

The final perspective on oxytocin assumes its effects on social cognition and behavior emerge because oxytocin up-regulates social approach towards positive cues, and inhibits withdrawal from negative cues (Kemp and Guastella, 2011). Consistent with this is a recent study of rhesus macaques, showing that oxytocin increases attention to faces and eyes and, importantly, reduces social vigilance for unfamiliar, dominant, and emotional faces (Ebitz et al., 2013; also see Parr et al., in press). Along similar lines, intranasal oxytocin in humans facilitates recognition of and (empathic) responses to positive social cues, yet does not alter recognition of, and responses to aversive social stimuli. From this, Striepens et al. (2012, p. 18147) concluded that oxytocin prepares for "approach and protective behavior, but with heightened caution" (p. 18147), a conclusion that fits well the "tend-and-defend" response triggered by oxytocin in intergroup competition (De Dreu et al., 2010; De Dreu, 2012b). Current results also subscribe to this hypothesis. In competitive interactions among humans, oxytocin does not alter preferences for withdrawal, and increases pro-social preferences but with caution; only when dealing with in-group members and not with competitors from a rivaling out-group does oxytocin promote pro-social approach.

4. Experimental procedures

4.1. *Participant recruitment*

The study was approved by the Ethics Committee of the University of Amsterdam, and all participants provided informed consent prior to participation. Male participants were recruited via an on-line recruiting system and offered a monetary reward of €10 (approx. 13 USD) for participating in a study on the effects of medication on test scores and decision-making. They filled out an on-line medical screening – exclusion criteria were significant medical or psychiatric illness, medication, smoking more than five cigarettes per day, and drug or alcohol abuse. Seventy-three participants were retained and instructed to refrain from smoking or drinking (except water) for 2 h before the experiment. A total of sixty nine participants were included in the final sample and analyses (two participants were excluded because they indicated themselves as very experienced poker players, and two other participants were excluded because of technical failures and missing data). There were no differences between the two treatment groups in medical screening responses. Participants averaged 21.51 ($SD=3.078$) years of age, and age did not differ across experimental conditions, all

$F(1, 65) < 0.52$, all $ps > 0.49$. On average, participants indicated they had moderate experience with poker ($M = 2.36$; with 5 = very much; $SD = 0.94$), and experience did not differ across experimental conditions, all $F(1, 65) < 2.10$, all $p > 0.15$.

4.2. Substance administration

Participants were randomly assigned to the oxytocin or placebo group (double-blind, placebo-controlled study design). Participants self-administered a single intranasal dose of 24 IU oxytocin (Syntocinon-Spray, Novartis; 3 puffs per nostril, each with 4 IU oxytocin) or placebo 30 min before the start of the experimental tasks (De Dreu et al., 2010; Kosfeld et al., 2005). To avoid any subjective effects (for example, olfactory effects) other than those caused by oxytocin, the placebo contained all the active ingredients except for the neuropeptide. The placebo was manufactured by Stichting Apothekers Haarlemse Ziekenhuizen (SAHZ) in coordination with the pharmacy at the Amsterdam Medical Centre (AMC), adhering to the guidelines on Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP). The placebo was produced using the exact same recipes and procedures used by Novartis Inc. to produce the carrier of Syntocinon – the synthetic analog of oxytocin. Placebos were delivered in the same bottles as Syntocinon. In short, the only difference between the placebo and treatment was the absence vs. presence of the active neuropeptide.

4.3. Experimental procedures and materials

Fig. 1 provides the time-line of the experimental procedures and tasks. Participants came in groups of six individuals to the laboratory, where they were seated in individual cubicles in front of a computer displaying all instructions and recording responses. Participants could neither see nor communicate with other participants, and worked independently and at their own pace.

Participants self-administered oxytocin (or placebo) under experimenter supervision. Thereafter, the experimenter unlocked the participant's computer for them to work on a series of unrelated tests, for a total duration of 30 min (this was done because effects of oxytocin emerge approximately 30–35 min past administration; Baumgartner et al., 2008). Embedded in these unrelated tests was a measure of social value orientation, which asks participants in nine decomposed games to choose between a cooperative and a non-cooperative distribution of outcomes between themselves and an anonymous other (see for more detail, De Dreu et al., 2010). To verify that randomization across experimental conditions was successful, we analyzed the number of cooperative choices (range 0–9) in a 2 (Treatment) × 2 (Antagonist's Group Membership) ANOVA. Neither factor had significant effects, alone or in combination, all $F(1, 65) < 2.34$, all $ps > 0.16$, indicating that prior to the (effective) manipulation of our independent variables, and the decision game itself, no differences in cooperative preference existed across the four conditions.

Thirty minutes past self-administration of oxytocin or placebo, the computer switched to instructions for the main experimental tasks. Participants read that they were about to engage in a series of decision making tasks, some of which would require two three-person groups. Participants were assigned to either Team "Triangle" or Team "Circle" on the basis of the order in which they signed-up for the experiment, and engaged in decision making in a between-group competition games (De Dreu et al., 2012b). This took approximately 15 min. Thereafter, they performed a short filler task asking about their current mood. They indicated for 8 positive and 10 negative mood states how they felt (e.g., concentrated; 1 = not at all, to 5 = very much). We created a positive affect index (8 items, $\alpha = 0.67$) and a negative affect index (10 items, $\alpha = 0.82$) and found no differences across the four conditions of our experimental design, all $F(1, 65) < 0.48$, $ps > 0.49$. On average, participants felt more positive ($M = 2.96$, $SD = 0.58$) than negative ($M = 1.33$, $SD = 0.43$).

Following the short filler task, participants were introduced to the two-person simplified online poker game with another participant who would remain anonymous. Participants played four rounds of poker. In each round, they started with 25 chips and were reminded that the earned chips would be converted 1:1 into lottery tickets, which would go into a raffle for one of four 25€ Euro prizes. Before each round started, they had to place a forced bet of five chips and read that from a standard deck of 52 playing cards, they and their antagonist would randomly receive one card. The antagonist was (unknowingly to participants) simulated and said to be a member of their own Team "Triangle", or of the rivaling other Team "Circle" (but different from the antagonist in the between-group competition games; we counterbalanced labels but this had no effects whatsoever). There was no feedback in between rounds–participants decided to fold, call or raise, and then immediately moved to the next round of the game.

After a practice trial, participants played four rounds of poker in which we varied participants' competitive strength. Participants received two low value cards (3 and 5), representing low competitive strength (the probability of winning, a draw, and losing, respectively, is 7.84%, 5.88%, and 86.27% for card value 3, and 23.53%, 5.88%, and 70.59% for card value 5). Participants received two high value cards (J and K), representing high competitive strength (the probability of winning, a draw, and losing, respectively, is 70.59%, 5.88%, and 23.53% for card value J, and 86.27%, 5.88%, and 7.84% for card value K). The color of the antagonist's chips was either red or white but because chip color did not interact with any of the variables, this variable is further ignored.

After the opponent placed a first bet of 10 chips, the participant had the choice between foldings (in which case the remaining 20 chips would be preserved, but five chips would be lost), calling (in which case 15 chips could be won, or 15 chips could be lost), or raising with a maximum of 10 chips in which case the opponent could either call the raise (depending on the amount raised, up to 25 chips could be won or lost), or fold, in which case the participant would win 15 chips. Note that the simulated poker game was an interpersonal (dyadic) game, with earnings from the game going only to the individual participant and not (also) to other members of his team and/or the (simulated) antagonist's team. Because no actual interaction took place, each participant received a fixed number of chips after the four rounds of the game, and each thus had the same probability of winning one of the raffle prizes.

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Research Report

Oxytocin eliminates the own-race bias in face recognition memory ☆

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ABSTRACT

The neuropeptide Oxytocin influences a number of social behaviors, including processing of faces. We examined whether Oxytocin facilitates the processing of out-group faces and reduce the own-race bias (ORB). The ORB is a robust phenomenon characterized by poor recognition memory of other-race faces compared to the same-race faces. In Experiment 1, participants received intranasal solutions of Oxytocin or placebo prior to viewing White and Black faces. On a subsequent recognition test, whereas in the placebo condition the same-race faces were better recognized than other-race faces, in the Oxytocin condition Black and White faces were equally well recognized, effectively eliminating the ORB. In Experiment 2, Oxytocin was administered after the study phase. The ORB resulted, but Oxytocin did not significantly reduce the effect. This study is the first to show that Oxytocin can enhance face memory of out-group members and underscore the importance of social encoding mechanisms underlying the own-race bias.

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1. Introduction

The neuropeptide Oxytocin (OT) has been implicated in complex emotional and social behaviors. Human and animal studies show that OT enhances a number of social interactions, reduces anxiety, increases trust, and in some species decreases social avoidance and aggression (Lee et al., 2009; Zak, 2012). More recently the effects of OT on human social cognition have been demonstrated as well (for reviews see Bartz et al., 2011; MacDonald and MacDonald, 2010). Rimmele et al. (2009) reported that pre-encoding intranasal doses of OT make faces more familiar during subsequent recognition tests, and the effect was unique to this social stimulus set; recognition of non-social stimuli (e.g., houses, sculptures, and landscapes) did not show a beneficial effect of OT. Thus, face identification may be facilitated by pre-encoding exposure to OT. In this study we examined the potential effects of this peptide on the own-race bias (ORB). The ORB is a phenomenon characterized by less accurate recognition of other-race than the same-race faces due to encoding failures. We predict that pre-encoding OT exposure will lead to improvements in recognition of other-race faces.

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1.1. Social-cognitive factors underlying the own-race bias

The ORB is a robust phenomenon demonstrated in numerous studies in the lab and real-world settings (Brigham et al., 2007). In a typical ORB study, participants view the same- and other-race faces. On subsequent recognition memory tests, the same-race faces are more accurately recognized than other-race faces by a number of groups (see Brigham et al., 2007; Pezdek et al., 2003). A principal explanation of the ORB posits that the effect results from social-cognitive factors that lead to differential processing of the same- and other-race faces (see Levin, 2000; Meissner et al., 2005; Sporer, 2001). When a face is perceived, an automatic social categorization process occurs such that the face is placed into an in-group or an out-group category. Race is one of a number of factors that can cue out-group categorization processes (Levin, 2000; Susa et al., 2010). As demonstrated by studies with ambiguous race faces, changing just one facial feature that stereotypically marks a race (e.g. hair style) can trigger face categorization processes (Maclin and Malpass, 2001). This categorization occurs with other in-group/out-group social categories as well. Shriver et al. (2008) showed that White participants remembered faces of White individuals more accurately if they believed them to be affiliated with their own rather than another university or social economic class.

Cognitively, the categorization of faces can be characterized as an economy of attentional resources. Whereas out-group faces are "cognitively disregarded" (Rodin, 1987) leading to decreased attention and shallow processing, in-group faces receive more attentional resources to individuating features diagnostic of recognition (Meissner et al., 2005). Indeed instructing participants to pay close attention to individual aspects of other-race faces substantially reduces the ORB (Hugenberg et al., 2007). Lebrecht et al. (2009) found that training involving an individuation task (attending to face differentiating cues) but not category tasks (deciding on race of face) reduced both the ORB and implicit racial bias. Thus, it appears that early processing dimensions of social categorization affect attentional allocation and to some extent attitudes toward out-group members. These mechanisms appear to underlie the bias in other-race face recognition memory.

1.2. Influence of Oxytocin on face processing

In humans, the impact of OT on social recognition and behavior appears to be moderated by contextual and individual difference factors (Bartz et al., 2011). Despite this, a recent meta-analysis of the effect of OT on *facial recognition of emotions* showed a modest significant effect size in the direction of OT-treated groups outperforming the placebo group (overall $d=.21$, $p<0.01$; Van IJzendoorn and Bakermans-Kranenburg, 2012). Similarly, four of the five published studies on *face recognition memory* show positive effects in the predicted direction (Di Simplicio et al., 2009; Guastella et al., 2008b; Rimmele et al., 2009; Savaskan et al., 2008). A reverse effect was reported by Herzmann et al. (2012). Thus, the overall pattern of result shows that OT enhances face processing and recognition.

Although the mechanisms by which OT facilitates face recognition are unknown, it has been suggested that OT may work by reducing social anxiety and stress via attenuation of amygdala activity, which induces autonomic responses to emotional experience (Kirsch et al., 2005). Using functional MRI, Domes et al. (2007a) showed that compared to a placebo group, OT-treated males had less right-sided amygdala activity in response to emotional face stimuli (showing angry, fearful or happy expressions) than neutral stimuli.

Another mechanism by which OT may enhance face memory is by facilitating eye-gaze to face regions conveying important social information. Guastella et al. (2008a) had participants in OT and placebo conditions view neutral faces. They recorded eye-gaze duration and fixation toward three face regions: eye, nose/mouth and forehead/cheek. Based on previous research indicating that the eye region is primary in social face perception, the authors hypothesized this region would be important in eye-gaze patterns. Compared to the placebo group, OT-treated participants gazed significantly longer and more frequently at the eye region of faces compared to other regions. These eye-gaze data, together with the face recognition studies, suggest that OT may facilitate encoding by inducing a face individuation orienting response.

1.3. Influence of Oxytocin on social categorization

Research investigating the influence of OT on social categorization in humans is sparse (de Dreu, 2012). However, recent research shows that OT may moderate socially relevant behaviors toward in-group and to some extent out-group members. Using measures of event-related brain potentials, Sheng et al. (2013) found greater neural response to in-group faces displaying pain expressions than neutral expressions. This empathy bias was enhanced by OT-treatment significantly more when viewing in-group faces than out-group faces. Similarly, de Dreu et al. (2011) reported that OT-treated groups made stronger positive implicit associations (e.g., ascribing words to targets) and benevolent decisions (e.g., reduced readiness to sacrifice targets) about the in-group compared to control conditions. Only in some conditions did OT-treated participants make negative implicit associations toward the out-group, a result that has not been specifically clarified and may be explained by out-group derogation (de Dreu et al. 2011) or a general OT-induced sensitivity to socially important information (Averbeck, 2010; Chen et al., 2011). In these social categorization studies OT had a greater effect on attitudes and behaviors toward in-group than out-group members. The potential effect of OT on face encoding and recognition memory for in-group vs. out-group members remains unexplored. Examining this relationship is a principal goal of the current study.

1.4. Current study

Given that OT can facilitate encoding of faces via a combination of social, neurological and cognitive processes, and the finding that the ORB results from encoding deficits for other-race faces in some of these same processes, the principal prediction in this study is that encoding of other-race faces

will be enhanced by the application of OT compared to a placebo control condition. In two double-blind experiments, participants were randomly assigned to an OT or placebo condition. Using a social orienting task they encoded own- and other-races faces followed by a recognition memory test. In Experiment 1, OT was administered prior to studying the faces to assess the effects of OT at encoding. We predict that OT will enhance face recognition overall. More important, we predict an interaction with greater improvements in recognition accuracy in the OT than the placebo condition for other-race than the same-race faces, effectively reducing the ORB. The application of OT is predicted to reduce the face categorization bias thereby resulting in more similar allocation of attentional resources to the same- and other-race faces. In Experiment 2, OT was administered after encoding faces to determine if OT affects the consolidation of the information processing stage.

2. Experiment 1 results and discussion

This study involves a 2 (Race of face: White or Black) by 2 (Condition: Placebo or Oxytocin), mixed design, with condition as the between-subjects factor. Measures from Signal Detection Theory (SDT; see Banks, 1970; Stanislaw and Todorov, 1999) were used to assess recognition accuracy for the same- and other-race faces (see Section 6 for explanation of stimuli and participants' tasks). The SDT measures were calculated by comparing test responses to previously seen faces ("old") and distractor faces presented only at test ("new"). A hit rate indicates the proportion of correct responses to previously seen faces; a false alarm rate indicates the proportion of incorrect responses to new faces. The d' rate is the standardized difference in accuracy between responses to old and new faces. The C rate, also known as response bias, is a measure of the tendency to respond "old" or "new" independent of accuracy. A C rate of zero indicates relatively equal distributions of "old" and "new" responses and therefore no bias in responding. A C rate smaller than zero indicates more "old" responses, and a C rate larger than zero indicates more "new" responses. A lower C rate is interpreted as a liberal response bias (more likely to respond "old" to both old and new faces), and a higher C rate is interpreted as a conservative bias (less likely to respond "old").

All statistical tests in this study were conservatively conducted as two-tailed. Degrees of freedom for tests vary because some participants did not provide responses in one or more conditions. Analyses of face recognition measures are reported first, followed by analyses of the social encoding task and self-reported perception of anxiety, mood and attention.

2.1. *Face recognition*

Fig. 1 presents the mean hit rate, false alarm rate, d' rate and C rate as a function of race of target and condition. On the d' data a 2 (Face: White vs. Black) × 2 (Condition: Control vs. OT) mixed ANOVA revealed a significant main effect of race of face and more important, an interaction with condition.

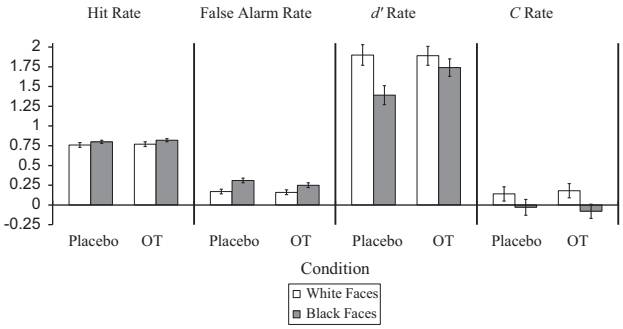


Fig. 1 – Experiment 1 (pre-encoding substance intake). Four dependent measures presented as a function of race of face and condition. Errors bars represent standard errors of the means. The principal finding on the d' rate shows the predicted interaction; whereas in the placebo condition the same-race faces were better recognized than other-race faces, in the Oxytocin condition the same- and other-race faces were equally well recognized, effectively eliminating the own-race bias.

Overall White faces ($M=1.89$, $SE=0.09$) were better recognized than Black faces ($M=1.56$, $SE=0.08$), F (1, 41)=14.22, $p=0.001$, $\eta_p^2=0.26$. The significant interaction, F (1, 41)=4.34, $p=0.044$, $\eta_p^2=0.10$, showed that whereas in the placebo condition, as predicted, White faces ($M=1.90$, $SE=0.13$) were better recognized than Black faces ($M=1.39$, $SE=0.12$); in the OT condition recognition accuracy for White faces ($M=1.89$, $SE=0.12$) and Black faces ($M=1.74$, $SE=0.11$) did not differ. It was specifically recognition memory for Black faces that was improved in the OT compared to the control condition, t (41)=−2.19, $p=0.034$, $d=-0.68$. No other effect was statistically significant on d' (highest $F=1.30$)

The 2 × 2 mixed ANOVAs on hits and false alarm data showed statistically significant effects of race of face only. Hit rates were significantly lower for White ($M=0.76$, $SE=0.02$) than Black faces ($M=0.81$, $SE=0.02$), F (1, 41)=6.81, $p=0.013$, $\eta_p^2=0.14$. However, false alarms were significantly higher with Black ($M=0.28$, $SE=0.02$) than White faces ($M=0.17$, $SE=0.02$), F (1, 41)=37.12, $p<0.001$, $\eta_p^2=0.48$. The finding that the ORB was more evident for false alarm than hit rate data is consistent with findings reported elsewhere (e.g., Meissner and Brigham, 2001). No other effect was statistically significant (highest $F=2.44$).

A 2 × 2 mixed ANOVA on C rates revealed a significant effect of race of face only. Participants were more liberal (more likely to respond "old" to both old and new faces) in their judgment with Black ($M=-0.05$, $SE=0.07$) than White faces ($M=0.16$, $SE=0.06$), F (1, 41)=12.48, $p=0.001$, $\eta_p^2=0.23$. No other effect was significant ($F<1$).

A multivariate analysis of confidence ratings in response to the four types of stimuli at test (old-White, old-Black, new-White, new-Black) as a function of condition revealed no significant effects, $F<1$.

2.2. *Social engagement during encoding*

A 2 × 2 mixed ANOVA on stimulus approachability ratings during encoding showed no statistically significant effects, $F<1$.

The overall mean approachability rating was relatively low (scale 1–10, $M=4.29$, $SE=0.22$), and in all conditions none of the correlations between face approachability rating and d' were significant ($p>0.05$). It is not clear why these results were not significant. Perhaps the task was only effective orienting participants to the faces but not sensitive enough to determine other relationships.

2.3. *Wakefulness, calmness, mood, and attention*

Two 2 (Condition) × 2 (Time: pre- vs. post-encoding) mixed ANOVAs on wakefulness and calmness ratings were conducted. A significant interaction on calmness ratings resulted, F (1,35)=8.37, $p=0.007$, $\eta_p^2=0.19$; whereas in the control condition calmness ratings were lower pre-test ($M=41.44$, $SE=1.58$) than post test ($M=44.94$, $SE=1.83$), (t (17)=−2.81, $p=0.012$ $d=-0.482$), in the OT condition pre- ($M=44.63$, $SE=1.19$) and post ($M=43.95$, $SE=1.17$) calmness ratings did not significantly differ, ($t<1$). No other effect was statistically significant (highest $F=3.79$).

The 2 × 2 ANOVAs on both affect ratings revealed a main effect of time on negative affect only. Negative affect ratings given prior to substance intake ($M=15.58$, $SE=0.78$) decreased after substance intake ($M=14.10$, $SE=0.78$), F (1,41)=7.62, $p=0.009$, $\eta_p^2=0.16$. No other effect was significant (highest $F=1.74$). Additionally, no significant effects were found for the attention measure, $F<1$. Together these results suggest that for the most part OT did not negatively affect participants' mood, anxiety or attention.

In Experiment 1, the principal analyses involving discrimination accuracy (d') revealed three important findings. First, the predicted interaction was confirmed; whereas in the placebo condition same-race faces were better recognized than other-race faces, in the Oxytocin condition Black and White faces were equally well recognized, effectively eliminating the ORB. Second, the main effect of OT was not significant. Overall better face recognition with OT was predicted from previous findings but did not result. Third, there was an overall ORB effect; the same-race faces were more accurately recognized than other-race faces. Finally, OT did not adversely affect participants′ anxiety, mood or attention.

3. Experiment 2

In Experiment 1, pre-encoding of OT significantly improved memory for other-race faces, thus confirming that OT improves face recognition memory at the encoding stage. However, Savaskan et al. (2008) reported that post-encoding of OT also improved face recognition memory, thus suggesting that OT may affect memory consolidation as well as encoding. The results of Experiment 1 and those of Savaskan et al. suggest that pre- and post-encoding OT administration may differentially affect various aspects of face recognition memory. Experiment 2 was conducted to assess if OT affected the own race bias at the consolidation stage in addition to the encoding stage. If so, the significant interaction of race by condition on d' data reported in Experiment 1 would be replicated in Experiment 2. The procedure of Experiment 2 was similar to that used in Experiment 1 except that the OT and placebo were administered after presentation of the target faces.

4. Experiment 2 results and discussion

Experiment 2 applies the same analytical procedures from Experiment 1.

4.1. *Face recognition*

Fig. 2 presents mean hit rate, false alarm rate, d' rate, and C rate as a function of the race of target and condition. Various 2 (Face: White vs. Black) × 2 (Condition: Control vs. OT) mixed ANOVAs on each measure showed statistically significant effects of race of face only; The d' analysis showed that White faces ($M=1.68$, $SE=0.11$) were better recognized than Black faces ($M=1.24$, $SE=0.09$), F (1, 42)=10.58, $p=0.002$, $\eta_p^2=0.20$. Consistent with Experiment 1, whereas hit rates were lower for White ($M=.71$, $SE=0.02$) than Black faces ($M=0.76$, $SE=0.02$), F (1, 42)=6.99, $p=0.011$, $\eta_p^2=0.14$, false alarms were significantly higher with Black ($M=0.34$, $SE=0.03$) than White faces ($M=0.18$, $SE=0.02$), F (1, 42)=51.17, $p<0.001$, $\eta_p^2=0.55$. No other effect on these three measures was statistically significant (highest $F=2.57$). Most critically, the interaction of condition by race of face was not significant on any of the recognition accuracy measures including d' rate ($F=1.50$, $p=0.227$).

A 2 × 2 mixed ANOVA on C rates revealed significant main effects of face and condition. Participants were more liberal in their judgment of Black ($M=-0.13$, $SE=0.06$) than White faces ($M=0.28$, $SE=0.06$), F (1, 42)=39.26, $p<0.001$, $\eta_p^2=0.48$, and participants were more conservative (less likely to choose "old") in the OT ($M=0.19$, $SE=0.07$) than placebo condition ($M=-0.03$, $SE=0.07$), F (1, 42)=4.81, $p=0.034$, $\eta_p^2=0.10$.

As in Experiment 1, a multivariate analysis of confidence ratings in response to the four types of stimuli at test, as a function of condition was not significant, $F=1.37$.

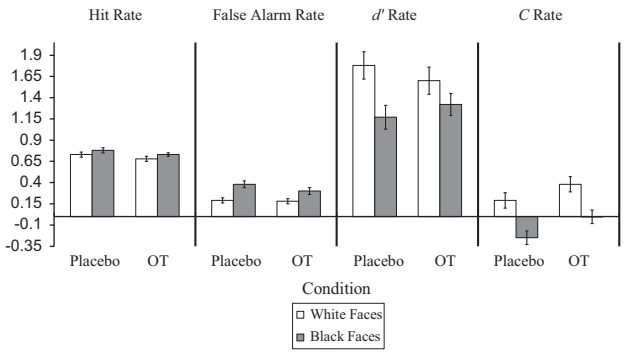


Fig. 2 – Experiment 2 (post-encoding substance intake). Four dependent measures presented as a function race of face and condition. Errors bars represent standard errors of the means. The principal finding on the d' rate shows a main effect of face but not a significant interaction. This indicates that the typical own-race bias occurred in both treatment conditions and post-encoding OT did not have a significant effect on recognition memory.

4.2. Social engagement during encoding

A 2 × 2 mixed ANOVA on stimulus approachability ratings during encoding showed a significant main effect of race of face despite an overall low mean rating (scale 1–10, $M=4.55$, $SE=0.21$). White faces received higher approachability ratings ($M=4.75$, $SE=0.23$) than Black faces ($M=4.36$, $SE=0.23$), F (1, 42)=5.75, $p=0.011$, $\eta_p^2=0.12$. The correlations between approachability ratings and d' measures were small; none were significant, $p>0.05$.

4.3. Wakefulness, calmness, mood, and attention

Two 2 (Condition) × 2 (Time: pre- vs. post-encoding) mixed ANOVAs on wakefulness and calmness ratings were conducted. Only a significant main effect of wakefulness resulted; pre-encoding ratings were higher ($M=43.31$, $SE=1.15$) than post-encoding ratings ($M=41.28$, $SE=1.32$), F (1,39)=5.42, $p=0.025$, $\eta_p^2=0.12$. No other effect was significant (highest $F=1.35$).

The 2 × 2 ANOVAs on both affect ratings revealed a main effect of Time on negative affect only. Negative affect ratings declined from pre-encoding ($M=15.42$, $SE=0.94$) to post-encoding ($M=13.78$, $SE=0.70$), F (1,41)=6.13, $p=0.018$, $\eta_p^2=0.13$. No other effect was significant (highest $F=1.27$) including results on the attention measure, $F<1$.

In Experiment 2 the principal analyses involving discrimination accuracy (d') revealed a significant ORB effect only. Unlike Experiment 1, in Experiment 2, when OT was administered post-encoding, the interaction of condition by race of face was not significant. This nonsignificant interaction in Experiment 2 suggests that OT affects recognition memory for other-race faces only when administered prior to encoding. This is consistent with social-cognitive models of the ORB and underscores the importance of encoding mechanisms involved in the ORB effect.

The main difference between Experiment 1 and 2 is the timing of the substance administration relative to the study phase. This procedure separates the OT encoding effects from consolidation effects. The effect of OT on consolidation processes independent of retrieval processes cannot be assessed in this study. It is likely that the OT substance was still present in the central nervous system at the time of the recognition memory test, as it takes a few hours to wash out of the body. Several studies have used longer delays (e.g., 24 h) for the recognition test (e.g., Guastella et al., 2008b; Rimmele et al., 2009), and Savaskan et al. (2008) used a short (30 min) vs. long (24 h) delay to assess potential interactive effects of OT with time intervals. Results from these studies showed no significant interactive effects, suggesting that OT did not directly affect retrieval processes. Despite this, it is possible that in the context of our study the lack of significant main effect of OT on face recognition memory may be related to the short delay interval.

5. General discussion

This study is the first to show that the neuropeptide, Oxytocin, reduced the own-race bias. The principal finding involved the significant interaction of condition by race of face in Experiment 1; compared to the placebo condition, pre-encoding intake of OT led to a significant increase in accuracy recognizing other-race faces. This interaction was not significant in Experiment 2 when OT was administered post-encoding of faces. These results suggest that the effect of OT on other-race face processing occurs primarily at the encoding stage and does not affect memory consolidation. These results are consistent with social-cognitive models of the ORB and in line with many behavioral studies demonstrating that the memory impairment of other-race faces occurs because of encoding failures. Contrary to predictions from the OT face recognition research, there was no significant effect of OT on recognition memory for the same-race faces.

In modeling the basic mechanisms underlying the ORB, Meissner et al. (2005) and more recently Susa et al. (2010) concluded that the cognitive processes involved in encoding the same-race faces are qualitatively different from that of other-race faces. Racial categorization plays a significant role in early stages of other-race face processing whereby an out-group label may "disrupt the successful encoding of individuating facial information" (p. 535). With the same-race faces a deeper processing involving the encoding of individuating features diagnostic of recognition occurs and can result in better memory. Our results are consistent with a differential processing of faces framework of the ORB. Given that OT facilitates attention to more socially significant face regions such as the eyes, it is possible that OT induced an orienting response to individuating encoding of other-race faces in our participants. Di Simplicio et al. (2009) reported that OT induced a slower processing speed for fearful facial expressions compared to other basic expressions. Thus it is possible that OT works to facilitate greater attention allocation to particular aspects of important stimuli and thereby strengthening encoding.

Emotions may play an important role as well. The emotional salience of Black faces to White participants was shown by Cunningham et al. (2004) with functional MRI. These researchers showed that during a fast-pace perception interval, amygdala activity increased more in response to Black than White faces, and this difference in activation was stronger in participants who exhibited greater racial bias toward out-group members. Because OT dampens amygdala activity in males (Domes et al., 2007a; Kirsch et al., 2005) it is possible that in our study, OT attenuated amygdala activity in response to emotion likely triggered by Black faces. This is possible given that the social group for most of our participants involved mainly Whites. Further research is needed to directly assess these potential relationships and importantly, female participants should be included. A different pattern of results may emerge or elucidate on the current findings, as in some cases female participants' amygdale activation differs from that of men. For example, Domes et al. (2010) found that compared to a control group, OT-treated females showed an increase in left amygdala activation in response to faces displaying a fearful expression. This increase in amygdala activation in females followed by OT treatment may reveal additional relationships between OT and the ORB. Perhaps the ORB will increase in females due to OT-induced activation of the amygdala. Alternatively, gender might moderate the

relationship between OT and ORB when faces displaying emotions are shown, but not when neutral faces (like the ones in the current study) are shown. Any of these findings would further our understanding of OT effects on the ORB.

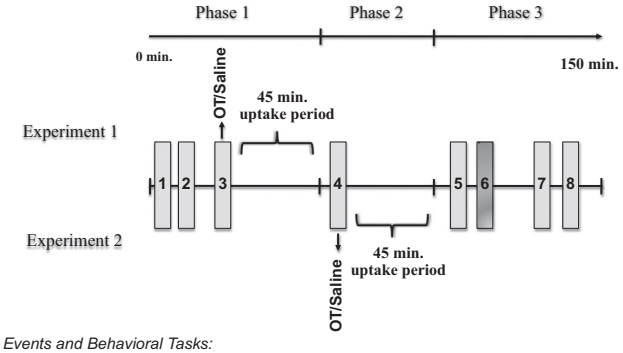
Together, these explanations help clarify the OT effect on memory for other-race faces, however, they do not account for the absence of an effect of OT on the same-race faces. Several contextual and individual difference factors have been noted to account for some inconsistent findings in studies of OT and social cognition (Bartz et al., 2011). One of those factors is task difficulty. Domes et al. (2007b) reported that participants in an OT condition performed better than controls on a difficult version of a mind reading task, however, the two groups performed equally well on the easy version of this task. Similarly, in the verbal memory domain, Heinrichs et al. (2004) showed that pre-encoding OT significantly impaired memory when the recall task was difficult (word generation) but not when it was easy (word-stem completion). Together these findings suggest that stimuli type, task type, and task difficulty may moderate the effect of OT on the same-and cross-race faces. Specifically, it is possible that in our study, OT had a greater influence on the more difficult other-race face memory task but not on the relatively easier same-race face memory task.

This study demonstrated that Oxytocin can enhance the encoding of out-group faces, a class of stimuli that typically receives less attention, is "cognitively disregarded" and processed at a shallow level. The mechanisms underlying these encoding effects need to be clarified in future studies, including the investigation of possible motivational factors driving attention allocation to out-group faces. This study also demonstrates the feasibility of a new methodology to test models of the ORB. Imaging studies have shed light on the neural structures associated with the same- vs. other-race face processing, behavioral studies have investigated the social-cognitive mechanisms involved in processing these two categories of faces, and the current study contributes to the understanding of the ORB from a neurochemical perspective. This furthers our understanding of the ORB and provides a more complete picture of its underlying mechanisms.

6. Experiment 1 method

6.1. Participants and design

Forty-three non-Hispanic Caucasian males (age $M=19.86$, $SD=1.68$) meeting criteria were included. They received $20 and course credit. Similar to other studies (e.g., Rimmele et al., 2009; Savaskan et al., 2008) participants' inclusion criteria were: no physical or mental illness, not taking prescription medication, non-smokers, and a normal heart rate and blood pressure at the time of the study. Participants reported normal sleep–wake cycle the day preceding the study, and no heavy consumption of alcohol or caffeinated drinks, or use of illegal drugs prior to testing. Three participants who showed deviant scores on hits or false alarm measures ($z>3.29$) were not included in analyses. A double-blind placebo-control design was used with 23 participants in the OT condition and 20 in the control condition. The main



Events and Behavioral Tasks:
1. Health questionnaire and BP/Heart Rate reading.
2. Psychological processes questionnaires.
3. Exp 1: OT or Saline administration. Exp 2: Study face stimuli.
4. Exp 1: Study face stimuli. Exp 2: OT or Saline administration.
5. Psychological processes questionnaires.
6. Test of face stimuli.
7. Contact and Knowledge questionnaires.
8. Debrief.

Fig. 3 – Events and behavioral tasks completed in each phase of Experiments 1 and 2.

design is a 2 (Race of face: White or Black) by 2 (Condition: Placebo or Oxytocin), mixed design, with condition as the between-subjects factor.

6.2. Materials and procedure

There were three phases, illustrated in Fig. 3. In phase 1, participants completed a questionnaire assessing their prior days' activities, followed by assessments of heart rate and blood pressure. Next, questionnaires assessing wakefulness, calmness (Steyer et al., 1997), mood (Positive and Negative Affect Scale, PANAS; http://ir.uiowa.edu/psychology_pubs/11) and attention (Brickenkamp and Zillmer, 1998) were completed self-paced. Immediately afterward, participants self-administered intrana sally, either 24 IU of Oxytocin (Syntocinon Spray by Novartis; three puffs of 4-IU in each nostril) or the placebo (saline) solution.

Using procedures similar to Rimmele et al. (2009) we allowed 45 min to ensure OT central nervous system effects. During this time participants completed distractor tasks. In phase 2, participants viewed 50 neutral-expression faces (25 Black, 25 White, in random blocks) for 2.5 s each, with instructions to study each face and indicate the extent to which they would like to approach the person (rating: 1=not at all; 10=very much). This orienting task (a) ensured that participants were attending to stimuli in a social manner, and (b) determine if OT has a greater effect than placebo on subjective perception of stimuli at encoding. Practice trials familiarized participants with the task. The face stimuli for both experiments were selected from the database of male faces with neutral expressions used by Meissner et al. (2005) and others.[1]

Immediately following, in phase 3, participants again completed the wakefulness, calmness, mood and attention questionnaires. They were then instructed on the test procedure and given practice trials. The test consisted of 50 old and 50 new face stimuli (50 Black and 50 White faces) presented for 2.5 s each and organized in blocks shown in random order. Participants' task was to decide if each face was old or new

[1]See: http://iilab.utep.edu/stimuli.htm.

and rate their confidence in that assessment (1=not at all confident; 10=very confident).

Participants then reported their contact with the same- and other- race groups; the majority (73%) reported that their social group included mostly Whites. Finally, they were asked to guess which condition they were assigned to. Only 17 provided a guess response. The proportion of those guessing correctly (47%) was not significantly different from those guessing incorrectly (54%), $Z=.34$, $p>0.05$.

7. Experiment 2 method

7.1. *Participants and design*

Forty-four non-Hispanic Caucasian males (age $M=19.57$, $SD=1.45$) participated. They received $20 and course credit. The same design, inclusion criteria, and prescreening used in Experiment 1 were used in Experiment 2.

7.2. *Materials and procedure*

In phase 1, all procedures followed in Experiment 1 were used except that participants studied the face stimuli in phase 1 rather than phase 2 (see Fig. 3). Similar to Savaskan et al. (2008), immediately following presentation phase, in phase 2, participants self-administered the substance and waited 45 min. In phase 3, participants again completed the wakefulness, calmness, mood and attention questionnaires and were then presented the face recognition memory test.

Next participants reported on their contact with the same- and other-race groups; 63% reported their social group to include mostly Whites. Finally participants were asked to guess which condition they were assigned to. Only 20 participants provided a guess response. The proportion of those guessing correctly (35%) was not significantly different from those guessing incorrectly (65%), $Z=1.90$, $p>0.05$

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Research Report

Oxytocin's role in anxiety: A critical appraisal

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ABSTRACT

A growing literature suggests that the oxytocin (OT) system may play a role in human anxiety states, anxiety-related traits, and moreover, that this system may be a target for the development of novel anxiolytic treatments. However, studies of OT's acute and chronic effects on various aspects of anxiety have produced mixed results. In this forward-looking review, we discuss the myriad phenomena to which the term "anxiety" is applied in the OT literature and the problem this presents developing a coherent picture of OT's role in anxiety. We then survey several different fields of research that support the role of the OT system in human anxiety, including evolutionary perspectives, translational and neuroimaging research, genetic studies, and clinical trials of intranasal OT. As an outgrowth of this data, we propose a "bowtie" model of OT's role at the interface of social attachment and anxiety. We next direct attention to understudied brain regions and neural circuits which may be important to study in OT experiments in humans anxiety disorders. Finally, we conclude by proposing questions and priorities for studying both the clinical potential of OT in anxiety, as well as mechanisms that may underlie this potential. Crucially, these priorities include targeted proof-of-concept clinical trials of IN OT in certain anxiety disorders, including investigations of individual moderators of OT's anxiolytic effects (i.e. sex, genetic factors, and early experience).

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1. Introduction

H.L. Mencken quipped that "for every complex problem there is an answer that is clear, simple, and wrong". Human anxiety disorders[1] are complex problems. Might OT be an answer? Though a growing literature discusses the relationship between OT and anxiety—and frequently states that oxytocin is "anxiolytic"—the answer to this question is neither clear nor simple. As a case in point, research from our own group has found both single-dose anxiogenic (Macdonald et al., 2013b) and chronic anxiolytic effects (Feifel et al., 2011) of IN OT in humans with psychiatric disorders. In this forward-looking review, we survey several literatures that inform the role of the OT system as a target

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[1]For the purposes of this review—and because most studies in humans have been done using the DSM IV system—unless otherwise specified, "anxiety disorders" refers to anxiety disorders in the DSM IV classification system. These include panic disorder (PD), obsessive-compulsive disorder (OCD), social phobia/social anxiety disorder (SOP), generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD). Recently, DSM 5 changed the classification of several of these disorders (notably, OCD and PTSD), added a diagnosis to the category (adult separation anxiety disorder) and changed the diagnostic criteria for several disorders (see Table 1).

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for novel anxiolytics and discuss a variety of ways that the OT system may be related to human anxiety-related traits and disorders. These bodies of research include: (1) evolutionary biological perspectives on anxiety and the OT/social neuropeptide system (including a bow-tie model of their overlap); (2) translational research on OT's relationship to mammalian fear and anxiety; (3) studies of genetic variation in the OT system; (4) neuroimaging studies of anxiety states, traits and disorders; (5) human experiments using intranasal (IN) OT. Building on these diverse literatures, we survey several brain "regions of interest" found to be important across human anxiety disorders, and propose them as future targets of study of the anxiolytic effects of OT. We conclude by emphasizing that a key therapeutic question—whether chronic OT or OT mimetics can give meaningful relief to humans with anxiety and stress-related disorders—is yet to be answered. Throughout this paper, though we emphasize the OT system, we acknowledge the dynamic interplay between OT and AVP systems (Neumann and Landgraf, 2012) (including the role of AVP receptors in some of OT's anxiolytic effects (i.e. Mak et al., 2012)). Among other reasons, this focus warranted by the fact that the majority of trials in humans that inform OTs anxiolytic effects have focused on the OT "half" of the social neuropeptide system.

1.1. *Overview: clinical anxiety disorders*

Broadly speaking, anxiety disorders are the most prevalent class of mental disorders, impose significant functional impairment, and typically have a chronic, recurrent course (Kessler et al., 2005a, 2005b; Ravindran and Stein, 2010). Myriad factors influence their development, including genetic and temperamental factors (Biederman et al., 2001; Ehringer et al., 2006; Fox et al., 2005; Hirshfeld-Becker et al., 2008; Kagan et al., 2001; Norrholm and Ressler, 2009; Stein et al., 2008). These factors interact in complex ways with early socioemotional experiences, resulting in the "programming" of hormonal systems like the HPA axis (Heim and Nemeroff (2001), Meaney et al. (2007), and Heim et al. (2008) for review) and the OT system (Champagne et al., 2001; Feldman et al., 2010; Macdonald, 2012; Pedersen and Boccia, 2002). Besides the categorical anxiety disorders, anxiety symptoms are a common, transdiagnostic, functionally-impairing component of other many disorders including depression and schizophrenia (D'Avanzato et al., 2013; Fava et al., 2008; Kessler et al., 2005b). Current pharmacological treatments for anxiety and anxiety disorders frequently have side effects or do not induce symptom remission, leading to a need for novel antianxiety agents (Carson et al., 2004; Davidson et al., 2010).

1.2. *Defining terms: what is anxiety? what is an anxiety disorder?*

Three linked topics contribute to a mixed perception of OT's anxiolytic potential. The first issue—common in the neurosciences (Kagan, 2008)— is linguistic, and concerns vagaries in the use of the term "anxiety". To wit, like the terms "prosocial" (Goodson, 2013), "trust" (Zak et al., 2004) and "love" (Young, 2009), the terms "anxiety" (and therefore "anxiolytic") are promiscuous and underspecified. In different contexts, these terms are used to denote a wide variety of anxiety-related phenomena in both animals and humans (Blume et al., 2008; Bosch, 2011; Grillon et al., 2013; Thompson et al., 2011; Weisman et al., 2013a). Table 1 sets down a number of these common anxiety-related terms and phenomena. As evidenced by the array of topics there, depending on the knowledge domain and research field, anxiety can refer to: (1) subjective/verbal statements (typically captured in self-reports); (2) behaviors in nature or the lab; and/or (3) biological and physiological measurements (i.e. elevated cortisol, sympathetic arousal, amygdala activation) (Kagan, 2008). Though these different domains all map onto a triparate model of human anxiety (Lang and Davis, 2006), these shifting referents contribute to lack of clarity in the OT-anxiety literature. Rather than proposing a solution to this "tower of Babel" dilemma, we simply highlight the importance of clear, domain-specific language, and alert the reader to this trend.

A second, related issue in the OT-anxiety literature is an often-mistaken perception that acute anxiolytic-type effects (i.e. short-term decreases in subjective fearful feelings or acute neural effects—i.e. amygdala downregulation)—are necessarily salutary, and the obverse: that acute anxiogenic-type effects are negative. As we have discussed in a prior publication (Macdonald et al., 2013a), the contrast between the acute subjective anxiogenesis and amygdala activation seen with SSRIs (Burghardt and Bauer, 2013; McKie et al., 2005; Ravinder et al., 2013) and these agent's later-onset symptomatic benefits highlights the problems with this assumption. Coming from the other side of the argument, agents that have reliable short-term subjective anxiolytic effects in humans (i.e. benzodiazepines) may impair fear learning (Stewart, 2005), and are not recommended in the treatment of certain stress-related disorders (Tol et al., 2013). Therefore, when considering the potential of OT in the psychopharmacological treatment of human anxiety states and disorders, its acute effects should be disambiguated from potential long-term benefits after chronic delivery.

A third contributor to the mixed perception of OT's promise as an anxiolytic agent has to do with the heterogeneous nature of the maladies classified as anxiety disorders (Craske et al., 2009). Though many of the DSM IV and DSM 5 anxiety disorders share phenomenological, psychological, and neurobiological features (Craske et al., 2009; Etkin and Wager, 2007; Menon, 2011; Mineka and Zinbarg, 2006; Sylvester et al., 2012), and though they are often treated with similar medication classes (i.e. SRIs) and therapies (i.e. exposure-based therapies) (Craske et al., 2009; Ravindran and Stein, 2010), from multiple other perspectives (i.e. phenomenology, factor analytical, genetics) they are a heterogeneous group. Reflecting this fact, several conditions classified in the DSM IV as anxiety disorders have been reclassified in DSM 5 (see footnote above). Not only are there significant within-category differences in the anxiety disorders, but these afflictions share significant overlap with mood disorders (Craske et al., 2009; Kendler et al., 2011; Kendler et al., 2003; Krueger, 1999; Watson, 2005), a reality reflected in the NIH RDoC "negative valence systems" category (Insel et al., 2010). Notably, the RDoC criteria place OT in two

Table 1 – Varieties of anxious experience: terms used in the OT literature related to anxiety and stress-related disorders.

Construct/term	Definition	References related to OT	Comments
"Anxiety" (and the related terms "anxiolytic" and "anxiogenic")	Underspecified: depending on the context, any of the below	See text	1. Neurobiologically, the activation or deactivation of some aspect of the brain's central "fear system" (acute, phasic responses to threat), or the related "anxiety system" (tonic, longer-term responses to anticipation of danger) (Barlow, 2002; Davis et al., 2010) 2. In emotion literature, anxiety is often considered a secondary emotion in response to a primary emotional reaction (anticipatory response to fear or pain) (Barlow, 2002) 3. Components of human anxiety: – Action tendencies (avoidance) – Appraisal/attention biases – Physiology (autonomic nervous system, HPA axis) – Expression (facial, vocal) – Cognitions (worry) – Subjective feelings states (i.e. interoception of somatic markers) (Barlow, 2002; Craske et al., 2009; Lang et al., 2000; Risbrough, 2010)
Fear	A phasic, primary, aversive state of the nervous system associated with threat to survival or pain	Guzman et al. (2013) and Knobloch et al. (2012)	1. In one influential model focusing on primary defensive states of the nervous system, fear is contrasted with anxiety, a tonic response associated with sustained fear and anticipation (Davis et al., 2010). In human research, anxious anticipation is sometimes called dread (Berns et al., 2006; Carter and Krug, 2009; Mobbs et al., 2007) 2. The mammalian fear system is subserved by highly conserved subcortical brain networks (lateral and central amygdala, anterior and medial hypothalamus, PAG) (LeDoux, 1996; Panksepp, 1998) 3. Activation of this system coordinates and mobilizes facets of the organism—physiology (sympathetic nervous system, HPA axis), behavior, facial expression—to cope with and communicate immediate threat 4. Symptoms of clinical anxiety disorders are better detected in sustained rather than phasic fear paradigms (sustained fear) (Davis et al., 2010)
Stress	First defined as the non-specific response ("general adaptation syndrome") of the body to noxious stimuli (Selye, 1936)	Cardoso et al. (2013), Skopek et al. (2012) and Taylor et al., 2000	1. Like "anxiety", an underspecified term whose experimental definition has been perennially problematic (Koolhaas et al., 2011; Selye, 1936) 2. Captured in the DSM 5 as part of "post-traumatic stress disorder" (American Psychiatric Association, 2013) 3. Related to disruption of homeostasis and the fight-or-flight response (Cannon, 1932) 4. Often recruits the neuroendocrine system, the autonomic nervous system and the immune system (Koolhaas et al., 2011). Key elements of a restrictive definition of stressful situations include (1) unpredictability, (2) uncontrollability, and (3) environmental demands which exceed individual capacity

			(Koolhaas et al., 2011)
Anxiety symptoms	Subjective symptoms related to anxiety or fear, typically collected via self-report (i.e. STAI)	Lawson et al. (2013)	1. Can refer to symptoms contributing to a DSM diagnosis of anxiety disorder 2. Single-question/Likert-type assessments of anxiety or fear (i.e. visual analog scales) do not tend to discriminate single-dose OT from placebo (MacDonald et al., 2011) 3. Dissociation between physiological/neurobiological signs of anxiety and subjective anxiety symptoms (response dyssynchrony) is common (see text for references and discussion)
Endophenotypes of anxiety disorders	A restrictive definition states that endophenotypes should be laboratory-based biomarkers that are (1) quantifiable; (2) associated with genetic risk for the disorder; (3) abnormal in patients and probands and (4) relatively invariant (Bearden and Freimer, 2006)	de Oliveira et al. (2012a, 2012b), Labuschagne et al. (2010, 2011) and Panksepp (2006)	The definition of endophenotype varies in the anxiety literature from more to less restrictive, with the less restrictive types sometimes called intermediate phenotypes (see footnote in text)
Anxiety-related behaviors/anxiety-like behavior	A variety of behavioral responses linked to anxiety disorders and used in animal and human models (i.e. fear-potentiated startle (FPS)) (see text)	Figueira et al. (2008), Grillon et al. (2013), Mantella et al. (2003) and Slattery and Neumann (2010)	1. Correlation of animal or human behavior with (1) subjective anxious feelings in humans; (2) human anxiety disorders; or (3) pharmacological agents used to treat human anxiety is imperfect (see discussion in Baas et al. (2009) and Fernando and Robbins (2011)) 2. The effects of OT on FPS in humans have been examined in several human studies (Acheson et al., 2013; Grillon et al., 2013). The FPS model has both advantages and disadvantages in terms of screening for anxiolytics (Grillon et al., 2009; Klumpers et al., 2010; Baas et al., 2009) (and see text) 3. The effects of OT have been examined in many animal models of anxiety (Lin, 2012; Rotzinger et al., 2010)
Separation anxiety[a]	"overconcern about their offspring and spouses… experience marked discomfort when separated from them"	Costa et al. (2009)	1. Though it has unclear homology to adult separation anxiety, animal models use maternal separation—which causes changes in OT systems (Kojima et al., 2012; Lukas et al., 2010)—to model early life stress (Zhang et al., 2012) 2. Adult separation anxiety disorder (ASAD) is not uncommon (Bogels et al., 2013), and is now listed in DSM 5 anxiety disorders (American Psychiatric Association, 2013) 3. Classification of behaviorally inhibited children at 2 years is composed of clinging to and remaining proximal to the mother and approach of novel stimuli (Schwartz et al., 2012)
Anxiety disorder	One of the anxiety disorders codified in the DSM system	Feifel et al. (2011), Guastella et al. (2008), Labuschagne et al. (2011) and Macdonald and Feifel (2013) for review	The DSM 5 recently reclassified several anxiety disorders (see footnote in text)
Anxiety-related temperaments			See text for discussion
Anxious temperament (aka "inhibited temperament")	A trait-like tendency to avoid novel or unfamiliar situations, and demonstrate increased physiological responsiveness and behavioral inhibition to mild threat	Poirier et al. (2013)	More than other anxiety-related temperaments, anxious temperament is related to behavioral observations, and therefore can be used in translational research in animals and very young (preverbal) humans (i.e. Oler et al., 2010)
Attachment anxiety			

Table 1 (*continued*)

Construct/term	Definition	References related to OT	Comments
	A trait measure of sensitivity to or worry about rejection or loss of relationships with intimates (Brennan et al., 1998)	Bartz et al. (2011), Kiss et al. (2011), Love et al. (2012) and Weisman et al. (2013a)	Along with attachment avoidance, one of the two attachment parameters demonstrated in some studies to moderate certain individual responses to oxytocin (see text)
Trait anxiety	Measured with STAI, trait version	Stuebe et al. (2013) and Weisman et al. (2013a)	One of a cluster of terms (see also "harm avoidance" and "anxious temperament") describing trait-like tendency toward tension, anxiety, and negative affectivity
Harm avoidance	A heritable temperamental trait assessed with Cloninger's temperament and character inventory (Cloninger, 1987), and associated with excessive worrying, cautiousness, pessimism, shyness and fearfulness	Stankova et al. (2012) and Wang et al. (2013)	Harm avoidance is associated with anxiety disorders (Ball et al., 2002; Wachleski et al., 2008), and a number of parameters of neurobiology (see text)

A variety of terms are used in the literature pertaining to OT's role in human fear, anxiety, and anxiety disorders. References in table refer to OT studies relating to that aspect of anxiety. See text for discussion.

[a] Based on DSM 5 definition.

domains: negative valence systems and social processes (Insel et al., 2010), creating a shared space of interest in terms of the role of OT in human anxiety (Figs. 1 and 2). In the future, human studies will likely use a combination of DSM 5 and RDoC-influenced criteria and endpoints (Insel et al., 2010), a dual agenda which will create both challenges and opportunities.

Ultimately, though the abovementioned issues are important, the largest and most glaring impediment to understanding the role of OT as a bona-fide treatment for human anxiety disorders is lack of direct clinical research. In fact, a search for published studies treating patients with anxiety disorders with chronic (multiple-week) OT yields a total of only 26 patients (Table 2). Almost half of these are negative studies of patients with OCD (den Boer and Westenberg, 1992; Epperson et al., 1996), a disorder now considered have significantly different neurobiological substrates than other anxiety disorders (Brennan et al., 2013; Saxena and Rauch, 2000). As such, though the studies reviewed herein suggest that the OT system may have a role in the treatment of anxiety disorders, with the exception of a few pilot trials (Feifel et al., 2011), studies that directly address key clinical questions about the role of OT in human anxiety disorders are still sorely lacking.

1.3. *Evolution, anxiety, and social neuropeptides*

The long evolutionary history of fear, anxiety, and the social nonapeptides (OT and AVP) strongly inform OT's potential as an anxiolytic agent. From this evolutionary and phylogenic perspective, it has long been noted that many human anxiety symptoms and disorders have their roots in highly conserved mammalian "defense systems" (Belzung and Philippot, 2007; Deakin and Graeff, 1991; Lang and Davis, 2006; Panksepp, 1998). The most ancient roots of these brain-based systems have both appraisal (i.e. low-level, reflexive valancing (Robinson, 1998)) and hormonal aspects which—like OT homologs—can be found in simple invertebrates (Beets et al., 2013; Belzung and Philippot, 2007; Panksepp, 1998; Yamashita and Kitano, 2013). Over millennia, these primitive mechanisms become intercalated in vertebrates with homeostatic mechanisms (i.e. the autonomic nervous systems), and in mammals, aspects of these systems are exapted, modified, and repurposed into mechanisms for social signaling, social perception, attachment, and pairbonding (Chang et al., 2013; Emery, 2000; Porges, 2003b; Shultz and Dunbar, 2007; Tomasello et al., 2007). Many of these defense and safety-related mechanisms (i.e. eye contact, vocalizations, facial expressions) have been shown to be correlated with or modified by OT (Domes et al., 2013b; Seltzer et al., 2010; Shahrestani et al., 2013). A critical aspect of the evolutionary advance in placental mammals was the comingling of brain reward mechanisms with chemistries related to sex, birth and nursing (including OT-related systems (Dolen et al., 2013)); these allowed infants and mothers to sustain dyadic behavioral "addiction" (Insel, 2003) and "symbiotic regulation" (Hofer, 1994b; Porges ad Carter, 2012). Importantly, development of these social attachments necessitated the modulation of older defense-related systems: deactivation of amygdala (Moriceau and Sullivan, 2005), regulation of

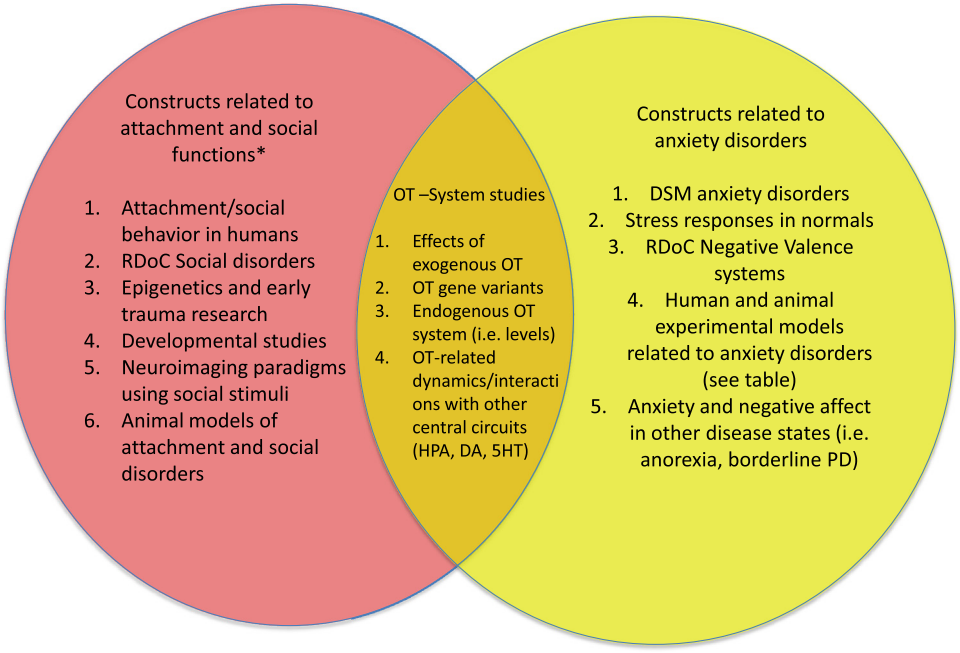

Fig. 1 – As captured in the RDoC criteria, different aspects of the larger field of OT-related research relate to both social/attachment functions, as well as anxiety and anxiety disorders. *Though attachment-related topics and social processes and behaviors are not synonymous, they are combined here for simplicity.

sympathetic tone via myelenated vagus (Porges and Carter, 2012), and relational entrainment of the HPA axis (Feldman, 2012; Hofer, 1994a; Insel, 2003). Here, in ancient brain reward and regulatory systems, we find the neural roots of sustained attachment bonds, as well as the microcircuitry wherein social attachments function as 'hidden' regulators of the physiology and behavior of offspring (Feldman, 2012; Hofer, 1994a; Porges and Carter, 2012).

From an evolutionary perspective, then, maternal-infant attachment became a new "safety signal", creating links between single-skull survival-oriented defense systems and OT-associated attachment systems (Hofer, 1994a; Panksepp et al., 1997; Porges, 2003a). This evolutionary fact introduces an interesting dialectic into OT research and social neuroscience: though for the developing infant attachment is a survival necessity, outside of this bond, and throughout the rest of mammalian life, conspecifics and other minded beings are a more ambiguous social signal, a potential source of reward and pleasure as well as competition, stress, and danger. This dialectic informs the potential "anxiolytic" effects of OT vis a vis its ability to increase the salience of social stimuli (Groppe et al., 2013). That is, increasing the salience of social stimuli in different contexts may have very different survival implications, as well as different implications for fear and anxiety.

A finally step in the evolutionary process discussed above came with the evolution of integrative cortical brain structures supporting second and third-level representations of body state, higher levels of consciousness, and more advanced social cognition. These include structures and "modules" that instantiate aspects of self-awareness, awareness of the minds of others, and future-oriented cognition (Belzung and Philippot, 2007; Brune and Brune-Cohrs, 2006; Chang et al., 2013; Panksepp and Northoff, 2009; Shultz and Dunbar, 2007; Tomasello et al., 2005). These cortical structures play a central role in our current understanding of human anxiety disorders (see Section 4.7), though our understanding of the role of OT in these areas is nascent (but see recent, seminal study of cortical effects of OT (Zheng, 2014)).

To summarize: tracing the phylogenic pathway of these two highly-conserved brain systems –defense and attachment—alongside the remarkably conserved OT system highlights several pathways through which OT may have effects on the expression, phenomenology and development of human anxieties at different levels of the evolved neural axis (Bethlehem et al., 2013; Kirsch et al., 2005; Riem et al., 2013; Zink and Meyer-Lindenberg, 2012). This idea is further developed in Section 3, in the context of a "bowtie" model of OT.

1.4. *Causal thickets: OT and levels of analysis*

Alongside the "long view" provided by a phylogenic and evolutionary perspective on OT's role in fear and anxiety, one can place a more present-oriented perspective on different "levels of analysis" present in the OT-anxiety literature (Table 3). In term of the broader goal of understanding OT's role in the development and treatment of anxiety disorders within a human lifespan, it is worth noting that the more we understand the details of a system, the greater the number of potential cross-level interactions, emergent system properties and feedback loops are created (Kendler, 2005, 2008). These complex interactions create recursive etiological pathways and complex "causal thickets" (Kendler, 2005, 2008). In the case of OT, these multi-level dynamics may be the best theoretical model with which to understand emerging studies of OT's role in gene x environment interactions (for example,

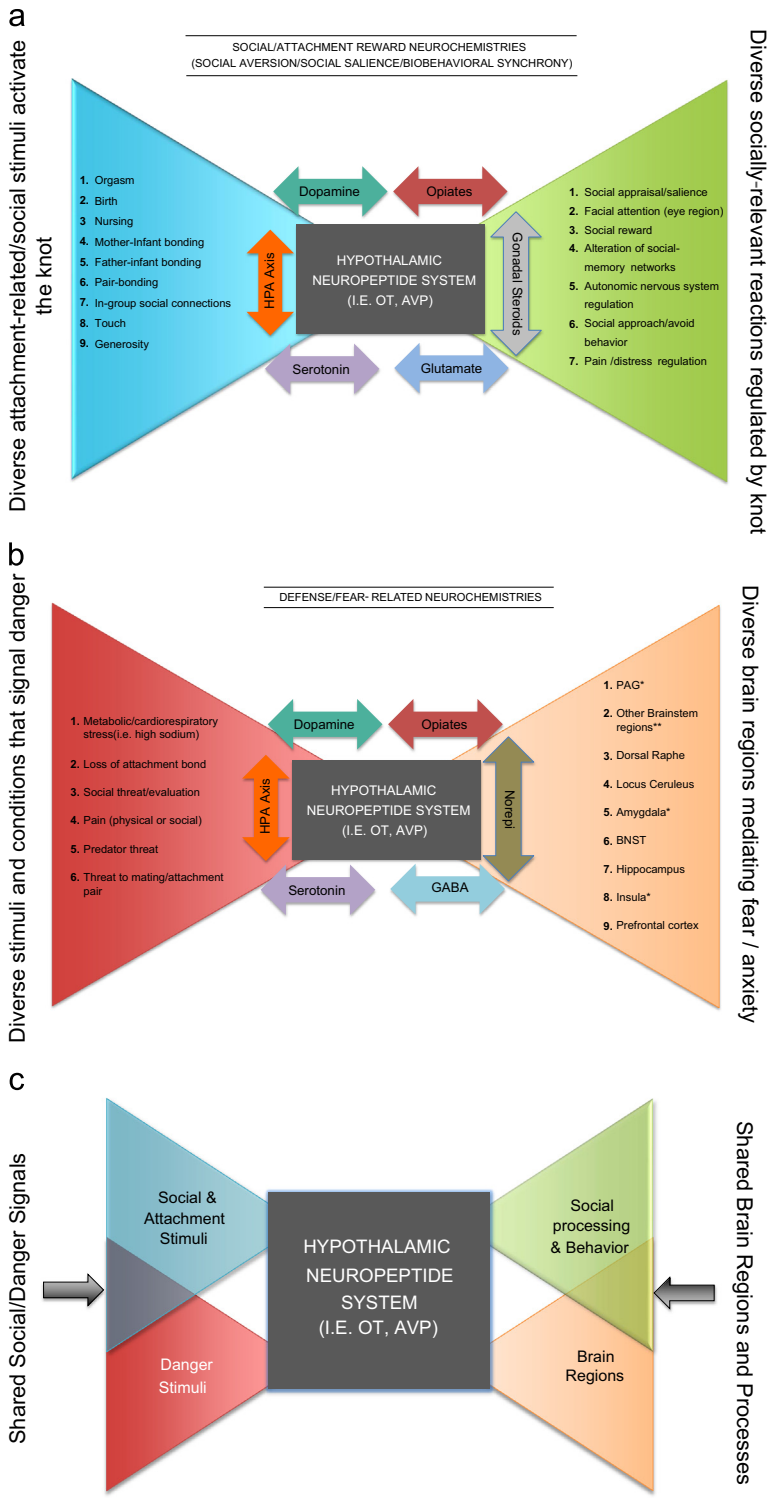

Fig. 2 – The central OT/social neuropeptide system is embedded in a layered, interactive central network, and is an example of the knot in a bowtie architectural structure. Bowtie architectures are a characteristic of robust, evolvable systems in biology (i.e. the social attachment system (a) and fear/defense system (b)), and have extensive 'fan-in' inputs and a diverse array of 'fan-out' outputs. Left and right sides of the bowtie are connected by a highly-conserved core network whose components have modular, weak linkages (double arrows). Notably, information does not flow solely from left to right: extensive local and global bidirectional influences (i.e. genetic and epigenetic differences within the OT system, hormone levels, and receptor densities) ultimately regulate its dynamics. The shared knot (c) between these evolved and highly conserved systems and the overlap between left and right sides illuminates how OT systems may play a role in human fear and anxiety. Overlapping areas on left of (c) are shared safety/social signals; overlapping areas on right are brain regions and reactions with relevance to both social processing and anxiety disorders. See text for discussion and references. ∗ Brain regions also associated with social processing; ∗∗See Fig. 3 for details. BNST=bed nucleus of the stria terminalis; GABA=gamma-aminobutyric acid; HPA=hypothalamic-pituitary axis; NE=norepinephrine, PAG=periaqueductal gray. Figure reprinted and modified with permission from Csete and Doyle (2004).

Table 2 – Human treatment studies of relevance to IN oxytocin's effects on anxiety.

Reference(s)	Population	N, sex, age (if < 18)	Parameter	Dosing	Findings
	Normals				
Heinrichs et al. (2003)[c]		37M	Subjective anxiety, CT response (TSST)	24 IU	After TSST, OT group showed lower CT and higher calmness ratings, similar to social support
Kirsch et al. (2005)[b]		15M	Brain responses to fearful or threatening visual images	27 IU	IN OT reduced connectivity between amygdala and brain stem regions involved in autonomic functions
Petrovic et al. (2008)		27M	Evaluative conditioning responses to faces, neural activity	32 IU	Post-acquisition OT diminished conditioned negative subjective responses and attenuated amygdala, anterior cingulate activation relative to PBO
Ditzen et al. (2009)		47M, 47F	Behavioral and physiological responses to conflict discussions	40 IU	OT significantly improved negative to positive communication ratio and salivary CT levels
Quirin et al. (2011)		36M	Stress-induced (TSST) CT increases based on (ERA)	24 IU	Individuals with lower ERA (based on Action Control Scale) showed blunted CT response after OT
de Oliveira et al. (2012b)		28M	Subjective anxiety, skin conductance, heart rate (SBP, DBP)	24 IU	OT caused decreased anticipatory (pre-test) subjective anxiety and decreased skin conductance prior to a validated model of public speaking test called the SPST (McNair et al., 1982) (see text for details)
de Oliveira et al. (2012a)		45M	Subjective anxiety, DBP, SBP, CT	24 IU	OT prevented increase in subjective anxiety induced by CO_2. See text for notes on CO_2 model (text)
Linnen et al. (2012)		48F, 48M	Affective and cortisol response to the YIPS task	24 IU	Task did not elevate CT, and IN OT did not impact mood. IN OT was associated with decreased CT over course of experiment (see text for discussion)
Sripada et al. (2012)		15M	Resting-state fMRI	24 IU	IN OT was found to significantly increase resting state connectivity between the amygdala and specific regions of the frontal cortex in normal subjects, while having only negligible effects on coupling with other brain regions
Rupp et al. (2014)		59F (29 postpartum, 30 nulliparous)	Amygdala sensitivity to negative visual stimuli (IAPS pictures). Urinary cortisol levels	24 IU	Both amygdala activation and subjective negative arousal demonstrated reductions in postpartum vs. nulliparous women. Postpartum women had lower stressed CT levels. IN OT eliminated the parturitional difference in stress response
Cardoso et al. (2013)		17M	Exercise-induced CT	24 IU, 48 IU	Exercise-induced CT increase attenuated by 24 IU but not 48 IU dose
Weisman et al. (2013a)		35M (fathers)	Fathers and infants CT response to social stressor	24 IU	IN OT increased paternal HPA responses to social stressor (still-face paradigm), and altered infant's CT response to still face stressor. Effects on infants moderated by quality of attachment relationship
Grillon et al. (2013)		19F, 24M	(FPS)	24 IU	Compared with PBO and AVP, OT increased FPS to unpredictable (but not predictable) shock
Acheson et al. (2013)		21F, 23M		24 IU	OT increased extinction recall, but did not facilitate extinction. OT had

Table 2 (*continued*)

Reference(s)	Population	N, sex, age (if < 18)	Parameter	Dosing	Findings
			Fear conditioning and fear extinction in FPS task		no effects on self-reported anxiety or expectancy
Single-dose trials in patients with brain-based illness					
Bartz et al. (2011)	Borderline personality disorder	10F, 4M	Neuroeconomic trust game	40 IU	OT impeded trust and prosocial behavior, moderated by attachment anxiety and avoidance
Simeon et al. (2011)	Borderline personality disorder	6F, 8M	Post stressor subjective mood, CT response	40 IU	OT attenuated of subjective post-stressor dysphoria, and caused a trend to decreased CT. Results moderated by trauma, self-esteem, and attachment style
Bertsch et al. (2013)	Borderline personality disorder	40F	Eye movements and fMRI responses to emotional faces	26 IU	OT normalized several disorder-specific responses to angry faces, causing a reduction in posterior amygdala hyperactivation, as well as a reduced attentional (visual) bias toward the eye region of angry faces
Hall et al., Reiss (2012)	Fragile-X syndrome	8M, age 13–28	Eye gaze frequency, HR, HR variability, CT	24–48 IU	Eye-gaze improved with 24 IU; CT decreased with 48 IU
Pincus et al. (2010)	Major depressive disorder	8F	Reaction time and brain responses (fMRI) to RMET	40 IU	Compared with controls, depressed patients doing the RMET activated higher order cognitive areas and insula with OT
MacDonald et al. (2013b)	Major depressive disorder	17M	Subjective anxiety (STAI)	40 IU	OT caused an increase in STAI over the course of a 20 min therapy session
McRae-Clark et al. (2013)	Marijuana dependence	12M, 4F	Stress responses, subjective anxiety, craving, CT, DHEA levels	40 IU	OT administered prior to TSST resulted in decreased MJ craving scores. Lower anxiety response to TSST was observed, but subjective stress ratings not reduced. DHEA levels decreased with IN OT
Koch et al. (2013)	Post-traumatic stress disorder	21M	Amygdala reaction to fearful and angry faces	40 IU	OT reduced right amygdala activation during fearful and angry faces
Pitman et al. (1993)	Post-traumatic stress disorder	43M	Physiologic responses (HR, GSR, facial EMG) to personal trauma prompts	20 IU	OT subjects had the lowest mean physiologic responses to personal combat imagery prompts, verses placebo and IN AVP-treated subjects
Labuschagne et al. (2010)	Social anxiety disorder (generalized)	18M	Brain responses (fMRI) to emotional face matching task with fearful, angry, happy faces	24 IU	Patients exhibited bilateral amygdala hyperactivity to fearful faces; OT normalized this effect
Labuschagne et al. (2011)	Social anxiety disorder (generalized)	18M	Brain responses (fMRI) to emotional face matching task of happy and sad (vs. neutral) faces	24 IU	Patients had heightened activity to sad faces in medial prefrontal cortex and anterior cingulate cortex; OT reduced this hyperactivity
Guastella et al. (2009)	Social anxiety disorder	25M	Self-rated aspects of social anxiety, speech performance and appearance	24 IU	OT-treated subjects demonstrated improved self-evaluation of appearance and speech performance; these benefits did not generalize into a sustained positive effect over exposure therapy alone
Multiple-dose trials/case reports					
Pedersen et al. (2013)	Alcohol dependence	9M 2F	Alcohol withdrawal scores, lorazepam use	24 Twice-daily for 3 days	OT-treated patients required less lorazepam, had lower alcohol

Table 2 (*continued*)

Reference(s)	Population	N, sex, age (if < 18)	Parameter	Dosing	Findings
					withdrawal scores, and lower subjective distress
Feifel et al. (2011)	Generalized anxiety disorder	7M, 6F	HAM-A	20 Twice-daily for 1 week, then 40 IU twice-daily for 2 weeks	Males showed significant decrease in anxiety at week 2, females showed trend increase in anxiety, with trend significance drug x gender interaction
Scantamburlo et al. (2011)[a]	Major depressive disorder	1M	HAM-D, STAI, Q-LES-Q	Up to 36 IU over several weeks	Adjunctive OT improved depressive and anxiety symptoms and quality of life over the course of weeks
den Boer and Westenberg (1992)	Obsessive compulsive disorder	3M, 9F	Obsessions and compulsions	(1) 18 IU IN for 6 weeks (dosed four times daily) (2) 2 M treated with 54 IU	No effect on symptoms
Epperson et al. (1996)	Obsessive compulsive disorder	3F, 4M	Obsessive compulsive disorder symptoms, anxiety, mood and memory	160 IU or 320 IU IN (divided four times daily) for one week	No change in obsessive-compulsive disorder symptoms. OT subjects had a statistically significant improvement in BDI
Macdonald and Feifel (2012)[a]	Social anxiety disorder	1M	Social anxiety symptoms, sexual function	20 IU twice daily over several weeks	Improvement in several areas of sexual function, though no benefit in social avoidance or anxiety
Epperson et al. (1996)[a]	Trichotillomania	2F	Trichotillomania symptoms	160 IU (divided four times daily) for one week	No difference in trichotillomania symptoms

Abbreviations: AVP = arginine vasopressin, BDI = Beck Depression Inventory, CO_2 = Carbon Dioxide, CT = cortisol, DBP = Diastolic Blood Pressure, DHEA = Dehydroepiandrosterone, EMG = electromyography, ERA = Emotion Regulation Abilities, F = female, fMRI = functional Magnetic Resonance Imagery, FPS = Fear-Potentiated Startle, GSR = galvanic skin response, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, HR = heart rate, IN = intranasal, IU = international units, M = male, OT = oxytocin, Q-LES-Q = Quality of Life Enjoyment and Satisfaction questionnaire, RMET = Reading the Mind in the Eyes Test, SBP = Systolic Blood Pressure, STAI = State-Trait Anxiety Inventory, YIPS = Yale International Stressor, TSST = Trier Social Stress Test.

[a] Case reports.

[b] Given the large number of neuroimaging studies showing OT effects on amygdala and other anxiety-relevant structures, only selected recent studies of these effects are included. Readers are referred to recent reviews for a complete list of relevant studies indicating these effects (Bethlehem et al., 2013; Zink and Meyer-Lindenberg, 2012).

[c] A large number of studies have examined IN OT effects on cortisol and the HPA axis in both normal populations and a wide variety of psychiatric populations (Burri et al., 2008; Cardoso et al., 2013; de Oliveira et al. (2012b, 2012a); Ditzen et al., 2009; Heinrichs et al., 2003; Linnen et al., 2012; Quirin et al., 2011; Simeon et al., 2011). For reasons of space, not all are listed here. See text for discussion.

see Brune (2012) and Nolte et al. (2011)). Examples of OT-related studies exploring between-level causal loops germane to human anxiety are: (1) translational studies examining the effects of OT knockout on maternal behavior (Macbeth et al., 2010; Pedersen et al., 2006); (2) experiments examining the epigenetic impact of maternal behavior on the development of stress systems related to anxiety (Champagne, 2008); (3) findings relating aspects of OT function to maternal depression which then influences children's later development of anxiety disorders (Apter-Levy et al., 2013; Jonas et al., 2013; Skrundz et al., 2011); (4) studies of the impact of early relational trauma on neural hubs (i.e. amygdala) where OT has prominent effects ((Dannlowski et al., 2012; Olsavsky et al., 2013), and see Nolte et al. (2011) and references therein). Each of these experiments explores different facets of the question "what is the role of the OT system in human anxiety?" In summary, examining aspects of the OT system at multiple levels and over multiple timeframes—from evolutionary (millennial) to developmental (individual lifespan) to dynamic (seconds to milliseconds)—informs our understanding of the microarchitecture and complex, multi-level interactions that may underlie different aspects of human anxiety and the OT system's role in it (Table 3).

2. Translational animal research on OT and anxiety

For reasons of space, we will not comprehensively review the large, diverse body of translational and basic science research that informs the role of the OT system in anxiety (readers are directed to Lin (2012), Neumann and Landgraf (2012), Rotzinger et al. (2010) and Stoop (2012)). In one recent review summarizing a variety of animal models of both trait-like

Table 3 – Oxytocin and anxiety: recursive interactions and levels of analysis.

Level of analysis	Factors relevant to OT and anxiety
1. Molecules/receptors	1a. OT, OT mimetics (Ring et al., 2010), OT releasers (Bagdy and Kalogeras, 1993), OTR gene variants (Kumsta et al., 2013; Walum et al., 2008) 1b. AVP receptor-mediated effects (Hicks et al., 2012; Mak et al., 2012; Poirier et al., 2013; Schorscher-Petcu et al., 2010; Zheng et al., 2013) 1c. Other aspects of OT system function (i.e. CD38 (Jin et al., 2007), second messenger systems (Okimoto et al., 2012; van den Burg and Neumann, 2011)) 1d. Regional distribution of OT receptors (Boccia et al., 2013; Liu et al., 2005; Zheng et al., 2013), different timescales of OT effects (wired vs. diffusion-mediated effects) (Ludwig and Leng, 2006; Stoop, 2012)
2. Cells	2a. OT neurons (Boccia et al., 2013; Huber et al., 2005; Knobloch et al., 2012; Viviani et al., 2011) and their regulation by sex hormones, monoamines, etc. (Brown et al., 2013) 2b. OT effects on CRF neurons (Dabrowska et al., 2011; Dabrowska et al., 2013) 2c. OT effects on 5HT neurons (Dolen et al., 2013; Eaton et al., 2012; Yoshida et al., 2009) 2d. OT effects on interneurons (Owen et al., 2013) 2e. OT effects on neurogenesis (Leuner et al., 2012).
3. Nodes and networks (within-brain dynamics)	3a. Functional impact of IN OT on evoked activity in amygdala, insula, mPFC (Koch et al., 2013; Labuschagne et al., 2010, 2011) 3b. Effects of OT on evoked amygdala-brainstem (Kirsch et al., 2005), amygdala-PFC (Sripada et al., 2012), and amygdala-insula (Riem et al., 2011) connectivity 3c. Effects of OT on resting state connectivity (DMN) (Sripada et al., 2012) and other functional networks 3d. Effects of genetic variation in OT systems (i.e. OTR) on connectivity, structure, function (Wang et al., 2013) 3e. Role of epigenetic changes in OT system on brain regions and network structure and function: canalization, plasticity, resilience (Brune, 2012; Jack et al., 2012; Kumsta et al., 2013; Unternaehrer et al., 2012; Veenema, 2011)
4. Neurobiology of attachment relationships (dynamics between bonded brains)	4a. Studies of OT and maternal (Ring Atzil et al., 2011; Strathearn et al., 2009), paternal (Kenkel et al., 2013; Weisman et al., 2013b) and infant behavior 4b. Effects of parental and infant OT genetic variation on future anxiety-related states (Rodrigues et al., 2009) 4c. Effects of early interpersonal trauma on anxiety-related networks (Burghy et al., 2012; Grant et al., 2011; White et al., 2012) and Nolte et al. (2011) for review 4d. Adult pair-bonding (Schneiderman et al., 2013, 2012) and social loss (Norman et al., 2010)
5. Neurobiology of social relationships (neural dynamics related to wider social networks)	5a. Effects of social support and social isolation (Grippo et al., 2012, 2009; Kim et al., 2010; Pournajafi-Nazarloo et al., 2013) 5b. In-group/out-group (De Dreu et al., 2011) and ethnic/racial effects (Inoue et al., 2010; Tost et al., 2011) on anxiety disorders 5c. Impact of social hierarchies/social defeat on anxiety disorders (Guzman et al., 2013; Lukas et al., 2011)

Data from multiple levels of analysis of the OT system inform our understanding of its role in the development and treatment of human anxiety states and disorders. Experiments informing these levels occur in a variety of different populations and models, including: (1) translational research in a variety of species; (2) anxiety/stress states in normal humans; (3) anxiety-related traits in non-clinical populations; (4) anxiety disorders in humans; (5) other disorders with anxiety as a component (i.e. borderline personality disorders, eating disorders). Importantly for an understanding of the role of the OT system in human anxieties, bidirectional, between- and within-level effects create complex, recursive causal loops (Kendler, 2008). See text for discussion

harm avoidance and conditioned fear extinction, a pattern of promising (but mixed) acute and chronic anxiolytic results emerged, overall supportive of future studies in humans (Rotzinger et al., 2010). Since this particular review, much important animal research informing OT's role as an anxiolytic has been done (Ayers et al., 2011; Guzman et al., 2013; Knobloch et al., 2012; Okimoto et al., 2012; Viviani et al., 2011) and (Neumann and Landgraf (2012) for review).

Though space does not permit a comprehensive review of the details of this vital body of preclinical work, we highlight three key issues that emerge from translational research germane to the topic of human anxiety disorders. First, animal research with OT is invaluable in our understanding of the OT system dynamics as it allows the disambiguation of separate neuropeptide receptor effects (through the use of directed application of OT agonists and selective vasopressin agonists (Mak et al., 2012; Smith and Wang, 2013)), the use of specific knockout strains of animals (Amico et al., 2004; Mak et al., 2012; Mantella et al., 2003), as well as other novel techniques unavailable in humans (i.e. optogenetics (Knobloch et al., 2012), gene deletion (Dolen et al., 2013), variations in maternal care (Champagne et al., 2001)). Secondly, though

mammalian defense and neuropeptide systems and circuitries have significant commonalities, there are also significant intraspecies differences in OT-related parameters including aspects of sociality (Goodson, 2013) and OT receptor density (Ophir et al., 2012; Rosen et al., 2008; Ross et al., 2009; Y. Wang et al., 2013; Young and Wang, 2004). This point suggests cautious extension of experimental findings between species. Third, translational research has uniquely informed our understanding of the difference between short-term and long-term OT treatment, as well as the potential longer-term impact of OT treatment during critical developmental windows. For example, in an evocative study with alcohol-preferring rats, OT given during a key developmental epoch altered behavior (beer intake), anxiety, and sociability later in life (Bowen et al., 2011). Studies using viral vectors to increase OTR density in the NAcc have demonstrated dissociation between acute effects of this intervention (increased partner preference) and chronic effects (modulation of alloparental behavior) (Keebaugh and Young, 2011). A final example in this arena are several recent, cautionary studies in which acute IN OT caused increases in the social behavior of male voles, whereas long-term treatment resulted in behavioral deficits (Bales et al., 2013; Huang et al., 2013) and reduction in brain OTRs (Huang et al., 2013). All told, then, though translational research has generated a promising signal regarding OT's anxiolytic potential, it has also raised several important concerns regarding long-term consequences and individual moderators of OT's effects.

3. OT, attachment, and anxiety: bow ties that bind?

As mentioned in Section 1.3, OT, fear and anxiety are yoked by the fact that over long spans of evolutionary time, neural systems with both unique and shared elements evolved to regulate both mammalian social reward/attachment[2] as well as defense/fear. Both of these systems demonstrate a fundamental feature of complex, evolvable systems: robustness (Belzung and Philippot, 2007; Deakin and Graeff, 1991; Porges, 1998; Young, 2002). Defined as the cross-species preservation of particular characteristics despite differences in specific components or the environment (Csete and Doyle, 2002; Kitano, 2004), robustness abets translational OT research. Both within and outside of biology, robust, evolved systems exhibit an architectural framework called a bowtie, which features fan-in, 'many-to-one' inputs, and fan-out, 'one-to-many' outputs, joined by a central 'knot' made of universal building blocks or common currencies (here, the social neuropeptide systems OT and AVP (Csete and Doyle, 2004; Kitano, 2004; Tieri et al., 2010)) (Fig. 2). It has been suggested that this bowtie pattern evolved to optimize survival in highly variable environments, constraining and organizing fluctuating inputs and flexible outputs through a relatively small number of central elements (Csete and Doyle, 2004; Kitano, 2004; Tieri et al., 2010). Bowtie architectures have been used to describe a variety of different biological systems, including metabolism (M. Csete and Doyle, 2004), the immune system (Tieri et al., 2010) and the interface of obesity and addiction (Volkow et al., 2013). Here, we propose that the conceptual model of a bowtie architecture can be helpful in organizing and understanding interactions between OT/AVP systems and the multi-component, multi-level neurobiological systems that subserve human fear and anxiety. As mentioned above, for simplicity we focus here on OT, though a balance between OT and AVP is an vital concept within the social neuropeptide knot (Neumann and Landgraf, 2012), and many of OT's central actions may be mediated through its binding to AVP1a receptors (Mak et al., 2012).

Regarding the characteristics of the central node of this architecture, the core of a bowtie is comprised of a densely connected, small-world network, which includes a variety of related, evolved control systems (surrounding arrows, Fig. 2) which have weak linkages with the core process (here, the OT/AVP system) (Brown et al., 2013; Kitano, 2004). These surrounding processes often perform similar roles (i.e. DA and OT both signaling salience), therewith creating redundancy or degeneracy: different biological elements demonstrating functional homology. This principle makes the system resistant to single-component failure and allows positive and negative feedback to amplify signal-to-noise ratios (Kitano, 2004; Tieri et al., 2010). In the case of OT, critical 'within-node' interactions include dynamic relationships with CRF, AVP, opiates, serotonin, dopamine, GABA, glutamate, and gonadal steroids (estrogen and testosterone) ((Brown et al., 2013)).[3] Multi-level, versatile,

[2] In the social neuropeptide literature, different terms are used for the suite of shared neural circuits that underlie cross-species social and attachment-related phenomena. These include: (1) the "social brain" (Dunbar, 2003); (2) the "social reward/attachment system", which undergirds maternal-infant and mating-pair bonds (Bartels and Zeki, 2004; Bowlby, 1969/1982; Feldman, 2012; Insel, 1992; Nelson and Panksepp, 1998; Panksepp et al., 1978); and (3) the "social behavior network", a collection of limbic forebrain regions which mediate a wider range of social phenomena (i.e. sexual, parental, aggressive behavior) (Newman, 1999). Due to the significant amount of translational research on OT's role in the mammalian attachment/social reward network (Feldman, 2012; Insel, 1997; Panksepp et al., 1997; Pedersen and Prange, 1979), we here refer specifically to the subcortical networks shared between more encephalized primates (including humans) and lower mammals.

[3] Anatomically, the paraventricular nucleus (PVN) of the hypothalamus is literally a "knot" in a neurobiological "bowtie": it receives direct and indirect input from a vast number of brain regions and exerts wide influence throughout the CNS by coordinating sensory, neuroendocrine, and behavioral responses at multiple levels of the neural axis (Argiolas and Melis, 2013; Swanson, 2000; Swanson and Sawchenko, 1983). Within the PVN are two populations of OT neurons: magnocellular secretory neurons (MSNs), and parvocellular neurons of two types: pre-autonomic and neuroendocrine (Luther et al., 2002; Swanson and Sawchenko, 1983). Details of the dynamic regulation of MSNs are beyond the scope of this review, (see Brown et al., 2013 for figure, references and a comprehensive review). Centrally-projecting parvocellular OT neurons coordinate information from the PVN to its targets via "wired", direct neurotransmission to areas like the brainstem and spinal cord, and receive both adrenergic and noradrenergic innervation from the brainstem, bed nucleus of the stria terminalis, and adjacent hypothalamic areas (Ludwig and Leng, 2006; Stoop, 2012; Swanson and Sawchenko, 1980). Regulation of the parvocellular arm of the central OT system has been less well-studied than regulation of MSNs, though extant evidence indicates a complex, dynamic regulatory system as well (Bali and Kovacs, 2003; Blevins et al., 2003; Hoyda and Ferguson, 2010; Hrabovszky and Liposits, 2008).

recursive control systems within and outside the knot ((Brown et al., 2013; Kitano, 2004) and (Table 3)) are important in terms of our global understanding of OT function, and highlight that bowtie architectures do not depict simple left-to-right information flow. Rather, extensive local and global feedback regulations are imposed at each step in the system. Regulation, then, occurs both within the central knot and between left and right sides (as explicated, for example, in Feldman's biobehavioral synchrony model (Feldman, 2007; Feldman et al., 2013)).

Conceptually, a bowtie model of OT provides a framework for future translational, preclinical, and clinical OT research, may aid our understanding the role of the OT system in a the development and treatment of a variety of other disorders (including addictions (McGregor and Bowen, 2012)), and may inform complex, interactive models of human development, attachment, and anxiety (Feldman, 2012; Milrod et al., 2014; Nolte et al., 2011). Conceptualizing the OT/social neuropeptide system as a shared knot between Figs. 2a and b underscores areas of overlap between the diverse literatures on human attachment, fear, anxiety disorders and OT (Belzung and Philippot, 2007; Esbjorn et al., 2012; Milrod et al., 2014; Nolte et al., 2011; Porges, 1998; Warren et al., 1997).

4. Human research: OT and anxiety

Above, we reviewed problems with the term "anxiety", a phylogenic and evolutionary perspective on OT's role in anxiety, translational OT research, and a conceptual model of the OT system's function as a biological 'bowtie'. Each of these related areas inform the next section: the direct study of OT's role in human fear and anxiety.

Though research on the human central OT system has mushroomed, a host of technical limitations still constrain our deeper understanding of its development, dynamics, and function. These include: (1) lack of a radioligand for OTR; (2) a limited understanding of functional role of OT genetic variants; (3) lack a centrally-active OT antagonist for human research; (4) lack of a clear understanding of the connection between central OT system activity and peripheral OT levels[4] ; and (5) lack of a deeper understanding of the pharmacodynamics, pharmacokinetics and mechanism of action of IN OT. In terms of pharmacological development, though treatment of anxiety disorders is typically chronic (multiple doses over weeks) very few clinical trials of chronic OT in humans with anxiety disorders have been performed (Table 2). The few studies that have followed this pharmacological standard of care have generated initial positive results in generalized anxiety disorder (Feifel et al., 2011) and negative results in obsessive compulsive disorder (den Boer and Westenberg, 1992; Epperson et al., 1996).

Much more numerous than clinical trials are pharmacological studies examining single-dose OT as a pharmacological probe. These studies have been performed in a variety of different models of anxiety, with different subjects (normals and patients), and show positive, neutral, and negative effects on different parameters of anxiety (Table 2). From our perspective—based on the data in this review—anxiety disorders worthy of exploratory proof-of-concept randomized clinical trials with chronic OT include posttraumatic stress disorder, social phobia, generalized anxiety disorder, and panic disorder. The converging fields of human OT research that support this contention include: (1) studies of genetic variants of the OT system; (2) studies of OTs impact on aspects of anxiety (i.e. hormone levels, neurobiological responses) in normal subjects; (3) studies using OT in laboratory models of anxiety disorders; (4) studies of OT in anxiety-disorders populations; (5) studies of OT in disorders in which anxiety symptoms play a role (eating disorders, borderline PD); (6) studies of the role of the OT system in intermediate behavioral phenotypes associated with anxiety. Auspicious signals from each of these arenas are reviewed below.

[4]In discussing the role of OT in anxiety, several significant caveats constrain conclusions supported by or derived from studies of OT levels, whether those levels are measured in CSF, plasma (pOT), urine or saliva (sOT). As discussed in a growing, cautionary literature on this topic (Kagerbauer et al., 2013; McCullough et al., 2013; Szeto et al., 2011; Young and Anderson, 2010), a host of assay validity issues in the measurement of OT mean that we "know less about the neurobiological and behavioral significance of peripheral levels of OT" than many reports imply (McCullough et al., 2013). Concerns around the measurement of OT levels include the fact that: (1) pOT levels differ significantly based on sample processing: levels from extracted samples often differ from unextracted samples by a factor of 10 (see McCullough et al. (2013) for references), and levels from extracted and unextracted samples do not correlate with each other (Szeto et al., 2011); (2) immunoassay methods like the commonly-used enzyme immunoassay (EIA) are based on the assumption that the target antibody is specific for only the analyte of interest (i.e., OT). In the case of the most-commonly used OT EIA, this assumption is dubious given that OT-degradation products may cross-react with the antibody (Szeto et al., 2011). Though these OT degradation products may have biological activity (i.e. activate the OT receptor), data on this have not been published. As such, radioimmunoassay (RIA) on extracted plasma (Zhang et al., 2011) is currently the consensus plasma assay of choice (Paul Zak, personal communication); (3) in humans, pOT and CSF OT levels—at least at baseline state—do not correlate (Kagerbauer et al., 2013) (but see Wang et al., 2013), and CSF OT levels best reflect central activity and release (Veening et al., 2010). This does not imply, though, that pOT levels are irrelevant to brain or behavior. Peripherally-delivered OT—which technically does not cross the BBB—has behavioral effects in animals (Feifel and Reza, 1999; Feifel et al., 2012) and humans (Hollander et al., 2003), perhaps mediated through the vagal nerve (Porges and Carter, 2012); (4) correlations between sOT levels and pOT levels do not approach those in other endocrine literatures (i.e. salivary cortisol or testosterone) (see McCullough et al. (2013) for references); (5) compared with urinary OT, pOT and sOT levels, relatively few papers examining CSF levels of OT in humans have been published (see Section 4.4) (Clark et al., 2013; Jokinen et al., 2012; Kagerbauer et al., 2013; Lee et al., 2009; Sasayama et al., 2012; Wang et al., 2013). Summing up this important aspect of the OT field, McCullough et al recently opined that "until methods for measuring OT in any human fluid are validated and standardized, interpretation of reported results remains murky at best" (McCullough et al., 2013). In the context of this review, these data encourage significant caution in interpreting the relationship between OT levels and anxiety states, traits and diagnoses.

4.1. *Genetic and epigenetic variations in OT systems and anxiety*

Like most psychiatric disorders, a substantial amount of the variance in the incidence of anxiety disorders is explained by genetic factors (Norrholm and Ressler, 2009). Speaking to the novelty of this area of research, however, a recent review of the topic did not mention OT (Norrholm and Ressler, 2009). This will surely change, for in recent years, a large number of studies have examined the relationship between common allelic variations in the OT system and a number of parameters of interest to anxiety disorders, including anxiety-related personality traits, brain structure, brain dynamics and responses to adversity and stress ((Bradley et al., 2011; Love et al., 2012; Rodrigues et al., 2009; Thompson et al., 2011; Tost et al., 2010; Wang et al., 2013a,b) and Brune (2012) and Kumsta and Heinrichs (2013) for review). Due to space constraints, we will not review these studies here (see Bakermans-Kranenburg and van Ijzendoorn (2013b) and Kumsta and Heinrichs (2013) for recent reviews).

Also important as regards the role of the OT in the development of anxiety disorders are converging findings that the OT system contains a degree of programmable, developmental-window specific plasticity conferred via epigenetic changes (Champagne, 2008; Kumsta et al., 2013; Mamrut et al., 2013; Murgatroyd and Spengler, 2011; Stolzenberg et al., 2012; Unternaehrer et al., 2012; Wang et al., 2013). These developmentally-canalized changes may occur at many levels of the system (Table 3), including OT's role in regulation of the HPA axis and its role in amygdala-anchored brain systems (see Section 4.7.3). We cannot do justice to this rich and rapidly developing literature, but recommend Kumsta et al. (2013), Nolte et al. (2011) and Veenema (2012) for recent reviews.

4.2. *IN OT in healthy humans*

A variety of anxiety-relevant studies in both healthy and psychiatrically ill humans using IN OT have been performed (Table 2). These studies have examined OT's role in the processing of disorder-specific stimuli (i.e. social approbation in social phobia) and more general threat-relevant stimuli (i.e. fearful and angry faces), as well as IN OT's action within a number of anxiety-related laboratory models. Using clinical anxiety disorders as our point of reference, we note significant variation in the association between different experimental factors linked to OT (i.e. amygdala hyperactivity, cortisol elevation, autonomic reactivity), anxiety disorders, and their treatments (Craske et al., 2009; Vreeburg et al., 2010; Watson, 2005).

4.2.1. *OT, facial stimuli, and anxiety*

Many short-term studies of IN OT have examined its impact on the processing of facial stimuli in normal populations (Shahrestani et al. (2013), Van IJzendoorn and Bakermans-Kranenburg (2012) for recent reviews). Face processing studies relate to human anxiety because human facial expressions—especially eye-region related signals—are evolved, reflexively-processed displays of the emotional and motivational states of others. As such, they reliably capture attention and activate fear-related brain systems and behaviors in observing others (Adolphs 2008, 2009; Todorov, 2008; Tomasello et al., 2007). Consistent with the evolutionary importance of this form of social signaling, for example, fearful faces consistently activate the amygdala (Adolphs, 2008), a hub of the brain's salience and danger-detection system, and known anxiolytics dampen these responses (Blair and Curran, 1999; Del-Ben et al., 2012; Paulus et al., 2005; Zangara et al., 2002). Within this context, some of IN OT's effects on brain response to certain facial emotions (downregulating amygdala activity) seem to indicate an anxiolytic effect, though mixed results are found, with other studies showing amygdala activation with social stimuli (Domes et al., 2013a; Zink and Meyer-Lindenberg, 2012).

Facial processing tasks reveals a fundamental conceptual challenge in interpreting this aspect of the OT literature: a diathesis between OT increasing social salience and its role in decreasing social anxiety. As discussed in Section 1.3, social stimuli are inherently ambiguous, and can be a signal of both safety and danger. The degree to which OT has a nonspecific effect (increasing social salience in general) verses its effects on the processing of stimuli with a certain valence (i.e. happy vs. fearful faces) is an active area of investigation (Domes et al. (2014), Marsh et al. (2010), Prehn et al. (2013), Radke et al. (2013), Shahrestani et al. (2013) for reviews, see Shahrestani et al. (2013) and Van IJzendoorn and Bakermans-Kranenburg (2012).

A last important distinction in this research arena is that although certain experiments have suggested OT has a benzodiazepine-like effect (de Oliveira et al., 2012a, 2012b; Pedersen et al., 2013), benzodiazepines cause impaired facial recognition (Coupland et al., 2003), but see Kamboj and Curran (2006) and Murphy et al. (2008). Serotonergic agents, on the other hand, often improve facial recognition, though these effects depend partly on duration of treatment ((Murphy et al., 2009; Norbury et al., 2009), and see Macdonald et al. (2013b) for discussion of clinical implications of OT and facial processing).

To summarize this important area, though it is clear that IN OT has an effect on the visual processing of human faces (Shahrestani et al., 2013), and though these findings may have relevance to OT's role as a therapeutic anxiolytic agent, specific details of these associations are yet to be elucidated.

4.2.2. *IN OT, anxiety, and social stress*

Besides static facial expressions, active social approbation and evaluation are potent activators of the stress response (Dickerson and Kemeny, 2004), and several studies evaluate OT's impact in these situations. Using a laboratory model of public speaking called the Simulated Public Speaking Test (SPST) (McNair et al., 1982), de Oliveira et all demonstrated that IN OT (1) significantly decreased subjective anticipatory anxiety and increased subjective sedation before the speaking task; as well as (2) decreased skin conductance at most time points throughout the experiment (de Oliveira et al., 2012a, 2012b). Notably, the effect of OT was similar to the effect of diazepam in the SPST model (Zuardi et al., 1993). In an earlier seminal experiment in this literature, Heinrich et al demonstrated that both OT and social support exerted subjective anxiolytic effects and attenuated cortisol responses to a social stressor (Heinrichs et al., 2003).

4.2.3. OT in conditioned fear experiments

Fear learning and fear extinction play in important role in the development and treatment of several anxiety disorders (Bishop, 2007; Indovina et al., 2011; Mineka and Zinbarg, 2006). Specifically in the case of PTSD, prolonged exposure therapy (with the expectation of extinction learning of conditioned fear responses) is one of the preferred treatments (Foa, 2006). In translational OT research, conditioned association experiments form part of the backbone of studies examining the acquisition, learning and extinction of anxiety (Milad et al., 2006; Myers and Davis, 2007). This research has demonstrated that OT plays a significant role in conditioned association and fear learning (Lukas et al., 2013), partly based on its role in the amygdala (Knobloch et al., 2012; Petrovic et al., 2008; Viviani et al., 2011; Viviani and Stoop, 2008).

Several groups have examined the role of IN OT in human fear learning. In an important experiment, Petrovic et al found OT given shortly after acquisition of conditioned exposure abolished conditioned fear responding via down-regulation of amygdala activity (Petrovic et al., 2008). Two other trials using a fear-potentiated startle experimental model found that OT exerted a facilitative effect on extinction recall (but not extinction) (Acheson et al., 2013), and that although OT did not increase startle to cued threat, it did have the "anxiogenic" effect of increasing potentiated startle responses to unpredictable threat (Grillon et al., 2013). These somewhat mixed results underscore two important points about the therapeutic role of OT. First, a simple "amygdala dampening" model of OT's activity needs revision (see Bartels (2012) for discussion); and (2) careful examination of the timing of OT exposure relative to cue presentation as well as the context of the experiment and nature of the cues (social vs. nonsocial) in these trials is critical (Acheson et al., 2013; Lahoud and Maroun, 2013; Toth et al., 2012). Recent concerns regarding the shortcomings of the fear extinction model of human anxiety disorders have recently been raised (Milrod et al., 2014), and are also germane here. Finally, it is worth noting different correlations between fear-related conditioning experiments and individual anxiety disorders, with most consistent results in PTSD (Craske Rauch et al., 2009). This may indicate that the role of OT in PTSD may differ from that in other anxiety disorders (Olff et al., 2010).

4.2.4. IN OT in other models of anxiety

Inhalation of 7.5 % CO_2 is an anxiogenic stimulus which serves as a preclinical model of generalized anxiety (Bailey et al., 2007). CO_2 inhalation increases heart rate, blood pressure and subjective feelings of anxiety, fear and tension (Bailey et al., 2005), and these responses are attenuated by both lorazepam and paroxetine (Bailey et al., 2007). In an experiment using this model, de Oliveira et al demonstrated that both OT and lorazepam attenuated the anxiogenic response to CO_2 (de Oliveira et al., 2012a, 2012b). Specifically, although physiological and hormonal anxiolytic effects were not seen in this experiment, OT significantly impacted subjective anxiety symptoms.

To summarize: OT has demonstrated anxiolytic-type effects in a number of preclinical human models, though some results in this area have been lukewarm and even seemingly contradictory (Grillon et al., 2013).

4.2.5. Oxytocin, anxiety and the HPA axis

Due to the role of the HPA system in stress responses (Carrasco and Van de Kar, 2003; Chrousos, 1995; Selye, 1936), activation of this system is considered an intrinsic part of mammalian defense systems, anxiety and fear. HPA activation is partially regulated by tonic inhibitory control and negative feedback from both the hippocampus and prefrontal cortex (Brake et al., 2000; Chrousos, 1995; Diorio et al., 1993; Herman and Cullinan, 1997). OT, notably, has interaction with several critical components of this axis including the BNST and PVN (the source of corticotropin-releasing hormone (Chrousos, 1995)) and the hippocampus (Stoop, 2012) (Fig. 3). Translational animal research on OT's effects on the HPA axis have clearly demonstrated its modulatory role (Amico et al., 2008; Neumann, 2002; Slattery and Neumann, 2010), and these endocrine effects are often cited as evidence of OTs inherent anxiolytic activity (Engelmann et al., 2004; Slattery and Neumann, 2008).

Outside of animal models (which allow direct access to the central arm of the HPA axis), a large number of studies in a variety of normal and psychiatric populations have examined IN OT's effects on cortisol levels, with mixed results that will not be reviewed in detail here (Burri et al., 2008; Cardoso et al., 2013; de Oliveira et al., 2012a, 2012b; Ditzen et al., 2009; Heinrichs et al., 2003; Linnen et al., 2012; Quirin et al., 2011; Simeon et al., 2011). Several caveats about the effect of IN OT on cortisol in humans, however, are warranted. First, peripheral markers of HPA axis activity (i.e. salivary or plasma cortisol levels) have both practical and theoretical limitations, including timing factors, stressor-related factors, and different HPA responses in different patient populations (Dickerson and Kemeny, 2004; Hellhammer et al., 2009). In terms of relevance to clinical treatment, though there is a predictable link between certain types of stressors and HPA activation in normal humans (Dickerson and Kemeny, 2004; Koolhaas et al., 2011), the link between human anxiety disorders and cortisol levels is variable (Hek et al., 2013; Vreeburg et al., 2013, 2010). Complexity is also introduced by evidence that stress-induced cortisol levels may influence the release of OT (Pierrehumbert et al., 2012; Tops et al., 2012), and data indicating complex relationship between acute stressors and changes in endogenous cortisol and OT levels (Tabak et al., 2011; Taylor et al., 2010).

A final important point regarding of OT's interaction with the HPA axis is that dysregulation of this axis and its consequences —impaired plasticity and neurogenesis—are one of the plausible mechanisms mediating the link between traumatic early experience and later psychopathology (Apter-Levy et al., 2013; Heim et al., 2010; Kendler et al., 2004; McCrory et al., 2012). For example, altered amygdala-prefrontal connectivity found in humans exposed to maternal deprivation is mediated by cortisol levels (Gee et al., 2013). These data and others mentioned throughout this review suggest that HPA-OT interactions may be a mediator of some of the effects of early adversity on the connectivity and development of key brain structures related to anxiety (Elton et al., 2013). This point also relates to psychiatric therapeutic agents, given that modulation of the HPA axis in considered an important component of the therapeutic action of the SSRIs (see Hesketh et al. (2005) for discussion).

To summarize: though significant preclinical literature indicates that OT-HPA interactions are important and that

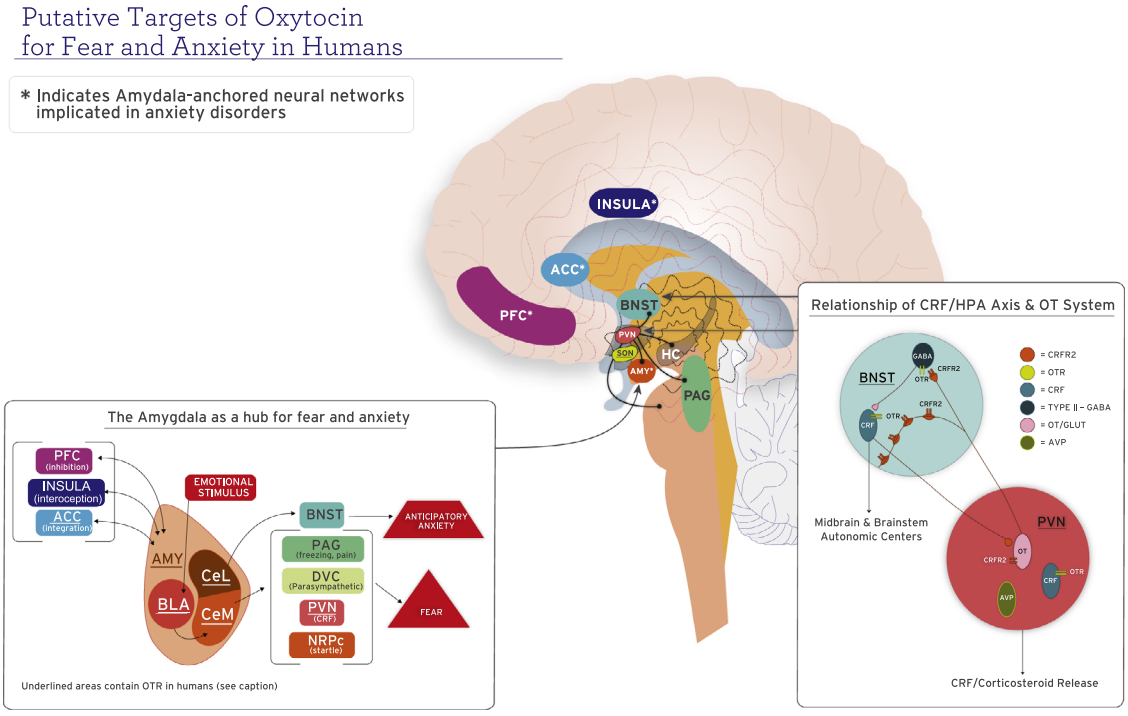

Fig. 3 – Brain nodes and networks implicated in OT's effect on anxiety symptoms and disorders in humans. Key nodes, based on both neuroimaging data using IN OT and OTR staining in humans include: (1) amygdala and bed nucleus of the stria terminalis (BNST) (left and right pullout); (2) hypothalamic-pituitary (HPA) axis (right pullout); (3) prefrontal-amygdala connectivity networks associated with regulation, second-order representation, and integration of information (left pullout and asterisks). Left pullout highlights key nodes and connections of an amygdala-anchored network as well as the distinction between fear—a phasic alarm response to present or imminent pain or danger—and anxiety—a more chronic, future-oriented anticipatory state (see text). Cortical areas with reciprocal connections to amygdala are on bracketed on left side of pullout, brainstem areas on the right. Underlined structures are those recently identified as containing OTR in cells or fibers in humans (see Boccia et al. (2013) for full list). Right pullout emphasizes BNST-PVN connections as key regions for crosstalk between OT and the HPA axis (reprinted with permission from Dabrowska et al. (2011)). Asterisks indicate areas identified in both neuroimaging experiments using IN OT and in anxiety disorders. Abbreviations:; ACC-anterior cingulate cortex; AMY-amygdala; AVP-arginine vasopressin; BLA-basolateral nucleus of the amygdala; BNST-bed nucleus of the stria terminalis; CeL/CeM-lateral/medial portion of the central nucleus of the amygdala; CRF-corticotrophin-releasing factor; DVC-dorsal vagal complex; GABA-gama-aminobutyric acid; GLUT-glutamate; HC-hippocampus; NRPc-nucleus reticularis pontis caudalis; OTR-OT receptor; PAG-periaqueductal grey; PFC-prefrontal cortex; PVN-paraventricular nucleus; SON-supraoptic nucleus. For references, see text and (Bethlehem et al., 2013; Boccia et al., 2013; Davis et al., 2010; Huber et al., 2005; Stoop, 2012; Viviani et al., 2011; Viviani et al., 2010; Zink and Meyer-Lindenberg, 2012).

IN OT may regulate this axis in certain states and human subjects, the relevance of these findings to the development and treatment of human anxiety disorders is still uncertain.

4.3. *IN OT in psychiatric populations with anxiety*

Very few treatment studies have been done in patients with anxiety disorders (Table 2). In one of the first, Pitman et al found that OT reduced physiological responding (HR, GSR, facial EMG) to personal combat imagery prompts (Pitman et al., 1993). More recently, functional imaging studies in PTSD patients indicate that OT reduces amygdala activation during the presentation of fearful and angry faces (Koch et al., 2013). Studies of fear learning in normals (reviewed above) are also important in terms of the use of OT in PTSD, as pharmacological augmentation of exposure therapies may be one of the more important roles of psychopharmacology in this condition (Olff et al., 2010).

Given its role in social learning and certain forms of prosocial behavior, social phobia (SOP) or social anxiety disorder is an auspicious target for OT. Though no chronic studies in SOP have been done, mixed results from single-dose trials exist. In one study, single-doses of OT were not found not to augment cognitive therapy for this disorder (save an improvement in self-rated performance) (Guastella et al., 2009), whereas imaging studies in patients SOP found OT reduced hyperactive amygdala responses (Labuschagne et al., 2010) and reduced hyperactive medial frontal and anterior cingulate responses to emotional faces (Labuschagne et al., 2011).

In one of the only double-blind, placebo-controlled studies of chronic OT in generalized anxiety disorder, Feifel et al gave 13 subjects twice-daily IN OT for 3 weeks, and demonstrated a trend-level dose-by-gender effect such that males treated with

OT showed a significant improvement in HAM-A scores at week 2, whereas females showed a tendency for increased anxiety (Feifel et al., 2011). The indication of a sex-dependent effect in this study is critical to follow up, given significant, converging data that sex is a critical individual variable in understanding the human OT system (Macdonald, 2012). Interestingly, recent work in invertebrates indicates that sex-specific OT effects extend as far back as the function of an OT-like precursor (nematocin) in *Caenorhabditis elegans*, where sex-specific effects on mating behavior in males are found (Garrison et al., 2012).

Ironically, at the time of this review, the largest anxiety-disordered patient group treated with chronic OT is patients with OCD (den Boer and Westenberg, 1992; Epperson et al., 1996), a disorder no longer categorized in the DSM anxiety disorder grouping. The two negative studies in this condition demarcated the start of significant pause in the clinical investigation of OT as a human anxiolytic.

4.4. *OT levels in patients with anxiety disorders*

Any discussion regarding OT levels must consider the significant caveats discussed in footnote 3. With these concerns in mind, several studies have indicated that endogenous OT plasma levels (pOT) are related to prosocial behaviors (Grewen et al., 2005; Light et al., 2005), and that lower OT levels occur in disorders with prominent social dysfunction (i.e. autism (Modahl et al., 1998), schizophrenia (Keri et al., 2009; Rubin et al., 2010), but see also Rubin et al. (2013)). Additionally, a mixed literature has shown that pOT levels vary as the result of stress, depending on individual and context factors (Light et al., 2005; Taylor et al., 2006; Turner et al., 1999). Few studies of OT levels in anxiety disorders exist. In OCD, patients were found to have higher CSF OT levels in one study (Leckman et al., 1994), but not a follow up (Altemus et al., 1999). Though an earlier study found no significant differences between pOT in patients with generalized social anxiety disorder and normals (Hoge et al., 2008), within the social anxiety group, pOT levels were associated with symptom severity. In a later study, Hoge et al reported decreased pOT levels in patients with generalized social phobia during a laboratory task of prosocial behavior (Hoge et al., 2012). Given the role of childhood trauma in the development of anxiety disorders (Milrod et al., 2014; Nolte et al., 2011), findings from a small study of 22 abuse victims showing inverse association between CSF OT concentrations and abuse are of interest (Heim et al., 2009). Altogether, extant literature examining OT levels in both normal and certain clinical populations (i.e. anorexia (Lawson et al., 2013), autism (Miller et al., 2013)) supports the idea that the peripheral release of OT system may be part of an acute stress response or anxiety states. Although there have been connections made between temperamental aspects of anxiety and pOT (Weisman et al., 2013a), direct correlations between anxiety disorders and OT levels is minimal.

4.5. *IN OT and OT levels in other populations with anxiety*

As mentioned above, anxiety is a transdiagnostic symptom and forms a clinical focus of treatment in several disorders outside of the codified anxiety disorders. As such, studies examining the effects of OT on anxiety and anxiety-related symptoms in other populations are relevant to the larger question of the role of OT in anxiety. One population that has been studied in this context is borderline personality disorder (BPD). Though BPD patient's affective experience includes irritability, dysphoria, and rage, many patients do suffer with disorganizing levels of anxiety and fearfulness (Leichsenring et al., 2011). Overall, mixed findings with OT in BPD exist, with single dose-studies demonstrating that IN OT impedes trust and prosocial behavior (Bartz et al., 2011), attenuates post-stressor dysphoria (Simeon et al., 2011), and normalizes amygdala hyperactivity in responses to angry faces (Bertsch et al., 2013). Importantly, effects in several of these studies were moderated by attachment parameters and early traumatic experience. These studies, though short-term, have generated interest in OT as a chronic treatment for BPD.

Anxiety is also an important feature of eating disorders, and the OT system is intercalated with central systems regulating ingestion and weight (Valassi et al., 2008; Wu et al., 2012). Several studies have related pOT levels to different aspects of anorexia nervosa (AN) (Lawson et al., 2013, 2011). Lawson et al recently reported that elevated subjective anxiety (STAI) levels were associated with elevated mean, nadir, and peak pOT in AN patients, and suggested that up to 51 % of anxiety symptoms (STAI trait) were directly attributable to OT secretion (Lawson et al., 2013). Besides BPD and AN, patients with the rare, inherited disorder called fragile X syndrome often manifest anxiety, and a small pilot study showed that IN OT improved certain parameters of social anxiety (eye gaze) and lowered cortisol levels (Hall et al., 2012).

In summary: OT and aspects of the OT system have been associated with anxiety and anxiety-related states in several human psychiatric disorders, but some of these findings are mixed and moderated by individual factors as well as concerns about the relevance of pOT levels (footnote 3).

4.6. *The role of OT in anxiety-related behavioral phenotypes*

Apart from categorical anxiety disorders, a final important arena that informs our understanding the role of OT in human fear and anxiety is OTs connection with anxious temperaments and personality traits. These more stable, chronic characteristics are measured using a variety of instruments including behavioral observations and self-reports[5] . They include (1) anxious temperament (aka "inhibited temperament"); (2) attachment anxiety; (3) trait anxiety; and (4) harm avoidance (see Table 1). Sometimes considered

[5]Importantly, though self-reports assay an important parameter of anxiety disorders, dissociation between physiological symptoms and self-reported anxiety (i.e. response dyssynchrony) is frequently reported in anxiety studies (Grillon et al., 2008; Hodgson and Rachman, 1974; Kemp et al., 2004; Ruys and Stapel, 2008; van Honk et al., 2005). A common distinction in this area assigns nonconscious manifestations of the anxiety/fear system to subcortical structures (i.e. amygdala, hypothalamus) and consciously perceived manifestations to cortical activity (Morris et al., 1999; Ribary, 2005; Ruys and Stapel, 2008).

endophenotypes[6] or intermediate phenotypes for anxiety disorders (Schwartz et al., 2012), anxiety-related personality traits are predisposing factors for both depression and anxiety-related disorders (Beesdo et al., 2010; Farmer et al., 2003; Ono et al., 2002; Rosenbaum et al., 1993; Starcevic and Uhlenhuth, 1996), supporting the "internalizing disorder" and RDoC negative valence categorization schemes discussed in Section 2. As they are related to the development of anxiety disorders and have links with OT, these data are worth considering in the broad spectrum of OT-anxiety research.

A frequently examined anxiety-related temperamental variation is inhibited temperament or "anxious temperament". Though this particular phenotype has not yet been directly related to OT in humans, experiments in rats demonstrate that only females with anxious temperament demonstrate alterations in AVPR-1a levels in the amygdala when subjected to male aggression (Poirier et al., 2013). Moreover, anxious temperament negatively correlates with prosocial traits like extraversion and cooperativeness (Zukerman and Cloninger, 1996), which have been related to OT levels and brain responses to IN OT (Andari et al., 2012; Groppe et al., 2013). This behaviorally-anchored temperamental variation—vital in our understanding of the development of human anxiety disorders (Biederman et al., 2001; Hirshfeld et al., 1992; Schwartz et al., 2012)—is an interesting target for future OT research.

Whereas inhibited temperament is measured using behavioral observations, the personality characteristic called trait anxiety is measured with the state-trait anxiety inventory (STAI) (Spielberger, 1983). Trait anxiety describes a stable tendency toward tension, anxiety, and negative affectivity, and is associated with anxiety disorders and functional abnormalities in amygdala and prefrontal cortex (Barrett and Armony, 2009; Bishop, 2009; Indovina et al., 2011; Otero-Garcia et al., 2013; Sehlmeyer et al., 2011). Phenomenologically, high trait anxiety and negative affectivity are common to all anxiety disorders (Clark et al., 1994; Watson, 2005). In terms of relationships with OT, trait anxiety was found related to pOT levels in a sex-dependent manner in one study of men and women (trait anxiety was lower among men with higher OT, and women with very high levels were much more likely to be highly anxious) (Weisman et al., 2013a), whereas pOT levels were inversely correlated with trait anxiety scores in breastfeeding women (Stuebe et al., 2013). Lastly, in a neuroimaging study illuminating the dynamic relationship between OT and dopamine systems, female C allele carriers of the rs4813625 allele of the OT receptor (OTR) had higher stress-induced dopamine release, higher trait anxiety scores and higher attachment anxiety (Love et al., 2012). These findings echo reports finding elevated pOT levels in distressed women (Taylor et al., 2006, 2010), and reports correlating pOT, trait anxiety and early life stress (Opacka-Juffry and Mohiyeddini, 2012).

Harm avoidance (HA) is a temperamental trait similar to trait anxiety, but measured using a different self-report, Cloninger's TCI (Cloninger, 1987). Like trait anxiety, HA is associated with being cautious, apprehensive and pessimistic and with anxiety disorders (Ball et al., 2002; Lochner et al., 2007; Starcevic and Uhlenhuth, 1996; Wachleski et al., 2008). HA is also associated with a variety of laboratory measures (i.e. startle, endocrine responses, functional and structural brain responses) connected with anxiety disorders (Corr et al., 1997; Tyrka et al., 2008; Van Schuerbeek et al., 2011; Yamasue et al., 2008; Baeken et al., 2009; Li et al., 2012; Westlye et al., 2011; Yang et al., 2009). Wang et al. studied the rs53576 variant of the OTR gene and found that HA was associated with this gene in females (homozygous A-allele had higher HA than G-allele carriers), and also that this gene variant was associated with significantly reduced gray matter volume in bilateral amygdala and reduced functional connectivity between amygdala and dlPFC (Wang et al., 2013a,b). In an earlier study, the same OTR gene was found to exert an effect on interregional coupling of amygdala during emotionally salient social cues (Tost et al., 2010). Moreover, G x E studies suggest that this gene or other OTR genes may function as factors in resilience to psychopathology (Bradley et al., 2013; Brune, 2012). In a second study of the common OXTR variants rs237900 and rs237902, a genotype-by-sex interaction was found to explain 11 % of the variance between levels of HA in females (Stankova et al., 2012). Overall, these findings suggest a possible mechanistic pathway from OTR genotype to anxiety-related traits (HA) to anxiety disorders, through modulation of prefrontal-amygdala coupling.

A final trait measure of interest in relation to OT and anxiety is attachment anxiety, a measure of sensitivity to or worry about rejection or loss of relationships with intimates measured using the experiences in close relationships questionnaire (ECR-R) (Brennan et al., 1998). In several studies, attachment anxiety (and the related parameter of attachment avoidance) have been found to moderate responses to IN OT (Bartz, 2012; De Dreu, 2012) and predicted trust-related OT responses (Kiss et al., 2011). Furthermore, attachment anxiety in women has been correlated with higher pOT levels (Weisman et al., 2013a). In a study mentioned above, C allele carriers of the rs4813625 C allele exhibited higher attachment anxiety (Love et al., 2012). A caveat to the relationship of attachment anxiety and anxiety disorders is that in a large sample of psychiatric outpatients, attachment anxiety correlated more strongly with mood and personality disorder symptoms than harm avoidance or anxious temperament (Macdonald, 2012), so the clinical significance of these

[6]As part of the goal of bridging the "gene-to-phene" gap, neuroscientists have searched for stable, reliably measurable traits called endophenotypes (from the Greek 'endos' or 'within'+'phainein', 'to show') (Bearden and Freimer, 2006; Gottesman and Gould, 2003; Waldman et al., 2006). In its most liberal definition, key characteristics of an endophenotype include a quality that is (1) quantifiable; (2) associated with genetic risk for a disorder; (3) abnormal in both patients and probands; and (4) relatively invariant (Bearden and Freimer, 2006). This definition includes certain behaviors, self-report measures and cognitive processes present in nonclinical populations, and therefore occurring "under the observable illness phenotype". Others have called these characteristics "intermediate phenotypes" (Stein et al., 2008), "exophenotypes" (Meyer-Lindenberg and Weinberger, 2006) or in the case of anxiety disorders, "anxiety spectrum phenotypes" (Hettema et al., 2008). A more restrictive definition for endophenotype—more applicable to translational neuroscience—opines that they should be laboratory-based biomarkers: processes occurring underneath observable/reportable behavior (i.e. Light et al., 2012).

findings in regards to the effects of IN OT in psychiatric disorders is unknown.

In summary: a review of the growing literature linking aspects of OT to anxiety-related temperamental variations supports the hypothesis that genetic variations in the OT system may play a role in the neurobiological substrates of anxiety-related predispositions, and—with caveats about OT levels (footnote 3)—that these levels may correlate with certain anxiety-related traits.

4.7. *Neural substrates for OT and anxiety: nodes and networks*

In this final section, we review both putative and proven neural substrates that may mediate some of OT's anxiety-related effects (Fig. 3). Though space does not permit a review of the similarities and differences in the brain regions implicated in different anxiety disorders (see Menon (2011) and Sylvester et al. (2012) for recent reviews), we highlight several key nodes and networks that inform the putative role of OT in anxiety disorders and warrant further investigation.

4.7.1. *Networks and hubs*

Our understanding of fear and anxiety disorders has been significantly influenced by systems neuroscience and the segregation of the human brain into functional networks: large and small-scale brain regions that demonstrate intrinsic functional connectivity (Menon, 2011; Seeley et al., 2007; Sylvester et al., 2012). These networks have critical "nodes" or "hubs", defined by both intrinsic properties as well as extrinsic connectivity (Honey et al., 2009; Passingham et al., 2002). Neural hubs coordinate and mediate alterations in and between different networks over multiple time scales (Honey et al., 2007; Sporns et al., 2007). Regions and nodes critical to an understanding of OT's role in fear and anxiety include (1) subcortical and brainstem structures which are part of the mammalian defense system (i.e., periaqueductal gray (PAG), hypothalamus, amygdala); (2) prefrontal cortical regions associated with modulation, integration and regulation of these regions (i.e., anterior cingulate cortex (ACC) and other prefrontal cortical regions (vmPFC)); and (3) cortical regions associated with integration of internal body states or "interoceptive prediction" (i.e., anterior insula) (Damsa et al., 2009; Deakin and Graeff, 1991; Etkin and Wager, 2007; Martin et al., 2009; McNaughton and Corr, 2004; Paulus and Stein, 2006; Shin and Liberzon, 2010) (Fig. 3). Elegant animal experiments using targeted delivery of OT agonists, antagonists, as well as optogenetics have allowed functional dissection of the microcircuitry of OT's anxiolytic effects, especially in the amygdala ((Huber et al., 2005; Knobloch et al., 2012; Viviani et al., 2011; Viviani and Stoop, 2008; Viviani et al., 2010) and Stoop (2012) for review). In addition, a growing human literature documents OT-mediated changes in functional activation of many of these brain regions in healthy controls (Bethlehem et al. (2013) and Zink and Meyer-Lindenberg (2012) for reviews) and in patients with anxiety disorders (Labuschagne et al., 2010, 2011).

Therefore, though for organizational purposes we focus on specific brain regions, we acknowledge the importance of a functional-network level of analysis. From this latter perspective, a variety of studies indicate that anxiety disorders are associated with dysfunctional connectivity of amygdala with prefrontal and brainstem regions, as well as aberrant amygdala connectivity within the central executive and salience networks (Blair et al., 2012; Campbell-Sills et al., 2011; Damsa et al., 2009; Etkin et al., 2010, 2009; Etkin and Wager, 2007; Kim et al., 2011; Kim and Whalen, 2009; Martin et al., 2009; Menon, 2011; Shin and Liberzon, 2010; Sylvester et al., 2012).

4.7.2. *Periaqueductal gray*

The periaqueductal gray (PAG) is a brainstem structure involved in fight-or-flight reactions to a proximal threat (Panksepp, 1998), sexual and maternal behaviors (Salzberg et al., 2002), anxious temperament (primates) (Fox et al., 2008), dread, threat imminence, sympathetic response to socioevaluative threat, and negative emotion (in humans) (Buhle et al., 2013; Craske et al., 2009; Hermans et al., 2012; Linnman et al., 2012; Mobbs et al., 2007; Tasker, 1982; Wager et al., 2009). The role of the PAG in anxiety and defensive responses has been much more well-studied in animals than humans, due to technical limitations in human neuroimaging, which have emphasized amygdala and cortical structures (but see Buhle et al. (2013), Damasio et al. (2000), Mobbs et al. (2007, 2010), Wager et al. (2009) and Linnman et al. (2012) for review). In an interesting recent study of relevance to OT, eye contact in people with PTSD from interpersonal trauma stimulated increased activation within the superior colliculus (SC) and periaqueductal gray (PAG) (Steuwe et al., 2014), both regions associated with OT activity (Gamer et al., 2010; Ge et al., 2002; Yang et al., 2011). Regarding OT's potential role in human anxiety, OT is found in the PAG of humans (Jenkins et al., 1984), though OTR are not (Boccia et al., 2013). Animal studies indicate that PAG has a role in some aspects of OT's regulation of the sympathetic response and anxiety-related behavior (Figueira et al., 2008; Viviani et al., 2011), as well as pain modulation (Ge et al., 2002; Tracey et al., 2002; Yang et al., 2011). Though the role of the PAG in human anxiety states and disorders has not been well specified (but see Buhle et al. (2013) and Hermans et al. (2012)), OT's effects in paradigms where PAG has been shown to be activated (Hermans et al., 2012; Mobbs et al., 2007; Steuwe et al., 2014) would be informative.

4.7.3. *Amygdala*

The amygdala is a key node in mammalian fear networks (LeDoux, 2003), in functional studies of human anxiety disorders (Etkin and Wager, 2007; Menon, 2011), and has featured prominently in both animal and human studies of the short-term effects of IN OT (Bethlehem et al. (2013), Stoop (2012) and Zink and Meyer-Lindenberg (2012) for reviews). It is widely thought that along with insula, amygdala registers and initiates a "first response" to a variety of fear-inducing stimuli as key nodes in what is called the salience network (SN) (which also includes dACC, substantia nigra, ventral tegmental area) (Martin et al., 2009; Etkin and Wager, 2007; Menon, 2011; Paulus and Stein, 2006; Seeley et al., 2007). Interestingly, despite its prominence in neuroimaging studies of humans treated with IN OT, until recently there was no direct evidence of OTR in human amygdala (but see Boccia

et al. (2013)). Effects of IN OT on the human amygdala likely occur due to a combination of direct (wired) transmission (via direct projections from the PVN) as well as diffusion effects from somatodendritic OT release (Ludwig and Leng, 2006; Stoop, 2012).

OT's role in human anxiety disorders is informed by studies indicating that IN OT impacts amygdala-anchored networks in normals (Kirsch et al., 2005; Sripada et al., 2012) and normalizes hyperactive amygdala responses to visual social stimuli in social anxiety patients (Labuschagne et al., 2010), patients with borderline personality disorder (Bertsch et al., 2013), and PTSD (Koch et al., 2013). These acute effects of IN OT on amygdala parallel the effects of some known anxiolytic agents like lorazepam (Paulus et al., 2005) and pregabalin (Aupperle et al., 2011), though other agents anxiolytic over the long term have short-term activating effects on amygdala (i.e. SRIs (Del-Ben et al., 2005; McKie et al., 2005)).

Aside from the evidence from functional neuroimaging studies with acute IN OT, other links between OT, amygdala and anxiety disorders comes from evidence that anxiety-prone individuals and patients with anxiety disorders demonstrate decreased amygdala volume (Spampinato et al., 2009) and that genetic variations in OTR are related to amygdala volume in some studies (Inoue et al., 2011; Wang et al., 2013a,b, but see Tost et al. (2011)). Moreover, as discussed above, in females, variants of the common rs53576 OTR gene affect (1) structural integrity in amygdala-prefrontal connectivity pathways; (2) trait anxiety (harm avoidance); (3) resting-state connectivity between PFC and amygdala (subsequently correlated with trait anxiety) (Wang et al., 2013a,b). Also worth noting are studies indicating that the structural and functional connectivity of the amygdala and mPFC are central to anxiety disorders (Kim et al., 2011; Kim and Whalen, 2009), and that this functional connectivity is impacted by both OT (Sripada et al., 2012) and AVP (Zink et al., 2010).

Crucially, in terms of the development of OT-targeted therapeutics, we are not aware of any functional imaging studies of the effects of chronically-dosed OT on amygdala function. Such studies are vital, given that certain premorbid functional states have shown promise as biomarkers of eventual therapeutic anxiolytic effects of a variety of anxiolytic treatments (Bryant et al., 2008; Nitschke et al., 2009; Phan et al., 2013; Whalen et al., 2008a).

Taking a developmental perspective, alterations in OT systems and their modulation of amygdala may also inform our understanding of the mechanisms wherein early traumatic experiences influences the development of anxiety and stress-related disorders (Apter-Levy et al., 2013; McCrory et al., 2012; Richter-Levin and Maroun, 2010). The burgeoning, cross-disciplinary field studying these mechanisms highlights the potential of OT research to inform questions about the key mediators between early experiences and the developmental of psychiatric disorders. Translational research has already demonstrated the role of OT in the intergenerational transmission of competent caregiving (Champagne et al., 2001; Champagne and Meaney, 2001; Meaney, 2001; Pedersen and Boccia, 2002) and the role of the amygdala in the development of attachment to traumatic caregivers (Moriceau and Sullivan, 2005; Raineki et al., 2010). In humans, early trauma and deprivations have been associated with loss of amygdala-based discrimination between mothers and strangers (Olsavsky et al., 2013), amygdala size (Mehta et al., 2009; Tottenham et al., 2010) and amygdala responses to emotional faces (Dannlowski et al., 2013, 2012). In a seminal study on the development of anxiety disorders, Burghy et al found early life stress to be associated with increased cortisol levels, resting-state amygdala-vmPFC connectivity and anxiety symptoms 14 years later (Burghy et al., 2012). En toto, this body of work informs human clinical research with OT, given that early experience is an individual factor that appears to influence responses to IN OT (Macdonald, 2012). It has even been hypothesized that the effect size of IN OT in certain conditions may be mitigated by neglect of this developmental factor (Bakermans-Kranenburg and van Ijzendoorn, 2013a).

4.7.4. *Bed nucleus of the stria terminalis*

Besides amygdala proper, an underexplored area in terms of human anxiety disorders and OT is the bed nucleus of the stria terminalis (BNST), considered a functional part of the "extended amygdala" (Davis et al., 2010; Veinante and Freund-Mercier, 1997). Together, amygdala and BNST serve as the primary output structures mediating the expression of fear responses via connections to the brainstem and hypothalamus (LeDoux et al., 1988; Oler et al., 2012; Stoop, 2012) (Fig. 3). Experiments in both humans and animals disambiguating amygdala from BNST have supported the distinction between amygdala—which mediates phasic fear responses—and BNST, associated with the transition from brief responses to tonic, long-duration anxiety states (Davis et al., 2010; Hammack et al., 2004; Lang et al., 2000; Pego et al., 2008; Ventura-Silva et al., 2012; Walker and Davis, 2008). Specifically, sustained input from the BLA to the BNST, mediated in part by corticotropin releasing hormone (CRF) (Lee and Davis, 1997), increases output from the BNST to the hypothalamus and brainstem regions associated with sustained anxiety (Walker and Davis 2008) (Fig. 3). Also important in this context is that a population of hypothalamic PVN OT neurons projects directly to the BNST (Buijs et al., 1980; Sawchenko and Swanson, 1983; Sofroniew, 1983), and human post-mortem studies found OTs in the human BNST (Jenkins et al., 1984) (but see Boccia et al. (2013)). Especially illuminating in this regard is Dabrowsa et al's recent examination of the role of PVN OT neurons in reciprocal regulation of CRF-induced anxiety states (and the HPA axis) via CRF neurons in BNST (see Fig. 1, R. pullout) (Dabrowska et al., 2011). This group has also noted that different populations of CRF neurons exist in the PVN and BNST, the former glutamatergic, the latter GABAergic (Dabrowska et al., 2013).

Despite the important role of the BNST, recent reviews of human imaging studies using IN OT do not mention this region (Bethlehem et al., 2013; Zink and Meyer-Lindenberg, 2012). Some of the reason for this neglect is technical; the BNST (like the PAG) is small and difficult to identify (but see Alvarez et al. (2011), Choi et al. (2012), Mobbs et al. (2010), Somerville et al. (2010), Straube et al. (2007) and Yassa et al. (2012)). In addition to technical challenges, much of the literature examining brain responses to OT have used short-term, evocative protocols, which by their nature are more likely to elicit amygdala than BNST. Recent imaging

studies utilizing advanced spatial resolution techniques have recently validated the role of the BNST in sustained, anticipation and monitoring of unpredictable threat vs. phasic fear in both trait-anxious and anxiety-disordered patients (Alvarez et al., 2011; Choi et al., 2012; Mobbs et al., 2010; Somerville et al., 2010; Straube et al., 2007; Yassa et al., 2012). For example, medication-free GAD patients in a high uncertainty gambling task showed decreased amygdala activity and increased activity in BNST (Yassa et al., 2012), and individuals with greater trait anxiety show more activity in BNST (and insula) when tracking threat proximity (Somerville et al., 2010).

Based on the above, we think it is likely that chronic OT modulates human BNST function, and suggest that investigation of the role of OT in BNST (perhaps with subchronic or chronic delivery, utilizing paradigms simulating prolonged anxiety states, and/or in patients who suffer with prolonged anxiety states (i.e. GAD)) may be illuminating.

4.7.5. *Insula*

Insula, especially anterior insula (AI), is part of the brain's salience network (SN) (Seeley et al., 2007). In conjunction with amygdala, with which it has significant connections, insula plays a role in ascertaining the significance of anticipated stimuli (Lovero et al., 2009; Paulus and Stein, 2006; Stein et al., 2007) and mediating predictive interoceptive signals of aversive body states associate with negative outcomes (Alvarez et al., 2011; Paulus and Stein, 2006). Hyperactivity of the AI node of the SN has been associated with anxiety disorders (Etkin and Wager, 2007; Menon, 2011) (but see also Blair et al. (2008)), anxiety sensitivity (hypervigilance for anxiety-related bodily sensations) (Domschke et al., 2010), social anxiety and neuroticism (Terasawa et al., 2013), and enhanced autonomic response and startle to threats (Melzig et al., 2008). In regards to OT, several recent imaging studies have found OT-induced modulation of insula and insula-amygdala coupling, though none of these have been examined in connection with anxiety disorders (Domes et al., 2014; Pincus et al., 2010; Riem et al., 2012; Rilling, 2013; Striepens et al., 2012). Based on this information, examination of the function of insula in anxiety disorder patients treated with OT would be informative.

4.7.6. *Prefrontal cortex (ACC, vmPFC, mPFC)*

A final set of regions associated with anxiety disorders and OT are the prefrontal cortices, including ACC, mPFC and vmPFC. In general, these regions are discussed in the context of "top-down" modulation of hyperactive or hypersensitive subcortical limbic structures and systems (Davidson and McEwen, 2012; Kim et al., 2011; Veer et al., 2012). Importantly, descending influences of the ventromedial prefrontal cortex (vmPFC) and other prefrontal structures on limbic structures (i.e. amygdala) have been identified in both rodents and humans (Bishop, 2007, Kalin et al., 2007, Peters et al., 2009, Soliman et al., 2010). Though significant differences between anxiety disorders exists, decreased activation of vmPVC has been shown in a variety of imaging studies of anxiety patients using different tasks (Killgore et al., 2014; Schienle et al., 2009; McClure et al., 2007; Krain et al., 2008; Blair et al., 2012). Speaking to the effects of medication treatment, a recent study by Phan et al. indicated that chronic SSRI treatment of generalized SOP changed threat-related activity in amygdala and vmPFC (Phan et al., 2013). Additionally, GAD subjects show abnormal function of anterior cingulate (ACC) (Blair et al., 2012; McClure et al., 2007), and in two studies of subjects with GAD, the degree of baseline activation of ACC was positively correlated with the likelihood of response to anti-anxiety medication (Nitschke et al., 2009; Whalen et al., 2008b).

In regards to OT and prefrontal cortex, OTR mRNA is found in the prefrontal and frontal cortex of animals (Gimpl and Fahrenholz, 2001; Smeltzer et al., 2006), and OTR are found in human cingulate cortex (Boccia et al., 2013). Human imaging studies have demonstrated OT-induced modulation of several prefrontal structures in both normals and patients with anxiety disorders (Bethlehem et al., 2013; Zink and Meyer-Lindenberg, 2012). Specifically, Labuschane performed functional imaging on 18 male social anxiety patients in the context of a face matching task and showed that in addition to reducing amygdala activation (Labuschagne et al., 2010), OT normalized hyperactive mPFC and ACC responses to sad faces (Labuschagne et al., 2011). In a second study examining resting-state effects of OT in normals, Sripada showed that OT improved connectivity between amygdala and medial frontal cortex (Sripada et al., 2012). Together, these studies invite future studies investigating the role of OT in modulating activity within prefrontal areas related to anxiety (see Bethlehem et al. (2013) and Zink and Meyer-Lindenberg (2012) for recent reviews).

In summary: though the study of the effects of OT on human brain is in its infancy, evidence reviewed above suggests that OT has effects on several key neural nodes and networks associated with human anxiety disorders, including PAG, BNST, amygdala, insula, and prefrontal cortices.

5. OT and human anxiety: conclusions and questions

Based on the heterogeneous nature of anxiety disorders and a growing body of data suggesting a complex and nuanced role of the OT system in different aspects of anxiety, we believe it is no longer viable to view or describe OT as simply "anxiolytic". That said, based on the diverse areas of convergent research reviewed above, we are optimistic regarding the potential for OT-targeted treatments for at least some specific anxiety disorders. Furthermore, we think the diverse literatures reviewed above suggest that similarly to the HPA and serotonin systems, aspects of the OT system will in the future play a central role in our understanding of the genetics, epigenetics and development of human anxiety and stress-related disorders. Despite the wealth of research above, it is still the case that our understanding of OT as a target for human anxieties is sorely understudied. The field needs refined translational studies and—most vitally—proof-of-concept randomized clinical trials employing chronic daily dosing and meaningful clinical endpoints to help establish OT as a bona-fide monotherapy or adjunctive anxiolytic treatment. Coming from a clinically-informed perspective,

Box 1–Questions for future work on OT and anxiety.

1. Can OT or OT mimetics (alone or adjunct to other medications) significantly reduce symptoms of specific anxiety disorders? What dose, duration and delivery system is optimal? What individual factors determine response? Are there biomarkers of salutary effects?
2. Can OT augment the efficacy of established psychological (non-pharmacological) treatments for anxiety disorders?
3. What role does the OT system play in human fear learning? How does its role in this process inform the role of OT in the development of different anxiety and anxiety-related disorders?
4. How does the OT system interact with different neurotransmitters and hormones (i.e. serotonin, dopamine, HPA axis) in the genesis and maintenance of anxiety states?
5. What is the role of OT in anxiety symptoms associated with non-anxiety disorders (i.e. MDD with anxious features, eating disorders, schizophrenia, addictions)? Might OT be a helpful adjunctive treatment in these conditions?
6. What is the role of the endogenous OT system in common conditions related to anxiety (acute stress responses, marital conflict, loss of partner)?
7. How do early experiences (traumatic and protective) canalize the OT system? How do these changes impact the incidence and emergence of anxiety disorders, including responses to OT?
8. How do OT and OT-related genes (i.e. CD38) modulate early experience and protect against or predispose to anxiety disorders?
9. How do individual differences in OT-related genes relate to individual temperamental variables associated with anxiety disorders (trait anxiety, neuroticism, extraversion, etc.)? How are sex differences in anxiety related? What brain systems mediate these differences?
10. How do changes in central and peripheral aspects of the human OT system (baseline or dynamic OT levels, receptor location or density, OT cell function, genetic variations in components of the OT system) relate to different anxiety disorders?

we close with a list of pregnant questions to direct future research in this area (Box 1).

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Research Report

Reading the mind in the infant eyes: Paradoxical effects of oxytocin on neural activity and emotion recognition in watching pictures of infant faces

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ABSTRACT

The neuropeptide oxytocin facilitates parental caregiving and is involved in the processing of infant vocal cues. In this randomized-controlled trial with functional magnetic resonance imaging we examined the influence of intranasally administered oxytocin on neural activity during emotion recognition in infant faces. Blood oxygenation level dependent (BOLD) responses during emotion recognition were measured in 50 women who were administered 16 IU of oxytocin or a placebo. Participants performed an adapted version of the Infant Facial Expressions of Emotions from Looking at Pictures (IFEEL pictures), a task that has been developed to assess the perception and interpretation of infants' facial expressions. Experimentally induced oxytocin levels increased activation in the inferior frontal gyrus (IFG), the middle temporal gyrus (MTG) and the superior temporal gyrus (STG). However, oxytocin decreased performance on the IFEEL picture task. Our findings suggest that oxytocin enhances processing of facial cues of the emotional state of infants on a neural level, but at the same time it may decrease the correct interpretation of infants' facial expressions on a behavior level.

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1. Introduction

Before the onset of speech infants have vocalizations and facial expressions at their disposal to communicate with the caregiver. The correct interpretation of these infant signals is essential for the caregiver in order to respond appropriately. Previous studies have shown that oxytocin, a neuropeptide that is involved in social affiliation (Carter, 1998), is also involved in the processing of infant vocal cues (Riem et al., 2011, 2012b). Moreover, oxytocin has been shown to facilitate mental state reasoning, defined as the ability to infer others' mental states, thought, feelings and intentions (Domes et al., 2007b; Riem et al., submitted for publication). However, the aforementioned studies focus on infant *vocal* expressions and *adult* facial expressions. It is not yet clear whether oxytocin plays a role in the interpretation of *infant facial* expressions.

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The current study is the first randomized controlled trial examining the influence of intranasally administered oxytocin on the neural mechanisms underlying emotion recognition in infant faces. We examined the neural response to infants' facial emotions with functional magnetic resonance imaging (fMRI).

Infant facial expressions provide important cues about an infant's emotional state and are used by parents in concert with infant vocalizations and contextual information to interpret the needs of their infant. The "Infant Facial Expressions of Emotions from Looking at Pictures" (IFEEL Pictures; Emde et al., 1993) have been developed to assess the perception and interpretation of infants' facial expressions (e.g., Siddiqui et al., 2000). It consists of 30 pictures of infant faces and requires participants to describe in one word the emotional expression of the infant. Several studies have shown that the test can be used to study individual differences in the interpretation of infant emotions. For example, research using the IFEEL pictures has shown that abusive fathers perceive infant emotions in a more negative light than non-abusive fathers (Francis and Wolfe, 2008) and that neglecting mothers are more inaccurate in labeling infant emotions (Hildyard and Wolfe, 2007).

Oxytocin is a neuropeptide that plays an important role in sensitive parenting. Previous research has shown that higher levels of maternal oxytocin across pregnancy predict higher quality of postpartum maternal behavior (Feldman et al., 2007) and that oxytocin has stress-reducing effects in breastfeeding mothers (Heinrichs et al., 2001, 2002). In addition, intranasal administration of oxytocin stimulates a range of social behaviors (for a meta-analysis, see Van IJzendoorn and Bakermans-Kranenburg, 2012), such as trust (Kosfeld et al., 2005) and empathy (Bartz et al., 2010). Domes et al. (2007b) showed that intranasal oxytocin also facilitates mindreading, assessed with the Reading the Mind in the Eyes Task (RMET; Baron-Cohen et al., 1997), a test that requires individuals to infer mental states by looking at photographs of the eye region of adult faces. This is in line with other studies showing that oxytocin stimulates emotion recognition in adult faces (Bartz et al., 2010; Marsh et al., 2010), possibly by enhancing activation in empathy-related brain regions (Riem et al., submitted for publication).

FMRI studies measuring brain activity by detecting associated changes in blood flow have shown that intranasal oxytocin facilitates sensitive responding to infant vocalizations by decreasing activation in the amygdala (Riem et al., 2012a), a brain region implicated in the experience of fear and disgust (LeDoux, 2000), and by increasing activation in the insula and inferior frontal gyrus (IFG) (Riem et al., 2011), brain regions involved in empathy, emotion recognition, and the processing of facial emotional expressions (Bernhardt and Singer, 2012; Carr et al., 2003; Keuken et al., 2011; Liakakis et al., 2011). Other studies also found activation in the anterior insula and IFG during the presentation of pictures of infant faces (for a review see Rilling, 2013). Insula and IFG activation may allow parents to internally simulate what a child is feeling. Indeed, in a previous study we found that intranasal oxytocin enhances activation in the insula during the Reading the Mind in the Eyes Task, thereby facilitating the interpretation of adults' emotions (Riem et al., submitted for publication).

The orbitofrontal cortex (OFC) has also been shown to be activated during the observation of infant faces (Rilling, 2013). The OFC shows a very specific, rapid response to infant faces, and it has been suggested that this may be the potential brain basis for the "innate releasing mechanisms" for nurturing of infants as described by Lorenz (Kringelbach et al., 2008). Intranasal oxytocin has been shown to reduce activation and connectivity of the globus pallidus with reward- and attachment-related brain areas in fathers who were exposed to pictures of their own child (Wittfoth-Schardt et al., 2012). It is as yet unknown how oxytocin influences neural responses to infant faces in women. Moreover, it is unclear whether intranasal oxytocin facilitates the ability to interpret infant facial expressions.

In this study, we examined the influence of intranasally administered oxytocin on neural activation during the IFEEL pictures task with fMRI in female adults. To our knowledge, this study is the first randomized controlled trial examining the influence of intranasally administered oxytocin on the neural mechanisms underlying emotion recognition in infant faces. We were especially interested in effects of oxytocin on the anterior insula, the inferior frontal gyrus pars opercularis (IFG), and the orbitofrontal cortex (OFC), since previous studies have shown that these regions play an important role in the perception of infant stimuli and can be affected by intranasal oxytocin (Riem et al., 2011, 2012b; Strathearn et al., 2009; Wittfoth-Schardt et al., 2012). In addition, we examined effects of intranasal oxytocin on the anterior superior temporal gyrus (STG) and the middle temporal gyrus temporo occipital part (MTG), because these regions have been shown to be activated during emotion recognition in adult faces (Adams et al., 2009; Pincus et al., 2010; Riem et al., submitted for publication). Furthermore, since previous studies have found moderation of oxytocin effects by early caregiving experiences (Bakermans-Kranenburg and Van IJzendoorn, 2013), we examined the potential moderating influence of experienced parenting on the effects of oxytocin. Finally, we expected that intranasal oxytocin would increase performance on the IFEEL picture task.

2. Results

In order to identify brain regions involved in reasoning about the emotional state of infants, we contrasted the emotional state condition with the gender condition. The whole brain analysis revealed three clusters in the placebo group with peak voxels in the left middle temporal gyrus and in the bilateral inferior frontal gyrus (see Table 1). The pattern of activation included the bilateral paracingulate gyrus, the temporal poles, the occipital poles, the bilateral occipital cortex, the left putamen, the left insula, the right orbitofrontal cortex, the bilateral fusiform gyri and the left thalamus (see Fig. 1).

To examine whether oxytocin affected brain activity during emotional state reasoning we contrasted the oxytocin group with the placebo group (Oxytocin $^{\text{Emotion}>\text{Gender}}$ > Placebo $^{\text{Emotion}>\text{Gender}}$ and Oxytocin $^{\text{Emotion}>\text{Gender}}$ < Placebo $^{\text{Emotion}>\text{Gender}}$). In the whole brain analysis no significant differences in brain activity were found between the

Table 1 – MNI coordinates, cluster size, and Z-max values for significantly activated clusters.

Contrast	Brain region	MNI coordinates			Cluster size	Peak Z
		x	y	z		
Placebo $^{\text{Emotional state}>\text{Gender}}$	L Middle Temporal Gyrus	−56	−48	6	14,702	6.42
	L Inferior Frontal Gyrus	−54	16	22	11,346	7.06
	R Inferior Frontal Gyrus	56	26	2	1703	5.58
	L Superior Temporal Gyrus	−48	0	−22	20	2.70[a]
Oxytocin $^{\text{Emotional state}>\text{Gender}}$	R Middle Temporal Gyrus	52	−46	6	10,561	6.26
	L Inferior Frontal Gyrus	−52	14	18	9472	7.63
	L Middle Temporal Gyrus	−52	−44	2	6043	7.09
	L Superior Frontal Gyrus	−4	14	58	1650	6.58
	L Superior Temporal Gyrus	−48	0	−22	147	5.70[a]

$p<.05$, corrected by whole brain cluster threshold ($Z>2.3$); use of oral contraceptives and menstrual cycle included as confound regressors in the model.
[a] Region of interest analysis, $p<.05$, corrected by cluster threshold ($Z>2.3$).

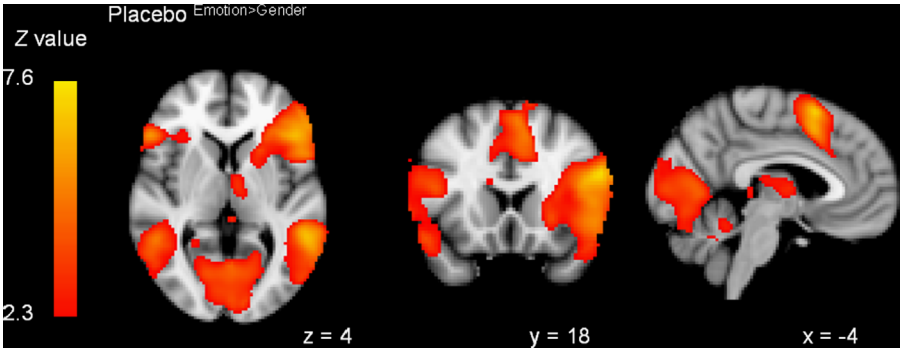

Fig. 1 – Significant activation during the emotional state reasoning condition compared to the gender condition in the placebo group (the left sight of the brain corresponds with the right hemisphere and vice versa). Statistical images were thresholded with clusters determined by $Z>2.3$ and a cluster-corrected significance threshold of $p<.05$.

oxytocin and the placebo group. Region of interest analyses were conducted to test for significant differences in activation during emotional state reasoning between the oxytocin and placebo group in the a priori specified regions of interest. Oxytocin significantly increased activation in the left superior temporal gyrus (cluster size=60, peak Z=2.87, $p=.0021$, MNI coordinates (mm)=−52, 0, −14), the left inferior frontal gyrus (cluster size=24, peak Z=2.64, $p=.0041$, MNI coordinates (mm)=−54, 12, 14) and the left middle temporal gyrus (cluster size=47, peak Z=2.71, $p=.0034$, MNI coordinates (mm)=−46, −54, 12) (see Fig. 2). Region of interest analyses with the right superior temporal gyrus, the right inferior frontal gyrus, the right middle temporal gyrus, the bilateral orbitofrontal cortex, and the bilateral insula did not reveal significant differences between the oxytocin and the placebo group. We examined the potential moderating influence of the difficulty of the pictures (ambiguity of the emotion) and participants' experiences with maternal rejection during childhood. Results were not significant.

There were no differences in basal levels of oxytocin between the oxytocin ($M=6.38$, $SD=4.96$) and placebo group ($M=5.02$, $SD=2.81$), $t(48)=1.19$, $p=.24$. A repeated measure analysis with time (before/after administration) as a within-subject factor and treatment (oxytocin/placebo) as a between-subject factor showed a significant interaction between time and treatment $F(1, 48)=12.28$, $p=.001$. Further analyses showed that the oxytocin level significantly increased from before ($M=6.38$, $SD=4.96$) to after administration ($M=822.11$, $SD=1163.16$) in the oxytocin group $F(1, 24)=12.27$, $p=.002$) whereas the oxytocin level did not significantly differ before ($M=5.02$, $SD=2.81$) and after placebo administration ($M=4.63$, $SD=2.01$) in the placebo group $F(1, 24)=.54$, $p=.47$.

With regard to the performance on the IFEEL picture task, we found no relation between basal oxytocin levels and performance ($r=-.18$, $p=.39$) in the placebo group. The oxytocin group was less correct in recognizing the emotions ($M=20.72$, $SD=2.49$) than the placebo group ($M=22.00$, $SD=1.89$), $t(48)=-2.045$, $p=.046$. Further inspection of the data was done by using a repeated measure analysis including the difficulty levels of the items (easy, medium and difficult). Results showed a main effect of oxytocin ($F(1, 48)=4.18$, $p<.05$), but no main effect of difficulty level ($F(2, 47)=.84$, $p=.44$), and no interaction of oxytocin with difficulty level ($F(2, 47)=.37$, $p=.69$). The basal level of oxytocin did not significantly add to the explained variance in neural activation (IFG beta=.210, $p=.148$; STG beta=.034, $p=.821$, MTG beta −.145, $p=.325$). There were no significant associations

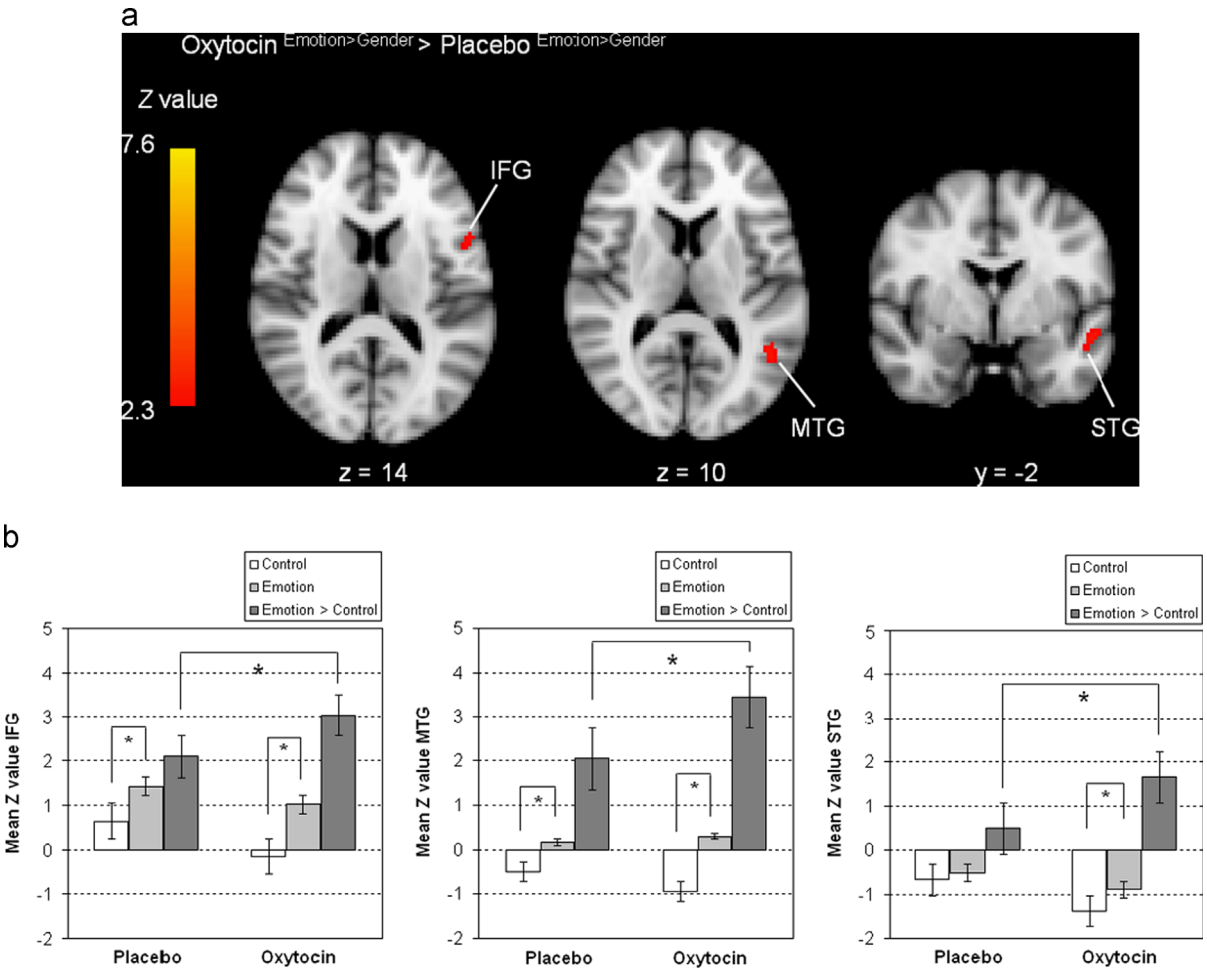

Fig. 2 – (a) Oxytocin effects on the left IFG, the left MTG and the left STG. Region of interest analysis, $p < .05$, corrected by cluster threshold $Z > 2.3$ and (b) Z values (M, SE) of the left IFG, left MTG and left STG activation for the emotion state, gender and emotion > gender condition.

between the number of correct responses and increased brain activation in the IFG ($r = -.08$, $p = .57$), the STG ($r = -.10$, $p = .48$) and the MTG ($r = -.02$, $p = .89$).

3. Discussion

We found that intranasally administered oxytocin enhanced activation in the left IFG, MTG and STG during emotion recognition in infant faces compared to gender identification. This is in line with studies showing neural activation in these areas during emotion recognition in adult faces (Adams et al., 2009; Critchley et al., 2000), and with studies showing that these regions are affected by intranasal oxytocin (Pincus et al., 2010; Riem et al., 2011). At the same time, oxytocin increased the number of mistakes in recognizing infant emotions in the IFEEL picture task.

The IFG is considered an important part of the human mirror neuron system (Gallese and Goldman, 1998) and has shown to be active during imitation and observation of emotional facial expressions of infants (Lenzi et al., 2009). Activation in the mirror neuron system facilitates the understanding of others' thoughts and feelings (Carr et al., 2003). Previous studies examining neural activation during emotion recognition in adult faces (e.g., Adams et al., 2009; Baron-Cohen et al., 1997; Critchley et al., 2000) and neural responses to infant faces (e.g., Leibenluft et al., 2004; Lenzi et al., 2009; Strathearn et al., 2008) also found activation of the IFG, the STG and the MTG. The MTG is part of the ventral visual processing pathway, which is involved in the conscious and explicit appraisal of facial expressions (Critchley et al., 2000). Increased activation in the MTG and the STG might indicate a more conscious evaluation of facial expressions and enhanced processing of facial emotions. Furthermore, we found that oxytocin had no effect on the insula, possibly because the insula is mostly involved in the perception of negative emotions (Lang et al., 2011). One explanation for the absence of oxytocin effects on the OFC may be that the OFC response to infant faces is too rapid and transient to be detected using fMRI (Kringelbach et al., 2008) and because scanning of the OFC is prone to artifacts due to its proximity to air-filled sinuses (Kringelbach et al., 2004).

In the current study we found that oxytocin primarily increased activation in the left hemisphere. Similarly, in a previous study we found that oxytocin effects on neural activation during the RMET were restricted to the left hemisphere (Riem et al., submitted for publication). There is some

evidence that suggests that positive facial expressions are processed primarily in the left hemisphere, in contrast to negative facial expressions, which are processed in the right hemisphere (Canli et al., 1998). This is consistent with the traditional view that the right hemisphere is specialized in handling negative emotions, whereas the left hemisphere specializes on handling positive emotions (Silberman and Weingartner, 1986). However, recent research indicates that differences in left and right hemispheric activation may relate to motivational direction rather than emotional valence. More specifically, greater activity in left frontal and anterior temporal regions has been shown to reflect approach motivation, whereas greater right activity reflects greater withdrawal motivation (Davidson, 1992; Harmon-Jones et al., 2010). Our finding that the effects of oxytocin are restricted to the left hemisphere might therefore indicate that oxytocin enhances approach-related behavior. Indeed, previous studies have found that oxytocin enhances heart rate variability, a psychophysiological marker of approach-related motivation (Kemp et al., 2012) and that it is involved in our motivation to be with others (for a review see Gordon et al., 2011).

In previous research with the IFEEL pictures parents showed an improvement in their ability to appropriately interpret infants' emotional cues after an intervention aimed at enhancing caregiving quality (Constantino et al., 2001). Moreover, neglectful mothers were less accurate in recognizing infant emotions than non-neglecting mothers (Hildyard and Wolfe, 2007). In contrast with our expectations, we found that oxytocin decreased emotion recognition performance. The effect was independent of the difficulty level of the items. Earlier studies found more pronounced oxytocin effects for difficult compared to easy items (Domes et al., 2007b; Marsh et al., 2010). These studies examined emotion recognition in adult faces while we examined emotion recognition in infant faces. It may be that the influence of oxytocin on emotion recognition with adult faces shows more variability depending on ambiguity of the emotion. Further research comparing adult faces and infant faces with varying levels of ambiguity of the expressed emotions may shed light on this issue. To our surprise we found that oxytocin *enhanced* neural activity in empathy-related brain regions during emotion recognition, while it *decreased* performance in emotion recognition.

We found no significant relation between brain activation and performance. This is in line with earlier studies in which RMET performance was not related to brain activity during the RMET task (Riem et al., submitted for publication, but see Adams et al., 2009) and neural responses to infant crying did not predict behavioral responses to crying (Riem et al., 2012a). Thus, there seems to be a transmission gap between task-related brain activity and actual behavior. Berkman and Falk (2013) recently discussed the *brain-as-predictor* approach with neural measures as independent variables in models with observed "real-world" outcomes as dependent variables. They describe established brain-behavior relations including neural signals that predict skill acquisition or cognitive decline. Future research may implement the brain-as-predictor approach in the investigation of parent–infant interactions and examine the relation between task-related brain activity and actual caregiving behavior.

The limitations of our study should be acknowledged. One limitation is that we used a between-subjects design to study the effects of oxytocin, which implies the risk of pre-existing differences between the oxytocin and the placebo group. Randomization and double-blind application have decreased this risk substantially. In addition, meta-analytic findings indicate that studies using between- or within-subject design to examine intranasal oxytocin influences show no significant differences in effect size (Van IJzendoorn and Bakermans-Kranenburg, 2012). Although we did not expect pre-existing differences in emotion recognition ability and tested for basal oxytocin levels between the two groups, there may have been differences between individuals in emotion recognition ability as related to genetic differences, e.g. in the oxytocin receptor OXTR gene polymorphism (Bartz et al., 2011). We found however no difference in basal oxytocin levels, no associations between basal oxytocin and emotion recognition, and in a meta-analysis differences in OXTR rs53576 and rs2254298 were not related to social-emotional behavior (Bakermans-Kranenburg and Van IJzendoorn, 2013). The inclusion of a sample of females without children is another limitation of this study. Earlier studies showed that oxytocin affects brain activity when looking at faces with emotional expressions differently in males and females (Domes et al., 2007a, 2010). Although the generalizability of our findings may be limited, examining oxytocin effects in women fills an important gap as long as most previous studies focused on the effects of oxytocin in men (Bos et al., 2012). In our sample, 70% of the participants used oral contraceptives. As contraceptives interfere with the endogenous steroid metabolism and steroids may interact with intranasally administered oxytocin, we took the use of oral contraceptives into account as a covariate. The covariate did not affect our results. Future studies may examine the possible interaction of intranasal oxytocin and the use of oral contraceptives in larger samples. Furthermore, we found no moderating effect of early childhood experiences on neural activation, and further research is needed to clarify whether and how the effects of oxytocin vary depending on individual factors.

We used intranasal oxytocin administration to examine changes in brain activation and behavior. It has been reported that related neuropeptides such as arginine vasopressin (AVP) can cross the blood brain barrier (BBB) and enter the brain directly from the nasal capillaries via the olfactory bulb neurons (Born et al., 2002). Other routes by which these neuropeptides may reach the brain are for example via the ventricular CSF followed by entering the extra-cellular space of the brain (Born et al., 2002), or via trigeminal nerve branches into the brain (Guastella et al., 2012). It is likely that multiple routes operate independently of each other (Neumann et al., 2013) and that the uptake of intranasally administered oxytocin by one or more of these routes shows inter-individual variation in relative contribution in the net uptake (Guastella et al., 2012).

A recent study with rodents showed that oxytocin levels in both the amygdala and hippocampus were increased after intranasal oxytocin administration, and that this increase in the brain was paralleled by changes in plasma levels of oxytocin (Neumann et al., 2013), but it is unclear whether

these findings generalize to humans. However, the results of our studies and those of others (for a review see Rilling, 2013) show that intranasal administered oxytocin does have effects on neural activity and behavior (for a meta-analysis, see Van IJzendoorn and Bakermans-Kranenburg, 2012). Moreover, elevated levels of oxytocin in saliva have been demonstrated up to seven hours after nasal administration (Van IJzendoorn et al., 2012). The persistence of intranasal oxytocin levels in saliva has been suggested to be caused by a feed forward mechanism in which treatment with intranasal oxytocin might lead to an increase in the production of endogenous oxytocin (Van IJzendoorn et al., 2012). These results support the validity of the procedure, but further research is needed to establish how exactly oxytocin enters the brain and in what amounts it reaches the receptors in which regions of the human brain.

In sum, this is the first randomized controlled trial examining the influence of intranasally administered oxytocin on the neural mechanisms underlying emotion recognition in infant faces. We found that oxytocin enhanced activation in brain regions implicated in empathy and emotion understanding when individuals infer the emotional state of infants with various facial expressions, which may facilitate the interpretation of the needs of infants and the selection of a sensitive caregiving response. Surprisingly, we found that oxytocin lowered performance in emotion recognition in infants and that performance and brain activation were not related. The paradoxical effects of oxytocin with enhanced neural activation of empathy-related brain regions on the one hand and lower performance on emotion recognition of infant faces on the other hand should be focus of further research.

4. Experimental procedure

4.1. *Participants*

A total of 343 female undergraduate students from the departments of education and child studies, and psychology at Leiden University participated in the first phase of the study. In this phase, the participants completed online questionnaires on experienced parenting and some demographic details. One participant was excluded due to random responses and five females with children of their own were excluded to avoid effects of parental experiences on the outcomes. One hundred eighty-six nulliparous females participated in the second phase of the study in which behavioral responses to infant crying were examined. Fifty-four participants with scores ranging from low to high on an experienced parenting questionnaire were selected to participate in the third phase of the study. The third phase consisted of a computer game designed to study prosocial helping behavior towards an excluded adult (without an fMRI component, see Riem et al., 2013), and the current fMRI study. Participants were screened for MRI contraindications, psychiatric or neurological disorders, hearing problems, pregnancy, and alcohol and drug abuse. Due to excessive head movement during fMRI scanning, four participants were excluded from the current analyses, resulting in a total sample of 50 nulliparous female participants. The participants were randomly assigned to the oxytocin ($n=25$) or the placebo condition ($n=25$). The mean age of the participants was 19.66 years ($SD=1.45$, range 18–27) and the majority (70%) used oral contraceptives. Permission for this study was obtained from the Ethics Committee of the Institute of Education and Child Studies of Leiden University and of the Leiden University Medical Centre.

4.2. *Procedure*

The majority of the participants (82%) were invited in the luteal phase of their menstrual cycle, which was assessed using self-report. It was not possible to determine menstrual phase for two participants because of use of Mirena intrauterine device. Participants took six puffs of nasal spray containing oxytocin (16 IU total) or placebo spray approximately 50–60 minutes before the start of the fMRI data acquisition for the IFEEL pictures task. The administration of the spray was done under supervision of the experimenter and drug administration was double-blind. After administration of the nasal spray, the participants completed some practice trials outside the scanner to become familiar with the task. Salivary oxytocin levels have been shown to remain elevated for more than seven hours after administration of nasal spray containing 16 IU of oxytocin (Van IJzendoorn et al., 2012) and effects of nasal spray with 16 IU of oxytocin on social behavior and neural activity have been reported in previous studies (Riem et al., 2011).

4.3. *Experimental task*

Participants performed an adapted version of the IFEEL pictures task (Emde et al., 1993). Participants viewed 30 photographs of infant faces in two different conditions, resulting in a total of 60 stimulus presentations. In the first condition, two emotion words accompanied each photograph and participants were asked to select the word that best described what the infant in the photograph was thinking or feeling. The selection of the two emotion words for each picture was based on scores of a reference group of 100 mothers of infants (Emde et al., 1993). For each picture, two emotion words were selected as the emotion words in the current fMRI study. The emotion that was more often chosen by the reference group (Emde et al., 1993) was considered the correct response, and the emotion that was less often chosen was considered the incorrect response. Correct and incorrect emotions were presented counterbalanced on the left and right side of the screen. In the control condition, the participants were asked to indicate whether the infant was a boy or a girl. Participants were asked to indicate the child's emotional state or to indicate the gender of the child by pressing buttons with the right hand. The photographs were presented in blocks of 5 trials. Each photograph was presented for 5 s (interstimulus time 1–2.5 s). To compare the responses to the relatively easy (unambiguous) and more difficult (ambiguous) pictures, we distinguished three groups: easy, medium and difficult. For each picture we calculated a difference score based on differences in frequencies of the alternatives in the reference group. For example, when for a specific picture 94% of the reference group chose “content”

and 5% chose "passive", the difference score was (94–5=)89. Ten pictures (with difference scores 31–90) were classified as easy, ten as medium (difference scores 12–30) and ten as difficult (difference scores 1–11). Menstrual cycle phase and oral contraceptive use had no influence on performance on the IFEEL pictures task.

4.4. *Maternal love withdrawal.*

Maternal use of love withdrawal was assessed using an 11-item questionnaire (Huffmeijer et al., 2011) based on the Child's Report of Parental Behavior Inventory (CRPBI; Beyers and Goossens, 2003; Schludermann and Schludermann, 1970) and the Parental Discipline Questionnaire (PDQ; Hoffman and Saltzste, 1967; Patrick and Gibbs, 2007). Each item (e.g. *My mother was a person who is less friendly with me, if I do not see things her way*) was rated on a 5-point scale ranging from *not applicable* to *fully applicable*. Due to a technical error one of the items was missing in some questionnaires. The score for this item was substituted with the mean score of the other items. Internal consistency of the scale was high (Cronbach's $\alpha = .92$).

4.5. *fMRI data acquisition and analysis*

Scanning was performed with a standard whole-head coil on a 3-T Philips Achieva TX MRI system (Philips Medical Systems, Best, the Netherlands) in the Leiden University Medical Center. First, a T1-weighted anatomical scan was acquired (flip angle=8°, 140 slices, voxel size.875 × 875 × 1.2 mm). For fMRI, a total of 186 T2*-weighted whole-brain echoplanar images were acquired (repetition time=2.2 s; echo time=30 ms, flip angle=80°, 38 transverse slices, voxel size 2.75 × 2.75 × 2.75 mm (+10% interslice gap)). All anatomical scans were examined by a radiologist in accordance with Leiden University Medical Center policy. No anomalies were found.

Data analysis was carried out using FEAT (FMRI Expert Analysis Tool) version 5.98, part of FSL (Smith et al., 2004). The following pre-statistics processing was applied: motion correction (Jenkinson et al., 2002), non-brain removal (Smith, 2002), spatial smoothing using a Gaussian kernel of full-width-at-half-maximum 8.0 mm, and high-pass temporal filtering (highpass filter cutoff=100.0 s). Functional scans were registered to the high-resolution EPI-images, which were registered to the T1-weighted images, which were registered to standard space (Jenkinson et al., 2002).

In native space, functional activation was examined using general linear model analysis. Each condition (emotional state, gender) was modeled separately as a square-wave function. Each predictor was then convolved with a double gamma hemodynamic response function and its temporal derivative was added to the model, giving four regressors. To be able to examine brain regions activated during the emotional state attribution we contrasted the emotional state attribution condition with the gender condition (emotion>gender).

The first-level contrast images and the corresponding variance images were transformed to standard space and submitted to second-level mixed-effects group whole brain analyses. Group means were tested using one-sample *t*-tests and we tested for group differences using two-sample *t*-tests on these contrasts with the oxytocin versus placebo group comparison (Oxytocin>Placebo and Oxytocin<Placebo). We included menstrual cycle (follicular or luteal phase) and use of oral contraceptives as confound regressors in the model in the analyses of the group means and group differences. Menstrual cycle and use of oral contraceptives showed no effects on neural activity during the task. The statistical images were thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p < .05$.

Region of Interest (ROI) analyses were conducted with *a priori* specified regions of interest based on previous fMRI studies (e.g., Adams et al., 2009; Castelli et al., 2010; Moor et al., 2012; O'Doherty et al., 2003). These regions were the anterior insula, the inferior frontal gyrus pars opercularis (IFG), the anterior superior temporal gyrus (STG), the orbitofrontal cortex (OFC) and the middle temporal gyrus temporo occipital part (MTG) (>75% probability, anatomically defined using the Harvard–Oxford cortical atlas, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). ROI analyses were limited to these regions, applying the same statistical threshold as for the whole brain analyses, but correcting only for the size of ROI volumes. The correction for multiple testing was done for all three ROIs separately. Mean *Z*-values for significantly activated voxels in the left IFG, the left STG and the left MTG were calculated for visualization purposes.

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Research Report

Schizophrenia and alcohol dependence: Diverse clinical effects of oxytocin and their evolutionary origins

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ABSTRACT

Beginning in 1979 with the first report that central administration of oxytocin stimulates maternal behavior in virgin rats, decades of animal research and more recent human studies have demonstrated that oxytocin has many pro-social effects. These many findings suggest that oxytocin may be an effective treatment for social deficits that are hallmark features of disorders such as autism and schizophrenia. Effects in preclinical animal models also imply that oxytocin may be an efficacious pharmacotherapy in a wide range of psychiatric disorders including psychoses and addictions. To date, 3 small clinical trials found that daily intranasal oxytocin treatment for 2–8 weeks significantly reduced psychotic symptoms in schizophrenia. Two of these trials also found improvement in social cognition or neurocognition, areas in which patients have significant deficiencies that do not respond to conventional antipsychotic treatment and contribute to disability. In another small trial, intranasal oxytocin potently blocked alcohol withdrawal. After reviewing the rationale for these trials, they are described in more detail. Questions are then asked followed by discussions of the large gaps in our knowledge about brain oxytocin systems in humans. The hope is to highlight important directions for future investigations of the role of oxytocin in the pathophysiology of psychotic disorders and addictions and to extend clinical research in these areas. Heretofore unrecognized roles for which oxytocin may have been selected during the evolution of placental mammalian maternal–infant and other social attachments are considered as possible origins of oxytocin antipsychotic and antiaddiction effects.

This article is part of a Special Issue entitled Oxytocin and Social Behav.

1. Evolutionary prologue

Chapter 2 (in this volume) discusses the evolution of oxytocin (OT) and its central roles in unique aspects of placental mammalian reproduction. These include milk ejection, which is essential for the success of lactation, and stimulation of uterine contractions, which facilitates parturition following fetal development within the uterus. Chapter 2 also emphasizes that OT was selected to activate avid and sustained maternal behavior in parturient females, another novel

Abbreviations: OT, oxytocin

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reproductive strategy that was essential for the successful evolution of placental mammals. It was hypothesized that the much higher quality maternal behavior exhibited by placental mammals required the evolution of new brain systems that could initiate and maintain a highly motivated social behavioral state, systems that OT activates at parturition. OT (as well as vasopressin) appears to have been selected to initiate other social attachments that evolved in placental mammals, such as monogamous pair-bonding. Evidence was reviewed that OT may also have been selected to regulate other social and emotion behavior control systems that emerged during placental mammalian evolution to enhance reproductive success. For example, OT has been strongly implicated in reducing anxiety and fear responses during parturition and lactation which enabled successful activation of offspring caretaking in parturient mothers, especially primiparous mothers in whom the novelty of parturition and newborns could produce aggression toward or avoidance of offspring. As is reviewed by MacDonald (in this volume), OT anxiolysis is not restricted to reproductively relevant states in animals, has been demonstrated in human subjects, and may be therapeutically beneficial in human anxiety disorders. Later in placental mammalian reproductive, central OT systems evolved to facilitate the formation of selective maternal–infant bonds by enabling mothers to learn the unique odors of their offspring.

Chapter 2 also speculates that the evolution of avid and sustained maternal behavior, as well as lactation and *in utero* fetal development, enabled, in multiple ways, the subsequent evolution of higher intelligence. The many recent reports that intranasal OT administration facilitates social cognition in human subjects (see Evans et al. (in this volume) as well as the review of these findings later in this chapter) suggest that OT may have been centrally involved in advances in cognitive ability, especially social intelligence, during the evolution of placental mammals.

The primary goal of this article is to review evidence that OT is a promising new treatment for schizophrenia and alcohol dependence. A secondary but still key aim is to propose that the seemingly unrelated antipsychotic and antiaddiction effects of OT may provide new insights into other OT mechanisms that may have been selected during placental mammalian evolution to facilitate the formation of social bonds. This argument is summarized here and restated at the end of the article. As is discussed in more detail below, the antipsychotic efficacy of OT may be based on enhancement of sensory-motor gating, *i.e.*, the ability to rapidly process the significance of sensory input and initiate appropriate behavioral responses. Successful evolution of avid and sustained maternal behavior in placental mammals may have required a considerable up-grade in sensory-motor gating ability. Effective mothering requires accurate perception of diverse sensory cues from offspring and swift mobilization of appropriate caretaking behaviors. The antiaddiction effects of OT appear to be based on inhibition of tolerance formation to addictive substances. The evolution of the ability to form lasting social attachments may have required selection of brain mechanisms that prevent habituation to the highly rewarding stimuli from reproductively important conspecifics such as offspring or pair-bonded mates. OT could have been selected to play this role. As a by-product, OT may block tolerance formation to other strong activators of reward pathways including addictive drugs.

2. Introduction

Three recent clinical trials have rapidly propelled OT into the forefront of schizophrenia research. All 3 trials found that twice daily intranasal administration of OT for 2–8 weeks as an adjunct to antipsychotic medication significantly reduced positive, negative and general symptoms in patients with schizophrenia (Feifel et al., 2010; Pedersen et al., 2011; Modabbernia et al., 2013). Furthermore, OT treatment but not placebo improved performance on tests of social cognition in the Pedersen et al. (2011) study and improved verbal learning but not working memory (Feifel et al., 2012). Patients with schizophrenia have deficits in these cognitive domains that profoundly impair their function and which do not respond to currently available antipsychotic medications (Harvey et al., 2006; Sergi et al., 2007; Penn et al., 2009). A recent preliminary trial suggests that OT may have efficacy in treating a quite different clinical disorder-addiction. Pedersen et al. (2013) discovered that twice daily intranasal OT for 3 days was markedly more effective than placebo in reducing withdrawal symptoms and the amount of benzodiazepine required for successful medical detoxification of alcohol dependent patients. This is the first evidence in human subjects that OT has therapeutic efficacy in a substance dependence disorder. Remarkably, intranasal OT treatment produced no increased side effects or adverse events in these clinical trials or other studies (MacDonald et al., 2011).

The sections below begin with reviews of animal and human studies that led investigators to test OT as a treatment for schizophrenia and alcohol withdrawal. The clinical trials are then described as well as relevant studies that have been published more recently. Questions are then posed about the large gaps in our current knowledge about OT systems in the human brain. These are discussed to highlight important areas for future research that will advance our understanding of OT in schizophrenia, alcohol dependence and other addictive disorders as well as other types of psychopathology (see Macdonald and Feifel (2013) for a comprehensive overview of unresolved issues relevant to the development of OT pharmacotherapeutics). Finally, roles for which OT may have been selected during the evolution of placental mammalian maternal behavior are considered as possible origins for OT efficacy in treating disorders as diverse as schizophrenia and alcohol dependence.

3. Oxytocin and schizophrenia

MacDonald and Feifel (2012) thoroughly reviewed evidence for therapeutic effects of OT in schizophrenia. We will briefly summarize and update that evidence and elaborate further on OT as a treatment for social cognition and function deficits in schizophrenia.

3.1. *The rationale for oxytocin treatment of psychotic symptoms in schizophrenia*

The strongest evidence that OT may have antipsychotic efficacy was studies employing several animal models of psychosis. The first animal model in which OT was tested is stimulant-induced hyperactivity that simulates the excessive dopaminergic activity which has long been hypothesized in schizophrenia (Carlsson, 1977; Carlsson and Carlsson, 2006). OT administration diminished cocaine or methamphetamine-induced hyperactivity (Sarnyai et al., 1990; Qi et al., 2008), effects that were localized to the striatum and nucleus accumbens, brain areas that have been implicated in schizophrenia (Meyer-Lindenberg, 2010). Subsequent studies were conducted in a rat model of psychosis in which prepulse inhibition (PPI) is disrupted by administering psychotomimetic drugs such as amphetamine or apomorphine that increase dopamine receptor stimulation or NMDA receptor antagonists like phencyclidine or MK801 (Geyer et al., 2001; Geyer and Ellenbroek, 2003). PPI is the capacity to suppress startle response to a strong stimulus (usually acoustic) when "warned" by a preceding mild stimulus (Braff et al., 2001; Geyer et al., 2001). PPI is mediated by neural circuitry that includes the nucleus accumbens, the hippocampus and the basolateral amygdala, all brain areas that have been implicated in the pathophysiology of schizophrenia (Koch and Schnitzler, 1997, Swerdlow et al., 2001). PPI performance is impaired in patients with schizophrenia which is thought to indicate aberrant sensory-motor gating in this disorder (Braff et al., 2001). PPI deficits are decreased by antipsychotic medication in psychotomimetic drug-treated rodents and in patients with schizophrenia. Both exogenous and endogenous OT have been shown to diminish PPI deficits in this model of psychosis, especially in animals given NMDA antagonists (Feifel and Reza, 1999; Caldwell et al., 2009). OT has also been tested in a third animal model that is based on evidence that the NMDA receptor is involved in psychosis. Specifically, chronic treatment with NMDA antagonists (PCP, ketamine, MK-801) produces a loss of social interest (a prominent negative symptom) (Sams-Dodd, 1999; Qiao et al., 2001) and PPI deficits. Chronic PCP administration was noted by Lee et al. (2005) to decrease anterior hypothalamic OT mRNA and to increase OT receptor binding in the central nucleus of the amygdala (CeA). Infusion of OT into the CeA fully restored social interest in chronic PCP-treated rats. The greater efficacy of OT in reversing NMDA antagonist-induced PPI deficits and chronic PCP-induced psychotic-like behavioral deficits in rats suggests that OT may exert its antipsychotic effects through interactions with glutamatergic systems. Koenig et al. (2005) found that offspring of rat mothers exposed to variable, unpredictable stress during the third trimester also had deficits in social interest and PPI. As in the chronic PCP model, these animals had diminished OT mRNA in the hypothalamic paraventricular nucleus (PVN), the site containing the largest number of centrally-projecting OT neurons, and elevated OT receptor binding in the CeA (Lee et al., 2007). Bilateral infusion of OT into the CeA restored normal social interest levels in these animals.

Other findings in animals have suggested that OT may exert effects in schizophrenia. The atypical antipsychotic drugs, clozaril and amperozide, but not haloperidol, were reported to increase plasma OT concentrations in rats (Uvnäs-Moberg et al., 1992). In addition, OT interactions have been reported with neurotransmitter systems that have been linked to schizophrenia; most importantly dopamine (Baskerville and Douglas, 2010; Shahrokh et al., 2010; Succu et al., 2007), glutamate (Hrabovszky and Liposits, 2008; Ninan, 2011), and serotonin (Emiliano et al., 2007). Estrogen has strong effects on CNS OT and OT receptors (Jirikowski et al., 1990; Bale et al., 1995; Shughrue et al., 2002; Patisaul et al., 2003; Choleris et al., 2008) which may be relevant to sex differences in the onset and severity of schizophrenia.

All but one published studies of OT parameters in the human brain have found differences between patients with schizophrenia and normal subjects. Two groups reported that CSF concentrations of OT or OT-associated neurophysin were elevated in patients (Beckmann et al., 1985; Linkowski et al., 1984) but a third group found no difference in OT concentrations (Glovinsky et al., 1994). Morphometric differences in OT-associated neurophysin-immunostaining cells as well as reduced cell density were also identified in the PVN of schizophrenic patient brains (Mai et al., 1993; Bernstein et al., 1998). Serum concentrations of OT-associated neurophysin were significantly higher in patients, especially those with paranoia (Legros et al., 1992). Plasma OT concentrations were lower in polydipsic, hyponatremic schizophrenic patients compared with polydipsic, normonatremic patients, non-polydipsic, normonatremic patients or healthy controls and did not differ among the latter 3 groups (Goldman et al., 2008). Rubin et al. (2010) found no difference in plasma OT concentrations between women or men with schizophrenia compared with normal controls but higher concentrations in female patients correlated significantly with lower total, positive and general Positive and Negative Symptom Scale (PANSS; Kay et al., 1987) scores and nearly significantly ($p=.06$) with negative PANSS scores. In addition, an OT gene variant (rs2740204) has been significantly associated with clinical improvement with clozapine (Souza et al., 2010). In the same study, some OT receptor gene polymorphisms were associated with improvement of positive psychotic symptoms with clozapine treatment while other receptor gene polymorphisms were associated with symptom severity. It should also be noted that studies conducted in the Soviet Union 3–4 decades prior to the recent era of intranasal OT clinical trials in schizophrenia found that repeated administration of intranasal or intravenous OT doses to severely, but rather imprecisely described, mentally ill patients, some probably with schizophrenia, improved symptoms and prevented hospitalizations (Bujanow, 1972; Bakharev et al., 1986).

3.2. *The rationale for oxytocin treatment of social cognition deficits in schizophrenia*

Social dysfunction is among the most disabling consequence of schizophrenia (Pinkham et al., 2003; Yager and Ehmann, 2006) and responds poorly to currently available antipsychotic medications (Buchanan et al., 1998; Kirkpatrick et al., 2000; Bellack et al., 2004; Penn et al., 2009). The loss of brain volume and decline in general mental abilities that occur in many individuals with schizophrenia appear to contribute

substantially to social dysfunction (Cahn et al., 2006). However, recent evidence indicates that aspects of mentation that facilitate social decisions and behavior are particularly impaired in schizophrenia (Phillips et al., 2003; Pinkham et al., 2003; Yager and Ehmann, 2006; Penn et al., 2008). This type of cognition, "social cognition," is comprised of emotion recognition (*e.g.*, identifying the emotional states of others from their facial expressions and other social cues), attributional style (beliefs about the causes of events) and theory of mind (inferring the thoughts and feelings of others), areas that are consistently impaired in schizophrenia (Green et al., 2005; Penn et al., 2006; Bora et al., 2009; Kohler et al., 2010), and which are related to real-world outcomes, such as social and community functioning(Couture et al., 2006; Pinkham and Penn, 2006; Fett et al., 2011). Unfortunately, there is no evidence that psychopharmacological treatment, such as currently available antipsychotic medications, improves social cognition in schizophrenia. Specifically, three large clinical trials (including the CATIE trial) found that typical and atypical antipsychotic medications did not improve social cognition in schizophrenia (Harvey et al., 2006; Sergi et al., 2007; Penn et al., 2009).

Decades of research in animals have established that CNS OT has many effects on social behavior including activation of key social attachments such as maternal behavior in several species, pair-bond formation in females of some monogamous species and olfactory-based social memory, a rodent model of social cognition (Pedersen et al., 1992; Carter et al., 1999; Gimpl and Fahrenholz, 2001; Lee et al., 2009). Over the past decade, human studies in which OT was administered in a nasal spray have found a wide range of pro-social effects (MacDonald and MacDonald, 2010). The advent of these studies was probably delayed by the inconsistent results of early studies employing the intranasal route of administration to determine if OT had amnestic effects previously found in animals (Ferrier et al., 1980; Fehm-Wolfsdorf and Born, 1991; Bruins et al., 1992) and by the negative results of two clinical trials testing whether sustained daily intranasal OT treatment improved symptoms in obsessive-compulsive disorder (den Boer and Westenberg, 1992; Epperson et al., 1996).

The current era of studying OT effects on human social behavior was ushered in by a particularly elegant and highly influential experiment conducted by Kosfeld et al. (2005) which demonstrated that a single intranasal dose of OT significantly increased interpersonal trust. Numerous studies published in the ensuing 5 years reporting that intranasal OT produced a variety of social behavioral and social cognitive effects in human subjects. These included mostly positive influences on social behavior including replication of the Kosfeld et al. (2005) finding of interpersonal trust enhancement (Baumgartner et al., 2008; Mikolajczak et al., 2010a, 2010b), increase in eye contact (Andari et al., 2010; Guastella et al. 2008), improved perception of and responsiveness to social cooperation in patients with autism spectrum disorder (Andari et al., 2010) but also amplification of envy and gloating at others' misfortune (Shamay-Tsoory et al., 2009). Other intranasal OT studies published during this time period found improvements in various domains of social cognition: face emotion recognition; theory of mind; and perception of the trustworthiness of faces and empathy (Domes et al., 2007a; Fischer-Shofty et al., 2010; Guastella et al., 2010; Hurlemann et al., 2010; Petrovic et al., 2008; Theodoridou et al., 2009). Plasma OT concentrations were reported to increase in participants in a trust game that received a high monetary transfer indicating trust and who then reciprocated generously (Zak et al., 2005). During trust-related interactions, plasma OT levels rose in healthy controls but not in patients with schizophrenia (Keri et al., 2009). In schizophrenia patients, plasma OT levels correlated positively with their accuracy in identifying facial emotions (Goldman et al., 2008). For more comprehensive reviews and critique of studies of intranasal OT on human social behavior and social cognition, including numerous studies since 2010, see Guastella and MacLeod (2012) and Evans et al. (in this volume).

Confidence that OT administered by the intranasal route enters the brain was increased by results published by Born et al. (2002). They found that CSF levels of vasopressin were markedly increased 10 min after intranasal administration and remained elevated for at least 80 min. This has led to the assumption that OT, which is structurally very similar to vasopressin, also readily enters the CNS after intranasal administration. Several fMRI studies have found that activation of the amygdala in subjects viewing unpleasant or frightening images is altered by intranasal administration of OT (Kirsch et al., 2005; Domes et al., 2007b, 2010; Zink and Meyer-Lindenberg, 2012). These results strongly support the conclusion that OT enters the CNS after intranasal administration.

3.3. *Clinical trials of oxytocin treatment of schizophrenia*

All 3 published studies were randomized, double-blind and placebo-controlled trials conducted in patients who met criteria for DSM-IV schizophrenia, were at least moderately symptomatic (total PANSS scores ≥ 55) and had been clinically stable and on the same doses of antipsychotic medications (atypicals in almost all cases) for at least 4 weeks prior to study entry. These studies found no differences between OT and placebo groups in side effects (including extrapyramidal symptoms) or laboratory measures over the treatment periods.

Feifel et al. (2010) were the first to conduct a clinical trial of intranasal OT treatment in patients who met DSM-IV criteria for schizophrenia. The study had a cross-over design and enrolled 15 adult patients (12 male, 3 female). The order of intranasal treatments (OT *vs.* placebo) was randomly assigned during an initial 3-week treatment period after which subjects received the other treatment during a subsequent 3-week period following a 1-week washout. Intranasal OT (Syntocinon Spray, Novartis, Basel, Switzerland) was dosed at 20 IU (5 insufflations) twice daily (BID) for 1 week and then 40 IU BID for 2 weeks. PANSS total scores, PANSS positive subscale scores, PANSS negative subscale scores as well Clinical Global Impressions-Improvement (Guy and Bonato, 1970) scores were significantly lower in the OT compared to the placebo group at treatment week 3 but not at 1 or 2 weeks (see Figs. 1–3). PANSS general subscale scores did not differ between treatment groups at 3 weeks (Fig. 4). There was a significant drug by time interaction for PANSS

total scores indicating there was greater decline in this measure from baseline to 3 weeks in the OT compared to placebo group.

Neurocognitive deficits, including impaired verbal and working memory, are common in schizophrenia and respond poorly to current antipsychotic medications (Keefe and Harvey, 2012). Intranasal administration of OT has been reported to have amnestic effects in some but not all human studies (Fehm-Wolfsdorf and Born, 1991; Bruins et al., 1992). Therefore, Feifel et al. (2012) also administered the California Verbal Learning Test (CVLT, Delis et al., 2000) and the Letter Number Sequencing Task (LNS, Wechsler, 1997), a test of working memory, in the cohort of 15 described above at baseline and at week-3 of each test treatment period. During administration of the CVLT, subjects read a list of 16 words over 5 trials, and then engage in recall tasks, including free recall, recall after an interference list is read, recall after different amounts of elapsed time (*i.e.* short and long delay) and discriminating between words from different lists. Each task generates a separate subscore. Administration of the LNS Task involves reading to subjects a series of lists of letters and numbers in mixed orders ranging in length from 2 to 8. After each list is read, subjects are asked to recall first the digits and then the letters in the order they were presented. Scores are the total number of correct responses on all of the lists. The CVLT total recall, short delay free recall and total recall discriminability measures were significantly improved by OT compared to placebo treatment and compared to baseline, although most of the improvement occurred in subjects who received OT during the second treatment period (Fig. 5). OT did not improve performance on the LNS Task compared to placebo or baseline (Fig. 5). The effects of 3 weeks of intranasal OT treatment on CVLT found by Feifel et al. (2012) in patients with schizophrenia contrasts with previous reports that a single intranasal dose of OT worsened verbal memory (Ferrier et al., 1980; Fehm-Wolfsdorf et al., 1984; Bruins et al., 1992; Heinrichs et al., 2004). However, these results suggest that OT treatment has the potential to improve some neurocognitive deficits in schizophrenia.

Pedersen et al. (2011) reported the results of a 2-week treatment trial conducted in 20 subjects (17 male and 3 female) with paranoid or undifferentiated schizophrenia who received BID intranasal doses of OT (24 IU/dose, $N=11$) or placebo ($N=9$). The PANSS, the Paranoia Scale (Fenigstein and Vanable, 1992), the Brüne Theory of Mind Picture Stories Task (Brüne, 2003) and the Trustworthiness Task (Adolphs et al., 1998) were administered at baseline and after 14 days of test treatments. Five additional subjects subsequently completed the protocol increasing the total cohort to 25 (OT=14 and placebo=11). Data analyzed in the larger cohort also included mean scores on 5 PANSS items relevant to social function (the average of the suspiciousness, hostility, passive/apathetic social withdrawal, uncooperativeness and active social avoidance items). The results from the larger sample are presented here and cited as Pedersen et al. (2011). The OT compared to the placebo treatment group had a significantly greater decline in total PANSS scores from baseline to 2 weeks (Fig. 1) as well as a trend toward a significant decline in PANSS general subscale scores ($p=.09$). PANSS total scores (Fig. 1) as well as PANSS positive (Fig. 2), negative

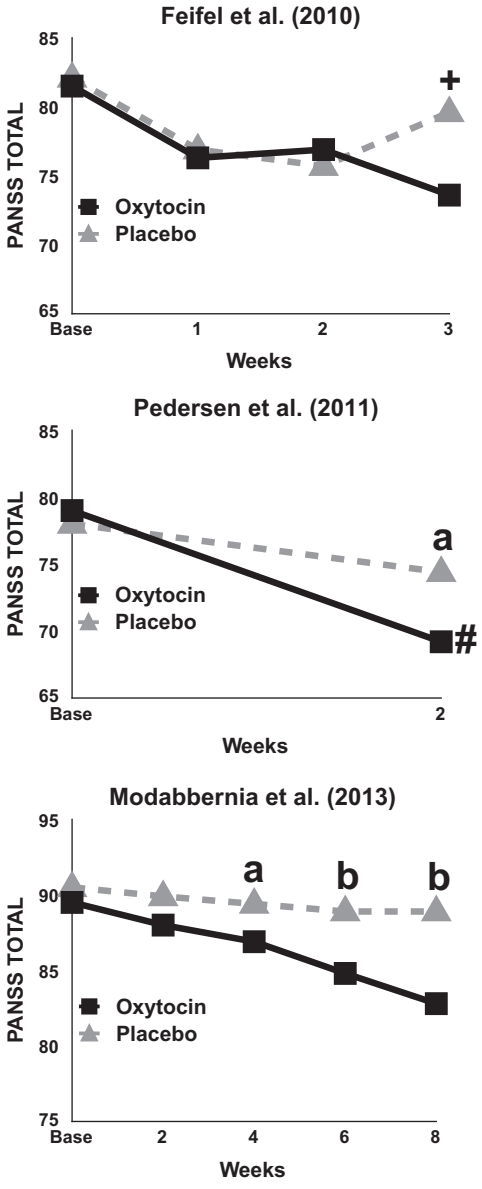

Fig. 1 – Mean PANSS total scores at baseline and at each assessment time point for the intranasal oxytocin and placebo treatment groups in three randomized clinical trials in patients with schizophrenia. a Denotes $p<.05$, b denotes $p<.001$ between treatment groups change from baseline,+ denotes $p<.001$ between treatment groups at 3 weeks, and # denotes $p=.0009$ within treatment group change from baseline.

(Fig. 3) and general psychopathology (Fig. 4) subscale scores fell significantly within the OT treatment group but not within the placebo group. Similarly, significant reductions in PANSS anxiety item scores and Paranoia Scale scores occurred solely in OT recipients ($p<.05$ for both measures). However, PANSS suspiciousness item scores declined significantly in both treatment groups. Also restricted to OT recipients were significant declines in PANSS social items mean scores (Fig. 6).

The Brüne Theory of Mind Picture Stories Task (Brüne, 2003) includes six 4-panel cartoons depicting interpersonal

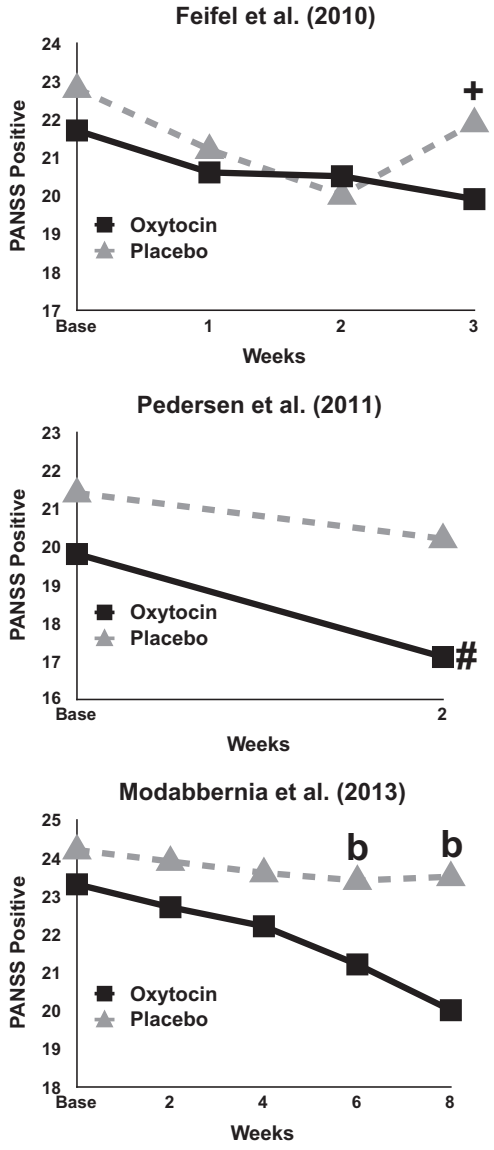

Fig. 2 – Mean PANSS positive subscores at baseline and at each assessment time point for the intranasal oxytocin and placebo treatment groups in three randomized clinical trials in patients with schizophrenia. b Denotes $p<.001$ between treatment groups change from baseline;+ denotes $p=.006$ between treatment groups at 3 weeks, and # denotes $p=.003$ within treatment group change from baseline.

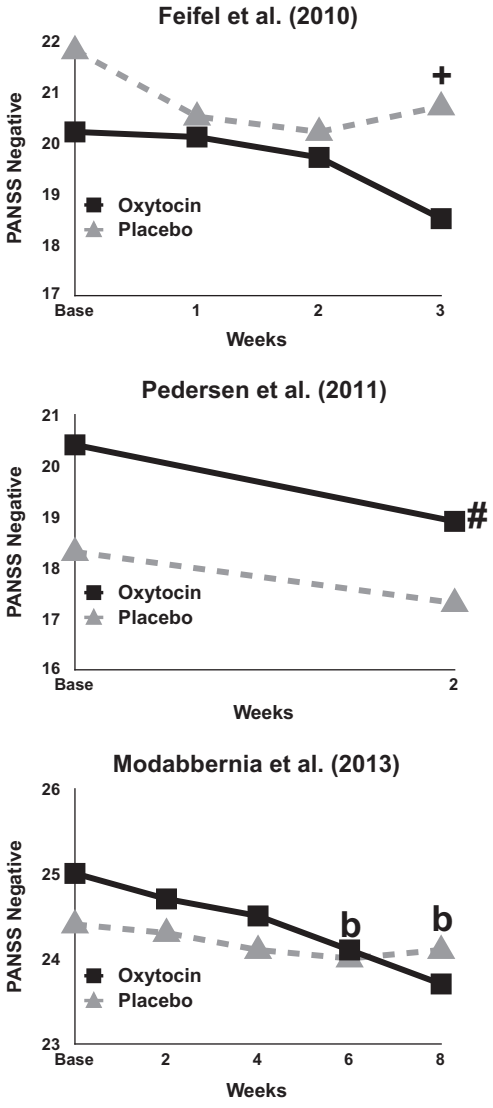

Fig. 3 – Mean PANSS negative subscores at baseline and at each assessment time point for the intranasal oxytocin and placebo treatment groups in three randomized clinical trials in patients with schizophrenia. b Denotes $p<.001$ between treatment groups change from baseline; + denotes $p=.023$ between treatment groups at 3 weeks; and # denotes $p=.025$ within treatment group change from baseline.

interactions that are sometimes deceptive and often produce false beliefs in specific characters. Questions are asked to determine subjects' understanding of the beliefs of cartoon characters and their intentions. As illustrated in Fig. 6, subjects in the OT group, but not subjects in the placebo group, improved significantly in accurately identifying second order false belief (*i.e.*, cartoon characters understood that other characters had false beliefs) and in accurately identifying third order false belief (*i.e.*, index cartoon characters understood that other characters erroneously believed the index characters had false beliefs). OT recipients also exhibited a trend toward significant improvement in accurately detecting deception in the Brüne Task (Fig. 6). The Trustworthiness Task (Adolphs et al., 1998) involves rating each face depicted in a series of pictures for trustworthiness on a scale ranging from −3 to +3. In the study conducted by the Pedersen group, Trustworthiness Task scores were based on ratings of untrustworthy faces (below the mean in a normal sample). The OT treatment group had a decline in untrustworthiness ratings that trended toward significance while untrustworthiness ratings changed very little in the placebo group (Fig. 6).

Modabbernia et al. (2013) conducted an 8-week clinical trial in which 40 subjects (33 male and 7 female) with paranoid, residual or undifferentiated schizophrenia, all of whom were on stable doses of risperdone, were randomized to OT (N=20) or placebo (N=20); 37 subjects completed the entire protocol. OT recipients received 20 IU BID during the first week and 40 IU BID for the remaining 7 weeks. PANSS

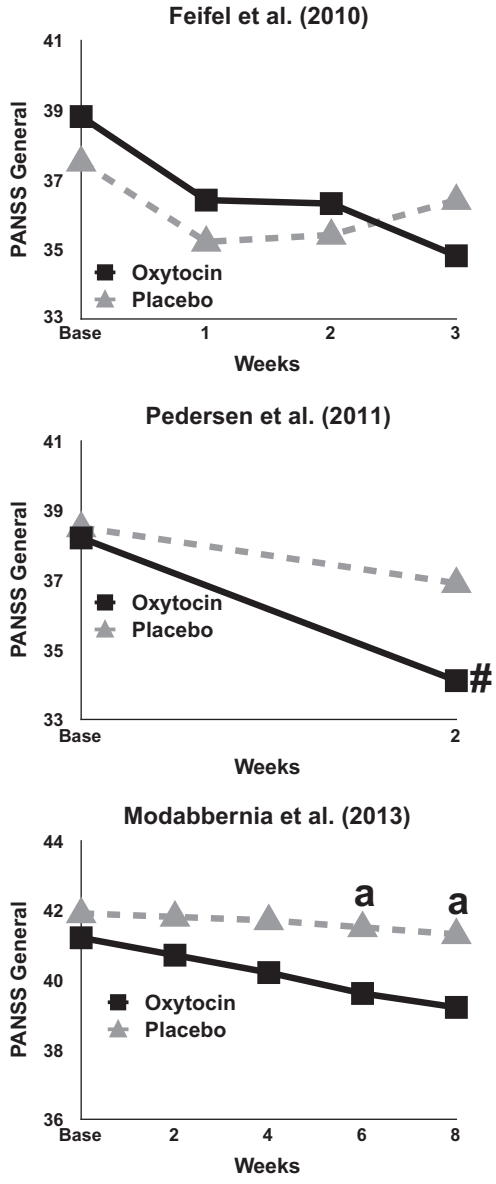

Fig. 4 – Mean PANSS general subscores at baseline and at each assessment time point for the intranasal oxytocin and placebo treatment groups in three randomized clinical trials in patients with schizophrenia. a Denotes $p<.05$ between treatment groups change from baseline; and # denotes $p=.011$ within treatment group change from baseline.

scores were obtained at baseline and every 2 weeks during the treatment period. As in the Feifel et al. (2010) and Pedersen et al. (2011) studies, PANSS total and subscale scores did not differ between treatment groups at baseline. The OT compared to the placebo group had significantly greater declines from baseline in (1) PANSS total scores at 4, 6 and 8 weeks of treatment (Fig. 1); and (2) PANSS positive (Fig. 2), negative (Fig. 3) and general subscale (Fig. 4) scores at 6 and 8 weeks.

The results of these 3 trials support the conclusion that intranasal administration of OT decreases psychotic symptoms in schizophrenia. However, this conclusion must be considered preliminary because of the small size of the studies. Baseline PANSS scores were similar in the Feifel et al. (2010) and the Pedersen et al. (2011) trials but somewhat higher in the Modabbernia et al. (2013) trial. Perhaps the most notable discrepancy among these trials is that OT treatment produced the greatest decline from baseline in total PANSS scores (9.8, 12.4%) in the Pedersen et al. (2011) study that administered the lowest dose of OT (24 IU BID) for the shortest period (2 weeks). Oxytocin treatment for 3 weeks and at a higher dose for the last 2 weeks (40 IU BID) resulted in a smaller reduction in total PANSS scores (7.9, 9.7%) in the Feifel et al. (2010) study, while OT treatment for 8 weeks and at a higher dose for the last 7 weeks (40 IU BID) produced a yet smaller decline in total PANSS scores (6.7, 7.5% [this percentage is based on data in the report but is lower than the 11.2% claimed by the authors]) in the Modabbernia et al. (2013) study. In contrast to the Pedersen et al. (2011) trial, 2 weeks of OT treatment did not significantly decrease PANSS scores in either the Feifel et al. (2010) or Modabbernia et al. (2013) studies. While OT produced significant declines in PANSS scores in all 3 trials, the discrepancies in the magnitude and latencies of the effects on psychotic symptoms underscore the importance of directly comparing a range of doses in future studies. The improvements obtained by Pedersen et al. (2011) and Feifel et al. (2012), respectively, in some social cognition and neurocognition measures are very exciting because deficits in these areas contribute to a high rate of disabling social dysfunction in schizophrenia and are not improved by currently available antipsychotic medications. Longer treatment trials will be necessary to determine if OT treatment produces further improvements in social cognition and neurocognition and perhaps reduces social dysfunction. See MacDonald and Feifel (2012) for an in-depth discussion of other important issues about the therapeutic use of OT in schizophrenia.

3.4. *Other recent oxytocin studies in schizophrenia*

There have been additional publications since the first clinical trial report by Feifel et al. (2010) that for the most part further support a significance role for OT in the pathophysiology and pharmacotherapy of schizophrenia. In a comparison of intranasal administration of two doses of OT (10 or 20 IU) or placebo among 5 polydipsic schizophrenia patients, 8 non-polydipsic patients and 11 healthy controls, Goldman et al. (2011) found that the lower OT dose decreased accurate identification of face emotions in patients while the higher dose increased accurate emotion identification in polydipsic patients, an effect largely attributable to decreased bias to identify fear in non-fearful faces. Averbeck et al. (2012) reported that a single intranasal dose of OT (24 IU) compared to placebo in a cross-over design significantly improved accurate emotion recognition in patients with schizophrenia shown images of morphed and unmorphed faces showing a range of emotions (anger, disgust, fear, happiness, sadness, and surprise) although OT did not significantly increase accuracy of identifying specific emotions.

Lee et al. (2013) conducted a placebo-controlled clinical trial in 28 subjects (12 inpatient and 16 outpatient) with schizophrenia or schizoaffective disorder testing BID intranasal OT (20 IU/dose) for 3 weeks on general psychiatric symptoms including a 4-item positive symptom score on

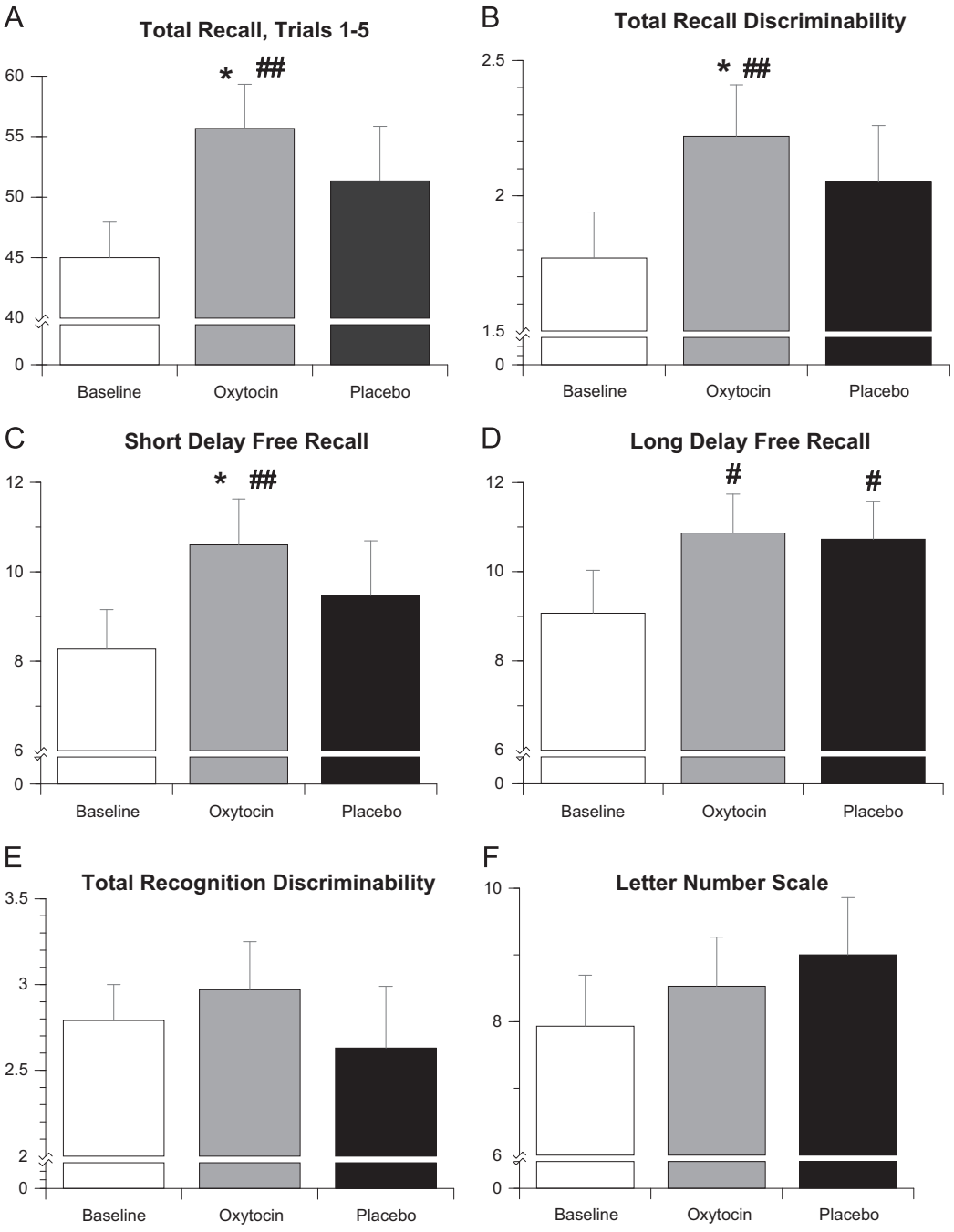

Fig. 5 – Mean (+SEM) performance on various measures on the California Verbal Learning Test (A–E) and the Letter Number Sequencing Task (F) at baseline and after 3 weeks of intranasal oxytocin or placebo treatment. Figure obtained from Feifel et al. (2012) with permission. * Denotes $p < .05$ difference from placebo; # denotes $p < .05$, and ## denotes $p \leq .001$ difference from baseline.

the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham, 1962), negative symptom ratings on the modified Scale for the Assessment of Negative Symptoms (SANS, Buchanan et al., 2007) as well as olfactory identification ability using the University of Pennsylvania Smell Identification Test (UPSIT, Doty et al., 1984). Olfactory identification ability has been reported to be particularly impaired in patients with negative symptoms and the deficit syndrome (Corcoran et al., 2005; Malaspina and Coleman, 2003; Moberg and Turetsky, 2003; Moberg et al., 2006; Strauss et al., 2010). Measurements were obtained at baseline as well as at 1 and 3 weeks during the test treatment period. Total BPRS scores decreased significantly more in the placebo than the OT group although there was no difference between treatment groups on change in positive symptoms. On the SANS, total scores and motivation-pleasure subscores were significantly better in inpatients after 3 weeks of treatment with OT compared to placebo. However, these measures did not differ between treatment groups at 3 weeks in the combined inpatient and outpatient sample. Among all subjects, total UPSIT scores and pleasant

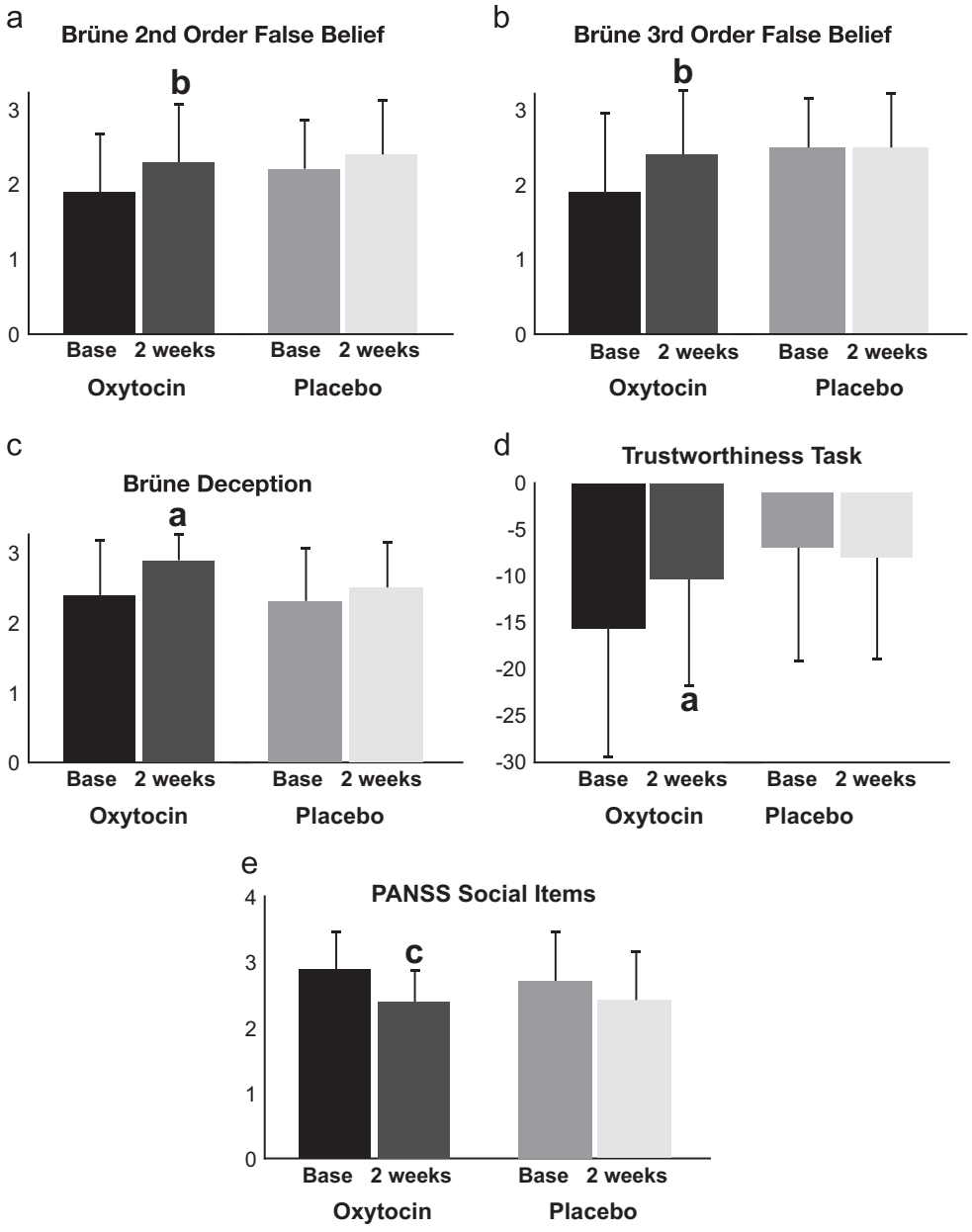

Fig. 6 – Mean (+SD) performance on various measures on the Brüne Theory of Mind Picture Stories Task (A–C) and on the Trustworthiness Task (D) as well as the mean (+SD) PANSS social item scores (E) at baseline and after 2 weeks of intranasal oxytocin or placebo treatment. a Denotes $p<.08$, b denotes $p<.05$, and c denotes $p<.001$ difference from baseline.

smell subscores improved significantly in the OT compared to the placebo group; there were no treatment group differences on neutral or unpleasant smell subscores.

Higher plasma OT concentrations were related to perceiving images of faces as happier in women with schizophrenia and healthy controls but not in male patients or controls (Rubin et al., 2011). Sasayama et al. (2012) found that CSF concentrations of OT in male schizophrenia patients correlated negatively with doses of atypical but not typical antipsychotic medications and also correlated negatively with PANSS negative subscale scores even after controlling for atypical antipsychotic doses. In a case-control design, comparison of 406 patients with schizophrenia and 406 healthy controls matched for age and gender, 2 single nucleotide polymorphisms (SNPs) of the OT receptor gene, rs53576 and rs237885, were found to be significantly associated with a diagnosis of schizophrenia and, respectively, with PANSS general and negative subscores in the patients (Montag et al., 2013). The same group also found that another SNP of the OT receptor gene, rs2254298, was associated with "empathic concern" but not with other dimensions of empathy measured on the Interpersonal Reactivity Index (Davis, 1983) in matched cohorts of schizophrenia patients and controls and, in the patients, was related to PANSS general psychopathology subscale scores (Montag et al., 2012).

3.5. *Questions to guide future research on oxytocin mechanisms in schizophrenia*

MacDonald and Feifel (2012) have summarized important areas for future research concerning OT pharmacotherapy in schizophrenia. Below we discuss other questions that are fundamental for understanding OT involvement in schizophrenia and other psychopathology.

3.5.1. *Where are oxytocin receptors in the human brain?*

It is of great importance to identify with precision where OT receptors are expressed in the human brain, especially in areas that have been implicated in schizophrenia and other psychopathology. In reviews of OT in human behavior and psychopathology, assertions are routinely made about the locations of central OT receptors. These assertions are based solely on autoradiographic studies in rodents and, to some extent, PCR studies in sheep or on early autoradiography studies in human brain that employed a radioligand that has since been shown to have poor selectivity for the human OT receptor (Loup et al., 1989, 1991; Toloczko et al., 1997). There are no definitive, replicated studies of OT receptor locations in the human brain or mammalian species other than rodents (rat, mouse, and vole) and sheep. Among rodent and other mammalian species, central OT receptor distribution varies widely (Tribollet et al., 1992; Hammock and Young, 2006). Therefore, findings from rodents and sheep can, at best, suggest where OT receptors might be located in the human brain.

Perhaps the best available evidence of where OT receptors may be in the human brain comes from fMRI studies of the effects of intranasal OT administration on brain activation by social stimuli or social interactions. The brain sites where OT has altered activation have varied among studies possibly because of differences in test conditions (Meyer-Lindenberg et al., 2011; Zink and Meyer-Lindenberg, 2012). The amygdala is the only area where activation was affected by OT in all studies. Also, OT has had strikingly contrasting effects on brain activation in men and women performing similar face emotion processing tasks (Domes et al., 2007b, 2010). OT decreased activation in the right amygdala and a few additional sites in men but increased activation of the left amygdala as well as numerous other sites in women. Inferences about the location of OT receptors from these investigations are limited to brain areas that are activated by social stimuli. Future studies are needed that examine OT effects on brain activation by a wider range of stimuli as well as determining OT effects in the absence of stimuli.

Unfortunately, selective radioligands for the human OT receptor have not yet been developed. Therefore, autoradiographic location and quantification of OT binding have not been possible in postmortem human brains. Even though antibodies that selectively bind human OT receptors have been used for two decades to visualize receptors in human reproductive tissues, they have only recently been employed to conduct immunohistochemistry localization of OT receptors in the human brain (see below). Surprisingly, immunohistochemical visualization of central OT receptors in other species, including rodents, has yet to be consistently achieved because reliable, selective OT receptor-directed antisera have not been developed (Yoshida et al., 2009). This has been a major obstacle to identifying OT-activated neural circuits involved in animal social behavior and will similarly impede investigation of OT mechanisms in preclinical animal models of psychosis, addiction and other psychopathologies. These methodological barriers to elucidate OT receptor localization and neural circuits that mediate OT effects in the CNS are discussed in detail by Pedersen (2013). Furthermore, attempts to develop PET ligands to locate OT receptors in the brains of living human subjects have had disappointing results (Smith et al., 2012).

In a promising new development, Boccia et al. (2013) have conducted the first study clearly demonstrating and locating OT receptors in the human brain with immunohistochemistry employing a monoclonal antibody developed by Takemura et al. (1994) that selectively binds OT receptor in human reproductive tissue. At autopsy, blocks of fixed brain tissue containing areas of interest were dissected from two deceased human females (44 and 28 years old). OT receptor immunostaining was visualized in discrete cell bodies and/or fibers in the central and basolateral regions of the amygdala (see front cover of this issue), medial preoptic area, anterior and ventromedial hypothalamus, olfactory nucleus, vertical limb of the diagonal band, ventrolateral septum, anterior cingulate cortex and hypoglossal and solitary nuclei. OT receptor staining was not observed in the hippocampus (including the CA2 and CA3), parietal cortex, raphe nucleus, nucleus ambiguus or pons. Unfortunately, tissue blocks that included regions that exhibit volumetric or connectivity abnormalities in schizophrenia, such as the prefrontal and superior temporal cortices as well as basal ganglia (Meyer-Lindenberg, 2010; Fitzsimmons et al., 2013), were not collected for this study. The Boccia et al. (2013) results suggest that there are some similarities, but also important differences, in the locations of OT receptors in human and rodent brains.

3.5.2. *Does oxytocin regulate brain development?*

Several lines of evidence suggest that OT is involved in brain development from early in ontogeny. The initial hints that this may be so were autoradiographic studies showing quite different OT binding patterns in the brains of neonatal compared to adult rat brains (Shapiro and Insel, 1989; Tribollet et al., 1989). Binding emerged early in the postnatal period in brain sites in which abnormalities have been found in schizophrenia. These include the cingulate cortex, caudate putamen, dorsal hippocampus and thalamus. Binding in these sites reached peak density at approximately age 14 days and then diminished and was no longer discernible by the end of the third postnatal week except for the persistence of weaker binding in the caudate putamen. The adult pattern of OT binding did not emerge until puberty. OT receptor mRNA has been found in the rat telencephalon as early as fetal day 12 although it is unclear if the receptor is expressed that early (Chen et al., 2000). Analogous with the results of autoradiography studies in postnatal rat brains, we have preliminary, unpublished evidence that OT receptor immunostaining in second trimester human fetal brain is located in sites, such as the hippocampus, where immunostaining was not found by Boccia et al. (2013) in the adult human brain.

These findings suggest that OT may play a role in early brain development including brain areas that have been implicated in schizophrenia. While there is considerable indirect evidence (see below), experiments to directly test this important hypothesis and to determine the specific neurodevelopmental processes that may be regulated by OT have not yet been conducted in rodents or other species. Research in this area could provide important new insights into mechanisms of great significance to the pathophysiology of schizophrenia.

A developmental role for OT in the fetal brain is supported by the marked social behavior abnormalities exhibited by mice with a null mutation of the OT gene (OT−/−, gestated in OT−/− mothers) or mice with a null mutation of the OT receptor gene, in which OT activity was absent from conception, compared to wild type (WT) mice or OT(−/−) mice gestated in OT (+/−) mothers that were exposed to OT *in utero* (Takayanagi et al., 2005). Further comparison with WT mice has identified a number of deficits in male OT receptor knockout (OTRKO) mice in reciprocal social interactions and in social communication in adulthood (Pobbe et al., 2012a, 2012b). In agreement with the initial report by Takayanagi et al. (2005), Dhakar et al. (2012) found elevated aggressive behavior in male OTRKO mice but no aggression differences from WT mice in conditional forebrain OTRKO mice in which the gene was not excised until postweaning (ages 21–28 days). Additional evidence has pointed toward a brain developmental role of OT in the postnatal–prepubertal period. A number of studies in monogamous prairie or Mandarin voles have established that a single dose of OT or OT antagonist shortly after birth alters, in a species, sex and dose dependent manner, adult expression of various dimensions of social behavior (Bales and Carter, 2003a, 2003b; Bales et al., 2004, 2007; Jia et al., 2008a, 2008b). OT regulation of human brain development is suggested by reports of relationships of specific OT gene or OT receptor gene SNPs with autism, symptoms in schizophrenia, profound abnormalities of child social behavior as well as emotionality, social behavior and stress responses (Beitchman et al., 2012; Wu et al., 2005; Jacob et al., 2007; Liu et al., 2010; Souza et al., 2010; Ebstein et al., 2012; Malik et al., 2012).

If OT regulates early brain development, deficits in OT or OT receptor expression could contribute to neurodevelopmental abnormalities that contribute to the onset of schizophrenia. A plethora of evidence has linked a wide variety of environmental insults from conception to adolescence to increased risk of developing schizophrenia (van Os et al., 2010; Brown, 2011). Brown (2011) has concluded that a large portion, if not the majority of schizophrenia cases can be accounted for by interactions between environmental and genetic factors and by other mechanisms involving the subtle interplay between environments and genes. Many of these environmental insults occur during pregnancy or early childhood (infections, toxins, nutritional deficits, *etc.*). Of great importance will be determining whether epigenetic mechanisms, such as methylation, impair OT or OT receptor gene expression in schizophrenia and if the degree of impairment is related to exposure to environmental risk factors. A high degree of methylation of the OT receptor gene has been reported in autism (Gregory et al., 2009).

3.5.3. *Does oxytocin ameliorate brain connectivity and plasticity deficits in schizophrenia?*

Many imaging studies have found impaired connectivity between numerous brain areas in schizophrenia, especially between prefrontal and limbic regions (Fitzsimmons et al., 2013; Schmitt et al., 2011). Considerable evidence suggests that neural plasticity, the ability of synapses to change their activity in response to altered afferent input, is also impaired in schizophrenia (Daskalakis et al., 2008; Goto et al., 2010; Hasan et al., 2011; Stephan et al., 2006, 2009). Cavus et al. (2012) recently reported that a 2-min period of high frequency visual stimulation increased subsequent visual evoked potentials (VEPs) in healthy control subjects but failed to increase VEPs in patients with schizophrenia.

Several fMRI studies have found that intranasal OT treatment has effects on connectivity between some brain areas implicated in schizophrenia that vary with the test situation (Bethlehem et al., 2013; Rilling et al., 2012; Sripada et al., 2013; Riem et al., 2012; Wittfoth-Schardt et al., 2012). Animal studies have demonstrated that OT alters neural plasticity in brain areas that exhibit abnormalities in schizophrenia such as the prefrontal cortex (PFC) and hippocampus. Specifically, OT perfusion of mouse brain slices for 1 hour converted long-lasting depression into long-lasting potentiation of glutamatergic neurotransmission in the infralimbic, medial PFC which is thought to play an important role in regulating social cognition (Ninan, 2011). Also, OT perfusion of hippocampal slices enabled long-lasting, long-term potentiation by one-train, rather than multiple-train, tetanus stimulation (Tomizawa et al., 2003). fMRI could be used to determine if intranasal OT administration during a clinical trial "normalizes" connectivity in the brains of schizophrenia subjects and if changes in connectivity are related to symptom improvement. The elegant method of Cavus et al. (2012) could be employed to determine if intranasal OT treatment improves neural plasticity in patients.

3.5.4. *Is OT regulation of stress relevant to the onset of schizophrenia?*

Abundant evidence indicates that stress contributes to the onset of psychosis in adolescents and young adults at high genetic risk for developing schizophrenia (Walker and Diforio, 1997; Walker et al., 2008; McEwen, 2000; Broome et al., 2005; van Os et al., 2005, 2010; Thompson et al., 2007a, 2013b; Arnsten, 2009; Brown, 2011). Stress responses increase during the normal postpubertal period. In agreement with findings in animals (Goldman et al., 1973; Vazquez and Akil, 1993; McCormick and Mathews, 2010), adolescents exhibit exaggerated stress responses compared to adults including (1) increased activity of the hypothalamic-pituitary-adrenal (HPA) axis around puberty (Walker et al., 2004), with a marked rise in salivary and urinary cortisol around 13 years of age that continues throughout adolescence (Kenny et al., 1966), and (2) greater social stress increases in heart rate and cortisol release (Buske-Kirschbaum et al., 1997). Increased stress-reactivity in adolescence has been attributed to immaturity of fronto-limbic circuits. Changes from shorter to longer-range connections that increase connectivity between limbic and prefrontal regions and enable greater efficiency in top-down regulation of limbic activity occur during this

developmental period (Fair et al., 2007; Kelly et al., 2008). Higher-order prefrontal areas involved in emotion and stress regulation mature relatively late during adolescence, contributing to emotion dysregulation and increased sensitivity to stress and emotion during this period (Galvan et al., 2006; Ganzel et al., 2007; Casey et al., 2010).

Dysregulated stress activation of the HPA has also been reported during the initial transition to psychosis and in asymptomatic individuals at high genetic risk for the disorder (Walker and Diforio, 1997; van Os et al., 2005; Thompson et al., 2007a, 2007b; Walker et al., 2008). During adolescence, glucocorticoids exert programming effects on neurocircuitry involved in higher cognitive functions. Sustained high levels of glucocorticoids may result in enduring changes in adult cognitive function (McCormick and Mathews, 2010). Consequences of frequent or sustained activation of the HPA axis also include damage to regions rich in glucocorticoid receptors, such as the hippocampus (Hoschl and Hajek, 2001; McEwen, 2002); damage to prefrontal cortex and its function (Arnsten, 2009); and poor hippocampal-frontal connectivity.

In addition to increasing glucocorticoid levels, acute stress exposure increases dopamine synthesis and release in the brain (Moghaddam, 2002; Czyrak et al., 2003; Dallman et al., 2004), especially in the mesolimbic system (Finlay and Zigmond, 1997; Marinelli et al., 2006). Hippocampal and prefrontal cortex pathophysiology leads to increased stress-induced dopamine release, which is associated with psychotic symptoms and increased salience of, and greater reaction to, emotional stimuli (Broome et al., 2005; Grace, 2004). Exposure to psychosocial stress can compromise fronto-limbic circuits through excessive dopamine activity, leading to relatively increased limbic activity with concomitant disruptions in prefrontal activity. Impairment in stress-regulation neural pathways may synergize with increased sensitization to dopamine during adolescence (Jezierski et al., 2007) to further adversely impact cognition and neural circuitry in high risk individuals.

Animal studies have shown that OT decreases all components of the stress response: HPA axis, sympathetic nervous system and immune activation as well as anxiety (McCarthy et al., 1996; Windle et al., 1997; Neumann et al., 2000; Bale et al., 2001; Mantella et al., 2003, 2004; Amico et al., 2004; Szczepanska-Sadowska, 2008; Wsol et al., 2008; Grippo et al., 2009; Cohen et al., 2010; Jankowski et al., 2010). Furthermore, OT has a calming effect by increasing parasympathetic activity (Michelini, 2007; Higa-Taniguchi et al., 2009). In human studies, acute intranasal OT administration decreased anticipatory stress-induced anxiety (de Oliveira et al., 2012) and had synergistic effects with social support in reducing stress-induced anxiety (Heinrichs et al., 2003). In fMRI studies, intranasal OT reduced amygdala activation by various stressful stimuli in men but had contrasting effects on amygdala activation by different stressful stimuli in women (Zink and Meyer-Lindenberg, 2012). Intranasal OT treatment also decreases cortisol release during and following psychosocial stressors (Heinrichs et al., 2003) and increases heart rate variability, an index of parasympathetic activity (Norman et al., 2011; Kemp et al., 2012). OT receptors are expressed in cultured human monocytes and macrophages and OT suppresses release of proinflammatory cytokines from those cells (Szeto et al., 2008). IV infusion of OT potently blocks endotoxin-induced release of a wide range of pro-inflammatory cytokines and other immune-activating factors (Clodi et al., 2008).

Also relevant are animal studies finding that OT regulates mesolimbic dopamine activity through effects in the ventral tegmental area and the nucleus accumbens (Succu et al., 2007; Melis et al., 2007; Shahrokh et al., 2010; Liu and Wang, 2003). In agreement with these findings, a recent fMRI study found that intranasal OT administration increased VTA activity in response to socially relevant visual cues (Groppe et al., 2013).

These considerations suggest that our understanding of the significance of stress for the onset of psychosis may be advanced by comparing endocrine, autonomic and brain activation responses to stress during adolescence between individuals at high and low risk of developing schizophrenia. Furthermore, investigating the effects of intranasal OT on stress responses from early to late adolescence may shed light on OT involvement in the development of stress responses during this critical period and determine whether OT "normalizes" aberrant stress responses that may be found in high risk individuals. The latter findings would suggest that OT treatment of high risk individuals during adolescence/early adulthood, especially those exhibiting prodromal subsyndromal psychotic symptoms, may protect them from conversion to psychosis.

4. The rationale for oxytocin treatment of alcohol withdrawal

Numerous studies in rodents found that OT treatment prior to each successive dose of alcohol, opioids or cocaine inhibited tolerance formation, *i.e.*, the typical decline in efficacy of the addictive substance following repeated administration of the same dose (Kovács et al., 1998). Specifically, peripheral or central administration of OT in mice blocked the development of tolerance to the hypothermic, myorelaxant, akinetic and hypnotic effects of alcohol (Rigter et al., 1980; Pucilowski et al., 1985; Szabó et al., 1985, 1989; Jodogne et al., 1991). OTKO compared to WT mice exhibited significantly more rapid tolerance formation to effects of repeated doses of alcohol (Vadlamudi et al., 2004). Withdrawal symptoms precipitated by picrotoxin treatment of alcohol-dependent mice or naloxone treatment of morphine-dependent mice were markedly reduced by OT treatment (Szabó et al., 1987).

4.1. *Oxytocin blockade of withdrawal in alcohol dependent patients*

To test whether OT inhibits alcohol withdrawal in humans, Pedersen et al. (2013) conducted a pilot randomized, double-blind 3-day trial of BID intranasal OT *vs.* placebo in 11 alcohol-dependent inpatient subjects undergoing detoxification with symptom-driven PRN (as needed) lorazepam. Individuals were recruited by advertising and evaluated at an outpatient visit where informed consent, medical, psychiatric and drinking history were obtained and blood and urine collected for laboratory tests. Subjects were recruited who

had been drinking heavily (8–30 standard drinks/day) for at least 2 weeks prior to recruitment, had previously experienced 2 or more days of debilitating withdrawal symptoms, but not delirium tremens or seizures, after a heavy drinking period, and had no unstable medical or psychiatric disorders based on interview and laboratory tests. They were admitted to an inpatient research unit. After obtaining baseline alcohol withdrawal symptom ratings using a modified (vital signs were included in the score) Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA, Sullivan et al., 1989), subjects received their first intranasal dose of the substance to which they had been randomized; OT (24 IU/dose) or placebo. They received intranasal test doses BID for 3 days. CIWA scores were obtained every 4 h throughout the trial except when subjects slept at night or whenever subjects reported or research nurses observed an increase in withdrawal symptoms. Lorazepam (2 mg) was given orally whenever CIWA scores were ≥ 12. Another CIWA score was obtained 1 h after each lorazepam dose. Lorazepam doses were repeated if CIWA scores remained ≥ 10. Subjects rated themselves on the Penn Alcohol Craving Scale (PACS, Flannery et al., 1999) and the Profile of Mood States (POMS, McNair et al., 1971) midday on admission days 2 and 3.

The mean number of standard drinks per day prior to enrollment did not differ between the OT ($N=7$) and placebo ($N=4$) groups (17.7 ± 6.0 [SD] *vs.*14.5 ± 1.7). The placebo group compared to the OT group required 5 times more total lorazepam to complete detoxification (Fig. 7). Mean CIWA scores were almost 3 times higher in the placebo compared to the OT group on admission days 1 and 2 (Fig. 8) but not on admission day 3. POMS Tension/Anxiety subscores were significantly lower on admission day 2 in the OT compared to the placebo group (10.3 ± 6.0 *vs.* 23.8 ± 6.7, $p=.007$) but did not differ significantly on admission day 3. PACS scores did not differ between treatment groups on admission day 2 or 3. Placebo recipients, all of whom had been drinking ≤ 16 mean drinks/day ($N=4$), required an average total of 16.5 ± 4.4 mg of lorazepam to complete detoxification. Oxytocin recipients who consumed ≤ 16 mean drinks/day ($N=4$), required no lorazepam ($p=.005$). CIWA scores were significantly lower on all 3 admission days in this OT subgroup. Oxytocin treatment was not associated with side effects or clinically significant changes in laboratory values. This is the first evidence that OT may potently block alcohol withdrawal in humans.

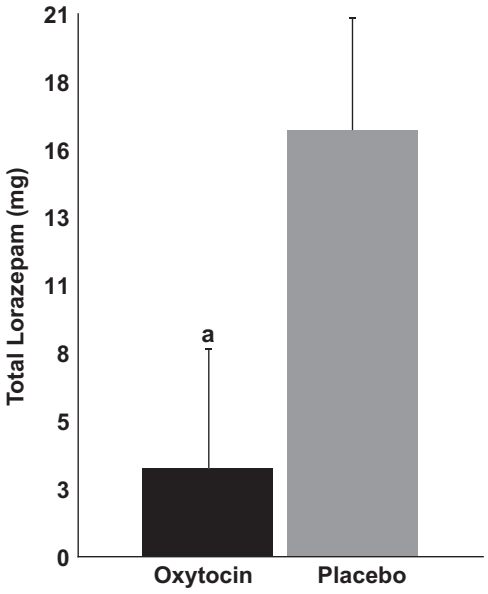

Fig. 7 – Mean (+SD) total lorazepam (mg) required to complete medical detoxification from alcohol during 3 days of intranasal oxytocin or placebo treatment. a Denotes $p=.0015$ compared to placebo.

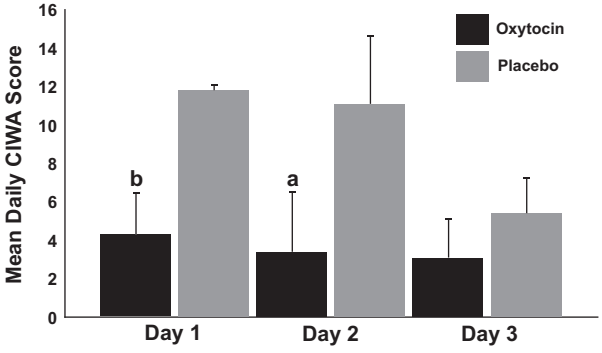

Fig. 8 – Mean (+SD) daily CIWA scores on inpatient admission days 1–3 in subjects receiving intranasal oxytocin or placebo. a Denotes $p=.0015$ and b denotes $p<.0001$ compared to placebo.

4.2. *Questions to guide future research on oxytocin mechanisms in alcohol and other dependence disorders*

4.2.1. *Will oxytocin treatment decrease drinking and craving in alcohol-dependent subjects?*

The Center for Disease Control places alcohol as the 3rd cause of preventable deaths following nicotine use and overweight (Centers for Disease Control and Prevention, 2009). The economic costs of alcohol misuse for 2006 are estimated at $223 billion/year (Bouchery et al., 2011). Epidemiological studies show that the 12-month prevalence rate for DSM-IV alcohol dependence in USA is 5–6% for men and 2–3% for women (Grant et al., 2004). Despite these grim statistics, treatment options are limited. Currently, treatment to decrease drinking in alcohol dependent individuals primarily consists of psychosocial interventions including 12-step programs and motivational interviewing though perhaps less than 25% of patients with alcohol dependence receive treatment (Hasin and Grant, 2004). Relatively recently, the FDA approved two drugs that have exhibited some efficacy in increasing partial or complete abstinence (Kranzler and Van Kirk, 2001): naltrexone, a μ-opioid receptor antagonist, and acamprosate, thought to modulate N-methyl-D-aspartate receptors. However, the use of these medications for alcohol dependence has been limited (Mark et al., 2009) because both have small to medium effect sizes (Kranzler and Van Kirk, 2001). Furthermore, it is suggested (FDA label) that patients be abstinent from drinking prior to starting naltrexone or acamprosate which adds another potential barrier in the clinical setting.

For several reasons, OT has a potentially attractive profile for the treatment of alcohol-dependent individuals. First, numerous animal and human studies consistently show that

OT is anxiolytic and reduces fear (McCarthy et al., 1996; Windle et al., 1997; Bale et al., 2001; Mantella et al., 2003; Heinrichs et al., 2003; Amico et al., 2004; Ring et al., 2006; Labuschagne et al., 2010; de Oliveira et al., 2012) including in the context of alcohol detoxification (see above) and in an animal model of relapse (see below). Anxiety is hypothesized to impede recovery and contribute to relapse (Kushner et al., 2000). In clinical and laboratory studies, alcohol has been shown to have both an acute anxiolytic effect and a delayed anxiogenic effect. This led Kushner et al. (2000) to propose a feed-forward cycle where the initial anxiolytic effect of alcohol is followed by an anxiogenic effect which then promotes the use of alcohol because of its anxiolytic effect. As shown in the clinical trial described above (Pedersen et al., 2013), OT potently reduces other withdrawal symptoms as well. Dependent individuals are often unable to refrain from drinking because withdrawal symptoms become unbearable. In the withdrawal treatment trial, intranasal OT was administered safely to subjects who had been drinking heavily until admission to the research unit. This indicates that a period of abstinence from alcohol may not be necessary prior to initiating OT treatment. Craving for alcohol, like withdrawal, may be related to tolerance formation. If OT blocks withdrawal by reversing neuroadaptation underlying tolerance, it may decrease craving by a similar mechanism. OT treatment also blocked increased alcohol intake in P (alcohol-preferring) rats subjected to repeated alcohol deprivation combined with restraint stress, an animal model of craving and relapse (Breese et al., 2004; Overstreet et al., 2007; Knapp et al., 2010). These considerations support the hypothesis that intranasal OT may decrease drinking and craving in alcohol-dependent individuals.

4.2.2. *Does oxytocin inhibit tolerance formation and reverse established tolerance in human subjects?*

The repeated demonstration in animals that OT inhibits formation of tolerance to alcohol suggests that OT may block alcohol withdrawal by reversing tolerance. This hypothesis should be tested by comparing the effects of intranasal OT administration on responses to repeated ingestion of a standard dose of alcohol in normal volunteers and alcohol-dependent subjects. The hypothesis would be supported if OT compared to placebo inhibits decline in the magnitude of ethanol effects in normals and increases sensitivity to ethanol effects in dependent individuals. Demonstrating that OT blocks tolerance formation in humans would reinvigorate investigation of the underlying mechanisms as well as the relationship of CNS OT to other neurochemical systems that have been implicated in alcohol dependence (Wee and Koob, 2010; Pava and Woodward, 2012; Roberto et al., 2012; Lovinger and Roberto, 2013).

This line of research may also have important clinical implications. OT could have advantages over benzodiazepines, the currently recommended treatment for alcohol withdrawal symptoms. While benzodiazepines are very effective and relatively safe (Mayo-Smith, 1997; Daeppen et al., 2002), they are, like alcohol, sedative-hypnotics and are known to have addictive properties and to enhance the depressant effects of alcohol. Furthermore, benzodiazepine treatment may maintain elevated sedative-hypnotic tolerance which could contribute to factors that increase vulnerability to relapse: persistent craving for alcohol; high anxiety; decreased ability to cope with stress; and consumption of large quantities of alcohol upon relapse. If OT treatment diminishes sedative-hypnotic tolerance, patients may be less likely to relapse after medical detoxification. This prospect is supported by the findings of Myrick et al. (2009) that treatment of alcohol withdrawal with gabapentin, a non-sedative-hypnotic drug, was as effective as lorazepam but resulted in less alcohol consumption after completion of detoxification. There are potential drawbacks to OT treatment of alcohol dependence. Rapid reduction of tolerance by OT could increase the vulnerability of heavy drinkers to toxic effects if they relapse and consume large amounts of alcohol. Also, it is unknown whether OT decreases risk of developing delirium tremens and seizures and should not be substituted for benzodiazepines, which are known to reduce these risks, in the treatment of patients with history of dangerous withdrawal.

4.2.3. *Does OT block withdrawal and decrease consumption of other addictive substances?*

Reports that OT inhibits tolerance formation to opioids and cocaine, reduces opioid withdrawal and exerts other anti-addictive effects in animals (Sarnyai and Kovács, 1994; Kovács et al., 1998; Yang et al., 2010; McGregor and Bowen, 2012) suggest that OT may be effective in treating a wide range of substance dependence disorders (McGregor and Bowen, 2012). Clinical trials testing OT on withdrawal from and consumption of opioids and cocaine as well as other addictive substances are of great importance. Demonstrating that OT is an effective treatment for multiple substance dependence disorders would be a major advance in addiction medicine and would inspire new research to determine if CNS OT is involved in pathophysiological mechanisms common to many if not all addictions.

5. Speculation on the evolutionary origins of oxytocin efficacy in schizophrenia and alcohol withdrawal

In Article 2 (in this volume), Pedersen et al. argue that the selection of OT to activate avid and sustained maternal behavior was essential for the evolution of placental mammals. Research in rodents and sheep indicate that in the sex hormone milieu of late pregnancy and parturition OT facilitates the onset of maternal behavior by enabling activation of reward pathways by stimuli from newborns and by expression of hard-wired, species-specific nurturing behaviors (Numan and Insel, 2003; Pedersen, 2013). However, OT may have been selected to play other roles that were important for the considerably higher quality of maternal behavior that was necessary for the evolution of placental mammals. Rapid and accurate perception of sensory cues from newborns and timely expression of appropriate caretaking behaviors in response to those cues may have required an up-grade of sensory-motor gating systems that enabled mothers to effectively nurture their offspring but also endowed placental mammalian brains in general with greater ability in this area. If neural systems were selected through which OT enhances sensory-motor gating in

mammals, especially mothers, perhaps it is through those neural systems that OT reverses deficits in PPI in animal models of psychosis and contributes to OT reduction of psychotic symptoms in schizophrenia. A potential test of this hypothesis in rodents would be to compare PPI in new mothers and nulliparous females and examine the role of endogenous OT in differences that may be discovered.

The success of mammalian mothering behavior requires that maternal care be sustained over extended periods until offspring can survive independently. Similarly, monogamous relationships in species such as the prairie vole require that selective attachments are maintained over periods as long as the lifetimes of the pair-bonded couples. Perpetuation of these reproductively critical attachments may have required the evolution of neural mechanisms by which OT prevents habituation to the rewarding stimuli from offspring or pair-bonded mates. These hypothesized mechanisms may underlie the efficacy of OT in reducing tolerance formation to addictive substances, all of which activate reward pathways. However, while central administration of OT antagonists potently disrupt the onset of maternal behavior acute ICV injection of OT antagonists only weakly inhibits some components of established maternal behavior in lactating rats (Numan and Insel, 2003; Pedersen, 2013), evidence that does not support a role for central OT in preventing decline in maternal responsiveness to offspring. The effects of central OT antagonist administration on established pair bonds have yet to be tested. It may require OT antagonist treatment for longer periods to adequately test whether central OT plays a significant role in maintaining established maternal behavior or monogamous pair bonds. Alternatively, the hypothesized role of OT in blocking habituation to stimuli from significant others may have evolved in mammalian species other than rodents in which long-term maintenance of social bonds increased reproductive fitness.

In the ways discussed above, recent discoveries of clinical efficacy of OT in schizophrenia and alcohol withdrawal may provide new insights into OT mechanisms which may have been selected for during the evolution of placental mammals to facilitate maternal-infant and other social attachments.

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