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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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Cort A. Pedersen*
Department of Psychiatry, University of North Carolina at Chapel Hill, CB 7160, Chapel Hill, NC 27599-7160, USA
E-mail address: Cort_Pedersen@med.unc.edu

Steven W.C. Chang
Center for Cognitive Neuroscience, Levine Science Research Center, Duke University, Durham, NC, USA

Christina L. Williams
Department of Psychological & Brain Sciences, Duke University, Durham, NC, USA

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*Corresponding author.