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Prefrontal circuits guiding social preference: Implications in autism spectrum disorder

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ABSTRACT

Although Autism Spectrum Disorder (ASD) is increasing in diagnostic prevalence, treatment options are inadequate largely due to limited understanding of ASD's underlying neural mechanisms. Contributing to difficulties in treatment development is the vast heterogeneity of ASD, from physiological causes to clinical presentations. Recent studies suggest that distinct genetic and neurological alterations may converge onto similar underlying neural circuits. Therefore, an improved understanding of neural circuit-level dysfunction in ASD may be a more productive path to developing broader treatments that are effective across a greater spectrum of ASD. Given the social preference behavioral deficits commonly seen in ASD, dysfunction in circuits mediating social preference may contribute to the atypical development of social cognition. We discuss some of the animal models used to study ASD and examine the function and effects of dysregulation of the social preference circuits, notably the medial prefrontal cortex-amygdala and the medial prefrontal cortex-nucleus accumbens circuits, in these animal models. Using the common circuits underlying similar behavioral disruptions of social preference behaviors as an example, we highlight the importance of identifying disruption in convergent circuits to improve the translational success of animal model research for ASD treatment development.

1. Main Text

Autism Spectrum Disorder (ASD) is a set of neurodevelopmental disorders characterized by aberrant social behaviors (American Psychiatric Association, 2013). ASD is caused by a combination of familial, heritable mutations to risk-associated genes, de novo mutations, and environmental factors that result in molecular, neurological, and behavioral changes (Geschwind, 2008). The social deficits associated with ASD can present in many ways, from difficulties with nonverbal communication and social gaze to decreased social reciprocity, approach, and motivation behaviors (Lord et al., 2000; Mottron and Bzdok, 2020). This review will focus on social preference in ASD.

Social preference refers to an individual's ability to perceive, evaluate, and respond preferentially to social stimuli (Chevallier et al., 2012; Ruff and Fehr, 2014). Individuals with ASD often show decreased preference for social stimuli compared to neurotypical individuals, and research implicates particular brain regions in social decision processes, including the nucleus accumbens (NAc), prefrontal cortex (PFC), amygdala, striatum, anterior insula, anterior cingulate cortex, and temporoparietal junction (Adolphs, 2009; Bault et al., 2011; Behrens et al., 2009; Gangopadhyay et al., 2021; Kelly et al., 2020; Lee, 2008; Ruff and Fehr, 2014; Seo and Lee, 2012; Tricomi et al., 2010). These areas are parts of or connected to specialized social preference circuits and seem to be altered in ASD (Gangopadhyay et al., 2021; Lockwood et al., 2020; Seo and Lee, 2012). Investigating these circuits in neurotypical individuals and those with ASD may lead us to a better understanding of the neurobiological basis of abnormal social preference in ASD.

Non-invasive neuroimaging techniques have allowed for significant progress in our understanding of the neural correlates of social preferences in humans. One such method, functional magnetic resonance imaging (fMRI), enables researchers to measure minute changes in blood

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flow through Blood-Oxygen-Level-Dependent, or BOLD, signaling, allowing for the identification of relatively activated or deactivated brain regions during social preference tasks. Human and nonhuman primate fMRI studies have implicated specific circuits, such as the PFC-amygdala and PFC-NAc circuits, in social preference behaviors (Kelly et al., 2020; Zhou et al., 2019). Human studies are largely limited, however, to correlational relationships, as ethical considerations prevent most direct manipulations in humans. Therefore, animal models of social preference are incredibly important. Chemogenetic and optogenetic activation in animal models permit direct, in vivo manipulation of neural processes (Huang et al., 2016; Kelly et al., 2020; Selimbeyoglu et al., 2017). Furthermore, the use of neuroimaging techniques and social preference tasks similar to those used in human subjects allow for meaningful comparisons to human studies. In fact, multiple recent studies have found that many distinct causes of ASD converge onto disruptions of similar circuit level pathways. Thus, focusing at this level could be a promising way to approach treatments of ASD. In this review, we will focus on social preference behavioral deficits in ASD and their underlying neural causes to demonstrate this idea of the importance of convergent pathways and how it can help us in treatment development.

Circuit-level research on rodent and nonhuman primate social preference behaviors has largely supported the involvement of the neural circuits encompassing the PFC and the amygdala (Allsop et al., 2018; Dal Monte et al., 2020, 2022; Gangopadhyay et al., 2021; Huang et al., 2016; Kelly et al., 2020; Selimbeyoglu et al., 2017) as well as the PFC and the NAc (Amadei et al., 2017; Block et al., 2007; Krishnan et al., 2007; Montaron et al., 1996; Murugan et al., 2017). The PFC-amygdala circuit is recruited in a range of social tasks across species from observational fear conditioning and social exploration in mice to vicarious social reward allocation in macaques (Allsop et al., 2018; Dal Monte et al., 2020; Selimbeyoglu et al., 2017), and the PFC-NAc circuit has been implicated in affiliative behavior and social avoidance in rodents (Amadei et al., 2017; Krishnan et al., 2007). Understanding how these specific prefrontal-subcortical circuits contribute to social preference behaviors could greatly assist applied clinical research on ASD. Circuit alterations could inform what interventions may be more effective in treatment development, while changes in or restoration of circuit activity levels could serve as a neurological marker for treatment efficacy in clinical trials of behavioral or molecular treatments. This is of note because the heterogeneity of the numerous genetic, molecular, and cellular causes of ASD lead to tremendous uncertainty for many of the individuals seeking treatment. Importantly, recent studies suggest that multiple genetic and neurological alterations may converge on similar targetable circuits, such as the ones covered in this review, further supporting the utility of ASD-relevant research at the circuit level (Kelly et al., 2020). Focusing on convergent circuit-level approaches could therefore lead to more broadly applicable treatments by possibly overcoming the molecular and genetic diversity in ASD through targeting a common circuit-level mechanism downstream of multiple genetic and molecular level alterations.

In this review, we will explore selected neural circuit research on social preference in the context of ASD. We will first describe the social preference paradigms typically used in humans and in common model organisms. We will then describe the neurobiological research that has been conducted regarding social preference in neurotypical and ASD animal models, focusing on two specific circuits: the medial prefrontal cortex (mPFC)-amygdala and the mPFC-NAc circuits. In doing so, we will compare and contrast social preference deficits across these common animal models and humans to better understand how circuit-level investigations in animals can inform research on pathophysiology and aid ASD treatment development and clinical interventions in humans.

2. Social preference behaviors

Social preference, which can be defined as an individual's tendency to preferentially engage with social stimuli or make a social choice in specific contexts, is necessary for survival in social species. Behaviors guided by social preference play a crucial role in complex social interactions and strategies leading to meaningful social relationships. Motivation to engage with social stimuli, for instance through processes of joint attention and communication, is foundational to forming relationships and engaging in meaningful collaboration (Chevallier et al., 2012; Dawson et al., 2007; Gale et al., 2019). Furthermore, without intact social motivation, individuals may show decreased social engagement or even social avoidance as compared to their typically developing peers. This deficit may contribute to development-related miswiring of circuits involved in social cognition, ultimately resulting in significant social deficits as seen in neurodevelopmental disorders such as ASD. In the following sections, we will focus on social preference behavior in humans and in the most common model organisms used in social preference research: rodents and nonhuman primates.

2.1. Social preference behaviors in humans

Humans begin to show social preference just days after birth, as demonstrated by newborns' preference for stimuli that mimic biological motion compared to scrambled and non-biological motion stimuli (Simion et al., 2008), preference for face stimuli over nonface stimuli (Johnson et al., 1991; Valenza et al., 1996), and preference for direct over averted eye gaze (Farroni et al., 2002). Social preference is thought to develop in a 'U-shaped' trajectory, decreasing from birth until around 2 months and subsequently improving as new neural connections are made and new abilities develop in the first years of life (Federici et al., 2020; Sifre et al., 2018). While some research has shown abnormal social behaviors within the first year of life in infants that later showed signs of ASD (Thorup et al., 2018), little research has been done on social preference in ASD prior to this 2-month-old developmental shift. This is largely because individuals are typically not diagnosed until at least 2 years old when the core diagnostic characteristics are apparent. However, several studies have found social preference deficits in at-risk infants, namely, children with older siblings diagnosed with ASD. One study found typical levels of fixation on the eyes of caregivers at 2 months old, followed by a sharp decline to around half the typical fixation levels by 24 months, with a greater eye fixation decline being associated with more severe social disability (Jones and Klin, 2013). Another study found deficits in social preference in 6–10-day old newborns at high-risk for ASD, with greater fixation on inverted face-like shapes and random motion compared to the typical fixation on upright face-like shapes and biological motion (Di Giorgio et al., 2016).

Neural studies of social preference behavior take many forms, as humans perceive and preferentially attend to social stimuli in a wide range of contexts and in many ways across development. Human interaction studies, while relatively uncommon due to methodological restrictions, have shown decreased joint attention and social gaze in children with ASD (Thorup et al., 2018). The most common human social preference tasks employ eye tracking during preference selection to investigate visual attention to images depicting social stimuli such as facial expressions, social scenes, and biological motion, as shown in Fig. 2 A (Dalton et al., 2005; Gale et al., 2019; Klin et al., 2009; Unruh et al., 2016). Image presentation studies, most of which simultaneously present individuals with a social and nonsocial stimulus, have found a reduced preference for attending to social stimuli and increased preference for nonsocial stimuli in young children with ASD (Di Giorgio et al., 2016; Gale et al., 2019; Klin et al., 2009; Ruta et al., 2017; Sifre et al., 2018; Unruh et al., 2016; Williams and Cross, 2018). These paradigms can be used with a variety of methodologies including, but not limited to, neuroimaging and lesion studies. When such a paradigm was used in fMRI investigations, researchers identified differential neural activation in the amygdala and fusiform gyrus during eye fixation in ASD individuals compared to neurotypical individuals (Dalton et al., 2005). Relatedly, studies of patients with amygdala and mPFC lesions have demonstrated that they have difficulty identifying emotions in

voice stimuli and images of facial expressions coupled with social attention deficits, highlighting the key role that these regions play in processing social information (Adolphs et al., 2002; Hornak et al., 2003; Pessoa and Adolphs, 2010). Although it is challenging to attribute impaired functions solely to damage in these specific regions without considering interconnected brain regions, evaluation of the effects of brain lesions in conjunction with neuroimaging studies can identify convergent functions of brain regions based on multiple types of investigations.

Even with the use of neuroimaging in humans, however, many questions remain unanswered. Consider the following example. In Dalton et al. (2005), amygdala BOLD activation was positively correlated with time spent fixating at eyes in individuals with ASD, but not in neurotypical individuals, suggesting systematic amygdalar hyperreactivity to faces specifically in individuals with ASD. In contrast, fusiform gyrus BOLD activity was positively correlated with time spent fixating at the eyes in both ASD and neurotypical individuals. Individuals with ASD fixated at the eyes in social images less than neurotypical individuals, and they tended to show weaker fusiform gyrus activation. This finding, due to its correlative nature, suggests that either a) decreased activation of the fusiform gyrus may lead individuals with ASD to fixate at the eyes less or b) decreased fixation at the eyes may cause decreased activation of the fusiform gyrus in individuals with ASD. This distinction may have important implications for treatment. If decreased activation of the fusiform gyrus drives reduced eye fixation, treatments targeting fusiform gyrus activation may help restore eye fixation behaviors. However, if decreased activation is a result of decreased eye fixation behaviors, for example, due to amygdalar hyperreactivity from eye fixation possibly related to amplified emotional processing, then a treatment targeting the fusiform gyrus may be ineffective. In this case, there is a possibility that a treatment targeting a different brain region, such as the amygdala, may restore both the behavior and the fusiform gyrus activity. This example case demonstrates the importance of pairing human studies with research approaches that allow for direct manipulation of circuit activation to answer questions that cannot be determined simply through observation of neural activation levels.

2.2. Animal models of social preference behaviors and ASD

Because studies with humans are mostly restricted to non-invasive research methodologies, animal models provide a useful tool for studying social preference behaviors. While social preference behaviors are present in many species, including birds, rodents, and primates (Klin et al., 2009; Rosa Salva et al., 2011), they may appear different, due to the ethological, neurological, cognitive, and sensory modality differences between species. For translational research, it is therefore important that social preference behaviors mimic those in humans as closely as possible for better translation. However, at the same time, failing to test social behaviors in contexts typical to the species may ignore the normal expression of their social preference behaviors and limit their utility as models altogether. Despite the species-specific expressions of social preference behaviors, there are analogies in the shared neural circuits that underlie these behaviors across commonly studied species, namely rodents and nonhuman primates.

Rodent models have become the standard animal model in ASD research, as both genetic manipulations, through mutant genetic strains and localized gene silencing, and neural manipulations, through optogenetic/chemogenetic activation or inhibition, are well-established (Guo et al., 2019; Ma et al., 2018; Phillips et al., 2019; Qin et al., 2018; Yoo et al., 2019a; Zhang et al., 2016). Basing animal genetic manipulations off human ASD gene associations allows for a higher likelihood that the model will result in an ASD-related phenotype, and investigations with these models have greatly improved our understanding of the neurobiological alterations underlying ASD. However, modeling ASD with monogenic rodent models does pose some challenges. Although rodents and humans share the majority of their protein-coding genes, genes that result in ASD-like social behaviors in humans and in rodents may not always correspond. Additionally, different manipulations to the same genes may also achieve distinct phenotypes. For example, in mice, one study found that a homozygous knockout of *Shank3* disrupted social behavior, as mice demonstrated decreased social approach and social novelty behavior (Peça et al., 2011), while another study found that a homozygous knockout specifically to exon9 of *Shank3* resulted in reduced dominance and cooperative behaviors but normal social approach and novelty behaviors (Han et al., 2020). Thus, it may be that knockout of the whole gene results in widespread molecular pathway dysfunction causing broad social behavior deficits, while knockouts of certain exons result in disruption of more specific neural mechanisms leading to deficits only in social behaviors that depend upon those pathways. This indicates that even within a particular gene, social ASD-phenotypes may be exon-specific and may differ from humans to nonhuman primates to rodents (Jiang and Ehlers, 2013). In contrast, there are also examples in which exon-specific deletions of genes implicated in ASD are sufficient to cause ASD-like deficits. This can be seen in rats with an exon 8-specific knockout of *Fmr1*, the gene associated with Fragile X Syndrome which is a monogenic disorder associated with ASD. These *Fmr1*-Δ*exon 8* rats show impaired social preference behaviors with decreased sniffing of and contact with unfamiliar mice in the three-chamber test (Hamilton et al., 2014; Schiavi et al., 2022). While this exon-specific *Fmr1* rat model of ASD will likely be a valuable tool in studying the neurobiology of ASD, it remains unclear how exactly this model will translate to *FMR1*-related cases of ASD in humans. Finally, given that hundreds of different genes are associated with ASD in humans, a single gene may be associated with only a small percentage of cases. Although mutations in the *FMR1* gene are one of the leading identified monogenic causes of ASD, they still only account for approximately 1–6% of cases (Schaefer et al., 2013). Similarly, mutations in *SHANK3*, which is one of the most well-studied ASD-associated genes and, as such, contributes to a large portion of animal models, only contribute to around 1% of human ASD cases (Awadalla et al., 2010; Boccuto et al., 2013; Gauthier et al., 2009; Moessner et al., 2007; Waga et al., 2011). This tremendous genetic diversity highlights the importance for animal model studies to validate that the genetic manipulations converge on similar neurological pathways to achieve behavioral changes.

In addition to genetic and circuit-manipulation models, environmental models of ASD help elucidate the genetic, molecular, and circuit alterations associated with environmentally-caused cases of ASD. Environmental models of ASD development typically fall under one of two categories: maternal immune activation or pharmaceutical agent exposure. The association between maternal immune activation and ASD has been documented in humans in the contexts of both stress and infection (Brown, 2012; Kinney et al., 2008; Newschaffer et al., 2007), and animal models typically involve maternal exposure to immune-activating synthetic RNA. Animal studies suggest that maternal immune activation can increase fetal and placental cytokine levels and inflammation, thus influencing fetal and postnatal neural development (Patterson, 2009; Meyer et al., 2009). Maternal immune activation models can result in abnormalities to structural morphology, cell density, and neurotransmitter and regulatory protein expression (Meyer et al., 2009). Most pharmaceutical agent models use maternal valproic acid (VPA) exposure, which is shown to increase the likelihood of ASD development in children (Roullet et al., 2013). VPA has been found to act on rodent embryos during neural development, and depending on the time of exposure, it can impact neuron density/number, brain volume, neurotransmitter levels, and cortical circuitry connections in specific brain regions. It is possible that circuit-level investigations of these environmental models will reveal if the neural pathways affected are shared with those in genetic models of ASD. Studying the underlying circuitry in environmental models in tandem with targeted genetic, molecular, and circuit-manipulation models should be a powerful resource for investigating the connection between circuitry and social preference

behavior in ASD (Potasiewicz et al., 2020; Schiavi et al., 2019; Zhang et al., 2019).

Since rodents demonstrate some social preference behaviors considered analogous to those of humans, these behaviors are often used to verify the applicability of a particular ASD-associated genetic or neural manipulation in modeling human ASD behavior. Additionally, established paradigms for measuring social preference in rodents, the most common of which is the three-chamber social preference task, allow for semi-standardized investigations across labs (Rein et al., 2020; Silverman et al., 2010). The three-chamber task mimics the simultaneous presentation of social and nonsocial stimuli in human tasks, giving rodents a choice to explore a chamber containing either another rodent or a nonsocial stimulus in the social preference task and either a novel or familiar conspecific in the social novelty task, as shown in Fig. 2D. The rodent's exploratory behavior is typically measured as time exploring each chamber, though some studies include more rodent-specific behaviors, such as sniffing or close contact with the conspecific (Allsop et al., 2018; Guo et al., 2019; Huang et al., 2016; Ma et al., 2018; Murugan et al., 2017; Phillips et al., 2019; Vialou et al., 2014; Vyas et al., 2020; Yang et al., 2020; Yoo et al., 2019b). While most social preference tasks in rodents use live interacting animals, some tasks have also used more reductive, rodent-specific stimuli including ultrasonic vocalizations or odorant cues like used bedding (Ryan et al., 2008; Yang et al., 2015). Overall, the three-chamber task is useful to the study of social preference behaviors in rodents, as it allows for both a similar structure to human social preference tasks and the testing of species-specific behaviors. Additionally, the ability to record and manipulate neural activation during the three-chamber task allows for further verification of the translational utility of the models through circuit-level investigations.

While the three-chamber task is a common standardized social preference paradigm in rodents, many other tasks have been developed that can reveal nuances in preference behavior. Three chamber tasks with weighted doors can compare the level of social reward to the reward of, for example, food, without requiring social memory (Borland et al., 2017). Alternatively, a socially conditioned place preference task eliminates the auditory and olfactory stimuli of a live rodent condition and relies on social preference memory, conditioning rodents to associate bedding of a specific color and texture to social/nonsocial conditions and measuring time spent in social/nonsocial-associated bedding chambers (Wei et al., 2015; Schiavi et al., 2019). Another conditioned task, the novel operant nose poke task, trains mice to voluntarily poke a port to lift a barrier to access a conspecific in a chamber (Szelenyi et al., 2021; Hu et al., 2021). Due to the additional effort required to poke the port, this task may speak more directly to motivation for social stimuli, rather than just a preference. Moreover, social play tests measure the engagement in and responsiveness to play behaviors, including pouncing and pinning, of the experimental rodent with a neurotypical rodent (Trezza and Vanderschuren, 2008; Schiavi et al., 2019; Veenema et al., 2013), and even more general free social interaction tests measure time spent interacting with or sniffing their neurotypical counterpart (Kazdoba et al., 2014). These paradigms, while less controlled, can be easily applied across model species and can approximate the typical situations in which animals, including humans, would interact.

Another advantage of using rodent models of social preference is the accessibility of the perinatal stages to neurobiological study. Naturalistic behaviors, like ultrasonic vocalizations and preference for social odors, can be used to investigate social preference in neonatal rodents, a particularly important timepoint given the challenges of studying the developmental trajectory of ASD in infancy and early childhood in humans. Rodent pups have complex social dynamics, both with their mother and the rest of the litter. For example, mothers engage in licking and grooming of pups, which establishes physical contact and olfactory memory (Lucion and Bortolini, 2014). Typically developing pups show maternal-odor preference even before the development of non-olfactory sensorimotor abilities, and pups deprived of maternal licking and grooming develop altered social preference behaviors (Cromwell et al., 2007; Harmon et al., 2008, 2009). Pups also produce ultrasonic vocalizations that may be involved in social communication; when pups are isolated from their littermates or mother, they emit vocalizations of specific length/frequency which elicit a maternal response (Cromwell, 2011; Boulanger-Bertolus et al., 2017; Manduca et al., 2020, 2021). Given their presence early in development, maternal-odor preference and ultrasonic vocalizations are used as indications of early social preference and have been explored in models involving altered maternal grooming/exposure, altered litter exposure, exposure to toxins, and exposure to stressors (Harmon et al., 2009; Cromwell et al., 2007; Cummings et al., 2005; Cromwell et al., 2011). Decreased ultrasonic vocalizations, indicating decreased social preference, were found in both maternal-immune activation and VPA exposure environmental models of ASD (Potasiewicz et al., 2020). Understanding the altered neurobiology and developmental trajectory of neural circuits that underlie the decreased social preferences seen in these early-life animal models of ASD may shed much-needed light on this understudied timepoint in human development.

Research with nonhuman primate models is a promising direction for improving human translation, as the social behavior and circuitry in humans is much more similar to that of other primates than rodents (Chang et al., 2013b). Though the genetic manipulations that make rodent models so attractive are more challenging in nonhuman primates, recent studies have used gene editing and silencing techniques to study associated alterations in behavior and neural signaling (Galvan et al., 2018; Zhao et al., 2019). Notably, using a combination of open field and eye tracking tests, researchers have demonstrated that macaque models of ASD that disrupt the *MECP2* and *SHANK3* genes show decreased or altered preference of social stimuli and decreased social approach and novelty behaviors (Liu et al., 2016; Zhou et al., 2019) consistent with the results seen in rodents and humans.

Just like in humans, social behaviors and the underlying neural mechanisms can be studied with eye tracking in nonhuman primates. This approach allows for precise behavioral measures and is analogous to the preference selection task used in humans, thus increasing translational value (Chen et al., 2017; Sliwa and Freiwald, 2017; Zhou et al., 2019; Dal Monte et al., 2022). However, typical eye tracking paradigms require restraining the head for high-precision tracking, which restricts natural head movements. Furthermore, these tasks often employ still images or videos of conspecifics, which lack the sensory features of live conspecific-to-conspecific interactions. Because of this, traditional eye tracking experiments face limitations in capturing naturalistic, species-specific social behaviors.

Nonhuman primate social preferences can also be studied through live interaction tests, where two primates are allowed to interact in a neutral, open field, as shown in Fig. 2 (Chen et al., 2017; Liu et al., 2016; Tu et al., 2019; Zhou et al., 2019). Their interaction is then scored for species-typical social behaviors, such as following, grooming, and play. The monkeys can exhibit a preference for social behaviors by approaching their conspecific and maintaining proximity to them, instead of not approaching the conspecific and/or choosing to spend time alone. These nonhuman primate tests are similar in concept to the three-chamber social approach test in mice in that they measure social approach frequency and quantify time spent interacting with, or not interacting with, a conspecific. When these behaviors are tested with no cage around the social stimulus, these paradigms can better mimic human interactions, bridging the gap between high-throughput rodent studies and human studies. However, these naturalistic studies can result in a high amount of variance in the experimental conditions and the animals' behavior, which can make results difficult to interpret. In certain situations, less naturalistic and more controlled tasks can be used to study specific facets of social behaviors more carefully. For instance, in the social reward allocation task, an actor monkey makes either a prosocial or an antisocial decision by choosing one or the other visual stimulus on a monitor screen to impact the reward outcome of a

conspecific monkey (Chang et al., 2013; Dal Monte et al., 2020). Tasks like this can enable more precise isolation of the specific behaviors that may underlie social preference and can be used to probe which specific alterations/dysfunction in brain regions and circuits lead to distinctive behavioral deficits commonly seen in ASD.

To conclude, careful consideration must be given to task design, naturalistic or controlled, to ensure that meaningful inferences can be drawn from behavior to the neural circuitry underlying it. Carefully weighing the balance between naturalistic contexts and experimental control (Fan et al., 2021) can help us to better understand how dysfunction in the brain leads to ethologically relevant disruptions in social behavior as well as to understand the specific processes that are being disrupted. This is especially true when considering animal models and human studies of social preference. Paradigms that involve explicit choice, such as measuring social approach in the three-chamber task, and those that do not, such as image-based eye tracking used in human studies, may be confounded by the difference in motivation required. In the latter, the subject is simply required to have a preference; in the former, the subject is required to act on it. Similarly, tasks that give animals the option to engage with a conspecific, such as free-interaction contexts, and those that force the subject to choose between a social versus nonsocial stimulus may not be perfectly comparable. By balancing tasks with ecological validity with tasks designed to measure some specific aspect of social preference, we can leverage animal models effectively to allow for the greatest translational validity.

3. Social preference circuits in the brain

Social preference behavior in humans is characterized by activation of a broad network of brain regions. Social cognition circuity is comprised of an array of both cortical and subcortical regions involved in social stimulus processing, emotion recognition and interpretation, and social decision making (Adolphs, 2009). Some areas are activated in highly specific contexts of perceiving social information, such as the fusiform face area for facial stimuli and the temporoparietal junction for perspective-taking, while other areas like the PFC are involved in many general aspects of social behavior (Adolphs, 2003a; Gangopadhyay et al., 2021; Ruff and Fehr, 2014; Seo and Lee, 2012). Preference and choice behaviors also recruit the brain's reward and motivational systems (Adolphs, 2003a; Gangopadhyay et al., 2021; Ruff and Fehr, 2014; Seo and Lee, 2012). The reward circuitry broadly encompasses several brain areas receiving or sending inputs from the dopaminergic ventral tegmental area and its downstream target, the NAc, and most relevant to the current review, this circuitry extensively interacts with the amygdala and multiple regions within the PFC (Chau et al., 2004; Pierce and Kumaresan, 2006). Thus, the brain regions specialized for social preference behaviors likely function at the "intersection" of social cognition and reward processing.

Several of the subregions of the PFC are involved in social preference behaviors, notably the medial PFC (mPFC), the prelimbic portion of the mPFC (PL) in rodents, the dorsolateral PFC (dlPFC), and the anterior cingulate cortex (ACC), of which the rostral part is often included in the mPFC region (Silvetti et al., 2014). The mPFC, a region critically involved in emotional response regulation and reward-guided learning (Etkin et al., 2011; Neubert et al., 2015), is active during social approach behaviors in rodents (Lee et al., 2016) and during prosocial preference behaviors and viewing of social interactions between conspecifics in nonhuman primates (Chang et al., 2013a; Sliwa and Freiwald, 2017). While this region has historically been poorly defined across species, new schemas connect the structure, function, and connectivity of the rodent mPFC/ACC regions to the primate ACC, specifically with regard to its social functions (Laubach et al., 2018; Burgos-Robles et al., 2019; van Heukelum et al., 2020). Further, lesions of the ACC in macaques have been shown to disrupt attention to social information and prosocial learning (Basile et al., 2020; Rudebeck et al., 2006), and lesions of the ACC in otherwise healthy humans have been shown to decrease social behavior and impair participants' ability to identify emotions in voices and faces (Hornak et al., 2003). The mPFC has also been shown to be involved in rewarding aspects of social interactions across humans, nonhuman primates, and rodents (Sumiya et al., 2020; van Kerkhof et al., 2013). More specifically to ASD, fMRI research in humans has demonstrated that, compared to typically developing individuals, individuals with ASD reported lower levels of social reward following positive social interactions accompanied by decreased mPFC activation compared to neurotypical individuals (Sumiya et al., 2020). Thus, dampening of mPFC-mediated social reward circuit activity could lead to decreased motivation towards social stimuli/interactions and, therefore, decreased social preference.

Subcortically, the amygdala and NAc, both of which are largely conserved across our model species, play a critical role in social processing as well as both general and social reward processing (Janak and Tye, 2015; Balsters et al., 2020). A well-established key mediator of social interactions, the amygdala also encodes values associated with social behaviors and decisions such as social rank, facial identity and expressions, and vicarious social reward (Putnam and Chang, 2021). Human lesion studies have highlighted the clinical importance of the amygdala in social behaviors, as patients with bilateral amygdala lesions have shown deficits in emotion recognition and social attention, impaired sense of interpersonal space, and atypical gaze patterns during social interactions (Kennedy et al., 2010; Adolphs et al., 2003b; Adolphs et al., 2002; Spezio et al., 2007). Relatedly, rhesus macaques examined in an open-field interaction test showed increased social behaviors following transient BLA inhibition and decreased social behaviors following transient BLA excitation (Wellman et al., 2016), suggesting that the BLA is involved in bidirectional modulation of social behavior. At the intersection of its reward and social processing functions, the amygdala has been found to encode social and nonsocial reward information. In a study investigating representation of social hierarchy and reward value in macaques, researchers found that the same subpopulation of amygdala neurons encoded both social hierarchy and reward association information in social and nonsocial reward tasks (Munuera et al., 2018). Relatedly, human fMRI studies demonstrated that increases in amygdala activation were associated with the anticipation of social reward and social punishment outcomes as compared to neutral feedback (Martins et al., 2021). Thus, decreased amygdala activation in anticipation of or during social interactions may result in altered social reward processing leading to decreased social preference in individuals with ASD.

The NAc has long been established as a key region in reward modulation and processing, and there is increasing evidence that it is also critically involved in social behaviors. For example, recent studies have highlighted the NAc's involvement in a variety of social behaviors across species including, but not limited to, social play in rodents, pair bonding in nonhuman primates, and prosocial choices in humans (French et al., 2018; Haruno et al., 2014; Vanderschuren et al., 2016). In ASD-specific studies of the NAc, researchers have found that individuals with ASD show decreased NAc activation relative to controls during reward-related tasks (Assaf et al., 2013; Damiano et al., 2015). A recent meta-analysis of fMRI studies investigating social and nonsocial reward-related activation demonstrated that, relative to neurotypical controls, individuals with ASD show NAc hypoactivation in response to nonsocial rewards but NAc hyperactivation in response to restricted interests (Clements et al., 2018). While this meta-analysis did not find altered NAc activation in response to social reward, broader changes in reward circuitry, such as that seen in the NAc, could still contribute to decreased social motivation by affecting general reward experiences. Further, because investigations of the NAc in social behaviors and reward are relatively recent, the specific function of the NAc in social reward in ASD is still not well hypothesized. However, research has shown that the NAc responds to anticipation of social reward and social punishment (Kohls et al., 2013), suggesting that atypical activation of the NAc could underlie social reward processing deficits in individuals

Table 1
Circuit Research Overview. This table describes the 6 highlighted studies on mPFC-Amyg and mPFC-NAc circuits.

Model Organism	Model Focus	Model Manipulation	Rescue Manipulation	Circuit Implicated	Social Preference Behavior (s) Affected	Reference
Mouse	ASD	Pten+ /-	DREADD inhibition of mPFC	mPFC-BLA activation	decreased social approach	(Huang et al., 2016)
Mouse	ASD	maternal immune activation	N/A	mPFC-BLA activation	decreased social approach	(Li et al., 2018)
Mouse	observational fear learning	ACC-BLA inhibition during observation of aggression	N/A	ACC-BLA inhibition	uninhibited social approach toward aggressor	(Allsop et al., 2018)
Prairie vole	prosocial behavior	mPFC-NAc activation in proximity of conspecific	N/A	mPFC-NAc activation	increased affiliative behavior	(Amadei et al., 2017)
Mouse	social defeat stress	10 days of social defeat stress	optogenetic activation of mPFC-NAc	mPFC-NAc inactivation	social avoidance	(Vialou et al., 2014)
Mouse	social-spatial learning/ preference	location-based PL-NAc inhibition	N/A	PL-NAc activation	social-spatial preference	(Murugan et al., 2017)

with ASD. Taken together, these findings suggest that decreased social preference in individuals with ASD could be in part driven by dysfunction in the NAc and its circuits causing decreased reward processing to social engagement or increased reward processing to nonsocial pursuits such as during restricted interest engagement.

Underlying the relationship between social reward processing and the reduced social preference seen in ASD is the social motivation hypothesis of ASD which posits that individuals with ASD experience diminished reward from social interactions and thus are less socially motivated than their typically developing counterparts (Chevallier et al., 2012). In fact, decreased activation in social reward circuitry has been considered as a common factor in individuals with ASD, supporting a link between the activation of these brain regions and (a)typical social behavior (Abrams et al., 2013; Dichter et al., 2012a, 2012b; Kohls et al., 2012). Thus, as regions involved in social cognition, reward processing, and social reward, the mPFC, amygdala, and NAc are likely to play a critical role in social preference behaviors. Additionally, the mPFC projects to both the core and shell of the NAc and shares reciprocal anatomic connections with the amygdala (Britt et al., 2012; Carmichael and Price, 1995). This further supports the importance of circuits connecting these regions in social disorders where social preference may be disrupted. In the following sections, we will review two PFC circuits, the mPFC-amygdala circuit and the mPFC-NAc circuit, and their involvement in social preference behaviors in ASD. We chose to focus on these two circuits due to their applicability to and novelty in ASD-specific research. Additionally, we will highlight animal models that rely on divergent methods of induction of social preference behaviors, but have convergent, downstream neural pathways (Table 1).

3.1. *Prefrontal cortex-amygdala circuit*

Projections and interactions between the mPFC and the amygdala have been associated with social learning, reward, and preference decisions in nonhuman primates, rodents, and humans (Allsop et al., 2018; Carmichael and Price, 1995; Dal Monte et al., 2020; Gangopadhyay et al., 2021; Huang et al., 2016; Kumaran et al., 2016; Putnam and Gothard, 2019). Thus, it is natural to investigate the potential implications of this circuit in social preference behaviors in ASD and in ASD model species.

In a 2016 study, researchers generated an ASD mouse model with a heterozygous mutation of *Pten* (*Pten*$^{+/-}$), a gene that encodes a lipid phosphatase that negatively regulates cell growth and proliferation (Huang et al., 2016; Skelton et al., 2019; Table 1). Loss of *Pten* is associated with increased excitatory synapse growth, and mis-wired and overgrown neural circuits in mice, along with reduced social preference in the three-chamber task (Skelton et al., 2019). Functionally, improper and excessive excitation can lead to seizures and a variety of behavioral alterations, including reductions in social novelty preference and impaired social recognition in mice and ASD-related social deficits in humans (Clipperton-Allen and Page, 2014; Hobert et al., 2014; Klein et al., 2013; Kwon et al., 2006; Marchese et al., 2014). In the study, researchers demonstrated that in *Pten*$^{+/-}$ mice, relative to in control mice, there was increased branching and connectivity of mPFC to BLA axonal projects and increased activation of the mPFC→amygdala pathway during social interactions (Fig. 1A, D, G). Next, researchers used a 'designer receptor exclusively activated by designer drugs' system (DREADDs) to partially inhibit BLA-projecting mPFC neurons and found restored three-chamber social approach behavior in these mice, demonstrating the causal role of the mPFC→amygdala circuit in social preference behavior.

A 2018 study used an environmental model of ASD and found the involvement of the mPFC→BLA circuit in the social deficits generated (Li et al., 2018; Table 1). Specifically, maternal immune activation to induce ASD-related changes in mice, a model based on the effect maternal immune signaling molecules can have on fetal neural development (Careaga et al., 2017). In this study, researchers induced maternal immune activation in mice to mimic an ASD-like behavioral phenotype, with decreased social approach behavior in a variant of the three-chamber task, wherein approach to a conspecific in a wire cage placed within an open field was measured. Accompanying this reduced behavioral preference, researchers found increased firing of BLA-projecting mPFC neurons (Fig. 1G), due to either increased connectivity of glutamatergic mPFC projections to the BLA (Figs. 1B, 1E) or decreased connectivity of GABA interneurons in the mPFC→BLA circuit (Fig. 1C, F), depending on whether subsequent postnatal immune activation was induced. Thus, evidence showing altered activation of the mPFC→amygdala circuit across ASD rodent models induced by distinct manipulations supports the theory that dysfunction in this circuit contributes broadly and causally to atypical social preference in ASD (Fig. 1A-G).

Another 2018 study examined the role of the ACC-amygdala pathway in regulating adaptive social preference and social avoidance (Allsop et al., 2018; Table 1). This study relied on observational learning, with a subject mouse observing an aggressive interaction between two conspecifics. When these mice engaged in the three-chamber task, with the aggressor mouse serving as a social stimulus, the subject mice preferred not to approach the aggressor mouse, showing adaptive social avoidance behavior. The researchers transiently optogenetically inhibited the ACC→BLA circuit in the subject mice while the mice observed the aggressive interaction between two conspecifics. When these mice engaged in a three-chamber social approach task, they displayed uninhibited social approach behavior and demonstrated a preference for the aggressive mouse. This indicates that inhibition of the ACC→BLA circuit was sufficient to induce atypical social preference. These findings suggest that ACC→BLA circuit activation may be necessary for adaptive social avoidance learning and, furthermore, that atypical activation of this circuit may be involved in the maladaptive social preference behaviors seen in ASD.

Taken together, these studies support the critical role of the mPFC-amygdala circuit in expression of normal social preference behaviors

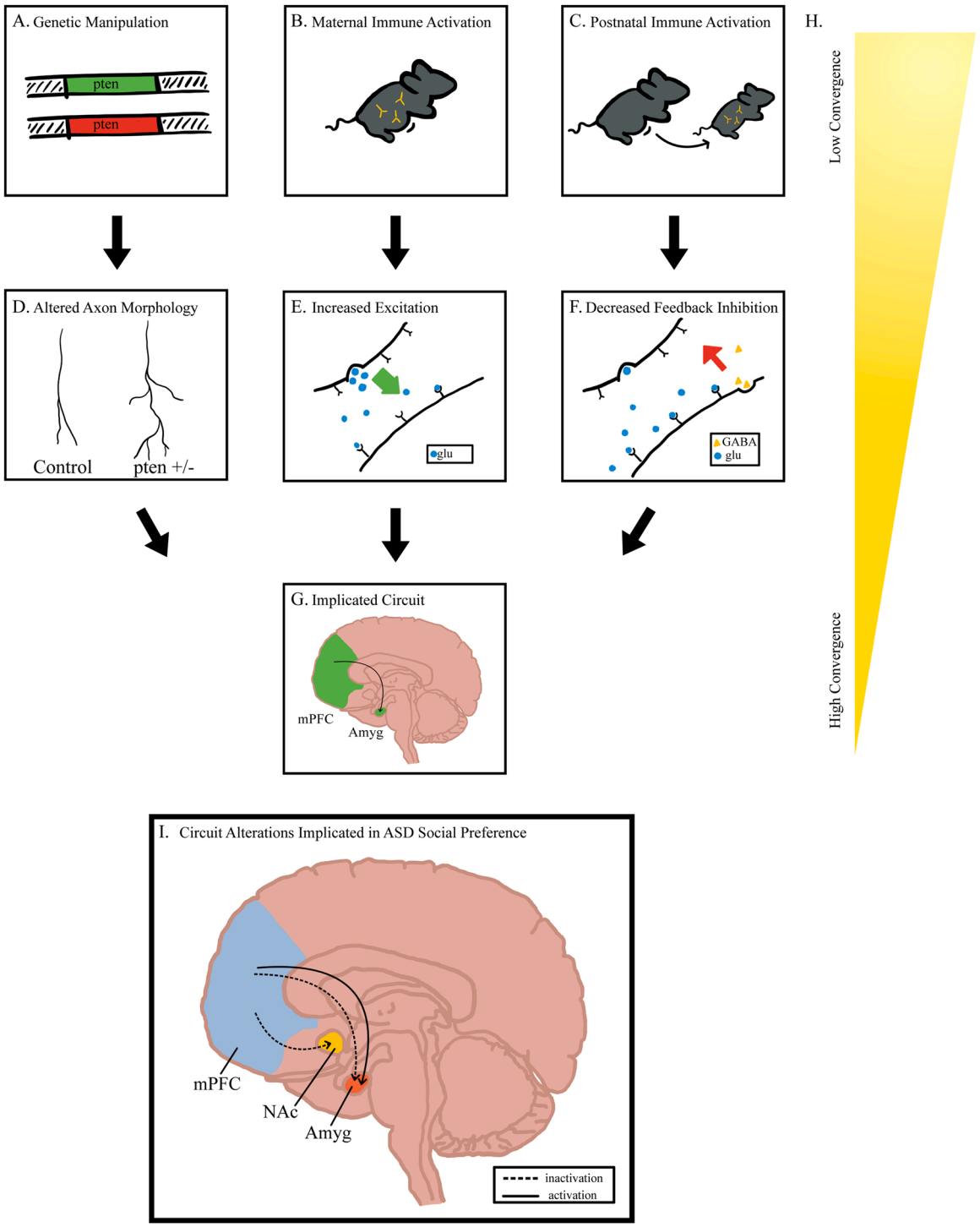

Fig. 1. : Convergence of circuit alterations implicated in social preference in ASD. A-C. Manipulations performed in three models of social preference in ASD. A. Heterozygous *Pten* knockout mouse model (Huang et al., 2016). B. Maternal immune activation (MIA) through injection of polyinosinic:polycytidylic acid (Li et al., 2018). C. Postnatal immune activation (PIA) through injection of lipopolysaccharides (Li et al., 2018). D-F. Molecular/cellular effects of the manipulations. D. Heterozygous knockout of *Pten* led to increased axon branching and synaptic boutons and hypertrophy of BLA-projecting mPFC neurons (Huang et al., 2016). E. MIA led to increased glutamatergic activation in BLA-projecting mPFC neurons (Li et al., 2018). F. PIA led to decreased GABA feedback inhibition in BLA-projecting mPFC neurons (Li et al., 2018). G-H. All three models led to hyperactivity of the mPFC-BLA circuit and social preference deficits, demonstrating functional convergence. I. Decreased mPFC-NAc activation and both increased and decreased mPFC-amygdala activation have been associated with altered social preference behavior in ASD.

and suggests that future research to better understand the underpinnings of this circuit could benefit our understanding of ASD pathophysiology.

Work done with nonhuman primates also supports a central role for the mPFC-amygdala circuit in social preference. In a 2020 study, Dal Monte and colleagues (Dal Monte et al., 2020) assessed social preference in rhesus macaques who had to choose between delivering juice to a conspecific partner monkey and wasting it into an empty bottle as well as between delivering juice to themselves and both to themselves and the partner. Monkeys displayed a prosocial preference in the former context (preferring to deliver juice to the partner), whereas they

displayed an antisocial preference in the latter context (preferring to deliver juice to only themselves). They found distinct activation and synchronization patterns between the ACC and the BLA for prosocial versus antisocial decisions, with selectively enhanced coherence between spiking activity in the BLA and local field potentials in the ACC as well as between spiking activity in the ACC and local field potentials in the BLA for prosocial preference. This study also determined that this enhanced neuronal coordination for expressing prosocial preference was associated with an increase in directionality of information flow from BLA to mPFC. It is important to note that most rodent research on the involvement of the prefrontal-amygdala circuit in ASD has focused on projections from the mPFC to the BLA. However, there is data to support a role for BLA projections to the mPFC. Felix-Ortiz and colleagues (Felix-Ortiz et al., 2016) used optogenetics to selectively activate or silence BLA projections to the mPFC and could bidirectionally alter anxiety-like and social interaction behavior. Activation of BLA→mPFC led to anxiogenic behaviors and reduced social interactions, while inhibition of BLA→mPFC led to the opposite. More research is needed to determine whether dysfunctional BLA→mPFC activation might also contribute to atypical social preference behaviors in both rodent and primate species.

Human research also supports the role of the PFC-amygdala circuit in social preference, analogous to what has been observed in animal models. Some studies found that individuals with ASD showed increased activation in the mPFC/ACC, dlPFC, and amygdala while engaging in social perception tasks (Critchley et al., 2000; Dalton et al., 2005; Dichter et al., 2012a, 2012b; Schumann et al., 2009), with some studies further demonstrating that social deficit severity was positively associated with amygdala activation in adults and amygdala volume in toddlers (Dalton et al., 2005; Schumann et al., 2009). However, there is also contrasting evidence showing hypoactivation across these regions in individuals with ASD. A meta-analysis analyzed fMRI studies employing social processing tasks and found that individuals with ASD showed decreased amygdala, perigenual ACC, and fusiform gyrus activity compared to neurotypical controls (Di Martino et al., 2009). Further, a recent resting-state fMRI study found significantly decreased mPFC-amygdala effective connectivity, a metric that captures the causal effect of one brain region on another in a direction-specific manner, in individuals with ASD as compared to neurotypical controls (Li et al., 2021). The researchers also found that this reduction in mPFC→amygdala influence was associated with social deficits in children with ASD. Although the similar social behavioral effects of decreased and increased activity of the PFC and amygdala may initially seem contradictory, Fernandez et al. (2018) explained this interesting dichotomy through understanding the functional effects of normal activation versus the two extreme abnormal activations (hypoactivation or hyperactivation). The first extreme would be a complete absence of amygdala activation in response to social stimuli. This would functionally correspond to an absence of emotional activation to and perceived importance of the social stimulus, ultimately resulting in a lack of motivation to attend to it. Thus, the deficient social preference would be due to a lack of prioritized circuit activation to the social stimulus. The second extreme would be hyperactivation of the amygdala as demonstrated in Huang et al. (Huang et al., 2016). This increased amygdala activation could result in excessive emotional activation, potentially leading to an aversive experience and thus an avoidance response. This would have a qualitatively similar behavioral response as decreased activation, a lack of social preference, but would now be due to social avoidance rather than indifference. Normal, balanced levels of activation, therefore, would be necessary for appropriate social preference behavior. While this logic explains why we may observe similar behaviors with opposing neural changes, note that most human neuroimaging studies have found decreased amygdala activation in ASD and most animal models of the PFC-amygdala pathway have focused on stimulating amygdalar pathways. It is important to keep in mind both the behaviors and circuits implicated in ASD animal models and the manipulation direction of circuit activation when creating translationally informative models.

3.2. Medial prefrontal cortex-nucleus accumbens circuit

The functional link between the PFC and NAc has been established for years (Montaron et al., 1996), and recent studies have begun to investigate the mPFC-NAc circuit in the context of social preference behavior. The NAc plays an important role in the motivation and behavioral coordination required to obtain a reward, and it has recently been theorized that the mPFC-NAc circuit may play a role in the rewarding aspects of social interactions. Additionally, several different animal models appear to recruit the mPFC-NAc pathway to affect social preference behaviors.

In a study using prairie voles and the formation of monogamous mating bonds, researchers recorded neural activity in the mPFC and NAc and found increased functional connectivity between these regions during prosocial behaviors (Amadei et al., 2017; Table 1). External activation of the mPFC-NAc circuit, through optogenetic stimulation while in proximity of a conspecific partner, resulted in increased affiliative behavior with the partner rodent. In addition, another study investigated the mPFC→NAc circuit in a mouse model where altered social preference was induced by exposing animals to chronic social defeat stress (Vialou et al., 2014, Table 1). The study looked at cholecystokin (CCK), which is an anxiolytic neurotransmitter that is highly prevalent in the limbic regions and cortex, and whose release during stressful or anxious situations is thought to decrease mPFC activation and increase anxiety behaviors (Becker et al., 2001, 2008; Rotzinger and Vaccarino, 2003; Vialou et al., 2014). In social situations, the release of CCK leads to avoidant behavior, and the study found that both the inhibition of mPFC CCK receptors and optogenetic stimulation of mPFC projections to the NAc reversed the social avoidance normally seen in the CCK model (Vialou et al., 2014). This study used another variation of the three-chamber test, where the enclosure with the social stimulus was part of one larger chamber with a designated social zone, rather than three separate chambers divided by walls (Krishnan et al., 2007). These results suggest that activation of the mPFC-Nac circuit contributes to social preference behaviors, and decreased activation of this circuit might decrease social preference.

Moreover, a study from Murugan and colleagues suggests that the contributions of mPFC-NAc circuit to social preference behaviors may be even more nuanced than previously shown (Murugan et al., 2017; Table 1). The researchers found that optogenetic activation of NAc projecting prelimbic (PL) mPFC neurons resulted in decreased social preference in a three-chamber test. This seems to contradict the previously discussed studies in which stimulation of this circuit resulted in increased social preference. However, when the researchers performed the three-chamber task, they found differential activation of subpopulations of neurons in response to not only the social stimulus but also the spatial location of the social stimulus. They hypothesized that when these subpopulations were indiscriminately stimulated, as in their first experiment, it may result in a uniform spatial preference, thus reducing the comparative preference for the social stimuli. Next, they created a new enclosure with two chambers, each with an encaged conspecific. When PL→NAc neurons were inhibited in one chamber but not the other, mice showed a lack of preference the next day for the social zone in which their PL→NAc pathway was inhibited, while showing normal preference for the social zone in which their PL→NAc pathway was not inhibited. These findings, paired with this circuit's involvement in reward-related behaviors, suggest that the PL→NAc pathway may influence social preference through its impact on social-spatial preference formation.

Due to the recency of the experiments looking at the mPFC-NAc circuit in social preference, there is not much human research on the role of this pathway on social preference in ASD. However, the potential importance of mPFC-NAc pathways is supported by clinically relevant

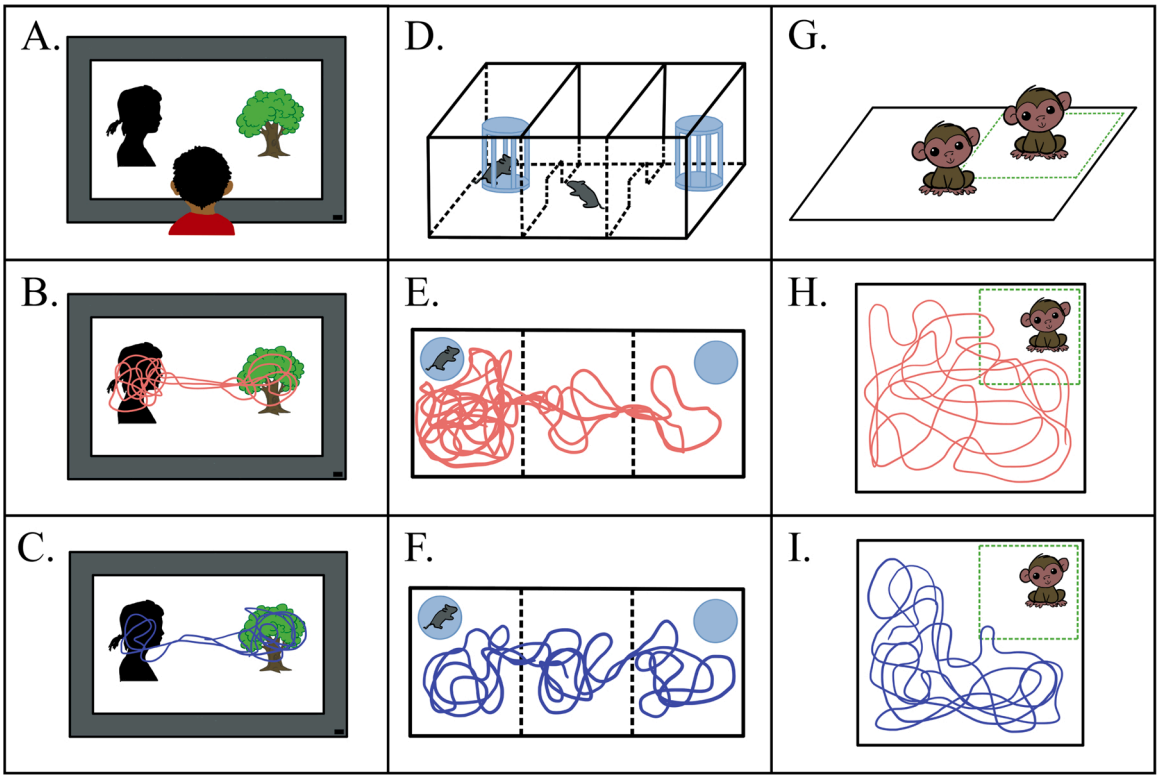

Fig. 2. : Representative examples of common social preference research paradigms and results in rodents, nonhuman primates, and humans. A. Eye tracking social preference test in humans. B. Eye tracking social preference test results in neurotypical humans. C. Eye tracking social preference test results in humans with ASD, which show increased preference for nonsocial stimuli, above chance (Di Giorgio et al., 2016; Jones and Klin, 2013). D. Three-chamber test in rodents. E. Three-chamber test results in neurotypical rodents showing a preference for the social chamber. F. Three-chamber test results in rodent ASD model show decreased social preference, nearing chance (Guo et al., 2019; Ma et al., 2018; Phillips et al., 2019; Qin et al., 2018; Yoo et al., 2019a; Zhang et al., 2016). G. Open field test in nonhuman primates. H. Open field test results in neurotypical nonhuman primates showing significant exploration and unhindered interaction with conspecific. I. Open field test results in nonhuman primate ASD model, which show decreased proximity to and interactions with the conspecific (Liu et al., 2016; Zhou et al., 2019). All traces are a representation, and not reproduction, of the traces observed in the studies mentioned.

studies that can be applied to the context of ASD in the future. Recent human studies have identified the mPFC and NAc as two of the core regions in social brain networks (Kiesow et al., 2021) and have demonstrated increased mPFC-NAc functional connectivity during salience processing (Richter et al., 2020). Additionally, research has demonstrated that the NAc shows increased activation during monetary reward, social reward, and social punishment anticipation, and the mPFC shows activation during reception of social reward in neurotypical individuals (Izuma et al., 2008; Kohls et al., 2013). In contrast, individuals with ASD show decreased activation of the NAc and ACC during monetary anticipation (Dichter et al., 2012b), but further investigation is needed to understand activation in these regions during social tasks in ASD. Given the importance of the mPFC-NAc circuit in affiliative behavior (Amadei et al., 2017), social avoidance/stress (Vialou et al., 2014), and social-spatial learning (Murugan et al., 2017), it is a likely candidate for involvement in the social preference deficits associated with ASD. Further supporting this, and suggesting treatment implications, animal studies have found increased social interaction with mPFC optogenetic and deep brain stimulation in mouse models of social avoidance using chronic social defeat stress (Covington et al., 2010; Veerakumar et al., 2014). More research on the mPFC-NAc pathway in the specific context of ASD could improve our understanding of ASD pathophysiology and help with developing treatments.

4. Implications of convergent circuits in ASD for treatment development

Throughout this review, we have discussed studies that generate animal models of ASD or of altered social preference using genetic, environmental, or circuit-level manipulations. Despite the diversity of the manipulations, these models seem to converge on a select few brain regions and neural pathways to result in disrupted social preference behaviors (Table 1). While we highlighted specific convergent circuits underlying social preference deficits, this may not be the only domain within ASD where this concept applies. In fact, there is evidence suggesting a similar convergence of distinct genetic causes onto the same circuits and, subsequently, behaviors. For example, both *Fmr1-Δexon 8* rat and *Shank3*-deficient rat models of ASD show similar deficits in sustained attention abilities with the former showing an altered mPFC transcriptional profile and the latter showing reduced synaptic plasticity in the mPFC (Golden et al., 2019; Harony-Nicolas et al., 2017). While an exact neural circuit underlying this behavioral deficit has not yet been identified, these results suggest a promising path forward for identifying another common circuit disruption leading to similar symptoms across various causes of ASD.

Furthermore, this shift in focus is in line with a movement from the NIMH to define psychiatric disorders according to broader spectrum of symptoms to facilitate the linking of behaviors and symptoms to neural circuits (Casey et al., 2014). The use of a dimensional approach based on observable behavior, in which behavior and cognition exist along a continuum rather than into discrete categories or diagnostic criteria, allows for increased capture of variation and its contributors. Applied to ASD, this dimensional approach would emphasize study of and treatment based on observed behavioral deficits rather than specific etiologies. This approach could also mitigate several challenges associated with treatment development for such a heterogeneous disorder. Studies

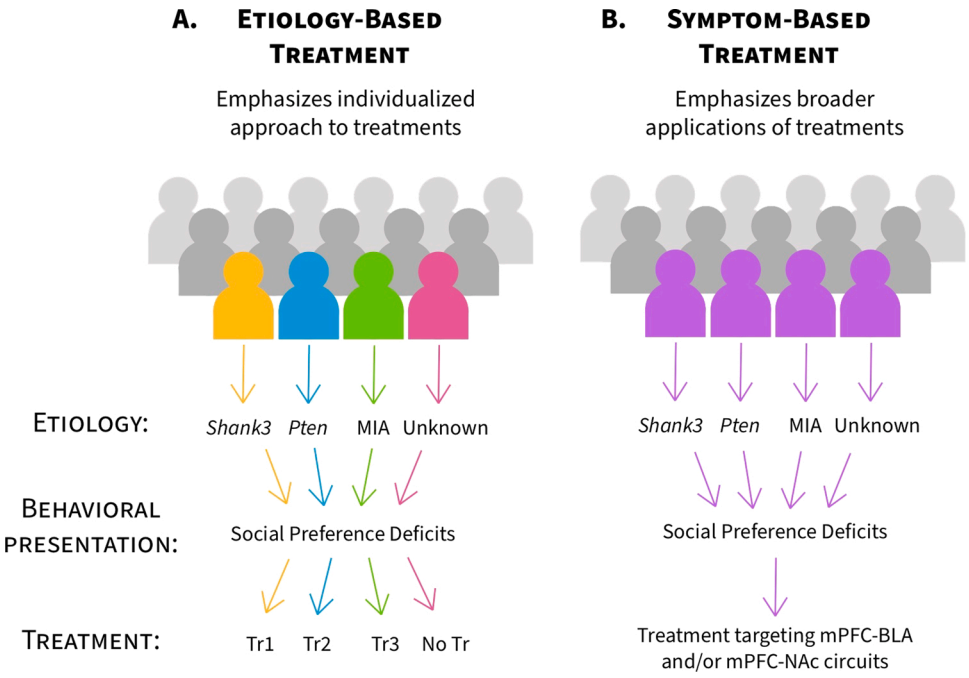

Fig. 3. : Schematic of etiology-based treatment versus symptom based-treatment in ASD. A. Etiology-based treatment calls for treatment selection based upon the underlying cause genetic, cellular, and/or molecular causes of ASD. These distinct causes may result in similar behavioral presentation, but treatments will still differ because they are based on etiology of the disease. This approach emphasizes individualized treatment plans with high specificity to specific causes of ASD. B. Symptom-based treatment calls for treatment selection based upon the behavioral presentation of ASD. With this approach, if individuals have distinct genetic, cellular, and/or molecular causes of ASD but show similar behavioral deficits, they would undergo the same treatment targeting the circuit underlying the behavioral deficit. This approach emphasizes wide applicability of treatments across diverse ASD cases.

of specific models of ASD, whether genetic, environmental, or others, have and will continue to inform our understanding of the neurobiological causes of behavioral presentations of this disorder and will likely lead to some successful, individualized treatment development (Fig. 3A). However, it may not prove feasible to develop a treatment for every single distinct cause of ASD. Moreover, therapies based upon a specific etiology may only be applicable for a small subset of cases and may not be more broadly applicable. Instead, if we can identify the common neural circuits upon which multiple etiological causes of ASD converge, we can focus on developing treatments that target circuit-level dysfunctions and will be generalizable across many causes of ASD. Ultimately, it may be possible to select treatments that have the potential to be effective across larger subsets of ASD patients despite heterogeneous, and often unidentified, underlying causes (Fig. 3B).

5. Conclusion

Evidence supports the PFC-amygdala and PFC-NAc circuits as being relevant to social preference behaviors. Studying these circuits in the context of ASD could provide insight into pathophysiology and allow for alternative or improved treatment development. Dissecting out the workings of these pathways is made more amenable by using animal models, notably rodent and nonhuman primate models. These animal models can be generated using a variety of manipulations – genetic, environmental, or with alterations at the level of brain regions and circuits. Similarly, the behavioral paradigms used to study social preference behaviors in these animal models can range from naturalistic to more controlled. Given the variability and flexibility available in using these models, it remains important to understand the commonalities between them to increase their translational potential. Circuit-level research has so far provided an improved understanding of the converging mechanisms underlying social preference differences across these different animal models and in ASD. This knowledge may better enable the future development of more broadly effective treatments to target these common pathways in a wider share of individuals with ASD caused by distinct pathophysiology.

Conflict of interest

The authors declare no competing financial interests.

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Author contributions

A.V.F., O.C.M., A.R.N., and S.W.C.C. wrote the paper.

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