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Neural Circuit Transitions Supporting Developmentally Specific Social Behavior

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Environmentally appropriate social behavior is critical for survival across the lifespan. To support this flexible behavior, the brain must rapidly perform numerous computations taking into account sensation, memory, motor-control, and many other systems. Further complicating this process, individuals must perform distinct social behaviors adapted to the unique demands of each developmental stage; indeed, the social behaviors of the newborn would not be appropriate in adulthood and vice versa. However, our understanding of the neural circuit transitions supporting these behavioral transitions has been limited. Recent advances in neural circuit dissection tools, as well as adaptation of these tools for use at early time points, has helped uncover several novel mechanisms supporting developmentally appropriate social behavior. This review, and associated Minisymposium, bring together social neuroscience research across numerous model organisms and ages. Together, this work highlights developmentally regulated neural mechanisms and functional transitions in the roles of the sensory cortex, prefrontal cortex, amygdala, habenula, and the thalamus to support social interaction from infancy to adulthood. These studies underscore the need for synthesis across varied model organisms and across ages to advance our understanding of flexible social behavior.

Introduction

For many species, flexible social behavior is critical for access to limited resources, such as food, protection, and mates. Social behaviors reciprocally impact and are impacted by social context, determined by both environmental conditions (e.g., group living) and partner behavior. This social context readily impacts the developmental trajectory of social behaviors that change over the course of the lifespan. While some social contexts promote sociability and age-specific social engagement, others have deleterious effects on brain and behavioral maturation, particularly during development. Although our understanding of these processes has been limited, recent advances in neural circuit dissection tools, as well as adaptation of these tools for use at early time points, has helped uncover several novel mechanisms supporting developmentally appropriate social behavior.

During early life, environmental demands are in constant flux and require a great deal of flexibility. For altricial species, born immature, the caregiver provides key resources, such as food, protection, and warmth; and as such, the social brain of the infant must support approach behavior toward the caregiver. As infants mature and prepare for independence, alternative neural circuits must be engaged to support distinct social behavior strategies. These circuits must support behaviors adapted to the world of the adolescent, where peers replace the caregiver as primary social partners. These social groups engage in a high degree of social play that is directly impacted by social circumstances supporting or impairing social engagement. Environments that disrupt social play have negative long-term consequences on brain maturation supporting behavioral flexibility into adulthood.

Adolescent social play gives way to complex group living structures in adulthood supported by mature cortico-centric circuitry. This behavioral repertoire includes forming and maintaining dominance hierarchies, identifying ingroup/outgroup members, and participating in collective behavior. It is now understood that inputs to and outputs from prefrontal cortical subregions regulate these forms of social decision-making. However, the detailed neural circuit mechanisms supporting these complex behaviors and

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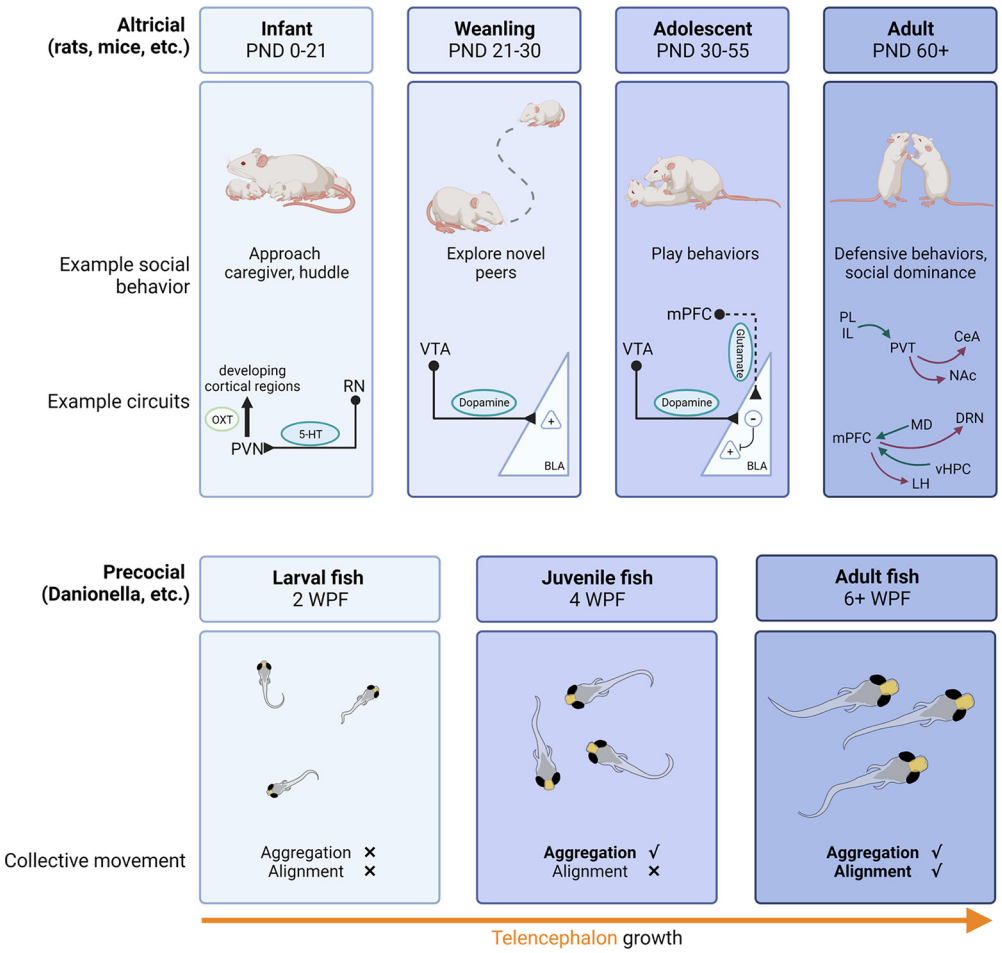

Figure 1. Social development is supported by distinct neural circuit functions across the lifespan. For altricial species, infant-caregiver interactions are supported by serotoninergic (5-HT) signaling originating from the raphe nucleus (RN) that modulates oxytocin (OXT) release to developing cortical regions via the paraventricular nucleus (PVN). This occurs alongside basal amygdala quiescence or caregiver regulation of endogenously increasing amygdala activity. Oxytocin signaling also supports the maturation of sensory cortices. Dopaminergic innervation from the VTA in the BLA is critical for the transition from caregiver approach to peer approach-avoidance in juveniles. Into adolescence, the underdeveloped amygdala can be characterized by a reduction in local inhibitory GABAergic function (represented as circles with minus signs) that is impacted by mPFC- and dopaminergic-amygdala circuitry. Amygdala underdevelopment may be a factor contributing to the increased incidence of social play in adolescence. As neural circuitry matures, play gradually declines and is replaced by complex group living and social decision-making. Here, PFC inputs (PL, prelimbic; IL, infralimbic) to PVT encode context-specific information and coordinate behavior selection. Divergent PVT outputs to NAc and CeA mediate defensive behavior flexibility. PFC inputs from mediodorsal thalamus (MD) show dominance related plasticity while input from ventral hippocampus (vHPC) plays a role in social memory. PFC outputs to lateral hypothalamus (LH) and dorsal raphe nucleus (DRN) also contribute to dominance behaviors. Aligned with this, some precocial species, such as fish, can increase in group synchrony over the course of development, involving aggregation and alignment of movement, as neural circuits mature from larval to adult stages (WPF, weeks post fertilization).

their development remain poorly understood. This review brings together cutting-edge work across the lifespan and across numerous model organisms to pinpoint the neural substrates supporting these age-appropriate behaviors and how these transitions can go awry.

Our goal is to highlight recent advances in our understanding of circuits supporting age-appropriate social behavior that are discussed in our 2023 Society for Neuroscience Mini-Symposium (summarized in Fig. 1). Our presentations will collectively outline developmental transitions in social behavior and the regulation of these behavioral transitions by maturing neural systems from infancy to adulthood.

Oxytocin-mediated neural circuits underlying the emergence of social touch

In rodents, touch is the first sense to form during fetal development and is among the most developed sensory modalities at birth (Bremner and Spence, 2017). During rodent infancy, social touch from caregivers is fundamental in developing secure attachment, which in turn significantly influences the emotional and cognitive development of the offspring (Kaffman and Meaney, 2007; Cascio et al., 2019). In neonatal rodents, tactile information from whiskers is critical to maintaining contact with and receiving milk from the dam, and early tactile sensory disruption, such as whisker trimming, can lead to long-lasting impairment in cognition, social behavior, and stress reactivity (Kaffman and Meaney, 2007; Landers and Sullivan, 2012; Soumiya et al., 2016). Notably, neurons in the adult primary somatosensory cortex (S1) can encode tactile stimuli from conspecifics (social touch), differentiating them from stimuli evoked by neutral objects (neutral touch) (Bobrov et al., 2014; Lenschow and Brecht, 2015). Despite the prominent role of tactile sensory processing in social behaviors, the neural mechanisms mediating this ability of cortical neurons to represent social touch are unknown.

Exogeneous oxytocin injections can promote learning social odor cues associated with the dam, forming tighter huddling in a litter, and suckling behaviors (Nelson and Panksepp, 1996;

Nelson and Alberts, 1997; Alberts, 2007; Kojima and Alberts, 2011), while knocking out oxytocin or oxytocin receptors (OXTRs) causes separation distress vocalizations in neonates (Insel and Winslow, 1991; Winslow et al., 2000; Winslow and Insel, 2002; Takayanagi et al., 2005). These findings indicate that oxytocin can enhance the required proximity to social cues that permit social learning in neonates. Therefore, oxytocin could act as an effector molecule mediating the entrainment of social touch because of its experience-dependent activity during this developmentally sensitive period.

Unpublished rodent data from the Che laboratory used longitudinal *in vivo* 2-photon imaging in developing mice to test the hypothesis that oxytocin is required for establishing proper synaptic connectivity in the developing S1 for both tactile sensory perception and social information processing. Che's group found that OXTRs are preferentially expressed in somatostatin (SST) interneurons in the developing S1, and the OXTR agonist TGOT induces large depolarizing currents as well as robust spontaneous firing in SST interneurons as early as postnatal day 9. Removing OXTRs specifically from SST interneurons results in persistent, oversynchronized spontaneous network activity *in vivo*, suggesting that oxytocin signaling might be involved in circuit desynchronization required for information processing. In addition, following the acute activation of SST interneurons, TGOT leads to long-lasting reduction in inhibitory synaptic transmission, suggesting that OXTR activation also has the capacity to further promote synaptic plasticity following network desynchronization. Che's ongoing work tests whether the presence of a social context (dam/dam odor), which activates oxytocinergic neurons, reduces synchronization and enhances sensory responses of L2/3 neurons in preweaning mice. Their unpublished findings indicate that oxytocin signaling can have profound influence on circuit assembly in the sensory cortex during early postnatal stage, providing a mechanism for how social features are encoded alongside tactile sensory inputs.

Infant social behavior: mesocorticolimbic circuits supporting caregiver approach

Sensing maternal cues is just the beginning of a circuit cascade that promotes approach toward a caregiver and ensures pup survival. Indeed, the neural circuitry supporting early social behavior reflects the unique social world of the developing individual. Unlike the adult rodent that participates in complex social hierarchies and seeks a mate, the primary social behavior for the infant rodent is learning attachment to a caregiver and seeking and maintaining proximity to them. While this proximity-seeking does not involve the basolateral amygdala (BLA) (Raineki et al., 2019), the learned caregiver does have the ability to partially or completely suppress infant BLA activity. This suppression of BLA activity and plasticity prevents rodent infants from learning to avoid cues paired with shock (Moriceau and Sullivan, 2006; Opendak et al., 2018, 2019; Robinson-Drummer et al., 2019). Instead of learning avoidance, fear conditioning in the presence of the caregiver actually engages attachment circuits to promote approach toward these conditioned stimuli — a phenomenon that has recently been demonstrated in children (Tottenham et al., 2019).

Recent circuit dissection work in rat pups has identified a role for dopaminergic projections from the ventral tegmental area (VTA) to the BLA in generating developmental transitions in social behavior (Opendak et al., 2021). Whereas preweaning pups demonstrate a strong bias toward approaching a caregiver, older rat pups show more inhibited social approach behavior toward novel peers. Optogenetic inhibition of BLA principal neurons or inhibition of VTA terminals in the BLA increased social approach in postweaning pups, while stimulation of these loci inhibited social approach. Inhibiting these circuits has no impact on social approach behavior in typically developing preweaning pups. Together, these results demonstrate that dopaminergic innervation of the BLA transitions a system biasing social approach toward the caregiver toward one favoring a balance of approach and avoidance as infants mature. This developmental trajectory is robustly impacted by early social adversity, with maltreated rats showing early emergence of avoidant behavior caused by amygdala hyperactivity and dopaminergic innervation of the BLA.

Recent work from the Opendak laboratory suggests that these circuit transitions may also involve an upstream modulator of VTA dopamine release, the lateral habenula (LHb). This region is an interface between the forebrain and the monoaminergic systems and is widely considered the brain's "anti-reward region," as it responds to aversive cues or the absence of expected rewards by suppressing DA release from the VTA (Baker et al., 2022; Mondoloni et al., 2022). Although this region is known to be important for adult social behavior flexibility (Benekareddy et al., 2018), our understanding of its role in development is limited. Opendak's laboratory assessed the role of this brain region in social behavior transitions using metabolic imaging and chemogenetics in the preweaning and postweaning rat pup. This unpublished work suggests that the LHb promotes a developmental transition in social behavior when threats are present. Specifically, when a threat cue is present, the LHb increases approach toward a social cue in preweaning pups, whereas the LHb inhibits approach in postweaning pups. As such, the LHb may be supporting developmentally specific social behavior: when the infant is threatened, approaching the social partner for safety (e.g., caregiver) is adaptive, whereas later in development, social partners are more ambiguous and may themselves be threats. Additional research highlights specific habenula circuits that promote this transition. Together, this body of work highlights specific neural circuit changes promoting unique social behavior strategies as environmental demands change.

Regulation of adolescent and adult social behavior by developing basomedial amygdala circuitry

From infancy to adolescence of the rat, amygdala function changes and its activity across ages regulates social behavior and behavior regulated by the environment (Varlinskaya et al., 1999; Varlinskaya and Spear, 2008; Arruda-Carvalho et al., 2017; Selleck et al., 2018; Ferrara et al., 2021). As a neuroanatomical corollary to these environmental changes, long-range infralimbic (IL) connections within the amygdala change from adolescence to adulthood (Arruda-Carvalho et al., 2017). These inputs are progressively pruned throughout adolescence, and their integration, strength, and capacity to activate amygdala neurons increase with rat age (Cressman et al., 2010; Selleck et al., 2018). The basomedial subdivision of the amygdala (BMA) displays a great deal of sensitivity and unique responsivity to social circumstances (Adhikari et al., 2015; Mesquita et al., 2016; Vitor-Vieira et al., 2021; Ineichen et al., 2022). In line with this, recent work from the Ferrara laboratory has demonstrated that repeated social defeat stress in the rat reduces both social interaction and BMA neuronal firing in adults, supporting the notion that BMA activation is directly tied to social state (Ritger et al., 2023). The rodent BMA is not only sensitive to

social stimuli, differentially responding to same- and opposite-sex partners and regulating physiological responses to social novelty, but is also an important site for environmental encoding (Rajbhandari et al., 2021; Mazuski and O'Keefe, 2022). Consistent with BMA activation, adolescent social development encompasses a heightened sensitivity to the social environment and a gradual decline in social play that is replaced by increases in preference for opposite sex partners (Meaney and Stewart, 1981; Thor and Holloway, 1984). Thus, the environmental sensitivity and differential activation to different partners in adulthood optimally position the BMA to regulate age-specific social behaviors in adolescents and adults. However, BMA regulation of social behavior and activation by the IL in adolescence are still unclear.

Ongoing work from the Ferrara laboratory investigates how the IL influences BMA activity from adolescence to adulthood to support transitions in social exploration that are impacted by the environment. Using a combination of fiber photometry and immediate early gene expression of BMA activity, Ferrara's unpublished work shows that BMA activity was elevated during and following adolescent rat social interaction to a greater extent compared with adults. To explore the necessity of the BMA in social development, Ferrara's laboratory used a chemogenetic approach to inhibit the BMA before social interaction, varying partner sex and environmental novelty. This work revealed that BMA inhibition reduced age-specific social interaction in a manner that depended on environmental novelty, suggesting that environmental circumstances guide BMA regulation of age-specific social behavior.

While many afferent projections may activate the BMA, maturational changes of prefrontal cortical-amygdala circuitry optimally positions IL regulation of the BMA in age-dependent changes in BMA function underlying rodent social development. To understand developmental differences in IL-BMA circuitry, Ferrara's laboratory used single-unit *in vivo* extracellular recordings. Unpublished data support the idea that the IL excites the BMA to a greater extent in adolescents relative to adults. Thus, BMA excitation may be directly tied to developmental decreases in approach that are sensitive to environmental novelty and become increasingly dependent on partners into adulthood. Together, this work suggests that IL engagement of BMA neuronal activity may underlie developmental differences in contextually-guided social behavior.

A putative role for paraventricular nucleus of the thalamus in adult social behavior

As individuals mature into adulthood, the navigation of new social environments is challenging, especially in cases where there is limited information or prior experiences to guide behavior. Situations like these, where decisions need to be made quickly, promote the use of heuristics (Tversky and Kahneman, 1974), a behavior selection strategy reliant on readily available cues. Social psychologists have explored how learning, perception, internal state, and context influence the selection of social behaviors (White and Kight, 1984; Bargh et al., 1996; Garcia et al., 2002; van Baaren et al., 2004), demonstrating a variety of ways in which social decisions can be biased. However, the underlying neural circuits and mechanisms modulating adult social decision-making and affiliated behaviors in novel contexts are not fully understood.

Behavioral adaptation to dynamic contexts across species requires multimodal sensory integration at a rapid time-scale in addition to filtering cues and information according to their relevance. Previous studies in rodents have demonstrated that the paraventricular nucleus of the thalamus (PVT) is a central node important for coordinating said responses (Otis et al., 2017; Engelke et al., 2021). In line with this, others have reported PVT involvement in associative learning, the detection of stressful stimuli, and selection of active and defensive behaviors (Beas et al., 2018; Zhu et al., 2018; Ma et al., 2021). However, all of these rodent behaviors were conducted in solitude, leaving the role of the PVT within a social context unknown. Given the PVT's functional and genetic diversity, and, similar to the BMA, its interconnectedness with amygdalar, hypothalamic, and IL regions (Gao et al., 2023; for review, see McGinty and Otis, 2020), it is well positioned to modulate the selection and initiation of social behaviors. Within the rodent PVT, sex steroid hormones may play an especially important role in navigating social context, as these hormones act through hormone receptors via genomic and nongenomic mechanisms to sculpt circuits important for social behaviors (Ervin et al., 2015). Estrogen receptor *Esr1*-expressing neurons, in particular, play a role in a myriad of social behaviors throughout the brain (Lee et al., 2014; Peña and Champagne, 2015; Hashikawa et al., 2017; Fang et al., 2018; Calvigioni et al., 2023) and are directly and indirectly regulated by circulating hormones. Thus, in an attempt to uncover a role for PVT in social contexts, work by Briones and colleagues has begun to interrogate *Esr1*-expressing neurons in the rodent PVT within novel social behavior assays.

Prefrontal control over social dominance via the hypothalamus

The complex neural transitions designed to support adult social decision-making are put to the test when adults encounter the challenge of the social dominance hierarchy. Most social species, from insects to humans, organize into social dominance hierarchies to decrease aggression, conserve energy, and maximize survival for the group (Dwortz et al., 2022). Individuals must consider their social rank in any social encounter and adjust their behavior accordingly. Despite social and dominance behaviors being critical for successful interactions with other group members, it is unclear how the brain encodes social rank (Zhou et al., 2018; Strauss et al., 2022). However, recent work has begun to unravel the neural substrates supporting this complex process.

The rodent medial prefrontal cortex (mPFC) has been implicated in social dominance across species. Optogenetic stimulation of mPFC neurons in mice increases dominance expression and can result in sustained increases in social rank (Zhou et al., 2017). Similarly, in humans playing a game that requires learning the ranks of different players, the rostral mPFC correlates with social rank learning and trans-magnetically stimulating rostral mPFC improves learning (Ligneul et al., 2016). Despite evidence linking mPFC to social dominance, how the mPFC encodes social rank and which circuits mediate this computation are unknown. To tackle this question, Padilla-Coreano et al. (2022) developed a social competition assay in which mice compete for rewards signaled by a tone. This assay allowed for the recording of mPFC single-neuron activity during a trial-based competition and to dissociate responses to competitive success from social rank differences. Padilla-Coreano et al. (2022) also developed a computer vision tool, Alphatracker, to track multiple unmarked animals and found that mPFC population activity is predictive of behavior during the social competition (Padilla-Coreano et al., 2022; Chen et al., 2023). This revealed that social rank and future competitive success are encoded by mPFC population dynamics,

with dominant mice having larger ensembles that encode competition relevant information. Finally, Padilla-Coreano et al. (2022) identified a subpopulation of mPFC cells that project to the lateral hypothalamus that drives dominance behavior during the reward competition. This work collectively links mPFC-hypothalamic circuitry to dominance behaviors underlying mouse social hierarchy formation.

Two studies point to the possibility of the mediodorsal thalamic input being part of this prefrontal circuitry that mediates social hierarchy formation. Prefrontal inputs from the mediodorsal thalamic show plasticity and strengthening after competitive success (Zhou et al., 2017), and silencing the mediodorsal thalamic prevents formation of social hierarchies in mice (Nelson et al., 2019). Although there is no direct evidence, the role of the rodent hippocampus in social memory and of the dorsal raphe nucleus in social stress make them likely to interact with the mPFC during social dominance control. Padilla-Coreano's ongoing work is assessing how this extended circuit may be working together to control social dominance and competitive success.

Neurodevelopment of collective behavior: schooling fish as a case study

Social behavioral dynamics within social units extend beyond hierarchies to group living, where animals form large collectives to jointly navigate their environments as a cohesive unit (Krause and Ruxton, 2002; Sumpter, 2010). These behaviors are a benefit to individuals in groups, using social cues to improve their ability to avoid predators (Sosna et al., 2019; Poel et al., 2022), forage for food (Handegard et al., 2012), and navigate noisy environments (Berdahl et al., 2013). These collective behaviors emerge as a consequence of individual interaction rules, including short-range avoidance, long-range attraction, and alignment with nearest neighbors (Krause and Ruxton, 2002; Couzin, 2009; Sumpter, 2010; Vicsek and Zafeiris, 2012).

Like many social behaviors in vertebrates (Adkins-Regan, 2013), collective movement emerges as animals develop and mature. This has been well studied in shoaling fish, particularly zebrafish (Buske and Gerlai, 2011; Orger and de Polavieja, 2017). Young larval zebrafish at 1 week after fertilization do not show social attraction (Dreosti et al., 2015; Hinz and de Polavieja, 2017; Larsch and Baier, 2018; Stednitz and Washbourne, 2020) but do engage in close-range social avoidance based on vision (Larsch and Baier, 2018; Harpaz et al., 2021) and mechanosensation (Groneberg et al., 2020). By 3 weeks of age, juvenile zebrafish show evidence of social attraction (Dreosti et al., 2015; Hinz and de Polavieja, 2017; Larsch and Baier, 2018; Stednitz and Washbourne, 2020; Harpaz et al., 2021), and preferentially aggregate in shoals of two or more fish. By presenting embedded juvenile zebrafish with biological motion stimuli, Kappel et al. (2022) identified the dorsal thalamus as a region enriched in neurons responsive to biological motion stimuli, and important for the attraction aspect of shoaling.

Shoaling fish, like zebrafish, show robust social aggregation but limited postural alignment, whereas schooling fish also show strong polarization, where nearby animals share common posture and heading direction. While much is known about the ontogeny of the shoaling zebrafish, less is known about the development of schooling and social polarization, despite seminal early work on the development of aggregation and alignment in schooling fish (Shaw, 1960, 1961). *Danionella cerebrum* are a promising model system for optical accessibility of neural processes throughout the lifespan during visually based schooling in the laboratory (Penalva et al., 2018; Schulze et al., 2018; Britz et al., 2021; Hoffmann et al., 2022; Rajan et al., 2022). Lovett-Barron's ongoing work studies the development of schooling in maturing *Danionella*, with a focus on the maturation of social interactions and neural encoding of biological motion.

Conclusion and Future Directions

The last several years have seen an explosion in the field of social neuroscience, supported by technological innovations permitting circuit dissection in freely behaving groups of animals. In parallel, circuit dissection tools have been adapted for early developmental time points to understand how social behavior patterns are formed in early life. Now is the time to synthesize this work across the lifespan to highlight specific mechanisms promoting adaptive transitions in social behavior. Our SfN Symposium collectively covers several developmentally regulated neural mechanisms, including the roles of the sensory cortex, the PFC, amygdala, and the thalamus that all play a role in social behavior from early life through adulthood. This work spans multiple time points and various model organisms to pinpoint specific neural substrates supporting developmentally appropriate social behavior, from sensing and approaching the caregiver to collective behavior in group-living adults.

However, numerous important questions remain concerning the development of adaptive social behavior. For example, does the mPFC-amygdala maturational trajectory align with social rank representation? Do early life experiences shape somatosensory cortical and cortical-amygdala circuits that subsequently influence social experience and aggregation or predispose the animal to be of higher or lower rank? In addition, identifying the mPFC inputs that encode social context may have a lasting impact on social maturation from early life into adulthood that in turn affects group living. To advance our understanding of flexible social behavior, it is clear that it will be necessary to leverage various model species evolved to meet the demands of their specific ethological niche.

Understanding the underlying features of social development and the reciprocal interactions with maturing neural circuitry has wide implications for a variety of neuropsychiatric disorders, where disrupted social behavior is a core feature of compromised mental health, including anxiety and depression. These alterations in social function provide a robust early diagnostic marker of disorders that emerge in later life. Yet, we have little understanding of the ontogeny of social behavior neural circuits or how environmental perturbation at different stages of development impacts emerging behavior. Continued research in this area will help identify the potential neural basis for comorbid sensory abnormalities and social deficits in neuropsychiatric disorders, such as autism spectrum disorder, schizophrenia, and major depressive disorder. Importantly, understanding the neural regulation of social maturation will provide a framework for the development of age-appropriate therapeutics and interventions for individuals with social behavior deficits emerging across the lifespan.

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