



Prefrontal-amygdala circuits in social decision-making

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An increasing amount of research effort is being directed toward investigating the neural bases of social cognition from a systems neuroscience perspective. Evidence from multiple animal species is beginning to provide a mechanistic understanding of the substrates of social behaviors at multiple levels of neurobiology, ranging from those underlying high-level social constructs in humans and their more rudimentary underpinnings in monkeys to circuit-level and cell-type-specific instantiations of social behaviors in rodents. Here we review literature examining the neural mechanisms of social decision-making in humans, non-human primates and rodents, focusing on the amygdala and the medial and orbital prefrontal cortical regions and their functional interactions. We also discuss how the neuropeptide oxytocin impacts these circuits and their downstream effects on social behaviors. Overall, we conclude that regulated interactions of neuronal activity in the prefrontal-amygdala pathways critically contribute to social decision-making in the brains of primates and rodents.

Recent years have seen an increased interest in investigating the neural bases of social cognition from a systems neuroscience perspective^{1–7}, moving away from phenomenologically mapping social functions to brain areas and toward parsing out mechanisms at the level of neural codes, inter-regional coordination, connections and cell types involved. This approach has advanced our knowledge beyond descriptive labels of areas belonging to the ‘social brain’.

Research has focused on examining the neurobiology of social behaviors in several model species including humans, non-human primates and rodents, each with their own advantages and disadvantages (Fig. 1). While the social repertoires of rodents largely involve grooming, sniffing, mating and aggression, this model allows dissection of the molecular and genetic contributions to social behaviors. For example, optogenetics in rodents has highlighted the roles of cell types and neuronal pathways *in vivo*. This technology is not currently optimized for primates, though significant advances are being made⁸. The social repertoires of non-human primates are more complex than rodents, and primate studies provide an opportunity to investigate human-like social cognition in individual neurons. Finally, through functional MRI in humans, blood-oxygenation-level dependent (BOLD) signals can be examined along with self-reported thoughts and feelings.

An integrative approach, considering research from distinct model systems, can be invaluable for understanding the neurobiology of social cognition. While there are vast interspecies differences in behavioral repertoires and investigative methodologies (Box 1), there are also significant commonalities in fundamental processes. In social decision-making, these processes can be broadly divided into the following stages: (i) social perception; (ii) social learning, valuation and reward; and (iii) social action or response. Of course, social processes are complex, and these stages are iterative and continuous. Still, organized by these themes, this review integrates literature across humans (Figs. 1a, 2a, 3a and 4a,b), non-human primates (Figs. 1b, 2b and 3b) and rodents (Figs. 1c, 2c, 3c and 4c–e) to discuss the neurobiological substrates in these

broadly defined aspects of social decision-making. We focus on the amygdala and prefrontal cortex (PFC) subregions, as well as on the functional interactions in the PFC–amygdala pathways (see Box 2 for an anatomical overview). We also examine the contribution of the neuropeptide oxytocin (OT) in the PFC–amygdala pathways under an integrative framework of OT in multiple stages of social decision-making⁹ (Figs. 4 and 5).

Social perception

The identification and recognition of a conspecific is critical for contextualizing social decisions. Depending upon an animal’s ethology, the process of social perception varies drastically. Social perception in primates relies heavily on vision, whereas in rodents it is primarily achieved by olfaction. In particular, the amygdala and PFC subregions, including the medial PFC (mPFC) and orbitofrontal cortex (OFC), have been found to play major roles in social perceptual processes in the primate and rodent brains^{10–14}.

Recognizing and perceiving social information. Faces and facial expressions are central to social recognition in primates¹⁵ and impact social decisions. Evidence supporting face selectivity exists in the hierarchical network of ‘face patches’ in the inferior temporal cortex and OFC of macaques, where the overwhelming majority of neurons within each patch has been shown to fire preferentially to faces and to modulate firing based on facial features and identity^{16–18}. In humans, the fusiform face area, in addition to face-selective prefrontal and temporal regions, is purported to be specialized for face perception^{15,19} (also see ref. ²⁰). In rodents, conspecific odors are often used to study social perception, and neurons in the medial amygdala have been reported to fire differentially to males, females, pups or non-social controls^{21,22} (Fig. 2c). Intriguingly, sexual experience and steroid signaling enhanced the neural discriminability of these stimuli²², suggesting an increased need to identify and discriminate between sexual partners with increased mating. In monkeys, many amygdala neurons have been shown to alter activity in response to faces¹³, but also to other variables like reward amount

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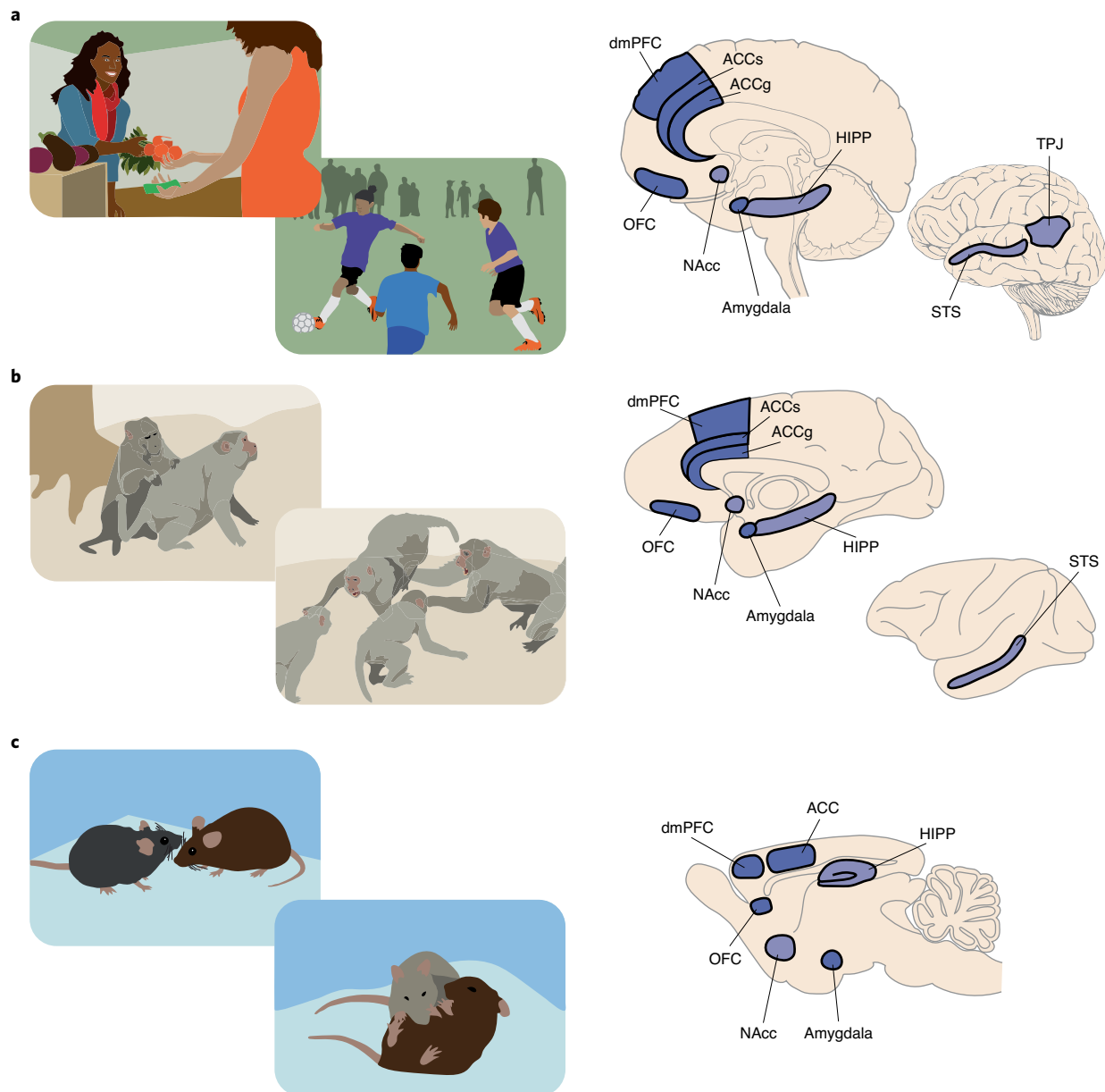


Fig. 1 | Behavioral ecology of social interaction and brain regions commonly recruited by social behaviors in humans, non-human primates and rodents. **a–c**, Behavioral illustrations (left) depict selected social interaction scenarios for humans (**a**), rhesus macaques (**b**) and mice (**c**), exhibiting different levels of complexity in social interactions. Brain illustrations (right) depict key brain regions that are discussed in this review (darker contrast) and other related regions briefly mentioned in connection (lighter contrast) that are implicated in various social behaviors in each species. TPJ, temporal parietal junction; HIPP, hippocampus. Social operations in these brain regions are being actively investigated at multiple neurobiological levels across humans, non-human primates and rodents.

and stimulus category¹⁴, suggesting that these individual neurons process social and non-social information in concert²³.

Lesion studies have been informative for testing the necessity of the amygdala and PFC subregions in social functions^{24–26}. For instance, monkeys with excitotoxic bilateral amygdala lesions spent less time looking at other's eyes compared to controls²⁷, suggesting a causal role of the amygdala in social attention. In the human brain, it has been reported that patient SM, who had bilateral amygdala lesions, performed poorly on recognizing emotion, particularly fearful expressions²⁸. Later, it was found that an instruction to attend to the eyes of stimuli restored her ability to judge emotion, suggesting that the amygdala is necessary for acquiring appropriate social information for emotion recognition²⁹. The amygdala also seems to

process perception of personal space, as amygdala BOLD activity in humans was shown to covary with perceived interpersonal distance, in which patient SM also exhibited impairments³⁰.

Categorizing and inferring from social information. Differentiating others by social status, familiarity, identity or other individual-level information helps constrain social decisions. In Capgras syndrome, study participants exhibit delusions in which familiar individuals have been replaced by imposters, possibly resulting from disrupted interactions between the amygdala and the inferior temporal cortex linked to face processing³¹. In mice, immediate early gene-based connectivity revealed that protein synthesis in the basolateral amygdala, mPFC, the anterior cingulate cortex

Box 1 | Important considerations when comparing across species and different methodologies

Comparing results across different species to investigate the neural bases of species-typical social behaviors can be extremely valuable. However, one must carefully account for distinct ethology and common methodologies used in different species. Each methodology and model system comes with its own advantages and disadvantages. The differences in social repertoire between species vary greatly, complicating cross-species comparisons. For example, while macaques and humans primarily use facial features for visual recognition of conspecifics, rodents predominantly use odor. This difference in the principal sensory modality involved in social perception limits direct comparisons of neurobiological processes during social recognition between primates and rodents.

In studies of non-human primates, the sample size of data is derived from the number of cells recorded while the number of animals studied is usually small (typically two), so correlations between neural activity and behavior need to be replicated over multiple studies to learn about any neural effects on social relationships and individual differences. The field of functional magnetic resonance imaging (fMRI), most commonly used in humans, has been criticized for low sample sizes in earlier studies, lack of replicability, inflated false positives¹³⁰ and dependence on particular analytic frameworks¹³¹, though constant progress is being made toward higher field-wide standards. For example, a newer approach involves scanning individuals at multiple time points, rather than just once, to establish more robust databases albeit with smaller numbers of unique brains^{132,133}. Still, fMRI provides a coarse image of a proxy for neural activity, and the difference in the temporal scales of the BOLD response and neuronal firing rates is considerable. Moreover, signal-to-noise ratios in fMRI signals are highly sensitive to geometric distortion and nearby draining veins, complicating the interpretation and comparison of BOLD responses in different cortical and

subcortical regions. For example, because of the anatomical locations of the OFC and the amygdala, BOLD signals obtained from these regions are particularly susceptible to such problems and may lead to biased interpretations in favor of large-scale signal changes. Similar concerns also exist for functional near-infrared spectroscopy (fNIRS), which also utilizes BOLD signals, though fNIRS presents opportunities to easily study face-to-face or group-based interactions coupled with easily wearable head caps. While other techniques such as electroencephalography (EEG) and magnetoencephalography (MEG) are also employed, with the advantages of much higher temporal resolution than fMRI or fNIRS, these techniques come with significantly poorer spatial resolution. Neuronal recording in people being treated for epilepsy provides a unique opportunity to obtain single-neuron electrophysiological data in humans, but comes with the inherent confound of a biased sample population and difficulty controlling desired experimental variables.

Cortical and subcortical lesions have also been frequently used in animal models for testing causal social functions of specific brain regions. However, critical caveats of lesion studies are that the downstream effects of lesioning are unknown; lesions induce adaptation and plasticity; and directly comparing studies is challenging due to differences in surgical techniques used to create focal lesions (excitotoxic vs aspiration). Indeed, most early lesions studies have employed aspiration lesions, which are prone to affecting fibers of passage, making it difficult to assign region-specific effects¹³⁴. Moreover, lesion studies have found factors like age at the time of lesioning, familiarity with conspecifics and the social structure at the time of experiments to influence the directionality and extent of changes in certain social behaviors^{24–26}. Still, lesion studies provide valuable evidence testing the necessity and sufficiency of a neural region's involvement in cognitive and behavioral processes¹³⁵.

(ACC) and hippocampus mediates remembering conspecifics³². Emotional discrimination is another important function mediated by the amygdala and mPFC. In mice, OT-induced neuromodulation in the central amygdala underlies the ability to discriminate emotional states of conspecifics³³. In macaques^{13,34} and neurosurgical patients^{35,36}, activity of neurons in the amygdala (and additionally ACC in macaques) was shown to categorize facial expressions, even when expressions were ambiguous^{35,36}. Human fMRI studies have extended the amygdala's role in categorizing socioemotional variables to categorizing individuals. BOLD responses in the amygdala were found to differentiate direct-gaze faces of racial in-group versus outgroup members³⁷. Further, amygdala BOLD responses were found to index subjective and implicit trustworthiness of faces^{38,39}. Evidence thus indicates a role for the amygdala in categorizing others, even based on incomplete information, implicating this region in facilitating social bias.

Inferring an individual's rank in the social hierarchy is another essential function of social perception, as quickly incorporating this information into decision-making can be critical for survival. The amygdala and mPFC have been shown to track the ranks of both oneself and others. BOLD signals from the human amygdala were found to correlate with the social rank of faces⁴⁰, even when the hierarchy was unstable⁴¹. Moreover, when learning the ranks of self and others, BOLD activity in the human mPFC correlated with hierarchy-updating learning⁴⁰. Further, psychophysiological interaction revealed increased functional connectivity between mPFC and the amygdala for updating estimates about one's hierarchical position⁴⁰, suggesting that mPFC–amygdala coordination might

facilitate social inference. The link between the amygdala and social status perception has also been found in non-human primates^{42,43} and rodents⁴⁴. For example, as a consequence of altered social hierarchies in macaques, the amygdala exhibited an increase in gray matter with increasing social status⁴².

Another important consideration is the size of social network, as larger groups require greater 'neural bandwidth' to recognize and identify others, track increasingly complex information about social ranks and infer meaningful information from frequent social encounters. In macaques, gray matter in the mid-superior temporal sulcus (STS) and rostral PFC was found to increase in accordance with increased social network size⁴⁵. Increasing group size also enhanced resting-state BOLD correlations between mid-STS and the gyrus region of ACC (ACCg) in monkeys⁴⁵, suggesting that larger social networks recruit communications between social perceptual processing in mid-STS and social valuation–reward processing in ACCg^{46–48}. Changes in functional connectivity in these regions have similarly been found in humans for social network size⁴⁹ (Fig. 3a) and may be linked to socioemotional understanding^{50,51}. Overall, PFC subregions and the amygdala in humans, non-human primates and rodents constitute crucial nodes in the networks that enable social perception and support the initial stages of social decision-making.

Social learning, valuation and reward

Social information leads to value judgements about potential rewards and punishments for self or others, which then are used to calculate future actions. These processes can be modeled in a

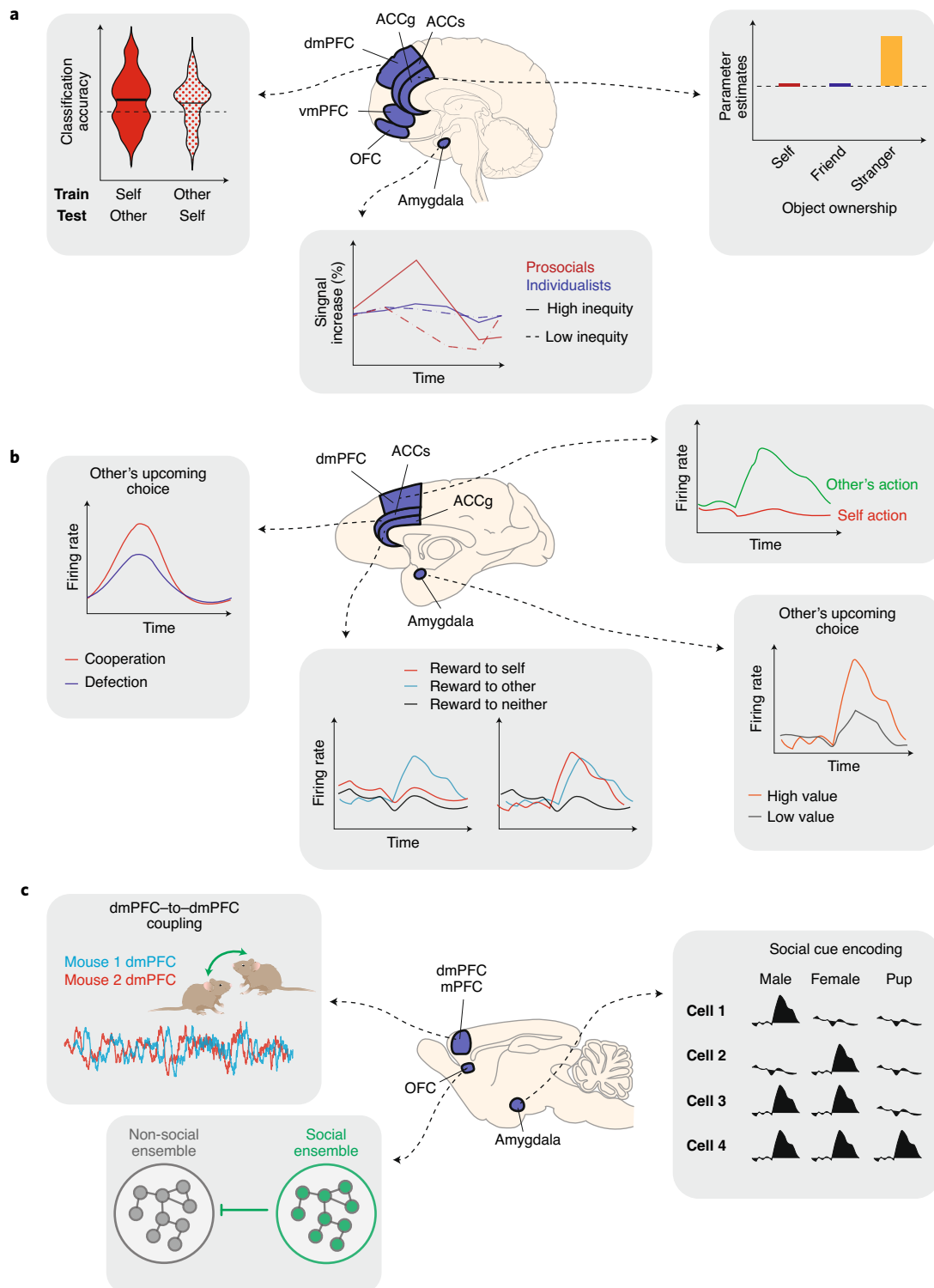


Fig. 2 | Illustrations of selected results demonstrating the importance of PFC and amygdala in social behaviors. Across humans, macaques and mice, summary diagrams illustrating selected findings from particular studies are shown with corresponding references. **a**, Left: in humans, dmPFC BOLD activations tracked subjective value for making decisions for self as well as on behalf of another individual in a shared manner⁶⁴. Middle: BOLD signals in the human amygdala showed different response patterns to high versus low inequity in reward outcomes between self and another individual for prosocial individuals⁶⁸. Right: BOLD activations in ACCg in the human brain signaled objects belonging to strangers but not to self or friends⁶¹. **b**, Left: neuronal activity in a population of ACC neurons in monkeys was found to predict whether a partner monkey was going to cooperate or defect in a prisoner's dilemma task⁶⁵. Middle: neuronal activity in a population of ACCg neurons either exclusively signaled conspecific's reward outcome or signaled the reward outcome of self or other in a comparable fashion⁴⁶. Top right: many neurons in dmPFC selectively increased activity to encode other's action in a turn-taking task between two monkeys⁷¹. Bottom right: activity of a group of amygdala neurons in monkeys was found to encode conspecific's upcoming choice when observing other's value-guided actions⁵⁷. **c**, Top left: during social interactions, mice exhibited dmPFC-to-dmPFC neuronal synchrony in behaviorally relevant manners⁹⁶. Bottom left: in the mouse OFC, neuronal ensembles selective for social behavior were shown to inhibit neuronal ensembles selective for non-social behavior¹². Right: neurons in the mouse amygdala were shown to discriminate social cues²¹.

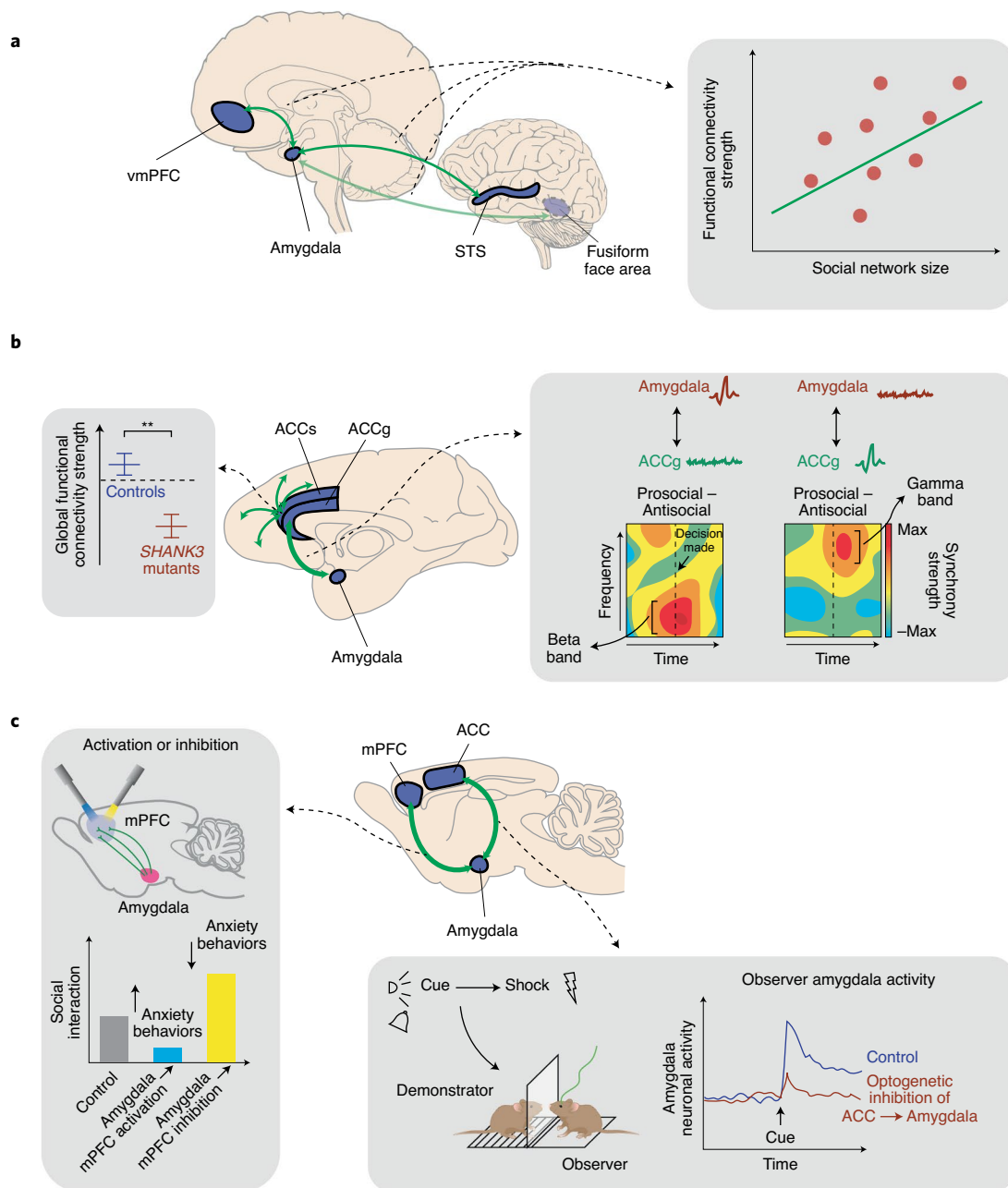


Fig. 3 | Illustrations of selected results demonstrating the importance of PFC-amygdala interactions in social behaviors. **a**, In humans, resting-state functional connectivity measures between the amygdala and vmPFC, between the amygdala and STS, and between the amygdala and the fusiform face area were shown to index individual participants' social network size⁴⁹. **b**, Macaques with *SHANK3* mutation, a model system frequently used to study autism spectrum disorder based on disrupted synaptic communication, exhibit abnormal global functional connectivity patterns involving ACC, among other regions⁹⁵. In addition, coherence between spiking activity and local field potential (LFP) signals between ACCg and the basolateral amygdala was enhanced during prosocial decisions compared to antisocial decisions in distinct frequency channels⁴⁷. **c**, In mice, optogenetic activation of basolateral amygdala (BLA) neurons innervating mPFC reduced social interaction (but increased anxiety behaviors), whereas inhibiting the same projection neurons enhanced social interaction (but decreased anxiety behaviors)⁹⁰. Moreover, ACC input to BLA neurons was found to be necessary for BLA neurons to signal observational fear cues, and optogenetically inhibiting these BLA-projecting ACC neurons prevented observational fear learning in mice⁷⁷.

value-based decision-making framework and serve as broad heuristics for social decision-making. However, definitional boundaries between these constructs are ambiguous, as they are often interdependent. Still, considerable anatomical, functional and genetic evidence suggests that many neural processes are largely conserved across species^{1,7,52,53}.

There are close conceptual and theoretical ties between social and non-social decision-making at the levels of value and reward

processing. While social and non-social stimuli are perceptually distinct by definition, value and reward related processes arising from such social and non-social stimuli are both eventually guided by goal-directed and internal representations. One theory proposes that neural valuation processes are co-opted in social contexts, arguing against social specializations^{1,2}. In this framework, social stimuli are themselves rewarding and recruit neurons that otherwise engage in non-social valuation and decision-making. For instance, a recent

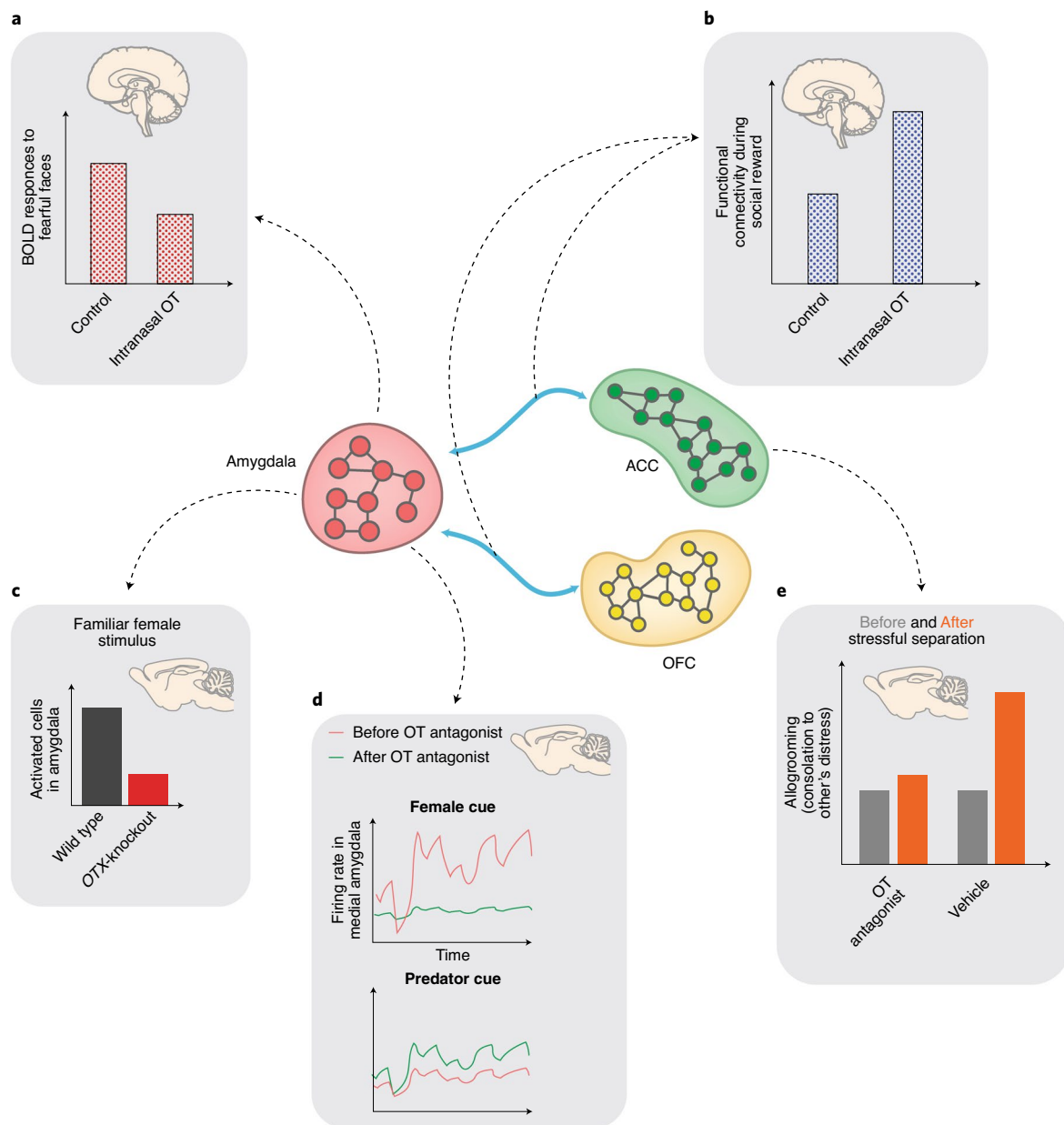


Fig. 4 | Illustrations of selected findings showing neuromodulation by OT in PFC-amygdala pathways. a,b, Intranasally administered OT in humans was shown to **(a)** attenuate amygdala BOLD responses to fearful faces¹¹⁴ and **(b)** modulate OFC-amygdala and ACC-amygdala functional connectivity strength when perceiving a socially rewarding stimulus (infant laughter)¹¹⁷. **c,** OT function in the medial amygdala is required for social recognition and for sex discrimination of social cues in mice¹²⁰. **d,** Blocking OT function in the medial amygdala in male mice reduced the processing of female cues but increased processing of predator cues¹²². **e,** In mice, OT processing in ACC is involved in partner-directed grooming behaviors to a conspecific under distress¹²⁴.

study found that the activity of the same amygdala neurons covaried with both reward value and the hierarchical rank or facial expressions of conspecifics, lending support to a common-currency valuation hypothesis⁴³. An alternative theory postulates that the brain developed socially specialized substrates, suggesting that the neural mechanisms underlying social and non-social decision-making are distinct^{1,2}. For example, the ACCg, compared to the sulcus of ACC (ACCs), is more specialized in encoding the reward outcome of a conspecific following prosocial decisions, compared to encoding one's own reward outcome^{4,46}. Additionally, in the aforementioned social hierarchy study, in neither OFC nor in ACC did neurons exhibit shared responses between social and non-social stimuli⁴³; this result is supported by another study reporting that

non-overlapping OFC neurons were modulated by juice value or the hierarchical rank of conspecific⁵⁴. Evidence for both hypotheses exists, but the answer may vary by brain region. To consolidate different views, a recent effort provided a novel framework regarding the 'social brain' by proposing that a process can be socially specific at different levels of explanation. That is, social specificity can be found at the algorithmic level for encoding a specific algorithm or rule (for example, reinforcement learning) that is similar or different between social and non-social domains⁵⁵. Social specificity can also be found at the implementational level where the same or different brain areas, circuits or cells perform social and non-social functions⁵⁵. Therefore, it is important to consider different levels of explanation at which social specificity operates in the brain.

Box 2 | Anatomical substrates of PFC–amygdala interactions

Neurons in the PFC, especially in the mPFC and the OFC, strongly project to the amygdala and also receive substantial projections from the amygdala^{136,137}. These pathways are evolutionarily conserved, as they are found in humans, non-human primates and rodents^{1,2,6,7,138}. The bidirectional communications between the amygdala and the PFC areas are theorized to mediate synergistic interactions to enable goal-directed behaviors based on affective and reward-related information¹³⁹. In addition to the direct amygdalocortical pathway, a distinct population of neurons in the amygdala also influences PFC through an indirect, amygdalothalamic pathway through the mediodorsal thalamus in both non-human primates and rodents¹⁴⁰. However, it remains to be elucidated how the amygdalocortical and amygdalothalamic pathways differentially contribute functionally to behaviors.

Projections from PFC areas to the amygdala predominantly originate from layer V, and the amygdala reciprocally projects to layers I/II and V/VI of PFC areas^{137,141}. In the amygdala, the basolateral subdivision, consisting of the lateral, basal and accessory-basal nuclei, is predominantly involved in bidirectional communications with PFC areas¹³⁶. The greatest number of projections from the amygdala to PFC areas is present in the orbital and medial PFC regions, including the rostral ACC^{137,141}. Furthermore, among the projections between the amygdala and PFC, there are differentiated anatomical projection patterns depending on PFC subregions, possibly laying the grounds for, or reflecting, functional differences of these connections. ACC neurons project more substantially to amygdala than vice versa, while amygdala neurons have larger and denser projections to OFC than to ACC¹³⁷. Among different PFC areas, mPFC and the medial aspects of OFC are inter-connected with all known limbic brain structures¹³⁶. These subregions of PFC receive much denser and more widespread anatomical connections from the amygdala, whereas lateral PFC areas and lateral and posterior aspects of the OFC instead receive most strong projections from parietal and temporal areas¹⁴². These anatomical characteristics suggest that coordination of neural activity in the limbic network involving the amygdala, mPFC and OFC integrate affective and reward information from the amygdala¹⁴³ (and from other subcortical limbic structures, such as the nucleus accumbens) with goal-directed and principally agent-specific processes by medial and orbital PFC regions⁵ to guide learning and decision-making in social contexts.

Agent specificity of decision variables. Learning from other's actions and outcomes is imperative for mastering one's environment, and in social species it is crucial for survival to balance information obtained by monitoring others against exploiting non-social resources or information⁵⁶. Integrating others' valuation and choices helps to predict others' future actions, and this provides valuable information for adapting one's own future action. Therefore, in social decision-making, the brain must track both self and others' decision variables, including reward probability, choices and outcomes. Considerable evidence implicates the amygdala, mPFC and OFC in value-based computations for social decision-making². Moreover, PFC subregions involved in learning and decision-making—dorsomedial prefrontal cortex (dmPFC), ACC, and OFC—display consistent intrinsic functional connectivity with the amygdala in both humans and non-human primates³⁷, suggesting evolutionarily well-conserved decision-making networks in primates.

The primate ACCg is a key node in processing other-referenced decision variables⁴. Single-neuron evidence for this was obtained

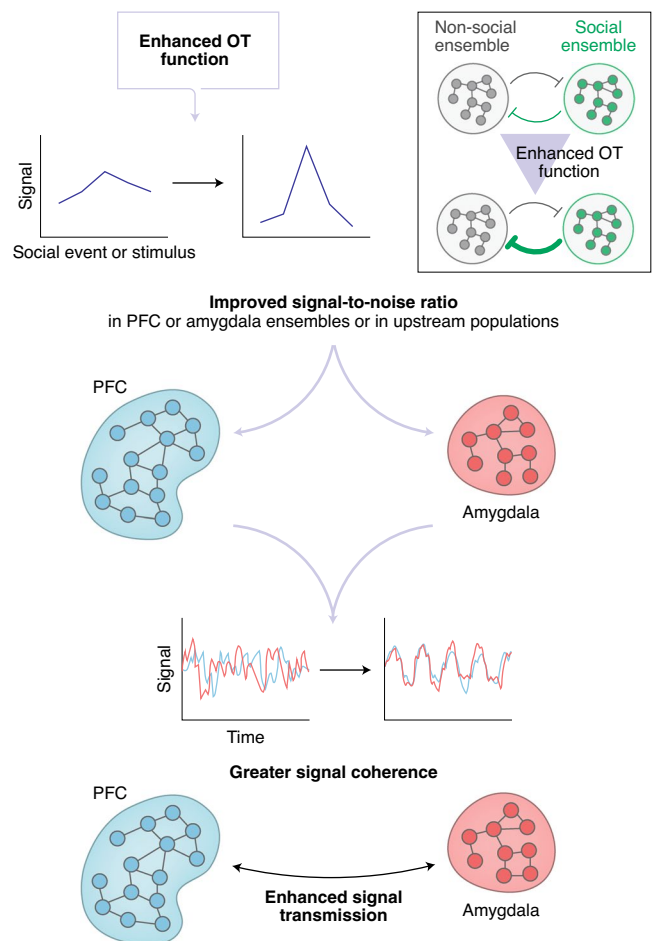


Fig. 5 | A hypothesized mechanism by which OT may enhance social functions in the PFC–amygdala pathways. OT may improve signal-to-noise ratio of neural signals¹²⁵ either in amygdala and PFC neural populations or in neural populations upstream to amygdala or PFC. Moreover, when there are mutual inhibition processes between neural ensembles linked to non-social behaviors and neural ensembles linked to social behaviors, OT may strengthen the inhibition of non-social ensembles by social ensembles (inset). As a result, OT would enhance neural signal transmission and possibly strengthen synchrony across neural ensembles between amygdala and PFC subregions. According to this hypothesis, OT would therefore enhance social functions that critically depend on PFC–amygdala interactions. Note that this mechanism is likely to be a general means by which many types of neuromodulators modulate various cognitive functions in multiple neural circuits.

in spike recordings from ACCg, ACCs and OFC during a social reward allocation task in which an actor monkey chose to deliver rewards to himself, a conspecific or no one. A greater proportion of ACCg neurons, compared to ACCs or OFC, signaled the reward outcome of the conspecific either exclusively or together with the reward outcome of self⁴⁶ (Fig. 2b), suggesting a role of ACCg in other-referenced reward processing. The necessity of ACCg for other-referenced reward processing and social valuation has also been examined. Upon measuring response time to reach for a reward in the presence of social and non-social stimuli, lesions to ACCg, but not ACCs or OFC, resulted in behaviors consistent with abnormal social valuation⁴⁸. A recent lesion study using a modified social reward allocation task found that excitotoxic lesions to the whole ACC in monkeys led to a specific disruption in learning a stimulus–reward association when the reward was for a conspecific monkey but not when it was for self⁵⁸. However, it remains to be

tested whether the lesion to ACCg, but not ACCs, was the reason for this other-referenced learning deficit. Research in humans also supports a role of ACCg in other-referenced processing. BOLD responses in ACCg were found to correlate with the value of others' rewards and prediction errors, and this relationship was moderated by trait-level empathy^{59,60}. Further, when participants learned about ownership of picture stimuli, ACCg signaled stranger's ownership, while ACCs exhibited greater activations to stimuli owned by self rather than others⁶¹ (Fig. 2a). Such findings^{1,4,55} support the notion that ACCg is specialized for other-referenced valuation and reward.

Self–other processing also engages other PFC subregions. In the social reward allocation task, the majority of OFC neurons were found to exclusively signal self reward⁴⁶, suggesting a role for OFC in self-referenced reward and modulations by social context. In line with this, activity of neurons in the monkey OFC was found to covary with reward size for self and was modulated by the identity and rank of the monkey with whom the reward was shared⁶², documenting one way by which reward signals in OFC are modulated by social context. Moreover, in dmPFC, 'self-type' and 'other-type' neurons were found to scale activity according to reward magnitudes exclusively for self and a conspecific, respectively⁶³. The human dmPFC and the ventromedial prefrontal cortex (vmPFC) are also implicated in self–other processing. When human participants made decisions on behalf of another, BOLD signals in dmPFC and vmPFC covaried with the decision value for the other^{64,65}. However, dmPFC, but not vmPFC, generalized subjective value representations between self and other based on classification accuracy⁶⁴ (Fig. 2a). Therefore, both dmPFC and vmPFC seem to compute other-referenced decision values, but these regions may differ on how they relate self and other.

The amygdala also signals reward variables for self and other. When monkeys made decisions for self or other, activity in basolateral amygdala neurons tracked reward value for both agents^{66,67}. However, it remains unknown how individual differences in social preference would affect such shared value tuning. Indeed, individual differences in social preference in humans might be mediated by the amygdala. For example, amygdala BOLD responses of individuals with prosocial orientation, but not individualists, were found to covary with the reward inequity between self and other⁶⁸ (Fig. 2a) (see also refs. 37–39). Future research should examine whether self–other processing in the amygdala is shaped through learning.

Learning from others. Monitoring and learning from others is essential for navigating social life⁶⁹. When monitoring other's choices, a subset of amygdala neurons in monkeys predictively tracked upcoming value-based choices of another monkey⁶⁷ (Fig. 2b). In humans, patients with amygdala lesions were unable to learn who to trust from observing others' decisions in a trust game⁷⁰. Evidence also supports a role of dmPFC in social monitoring: during turn-taking interactions that required monitoring others' choices, many neurons in the monkey dmPFC encoded others' actions or errors^{71,72} (Fig. 2b), even when monitoring the actions of a human experimenter⁷³.

Across species, the role of the ACC in observational learning is well-conserved^{74,75}. In observational fear learning in rodents, an observer learns an association between a cue and electric shocks by observing the freezing of a demonstrator. After observation, the observer exhibits freezing to the same cue without ever experiencing the shocks. Inactivating ACC in mice or genetically reducing ACC activity was shown to impair this learning⁷⁶. A subsequent study found that a population of ACC neurons projecting to the basolateral amygdala causally contributed to acquisition, but not recall, of observational fear learning⁷⁷ (Fig. 3c). It remains to be tested, however, whether this pathway also mediates learning from others' positive outcomes, for example, in observational reward learning. The primate ACC is similarly implicated in social

learning. As mentioned earlier, ACC lesions in monkeys led to a deficit in other-referenced reward learning⁵⁸. In humans, BOLD signals in ACCg were shown to be correlated with learning from the perspective of another individual. When evaluating another's advice for making reward-maximizing decisions, the volatility associated with learning from a confederate was signaled by ACCg⁷⁸. In teaching, ACCg BOLD activity in teachers also signaled prediction errors of student's learning⁵⁹. Therefore, ACC in both primates and rodents seems to be important for learning from, and perhaps also about, others.

Social behaviors require integrations of multiple cognitive and affective operations that necessitate interareal coordination. Functionally relevant regions exhibit correlated activity at temporal scales ranging from milliseconds to several seconds⁷⁹. Oscillatory coupling is proposed to facilitate cognitive functions by enabling interactions within and across local circuits^{80,81}. A study in prairie voles provides an example of how interregional coordination promotes social decision-making. This study found that cross-frequency coupling between mPFC and the nucleus accumbens (NAcc), a region implicated in pair-bonding in monogamous voles⁸², facilitated affiliative behaviors in females and promoted social bonding⁸³, indicating a role of interregional coordination involving mPFC in species-typical social functions. In addition, reciprocally connected pathways between the amygdala and mPFC–OFC regions have been implicated in fundamental aspects of valuation, learning and decision-making⁸⁴. In concert with the significance of mPFC and the amygdala in social decision-making, a recent study found that oscillatory interactions between these areas guided prosocial decision-making. When monkeys made decisions on whether or not to deliver juice rewards to a conspecific, neuronal synchrony between the amygdala and ACCg was enhanced for making prosocial decisions but suppressed for antisocial decisions⁴⁷ (Fig. 3b). This interaction was frequency-specific, occurring in beta and gamma frequency bands depending on the area contributing the spikes (Fig. 3b), and exhibited increased directionality from the amygdala to ACCg for prosocial decisions⁴⁷. Although there is still much to learn, existing evidence supports a specialized role of interaction dynamics between mPFC and subcortical regions, such as the amygdala and NAcc, in facilitating social decision-making.

Social action or response

The final step in social decision-making involves selecting an action or response that maximizes reward or minimizes harmful consequences. Strategic social decision-making has been studied using interactive games. During a prisoner's dilemma task, spiking activity in the primate ACC predicted whether the opponent's upcoming decision was to cooperate or defect⁸⁵ (Fig. 2b). Microstimulation of these neurons reduced the number of cooperative choices following a cooperative choice from the other player, suggesting a causal role of ACC in reciprocal cooperative interactions⁸⁵. In a prisoner's dilemma task in humans, mutual cooperation activated OFC, which could suggest that OFC has a role in processing reinforcing aspects of cooperation^{86,87}. NAcc and the caudate nucleus were also co-activated with OFC, highlighting how mutual cooperation recruits reward-related networks⁸⁷.

In rodents, social responses typically involve affiliative or aggressive behaviors, in which both the amygdala and PFC are implicated. For example, aromatase-expressing⁸⁸ as well as GABAergic and glutamatergic neurons⁸⁹ in the mouse medial amygdala regulate aggression, potentially by moderating anxiety-like behaviors. Interestingly, GABAergic and glutamatergic populations oppositely regulated social and repetitive non-social behaviors⁸⁹, suggesting an antagonistic mechanism of social and non-social behaviors implemented via distinct cell types. As another example in mice, selective inactivation of amygdala neurons projecting to mPFC increased social interactions but decreased anxiety-like behaviors, whereas

the reverse behavioral pattern was observed when this pathway was activated⁹⁰ (Fig. 3c). Evidence for a regulatory association has also been found in the mouse OFC: activation of socially selective OFC neuronal ensembles led to inhibition of feeding behavior¹² (Fig. 2c), again suggesting that social and non-social behaviors might be interrelated in certain circuits. Taken together, these findings support the novel hypothesis that social and non-social behaviors might be tightly regulated in an antagonistic manner in the brain. Based on potential competition between functional signals from separate but spatially proximate population of neurons, we speculate that during evolution, cells specific to social behavior were repurposed from non-social cells in the overlapping population and that the resulting two populations developed a mutually inhibitory relationship because of the functional tradeoff or behavioral conflicts. It is worthwhile to note that antagonistic implementations have also been found between two opposing social behaviors: in the ventrolateral subdivision of the mouse ventromedial hypothalamus, a population of neurons that are activated during male aggression have been found to be inhibited during mating⁹¹. Therefore, such an antagonistic regulation may reflect a more general implementational principle in the brain between two functionally conflicting behaviors.

Evidence also suggests that intricate balance within neural activity, such as that mediated by excitation–inhibition balance, may critically regulate social functions. Increasing, but not decreasing, the excitation–inhibition balance in mPFC resulted in reduced exploration of a novel mouse over a wire mesh cup in a three-chamber task, suggesting impaired social preference⁹². Parvalbumin interneurons in the mouse mPFC seem to contribute to the excitation–inhibition balance, as they selectively increased firing for interacting with a novel conspecific over a novel object⁹³. Important insights into how social functions in the PFC–amygdala pathways are regulated by neural activity have also come from transgenic animal models with social deficits. Mice lacking the autism-linked gene *CNTNAP2*, which encodes a cell-adhesion protein, show cortical hyperactivity and impaired social behavior, and optogenetic stimulation of mPFC parvalbumin interneurons restored both the excitation–inhibition balance and the social exploration deficit⁹³.

The importance of mPFC–amygdala interactions in social behaviors is also apparent in animal models of autism spectrum disorder. For example, *Pten*^{+/-} mice, which lack one copy of an autism-linked gene important for neuronal arborization, show impaired social preference that is driven by both the anatomical hyper-connectivity between mPFC and the basolateral amygdala and the hyperactivity in these brain regions⁹⁴. In non-human primates, transgenic cynomolgus macaques with a mutation in *SHANK3*, which encodes a synaptic protein, showed impairments in social interaction as well as dysregulated global BOLD connectivity involving dmPFC and rostral ACC⁹⁵ (Fig. 3b). These findings further reinforce the notion that mPFC–amygdala interactions regulate social behaviors.

Finally, the impact of social interactions extends beyond affecting the neural activity of just one recorded individual. Exciting recent studies have reported that two socially interacting mice⁹⁶ (Fig. 2c) or bats⁹⁷ show interindividual PFC synchronization that is further modulated by social context, a phenomenon also observed in human research⁹⁸. These studies in mice and bats document the first direct evidence of inter-brain synchrony at the neuronal level in social interactions. Continued research into the contributions and necessity of brain-to-brain coordination will enhance our understanding of the neural substrates of social interaction.

Oxytocin modulations in amygdala and PFC functions

Multiple neuromodulators shape social behaviors, including OT, vasopressin and testosterone, among others. OT and vasopressin have been studied extensively in the context of affiliative and prosocial behaviors⁹⁹, whereas testosterone has long been regarded

as a major contributor to aggression and competition, possibly for the purpose of seeking and maintaining social dominance¹⁰⁰. However, it remains largely unclear at which stages or aspects of social decision-making these neuromodulators exert their effects. What is clear is that no single neuromodulator system works independently of others. In this section, we discuss how OT regulates social decision-making in the amygdala and mPFC.

Role of OT in different aspects of social decision-making. OT is an evolutionarily conserved neuropeptide with major functions in birth, parental and non-parental behaviors¹⁰¹. OT was repurposed during evolution from non-social functions, such as water regulation and anxiolysis, to social functions, such as parenting and social bonding^{1,99,102}, and the distributions of OT receptors in the mammalian brain generally support species-typical social functions¹⁰³ (Box 3).

OT seems to act on multiple aspects of social decision-making⁹. For example, at a sensory stage, OT processing in mice sharpens the tuning of auditory cortical neurons to pup calls and promotes pup-retrieval decisions by increasing the saliency of acoustic stimuli triggered by the calls¹⁰⁴. At a more perceptual stage, OT influences the representation of socioemotional stimuli in the human amygdala by attenuating the response to fearful expressions^{105,106} or increasing the response to happy expressions¹⁰⁵. At the valuation stage, OT-mediated plasticity in NAcc is necessary for the development of reinforcing properties of social interaction in mice¹⁰⁷, and OT in NAcc is necessary for pair-bonding in monogamous voles⁸². In macaques, intranasal OT was shown to amplify social decision preference and attention to others^{108–110}. In humans, OT-induced changes in social attention were associated with increased functional connectivity between amygdala and the superior colliculus¹⁰⁵. Thus, rather than conceptualizing OT as being specific to just one category of social function, it is more appropriate to consider OT as impacting different aspects of social decision-making processes⁹.

Influence of OT in social functions of amygdala and mPFC.

Several studies have examined how intranasal OT affects BOLD signals in the amygdala and PFC subregions in humans. Although intranasal OT administration increases OT concentrations in the primate brain¹⁰⁸, with this method it is difficult to control the amount of exogenous OT reaching the brain or to study region-specific effects. Concerns also exist with respect to replicability, effect size, confounding factors due to changes in peripheral OT levels and lack of proper dose–response quantifications^{111,112}. With these caveats in mind, studies combining intranasal OT and socioemotional tasks have found that OT alters BOLD responses in limbic regions implicated in social behaviors, including insula, OFC, ACC, mPFC, hippocampus and hypothalamus¹¹³. Among those, the most consistent neural effect from intranasal OT seems to be its effect on altering amygdala BOLD signals to socioemotional stimuli^{105,106,114} (Fig. 4a).

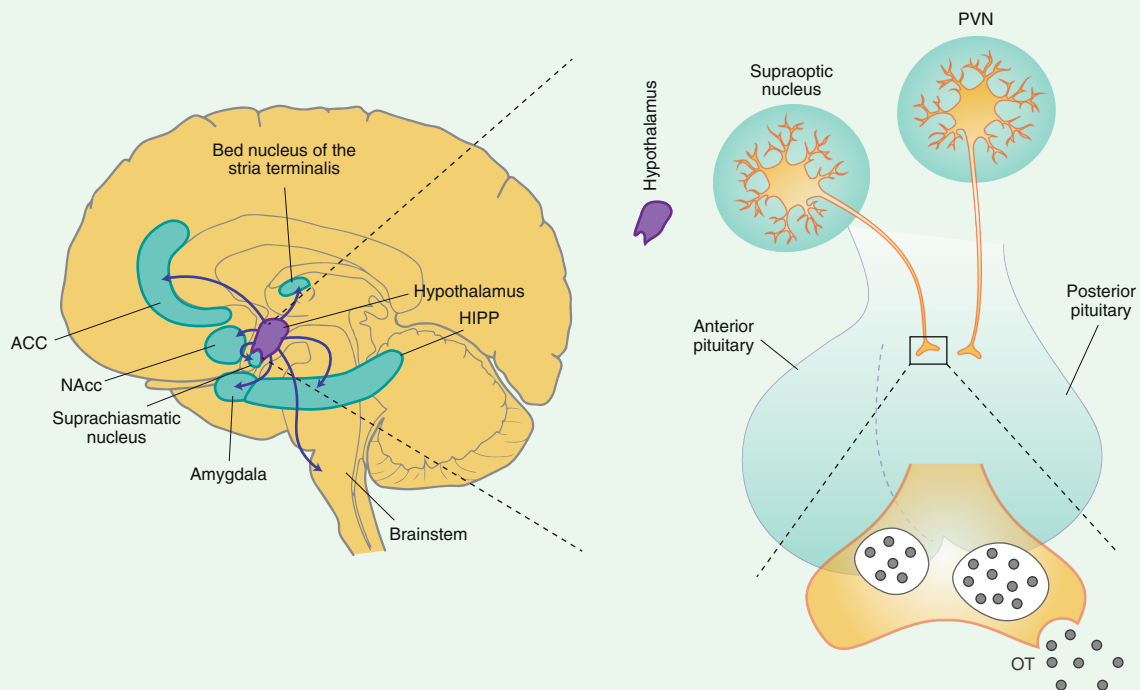
Generally speaking, however, it remains unclear how OT affects a wide array of social behaviors. One likely possibility is that OT modulates neural activity in multiple brain areas that participate in processes precipitating social decision-making⁹ and facilitate inter-regional coordination. Indeed, OT has been shown to affect the strength of resting-state connectivity between mPFC or ACC and amygdala^{115,116}, although the direction of this effect may depend on individuals. For example, OT increased amygdala–ACC or amygdala–mPFC resting-state connectivity in participants with generalized anxiety, but decreased it in healthy individuals¹¹⁶. Moreover, when presented with socially rewarding stimuli, like infant laughter, functional connectivity of the amygdala with ACC and OFC was increased after intranasal OT¹¹⁷ (Fig. 4b). Although the mechanisms underlying OT-induced changes in interregional coordination remain unclear, these findings advance exciting avenues for future research.

Box 3 | Species difference in OT receptor distribution

The neuropeptide OT is primarily released from the hypothalamus–posterior pituitary pathway¹⁰², and its receptors are predominantly localized in limbic regions of the brain (Box Fig.). There are notable species differences in the brain regions that are modulated by OT¹⁰³. The best-documented evidence comes from pair-bonding literature in voles. Monogamous prairie voles express abundant OT receptors in NAcc, mPFC and caudate nucleus, whereas non-monogamous montane voles do not⁸². Indeed, it was demonstrated that OT action in NAcc is required for social bonding in voles⁸² and social preference formation in mice¹⁰⁷. These findings not only show the importance of OT in mediating social reward in certain species, but also the role of OT in enhancing reward value of social stimuli or agents, a process that is important for guiding decisions concerning conspecifics in multiple species.

Our knowledge of OT receptor distributions in humans and non-human primates are generally limited compared to those in rodents. Moreover, OT also binds to arginine vasopressin receptors, which are more widely expressed in the primate brain than OT receptors¹⁴⁴, making it challenging to elucidate OT-specific functions in the brain. Importantly, based on existing literature, OT receptor distributions in different species seem to critically depend on the dominant sensory modality that guides

social interaction in any particular species. In fact, strong OT receptor expression in mice is found in brain areas involved in olfactory processing, the main sensory modality in guiding social behaviors in this species¹⁰³. In rhesus macaques, OT receptor expression is particularly high in the nucleus basalis of Meynert, superior colliculus and ventromedial hypothalamus, among other regions, all implicated in visual orienting behavior¹⁴⁴, which is critical for macaques in navigating their social environments. Likewise, in humans and marmosets, OT receptors are robustly present in brain regions involved in visual orienting, such as the superior colliculus and the nucleus basalis of Meynert^{145,146}. The OT fibers from brain regions with high levels of OT receptors often innervate several brain regions involved in multiple aspects of social decision-making. In primate brains, for example, OT cells in the nucleus basalis of Meynert project to the amygdala, and these innervations are thought to directly regulate social functions in the amygdala^{1,147}. Taken together, the anatomical distributions of OT receptors generally correspond to the dominant social modality (for example, OT receptors are abundantly present in brain regions involved in visual orienting in primates) as well as ethology in different species (for example, OT receptors are abundantly present in reward related regions in pair-bonding monogamous voles)¹⁰³.



Research in rodents has provided direct evidence that OT influences social functions in the PFC–amygdala pathways. It is well-established that OT in the amygdala is required for recognition and memory of conspecifics in mice¹¹⁸. For example, mice lacking the *OXT* gene failed to recall familiar conspecifics after repeated social exposures^{119,120}. Importantly, this deficit was linked to reduced neuronal activity in the medial amygdala^{119,120} (Fig. 4c). Moreover, focal infusions of OT in the medial amygdala rescued social recognition in the *OXT* knockout mice, whereas focal infusions of an OT antagonist induced similar social deficits in

wild-type mice¹²⁰, supporting the notion that OT processing in this region is both necessary and sufficient for social recognition leading to social memory.

OT effects are often sexually dimorphic in rodents. For example, time spent interacting with juveniles correlated positively with OT receptor density in the medial amygdala of male rats but negatively in the central amygdala of females¹²¹. The presence of OT receptors in aromatase-expressing neurons of the medial amygdala was required for male mice to preferentially interact with a female over another male¹²². In the absence of OT receptors in aromatase

neurons, however, female-evoked neural responses were reduced while activity to predator odor cue was enhanced¹²² (Fig. 4d), suggesting that OT tunes neural activity in the medial amygdala toward behaviorally preferred social stimuli (female conspecifics) over other relevant stimuli. In addition to the medial amygdala, OT is involved in social learning in ACC. For example, when an observer mouse was exposed to either a familiar or unfamiliar conspecific in distress, intranasal OT in the observer acutely increased activity of ACC neurons during observational fear acquisition and caused the observer to better acquire fear from the unfamiliar conspecific¹²³. Therefore, observational learning requires not only ACC and its functional interactions with the amygdala^{76,77}, but also the regulation of ACC by OT. Moreover, in prairie voles, ACC activity was increased when a familiar conspecific was in distress, and focally infusing OT receptor antagonists into ACC abolished partner-directed grooming toward the distressed conspecific¹²⁴ (Fig. 4e), supporting the role of OT in ACC for promoting empathetic responses to others.

Together, evidence from humans, non-human primates and rodents suggests that OT is critically involved in multiple aspects of social decision-making in the mPFC–amygdala pathways. How OT impacts neuronal activity and local and global information transmission remains to be better understood. A study in mouse hippocampal slices showed that OT increases fast-spiking interneuron activity, improving the signal-to-noise ratio¹²⁵. This mechanism may underlie certain social effects of OT by enhancing neural information transmission¹²⁵ and facilitating interareal communications, including in the mPFC–amygdala pathways (Fig. 5).

Concluding remarks

We have focused on studies that took a systems neuroscience approach to social cognition. The evidence discussed here supports the notion that neural activity in medial and orbital PFC areas and the amygdala, as well as interactions between these areas, contribute to social decision-making. The topics covered here are by no means exhaustive; for example, corticostriatal circuits also importantly contribute to social learning and reward^{83,126} and likely contribute to simulating and understanding others³. Moreover, cell-type- and projection-specific interactions within subcortical areas are known to regulate social functions¹²⁷. Finally, although we have focused on medial and orbital PFC regions, socially relevant signals are certainly processed in lateral PFC regions^{128,129}.

Social functions in the mPFC–amygdala pathways may be under oxytocinergic influence, although more research is needed to understand how OT modulates neuronal activity guiding social decision-making, especially in the primate brain. As existing studies in humans and non-human primates have mostly used intranasal OT, there remains a gap in understanding how the resulting changes in central OT concentration impacts functions in specific regions and circuits. Future efforts in primate OT research should examine causal changes in neuronal activity and interregional coordination in the mPFC–amygdala pathways following site-specific pharmacological or genetic manipulations. Together with the translational advantage of intranasal OT, region- and/or circuit-specific approaches in non-human primates will provide novel knowledge toward understanding and treating social dysfunction.

Looking ahead, experiments in more naturalistic settings may reveal novel insights that might not be easily tractable in typical laboratory conditions. Indeed, the field is beginning to reflect this concern. Navigating the intricate tradeoff between rigorous control and naturalistic implementations undoubtedly presents a challenge. Understanding similarities and differences in neural functions during experimentally controlled behaviors versus natural, spontaneous behaviors is an important topic for future research.

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Additional information

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