Trends in Cognitive Sciences

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Review

Social Decision-Making and the Brain: A Comparative Perspective

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The capacity and motivation to be social is a key component of the human adaptive behavioral repertoire. Recent research has identified social behaviors remarkably similar to our own in other animals, including empathy, consolation, cooperation, and strategic deception. Moreover, neurobiological studies in humans, nonhuman primates, and rodents have identified shared brain structures (the so-called 'social brain') apparently specialized to mediate such functions. Neuromodulators may regulate social interactions by 'tuning' the social brain, with important implications for treating social impairments. Here, we survey recent findings in social neuroscience from a comparative perspective, and conclude that the very social behaviors that make us human emerge from mechanisms shared widely with other animals, as well as some that appear to be unique to humans and other primates.

Trends

Evidence converging from several animal models of social interactions offers an unprecedented view of the brain areas and networks involved in social cognition.

Experimental manipulation of social brain networks in human and nonhuman animals offers new causal insights that go beyond mere correlation between brain and social behavior.

Neuropeptides, such as oxytocin, offer great promise as modulators of social behavior in humans. However, experts ask for cautious interpretation of the literature in humans and request more research in nonhuman primates.

Behavioral and neurobiological investigations of social behavior across species are beginning to reveal more continuity between humans and other animals than ever before imagined.

The Human 'Social Brain'

Consider the following common scenario (Figure 1): you step into a busy outdoor market on a Saturday afternoon to purchase some fresh fruit from a local farmer. You are looking for a particular vendor with whom you have done business before, and whom you know is open to concede some discounts if you buy a lot of fruit. Upon arrival, you notice that the vendor is in a bad mood and that his fruits are not particularly appealing. You vacillate between bargaining with him for a lower price and switching to another vendor who might be more willing to offer a better deal. However, you also fear that, if your preferred vendor sees you dealing with his competitor, this might impair the privileged relationship you have with him. In this situation, as in many other social dilemmas, the best decision is complicated by many variables, including the unknown mental state of the persons with whom you interact or the reactions they might have towards your decision. To make an adaptive choice in this context, you must leverage the support of brain systems that identify social contexts, make inferences about the mental states and likely behavior of others, estimate and compare the costs and benefits of different transactions, make decisions, and learn from these interactions.

Recent research in humans, largely using **blood-oxygen-level dependent** (BOLD; see Glossary) functional magnetic resonance imaging (fMRI), has uncovered a set of brain regions reliably engaged by social decisions such as that depicted in Figure 1A. The crucial first step of identifying the social context, including recognition of agents and recall of past interactions with them, is robustly associated with activity in the medial temporal lobes and fusiform gyrus [1,2]. Next, the process of inferring the intentions of the other person based on perception of his or her current state (known as theory-of-mind or mentalizing) is known to engage the posterior superior temporal sulcus (STS), the temporoparietal junction (TPJ), the rostral anterior cingulate

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cortex (rACC), and the medial prefrontal cortex (mPFC) [3–5]. Making a purchase in a market also requires computing how much you value the goods on offer, a process that reflects your personal preferences and internal state. Brain areas involved in personal valuation primarily include the ventromedial PFC, orbitofrontal cortex, and ventral striatum [6], although other value signals have also been identified in an array of other regions [7]. Current evidence suggests that the same brain regions also compute the value of social factors (e.g., the value of a relationship), which need to be considered along with the value of goods to make a decision [8,9]. Finally, a decision needs to be taken. Several neurocomputational models of decision-making have been proposed, most notably the accumulation of evidence towards a decision threshold [10,11], a process scaled by the value of available options and divisively normalized by their number [12]. The outcome of this process (namely whether it turned out better or worse than expected) provides important information that one can use to update the model of the decision context, a learning process that appears to depend on the dopaminergic midbrain, striatum, ACC, and dorsolateral PFC (DLPFC) [13,14].

Despite this success in using functional and structural imaging to predict individual variation in social behavior, the framework remains incomplete. Spatial and temporal limitations inherent to BOLD imaging preclude understanding neural mechanisms unfolding at the cellular and molecular scale with millisecond timing. Indeed, single neurons a few microns apart can signal widely different properties both in cortex [15] and basal ganglia [16], and these responses change dynamically within the time course of a single decision [17]. Moreover, signals related to value can easily be confounded with signals related to attention and arousal [18]. Finally, practical and ethical considerations make it difficult to functionally test this model by inactivating or stimulating neuronal populations with temporal and spatial specificity in humans. These challenges make animal models of social interactions critical for developing a fully mechanistic account of human social behavior.

Deep Homology in the Social Brain

Choosing with whom to compete, with whom to mate, and with whom to cooperate are critical decisions for many animals that strongly impact survival and reproductive success [19,20]. Selective pressure on neural circuits supporting social behavior may generate similar solutions based on either convergence in the absence of shared ancestry [21] or elaboration of traits shared by common descent [22]. Homology is defined as shared ancestry in traits between different species. Deep homology extends the concept of homology to describe traits that are shared across a wide range of species and develop and differentiate under the control of the same genetic mechanisms [23]. An example of deep homology is the role of *PAX* genes in the development of eyes in vertebrates and insects; despite their differing outward appearance, these organs share a common developmental pathway [23].

Emerging evidence supports the hypothesis of deep homology in some of the fundamental mechanisms mediating social behavior [24]. A recent study found remarkable overlap in the expression profile of neurochemical genes across 12 brain regions involved in social decision making in 88 species of vertebrates [25]. Analysis examining the changes in gene expression patterns since the time when tetrapods and ray-finned fishes shared a common ancestor (about 450 million years ago) identified the basolateral amygdala and the **oxytocin** (OT) and progesterone receptor distributions to be the most conserved through evolution (Figure 2). The authors also reported significant variability in the site of production of neuroendocrine ligands compared with the highly conserved distribution profiles of receptors, which they proposed may explain variation in the way in which social signals are weighed and processed, while conserving the responses to similar environmental challenges across species [25]. Despite the apparent similarities endorsing some deep homologies in the biological basis of social behavior, important behavioral differences exist between many of these species and humans [26,27].

Glossary

Blood-oxygen-level dependent (BOLD) imaging: a non-invasive functional neuroimaging method that maps the flow of deoxygenated hemoglobin molecules in small blood vessels across the brain. This hemodynamic response is associated with single neuron spiking and dendritic potentials averaged over large volumes of tissue (voxels), each containing hundreds of thousands of cells often with different physiological properties.

Dictator game: an economic game in which one participant, called the dictator, is given an amount of goods that they need to split between themselves and another participant. The dictator can choose to allocate any amount to the other participant, including giving nothing, and the other cannot have any impact on their decision. Human participants rarely comply with theoretical predictions of total selfishness, showing an aversion to unfairness.

Electrophysiology: single-cell electrophysiology refers to a neural recording technique whereby high-impedance electrodes are lowered into the brain to monitor the voltage fluctuations either inside or outside neurons. Using electrical amplification, filtering, and thresholding, the action potentials of neurons can be recorded with sub-millisecond time resolution.

Gaze following: social behavior in which an animal infers the object of attention of another individual by looking at its eyes. Gaze following is observed in numerous species of mammals and appears to indicate interest in the mental state of others. It is impaired in patients with autism spectrum disorders.

Muscimol: a potent, selective agonist for the $GABA_A$ receptor. The receptor is naturally activated by the principal inhibitory transmitter of the brain, GABA. When directly injected into the brain, muscimol disrupts neural activity over a volume of several cubic millimetres of tissue, permitting causal brain–behavior relationships to be established.

Optogenetics: neural manipulation technique that involves the use of light to activate or deactivate groups of neurons with high temporal and spatial resolution. These neurons are rendered sensitive to light of a

Among mammals, some species of rodents engage in social behaviors shared with humans and other primates, including play and laughter [28], status recognition and hierarchical behavior [29], rudimentary empathy [30], and adapting their social structures to environmental challenges [31]. In a remarkable recent study, neuroscientists demonstrated that prairie voles (an animal that forms strong pair bonds between males and females) show consolation behavior towards other voles [32], a behavior typically observed in great apes [33] and other animals, such as corvids, elephants, and canids [34–36]. Prairie voles increased grooming of a familiar vole, but not a stranger, that had experienced an unobserved stressful event. Furthermore, voles matched their own stress response to the stress level of their partner, as indexed by increases in corticosterone and anxiety-related behaviors [32]. Together, these findings endorse previous studies suggesting that some species of rodents, including mice and rats, display emotional contagion [37–39], which is thought to be a precursor for affective empathy in humans.

The neural basis of empathy appears to be partly regulated by an evolutionarily conserved peptide across some mammalian species. The neuropeptide OT is robustly associated with empathy-like behaviors in small rodents [32,40–44], and some evidence suggests that this association is conserved in humans [45–48]. These findings invite the hypothesis that OT shapes empathy behavior in part by acting either directly or indirectly on brain regions implicated in empathy, such as the ACC [49]. Consistent with this hypothesis, exposure to a stressed cagemate increased activity within the ACC and OT antagonists infused into ACC abolished consolation behavior in the monogamous prairie voles [32]. Recent studies suggest further parallels between rodents and humans in the interactions between empathy and the social environment. By pharmacologically blocking glucocorticoid synthesis or receptors for adrenal stress hormones, researchers were able to reduce the level of stress experienced by mice and humans partnered with a stranger. This manipulation elicited emotional contagion between strangers, a form of empathy-like behavior typically observed only between familiar mice and not between stranger mice [50]. Notably, the authors found the same effect of social stress on empathy for pain in young human adults, suggesting an evolutionarily conserved role for stress in emotional contagion and empathy between unfamiliar individuals across species [50]. These observations invite the possibility that empathy between human strangers could be enhanced through interventions that reduce stress. It is worth noting that OT has anxiolytic properties in addition to its direct effects on social function [51], offering the potential for both direct and indirect modulation of empathy.

Interestingly, OT binding in medial amygdala has also been reported to facilitate social recognition in rodents [52], a process that was abolished by selective application of OT antagonists via disruption of synaptic plasticity [43]. The amygdala may mediate social facilitation, in part, via projections to the ventral hippocampus. In a recent study, neuroscientists **optogenetically** manipulated the projections from pyramidal neurons in the basolateral amygdala to the ventral hippocampus in mice performing social interaction tests [53]. Deactivation of these projections significantly increased social interactions, whereas activation of the projections decreased social interactions [53]. These results indicate that social tendencies are modulated by precise departures from a resting-state level of interaction between these two brain regions.

Primate Specializations in Social Behavior and Cognition

Despite growing evidence for deep homologies in biology and social behavior across vertebrates, many of our most complex, flexible, visually guided, and strategic social behaviors appear to be restricted to other primates [54]. For most primates, social bonds are crucial, shaping the reproductive success of males [55], females [56], and offspring [57]. Variation in

specific wavelength by genetically engineered viral vectors carrying genes encoding light-sensitive ion channels, called opsins.

Oxytocin (OT): a brain peptide produced and released by the hypothalamus with receptors located both inside and outside the central nervous system in mammals. OT is important for social bonding, maternal behavior, aggression, and territoriality in small mammals. Evidence suggests that these roles are conserved to some degree in monkeys and humans.

Prisoner's dilemma game: economic game in which two individuals choose between options with outcomes crucially dependent on the unknown intention of the other to cooperate or not. In this game, mutual cooperation provides the highest payoff for both partners over repeated iterations of the game, but most people defect to avoid the risk that their partner will fail to cooperate.

Statistical power: the statistical power of a study refers to its capacity to detect a significant effect of the independent variable under study, assuming that the effect of this variable truly exists in reality. The power of a study depends on the sample size, the size of the true effect, and the scatter of the data. To be properly powered, a study needs to have at least 80% chance of detecting the effect, assuming it exists.

Transcranial direct current stimulation: a neurostimulation technique that uses a constant, low-current stimulator comprising an anodal and cathodal electrode placed on the scalp of subjects to modulate large brain regions of interest. Cathodal stimulation is thought to slightly depolarize neuronal populations, thus increasing their likelihood of firing, while anodal stimulation is thought to hyperpolarize the membrane of neuron.

Zero-sum game: a family of economic games in which the gains of one participant are exactly counterbalanced by the losses of the other participant. Example zero-sum games are competitive sports such as tennis. When playing doubles in tennis, however, a player engages in a non-zero-sum game with his teammate.

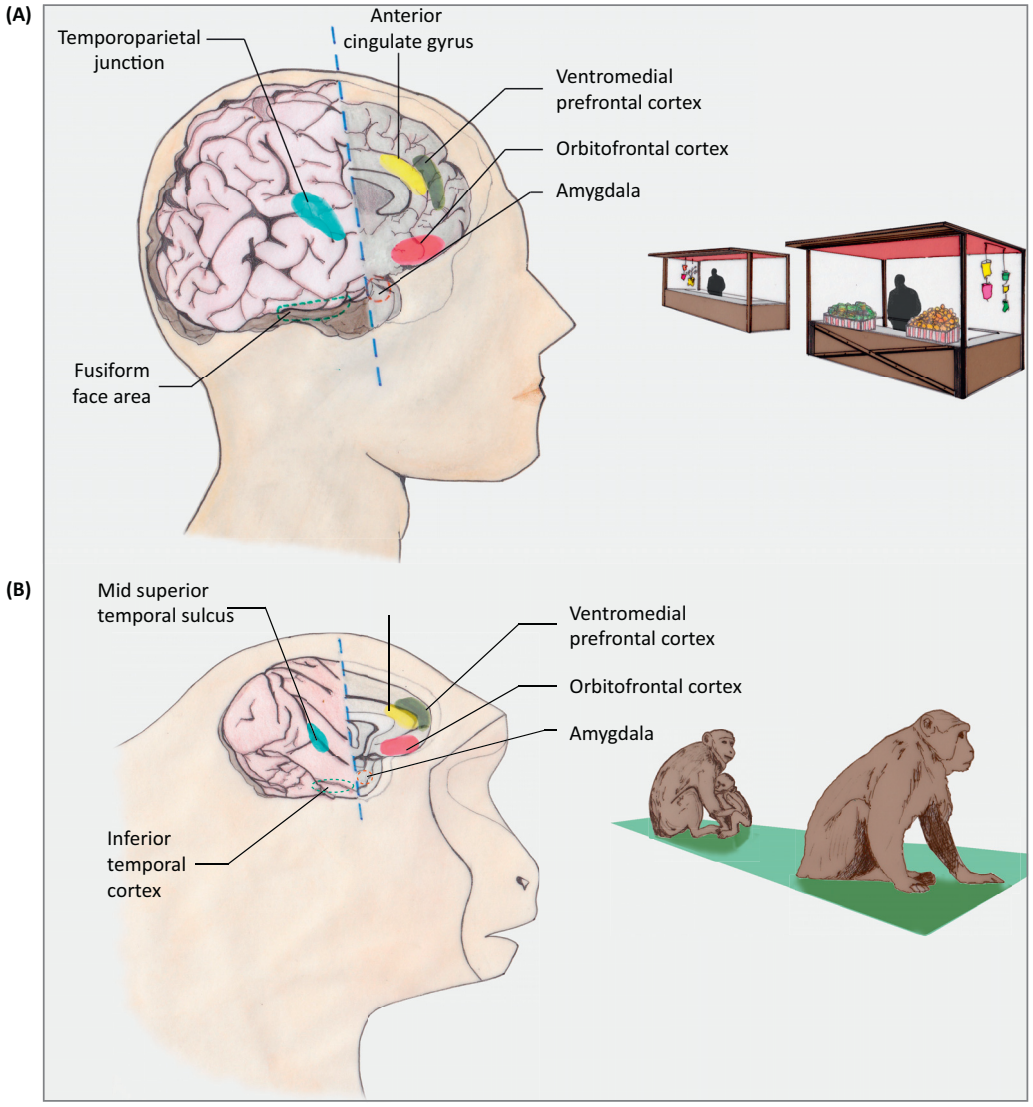

Figure 1. Social Dilemmas and the Primate Brain. (A) When faced with a social dilemma, such as choosing whom to deal with at the food market, several brain areas process social information to guide the decision (B). These social dilemmas are also part of the life of other species, such as monkeys living in large groups. Whether to cooperate with another male or to help care for the offspring of a female member of the group might have different payoffs in the short and long term that are hard to predict. Homologous brain areas responsible for social cognition can be studied in animal models to understand both function and dysfunction in the human brain.

social skills among human primates [58,59] and nonhuman primates [60,61] is directly related to observable variation in brain anatomy, opening the door to studying interindividual differences in social skills. The social skills of primates are complex; individuals make concessions to maintain power [62], unite to defeat a common opponent [63], and place high value on social information [64]. Although some of these complex skills can be found in other species [65], their combination into a rich social cognitive and behavioral repertoire appears, to date, to be unique to primates (Box 1).

Similar to humans, monkeys take into account the well-being of others when they make decisions. When interacting with friends, for example, rhesus monkeys worked to avoid delivery

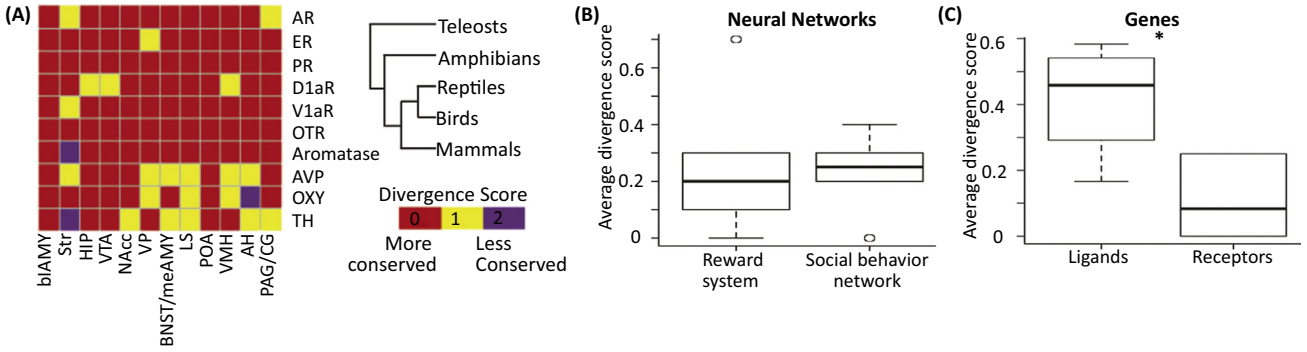

Figure 2. Conservation of Neurochemical Genes Regulating Social Behavior across Vertebrate Lineages. (A) Genetic divergence score for each gene (rows) in each brain region (columns) across a parsimonious model of vertebrate phylogeny (top-right). Red squares indicate a divergence score of 0, meaning that this gene has been highly conserved over the past 450 million years of evolution. Purple squares indicate a score of 2, meaning that this less conserved gene has undergone at least two changes over the same period. (B) The average divergence score for each brain region within either the mesolimbic reward system (VP, Str, LS, BNST/meAMY, VTA, HIP, NAcc, and bIAMY) or the social behavior network (VWH, BNST/meAMY, AH, LS, PAG, and POA) indicate that both systems evolved at the same slow rate over the course of vertebrate evolution. (C) Averaging the divergence score for each neurochemical gene across brain regions reveals that the sites of ligand production are more evolutionary flexible than where their receptors are expressed. Regions: AH, anterior hypothalamus; bIAMY, basolateral amygdala; BNST/meAMY, bed nucleus of the stria terminalis/medial amygdala; HIP, hippocampus; LS, lateral septum; NAcc, nucleus accumbens; PAG, periaqueductal gray/central gray; POA, preoptic area; Str, striatum; VWH, ventromedial hypothalamus; VP, ventral pallidum; VTA, ventral tegmental area. Genes: AR, androgen receptor; AVP, arginine vasopressin; D1aR, dopamine D1 receptor; ER, estrogen receptor; OTR, oxytocin receptor; OXY, oxytocin; PR, progesterone receptor; TH, tyrosine hydroxylase; V1aR, vasopressin 1a receptor. Adapted, with permission, from [25].

of an unpleasant air puff to their partner and work to deliver a reward instead [66]. This sensitivity decreased proportionally with social distance between the two monkeys, as measured in their home environment, and was correlated with the amount of mutual gaze and mutual eye blinking observed between partners [66]. In a similar experiment, researchers trained rhesus macaques to play a modified version of the classic **dictator game** while recording from single neurons in the basolateral amygdala [67]. The authors identified neurons that signaled the value of rewards for both self and for a social partner when dictators made overt decisions to give or withhold reward but not when the computer made the decisions, suggesting an active role for these neurons in social decision-making. The authors further showed that unilateral infusion of OT into the basolateral amygdala increased prosocial behavior, but equivalent injections into the DLPFC did not [67]. Effective OT-induced enhancement in prosocial behavior was also accompanied by increases in attention to the partner.

In addition to sensitivity to the welfare of others, monkeys and apes, similar to humans, also make inferences about the mental states of others. **Gaze following** is an important developmental and evolutionary precursor to theory of mind [68,69], the process of inferring the mental state of another individual. Both chimpanzees and rhesus macaques follow the gaze of others to obtain information about hidden objects and events [70]. As in humans, gaze following by rhesus macaques involves both overt gaze shifts and covert changes in the allocation of attention [71]. Gaze following also appears to follow a similar developmental time course in monkeys and humans. Primatologists tracked the gaze of 481 rhesus macaques ranging from infancy to old age and found that gaze following arose in infancy, peaked during the juvenile period, and declined with normal aging [72]. Notably, this developmental trajectory goes awry in disorders such as autism, which are defined in part by social impairments [73]. **Electrophysiological** studies in monkeys identified neurons in the amygdala [74] and the posterior STS [75] that detect and track the gaze of others. Moreover, neurons in the lateral intraparietal cortex, an area implicated in orienting attention, 'mirror' the gaze of other monkeys [76].

Box 1. Genes and Social Behavior in Primates

Genetic influences have an important role in modulating the activity of brain areas involved in social cognition. For example, interindividual variability in social phenotype can be traced back to polymorphisms in the OT and vasopressin receptor gene and/or promoter region [115,116]. Moreover, the sensitivity to exogenous administration of OT appears to be modulated by similar genetic factors [117], which has important implications for future personalized treatment approaches. More molecular genetic research is needed to identify novel genetic variations that can explain both normal and abnormal interindividual variations in sociobehavioral phenotype.

Recently, nonhuman primates have emerged as potential models for unraveling the genetics of individual variation in complex social behavior. Capitalizing on naturally occurring behavioral and genomic variation, researchers studied the interindividual interactions of a large colony of free-ranging macaques and mapped their social network ties based on grooming, an important affiliative behavior that serves to build and maintain bonds between individuals [118]. The authors found that social network position, that is, how many friends and allies each individual had, was not only heritable, but also linked to polymorphisms in two genes that regulate serotonin function, which has been implicated in depression, addiction, and autism in humans [118]. Since social network position itself cannot be heritable, these results imply that aspects of social temperament and social skill useful in building connections with others have a genetic basis, which holds the potential of clear translational value for understanding the biological bases of human disorders attended by social impairments. This and another study [119] endorse the potential power of exploiting naturally occurring variation in genomics and social behavior to understand and develop new treatments for human social pathology. While using this approach, however, researchers will have to be careful about potential epigenetic effects on the expression of those genes, including the OT receptor gene, and their associated sociobehavioral phenotype [120].

A complementary approach is to engineer primates with genetic variants implicated in human disorders characterized by social impairment. In a remarkable achievement, scientists used a lentivirus to deliver the human Methyl-CpG binding protein 2 (MeCP2) variant, which causes Rett syndrome in humans, to long-tailed macaque (*Macaca fascicularis*) embryos, which resulted in expression of the variant MeCP2 in the brains of infant monkeys [121]. Previous attempts to model MeCP2-induced Rett syndrome in mice induced repetitive behavior, but failed to replicate concomitant social impairment. The transgenic monkeys showed an autistic phenotype, including repetitive behavior and reduced social interactions with peers. Importantly, the MeCP2 variant and attendant phenotype were also expressed in offspring of the transgenic parents, permitting breeding of these animals for subsequent studies of the neural mechanisms leading to MeCP2 Rett syndrome. These findings strongly support the use of genetic engineering techniques to generate and study primate models of psychiatric conditions that are poorly recapitulated in standard small animal models, such as mice and rats.

Mentalizing in nonhuman primates appears to go beyond mere gaze following. Chimpanzees, marmosets, tamarins, and rhesus monkeys, to name just a few species, all show evidence for at least a rudimentary capacity to make inferences about the mental state of another individual, and can use that information, for example, to motivate cooperation [77–79]. Recent evidence even suggests that great apes can infer false beliefs that a peer might hold, as well as anticipate errors that are consequent of this false belief [80]. In a remarkable recent intracranial recording study, neurophysiologists investigated the neural correlates of intention inference in macaques. The authors trained rhesus monkeys to play an iterated **prisoner's dilemma game** while recording neuronal activity via a multielectrode array in the dorsal ACC (dACC) of one player. Monkeys decided between defecting for a small certain reward or choosing to cooperate and receive a larger uncertain reward [81]. The authors identified some neurons selective for the monkey's own choice, some selective for the partner's choice, and a third subgroup of neurons selective for the predicted choice of the partner monkey. Neurons selective for the predicted intentions of others might contribute to the computations necessary for strategic social behavior. The authors tested this idea by using microstimulation to disrupt normal patterns of neuronal activity in dACC, which impaired cooperation [81]. This deficit was specific to cooperative interactions, but did not impair the capacity to retaliate following defection by the partner, or to engage in **zero-sum behavior,** in which there was no possibility of mutual benefit. These results strongly implicate the dACC in computations necessary for strategic cooperation, and echo results of Chang and colleagues that neurons in dACC and gyral ACC, as well as orbitofrontal cortex, carry signals associated with prosocial decisions made by rhesus monkeys playing a dictator game [82].

Another noteworthy aspect of primate social behavior is our tendency to make strategic decisions based on perceived long-term societal implications. For example, experimental psychologists [83] applied **transcranial direct current stimulation** (tDCS) over the right lateral PFC to human participants playing an economic game and found that anodal stimulation (thought to increase neural excitability [84,85]) led to an increase in norm-compliant behavior when social punishment threats were present and a decrease in norm-compliant behavior when these threats were absent. Despite these changes in behavior, stimulation did not change how participants perceived the fairness of these exchanges or what they expected for not complying with the social norm. In another study, researchers asked human participants to make blameworthiness and punishment judgements [86]. Based on a model of social norm enforcement [87], the authors hypothesized that the DLPFC acts as 'node' that receives and integrates harm and blameworthiness signals when individuals decide whether to mete out punishment. As predicted, the authors found that repetitive transcranial magnetic stimulation (rTMS) over both right and left DLPFC evoked a departure from normal punishment behavior without affecting judgements of blameworthiness, implicating a role of DLPFC in norm enforcement. Although we believe testing this hypothesis using a nonsocial control condition would have further strengthened these results, these studies have taken a step forward in highlighting the neural circuits regulating complex social decisions in primates.

Translational Applications

Ultimately, furthering our basic understanding of the social brain will provide new targets and opportunities to treat humans with social impairments. Research across several species of mammals has identified a highly conserved social modulator in the neuropeptide OT, provoking a recent surge of excitement about its therapeutic potential (Figure 3) [88]. Numerous studies have found that intranasal administration of OT (IN-OT) enhanced a range of complex social cognitive processes in both healthy humans and patients [45,89,90]. A recent meta-analysis of human IN-OT studies found that OT increased the recognition of facial expressions of emotions (Cohen's $d = 0.21$) and increased trust towards members of one's group (Cohen's $d = 0.43$) [91]. Another meta-analysis examined the effects of IN-OT on autism spectrum disorder (ASD), schizophrenia, and social anxiety, and reported a combined effect size of $d = 0.32$ on a variety of outcome measures important for social interactions, including social anxiety and emotion recognition [92]. Encouraging findings such as these have inspired a large number of clinical trials to document the efficacy of OT for improving social functions in psychiatric populations. According to the US National Institutes of Health (NIH), there are currently 39 active clinical trials studying the effects of OT on social cognition in patients, 13 of which are in children with ASD (ClinicalTrials.gov, 2016). In most of these trials, OT is administered using a nasal spray. Many parents, patients, and clinicians eagerly await the results of these clinical trials.

Despite this optimism, experts have raised several concerns about the validity of results emerging from OT studies in humans [47,93–97]. For example, a team of OT researchers [97] conducted a meta-analysis of all meta-analyses examining the effects of OT on cognitive and behavioral variables in humans. They found that the average effect size was $d = 0.28$, or a quarter of a standard deviation difference between OT and control groups. Given such a small effect size of OT, sample sizes of over 300 participants would be required to detect its effects reliably, that is, with a **statistical power** equal or above 80%. Yet, the average sample size in these studies is under 50 participants, making it unlikely that any given study would detect a true effect of OT (12–16% chance of finding a true effect, given these small sample sizes) [97]. Thus, it is puzzling that 88% of published studies report a significant effect of OT in humans [97]. With such small sample sizes, methodologically sound studies should fail to detect effects of OT more than 80% of the time for statistical reasons alone. Therefore, either most OT studies ever conducted in humans were never published (i.e., file-drawer effect) [98] or most published studies have hidden methodological issues that undermine their conclusions [99,100].

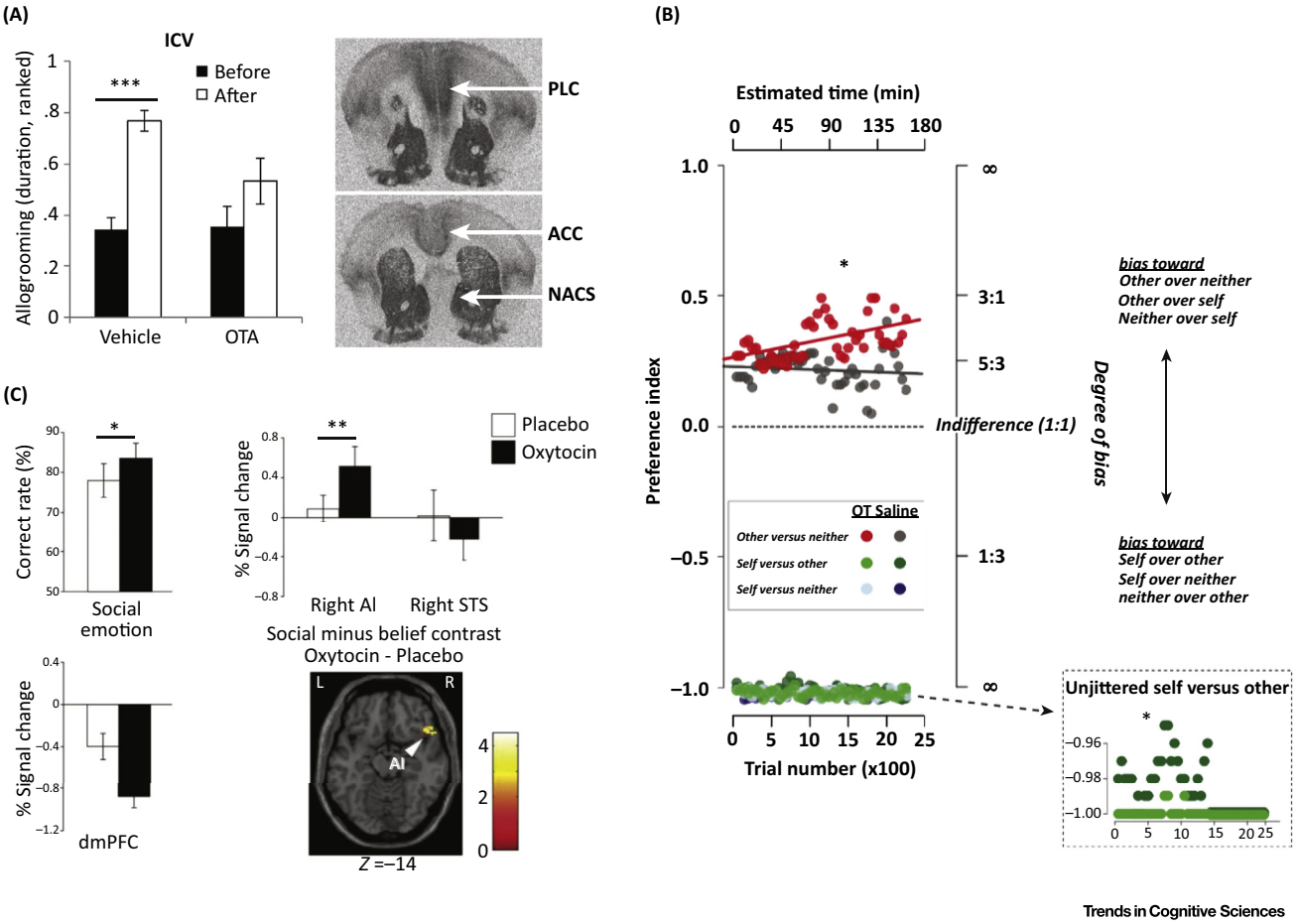

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Figure 3. Phylogenetically Conserved Effects of Oxytocin (OT) on Prosociality in the Rodent, Monkey, and Human. (A) Prairie voles naturally exhibited prosocial consolation behavior towards a peer that underwent a stressful event (white bars), but not if an OT antagonist was administered intracerebrally before the consolation test (OTA). Autoradiographs (right) show the distribution of OT receptors in the anterior cingulate cortex (ACC), nuclear accumbens (NACS), and paralimbic cortex (PLC) of the prairie vole [32]. (B) Rhesus macaques exhibited an increased preference towards rewarding a peer versus rewarding no-one following intranasal administration of OT via a pediatric nebulizer (red dots versus gray dots) [105]. (C) Human children with autism showed a slightly better aptitude at identifying social emotions in conspecifics following intranasal administration of OT using a nasal spray. This behavioral increase was paralleled by an increase in blood-oxygen-level dependent (BOLD) activity in the right anterior insula of patients with autism, but not in the dorsomedial prefrontal cortex (dmPFC) or the right superior temporal sulcus (STS), which were abnormal at baseline in this sample [90]. Reproduced, with permission from [32] (A), [105] (B), and [90] (C).

Therefore, large-scale, multicenter studies with appropriate statistical power are urgently needed to resolve this important issue [101].

A second concern is the penetration of OT to the central nervous system when administered intranasally in humans [94]. OT is a large peptide that does not cross the blood–brain barrier readily [102]. OT and other drugs delivered through the nose are thought to be translocated to the brain via the olfactory and trigeminal nerves [103], which lie deep within the nasal cavity and sinuses. It remains unclear precisely how effectively OT can reach receptors in the brain when administered by nasal spray, as done in human trials [95], compared with other modes of delivery, such as aerosolization. Recent studies in rhesus macaques found that an intranasal spray of OT did not lead to detectable increase of the peptide in the cerebrospinal fluid (CSF), casting doubts on the results of human studies using this route of administration [104]. Neurobiologists showed that using a pediatric nebulizer to deliver aerosolized OT [105] instead of a nasal spray significantly increased CSF levels in two monkeys. Subsequently, an independent group of researchers replicated the results from the latter study using a larger sample

size (eight monkeys; four OT, four placebo) and a within-subject design for baseline comparison [104]. These encouraging results invite the possibility that some of the variability in findings across studies of OT administration in humans reflect differences in the success of intranasal delivery.

Adding to the complexity of the translational impact of OT therapy, a recent study found that the distribution of OT receptors was more restricted than that of vasopressin receptors in macaques, and was mainly limited to deep structures of the diencephalon and brainstem, including the nucleus basalis of Meynert and the superior colliculus as well as amygdala [106]. Unfortunately, observations of increased OT levels in the CSF or blood plasma following nasal administration do not guarantee that exogenous OT reaches its target receptors in the deep nuclei of the brainstem, or that it does so in sufficient concentrations to trigger a positive behavioral effect [93]. Noteworthy is the fact that OT is also produced outside the brain in the heart, testes, uterus, gastrointestinal tract, and several other structures [107], which can bias plasma measurements of OT in social experiments [108]. A better way to activate central OT receptors might be to stimulate endogenous pituitary OT release using a pharmacological agent rather than exogenously administering it through the intranasal route [109].

Despite the efforts of many research groups to develop OT-based treatments for social impairments in clinical populations, there remain serious doubts whether and how IN-OT administration can stimulate prosocial behaviors in humans. Whereas the literature in rodents and other small mammals is uncontroversial [32,40–44], more research is needed to uncover the neural mechanisms by which OT affects the primate brain. Due to both neuroanatomical and behavioral similarities to humans, nonhuman primates are an excellent model to assess the efficacy and safety of chronic OT administration [110,111] as well as deepen our understanding of the mechanisms mediating the effects of OT in the human brain help us design improved and potentially personalized treatments for individuals with disorders in which social function is impaired.

Concluding Remarks

Social neuroscience is still in its infancy (see Outstanding Questions). Despite this early stage, groundwork has been laid for a basic framework in which different brain areas and circuits contribute selectively to the perception, recognition, selection, and recall of socially relevant information. Insights from research conducted in various species, including humans, has highlighted significant convergence in the neuroanatomy and neurophysiology of these brain circuits, as well as in the underlying genetics that shape neural structure and function, which encourages further comparative research. Importantly, new gene-editing technologies, such as CRISPR [112], may soon allow study of primate-specific social behaviors by harnessing the power of molecular genetics, an investigative tool heretofore limited to rodents, worms and flies, with potentially far-reaching translational implications [113,114]. Based on the foregoing, we advocate a collaborative, comparative approach, in which social neuroscientists continue to integrate insights from humans with complementary insights from animals, to understand what is in essence the foundation of human society and its potential for harmony or discord, with hopes for the benefit of all.

Acknowledgments

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Outstanding Questions

How does OT modulate social behavior in the primate brain? What are the neurophysiological and cellular-level mechanisms that lead to these effects? What brain regions are causally involved in this OT-mediated modulation and which ones are modulated only indirectly via other connected areas?

Does intranasal-OT administration really have a beneficial effect in human clinical populations? If so, how does OT reach deep brain receptors using this administration technique? Would stimulating endogenous OT release be a better strategy for clinical applications? How safe is a life-long OT treatment? What are the secondary effects of this systemic administration?

Can the CRISPR gene-editing technology be used in rodents and nonhuman primates to generate other novel models of psychiatric and neurological disorders? Will these primate models be produced at an affordable price so they can become part of common research methods in neuroscience labs?

What other animals could be used to model and study human social cognition? What makes a good model of social interaction and what makes a bad one? To what extent can biological homologies be ascertained when comparing the social behavior of humans and other animals? How can we rule out the possibility that biological analogies, rather than homologies, explain similar social behaviors between two species?

In brain regions identified using BOLD imaging, are different neuronal subpopulations playing different roles during social decision making?

If so, how should we interpret a change in BOLD signal in these heterogeneous areas? Can we resolve this issue by using single-cell neurophysiology in nonhuman animals?

How can the nonsocial and social functions attributed to some well-studied structures, such as the amygdala, coexist in the same area? Are different neuronal sub-populations within the same area responsible for social and nonsocial signals? Is the same circuitry

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responsible for both functions, performing the same computation regardless of the social nature of the stimuli?

How useful is the notion of a 'social brain'? Are there really brain regions or cell populations that are exclusively involved in social computations and not other tasks? Is it more parsimonious to assume that brain areas apply the same computation regardless of whether the input information is of social or nonsocial origin? Can differences in other factors (say, task difficulty or environmental complexity) between social and nonsocial paradigms explain differential activation in 'social brain' areas?

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