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How social information impacts action in rodents and humans: the role of the prefrontal cortex and its connections

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Abstract

Day-to-day choices often involve social information and can be influenced by prior social experience. When making a decision in a social context, a subject might need to: **1)** recognize the other individual or individuals, **2)** infer their intentions and emotions, and **3)** weigh the values of all outcomes, social and non-social, prior to selecting an action. These elements of social information processing all rely, to some extent, on the medial prefrontal cortex (mPFC). Patients with neuropsychiatric disorders often have disruptions in prefrontal cortical function, likely contributing to deficits in social reasoning and decision making. To better understand these deficits, researchers have turned to rodents, which have revealed prefrontal cortical mechanisms for contending with the complex information processing demands inherent to making decisions in social contexts. Here, we first review literature regarding social decision making, and the information processing underlying it, in humans and patient populations. We then turn to research in rodents, discussing current procedures for studying social decision making, and underlying neural correlates.

Keywords

prelimbic; infralimbic; anterior cingulate; vmPFC; dmPFC; operant; social decision-making; sociability; choice

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INTRODUCTION

Social experiences color our choices. From simple day-to-day choices such as what to have for dinner, to incredibly complex choices such as with whom to partner, social experiences affect how we behave and navigate a changing environment. This phenomenon extends to all mammals, as a degree of "social competence" is necessary for survival[1]. Thus, it is critically important that mammalian brains can contend with the complexities inherent to decision making, which involves the perception and integration of multiple sensory cues with historical knowledge and information about current internal states, ultimately guiding choices and behavior. In social contexts, this already complex process must also combine internal decision-making strategies with the perceived motivations and emotions of a dynamic group of agents. Many psychiatric illnesses are either co-morbid with, or defined by, disruptions in social behavior, including in decision making related to social experiences. Thus, it is imperative to investigate and uncover the neural processes inherent to this complicated and integrative process to further understand and develop new therapeutic avenues.

Across mammalian species, the prefrontal cortex, specifically the medial prefrontal cortex (mPFC), has emerged as a key regulator of the information processing demands necessary for decision making in social contexts. Historically, investigations of the mPFC focused on its function in adaptive control of behavior: utilizing motivationally salient information to guide decisions, and then altering decisions based on feedback[2]. This model applies to social situations; generally speaking, the mPFC functions within a "cognitive social brain" network[3], exerting "top-down" cognitive control over decisions that involve social information in humans[4], non-human primates[5], and rodents[6]. These functions can be contrasted with the more innate social behaviors, such as aggressive or sexual responses, which are predominantly controlled by subcortical structures like the hypothalamus[7, 8], and will largely not be discussed in this review.

Here, we review literature that deconstructs the complex information processing involved in social decision making in humans. We discuss three essential elements: *social/emotional recognition*, *empathic processes*, and *social incentive/action selection*. These three components of social information processing are controlled by overlapping but partially distinct circuits in the brain. As almost every neuropsychiatric disorder involves some degree of impairment in social decision making, better understanding the origins of impairment through investigations of social/emotional recognition, empathic processes, and social incentive/action selection is of utmost therapeutic importance. Finally, we discuss the tractable rodent models for understanding the precise functions of the mPFC in the information processing required for decisions in social contexts and discuss areas where future rodent studies could be translatable and beneficial.

SOCIAL DECISION MAKING IN HUMANS

Decision making in social contexts: deconstructing a complex process

Social interaction involves a very complex set of information-processing demands. To better understand how a social decision might be dissected, we turn to an example (modified

from[9]): going to a bake sale fundraiser for your child's school. As you walk by a stand, a fellow parent calls you over, attempting to persuade you to purchase their cookies. The first component of the interaction is *social and emotional perception*: do you recognize this person? Have you interacted with this parent before? Do they seem disappointed that nobody is at their stand? After you walk over to their stand, you infer the intentions of another person based on your perception of them, using *empathic processes*. Do you feel sorry for the parent who may not be selling as many cookies as they had hoped? Are you wondering whether they are trying to swindle you into purchasing overpriced cookies? At the same time, you are computing the value of the potential decisions you have in front of you. Importantly, this valuation must integrate not only the cost of the cookies, but the current "cost" of the relationship with the parent, and any other agent who might be paying attention to this interaction. Further, historical social associations with the food, such as enjoying these cookies with your child last year, might encourage you to buy them. As such, our brains are computing the *social incentive* of the interaction, alongside any non-social valuation. Lastly, you must *select an action*. You weigh the potential costs and benefits of purchasing the cookies from the parent, and you balance the social and non-social valuations of the interaction and reach a decision threshold as to whether you will purchase the cookies. In this relatively simple example of buying cookies at a bake sale, we are able to distinguish three elements of information processing when making a decision in a social context: social/emotional recognition, empathic processes, and social incentive/action selection[9, 10].

Social decision making as an endophenotype for neuropsychiatric disease

"Endophenotype" refers to neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological processes that are stable and have known or likely genetic causes; they are measurable processes that are associated with disease symptomatology, and understanding their mechanisms may provide insight into the etiology of a disease syndrome itself[11]. Deficits in the capacity for social decision making are prominent in many, if not all, neuropsychiatric conditions and are predictors of overall mortality, due to effects of diminished interpersonal relationships on overall health[12, 13]. This notion has led many clinicians to posit that investigations into social decision making may reveal potential endophenotypes more predictive of disease progression or treatment course than current diagnostic criteria. This is reflected in the National Institute for Mental Health's strategic plan, which has transitioned from emphasizing traditional disease diagnostic criteria, as reported in the Diagnostic and Statistical Manual of Mental Disorders (DSM), to the neurobiological construct-based Research Domain Criteria (RDoC), which includes "social processes" as one of its key Domains[14]. For instance, neuroimaging studies are already being conducted using social interaction as a putative endophenotype for neuropsychiatric illness[15]. However, the ubiquity of social behavioral difficulties among clinical populations poses a significant challenge to these studies. Given that decisions in social contexts impose demands on a large number of interconnected brain structures, dissecting this process into more discrete component parts may be necessary to inform endophenotypes[16]. This next section will take a more in-depth look at the brain structures underlying social/emotional recognition, empathic processes, and social incentive/action selection, and emphasize how functional impairments can manifest in neuropsychiatric

illnesses such as autism spectrum disorders (ASDs) and schizophrenia spectrum disorders (SSDs).

Anatomical and functional subdivisions of the mPFC in humans/primates

Understanding the neural correlates of social decision making requires a brief orientation to the subdivisions of the mPFC in humans (fig.1), which is involved in social decisions. Parcellation of the prefrontal cortex has proven to be a divisive endeavor; complexity in structure and function is the rule, not the exception[17]. The mPFC of humans classically consists of Brodmann areas (BAs) 9 and 10, 24, 25, and 32, with 11 and 14 constituting the medial orbital cortex[4, 18]. Major afferents to the mPFC come from the dorsolateral prefrontal cortex, temporal pole, anterior superior temporal gyrus, parietotemporal cortex, and posterior cingulate cortex (PCC). Connectivity of the mPFC broadly follows two axes: a dorso-ventral axis and a rostro-caudal axis[19]. The rhinal cortex, which acts as a gateway to hippocampal input and output, is more densely connected with the ventral mPFC (vmPFC) than the dorsal mPFC (dmPFC), which instead shares connections with the lateral premotor cortex, the supplementary motor area, and the cingulate motor area[20]. Further, the vmPFC, but not dmPFC, sends monosynaptic projections to the ventral striatum. Meanwhile, the amygdala has strong inputs to the more caudal anterior cingulate regions, also known as the anterior cingulate cortex (ACC; BAs 24, 25, and 32)[21], but much weaker inputs to the frontopolar regions. Dorsocaudal regions (BAs 24 and 32) have robust connections with the premotor cortex[22].

Canonical experiments focused on human and non-human primate PFC functions investigated non-social roles in working memory[23, 24] and attention[25]. In social neuroscience, a functional distinction is often made between the ventral (BA10, 24, 25, parts of 32) and dorsal (BA9, parts of 32) regions of the mPFC along various spectra: such as emotional *vs.* cognitive[26], or self-reliant *vs.* other-relevant social cognition[27, 28], respectively; illustrating the lack of clear agreement as to their functions (fig.1; to see a more exhaustive review of functional axes in the prefrontal cortex, see[29]). Broadly, the dmPFC is preferentially connected to high-order association cortical areas of the lateral frontal, temporal, and parietal lobe, while the vmPFC is preferentially connected to limbic and reward-related medial brain areas[30].

Social and emotional recognition in humans

Neural correlates.—Humans display a remarkable capacity for facial recognition, instantaneously discriminating between the relative similarity of human features while interpreting the vast complexity of information that can be transmitted through faces. This capacity appears to be intact from a very young age, as newborns will preferably look at photographs and cartoons of faces rather than objects or inverted faces[31]. The ability to identify a social context, including recognition of agents and recall of past interactions with them, is associated with activity in the medial temporal lobes and the fusiform gyrus (fig.1). In fMRI studies, several areas demonstrate a selective response to faces, including the fusiform face area (FFA), the lateral occipital lobe, the posterior superior temporal sulcus (pSTS), and the occipital face area[32–34] (fig.1; reviewed in[35]).

The pSTS belongs to another network as well, which recruits the amygdala and the vmPFC to process the emotional or affective value of observed stimuli (fig.1)[36–39]. Specifically, the amygdala is consistently recruited when emotional recognition provides motivational salience[40], such as when the perceived emotion predicts danger[41]. In contrast, investigations of the vmPFC in emotional perception have been more equivocal: patients with vmPFC lesions have exhibited impairments in emotional recognition[42], or exhibited no difference from controls[43]. More recent results suggest that the vmPFC coordinates visual attention to emotionally salient stimuli, particularly in the context of negative emotions, such as anger[43]. Thus, imaging studies suggest that typical facial recognition relies on the FFA and its accessory areas, while more salient stimuli, like an angry face, recruit the amygdala, and possibly, the vmPFC.

Alterations in ASDs and SSDs.—Both social recognition and emotional recognition are often impaired in neuropsychiatric and neurodevelopmental disorders and are necessary for typical decision making in social scenarios. Individuals with ASDs seem to lack early predispositions for social stimuli, and actually exhibit superior performance in the ability to match upside-down faces, consistent with the notion that these individuals may identify faces based on component parts as opposed to a gestalt[44]. A meta-analysis demonstrated that ASDs are consistently associated with facial and emotional recognition deficits, that the magnitude of these deficits increase with age, and that the deficits cannot be explained by levels of intelligence[45]. Indeed, face perecption in ASDs is accompanied by abnormal ventral temporal cortical activity, suggesting perhaps that patients with ASDs view faces similar to how neurotypical individuals view objects[46].

Patients with SSDs cite interpersonal problems as among the most debilitating of the disorder[47]. Evidence suggests non-emotional facial processing might be impaired in schizophrenia[48], but the neural bases underlying this deficit remain unclear, as FFA activation remains unchanged in patients with SSDs[49]. Comprehensive meta-analyses of facial affect research in SSDs confirmed that emotional recognition is a consistent and robust deficit, and that these deficits are predictive of deleterious outcomes in community functioning[50]. Deficits in emotional recognition are accompanied by decreased activation of the amygdala and the ACC and mPFC, with increases in areas outside those traditionally associated with emotional processing (such as the parietal lobule and cuneus), possibly representing compensatory processing[51, 52]. However, it is important to note that many studies of facial and emotional recognition in neuropsychiatric disorders suffer from inadequate validation in clinical settings (as discussed in[53]), pointing to fertile ground for new diagnostic and therapeutic approaches.

Empathic processes in humans

Neural correlates: Empathy is considered by many to be a uniquely human trait. However, pro-social behaviors in non-human primates and rodents suggest that some empathic capacity may predate humans evolutionarily[54]. Frans de Waal posits a multi-level theory of empathy[55], whereby the lowest common denominator of all empathic processes is when an individual is affected by another's emotional state, a phenomenon called emotional contagion. Empathic processes then extend in a continuum, with the more

complex levels involving concern about another's state and attempts to ameliorate that state, and subsequently, at the most elaborate level – attributing another's emotional state to oneself (*i.e.,* putting yourself in someone else's shoes).

Emotional contagion (also known as vicarious perception) is the notion that the observation of affective states in another induces a shared internal state in the observer[56]. Imaging studies have examined the brain regions that are activated when an observer watches someone taste the contents of a cup and look disgusted, and noted the same activation patterns when the observer themself tasted an unpleasant bitter liquid[57]. The functional circuits activated by both experiences have often been called the "emotional mirror neuron system" in the brain, relying on the activity of the ACC and the anterior insula[56, 58]. Most contend that emotional contagion, although likely fundamental to empathy, does not encompass the full empathic experience, as it does not involve a self-other distinction. In other words, a subject might become disgusted reflexively, without any real concern or understanding of another's experience. As such, de Waal's description of emotional contagion may constitute a "bottom-up" model of empathy, in which automatic responses are then sent to higher-order processing areas[59]. This model functions in tandem with the concept of "perspective taking," or "top-down" executive control of cognition and emotion through selective attention and self-regulation, mediated by the prefrontal and cingulate cortices. These "top-down" processes are continuously updated by "bottom-up" signals and provide important feedback, adding flexibility and modulation to empathic processes[56].

Prefrontal- and cingulate-mediated "top-down" executive control of empathy, or perspective taking, is often divided into two components: cognitive perspective taking (*i.e.,* inferring what another *thinks*), and an affective perspective taking (*i.e.,* inferring what another *feels*)[56, 60]. In this review, we will use the term "affective perspective taking" when tasks differentiate between the cognitive and affective components of "top-down" empathic processes. Otherwise, we will use "cognitive perspective taking," which can also be called mental state attribution, or mentalizing. Both affective and cognitive perspective taking require intact Theory of Mind (ToM), or the ability to differentiate the beliefs of another from oneself. Investigations into the neural correlates of cognitive perspective taking have observed a characteristic network of activations when participants read stories about social interactions, including the temporo-parietal junction (TPJ), the STS, the temporal poles, the PCC, and the mPFC (fig.1)[61–63]. The dmPFC subnetwork, which is more strongly connected to these high-order association regions, is more heavily associated with cognitive perspective taking than the vmPFC[64]. In contrast, affective perspective taking preferentially activates the vmPFC[65]. Patients with vmPFC lesions demonstrate a functional dissociation in their perspective taking processes: they exhibit intact cognitive perspective taking but impaired affective perspective taking[60]. Thus, "top-down" regulation of cognitive and affective perspective taking may be dissociable functionally in the mPFC, requiring input from the dmPFC and vmPFC, respectively.

Alterations in ASDs and SSDs.—Empathic processes are altered in many neuropsychiatric disorders, most notably ASDs and SSDs[66]. In ASDs, there is no clear consensus as to what may underlie changes in empathic processes. Emotional contagion may be atypical in ASDs, but studies of vicarious pain have demonstrated reduced,

similar, and increased brain responses to other's pain in the ACC and AI[58]. A number of studies have demonstrated reduced cognitive perspective taking[67], but not affective perspective taking[68, 69], in patients with ASDs. In keeping with this perspective, patients with ASDs exhibit reduced covariance in networks centered on the dmPFC and TPJ, but not fronto-insular connectivity, suggestive of a dissociation between cognitive and affective networks. This perspective has come under question in recent years, however, with other studies finding intact cognitive perspective taking and even enhanced affective perspective taking[70, 71].

In patients with SSDs, emotional contagion appears to remain intact, with comparable activation patterns to healthy control participants in the affective mirror neuron system during the observation and execution of complex facial emotional expressions[72], despite lower self-reports of empathy. In contrast, there is robust evidence of changes in both cognitive and affective perspective taking[73–75]. When making judgments requiring either cognitive or affective perspective taking, patients with SSDs exhibit hypoactivation of the mPFC and the TPJ[76], and decreased fronto-temporal connectivity[77]. Evidence suggests that inability to appreciate one's own and others' mental states is the single best predictor of poor social competence in SSDs[78], which is consistently correlated with the functional disability of patients[47]. As such, determining the neurobiological etiology of empathetic impairments in SSDs, and using this knowledge as the basis for therapeutic interventions, may improve patient outcomes.

Social incentive and action selection in humans

Neural correlates.—Historically, non-social valuation research (*i.e.,* responding for food or money) has focused on neural computations signaling rewarding properties of the choice options. This research has revealed a framework of brain structures known as the "brain valuation system." Interestingly, many investigations into the neural correlates of the incentive value of social interactions have found overlap between the areas activated by social and non-social rewards. Meta-analyses comparing anticipation of monetary or social rewards found a consistent overlapping valuation network, including the ventral and dorsal striatum, the amygdala, the insula, and the supplemental motor cortex[79] (fig.1). These studies have led many to contend that the brain utilizes a "common currency" to encode and utilize *any* reward information (social or non-social) to make decisions[80, 81]. The "common currency valuation" hypothesis suggests that a unified brain system that calculates value is utilized to determine the motivational salience of all stimuli, regardless of social nature (reviewed in[82]).

Another theory, "social-specific cognition," asserts that social rewards and values are processed by a dedicated neural circuity that evolved specifically to deal with interactions with others. There are multiple derivations of how social-specific cognition may be encoded neurobiologically. Some contend that two types of neurons – those conveying social and non-social value information – might reside in different brain regions. For example, when subjects make decisions regarding a reward for themselves, the vmPFC is engaged, while making altruistic choices preferentially engages the TPJ[83, 84]. Social-specific cognition may involve the consistent differential activation of brain regions: although social and monetary

rewards both activate the ventral striatum, social stimuli are more associated with amygdala activation whereas monetary rewards were more associated with thalamus activation[85]. Another possibility is that social-specific cognition may involve the same brain regions, but reside within distinct neuronal population codes[82]. Consistent with this notion, a recent multivariate pattern analysis identified distinct non-overlapping neuronal representations in the ACC following social rejection or physical pain[86]. Thus, there is still an open debate as to how social-specific value is encoded in the brain, and how that value guides decisions.

For a social decision to be performed, regardless of whether social or non-social circuitry is distinct or coalesced, putative values for each choice option must be computed, and an action must be selected. To operationalize decision making in a social context in humans, neuroscientists have adopted the tools of Game Theory, which is based on models aiming to identify the optimal choice for interacting agents. Typical examples of prosocial attitudes are investigated in tasks using two or more interacting players. One popular example is the Ultimatum Game, in which two players split a sum of money. The *proposer* offers a division, and the *responder* can accept or reject this. The Ultimatum Game thus relies on normative social principles of fairness as motivators of decision making, and involves the activation of the dlPFC and the anterior insula in normal contexts (fig.1), with heightened activity in the anterior insula when the responder rejects unfair offers[87]. In a modification of the Ultimatum Game, called the Dictator Game, the responder has no power to control the outcome of the bargain. The Dictator Game is thus used to evaluate the proposer only, demonstrating that even without responder input, a dictator will donate 20–30% of their earnings[88]. Another example, the Trust game, relies on interpersonal reciprocation[89]. In the Trust game, a first agent, the *trustor*, is given money and can choose what percentage of it goes to a second agent, the *trustee*. Before the transfer occurs, it is magnified by a certain factor (*i.e.,* doubled or tripled). Lastly, the trustee can choose to either keep the whole amount or honor the initial sacrifice of the trustor and send a fraction of their earnings back. fMRI studies have exhibited higher mPFC activity when playing with a partner *vs*. a computer[90], and that the TPJ, anterior insula, and ACC were activated by reciprocation of trust[91].

Human choice behavior in the Ultimatum or Trust game can be understood using a reinforcement learning (RL) framework[82, 92, 93]. In RL, social and non-social factors have *expected values*. *Expected values* are then used to compute the *reward value* associated with the outcomes generated by the choice. Lastly, the expected value and the reward value are compared, resulting in a computed *reward prediction error* (RPE). For example, if the reward value far exceeds the expected value, a positive RPE is signaled in the ventral striatum and dopaminergic midbrain[94]. Subsequently, this RPE will reinforce the choice that led to it, guiding future decision making; this use of RPEs to guide decisions requires the vmPFC[95]. Imaging studies have combined variants of the Ultimatum Game with RL to analyze the social influences of decision making: the conversion of social value to a “social RPE” engaged the TPJ, the dlPFC, and the ACC[96–99]. This social RPE is then converted into a more generalized computational value in the vmPFC that guides decisions[97, 98, 100]. Thus, although social and non-social influences of decision making might engage different areas of the brain, these processes appear to converge onto the vmPFC before a decision is made. Perhaps unsurprisingly, patients with lesions in the vmPFC demonstrate deficits in

outcome valuation-guided decision making in both non-social and social reward, suggesting a potential function in common currency valuation of decision making[101].

Alterations in ASDs and SSDs.—In multiple clinical populations, there are specific reductions in the ability of individuals to find social stimuli incentivizing or motivating, typically termed social anhedonia, which is a distinct compared to general, or physical, anhedonia[102]. For example, the social motivation theory of ASDs posits that disruptions in social motivation constitute a primary alteration in ASDs, ultimately resulting in fewer experiences with social sources of information and decreased social learning[103, 104]. As discussed previously, very young children with ASDs exhibit decreased orienting to social stimuli[105]. This lack of social incentive over time decreases chances for social learning, decreasing social competence later in life[106]. Children with ASDs respond faster for monetary rewards than social ones[107]. Similarly, patients with SSDs rate genuine smiles as less rewarding than healthy controls, despite showing the same preference for monetary rewards[108]. Further, levels of social anhedonia in college undergraduates predict the development of later SSDs[109, 110], suggesting that social amotivation may be a prodromal symptom of the disorder.

Performance in neuroeconomic games has also been informative in the analysis of patients with ASDs and SSDs[89]. In patients with ASDs, deficits emerge when subjects serve in the *responder*, but not proposer, role of the Ultimatum Game[111, 112], and when serving in the *trustee*, but not trustor, role of the Trust Game[113]. In either game, there is a reduced responsivity to reciprocal cooperation or fairness, but the reasons for this are unclear. There is evidence that children with ASDs exhibit diminished middle cingulate cortex responses while playing the trustee in the Trust Game[113], and reduced BOLD responses in regions associated with cognitive perspective taking (*i.e.,* amygdala, insula, TPJ) during a variant of the Trust Game called the Prisoner's Dilemma[114]. These findings have led researchers to speculate that alterations observed in neuroeconomic games may be attributable to reductions in cognitive perspective taking and ToM, resulting in the observed reductions in sensitivity to reciprocal fairness[89, 112].

Patients with SSDs exhibit a similar deficit in perceived reciprocal fairness: accepting more unfair offers and rejecting more fair offers in the Ultimatum game[115–117]. In addition, patients with SSDs act less strategically as proposers – making higher offers in the Ultimatum Game – and exhibit less trust than control counterparts[116, 118]. Patients with SSDs also demonstrate a lack of flexibility or adaptive control in decision making in social contexts, failing to adapt to the availability of contextual information, or their partner's emotions or performance[115, 116]. However, the reasons for these deficits are still unclear, and may emerge from a multifactorial combination of reduced social incentive, poor ToM, or poor integration of cognitive and affective information[89]. Notably, behavioral performance on these tasks correlates with symptom severity: patients with greater social deficits exhibit a higher degree of positive symptom severity[119]. Thus, a fine-tuned approach is needed to better understand how social decision making could function as an endophenotype for neuropsychiatric disorders.

CAN RODENTS REALLY BE USED TO STUDY SOCIAL DECISION MAKING?

Non-human primates exhibit a robust repertoire of social behaviors with undeniable translational potential[120], but a smaller genetic toolbox relative to other experimental systems prohibits in-depth investigation of mechanistic factors in behavior – for example, functional analysis of projections between specific interconnected cortical, striatal, and limbic brain regions likely controlling social/emotional recognition, empathic processes, and social incentive/action selection. Rodents serve as a valuable complementary tool to non-human primates but are often dismissed as viable model organisms for studying complex social behaviors. This notion persists despite an emerging body of literature describing complex social behaviors in rodents, including sophisticated reciprocal interactions with conspecifics[121].

Neural processes dedicated to social decision making appear to be remarkably conserved over the course of evolution, from rodents to humans[122, 123]. Still, how social information is processed in the rodent brain is a subject of debate. An obstacle in understanding the anatomical correlates underlying decision making in the rodent is that several parallel processes occur at once. To make a decision in a social context, a rodent must perceive and prioritize the sensory cues emitted by a conspecific, render those cues as relevant, use those cues to motivate behavior or encode reward, and generate a behavioral response. In this section, we will review how researchers have deconstructed social decision making in the rodent.

Anatomical and functional subdivision of the mPFC in rodents

Anatomical homologies between human and rodent mPFC have historically been a point of contention between researchers (for lively discussion, see[18, 124, 125]). Studies of functional homologies have been similarly fraught, but certain non-social functions of the human PFC, such as working memory[126], behavioral flexibility[127, 128], attention[129], and impulse control[130] have been localized to the rodent PFC. Nevertheless, we will briefly orient the reader to generally agreed upon subdivisions of the rodent mPFC before delving into their putative roles in social behavior. Historically, the rodent mPFC has been subdivided into five subregions along a dorsal-to-ventral axis: the supplementary motor area (M2; putatively homologous to BA6 or BA8, as this region is plagued by confusing nomenclature, for review, see[131]), the ACC (putatively homologous to BA24), the prelimbic cortex (PL; putatively homologous to BA32), the infralimbic cortex (IL; putatively homologous to BA25), and the medial orbitofrontal cortex (MO; putatively homologous to BA11/BA14) (fig.1)[125, 132, 133]. All subregions receive projections from adjacent regions of the mPFC, insular and entorhinal cortices, mediodorsal thalamus, amygdala, dorsal raphe, ventral tegmental area (VTA), and locus coeruleus (LC). Major inputs to the dorsal mPFC – M2 and caudal ACC – of rodents include cortical and thalamic sources, while the ventral mPFC – rostral ACC, PL, IL, MO – is more highly innervated by limbic sources and the midline thalamus (for extensive review, see[133–135]). Recent studies have highlighted antagonistic roles in cognition between the PL and IL in fear conditioning, with PL promoting fear expression while IL promotes fear extinction[136]. A similar dichotomy has emerged in the context of cortico-striatal control of action selection strategies: activation of PL supports

flexible decision making, whereas activation of the IL supports inflexible (or habitual) behavior[128, 137, 138].

Historically, studies examining the ACC in rodents have relied on distinguishing the region along a dorso-ventral axis, into the Cg1/Cg2 subregions, where Cg1 encompasses human BA24b and 24b' while Cg2 encompasses BA24a and 24a'[139]. This has been observed to not be structurally or functionally homologous to the ACC/midcingulate cortex (MCC) distinction used in humans, which has led to a shift in rodent nomenclature such that the ACC/MCC distinction is made rostro-caudally, with rostral ACC encompassing putatively homologous parts of human BA24a-b, 25, and 32, whereas the caudal MCC is comparatively uniform and as such does not contain subdivision[139]. The rostral ACC shares reciprocal connections with the BLA, and dopaminergic centers, which may underlie functions in working memory and decision making[140].

Social and emotional recognition in rodents

Tasks to test social recognition.—Perhaps the largest limitation in studying rodent social perception, from a translational perspective, is that the most salient sensory cues for the rodent differ significantly from that of humans[141]. In contrast to visual cues leading to neurobiological demands such as facial processing by the FFA, rodents rely much more heavily on the olfactory signatures and chemosensory cues emerging from social stimuli[142 143]. This is not to say that visual cues play no role in social recognition in rodents, as recent evidence suggests that integration of multiple sensory modalities is necessary for proper social recognition[144, 145].

Many tasks have been developed to better understand social recognition in rodents (table 1). The first of which, the *habituation/dishabituation task*, was introduced in 1982 in rats[146] (and subsequently adapted for use in mice[147]). In this task, the experimental subject is repeatedly exposed to an unfamiliar stimulus animal in a series of habituation sessions, interleaved by intervals in which the experimental animal is left in its home cage. Direct sniffing of, and interaction with, the stimulus animal is recorded, and a typical subject will decrease social investigative responses with repeated sessions. In the last phase of the task, termed "dishabituation," a novel unfamiliar animal is introduced, and a typical subject will reinstate high levels of social investigation. This test is robust, but it does not control for any preference for novelty that may guide behavior in the last phase. Further, it has a limited ability to differentiate between short-term and long-term memory[148].

These limitations led to the development of the *social discrimination task*, perhaps the most widely used test of social recognition in rats and mice[148, 149]. This procedure consists of two sessions. In the first, a novel stimulus animal is introduced to the cage of the experimental animal, allowing for the acquisition of its olfactory signature. In the second, separated by any desired time interval, two stimulus animals, one familiar and one unfamiliar, are introduced at the same time to the experimental subject's home cage. A typical experimental animal will spend more time with the unfamiliar stimulus animal than the familiar stimulus animal. This procedure is typically preferred over the habituation/dishabituation task as it can be used to test short-term memory or long-term memory, given that the period between the two sessions can be short or long.

Since the introduction of the social discrimination task, variants have been introduced in which the stimulus animals are confined in wire cups, or a three-chamber apparatus is used, called the *social novelty test* or *social choice test*[149, 150]. These variants limit the ecological validity of the test because the stimulus animals are constrained, but they reduce the complexity of the social interactions and are considered decent substitutes for more naturalistic approaches if the experimental subject can fully smell and interact with the olfactory signatures of the familiar and unfamiliar animals. The olfactory information emitted by a conspecific does appear critical for social recognition and approach in mice and rats, as tested in the *odor block test*. In this variant, an experimental animal is presented two wooden blocks: one scented with its own bedding or that of a conspecific. A typical experimental animal will prefer to engage with the block scented with the odor of the conspecific (table 1;[151]).

Other notable tests of social recognition include the *partner preference test*, which has been used in monogamous prairie voles[152, 153]. These monogamous voles, once they have formed a pair bond, will spend significantly more time with their partners than with strangers[154]. Also notable is the spontaneous formation of *social hierarchies* within colonies of mice[155] and (although less aggressive and territorial) rats[156], thought to maintain order and improve mating chances of community members with higher rank. Social hierarchies are typically determined using the *tube test*, whereby two mice are placed in opposing directions at either end of a narrow tube; the mouse that successfully pushes the other mouse out of its way is considered the successor and more dominant within a hierarchy[157, 158]. These dominant-subordinate relationships can be transmitted through olfactory signatures and appear to be regulated by prefrontal cortical circuits. Several studies have also investigated social recognition through the measurement of ultrasonic vocalization (reviewed in[159]).

Neural correlates.—For the purposes of this review, we will focus on one stream of sensory information – olfactory – as it reaches higher order processing areas responsible for social recognition (for a review of multisensory integration in social decisions, see[145]). The neural circuitry underlying olfactory social recognition in rodents begins in the accessory olfactory bulb (AOB; fig.1). The AOB houses a glomerular map for both the main olfactory epithelium (MOE), which detects olfactory signals, and the vomeronasal organ (VNO), which detects chemosensory signals. The MOE and VNO are both crucial for a wide variety of social behaviors in rodents[160]. For instance, ablation of the MOE or VNO decreases sexual behaviors in both sexes of mice[161, 162].

From the AOB, projections reach the cortex or hypothalamus, while VNO outputs converge on the medial amygdala, which acts as a major site for the integration of olfactory output[163]. The medial amygdala subsequently activates following exposure to chemosensory stimuli, and blocking medial amygdala activity impairs social recognition memory in mice[164]. The entorhinal cortex, which receives inputs from the perirhinal cortex, the amygdala, the thalamus, and the hypothalamus, acts as a gateway to the hippocampus, as well as its primary output. Lesions of the entorhinal cortex cause deficits in short-term odor memory[165]. In contrast, the neighboring perirhinal cortex, which receives sensory information from the olfactory cortices, is involved in the social recognition of hamsters, and appears to be required for the long-term storage of olfactory signals[166].

Surprisingly, initial studies in which lesions were placed in the hippocampus did not document impairments in social recognition memory[167, 168]. Subsequently, inactivation of the hippocampal CA2 subregion resulted in a pronounced loss of social memory with no effect on general sociability[169, 170]. Investigations of the CA1 region of the hippocampus, and its projections to the nucleus accumbens (NAc), documented higher neuronal activity in response to a familiar mouse relative to an unfamiliar mouse. In a so-called "social memory inception" protocol, activity-dependent labeling was used to "trap" CA1 neuronal ensembles during a novel experience with a stimulus mouse. Experimenters then optogenetically re-activated these CA1 ensembles previously activated by this stimulus mouse during a foot shock or cocaine exposure. Such experiences created "fake social memories" in the experimental mouse, causing avoidance or approach of the stimulus mouse in a subsequent social discrimination task, despite not having interacted with the stimulus mouse since that original contact[171]. Thus, the hippocampus appears to store manipulable ensembles encoding distinct social memories, or "engrams," specific to certain individual social experiences (fig.1).

The consolidation of memory with social content increases protein synthesis and immediate early gene (IEG) activity in the basolateral amygdala (BLA), the mPFC and ACC, and the hippocampus, revealing the involvement of amygdalo-cortical structures in social recognition[172]. Chemogenetic excitation or inhibition of ventral hippocampal projections to the mPFC impairs social recognition[173], and silencing of PL efferents to either the BLA or NAc can also reduce social recognition, highlighting an important role of the mPFC in this process, although more studies are needed to clarify its contributions[174, 175].

Empathic-like processes in rodents

Tasks to test empathic-like processes in rodents.—Some of the first evidence that rodents were capable of emotional contagion came from an experiment demonstrating that rats, trained in a lever-press task to receive food, inhibited this behavior when viewing a shocked rat[176] (table 1; for a review on rodent models of empathy, see[177]). The authors speculated that this phenomenon reflected emotional state matching between individual rodents. The most studied type of emotional contagion in rodents is called *vicarious freezing*, which is represented by a freezing response in a rat witnessing a conspecific being shocked and displaying fear responses[178, 179]. Mice also exhibit vicarious freezing responses[180], and recent elegant studies demonstrated that emotional contagion in mice extends beyond fear, to feelings of pain and analgesia[181].

Several other procedures provide evidence that rodents can use emotions, fear in particular, to socially transmit information[182]. In vicarious learning procedures, such as *fear conditioning by proxy*, a rat exposed to a novel tone in the presence of a cage-mate previously conditioned to that same tone will freeze[183]. In another variation of this type of procedure, termed *social harm aversion*[184], rats will inhibit a behavior if this behavior is associated with harm to others. This phenomenon is bidirectional, in that the frequency of a behavior will increase if the behavior is associated with rewards to others[185].

Two tasks have been recently developed specifically to test the ability of rodents to recognize the emotional states of conspecifics, and thereby guide behavior (table 1).

The first of these tests is the *affective state discrimination task* (ADT). ADT allows for discrimination based on positive affective state, as an experimental mouse will prefer to investigate a "relieved" demonstrator – a conspecific that just received water after 24 hours of water deprivation – over a control mouse. ADT can also test detection of a negative affective state, as an experimental mouse will prefer to spend time investigating a "stressed" control mouse over a neutral demonstrator[186]. In an alternative to ADT, the *social affective preference* (SAP) test, adult rats will approach a stressed juvenile, but avoid a stressed conspecific adult[187]. Thus, the ADT and SAP provide avenues by which to investigate the neural correlates of emotional recognition and discrimination in rodents.

If we apply de Waal's multi-level theory of empathy, all of the behaviors described so far in this section can be explained through variants of emotional contagion, the "lowest common denominator" of empathic-like processes[55]. To anthropomorphize, subjects could simply be performing a behavior to reduce the stress they feel by having to watch another in stress. According to de Waal, the next evolutionary step occurs when emotional contagion is combined with an understanding of the other's situation and attempts to understand the cause of the other's emotions. Two elegant procedures recently demonstrated evidence of this more advanced level of empathy in rodents. This first describes *rescue behavior*, in which a free-roaming rats exhibit motivation to liberate a caged conspecific[188]. When given the choice between chocolate and a caged conspecific, the subject will choose to liberate at the same latency as retrieving a food reward, and will subsequently *share* the food reward with the recently freed conspecific[188].

Another study in prairie voles demonstrated *consolation-like behavior*[189]. In this protocol, two prairie voles were given the opportunity to form a pair-bond prior to being separated. One of the two (the demonstrator) would receive foot shocks, while the other (the observer) would remain in the home cage. Following their reunion, the observer would greatly increase allogrooming behaviors towards the demonstrator, in comparison to a variant in which the demonstrator did not receive any shocks. No increase in grooming behaviors was observed when the demonstrator was an unfamiliar vole. Strikingly, the observer would continue this behavior, alleviating the plasma corticosterone levels of the demonstrator, apparently *even at the cost of* raising their own stress, as observers had significantly elevated plasma corticosterone following the interaction. These studies problematize the notion that rodents are not capable of more nuanced empathic-like behaviors and demonstrate the importance of generating tasks aimed at better understanding them (table 1).

Neural correlates.—Rodent studies have consistently connected empathic-like behaviors to ACC and prefrontal cortical function (table 2). The ACC is a hub of "emotional mirror neurons" in rodents, which are activated both by the self-experience of pain and witnessing pain in another[190, 191]. Inactivation of the ACC reduces emotional contagion, causing observers to freeze less while witnessing a demonstrator receiving foot shocks[192], and vicarious freezing, causing observers to freeze less in the *environment* in which they had witnessed the demonstrator receiving foot shocks[190]. Meanwhile, consolation behavior in prairie voles requires oxytocinergic tone in the ACC[189]. Further, emotional discrimination in mice requires somatostatin-expressing interneurons, but not parvalbumin-expressing interneurons, in the mPFC[186].

An understanding of the neural network responsible for empathic-like behaviors in rodents is starting to emerge (fig.1). Projections from the ACC to the BLA are necessary for observational fear conditioning[181, 193], while projections from the ACC to the NAc are necessary for the social transmission of pain[181]. The insular cortex, a site of multisensory integration with outputs to limbic, reward, and executive systems (reviewed in[145]), is implicated in emotional contagion. Inactivation of the insular cortex reduces the pain response induced by cohabitating a subject with a conspecific experiencing chronic pain[194]. Also, pharmacological or chemogenetic inactivation of the anterior insula leads to diminished helping behavior in a rat model of targeted helping[195]. Further, parts of the amygdaloid complex are involved in emotional contagion: inactivation of the lateral and medial amygdala reduces emotional contagion[196]. Lesions of the BLA reduce a rat's preference for actions that reward themselves and another rat, over those that just reward themselves[197].

Social incentive and action selection in rodents

Tasks to evaluate social incentive and action selection.—Rodents are incredibly social creatures, with maternal contact, social play behavior, and sexual behavior being the most intensively researched forms of pro-social interactions in rats and mice (reviewed in[198, 199]). Some of the most common assays of rodent social behavior are derivations of the *social approach test*, which was first developed as an assay of anxiety-like behavior in 1978[200] (table 1). Modern variants detect an experimental subject's preference for investigating a novel conspecific compared to a novel object, typically in a three-chamber apparatus similar to the one used for the social discrimination task described above[201]. This task defines "sociability" as the propensity to spend time with another animal, as opposed to time spent in an identical but empty chamber. In a variation of this social approach task, a T-maze is used, and subjects will choose to spend time with a social stimulus over a non-social stimulus. Mice and rats will retrieve pups or find a mate in a T-maze[198], and adolescent rats will prefer one end of the "T" over another to participate in social play[202].

One limitation of social approach tasks is that "sociability" is a relatively abstract concept, as it is unclear if an individual actually *values* the social experience, or simply finds it more stimulating than an empty chamber. Dissecting the "value" of social interaction (or, in an RL framework, the *expected value* of a social experience used to compute a generalized common effective state to guide decisions) is inherently trickier. Historically, a way to infer the "rewarding" properties of social interaction in rodents was borrowed from the drug addiction literature: *conditioned place preference (CPP)*[203]. CPP uses Pavlovian conditioning principles whereby neutral environmental cues gain salience after being repeatedly paired with a rewarding stimulus. In this procedure, the rewarding event serves as the unconditioned stimulus (US), while the neutral environment functions as the conditioned stimulus (CS). Thus, a rodent will choose to spend more time in the previously neutral environment following CS-US pairings. Postpartum rat dams deprived of their pups, but not virgin females, exhibit social CPP (sCPP) when one chamber is paired with reunion with pups[204], and this effect is dependent on the olfactory signature of the pups[205]. sCPP has also been demonstrated in adolescent rats when one chamber is paired with social play[206], an age-matched conspecific[207], or aggression-related reward behavior[208]. sCPP has been

adapted for use in mice[209], but with varying degrees of success, as the effect has been found to be more spurious[210].

Along the lines of sCPP, researchers have attempted to compute the value of a social interaction by showing how it influences a decision and/or elicits a behavior. Most times, that social interaction is either an affiliative or aggressive interaction[8]. But other times, rodents must take information from a social experience and use it to guide a non-social decision. For example, rodents use information from others to learn where, what, how, and even when to eat[211]. In the *social transmission of food preference* task, the olfactory cues from the breath of conspecific mice and rats can induce food preferences that even overrule innate preferences[212] (table 1). In this task, the olfactory cues from social investigation provide information regarding safety and palatability and thus will alter the decision to consume a typically avoided novel food.

Another form of ascertaining the reinforcing properties of social interaction on behavior in rodents is to see if they will perform an action to obtain a social interaction, which can be assayed through *operant conditioning*. Rats will lever-press to retrieve pups[213, 214], and male rats will lever-press for the opportunity to play with a juvenile conspecific[215], to gain access to a sexually receptive female[216], or to act aggressively[217, 218].

Another operant-based task, deemed *Operant social preference (OSP),* has been validated in adult male Syrian hamsters[219]. The apparatus in OSP consists of a main chamber with two small adjacent chambers, separated from the main chamber by a one-way vertical-swing door. The vertical swing door could be attached to weights, increasing the amount of effort needed to enter one of the side chambers. When tested, animals entered the chamber containing a conspecific significantly more than an empty chamber, and the motivational effort to obtain social interaction and food were similar[219]. A limitation of OSP is that hamsters are not asked to choose between different rewards; they are instead either entering a chamber with a novel stimulus hamster or food, as compared to an empty chamber. This limitation was addressed by Venniro and colleagues (2018), who developed a procedure in which rats could lever press for access to a novel conspecific, and strikingly, demonstrated that rats chronically exposed to cocaine or methamphetamine would still prefer to lever press for social interaction over drug exposure[220]. This report was particularly notable for introducing discrete choice at the time of tests: rats could choose social interaction *or* drug exposure and consistently chose social interaction over cocaine or methamphetamine[220]. This study demonstrates the intensely reinforcing nature of social interaction in rats.

In contrast to investigations in rats, the current repertoire of tasks validated to investigate social influences on non-social behaviors and action selection strategies *in the mouse* is limited (table 1). To add to this repertoire, our group devised a new task, *social incentivization of future choice* (SIFC)[221]. In SIFC, a female mouse is trained to nose poke on two distinct nose poke apertures for two distinct food rewards, either grain or chocolate. Once trained, the mice undergo social conditioning, whereby one of those two pellets is paired with a social experience with a novel conspecific, while the other is paired with a novel object. This social experience is sufficient to incentivize responding on the nose poke aperture predictive of the “social” pellet[221]. Said another way, the value of the social

experience may be transferred to an external reward, biasing responses towards that pellet. SIFC is pervasive, expressed after varying social experiences, even presumably aversive ones, such as a social experience with a shocked conspecific or a sexually experienced unknown male. Our interpretation is that the opportunity to gain novel social information, writ large, is adaptively valuable, and that SIFC reflects that value, rather than strictly the affiliative properties of the social interaction itself. We find that SIFC cannot be attributable to olfactory or warmth cues alone and does not rely on any single behavior (e.g., anogenital sniffing) exhibited during social conditioning. As such, SIFC provides a new tool to examine the influence of social behavior on instrumental action in mice[221]. We imagine that it could have utility in rats, as well, given that rats can readily perform all aspects of this task. Further, this SIFC task was directly inspired by the classical operant conditioning assay termed Pavlovian-to-instrumental transfer (PIT), which has historically been tested in rats[221].

Scheggia and colleagues also recently developed a mouse version of the Ultimatum/Dictator's Game, deemed Social Decision Making (SDM), to analyze social influences of operant choices. Using a modified instrumental conditioning chamber with a connected chamber and magazine for a cagemate conspecific, mice could either act to gain a food reward for themselves (e.g., act in a *selfish* manner), or act to also provide a food reward for their neighbor (e.g., act in an *altruistic* manner)[222]. Interestingly, male mice were more likely to act altruistically than female mice, and altruism-like behavior varied based on the hunger state, familiarity, and hierarchical status of the neighbor[222]. Further, mice particularly susceptible to observational fear learning were more likely to act in an altruistic manner, suggesting a connection between emotional contagion and "altruism." Thus, prosocial and "altruistic" behaviors are being identified and elucidated in species previously believed too primitive to perform such actions, mainly due to nuanced behavioral paradigms that lend themselves to larger scale rodent investigations. Future studies using these paradigms should aim to better understand the mechanisms underlying and evolution of altruism and prosociality in rodents.

Neural correlates.—How the incentive value of social interaction is encoded in the brain of rodents has only recently come more into focus (table 2; fig.1). In 2011, Yizhar and colleagues used a fine-tuned set of stable step-function opsins (SSFOs) to activate or inhibit excitatory or inhibitory neurons in the PL and IL, thereby disrupting the excitatory/inhibitory (E/I) balance. Elevation of the E/I balance in the mPFC through excitatory activation disrupted social interaction, an effect that could be partially ameliorated by increased inhibitory activation[223]. It was subsequently demonstrated that a subset of mPFC neurons elevates in discharge rates when an experimental subject approaches a stranger mouse but not an empty cup, suggestive of a role for the mPFC in social approach[180]. Recent real-time investigations have established that projections to the NAc[224], to the VTA[225], to the medial zona incerta (ZIm)[226], and to the paraventricular thalamus (PVT)[227] are among those active during social interaction. In a remarkable study, microendoscopic calcium imaging was used to monitor activity from hundreds of dmPFC neurons of two interacting mice in an open arena[228]. Kingsbury and colleagues computed aggregate signals of dmPFC activity to compare the "interbrain synchrony" between these two

mice. Strikingly, much higher levels of interbrain synchrony were observed during social behaviors compared to non-social behaviors. Further, interbrain synchrony depended on cells responsive to specific social behaviors in the subject, as well as cells responsive to specific social behaviors in their partner[228].

Rodent studies examining sociability identify a functional network of connectivity surrounding the PFC. Firstly, many studies have established a circuitry including amygdalo-cortical projections, and cortico-striatal projections in typical social interactions. Excitation and inhibition of BLA→PFC projections can decrease or increase social interaction, respectively, similar to the bidirectional control of these projections in anxiety-like behavior[229, 230]. Remarkably, PL→NAc projections can encode socio-spatial associations in a modified three-chamber task, meaning that a large proportion of PL→NAc neuronal ensembles preferentially fire in response to a social target in one spatial location (either the right or left side of the chamber)[224]. Further, Murugan and colleagues (2017) showed in a modified sCPP task that inhibiting PL→NAc ensembles can inhibit the development of sCPP, and, when activated, can enhance sCPP. The involvement of the NAc in sociability is perhaps unsurprising, as oxytocinergic tone in the NAc is required for intact sociability[231] and inactivation of the NAc in rats abolishes approach toward stressed juveniles, but not avoidance of stressed adults, in the SAP task[232]. In prairie voles, *in vivo* miniscope imaging has revealed that distinct ensembles in the core of the NAc increase in firing during approach towards partners, but not novel conspecifics[233].

New tasks investigating social influences of action have centered on the PL and its connections with subcortical structures. In SIFC, the PL is necessary for rodents to motivate instrumental responding based on previous social experiences, but not the neighboring orbitofrontal cortex (OFC)[221]. In contrast, classical non-social PIT requires the OFC but not the PL[234 235], suggestive of unique recruitment of PL circuits in decision-making behavior involving social content. Further, BLA→PL→NAc circuitry is required for social experiences to incentivize instrumental responding in SIFC, and immediate-early gene levels in the BLA predict the degree of SIFC expressed[221]. In SDM, BLA→PL connections mediate “altruistic” behavior in mice, while projections from the PL→BLA mediate “selfish” choices, suggesting dissociable circuitry underlying the decision to help a conspecific[222]. As BLA→PL projections appear to be necessary for social memories to guide future choices, and for mice to act “altruistically,” future studies should aim to understand the time course of BLA→PL ensembles in social decision making, and what molecular mediators within the BLA may underly its ability to signal the social salience necessary to guide actions.

Regions outside amygdalo-cortical-striatal circuits also of course exert control over rodent sociability. Social interactions in the rodent activate dopaminergic cells in the ventral tegmental area (VTA), which densely project onto the NAc[236]. Further, optogenetic activation of VTA-NAc cells facilitates social approach, whereas inhibition decreases it[236]. The insular cortex is similarly emerging as an area necessary for rodent social behavior (reviewed in[145]). In the SAP procedure, chemogenetic stimulation of insular cortical projections to the NAc increased approach towards stressed juveniles while inhibition reduced this behavior[187]. The volitional social interaction model shown to be protective

against addictive drug seeking described above relies on activation of central amygdala inhibitory neurons and inhibition of anterior insular cortex activity[220]. Importantly, the mPFC, NAc, VTA, and amygdala have all been implicated in non-social reward systems as well[237].

Some evidence suggests that amygdalo-cortical circuits might encode social and asocial behaviors in an antagonistic manner. For example, an inhibitory GABAergic neuronal ensemble in the MeA promotes aggression and mating behaviors, while a glutamatergic population promotes repetitive self-grooming. Moreover, this glutamatergic subpopulation inhibits social interactions independently of its ability to promote self-grooming, while the GABAergic subpopulation inhibits self-grooming[238]. In the OFC, distinct neuronal ensembles fire in response to food or social stimuli. While activity of food-sensitive neuronal ensembles facilitated feeding behavior, the activity of socially-selective neuronal ensembles exerted inhibitory control over feeding behavior[239]. In both cases, activity in neuronal ensembles required for a social behavior inhibited a non-social behavior, suggesting that social and non-social behaviors might be regulated to some extent in an antagonistic manner in some regions of the brain. However, future studies will be needed to better understand the divergent and convergent processes the rodent brain uses to evaluate and act upon social vs. non-social information.

Next steps: translational studies aimed at understanding social decision making

In both humans and rodents, the dissection of social decisions into their component parts – social/emotional recognition, empathic processes, social incentive/action selection – has allowed researchers to investigate the underlying brain regions, circuits, and neurochemical events necessary for incredibly complex social behaviors to occur. Human subjects-focused work can capture the nuanced interpersonal landscape contained within the human social world and can translate experiments to clinical populations such as individuals with ASDs and SSDs, for which animal models are limited. Meanwhile, rodent-focused work can function at sub-second timescales, using novel genetic approaches to better understand circuit function at a resolution currently untenable in human studies. Further, hypotheses concerning specific genetic and/or biochemical mechanisms can be empirically tested. The concomitant use of non-human primates in social neuroscience research (which has not been discussed in the current review, but see[5]) may also be imperative to better understanding complex social cognitive processes, given the ever-growing toolbox allowing for genetic access to specific cell types and circuits in these sophisticated organisms[240].

Future investigations into social decision making would do well to integrate cross-species research strategies to improve mechanistic and translatable knowledge, hopefully to ultimately improve treatment for illness. In one recent report, humans and mice with less bioavailable Brain-derived Neurotrophic Factor (BDNF) appeared to detect negative social information in experiences that control organisms deemed neutral. In mice, social information processing could be normalized by replacing BDNF during development in the MO, a cortical region argued to have a high degree of functional homology between organisms[241]. This cross-species investigation suggests that bioavailable BDNF during postnatal development is a fundamental building block for social information processing.

The val66met *BDNF* gene variant is associated with worse long-term psychiatric outcomes for individuals who suffer early-life adversity.[242] Thus, understanding BDNF control of social information processing may shed light onto disease mechanisms.

In this review, we attempted to identify human-rodent homologies in the mechanistic factors necessary for decisions to be made in social contexts. Connections between the vmPFC and amygdala routinely appear important for detecting salience in social contexts, with subsequent incorporation of information from reward systems (e.g., VTA) prior to engagement of downstream motor systems (e.g., striatal structures) as social information guides actions. The PL and ACC also recur as key social information processing hubs in rodents, corresponding with the aspects of the mPFC and ACC in humans, respectively. Future studies will be needed to better understand how social information is processed and valued in humans and rodents – are the neurobiological processes (from circuits to intracellular mechanisms and beyond) occurring within these structures conserved or divergent between species?

The last decade of rodent social neuroscience research has disabused the notion that rodents do not utilize complex social information to inform their choices, and/or that these processes cannot be systematically detected, quantified, and investigated. For instance, efforts aimed at translating social decision-making tasks across species have resulted in rodent versions of the Dictator's game[222]. These efforts are reminiscent of other explorations of decision making *outside* of social contexts, including investigations concerning complex "human" phenomena such as paranoid beliefs. One theorized mechanism contributing to paranoia is the propensity of an individual to re-categorize held beliefs in the face of uncertainty. Specifically, in situations when one is presented with uncertainty, beliefs may be recategorized (e.g., my friend is actually my enemy). To investigate learning styles in humans with paranoid beliefs and rodents with altered expectancy updating (e.g., post-methamphetamine exposure), researchers can carefully quantify responses to uncertainty utilizing probabilistic reversal learning in parallel cross-species investigations[243]. In the human subjects research domain, interesting recent investigations have combined machine learning with virtual reality and eye tracking to better understand empathic processes[244]; with the recent advent of virtual reality protocols in rodents[245], translational approaches could be similarly employed to dissect underlying neural circuits in rodents. This translation could be bidirectional, with the upscaling of certain rodent tasks (such as ADT or SIFC) for use with clinical populations. Cross-species investigations could help to determine whether: **1)** comparable brain regions are involved or implicated in decisions made in social contexts, and/or **2)** how current or novel pharmacotherapeutic and psychotherapeutics could be leveraged to ameliorate specific deficits in social decision making.

Conclusions

Social interactions, and how they affect our decisions, are difficult to dissect, even in controlled laboratory settings. This is due to a large dynamic environment of multiple agents, each with their own internal states, desires, and histories. It is perhaps unsurprising that deficits in social interactions, and social decision making, emerge in practically every neuropsychiatric disorder[246], given how many underlying components must co-occur

for social behaviors to be expressed typically. Even then, defining a “good” or “fair” (even “typical”) decision in a social context inherently includes some moralistic view of how individuals *should* act, which makes the study of social behavior all the more complicated. As genetic and physiological tools to manipulate specific neuronal ensembles and projections become more refined, so should the behavioral tasks that examine social behavior. Rodents provide a valuable tool to examine social decision making at a cellular and molecular level and can likely shed light on dysregulatory processes that characterize neuropsychiatric disorders.

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Highlights

- Many illnesses are co-morbid with, or defined by, disruptions in social behavior.
- Rodents are a viable tool for studying decision making related to social experiences.
- This review breaks down “social decisions” into their component parts.
- We discuss social/emotional recognition, empathy, and social incentive/value.
- We also pay homage to investigations that paved the way for current knowledge.

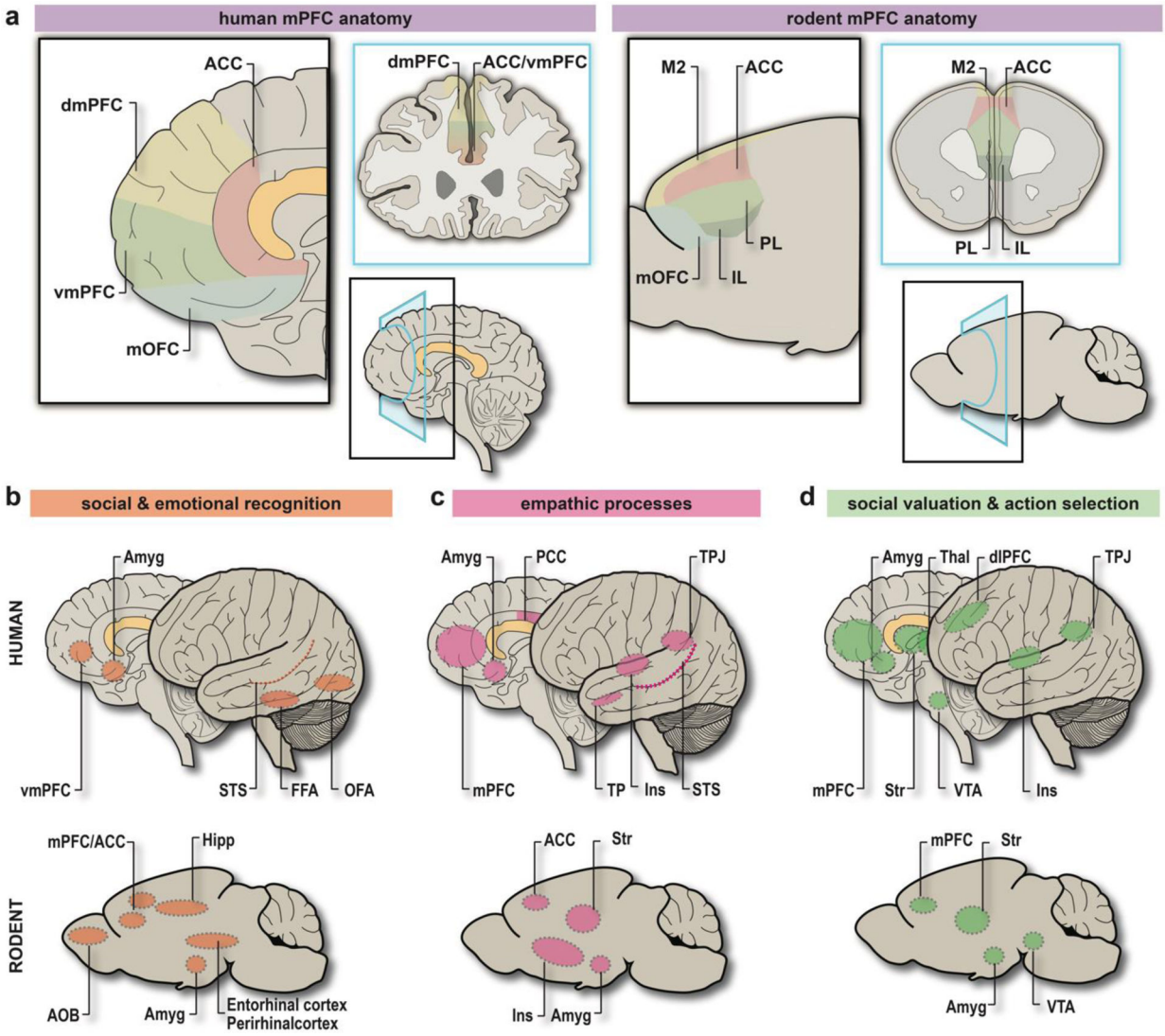

Figure 1. Comparative structural and functional anatomy of the "Social Brain" in humans and rodents.

a. (**left**) Diagram detailing human mPFC anatomy from the sagittal (black) and coronal (blue) perspective. Corresponding BAs: ACC = BA24, BA25, BA32, dmPFC = BA9, BA10, vmPFC = BA10, BA32, mOFC = BA11, BA14. (**right**) Diagram detailing rodent mPFC anatomy from the sagittal (black) and coronal (blue) perspective. Putative homologies to BAs: M2 = BA6 or BA8, ACC = parts of BA24a-b, 25, 32; PL = BA32; IL = BA25; mOFC = BA11, BA14. **b**. Brain areas involved in social and emotional recognition in humans (**top**) and rodents (**bottom**). **c**. Brain areas involved in empathic processes in humans (**top**) and rodents (**bottom**). **d**. Brain areas involved in the incentive valuation of social interaction, and subsequent action selection in humans (**top**) and rodents (**bottom**). Abbreviations: anterior cingulate cortex (ACC), anterior olfactory bulb (AOB), amygdaloid complex (Amyg), Brodmann area (BA), dorsolateral prefrontal cortex (dlPFC), dorsomedial prefrontal cortex (dmPFC), fusiform face area (FFA), hippocampus (Hipp), infralimbic subregion of mPFC (IL), insular cortex (Ins), medial orbitofrontal cortex (mOFC), medial prefrontal cortex

(mPFC), occipital face area (OFA), posterior cingulate cortex (PCC), prelimbic subregion of mPFC (PL), thalamus (Thal), temporal pole (TP), temporo-parietal junction (TPJ), striatum (Str), superior temporal sulcus (STS), secondary motor cortex (M2), vmPFC = ventromedial prefrontal cortex (vmPFC), ventral tegmental area (VTA). Image created by author HK using Adobe Illustrator.

Table 1.

Tasks used to investigate components of social information processing in the rodent.

Behavioral Task	Species	Experimental Outcomes	Citation
Social recognition			
Habituation/ dishabituation task	Long-Evans rats, CD1, C57BL, DBA/2 mice	• Subjects will reduce time exploring a juvenile upon second exposure • Higher interexposure intervals (IEIs) led to higher investigation during the second exposure to the same juvenile • Mature subjects exposed to social experience engaged in significantly longer investigation of a juvenile than those with no experience	146, 147
Social recognition test/ social novelty test	Wistar rats, CD1, C57BL, DBA/2 mice	• Subjects prefer to engage with an unfamiliar juvenile as opposed to a familiar juvenile • Replicated the finding that longer IEIs diluted social memory. Sexually naïve subjects demonstrate juvenile recognition, previously hypothesized to be masked by sexual/aggressive behavior towards intruder, possibly mitigated by concomitant administration of two conspecifics	148, 149
Odor block test	Mixed C57/129SvJ, C57BL/6J mice	• Subject is presented two wooden blocks: one scented with its own bedding *vs.* that of a conspecific • Subject will prefer to engage with the block scented with the odor of the conspecific • Dopaminergic deficits lead to impairments	151
Partner preference test	Prairie voles	• Subjects will spend more time with a partner over a stranger vole • Mating was not essential for partner preference, but aided its formation	153
Social hierarchies	A/alb, 03H, DBA/8 mice	• Social dominance hierarchies can be probed using a tube test • Two food-deprived mice were trained to move through a long tube to obtain a food reward; on a dominance trial, mice were placed on either end of the tube, and one forced the other to retreat backward • This task was used to measure social dominance within lab strains	157
Emotional recognition			
Social affective preference test (SAP) Affective state discrimination task (ADT)	Sprague-Dawley Rats C57BL/6J mice	• Subjects will approach a stressed juvenile but avoid a stressed adult • Subjects prefer to approach a “relieved” demonstrator that had just received water after 24hr water deprivation over a neutral demonstrator • Subjects prefer to approach a “stressed” demonstrator over a neutral demonstrator	187 186
Empathic like processes - *emotional contagion*			
Emotional reactions to the pain of others	Sprague-Dawley Rats	• Subjects decrease lever pressing for food in reaction to the unassociated pain responses of another animal	176

Behavioral Task	Species	Experimental Outcomes	Citation
Social recognition			
		• Subjects exhibited further decreases if they had experience being shocked themselves	
Social modulation of learning	Wistar rats	• Subjects paired with a shocked conspecific exhibit increased exploratory behavior, startle response, increased conditioned freezing	247
Vicarious freezing	C57BL/6J mice	• Subjects developed freezing behavior by watching other mice receive foot shocks	179, 192
Fear conditioning-by-proxy (FCbP)	Sprague-Dawley rats	• Cagemates of subjects conditioned to freeze to a tone demonstrated freezing to tone without any shock experience	183
Social harm aversion	Sprague-Dawley rats	• Subjects avoid actions that harm familiar and unfamiliar conspecifics	184
Empathic-like processes - *more advanced*			
Rescue behavior	Sprague-Dawley rats	• Free-roaming subjects in an arena with a cagemate trapped in a restrainer will work to free them	188
Consolation-like behavior	Prairie voles	• Subject greatly increases partner-directed grooming behavior after partner has experienced a stressor	189
Social valuation and action selection - *approach behaviors*			
Social approach/social proximity	Hooded rats, BTBR T+ tf/J, Swiss albino, mice	• Reciprocal interactions between two conspecifics • Maximum interaction under low light in familiar context • Initially used as a measure of anxiety	150, 200, 248, 249
Three-chamber test	C57BL/6J, DBA/2J, FVB/NJ, and B6129PR2/J mice	• Four strains spent more time in a chamber with a novel conspecific than an empty chamber sociability; A/J did not	201
Social preference/ avoidance test	C57BL/6J mice	• Subject is exposed to non-social stimulus, and then the non-social stimulus is replaced by a social stimulus • Subject will typically increase investigation time of social stimulus • Social defeat reduces preference in a neurotrophin-dependent manner	250
T-maze learning	Lister hooded rats	• Subjects chose in a maze to approach conspecifics	202
Social conditioned place preference (sCPP)	N:NIH rats	• Subjects will choose to spend time in a location that has been historically paired with a social experience	206
Transmission of food safety preference	Blue Spruce rats	• Subjects will learn to consume a previously avoided food after investigating a conspecific that recently ingested it	212
Incentive value of social interaction and action selection - *operant behaviors*			
Operant conditioning for social play	Wistar rats	• Subjects will lever press for the opportunity to access a juvenile conspecific and engage in play behavior	215
Operant social preference (OSP)	Syrian hamsters	• Subjects must press against a weighted door to receive access to a novel conspecific	219

Behavioral Task	Species	Experimental Outcomes	Citation
Social recognition			
Volitional Social Interaction	Sprague-Dawley rats	• Subjects could lever press for access to a novel conspecific or cocaine/methamphetamine exposure	220
Social incentivization of future choice (SIFC)	C57BL/6J mice	• Experience with a novel conspecific and food pellet will incentivize operant responding for that pellet	221
Social Decision Making (SDM)	C57BL/6J mice	• Mice will operantly act to either receive a pellet or to share a pellet with a neighboring mouse	222

Each row describes a task. Multiple citations are included if validated in different model organisms. Tasks designed to examine social stress response, aggressive behaviors, or mating behaviors are not discussed in this review.

Table 2.

Prefrontal cortical control of social information processing in rodents.

Species, Strain	Sex	Region	Stereotactic Coordinates			Manipulation or Measure	Findings	Cit.
			A/P (+)	M/L (±)	D/V (−)			
Social recognition and memory								
Lister hooded rats	M	ACC, OFC	2.3–0.9 4.0–3.2	0.5 2.6–0.8	0.2–2.0 4.4–3.4	lesion lesion	↓ social memory = social memory	251
C57BL/6J mice	M	mPFC, ACC	2.10–1.98 0.8–1.0	--	--	IEG analysis	↑ c-Fos and Arc	172
C57BL/6J mice	M	PFC	2.25	0.45	1.4	↑ OXTR+ neurons, PL→BLA OXTR+ neurons	↓ social recognition	174
C57BL/6J mice	M	IL	1.97	0.3	3.0	*In vivo* recording	↑social olfactory cues OR ↑non-social olfactory cues with experience-dependent sharpening of representations	229
C57BL/6J mice	M	mPFC	1.45	0.5	1.45	↑↓vHC→mPFC	↓↓ social recognition	173
C57BL/6J mice	M	PL	1.9	0.3	2.3	↓vHC→mPFC (PV interneurons)	↓ social recognition	252
C57BL/6J mice	M	PL	1.9	0.25	2.0	↓ PL→NAc	↓ social recognition	175
C57BL/6NHsd mice	M	IL	2.4 (10°)	1.0 (10°)	2.3	IEG analysis of IL→NAc ↓ IL→NAc	↑ social recognition ↓ social recognition	253
Emotional recognition								
C57BL/6J mice	M, F	mPFC	1.9	0.3	2.4	*In vivo* recording ↓ of SST+ interneurons	↑ in PL activity during ADT ↓ ADT	186
Empathic-like processes								
Long-Evans rats	M	PL/IL	2.7–3.2	--	--	IEG analysis	↑ c-Fos in PL/IL in subjects paired with shocked demonstrators	254
Sprague-Dawley rats	M	ACC	1.8 (18°)	1.6 (18°)	1.6	IEG analysis ↓ACC	↑ FCbP ↓ FCbP	255
Long Evans rats	M	ACC	1.7 (20°)	1.6 (20°)	1.8	*in vivo* recording ↓ACC	↑ unit activity when experiencing pain or observing another in pain ↓ OFL to observation of pain experience or associated CS+	190
Sprague-Dawley rats	M	ACC	1.35	0.6	2.4	fMRI scanning ↓ACC ↓↑ACC→MDL	↑ ACC activity ↓ OFL ↓↓ OFL	256
Sprague-Dawley rats	M,F	ACC	1.17 (20°)	1.16 (20°)	1.8	↓ACC	↓ social harm aversion	184
C57BL/6J mice	M	ACC	1.0	0.2	1.2	↓ACC	↓ OFL	192
C57BL/6J mice	M	ACC	1.0	0.3	1.2	↓↑rACC ↓↑IACC	↓↑ OFL == OFL	257
C57BL/6J mice	M	ACC	1.0 1.0	0.3 0.25	2.1 2.1	*In vivo* recording ↓ACC→BLA	↑ activity ACC→BLA during OFL ↓ acquisition, but not	193

Species, Strain	Sex	Region	Stereotactic Coordinates A/P (+)	M/L (±)	D/V (−)	Manipulation or Measure	Findings	Cit.
Social recognition and memory								
							expression, of cue-induced OFL	
C57BL/6J mice	M	ACC	1.0	0.3	1.5	↓↑ SST+ interneurons ↓ PV+ interneurons	↑↓ OFL = OFL	258
C57BL/6J mice	M, F	ACC	0.98	0.278	0.78	IEG analysis ↓ACC, ACC neurons "trapped" during social interaction ↓↑ACC→NAc ↓ACC ; ↓ACC→NAc ↓ACC→BLA ↓ACC→BLA	↑ACC→NAc by social transfer of pain ↓ social transfer of pain ↓↑ social transfer of pain ↓ social transfer of analgesia = social transfer of pain ↓ retrieval of context-induced OFL	181
C57BL/6J mice	M	mPFC	0.86–1.78	0.3	2.0	*In vivo* recording from single neurons	↑ self representation ↑ other representation	259
Prairie Voles	M,F	ACC PL	1.4 2.4	0.8 0.8	1.3 2.2	IEG analysis OT Ø in ACC IEG analysis OT Ø in PL	↑ during consolation ↓ during consolation = consolation = consolation	189
Sociability, social approach, incentive value of social interaction								
Lister hooded rats	M	ACC, OFC	2.3–0.9 4.0–3.2	0.5 2.6–0.8	0.2–2.0 4.4–3.4	lesion (excitotoxic) lesion (excitotoxic)	↓ social interaction = social interaction	251
Sprague-Dawley rats	M	PL/IL	2.9	0.5	2.9	inactivation (muscimol)	= social interaction	260
Sprague-Dawley rats	M	mPFC	3.0	0.8	2.5	*In vivo* recording	↑social interaction (32%) ↓social interaction (8%) =social interaction (60%)	261
Sprague-Dawley rats/ Long-Evans rats	M,F	IL	2.7	0.5	5.0	§ ↑excitability	↓ social interaction	262
C57BL6/J mice	M	PL, IL	1.8	0.35	2.85	§↑↓ excitability	↓= social interaction	223
C57BL/6J mice	M	PL	1.9–2.8.	0.3–0.4	2.5–1.5	lesion IEG analysis	↑ social interaction ↑ c-Fos during social interaction	263
C57BL/6J mice	M	mPFC	1.7	0.3	1.8–2.5	*In vivo* recording	↑ firing during social approach behavior	180
C57BL/6J mice	M	mPFC	1.7	0.3 0.9 (10°)	1.9 2.1 (10°)	↑↓ BLA→PL	↓↑ social interaction	230
C57BL/6J mice	M,F	PL	1.8	0.5	2.5	↑↓ PL→NAc	↓= social interaction	224
C57BL/6J mice	M	PL	1.9	0.3	1.7	*In vivo* recording *In vivo* recording	↑or↓ during social approach (ON and OFF ensembles) ↑to novel stimulus (ON ensembles sensitive to novelty)	264
C57BL/6J mice	M	ACC	1.0	0.25	2.1	↓↑ ACC→BLA ↓ BLA→ACC	↓= social interaction = social interaction	193
C57BL/6J mice	M	OFC	2.6	1.26	2.8	*In vivo* recording ↑"trapped" social ensembles ↑"trapped" feeding ensembles	↑social behavior ↑feeding behavior ↓feeding behavior ↑feeding behavior	239
C57BL/6J mice	M	IL	1.97	0.3	3.0	*In vivo* recording	↑activity to social odors	229

Species, Strain	Sex	Region	Stereotactic Coordinates			Manipulation or Measure	Findings	Cit.
			A/P (+)	M/L (±)	D/V (−)			
Social recognition and memory								
C57BL/6J mice	M	ACC	1.0	0.35	2.0	↑ACC	↑social interaction	265
C57BL/6J mice	M	dmPFC/PL	2.0	0.3	1.8	*In vivo* calcium imaging	Interbrain activity correlations of interacting mice	228
C57BL/6J mice	M,F	mPFC	1.9	0.3	2.4	↓ PV+ interneurons	↓ social interaction	186
C57BL6/J mice	M, F	dmPFC	2.0	0.3	1.8	*In vivo* calcium imaging	Single neurons selectively responsive to conspecific sex	266
C57BL6/J mice	F	PL IL	2.2 2.2	0.4 0.4	2.1 2.8	↑↓PL→BLA ↑↓IL→BLA ↑"trapped" PL→BLA during footshock	↓=social interaction =↓social interaction ↓ social interaction	267
C57BL6/J mice	M	mPFC	1.95	0.3	2.1	*In vivo* calcium imaging of mPFC→VTA neurons	↑social interaction	225
C57BL6/J mice	M, F	PL	1.9	0.4	2.0–2.2	*In vivo* calcium imaging of PL→ZIm neurons ↓PL→ZIm	↑social interaction ↓social interaction	226
C57BL6/J mice	M	mPFC	1.3–2.3	0.4	1.0–1.7	↑↓mPFC→PVT	↑↓social interaction	227
C57BL6/J mice	F	PL OFC	1.7 2.6	0.17 1.2	2.5 2.8	↓BLA→PL, ↓PL→NAc ↓PL ↓BLA→PL, ↓PL→NAc ↓OFC	=social interaction ↓SIFC ↓SIFC = SIFC	221
C57BL6/J mice	M, F	PL	2.0	0.25	2.4	↓BLA→PL ↓PL→BLA	↓"altruistic" choices ↓"selfish" choices	222

"Region" is indicated as per author nomenclature, given the lack of coherence in prefrontal cortical nomenclature in the field[125]. Stereotactic coordinates are expressed in mm from lambda, ranges are provided for larger lesions or multiple infusions. For the Manipulation column, *in vivo* recording indicates calcium imaging or electrophysiological recording, ↑ indicates optogenetic or chemogenetic activation, ↓ indicates optogenetic or chemogenetic inhibition, Ø indicates the use of a pharmacological antagonist, § indicates the use of an SSFO to manipulate excitability of local cells[223]. For Findings column, ↑ indicates increase in measure, ↓ indicates decrease in measure, = indicates no change in measure. Tasks examining social stress response, aggressive behaviors, or mating behaviors are not discussed in this review. Specific protein knockouts, developmental insults, and models for disease are not included. Abbreviations: affective discrimination test (ADT), anterior cingulate cortex (ACC), basolateral amygdala (BLA), dorsomedial prefrontal cortex (dmPFC), fear conditioning-by-proxy (FCbP), immediate early gene (IEG), immunohistochemistry (IHC), infralimbic subregion of medial prefrontal cortex (IL), left anterior cingulate cortex (lACC), medial prefrontal cortex (mPFC), medial zona incerta (ZIm), observational fear learning (OFL), orbitofrontal cortex (OFC), oxytocin (OT), nucleus accumbens (NAc), paraventricular thalamus (PVT), parvalbumin (PV), prelimbic subregion of medial prefrontal cortex (PL), right anterior cingulate cortex (rACC), somatostatin (SST), ventral tegmental area (VTA).