

Shedding Light on Social Reward Circuitry: (Un)common Blueprints in Humans and Rodents

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Shedding Light on Social Reward Circuitry: (Un)common Blueprints in Humans and Rodents

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Abstract

Human behavior is strongly influenced by our motivation to establish social relationships and maintain them throughout life. Despite the importance of social behavior across species, it is still unclear how neural mechanisms drive social actions. Rodent models have been used for decades to unravel the neural pathways and substrates of social interactions. With the advent of novel approaches to selectively modulate brain circuits in animal models, unprecedented testing of brain regions and neuromodulators that encode social information can be achieved. However, it is unclear which classes of social behavior and related neural circuits can be generalized across species and which are unique to humans. There is a growing need to define a unified blueprint of social brain systems. Here, we review human and rodent literature on the brain's social actuators, specifically focusing on social motivation. We discuss the potential of implementing multimodal neuroimaging to guide us toward a consensus of brain areas and circuits for social behavior regulation. Understanding the circuitual similarity and diversity is the critical step to improve the translation of research findings from rodents to humans.

Keywords

social behavior, social reward, social motivation, fMRI, translational neuroimaging, rodent, human

Introduction

Why do humans engage and invest in social interactions? How do brain circuits drive us to act in a cooperative or competitive manner? Throughout this review, we define social behavior as any modality of communication and/or interaction between two or more conspecifics (Crespi 2001; Ebstein and others 2010). For this purpose, species-typical signals such as body language, facial expressions, or vocalizations act as mediators to build and maintain social bonding and social networks. However, social signals can display considerable variability across species, in part dictated by the individual's ability to recognize, evaluate, and possibly react to them. In social science the ability to infer what another conspecific is thinking, feeling or perceiving, is often referred to as “theory of mind” (Baron-Cohen and others 1985). In humans, research has shown that *motivation* to seek out social cues at an early age plays a key role in developing social skills such as theory of mind. Infants rapidly recognize faces and display a visual preference for them (Walton and Bower 1993). Particularly attending to and responding to gaze are crucial for successful joint attention as well as social orienting and ultimately guide the development of social relationships (Baron-Cohen 2000;

Williams and others 2001). Individuals who fail to extract and process social information as a result of impaired *social motivation*, might not experience social contact as positively reinforcing (*rewarding*) and are therefore less likely to pursue it in the future (Dawson and others 2002). These patterns are commonly observed in socially debilitating disorders like autism spectrum disorders (ASD) (Chevallier and others 2012), schizophrenia (Fulford and others 2018), and psychopathy (Lockwood 2016; Viding and McCrory 2019).

Humans are not the only species to display social seeking behaviors. Instead, several forms of sociality have evolved in non-human primates and rodents as well (Watson and Platt 2012). One hypothesis proposes that social behavior, regardless of the nature of social signals,

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is processed by a shared set of brain regions, which are activated upon the sensorimotor transformation of socially encoded information (the “social brain”) along with the tuning action of neuromodulators (O’Connell and Hofmann 2011, 2012). Despite increasing evidence, there is no consensus on a unified blueprint describing the brain systems that govern social behavior across species. Instead general confusion and disagreement still exists on which classes of social behavior can be generalized to other species and which are seemingly unique to humans (Kondrakiewicz and others 2018). Resolving these questions and thereby defining a common baseline for preclinical and clinical research promises a great

advance in our understanding of social behavior and its regulation in health and disease.

In this review, we focus on social reward as a conceptual model of social behavior (Box 1). We first discuss its psychological and molecular basis as well as the extent to which these patterns are conserved across species. Drawing on recent studies, we present both correlational and causal evidence of network and circuitual mechanisms that modulate social motivation in humans and in rodents. Finally, we aim to review the use of multimodal neuroimaging to understand socio-behavioral patterns on a network level and discuss this approach as a way to bridge preclinical findings with clinical findings in humans.

Box 1. Social Reward as a Conceptual Model of Social Behavior.

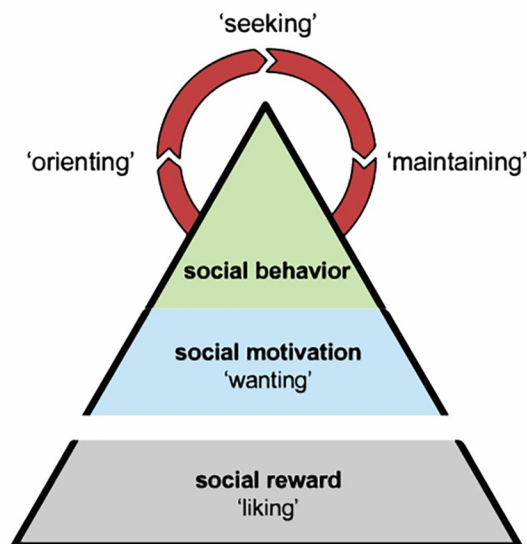
“Wanting”: “Wanting” or mesolimbic incentive salience is a form of motivation that is largely generated by the mesolimbic dopamine system. It is typically less linked to cognitive goals but rather triggered in pulses by reward cues or imagery about the reward. The intensity of the triggered “wanting” urge depends for one on the current state of the individual’s dopamine system and on the cue-reward association. This allows for state-dependent amplification of “wanting.” Particularly in stressful states this process can increase vulnerability to relapse in addiction or related disorders.

“Liking”: “Liking” comprises the actual pleasurable impact of reward consumption. Contrary to “wanting,” “liking” does not depend on dopamine and is mediated by small hedonic hotspots scattered throughout the brain. These hedonic hotspots can amplify “liking” responses if neurochemically stimulated and form a hedonic circuitry that may be shared by diverse pleasures.

Social Reward: Reward and its role for goal-directed behavior can generally be described in two dissociable psychological reward dimensions: “liking” and “wanting,” both of which are applicable to social signals. The “liking” component refers to the hedonic value of said signals, that is, perceiving social stimuli as rewarding. Social reward is mediated via activity in the mesolimbic network and is generally thought to be conserved across species. Social rewards include group affiliation, emotional support, as well as social status and salient identity.

Social Motivation: A social stimulus that is “liked” is then typically “wanted.” The “wanting” component refers to the incentive salience of the reward (i.e., social stimulus), which drives an incentive *motivation* to approach/seek and consume the reward. Social motivation constitutes an evolutionary adaptation to secure an individual’s ability to function in a collaborative environment.

Social Behavior: Social behavior comprises a range of behavioral outputs mediated by social reward and social motivation including social orienting, social seeking, and social maintaining. Not only are social signals prioritized by attention (*social orienting*) but are typically the preferred stimulus to attend to as well (*social seeking*). In an attempt to engage/interact with others (social interaction) over an extended period of time, an individual develops maintaining strategies enabling him to establish and enhance interpersonal relationships (*social maintaining*).



What Is Social Reward?

What makes a social stimulus rewarding and which mechanisms drive seeking this sensation time and time again? To understand the concept of reward and its role for goal-directed behavior, Berridge and others (2009) described two dissociable psychological reward dimensions: “liking” or the conscious experience of pleasure and “wanting” or the incentive motivation which promotes approach/consumption of rewards. Any type of reward that elicits “liking” is then typically “wanted.” This general motivation system, which drives *attention* toward pleasant stimuli and avoidance of unpleasant/stressful stimuli, varies in power and correlates with the individual’s reward responsiveness and level of perceived *reward value* (Laricchiuta and Petrosini 2014). With regard to situations in which higher-order goals or social motives differ from initial desires (maybe undesirable ones even), dissecting reward-processes into “liking” and “wanting” proves particularly useful in explaining reward-orientation: drug seeking, binge eating, or sexual desire being just a few examples where liking is no longer a synonym of wanting (Finlayson and others 2011; Krishnamurti and Loewenstein 2012; Robinson and Berridge 1993). The described behaviors describe a state of “wanting” that is largely (and subconsciously) driven by the mesolimbic dopamine system. These may, however, conflict with the actual conscious goals and preferences of an individual, that is, “liking” (Mier and Kirsch 2017). In social psychology, prosocial behavior is assumed to have rewarding quality (“social reward”) based on the display of a strong motivation to seek social relationships, support and understanding (Eisenberg and others 2010). Notably—but beyond the scope of this review—, social behavior might also be susceptible to states where “liking” no longer reflects “wanting” if we think of social media addiction or the upkeep of abusive relationships. During the past decade, the questions of *where* and importantly, *how* the brain encodes reward during social behavior have met extensive research efforts: data mostly from the field of cognitive neuroscience suggest the notion of a “social brain” where a network of brain regions displays specificity toward assigning reward values to *social* signals (Frith 2007).

The “Social” Brain

In humans, the medial prefrontal cortex (PFC), the temporoparietal junction (TPJ), subcortical structures, and the cerebellum can be considered social hub regions of the brain. Associated with social information processing, social cognition, and theory of mind, the functional

interplay of these key nodes helps individuals adapt to and navigate the social world (Joiner and others 2017; Olsson and others 2020; Ruff and Fehr 2014; Wittmann and others 2018). Here we will focus on the key human brain regions linked to both reward and social processing.

Medial Prefrontal Cortex. The medial regions of the prefrontal cortex (mPFC) take on an important role in gating and mediating social behaviors within all levels of social cognition. The dorso-medial PFC (dmPFC), ventromedial PFC (vmPFC), and the anterior cingulate cortex (ACC) have been implicated in processes of social reward, punishment, and motivation (de Quervain and others 2004; Fehr and Camerer 2007; Kohls and others 2013).

The dmPFC has often been implicated in social processing, in particular “mentalizing” and theory of mind (Frith 1996) as well as integrating social information from other conspecifics (Martino and others 2017). Multiple studies showing increased activation of the dmPFC during joint attention tasks (shared focus of two or more individuals on an object/each other), as opposed to solo attention tasks (non-shared attention toward an object), have indicated that these regions are concerned with aspects of moral decision making and cooperative behavior (Amodio and Frith 2006; Redcay and others 2013). The vmPFC (including the subgenual anterior cingulate cortex [sgACC] and medial orbito-frontal cortex [OFC]) has repeatedly been associated with the encoding of self-referenced rewards, choosing between rewarding options and positive explicit evaluation of others (Dang and others 2019; Rushworth and others 2011). However, it has also been implicated in social motivation and reward: vmPFC damage due to stroke has been shown to result in social isolation, apathy and decreased prosocial behavior in human patients (Barrash and others 2000). Interestingly, another subregion of the mPFC, the gyral surface of the anterior cingulate (ACCg), encodes reward-related information for *other* individuals (Apps and others 2012; Behrens and others 2008; Lockwood and others 2015). This way the ACCg compares the expected and actual outcome of another person’s decision, referred to as social prediction errors (Apps and others 2013; Apps and others 2015; Balsters and others 2017; Hill and others 2016). The ACC, along with the orbitofrontal and vmPFC, are generally thought to mediate the rewarding nature of cooperation, which could drive social motivation (Luo 2018). Anatomically, subregions of the mPFC are densely interconnected and further connected with several other hub-regions of the “social brain,” like the ventral striatum (VS)/nucleus accumbens (NAc), the ventral tegmental area (VTA), the amygdala, and cerebellum (Ghashghaei and others 2007; Kelly and Strick 2003; Middleton and Strick 2000; Passingham and others 2002; Schmahmann 1991).

Temporoparietal Junction. The TPJ is considered a further key node within the ‘social brain’. It comprises the supramarginal gyrus, caudal parts of the superior temporal gyrus and dorso-rostral parts of the occipital gyrus and integrates input from lateral and posterior thalamus, as well as auditory, visual, limbic, and somatosensory areas (Decety and Lamm 2007; Mars and others 2012). As part of the mentalizing system, neuroimaging studies have implicated the TPJ with social cognition and theory of mind (Hooker and others 2010; Mars and others 2012; Young and others 2010). Specifically, the right TPJ is associated with understanding others’ mental states such as moral stances, thoughts, beliefs, and feelings (Frith and Frith 2006) and through its role in empathy processing, it may encourage prosocial behavior: Zanon and others (2014) investigated functional connectivity in brain networks of self-benefitting and altruistic participants during a life-threatening simulation. While the selfish individuals exhibited increased functional connectivity in the salience network, prosocial individuals presented with more integrated communication between the mPFC and the rTPJ. Interestingly, voxel-based morphometry (VBM) showed that gray matter volume in the rTPJ is strongly associated with an individual’s level of altruism (Morishima and others 2012). Anodal transcranial direct current stimulation (tDCS) of the rTPJ for 20 minutes prior to a perspective-taking task enhanced the ability to take the visual perspective of another, though mentalizing ability was surprisingly unaffected (Santesteban and others 2012). A 2018 study by Blair-West and others used active anodal tDCS to the rTPJ in a social decision-making task to potentially enhance prosocial decision making but failed to find a significant effect. Contrary to numerous neuroimaging studies demonstrating heightened rTPJ during social decision making (Guo and others 2014; Halko and others 2009; Rilling and others 2004; van den Bos and others 2014), this may reflect methodological considerations to using tDCS. Transcranial magnetic stimulation (TMS) of the rTPJ, on the contrary, successfully modulated mentalizing and sociocognitive processes in a number of studies (Bardi and others 2017; Baumgartner and others 2014; Hill and others 2017; Jeurissen and others 2014; Kelly and others 2014). Activation likelihood estimation (ALE) meta-analyses on VBM studies suggested that the posterior part of the rTPJ takes on an exclusive role in the social domain (Krall and others 2015). Complemented by meta-analytic connectivity mapping (MACM) and resting-state functional connectivity analysis, Krall and others (2015) found that the posterior rTPJ coactivates with typical ToM regions, while the anterior part shares connectivity patterns with the attentional network. Mars and others (2013) took the connectivity profile of the human TPJ to

cortical areas and attempted to find relations to known homologues in the macaque temporal and parietal cortex. Their results suggested that macaque face processing areas and human mentalizing areas might share a similar evolutionary precursor.

Subcortical Structures

Basal ganglia. Electrophysiology and connectivity of the VS suggests that it encodes a variety of reward dimensions, including those of hedonic and motivational value (Daniel and Pollmann 2014). The feeling of being understood, receiving positive feedback or even the mere prospect of receiving positive feedback, the display of smiling faces as well as verbal praise all correlate with increased activity within the VS (Kirsch and others 2003; Rademacher and others 2010). With its central position in the mesolimbic pathway, the VS likely encodes the rewarding nature of cooperative behavior and thereby gates the motivational value of *acting* prosocially, that is, helping others (Bhanji and Delgado 2014). The NAc, prominently included in the VS, is also situated ideally to play a key role in processes of different reward dimensions, including those of a social nature (Meshi and others 2013). Spreckelmeyer and others (2009) reported activation of the NAc during the anticipation of positive social feedback, similar to anticipation of non-social outcomes like food (McClure and others 2007) or money (Knutson and others 2000). Kohls and others (2013) further implicated coordinated activity of NAc in the pursuit of social reward as well as the avoidance of social punishment. An investigation of cortico-striatal connectivity in a large sample of individuals with ASD (N = 130 per group) found there were significant differences in striatal connectivity patterns (Balsters and others 2018). Specifically, individuals with ASD did not show age-related changes in connectivity between the NAc and amygdala, or NAc and the frontal pole. In addition, the anterior and posterior sections of the putamen displayed unique connectivity patterns in typically developing individuals but not in ASD. This is particularly relevant in light of Pauli and others (2016) who suggested based on 5,809 human functional magnetic resonance imaging (fMRI) studies that activations in the anterior putamen are linked to social and language functions. Balsters and others (2018) suggest that the absence of unique connections to the anterior putamen could explain social and language deficits seen in ASD.

Ventral tegmental area. General acts without any direct beneficial outcome for oneself strengthen the assumption that pro-social behavior has an intrinsic motivational value: charitable behavior like donating and monetary pay-offs to charities activate the VTA

comparable to monetary rewards to oneself (Moll and others 2006). Situated on the floor of the midbrain, the VTA harbors the majority of dopaminergic cell bodies of the mesolimbic pathway, which is strongly implicated in the natural as well as drug reward circuitry of the brain (Russo and Nestler 2013). Using a norm adaptation paradigm and an imaging approach tailored to detect activation within midbrain structures, Héту and others (2017) suggested the substantia nigra (SN)/VTA complex and its dopamine system to be involved in social norm processing. Other human imaging studies found activation of the SN/VTA complex to reflect salience of a stimulus predicting reward and novelty seeking behavior, which could both be pharmacologically manipulated with dopaminergic agents (Menon and others 2007; Riba and others 2008).

Amygdala. In conjunction with the aforementioned areas of the mPFC, amygdaloid activity is further central to handling the demands of complex social life. In fact, individual differences in amygdala volume predict variations in social network size and complexity (Bickart and others 2011). Based on its anatomical connections with almost every other brain region implicated in the “social brain” (as obtained from tract-tracing studies in non-human primates), it can be considered a hub within the “social brain” (Freese and Amaral 2009). Noninvasive functional neuroimaging studies have repeatedly indicated activation of the amygdala corresponds to complex social judgments (e.g., trustworthiness of another individual) (Winston and others 2002) and a variety of social signals (Morris and others 1996; Morris and others 1998). Adverse early-life experiences (e.g., motherly maltreatment) negatively affect the development of the amygdala and increase the risk of developing social impairments (Alink and others 2012; Lansford and others 2002; Ometto and others 2016), which typically precede adult-onset psychopathology (Mazza and others 2014). A recent study from Rausch and others (2018) showed significant differences in the connectivity-based parcellation of the amygdala in ASD, including reduced connectivity with the vmPFC.

Cerebellum. Despite being most appreciated for its role in sensorimotor control (Schmahmann 2004), ample evidence suggests cerebellar contribution in social behavior: functional neuroimaging studies find robust activation within the cerebellum associated with social cognition (Carta and others 2019; Moreno-Rius 2019; Van Overwalle and others 2015) and processing of primary emotions (Schmahmann and Caplan 2006). Overlaps between cerebellar activations for particular

emotion categories (i.e., happiness, anger, disgust, fear, and sadness) imply the existence of shared neural networks across social and emotional dimensions (Baumann and Mattingley 2012). Lesions or resections can elicit cognitive impairment and abnormal social behavior (Schmahmann and Sherman 1998). Two key disorders of social cognition (ASD and schizophrenia) have been linked to cerebellar abnormalities (Andreassen and others 2008; Courchesne and others 1988; Wang and others 2014). Resting-state fMRI in patients with antisocial personality disorder (APD) revealed significantly reduced amplitude of low-frequency fluctuations in both the posterior cerebellar lobe (lobule Crus I) and OFC (Liu and others 2014).

Do Rodents Have Homologous “social” Brain Circuits?

Rodents like humans are socially engaged and show social behavior, though it presents in different forms. Depending on environmental contexts, rodents can display reciprocal interactions with conspecifics (Ben-Ami Bartal and others 2014), territorial aggression, mating via transmission, and interpretation of olfactory signatures (Rennie and others 2013), emotional contagion (Atsak and others 2011; Han and others 2019) and communication via ultrasonic signaling repertoires (Sangiomo and others 2020; see Chen and Wong 2018 for an extensive review). Therefore, rodent models are commonly used to investigate the neural correlates of both normal and abnormal social interaction. Preclinical research has already provided valuable insight into the cellular and neuromodulator mechanisms that fine-tune subregions of the “social brain.” Using behavioral test paradigms, which selectively probe for different dimensions of social behavior such as emotional contagion or social and observational learning can then assess manifestation of the final behavioral output (Box 2). Recently, rapidly evolving cutting-edge neuromodulation technologies like opto- and pharmacogenetics (see Sternson and Roth 2014; Yizhar and others 2011 for extensive reviews) have enabled the manipulation of specific cell-populations in a defined brain region, i.e. in a spatially and temporally controlled manner. These techniques allow for bottom-up research approaches, allowing us to go from cell to behavior, putting us in an ideal situation to investigate causality of brain-behavior interactions (see Fig. 1). Our understanding of complex behaviors, which are characterized by distinct internal states and switches thereof (Kaidanovich-Beilin and others 2011), can greatly improve using chemo- and optogenetic modulation.

Box 2. Social Behavior Tests in Rodents.

Reciprocal Social Interaction Test: The test assesses direct social interaction in rodents. It can extract naturalistic social behavior phenotypes of the “resident” to an “intruder/stimulus” subject by direct contact. A “resident” subject is habituated to a new, cage-sized, and bedded arena before an unfamiliar “intruder” is introduced. Commonly observed social behaviors include nose-to-nose or oral-to-oral contact, sniffing, following, pushing over, crawling under, and potentially aggression. Manual scoring and/or tracking software can be used to identify and quantify these specific social behaviors. Notably, the test does not allow to distinguish between, e.g., lack of social motivation and impaired social cognition in rodent models, making translatability to human socially debilitating disorders difficult.

Three-Chamber Sociability and Social Novelty Task: The test assesses cognition as per general sociability and social novelty interest in rodent models of health and disease. Based on two inclinations, i.e., preference toward spending time with another rodent and social novelty preference, this test can help identify rodents with sociability/social novelty deficits. In three testing sessions, mice are placed into a three-chambered box with openings between chambers. After habituation to an empty box, the sociability session follows: the “resident” mouse encounters an “intruder” mouse placed under a transparent cup and an empty transparent cup in separate chambers. In the social novelty session, the “resident” mouse then encounters the familiar “intruder” mouse placed under a transparent cup and a novel “intruder” mouse also placed under a transparent cup. Out-read parameters for sociability and social novelty preference are time spent sniffing each transparent cup, time spent in each chamber and number of entries into each chamber. This way deficits in social behavior of disease models can be quantified and pharmacological agents can be tested for their effect on social behavior.

Social Conditioned Place Preference (sCPP): This test is a form of Pavlovian conditioning and can be used to measure motivational effects of social encounters/experiences. For the acquisition of sCPP, the conditioning procedure is carried out in an apparatus of two or more compartments. Both compartments can be discriminated by the subject via differently patterned/textured floors or walls. Testing comprises three stages: a habituation session on day one, training sessions on consecutive days and a sCPP test on the final day, all of the same session duration. During habituation the subject can freely explore all compartments to reduce novelty effects. A baseline preference toward either compartment is obtained by measuring and comparing the time spent in each compartment. For the conditioning sessions an unconditioned social stimulus (conspecific) is placed into one compartment. Throughout this phase the testing subject has access to this compartment only, which will result in association of this compartment with the social stimulus. During the sCPP test, the subject has unrestricted access to all compartments. As an out-read of preference, the time spent in both compartments is measured and compared with the baseline.

Ultrasonic Vocalization: Communication among rodents includes calls in the ultrasonic range. Shortly after birth pups start calling and elicit maternal licking, pup retrieval by the dam, and crouching behavior. Social communication under these terms can be measured by means of number, duration, frequency, and amplitude of calls. To investigate, e.g., pup communication, a single pup is placed into a Styrofoam chamber equipped with a microphone and recorded calls are analyzed with an appropriate program. The test can be repeated over the course of several days to record changes in communication. Rodents show a repertoire of ultrasonic vocalization which is increasingly as a readout of sociability given the caveats of behavioral social interaction tasks in general.

The Rodent “Social” Brain

Prefrontal Cortex. Most theories on the functions of key “social” brain areas have been derived from studies in humans and non-human primates. Therefore, true value of translatability between human and rodent research can only be ensured once similarities or homologues of key “social” brain areas have been defined. Arguably, the most intense debate has focused on translatability of functions of the prefrontal cortical areas across species. Although many behaviors attributed to the PFC are thought to be unique to humans, it is commonly accepted that rodents are still a valuable model for understanding the functions of frontal areas emerging before evolutionary separation (Carlén 2017; Laubach and others 2018; Wallis 2007, 2011). Cumulative evidence suggests that the infralimbic (IL) region in rodents and area 25 in non-human primates can be considered homologues (see Alexander and others 2019 for an extensive review; Heilbronner and others 2016; Vogt and Paxinos 2014).

Furthermore, prelimbic (PL) and cingulate areas (Cg) are believed to be homologues of areas 32 and 24, respectively, in non-human primates (Aron and others 2004; Barbas and Pandya 1989; Bartra and others 2013; Bechara and others 2000). These homologies are further supported through lesion studies of the rodent PFC and its role in regulation of social reward processing. Findings of Cg involvement in social memory and interest as well as PL involvement in regulation of social investigation all point to the necessity of the rodent PFC in regulating social motivation (Avalle and others 2011; Rudebeck and others 2007). Optogenetic manipulation of inhibitory parvalbumin (PV) interneurons and excitatory pyramidal neurons in the mouse PFC disrupted social motivation during the three-chamber task of social preference: Shifting the balance toward excitation resulted in reduced attendance of the social compartment, while no effect was observed once the excitatory/inhibitory (E/I) balance was shifted toward inhibition. Simultaneous activation of excitatory pyramidal neurons and inhibitory PV interneurons in the

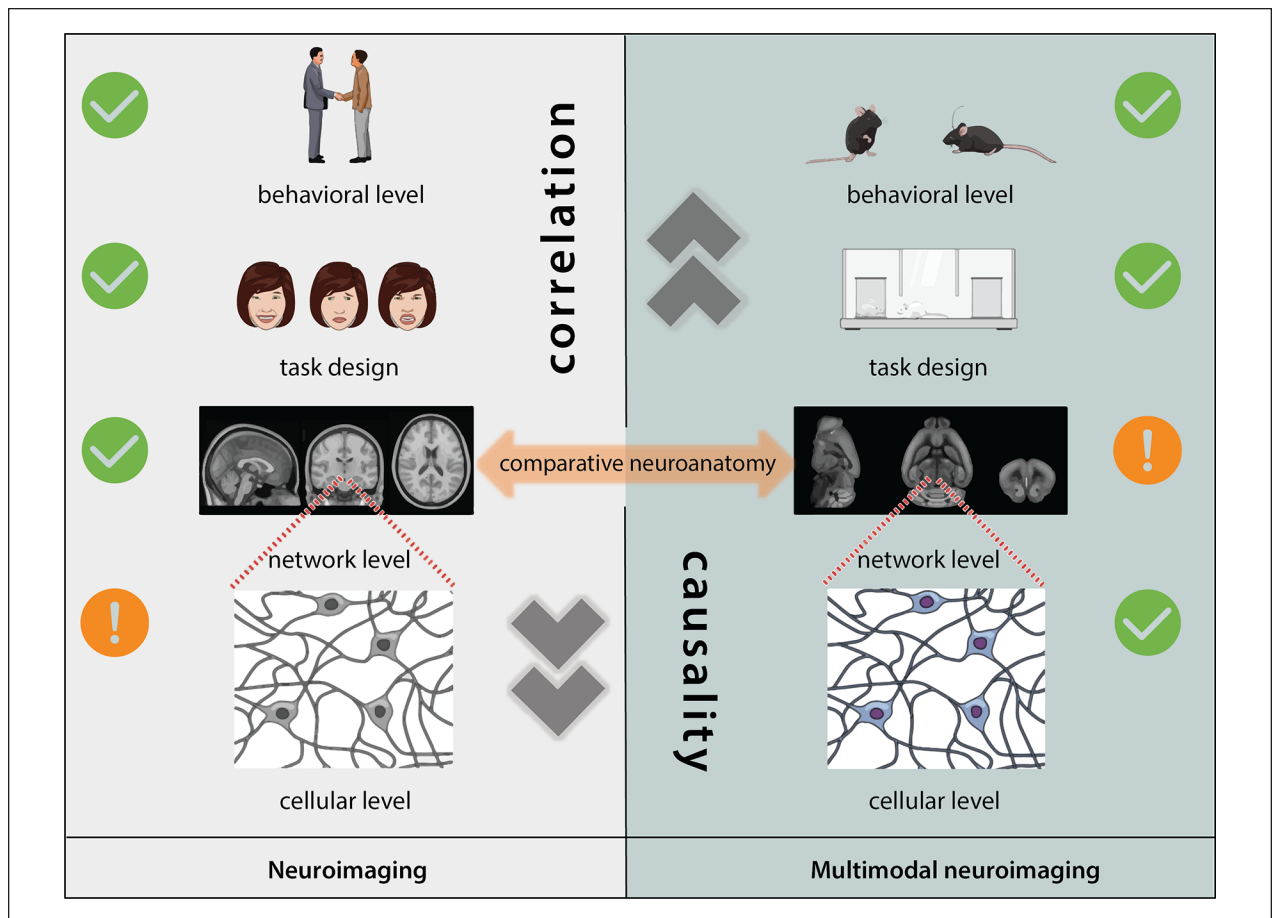


Figure 1. Translational neuroimaging can bridge research of functional connectivity across species and levels of inquiry. Rodent models present an ideal system to test research hypotheses from bottom to top, that is, understanding neural processes from synapses to circuits to behavior. While efforts have been made to create a common ground for data acquisition (i.e., task design) and defining homologies in behavior, the shared biophysical principle of functional neuroimaging can ultimately provide insight to common and unique blueprints in brain activity patterns. With recent advances in rodent functional neuroimaging, the effect of different neural states is now accessible on a network level. The implementation of targeted manipulations (e.g., chemo-, optogenetics, genetic manipulation) further allows to causally explain changes in brain activity patterns, rather than correlational as in human research. This way, combining human and rodent neuroimaging research from top-to-bottom and bottom-to-top, respectively, we can systematically elucidate neurological underpinnings and their causal role within brain circuits of health and disease.

PFC, however, did not show an effect on social motivation in the three-chamber social task (Yizhar and others 2011). How PV interneurons in the dmPFC exert long-term impacts on social behavior has been elucidated via opto- and chemogenetic manipulation. Bicks and others (2020) discovered that brief optogenetic stimulation of dmPFC PV interneurons triggered active social approach to promote overall sociability. Chemogenetic activation of dmPFC PV interneurons, on the other hand, mitigated social deficits induced by juvenile isolation in adult mice. A recent study with multiplexed DREADD experiments bidirectionally modulated PFC activity to measure the effects on a behavioral and functional level (Benekareddy and others 2018): PFC hyperactivity suppressed the

preference of social contact in a three-chamber social task and modulated activity in a subset of regions associated with emotional behavior. Bidirectional PFC modulation further identified the lateral habenula to receive direct prefrontal inputs which upon activation or inhibition suppress or promote social preference, respectively. Other studies found that the behavioral capacities related to social reward motivation and self-reward value assignment that have been attributed specifically to the human ventromedial prefrontal cortex (vmPFC), are localized to the rodent prelimbic (PL) and infralimbic (IL) areas (Bicks and others 2015). Anatomically, tracer studies show dense interconnections among subregions of the rodent mPFC, along with projections to the VS/NAc, the

VTA, and the amygdala (Gross and Canteras 2012; Vazdarjanova and others 2001). Human data have consistently implicated the ACCg in reward motivation of others (Apps and others 2016) and linking social agents to particular stimuli (Lockwood and others 2018). In rodents a potentially homologous area has been located in the ACC: Electrophysiological recordings in the ACC Cg1/Cg2 region of freely moving rats revealed that a large proportion of neurons coded the net-value of competing for a reward as long as competition with a conspecific was required (Hillman and Bilkey 2012). Lesioning of these subregions resulted in disruption of both cost-benefit decision making (Rudebeck and others 2006) as well as taking interest in other rats (Rudebeck and others 2007). This would suggest sub-regions of the ACC to be particularly important in learning about the behaviour of conspecifics and the cost-benefit information about an animal's own behavior (Apps and others 2016).

Subcortical Structures. Similar to humans, the contribution of reward mediating subcortical areas like the VS/NAc and the VTA further strengthen prosocial functioning in rodents (Gunaydin and others 2014; Kas and others 2014).

Ventral striatum. The rodent striatum, similar to the human striatum, is held as a general-purpose subcortical region which can translate social information into measures of social action and reward (Bariselli and others 2016). In particular, the VS shows specific involvement at the social level: Social isolation experiments in rats produced a “hypersensitive” VS, where events that would naturally trigger dopamine release resulted in an exaggerated effect possibly through increased expression levels of dopamine D2 receptors within the VS (Hall and others 1999; Howes and others 2000). Additionally, as part of the VS, NAc activity also proved to be relevant in processing of social reward (Walsh and others 2018) and in facilitating social behaviors (Kohls and others 2013).

Ventral tegmental area. Increased activity within the VTA was found to be necessary to promote social exploration (Gunaydin and others 2014). Mouse models with deficits in postnatal development of excitatory transmission onto VTA neurons display sociability deficits later on, which could be restored upon early administration of a pharmacologic modulator postnatally (Bariselli and others 2016). Lang and others (2019) examined male prairie voles' brain response to infant-related odors and found female cues (i.e., female cohabitation) to enhance *fos* activity in the VTA on exposure to infant cues.

Amygdala. Besides its role in fearful behaviors, lesion studies have causally linked the amygdala to social

deficits (Daenen and others 2003). Optogenetic manipulation of direct BLA-mPFC projections could bidirectionally modulate social behavior and produce/mitigate anxiogenic effects (Felix-Ortiz and Tye 2014). Exploration of resting-state fMRI data of an early-life stress mouse model focused on fronto-limbic connectivity compared with a control group and found amygdala-PFC hyperconnectivity, which highly correlated with anxiety-like behavior (Johnson and others 2018).

Cerebellum. Similar to the evolving trend in human research, cerebellar function has recently been put into context with social behavior in rodents as well. Carta and others (2019) demonstrated a direct regulatory role of monosynaptic connections onto VTA activity and thereby could regulate decision-making and emotional control: Optogenetic activation of the cerebello-VTA projections powerfully activated the reward circuitry. The authors additionally found increased activity of these projections upon exploration of conspecifics. Chemogenetic inhibition of Purkinje neurons (PN) within the Right Crus I (RCrusI) region of the cerebellum produced robust ASD-related social, repetitive and restricted behaviors (Stoodley and others 2017). Stimulation of these neurons in a genetic mouse model of ASD rescued its social impairments, warranting the therapeutic potential of cerebellar neuromodulation in ASD. Furthermore, chemogenetic perturbation of Crus I/II molecular layer interneurons in juvenile mice produced altered social preference throughout adult life (Badura and others 2018).

Overall, cumulative evidence points to a conserved set of brain regions involved in processing of and assigning value to social information in rodent and human (see Fig. 2, Table 1; see Prounis and Ophir 2020 for a critical view on the social brain). These homologies set a first basis for translational research on social behavior in health and disease. However, social interaction involves cognitive and emotional processes that may not be “social” per se, which makes it difficult to control for during experiments. Ensuring adequate assessment of attention during short-term habituation, reward and saliency processing and appropriate levels of anxiety versus exploratory drive are just a few of the measures that must be taken to reduce false-positive reports on sociability. Nevertheless, by making use of our ability to target specific cell-populations in rodents, we are able to add another layer of complexity through the determination of their dedicated role in complex behaviors.

Comparable Neurotransmitters to Regulate Social Reward Value

Neuromodulators primarily act on slow acting receptors through which they regulate diverse neuronal populations

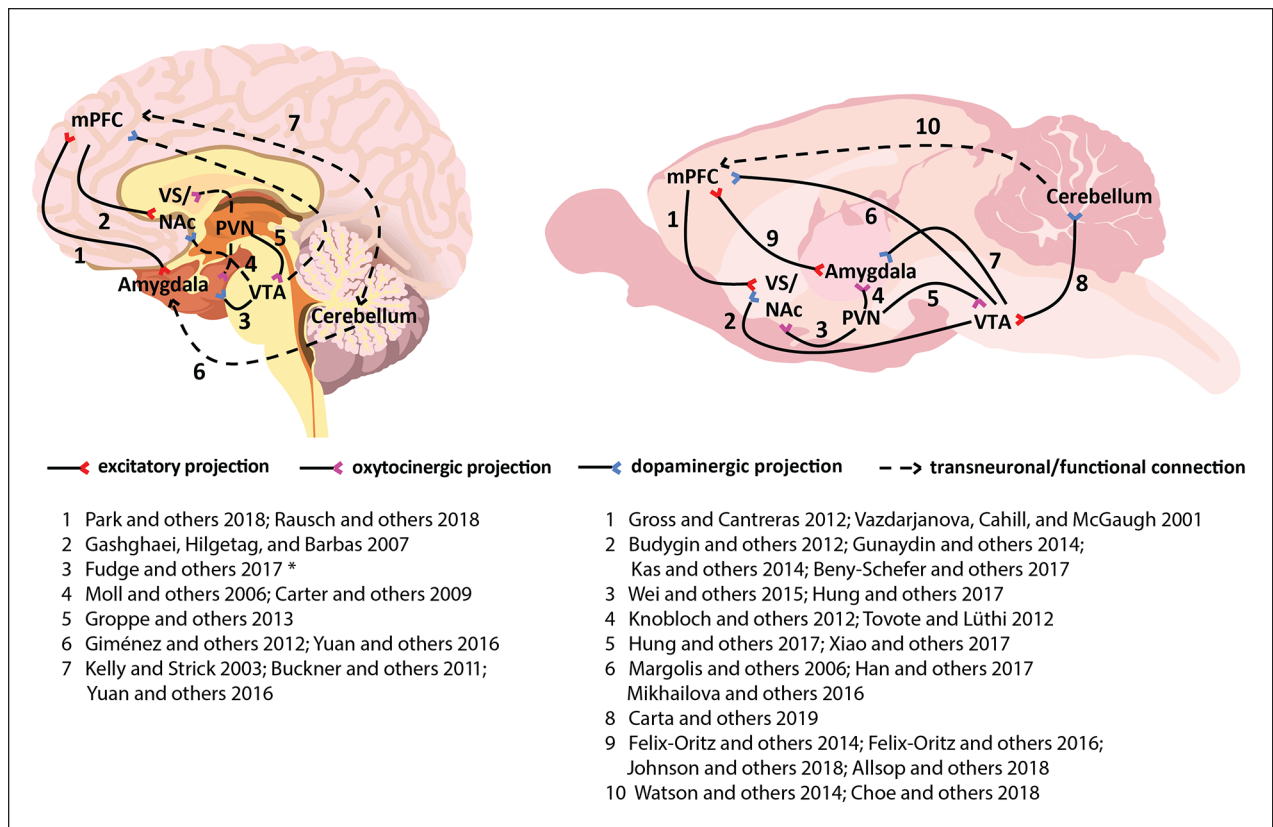


Figure 2. Comparable social actuators in the human and rodent brain. Indicated here in sagittal are areas comprising the social brain and their interconnections as described in human and rodent research (numerical index). Human neuroimaging and rodent research using neuromodulation and electrophysiology has established relationships between various social behaviors and activity in specific neural circuits. Furthermore, the critical role of neurotransmitters and hormones like dopamine (indicated in blue) and oxytocin (indicated in purple) in gating/tuning social behavior within these circuits have been subject of investigation. While social hubs such as the VTA, VS/NAc, PVN, and amygdala have been established in both human and rodent, the role of the mPFC or the cerebellum are less defined. Notably, detailed circuit connectivities (dashed lines) and directionality of connections are still to be characterized with help of rodent models across different levels of inquiry. mPFC, medial prefrontal cortex; VS, ventral striatum; NAc, nucleus accumbens; PVN, paraventricular nucleus; VTA, ventral tegmental area. *Non-human primate tracer studies.

and modulate their response patterns to specific stimuli. In a social context, dopamine (DA) and oxytocin (OT) are repeatedly reported to be involved in information processing and behavioral output in both rodents and humans (see Goodson 2013). In the mammalian brain, two adjacent midbrain regions, the VTA and substantia nigra pars compacta (SNc), comprise the majority of DA neurons. VTA-DA neurons are well known to project broadly throughout the brain, including the mPFC, NAc, and amygdala (Brischoux and others 2009; Budygin and others 2012; Chaudhury and others 2013; Lammel and others 2008). Early studies implicated strong phasic activity of DA neurons (“dopamine transients”) as a response to reward stimuli in rodents (Berridge and Robinson 1998; Schultz and others 1997). In vivo neurochemical methods revealed that phasic dopamine signals in the VS, possibly influenced by midbrain, amygdaloid and vmPFC inputs,

correlated with reward-seeking behaviors (Robinson and others 2011). Optogenetic phasic activation of mouse VTA-DA neurons was found to drive behavioral conditioning in a conditioned place preference task (Tsai and others 2009). Moreover, on phasic firing, DA terminals in the NAc appear to corelease glutamate, thereby activating fast ligand-gated ion channels and allowing transients to be truly time-locked to stimuli and reward (Stuber and others 2010; Tecuapetla and others 2010). While tracking subsecond DA fluctuations is not possible in humans, with recent studies implementing adaptations of fast-scan cyclic voltammetry (FSCV) to measure neurotransmitter changes in deep-brain structures (Kishida and others 2016; Kishida and others 2011), phasic DA signals are now commonly described as encoding of reward signals or the motivational component of reward (“wanting”) (Berridge and Robinson 2003). Genetic and

Table 1. Opto- and Chemogenetic Manipulation of Rodent Social Behavior.

Study	Manipulation Design	Rodent Model	Target Region	Behavioral Task	Results	Rescue Approach
Yizhar and others 2011	Optogenetically evoked shift in E/I balance	PV:Cre mice	mPFC	3-chamber social task	↑ Preference for social novelty chamber	Simultaneous activation of pyramidal cells and PV interneurons: ↑ preference for social chamber
Gunaydin and others 2014	Optogenetic activation/inhibition of VTA-DAergic NAc projections	TH::Cre mice	VTA	Social interaction test	↑ Social interaction upon optogenetic activation ↓ Social interaction upon optogenetic activation	—
Felix-Ortiz and others 2014	Optogenetic activation/inhibition of BLA-vHCP projections	C56BL/6 mice	BLA	Social interaction test 3-chamber social task	↑ Social interaction upon optogenetic inhibition ↓ Social interaction upon optogenetic activation ↓ social chamber preference and ↑ exploration of object chamber upon optogenetic activation	—
Hong and others 2014	Optogenetic activation of GABAergic and glutamatergic neurons in MeA Chemogenetic activation of glutamatergic neurons in MeA	C56BL/6N mice vGAT ^{Cre/+} mice vGLUT2 ^{Cre/+} mice	MeApd	Resident-intruder assay Modified resident-intruder task	↑ Aggression toward intruder upon optogenetic activation of GABAergic neurons Interruption of attack upon optogenetic inhibition of GABAergic neurons ↓ Social interaction and mounting behavior upon optogenetic activation of glutamatergic neuron ↓ Social interaction upon chemogenetic activation of glutamatergic neurons	—
Peňagarikano and others 2015	Chemogenetic activation of PVN-OT neurons	<i>Cntnap2</i> KO mice	PVN	3-chamber social task	No preference for social novelty chamber	—
Ferenczi and others 2016	Chronic optogenetic activation of glutamatergic pyramidal neurons in mPFC	Sprague-Dawley rats	mPFC	Social interaction test	Social interaction comparable to control group	—
Bariselli and others 2016	Optogenetic activation of DA neurons	Shank3-deficient DAT-Cre mice	VTA	3-chamber social task	↓ Preference for social novelty chamber compared to control group level	—
Siuda and others 2016	Chemo- and optogenetic activation of Gαs signaling in BLA	C57BL/6j mice	BLA	3-chamber social task	↑ Preference for social novelty chamber ↓ Preference for social chamber upon chemo- and optogenetic activation ↓ distance traveled in presence of conspecific upon chemogenetic activation	—

(continued)

Table 1. (continued)

Study	Manipulation Design	Rodent Model	Target Region	Behavioral Task	Results	Rescue Approach
Hung and others 2017	Optogenetic soma activation of PVN-OT neurons	OXT ^{ires} Cre mice	PVN	sRT-CPP task over 2 days	↑ Preference for social contact on day 1	—
	Optogenetic activation of PVN-OTergic-to-VTA projections	OXT ^{ires} Cre mice	VTA	sRT-CPP over 2 days	↑ Preference for social contact on day 1	Administration of an OT-receptor antagonist prevents social preference in sRT-CPP task on day 2
Selimbeyoglu and others 2017	Reduction of E/I balance by optogenetic PV interneuron activation	PV::Cre/Cntnbp2 KO mice	mPFC	Social interaction test	↓ Duration of social interaction	Normalized social interaction to control group level upon optogenetic activation
	Reduction of E/I balance by optogenetic decrease of pyramidal cell excitability	Cntnbp2 KO mice	mPFC	Social interaction test	↓ Duration of social interaction	Normalized social interaction to control group level upon optogenetic activation
Brumback and others 2018	Optogenetic activation and inhibition of D2R-expressing neurons in VPA-exposed mice	In utero VPA exposed Drd2-Cre mice	mPFC	Social interaction test	↓ Duration of social exploration	—
					↑ Social exploration upon optogenetic inhibition ↓ Social exploration upon optogenetic activation in VPA and non-VPA exposed mice	—
Benekareddy and others 2018	Chemogenetic bidirectional modulation of PFC pyramidal neuron activity	Emx1::Cre mice Sprague-Dawley rats	PFC	3-chamber social task	↓ Social novelty chamber preference upon chemogenetic activation	Chemogenetically induced decrease in sociability reversed with SALB/KORDi
Wang and others 2018	Chemogenetically mediated increase of pyramidal neuron activity	<i>l6p11</i> ^{+/-} mice	mPFC	Social interaction test	↓ Duration of social exploration	Normalized social interaction to control group level upon chemogenetic activation
Badura and others 2018	Chemogenetic inhibition of interneurons in juvenile cerebellum	C57/BL6 mice L7::Cre;Tsc1 ^{fllox/fllox} mice	Cerebellum	3-chamber social task	↑ Preference for social novelty chamber	—
					No preference for social or non-social chamber in juvenile-life inhibited Crus II Crus II adult mice	—

(continued)

Table 1. (continued)

Study	Manipulation Design	Rodent Model	Target Region	Behavioral Task	Results	Rescue Approach
Tan and others 2018	Optogenetic restoration of E/I imbalance in mPFC	TrkB cKO mice	mPFC	Tube test	↑ Intermale social dominance behavior in TrkB cKO mice compared with control group	Normalized social dominance behavior upon optogenetic silencing of mPFC excitatory pyramidal neurons
Cao and others 2018	Optogenetic activation of PV interneurons in mPFC	NL3 R451C KI mice	mPFC	3-chamber social task	↓ Preference for social novelty chamber	↑ Preference for social chamber upon optogenetic stimulation at 40 Hz nested at 8 Hz
Bariselli and others 2018	Chemogenetic inhibition of VTA-DA neurons	DAT::Cre mice	VTA	3-chamber social task	↑ Preference for social novelty chamber	↓ Preference for social novelty chamber and distance moved upon chemogenetic inhibition
Carta and others 2019	Optogenetic inhibition and activation of cerebello-VTA pathway	C57/BL6 mice DAT::Cre mice	VTA	3-chamber social task Social interaction test	↑ Preference for social novelty chamber No preference for object chamber Social interaction comparable to control group	↓ Social novelty chamber preference upon optogenetic inhibition ↑ Object chamber preference upon optogenetic activation No increase in social interactions upon optogenetic activation
Javaheri and others 2019	Optogenetic activation of ACC neurons in adult MD rats	Wistar rats	ACC	3-chamber social task	↓ Preference for social novelty chamber and ↑ stereotypical behavior	↑ Social novelty chamber preference and ↓ stereotypical behavior after chronic optogenetic stimulation
Qin and others 2019	Chemogenetic activation of pyramidal neurons in mouse mPFC	Shank3-deficient mice	mPFC	3-chamber social task Social approach assay	No preference for social novelty chamber ↓ social preference	↑ Social novelty chamber preference ↑ Social preference

E/I = excitatory/inhibitory; ↑ = increase; ↓ = decrease; mPFC = medial prefrontal cortex; PV = parvalbumin; DA = dopamine; NAc = nucleus accumbens; TH = tyrosine hydroxylase; VTA = ventral tegmental area; BLA = basolateral amygdala; vHCP = ventral hippocampus; GABA = gamma aminobutyric acid; MeApd = posterior dorsal subdivision of medial amygdala; vGAT = vesicular GABA transporter; vGLUT = vesicular glutamate transporter; PVN = paraventricular nucleus; OT/OXT = oxytocin; Cntnap2 = contactin-associated protein-like 2; KO = knock-out; sRT-CPP = social real-time conditioned place preference; *Gras* = G-protein alpha signaling; DAT = dopamine transporter; D2R = dopamine-2 receptor; VPA = valproic acid; Drd2 = dopamine receptor D2 gene; *Emx1* = empty spiracles homeobox1; *SALB* = salvinorin B; *KORDi* = Gi-coupled kappa-opioid receptor; *Tsc1* = tuberous sclerosis 1 gene; TrkB = tropomyosin receptor kinase B; cKO = conditional knock-out; N13 = neurotrophin-3; ACC = anterior cingulate cortex; MD = maternal deprivation.

pharmacological studies in both humans and rodents have also proven a critical role of the DA system in social interaction: human carriers of the nine-repeat allele of DAT1, a DA transporter, were reported to show stronger social approach tendency, while increase of DA concentration through a pharmacological agent improved learning about pro-social preferences of a partner (Eisenegger and others 2013; Noritake and others 2018). Additionally, human gender differences in social preferences were recently attributed for the dopaminergic reward system: pharmacological reduction of receptor-type specific actions of dopamine resulted in more selfish decisions during an interpersonal decision task in women while male participants exhibited an increase in prosocial decisions (Soutschek and others 2017). In rodents, FSCV measurements demonstrated increased DA transient frequency throughout the dorsal and ventral striatum on investigation of a novel conspecific (Robinson and others 2002). More targeted recordings from the NAc revealed DA release when animals were orienting toward and experienced initial contact with the conspecific, which would cease or rather habituate on subsequent contact (Robinson and others 2011). Despite accumulating evidence of DA's critical role in the brain's reward circuitry, a central question remains: what *mechanism* is tuning or rather gating VTA-DA neuron activity during social behavior? A first insight into the natural and causal circuit dynamics which underlie the modulation of social behavior was given by Gunaydin and others (2014), who found that the dynamics of VTA to NAc projections are both encoding and predictive of social interaction in mice. This finding was supported by evidence that VTA-DA neurons are implicated in the mediation of motivated behavior via a top-down reinforcing circuit from the anterior cortex, including the mPFC and orbitofrontal cortex, to lateral NAc (Beier and others 2015). Given the diversity of connectivity patterns and the large number of downstream VTA targets, understanding what is happening upstream of VTA-DA neurons might help pinpoint connectivity patterns that contribute to modulation of reward and aversion.

Besides DA, the neuropeptide OT, which is synthesized in the paraventricular nucleus (PVN) and supraoptic nucleus of the hypothalamus, has been often associated with social motivation in both humans and rodents (Lukas and others 2011). Initially proclaimed as a hormone strongly affected in social bonding, OT is now known to play a key role in several dimensions of social functioning, including fear responses, emotional memory, and social reward processing (Hu and others 2015; Knobloch and others 2012; Marlin and Froemke 2017). OT reportedly modulates E/I balance in the auditory cortex of female mice in response to pup calls and thereby enables pup retrieval behavior (Marlin and others 2015). The

neuropeptide also showed critical involvement in the development of all sensory cortices upon early sensory experience (Zheng and others 2014). In vivo OT injection together with increased sensory experience rescued effects of sensory deprivation by elevating excitatory synaptic transmission. Furthermore, OT receptor-expressing somatostatin (SST) interneurons within the mPFC show a differential response to OT in male vs female mice: in female mice these OT receptor (OTR) expressing neurons drive motivation to interact with male mice during estrus, while no changes in motivation were observed toward other females (Nakajima and others 2014). DREADD-driven excitation of OTergic neurons in the PVN of a mouse model of ASD was able to rescue social behavior in the 3-chamber task as assessed with normalized social interest (Peñagarikano and others 2015). Wei and others (2015) further reported these neurons to convey information about the rewarding properties of social interaction via cannabinoid-mediated signaling in the NAc (Wei and others 2015).

Since DA receptors are present on OT neurons and OT receptors can be detected in the VTA and SNc, a reciprocal modulation of both neuromodulator systems seems apparent (Baskerville and Douglas 2010; Grinevich and Stoop 2018). Consequently, the precise DAergic circuits which are involved in OT-sensitive behaviors should be questioned: How do DAergic and OTergic outputs guide social interactions? A recent study in mice reported a mechanistic link between VTA-projecting OT neuron activity in the PVN and social reward: OT release in the VTA enhanced the activity of reward-specific DA neurons, which could possibly correlate with the reinforcing component of social interactions via increased DA release in the NAc (Hung and others 2017). Ex vivo electrophysiological recordings of mouse VTA-DA neurons further showed the diverse functions of OT, whereby it could enhance the salience of partner-directed versus exploratory behavior by increasing DA neuron activity in the VTA but downregulating it in the substantia nigra pars compacta (SNc) (Xiao and others 2017). Indeed, while VTA-DA neuron activity might enhance social interest, DA neuron activity in the SNc could presumably dampen contextually irrelevant exploratory behavior via controlling motor activity (Gunaydin and others 2014; Patel and others 2012). OT release in the VTA and SNc might therefore be a crucial factor in estimation and modulation of the salience of a social encounter or possible prosocial behaviors.

While in rodent studies evidence of OTergic modulation of social reward processing accumulates, its role in human social behavior is less definite. Imaging studies report that upon social stimuli OT preferentially enhances connectivity of the brain's reward processing system (Gordon and others 2016). Similar to animal literature,

Groppe and others (2013) described the VTA as the brain region where OT modulates the salience to socially relevant cues via mesolimbic dopamine projections. More specifically, they observed intranasal OT application to increase the VTA BOLD (blood oxygen level dependent) response to socially rewarding and punishing cues in a social incentive delay fMRI task. OT was also reported to facilitate learning by giving feedback of both socially rewarding and punishing modalities (Gregory and others 2015). Liu and others (2019) found intranasal OT application to amplify social value representations within the amygdala (i.e., value of one's own interest relative to interest of others), resulting in more prosocial behavior in more individualistic rather than social subjects. Quintana and others (2017) characterized the distribution of three genes involved in the OT signaling pathway across the brain and assessed associations between gene expression patterns and mental states via large-scale fMRI meta-analysis. The expression maps of OXT (structural gene for oxytocin), OTR, and CD38 (central oxytocin secretion) showed an increase in central, temporal, and olfactory regions, which corresponded with motivation and emotion processing. Given its relevance in prosocial engagement, research on OT's regulatory processes in disorders of social dysfunction like ASDs has gotten more and more attention. However, only few clinical studies have directly linked autism-like phenotype to problems in OT signaling: While clinical application of intranasal OT at a single dose promoted prosocial behavior in high-functioning autism patients (Aoki and others 2014; Anagnostou and others 2012; Andari and others 2010), further doses of the agent failed to replicate these effects (Guastella and others 2015). At first glance, OT might appear to be just the missing agent to successful pharmacological treatment, however, consistent and reproducible data regarding its effects on regulation of social behavior are still missing (Miller 2013).

The sum of preclinical and clinical studies on the "social brain" and its neurotransmitter systems (see Fig. 2) have given great insights as to what is contributing to sociability, the value we assign to social interaction which ultimately motivates us to seek out social contact. Still, work on social reward in rodents has mostly focused on deciphering its molecular and neural basis and how it translates to behavior, while human research is limited to set the behavioral phenotype as a basis and investigate it on a network level. From a translational perspective the key macroscopic difference here becomes clear: in all these years of research we have yet to establish a "common language" between human and rodent studies, both in terms of neuroanatomy and behavior. Including the *network*-level characterization of circuit- and cell-specific stimulation in rodent models, that is, combining optogenetic or chemogenetic with the same neuroimaging

readouts as in human studies might just be that connective which enables us to translate findings from rodent to human research, and vice versa.

Translational Neuroimaging: Bridging the Gap

Multimodal approaches that include optogenetics and/or chemogenetics with fMRI could provide the interface to enable proper communication between clinical and preclinical research (Fig. 3). Today, optogenetics and chemogenetics allow the manipulation of virtually any chosen brain area or pathway and can model the neural dynamics observed in awake animals during a particular behavioral paradigm (Christie and others 2017; Lee 2012; Lee and others 2010; Rungta and others 2017). Measuring the whole-brain fMRI responses allows to parameterize the causal relationships between a specific input and the response of a distributed network of brain areas (Bernal-Casas and others 2017), including those of downstream connected circuits (Lee 2012), and overcomes the need to design a task-paradigm *during* the scan. These define the opto-fMRI as a powerful tool suitable for testing the circuit hypothesis within the framework of social reward and social motivation in rodents, describe their effects at the network level, and used to explain the data from human literature. For example, Ferenczi and others (2016) were the first to demonstrate the utility of opto-fMRI for testing a systemic hypothesis on reward processing—adapted from human imaging data—and found the rat mPFC to exert top-down control over interactions among subcortical striatal regions which govern general reward-related responses (Ferenczi and others 2016). Lohani and others (2017) next embarked on VTA-DA neuron activation in rats and showed how this influences regional and global fMRI signals. Specifically, they found that phasic activation increased BOLD and cerebral blood volume (CBV)-weighted fMRI signals in limbic regions innervated by the VTA, such as the NAc. It came as a surprise, however, that sparsely VTA-DAergic innervated regions of the basal ganglia (dorsal striatum, globus pallidus) also showed activation. Indeed, the most prominent fMRI signal increase came from the dorsal striatum, a region generally not associated with VTA-DA neurotransmission, which suggested a functional connection of meso- and non-limbic basal ganglia DA circuits (Lohani and others 2017).

Rodent and Human Circuit Homologies?

Given the similarity of activated networks to what is reported from human fMRI data, neuroimaging can be credited as a powerful translational tool that can be applied to examine homologies and differences between

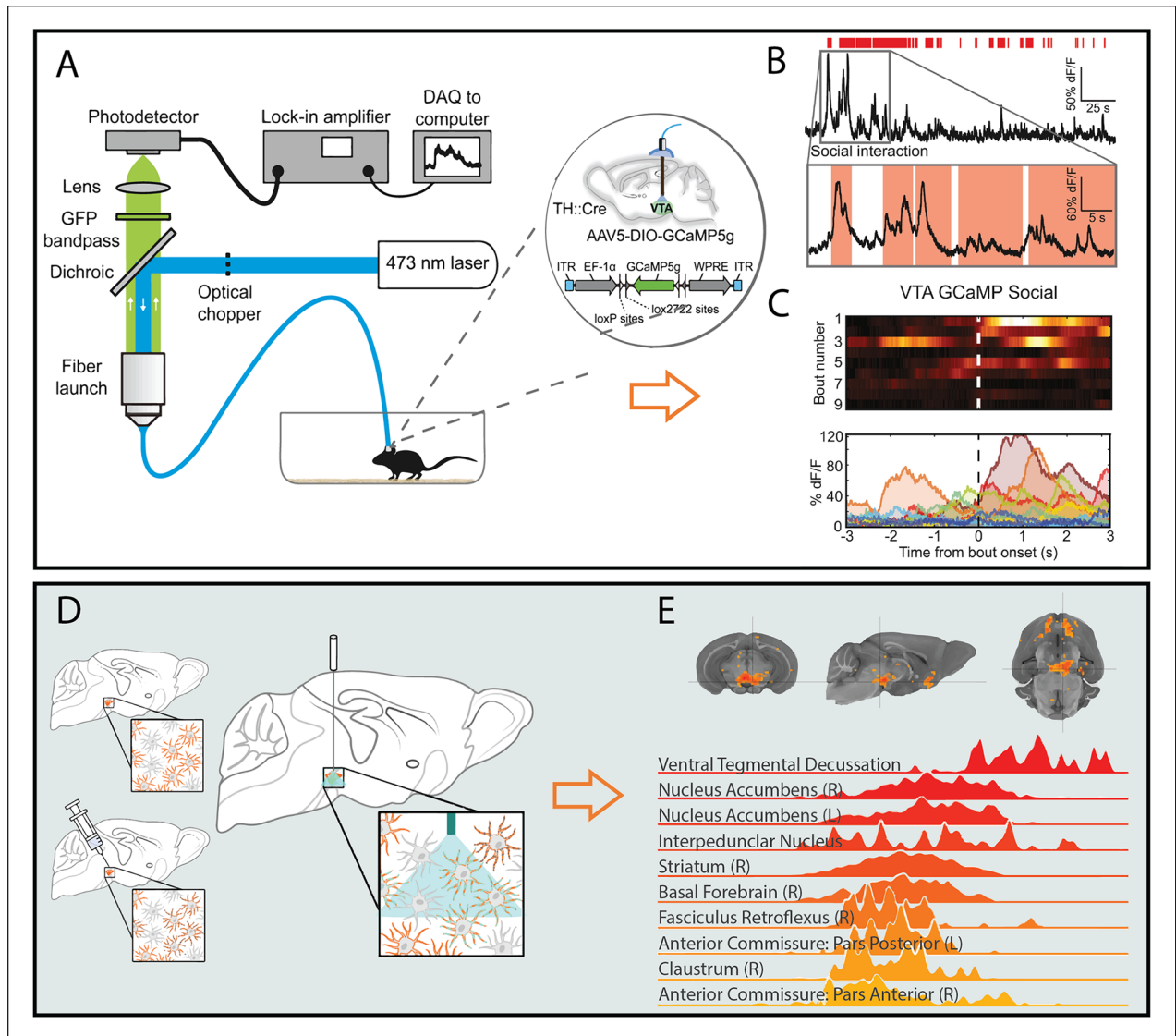


Figure 3. Multimodal measurement of neural dynamics in rodents. (A) Cutting-edge optical imaging techniques have enabled the detection of real-time activity of specified neural projections in socially interacting animals. A photometry setup enables optogenetic excitation and/or fluorescence emission recordings of targeted neuron through a single 400 μm fiber-optic implanted in ventral tegmental area (VTA). (Right) Viral targeting of GCaMP5 to VTA-DA neurons. (B) Photometry traces from mice expressing GCaMP5g in VTA during social behavior. (Red dashes) Interaction bouts. (Bottom) Zoom-in of gray box from above relating VTA-DA GCaMP signal and social interaction (colored boxes). (C) Example heatmaps (top) and peri-event plots (bottom) aligned to start of interaction for mice expressing GCaMP (left). (Heatmaps) Warmer colors indicate higher fluorescence signal; (peri-event plots) warmer colors represent earlier interaction bouts. (D) The combination of targeted neuronal modulation (e.g., chemogenetics, optogenetics) with fMRI brain-wide readout allows researchers to investigate the effects of acute neuromodulation not only in the targeted region(s) but also in downstream connected circuits; this may overcome a current limitation of single-cell and electrophysiological recordings, which assume a direct relationship between the manipulated brain area and behavioral changes. This approach proves to be particularly valuable in understanding how complex behaviors arise from cellular processes to connectional changes to inter-regional activity changes at the whole-brain level. Selective targeting of dopaminergic neuron is achieved using AAV5-DIO-channelrhodopsin2 viral delivery in the VTA of DAT-Cre mice. (E) General linear modeling (GLM) of stimulus-evoked activity followed by a mass univariate regression analysis produced voxelwise spatially resolved opto-fMRI activation maps. Representative distribution densities of statistic values from block-stimulus-evoked activity analysis. Depicted are the 10 most strongly activated areas. Figures adapted from Gunaydin and others 2014; Horea and others 2020 (in revision) with permission.

species. But which are the brain networks that have been maintained through evolution in humans and rodents? Are reward and social motivation circuits among them? An answer to these outstanding questions is given by *comparative functional neuroanatomy*, a branch of neuroscience that studies the organizational level of the central nervous systems from an evolutionary perspective and aims to identify which functions of the brain are conserved or unique across species. However, only recent attempts have been made to study similarities and differences between rodents and primates in their neuroanatomy as well as in the physiology of their brain networks. In 2014, Stafford and colleagues used functional brain imaging to compare the topology of the “default mode network” (DMN)—a set of regions that have been linked to social cognition and understanding of others (Laird and others 2011; Li and others 2014; Mars and others 2012)—in mice and humans in detail (Stafford and others 2014). Their results show striking similarities in the way DMN is connected to the anterior cingulate, retrosplenial, orbitofrontal, and parietal cortex. However, prefrontal components such as the posterior cingulate cortex (likely area 23) do not have a clear correlate in the mouse. In our recent study, we compared cortico-striatal connectivity profiles in mice, macaques, and humans with resting fMRI (Balsters and others 2019). These results suggest that connectivity models for both the nucleus accumbens—a hub for reward processing—and the cortico-striatal motor circles (posterior/lateral putamen) have been preserved, making them reliable targets for comparing species. However, a large area of human (85%) and macaques (69%) striatum does not have a clear mouse homolog. These areas were located in the caudate nucleus and anterior putamen, overlapping the executive function and the social / linguistic regions of the striatum, and connected to prefrontal-projecting cerebellar lobules and anterior prefrontal cortex, forming circuits that seem to be unique for non-human primates and humans. We attributed these differences to the expansion of the frontal cortex and parietal frontal lobes in humans. Taken together, these studies suggest that functional systems that relates to social cognition can be seen in mice, but they are often not present to the fullest extent as observed in primates. Further studies need to be carried out to refine the existence of similarities and differences between species in cycles that are relevant to specific aspects of behavior, including social behavior. We propose that this information is essential for assessing the human translation potential of circuit manipulation studies in rodents. Only if good agreement is observed can we guarantee that a particular process or behavior emerges from the same circuit, and therefore the theories developed in human studies can actually be used for rodent research—and vice versa.

Future Directions

The preclinical application of fMRI in combination with specific neural stimulation techniques is a foreseeable strategy for modeling, examining, and comparing the network signatures of human behavior, including those that are related to reward processing and its manifestation in social behavior. This has the potential to answer fundamental questions about the origin and physiological meaning of social behavior by integrating targeted and causally explainable manipulations of specific neurobiological pathways into the same fMRI design scheme as human studies. For example, it allows to assess whether the activation (or deactivation) of a particular structure, pathway, or modulatory system gives rise to similar network-level changes between rodents and humans. This overcomes the need to evaluate the similarity of results using complex and often not comparable behavioral assays. These observations form the basis of a new branch of neuroscience—comparative functional neuroanatomy—and provide insights into the neural mechanism that are evolutionary preserved (or not) between species. As this is an emerging research field in its infancy, there are many unknowns that need to be addressed, starting from mechanistic insights linking fMRI biomarkers to neural signaling. With careful interpretation of obtained results, comparative functional neuroanatomy may greatly advance translatability of preclinical studies in rodents toward humans.

Conclusion

Understanding the neural mechanisms conveying social functioning is key for the development of effective therapeutic interventions in socially debilitating disorders. Despite intensive research in a healthy and diseased state, it remains of question whether the observed activity patterns are causative or a by-product of information processing. As a complement to human studies, rodent studies can provide just that: Specific gene mutations can be created, molecular pathways can be targeted, and microcircuits can be manipulated, all while the observed effects can be *causally* explained. Using neuroimaging as an objective method of data readout and analysis is proving promising in understanding the brain functional basis of sociability as well as for monitoring the effectiveness of therapeutic interventions. Furthermore, these studies offer the possibility of studying network-level analogies between multiple species, filling the vital need to harmonize the results on the mechanisms of the social brain measured in rodents with the theories on the functioning of the social brain established in humans.

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