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Imaging the Neural Circuit Basis of Social Behavior: Insights from Mouse and Human Studies

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Abstract

Social behavior includes a variety of behaviors that are expressed between two or more individuals. In humans, impairment of social function (i.e., social behavior and social cognition) is seen in neurodevelopmental and neurological disorders including autism spectrum disorders (ASDs) and stroke, respectively. In basic neuroscience research, fluorescence monitoring of neural activity, such as immediate early gene (IEG)-mediated whole-brain mapping, fiber photometry, and calcium imaging using a miniaturized head-mounted microscope or a two-photon microscope, and non-fluorescence imaging such as functional magnetic resonance imaging (fMRI) are increasingly used to measure the activity of many neurons and multiple brain areas in animals during social behavior. In this review, we overview recent rodent studies that have investigated the dynamics of brain activity during social behavior at the whole-brain and local circuit levels and studies that explored the neural basis of social function in healthy, in brain-injured, and in autistic human subjects. A synthesis of such findings will advance our understanding of brain mechanisms underlying social behavior and facilitate the development of pharmaceutical and functional neurosurgical interventions for brain disorders affecting social function.

Keywords: autism, calcium imaging, fMRI, mice, stroke

Introduction

Social behavior refers to a variety of behaviors that are expressed between two or more individuals of the same species and is commonly observed in many animal species. Clinically, social behavior is often impaired in neurodevelopmental and neurological disorders including autism spectrum disorders (ASDs) and stroke, respectively. In particular, ASDs are characterized by social interaction and social communication difficulties and restricted and repetitive patterns of behaviors, and the elucidation of their pathophysiology is still fragmentary. Although the possibilities of treating ASDs with neuropeptides such as oxytocin (OT) and vasopressin have been studied,[1–3] potential molecular targets for pharmaceutical treatment of social deficits have not been fully identified. Therefore, elucidation of social neural circuit mechanisms may bring them within a range of application of functional neurosurgery such as brain stimulation therapies. Since the neural basis of social behavior is complex and widespread across the brain, multiple experimental approaches including behavioral, genetic, pharmacological, and electrophysiological techniques have been employed for its understanding.[4] Imaging has also recently emerged as a technology that can visualize the activity of numerous neurons within the brains of animals during social behavior. In this short review, we first overview some recent findings obtained by

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applying this powerful methodology to studies exploring the neural circuit basis of rodent social behavior. We also discuss human clinical and functional imaging studies that sought to investigate the neural basis of social function.

Whole-brain Mapping of Neural Activation Evoked by Social Behavior

Fluorescence monitoring of neural activity optically records signals of fluorescent neural activity reporter molecules within neurons.[5] This technique can be classified into two types in terms of the size of the areas monitored: whole-brain versus local measurements. Recent whole-brain mapping technologies aim to conduct automated, comprehensive mapping of changes in brain activity across the brain at the cellular level. They are usually achieved by combining immediate early gene (IEG)-mediated neuronal activity mapping with whole-brain reconstruction using serial sectioning or tissue clearing methods.[6] IEGs such as transcription factor *c-fos* are a group of genes whose expression is rapidly induced in response to strong neuronal activation.[7] Their expression is considered as a molecular hallmark of significant neural activity that is observed minutes to hours after the increased neural activity during behaviors. In practice, activity-dependent IEG expression is visualized as IEG promoter-driven expression of fluorescent marker proteins in transgenic mice, which is considered to reflect most, if not all expression patterns of endogenous IEG products. Although whole-brain mapping only provides a snapshot of brain activity in fixed brain samples and essentially lacks fine temporal resolution, it allows investigators to simultaneously screen the activation of many brain areas, including those that have not been extensively investigated in previous studies during a particular behavior of interest.

Kim et al.[8] visualized whole-brain activation in response to sex-specific social behavior using serial two-photon tomography and automated analysis of IEG expression in male transgenic mice expressing green fluorescent protein (GFP) under the *c-fos* promoter. A comparison of GFP expression patterns 3 hours after the 90 second encounter with a male or a female intruder revealed shared and distinct activation patterns. Specifically, a wide range of projection areas of the main olfactory bulb (MOB) and the accessory olfactory bulb (AOB), which are involved in processing odorant signals and pheromonal signals, respectively, were activated by social interaction.[9,10] The interaction with males elicited activation biased toward downstream areas of the MOB, while AOB revealed a strong bias toward female interaction. The sensing of nonvolatile pheromones by the AOB has been proposed to play a critical role in mate recognition.[11]

Furthermore, the activation of striatopallidothalamocortical circuitry, which includes the ventral striatum, ventral pallidum, thalamus, and the prefrontal cortex, and is considered to be involved in behavioral motivation, was observed during interaction with female but not with male mice. In the hypothalamus, the medial preoptic nucleus and ventral premammillary nucleus were only activated during interaction with female mice, whereas the ventrolateral part of the ventromedial nucleus (VMHvl) was activated by interaction with both male and female mice. This study demonstrates that IEG-based whole-brain mapping can be used for screening of brain regions activated by specific aspects of social behavior, such as sex discrimination and social recognition. Although the temporal resolution of this technique is not as high as calcium imaging, the information obtained by this technique is valuable for subsequent in-depth studies of identified brain regions (Fig. 1).

Social behavior at the whole-brain scale has also been investigated with non-fluorescence imaging techniques. Resting-state functional magnetic resonance imaging (fMRI), which is now widely used in research on functional connectivity in the human brain, is beginning to be used in investigating mouse models of brain disorders, particularly mouse models of ASDs.[12] Liska et al.[13] reported that homozygous Cntnap2-deficient mice exhibited impaired social investigation and reduced long-range and local functional connectivity in prefrontal and midline brain connectivity hubs. In addition, fMRI in awake mice that bear paternal duplication of the human chromosome 15q11-13 syntenic region revealed whole-brain functional hypoconnectivity and absence of fMRI responses to odors of stranger mice.[14] Although fMRI also lacks cellular resolution, it may complement IEG mapping by providing a more dynamic picture of brain activation in living mice.

Monitoring Social Behavior-related Local Circuit Activity in Freely Moving Mice

Fiber photometry

The fluorescence changes of calcium indicators are monitored at the local circuit level in freely moving animals by fiber photometry or by miniaturized head-mounted epi-fluorescence microendoscopy, or in head-fixed animals by two-photon laser scanning microscopy, as reviewed elsewhere.[5,15]

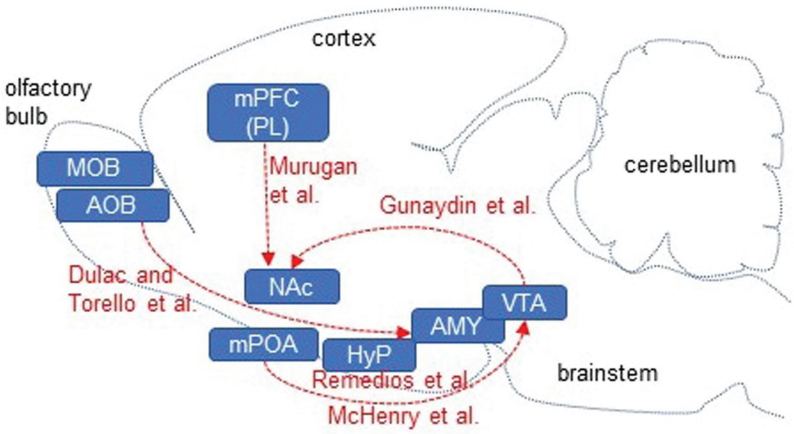

Fig. 1 An illustration of social behavior-related brain circuits discussed in this review. Red dotted arrows show projections. AMY: amygdala, AOB: accessory olfactory bulb, HyP: hypothalamus, MOB: main olfactory bulb, mPFC: medial prefrontal cortex, mPOA: medial preoptic area, NAc: nucleus accumbens, PL: prelimbic cortex, VTA: ventral tegmental area.

Fiber photometry optically monitors the average activity of multiple cells nearby a single optical fiber probe. Gunaydin et al.[16] were the first to use fiber photometry in the study of social behavior. They expressed the fluorescence calcium indicator protein GCaMP in the ventral tegmental area (VTA) dopaminergic (DA) neurons in mice and examined their activity during social interaction. DA neurons in the VTA are involved in processing of emotionally salient stimuli and reward, and project to widespread brain regions.[17,18] Fiber photometry revealed that these neurons responded to contact with either stranger mice or novel objects, but the dynamics of their activity differed between social interaction and novel object investigation. Consistently, the dynamics of DA neuron activity could predict social interaction and novel object interaction on a trial-by-trial basis. Direct optogenetic control of DA neuron activity bidirectionally modulated social behavior. Importantly, fiber photometry further revealed that activity dynamics of DA projection to the nucleus accumbens (NAc) could encode social, but not novel object interaction (Fig. 1). Direct observation of projection-specific activity by fiber photometry thus enables separate investigations of their roles in social behavior.

The medial prefrontal cortex (mPFC) is a cortical area that has been relatively well studied for its involvement in social behavior. Reciprocal connections with the mPFC involve diverse subcortical structures, including the amygdala, the hypothalamus, the hippocampus, the NAc, and regions of the cortex that process sensory and motor inputs and outputs.[19] mPFC lesions and optogenetically induced excitatory–inhibitory (E/I) imbalance in mPFC have been reported to impair social interaction in mice,[20,21] consistent with altered E/I balance in mouse models of ASDs.[22,23] Using fiber photometry, Selimbeyoglu et al.[24] found impaired activity of parvalbumin-expressing inhibitory neurons during social exploration in the mPFC of Cntnap2-knockout mice. Specifically, the activity of these neurons was higher during interaction with a novel mouse than with a novel object in wild-type mice, whereas this increase was not observed in Cntnap2-knockout mice. This finding suggests that dynamic modulation of E/I balance in the mPFC fails to occur during social interaction in autism-model mice.

Calcium imaging using a head-mounted miniaturized microscope

Activity of deep brain circuits can be visualized by implanting a micro gradient refractive index (GRIN) lens into the brain of the mouse and attaching to the head a miniaturized fluorescence microscope that consists of a built-in optical equipment and a complementary metal oxide semiconductor sensor (Fig. 2). The head-mounted, integrated microscope is small and light enough that it practically does not hinder the behavior of the mouse, which is favorable for studying social behavior in laboratory settings (Fig. 3). Excitation light and emitted fluorescence pass through the micro GRIN lens, enabling calcium imaging of the deep brain activity at cellular resolution. Although the field of view is typically limited to the scale of local circuits containing tens to hundreds of neurons, these methods can reveal how information associated with the behavior of interest is coded by a population of neurons in local circuits of particular brain areas on a millisecond scale temporal resolution.

Pheromonal signals play a central role in the recognition of other individuals in mice. Their

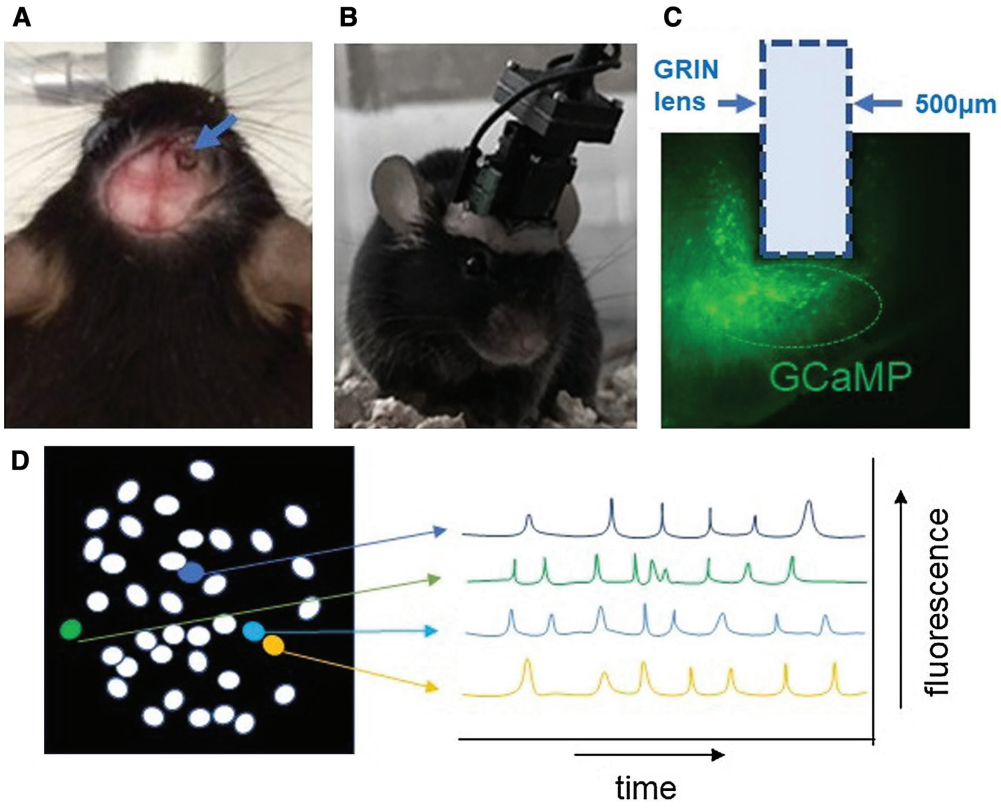

Fig. 2 Microendoscopic calcium imaging using a miniaturized head-mounted fluorescence microscope. (A) A GRIN lens implanted into the mouse brain (arrow). (B) Mouse with a head-mounted fluorescence microscope attached onto its head. (C) A brain section showing a neuronal population that was labeled with the fluorescent calcium indicator protein GCaMP and imaged through a GRIN lens. The diameter of the GRIN lens in this example is 500 μm. (D). An illustration of microendoscopic calcium imaging through a GRIN lens. Morphology and time-varying changes in GCaMP fluorescence intensity of individual neurons are analyzed from a time-lapse movie. GRIN: gradient refractive index.

signals are sensed by a specialized organ called the vomeronasal organ located in the nasal cavity, and the information is sent to the amygdala via the AOB (Fig. 1).[25–28] Thus, the amygdala is thought to represent information regarding other individuals. However, how such information is coded by neuronal ensembles in the amygdala was unclear.[29,30] Li et al.[31] imaged neuronal activity of the medial amygdala (MeA) during social and sexual behaviors using fluorescence microendoscopy. Individual cells of the MeA responded specifically to same-sex mice, opposite-sex mice, predator cue (rat bedding) or pups, while some cells responded to more than one category, showing that discrimination between the same-sex, opposite-sex, and pups at a neuronal population level was not completely differentiated. However, after sexual behavior, the proportion of cells that responded specifically to each category increased, and the neuronal population became distinguishable between these three categories. In males, this sexual experience-dependent change was suppressed by intraperitoneal administration of an OT receptor antagonist. From a mechanistic point of view, the plastic changes in MeA could be caused by the modulation of the upstream AOB by sex hormones.[32–34] In addition, endogenous OT may directly act on OT receptors expressed in the MeA circuitry,[35] although OT is also known to induce plasticity in the sensory cortex and the NAc.[36,37] Overall, this paper reveals that MeA neurons are selectively excited or inhibited by social cues and information about these behavioral events is present in some individual neurons, although it is significantly more robust and reliable at the population level. This information is also shaped by sexual experience and by OT in males.

Brain plasticity is usually investigated in the context of learning and memory. However, it is intriguing that sexual behavior induces long-lasting changes in the evolutionarily ancient subcortical brain regions such as the amygdala. Similar plasticity was also recently reported in the ventromedial

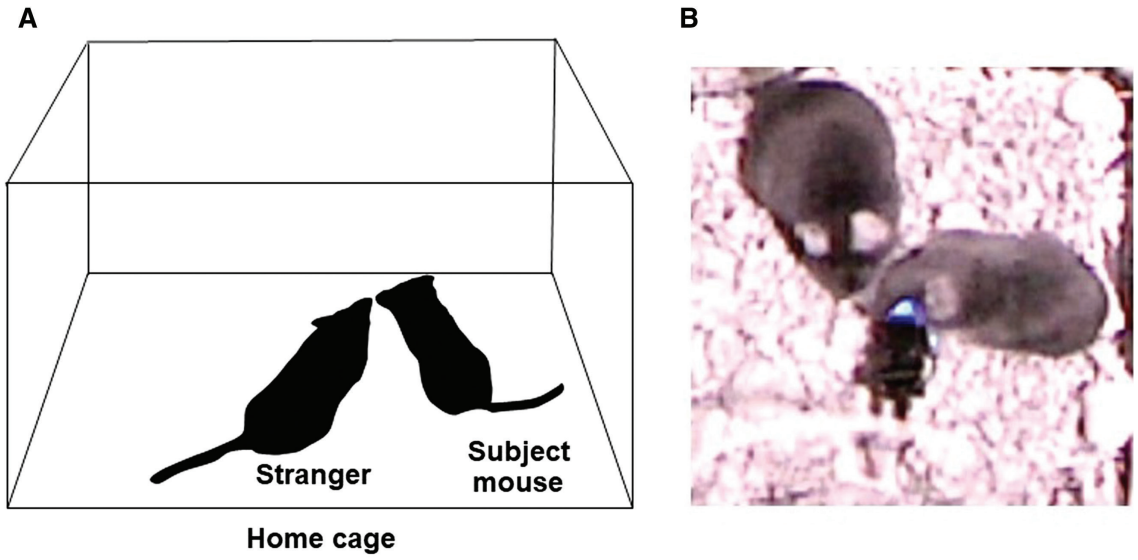

Fig. 3 Imaging local brain circuit activity during social behavior. (A) The home cage intruder test. A stranger mouse is introduced into the home cage of a subject mouse, and the behavior of their interaction such as physical contact is analyzed. (B) Microendoscopic calcium imaging experiments conducted during the home cage intruder test.

hypothalamus.[38] Using microendoscopic calcium imaging, Remedios and colleagues examined the activity of Estrogen receptor 1-expressing neurons in the VMHvl of the hypothalamus, which are involved in innate social behaviors such as mating and fighting.[39] When naïve adult male mice interacted with either male or female mice, cell ensembles activated by each conspecific sex were overlapping with each other. However, as they acquired sexual and social experience, these cells began to respond specifically to interaction with either male or female mice. This plasticity required direct contact with conspecifics. This study demonstrates that the formation of hypothalamic cell ensembles involved in recognition of sex occurs via experience-dependent processes. Collectively, microendoscopic calcium imaging in freely moving animals can thus reveal novel social experience-dependent plasticity in previously inaccessible deep brain regions.

Microendoscopic calcium imaging has also been utilized in the cortex. Liang et al.[40] imaged activity of mPFC neurons when mice freely explored restrained male social targets using fluorescence microendoscopy. Activity of principal neurons in the dorsal prelimbic (PL) cortex in male mice revealed that the latency at which neuronal activity increases or decreases varied between individual cells during social exploration. Interestingly, about 10% each of cells exhibited higher (ON ensemble) or lower activity (OFF ensemble) during social behavior, and it was possible to decode social exploration behavior from the observed activity of these ensembles. Neuronal members in the ON and OFF ensembles did not always belong to the same ensembles in different tasks or on the same task conducted on different days, but the frequency of such recurrence and the rate of overlap were shown to be higher than chance. Furthermore, psychiatric disorder-related changes in social behavior and mPFC ensemble activity were evaluated after administration of phencyclidine (PCP), an NMDA receptor antagonist that elicits schizophrenia-like symptoms. In contrast to behavior and neuronal activity without PCP, PCP administration reduced interest in stranger mice and decreased the recurrent probability of ON and OFF ensembles to chance levels, suggesting a close association between mPFC ensemble activity and social behavior. In summary, the distinct and dynamic ON and OFF ensembles in the mPFC encode real-time information during social exploration behavior. Similar neuronal ensembles are also found in the insular cortex.[41]

Microendoscopic imaging of projection neuron activity has also been reported in the mPFC. Murugan et al.[42] performed retrograde tracer experiments that identified the NAc, VTA, and the amygdala as targets of projection from the PL (Fig. 1). RNA sequencing revealed that these three types of projection neurons have different gene expression profiles, and optogenetic experiments demonstrated that the neurons that project to the NAc, a brain region involved in reward-related learning,[43–47] were causally implicated with social behavior. They then specifically labeled the PL-NAc projection neurons with Cre-dependent

GCaMP expression and monitored their activity during social behavior with microendoscopic calcium imaging in the PL. They found that a subset of PL-NAc projection neurons responded to social interaction, only when the conspecifics were present at certain locations. Furthermore, spatially specific manipulation of their activity bidirectionally modulated social-spatial learning. This study shows that PL-NAc projection neurons encode a combination of social and spatial information that may support a formation of social-spatial association.

Monitoring Social Behavior-related Local Circuit Activity in Head-Fixed Mice

Two-photon calcium imaging

Two-photon microscopy utilizes the principle of two-photon excitation, in which fluorescent molecules are excited by simultaneous absorption of two near-infrared photons of half the energy compared to single-photon excitation. Near-infrared lights have higher permeability into living tissues, and thus enable to excite fluorescent molecules deep within the tissue. Two-photon calcium imaging generally has a high resolution capable of calcium imaging of dendritic spines, although the head of the mouse has to be fixed under the microscope objective, which may limit the experimental design for social behavior.

McHenry et al.[48] imaged responses of neurons in the medial preoptic area (mPOA) to social odor cues using two-photon calcium imaging in awake head-fixed mice. mPOA neurons in the hypothalamus express estrogen and progesterone receptors and are involved in hormonal control of sexual behavior.[49] Importantly, a subset of these neurons project to the VTA which plays a pivotal role in control of social behavior, as mentioned earlier.[16] McHenry and colleagues found that these VTA-projecting mPOA neurons express neurotensin, a neuropeptide localized in the mPOA. Two-photon calcium imaging of neurotensin-positive mPOA neurons through an implanted GRIN lens in preestrus female mice revealed that attractive male urine odor recruited activity of more cells than female urine odor or nonsocial attractive odor in an estrogen-gated manner. Optogenetic activation of VTA-projecting neurotensin-positive mPOA neurons increased DA release in the NAc and social approach to males, suggesting that activation of VTA projecting mPOA neurons has rewarding effects. The imaging experiments in this study demonstrate the usefulness of head-fixed two-photon calcium imaging in characterizing neuronal responses to social stimuli.

Jennings et al.[50] observed activity of neuronal populations in the orbitofrontal cortex (OFC) during social interaction by GRIN-lens-mediated two-photon calcium imaging. They developed a new social interaction paradigm for head-fixed mice, in which a juvenile stimulus mouse placed in a tubular circular social arena in front of the head-fixed subject mouse could freely interact with it through an opening in the tube. The authors found that distinct neuronal populations responded to caloric rewards and social stimuli, and single-cell resolution activation of feeding-responsive neurons causally promoted feeding behavior, whereas social-responsive neurons inhibited feeding behavior. Their findings demonstrate that these two types of OFC neurons form distinct subnetworks that bidirectionally control feeding behavior. Technically, the combination of two-photon calcium imaging with single cell optogenetics and a head-fixed social behavioral task greatly expands its potential for precise observation and manipulation of neuronal activity during social behavior.

Research on Human Social Cognition and Behavior

Social function in humans is more complex than in mice. Human social cognition consists of various different aspects,[51] and as a way to understand it, Henry et al.[52] have proposed to divide it into four categories: theory of mind (ToM), social perception, affective empathy, and social behavior. ToM is the ability to think from the viewpoint of another person and is based on the recognition that their mental state is different from one's own, as assessed by the False-belief task.[53] Social perception is the ability to interpret clues to guess emotions and is evaluated by a test in which a subject guesses emotions from face photographs of various expressions.[54] Affective empathy is an emotional response to another person's situation, as measured by the Empathy Quotient[55] and the Empathic Concern subscale of the Interpersonal Reactivity Index.[56] Social behavior is behavior during interactions with other people, and can be evaluated by the Frontal Systems Behavior Scale.[57]

Social cognition in patients with brain injury has been studied in various cases in which left, right or both sides of the brain were damaged. Adams et al.[58] have conducted a meta-analysis of social cognition in stroke patients. They compared the aforementioned four categories of social cognition in 937 stroke patients and in 1630 healthy subjects. They found that ToM, social perception, and social behavior were significantly impaired in stroke patients, whereas affective empathy was maintained. Regarding laterality, ToM was impaired more severely in right-sided lesion cases than in left-sided lesions, while the impairment

of social perception was more severe in bilateral lesions than in unilateral cases. Whether the effects of laterality on social function remains inconclusive, as there are a few reports that lesions on the right side affect social function more severely than those on the left side,[59,60] while Samson et al. show that impairment of the left temporoparietal junction (TPJ) reduces the performance of the False-belief task.[61]

An attempt to determine which brain region is responsible for social perception was made by Adolphs and colleagues.[62] They conducted computed tomography and MRI in addition to social perception tests in 108 local brain injury and in 30 healthy subjects. Intriguingly, they reported that right somatosensory-related cortices (S1, S2, and anterior supramarginal gyrus) are important for the ability to visually recognize emotions from other people's facial expressions, suggesting that reading the emotions of others may require their own internal somatosensory representations.[63]

fMRI performed on healthy subjects revealed that the mPFC, anterior cingulate cortex (ACC), TPJ, and superior temporal sulcus (STS) are implicated in ToM.[64–66] The STS is an area that directly receives input from the primary visual and auditory areas and is involved in processing of face, voice, and eye gaze stimuli.[67–70] Isik et al.[71] reported that activity of right posterior STS (pSTS) shows high sensitivity to visual stimuli depicting social interaction. In this study, 14 normal subjects were shown videos in which point-lights or two animate shapes moved in ways that reminded subjects of social interaction such as helping and hindering while fMRI was performed to examine activity of multiple regions including the pSTS. They found that the right pSTS showed strong responses to videos suggesting social interaction, but the responses declined otherwise. In contrast, activities of the nearby TPJ and middle temporal region were not specific to social interaction stimuli.

Using fMRI, Watanabe et al.[72] reported that reduced brain activity in the right inferior frontal gyrus, bilateral anterior insula, ACC/ventral mPFC, and dorsal mPFC (dmPFC) was associated with impaired social judgments of incongruent verbal–nonverbal information in individuals with ASD. Moreover, intranasal administration of OT mitigated this autistic behavioral deficit and restored the activity in ACC and dmPFC, as demonstrated in a randomized double-blind placebo-controlled trial.[73] Interestingly, evidence from MRI indicates that alteration in structure and function of the mPFC, hypothalamus, and amygdala are associated with genetic variants of OT receptor gene that confer risk for social behavioral deficits and ASD.[74,75] These findings suggest that the brain regions involved in rodent social recognition and behavior may also be implicated in social function in humans.

Conclusions and Perspectives

In this review, we overviewed recent imaging studies in rodents that investigated brain activity during social behavior at the whole-brain and local circuit levels, and some noteworthy studies in brain-injured, in autistic, and in healthy subjects that sought to explore the neural basis of social function and its impairment in humans. Rodent studies incorporate invasive techniques and rapidly developing state-of-the-art technologies for visualizing and manipulating brain circuit activity, which will continue to elucidate the comprehensive picture of social brain networks (Fig. 1). Technological refinements in human brain imaging and manipulation of brain activity, such as transcranial magnetic stimulation used clinically to treat depression,[76] will be expected to reveal a causal relationship between brain activity and social function in humans, albeit with less specificity compared to rodent studies. Studies in rodents and humans will thus go hand in hand to advance our understanding of and the development of therapies for brain disorders affecting social function.

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Conflicts of Interest Disclosure

All authors have no conflict of interest.

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