Social Neuroscience and Psychopathology:

Identifying the relationship between neural function, social cognition, and social behavior

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Learning Goals:

1. Identify main categories of social and emotional processing and primary neural regions supporting each process.
2. Identify main methodological challenges of research on the neural basis of social behavior in psychopathology and strategies for addressing these challenges.
3. Identify how research in the three social processes discussed in detail – social learning, self-regulation, and theory of mind – inform our understanding of psychopathology.

Summary Points:

1. Several psychiatric disorders, such as schizophrenia and autism, are characterized by social functioning deficits, but there are few interventions that effectively address social problems.
2. Treatment development is hindered by research challenges that limit knowledge about the neural systems that support social behavior, how those neural systems and associated social behaviors are compromised in psychopathology, and how the social environment influences neural function, social behavior, and symptoms of psychopathology.
3. These research challenges can be addressed by tailoring experimental design to optimize sensitivity of both neural and social measures as well as reduce confounds associated with psychopathology.
4. Investigations on the neural mechanisms of social learning, self-regulation, and Theory of Mind provide examples of methodological approaches that can inform our understanding of psychopathology.
5. High-levels of neuroticism, which is a vulnerability for anxiety disorders, is related to hypersensitivity of the amygdala during social fear learning.
6. High-levels of social anhedonia, which is a vulnerability for schizophrenia-spectrum disorders, is related to reduced lateral prefrontal cortex (LPFC) activity

during the up-regulation of positive social signals. Individuals with higher social anhedonia and lower LPFC activity to positive social signals have the worst schizophrenia-spectrum symptoms. Thus, deficits in LPFC up-regulation of positive emotion during social interactions could contribute to social problems in schizophrenia.

7. The ventromedial prefrontal cortex (VMPFC) facilitates theory of mind (ToM) skills. Structural and functional deficits in VMPFC in schizophrenia contribute to ToM deficits and related social problems associated with schizophrenia disorder.
8. Moving forward requires the continued development of new approaches so that social neuroscience research can inform intervention techniques that improve social functioning in both healthy and disordered populations.

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Introduction

Social contact is a fundamental human need, crucial for health and well-being. Indeed, the desire for social relationships is so universal that forced deprivation, such as solitary confinement, is a form of punishment worldwide, and commercial products aimed at improving relationships are a driving economic force. However, as a quick glance of self-help books will demonstrate, the desire for social relationships and the ability to develop and maintain them varies widely across individuals. Extremes on either end of the distribution indicate the risk and/or expression of mental illness. Excessive dependence on others and fear of interpersonal rejection are associated with social anxiety, depression, and borderline personality features. Whereas disinterest in social relationships, lack of close friends, and deficits in social skills are associated with autism- and schizophrenia-spectrum disorders.

Social problems are especially harmful for psychiatrically vulnerable populations. Compromised social support systems expose vulnerable individuals to the negative impact of stressful life events (Horan et al 2006, Penn et al 2004). Social deficits can also irritate other people and exacerbate interpersonal conflict (King 2000). The potential consequences of these negative interactions are significant since interpersonal conflicts, especially those characterized by criticism and hostility, precipitate the onset, relapse, or exacerbation of psychiatric symptoms (Hooker et al 2014, Hooley 2007). (Also see chapter by Hooley in this volume).

Yet, although social relationships are central to the human experience, relatively little is known about the neural systems that support social behavior, and, this limited knowledge hinders the development of interventions to improve social deficits. The complexity of social behavior – a dynamic process in which multiple social and emotional skills influence relationships over time - creates several research challenges.

This chapter is a selective review, with an emphasis on research challenges and methodological strategies, of 1) the neural systems that support social behavior; 2) how these neural systems are compromised in mental illness, particularly schizophrenia-spectrum disorders; and 3) how this information can facilitate treatment of social deficits.

The Neuroscience of Social Functioning: What are the challenges?

A tenet of scientific research is to isolate the process under investigation and control for all other variables; yet, social behavior is not an isolated process. Interpersonal interactions are dynamic, reciprocal, and context dependent events in which the behavior of one individual is influenced by the other. Research on neural systems of social behavior must account for and/or examine the influence of these variables. Research must also account for potential discrepancies between social ability and social motivation. Ability is usually assessed with laboratory tests of social cognition, such as ability to accurately recognize pictures of facial expressions or identify the intentions of different people in a social scenario (see chapter by Lee, Horan & Green). However, just because someone has the capacity to understand complex mental states and interpersonal dynamics, does not mean that they will apply those skills equally in all relationships or use their skills with prosocial intentions. So, while the laboratory offers the benefits of tightly controlled experiments, the information gained from them is limited, if it doesn't apply to real-life behavior.

Although social psychologists have sophisticated methods to measure interpersonal dynamics, the main tools of neuroscientists, such as functional magnetic resonance imaging (fMRI) and other neuroimaging techniques, have unique constraints. Participants in an fMRI experiment, for example, are squeezed into a tight horizontal tube with their head restrained and body immobilized; the room is dark, the scanner loud, and behavioral responses are often confined to a button press – five buttons at most. This is a difficult environment to identify social phenomena that are even

remotely ecologically valid. Social neuroscience requires new and creative methods to connect neural function to real-life social behavior. Thus far, research in social neuroscience has focused on, and effectively established, the neural systems that are involved in core, laboratory-based skills for processing social and emotional information, such as face perception, emotion recognition, emotion regulation, and other aspects of social cognition. Moving forward will require the integration of multiple methods to capture the complexity of social behavior and offer an ecologically valid model of brain-behavior relationships.

Research on the social neuroscience of psychopathology faces additional challenges. People with severe disorders, such as schizophrenia and autism, have deficits in multiple (non-social) cognitive skills that can contribute to poor performance on social cognitive tasks and obscure associated neural systems. The most severe psychiatric patients may not be able to complete certain social cognition tasks at all, raising concerns about how well results generalize to the entire patient population. Alternatively, those individuals with intact cognitive skills may recruit brain regions normally dedicated to non-social processes to compensate for dysfunction in social systems. Cultural background, socio-economic status, and stigma associated with mental illness can also influence social cognitive processes and associated brain mechanisms (Chiao & Mathur 2010, Hackman et al 2010, Krabbendam et al 2014). Moreover, neural dysfunction can manifest in a number of ways. Hypoactivity can indicate neuropathology preventing activity or problems employing a psychological

strategy that engages activity, whereas hyperactivity can indicate inefficient neural processing or additional effort (Callicott et al 2003, Poldrack 2014). These different manifestations of neural dysfunction can vary across individuals, effectively canceling out group differences when comparing individuals with and without the disorder. Failure to account for these limitations and potential confounds can lead to faulty conclusions about which brain areas are supporting a specific social behavior. Since information about neural mechanisms of social behavior is used to guide treatment development, faulty conclusions can be costly mistakes.

Several methodological strategies can be used to address these challenges. First and foremost, interpretation of brain function is greatly enhanced if neural measures are tied to behavior – i.e. variation in neural structure or function should predict variation in the target social behavior. While this sounds obvious, combining fMRI and behavioral methods effectively requires careful consideration of experimental design so that appropriate variation is elicited in each domain. One strategy is to first isolate a targeted brain function using controlled laboratory-based experiments and then investigate whether it predicts more ecologically-valid measures of social behavior. The latter measures include experience sampling methods (ESM) in which people are prompted to report on their thoughts, feelings and behaviors at various times during the normal course of their day(Hooker et al 2014, Hooker et al 2010a), or video-recordings of real-life social interactions that are subsequently coded for specific social

behaviors. This multi-method approach optimizes sensitivity of both neural and social measures.

A technique, often used in psychopathology research, is to manipulate or statistically control for behavioral performance on fMRI tasks in order to minimize confounds associated with different skill-levels. For example, although participants with schizophrenia usually perform worse than healthy controls on social cognitive tasks, an experimenter might adjust task-difficulty or require a performance criterion prior to scanning, so that both groups perform the task equally well (Manoach 2003, Thermenos et al 2005). Thus, hyperactivity in the schizophrenia group can be interpreted as neural inefficiency since more neural resources are required to achieve the same level of performance as controls. Another strategy to reduce confounds related to psychiatric illness is to study social neuroscience processes in individuals at risk for developing the disorder, such as first-degree relatives, or with a specific vulnerability related to the disorder, such as high levels of personality traits related to psychopathology. Examples of these strategies are described below.

The Building Blocks of Social Functioning

From a neural systems perspective, the core social and emotional processes can be grouped into four broad categories based on the network of brain regions that are preferentially recruited to support the process. 1) Social perception, the accurate perception and interpretation of social cues, including the perception of socially-relevant stimuli, such as face identity, gaze direction, and communicative gestures.

Neural regions involved in social perception include the fusiform gyrus, superior temporal sulcus, and the lateral occipital cortex; 2) Emotion processing, including emotional experience, expression, recognition, and learning. Neural regions involved in emotion processing include the amygdala, ventral and orbital prefrontal cortex, insula, somatosensory cortices, and subcortical structures, such as the striatum, and thalamus. 3) Self-regulation, including the regulation of internal emotional states as well as the influence of social and emotional information on behavior. Neural regions involved in self-regulation include regions typically associated with cognitive-control, such as the lateral prefrontal cortex (LPFC) and anterior cingulate cortex (ACC). 4) Mental state attribution, referred to as Theory of Mind (ToM) or mentalizing, which broadly includes the understanding and reasoning about one's own mental state and the mental states of others. Neural regions involved in ToM include superior temporal cortex (STC), temporoparietal junction (TPJ), medial prefrontal cortex (MPFC), precuneus, and the temporal poles. [See review articles (Adolphs 2009, Barrett et al 2007, Calder & Young 2005, Heatherton 2011, Lieberman 2007, Ochsner & Gross 2005)]. The social processes and associated networks listed here are neither exhaustive nor exclusive. Social behavior is psychologically complex and draws upon multiple interacting brain regions depending on the combination of psychological processes involved. Emotion regulation, for example, includes both emotion processing and self-regulation, and could be listed in either category above. Other important social processes (not listed here), such as empathy, attributional style, attachment, and social dominance involve

multiple behavioral processes and neural systems. (See Lee, Horan, and Green for additional discussion on empathy and attributional style).

Emotion Processing in Social Contexts: Role of the Amygdala

An immense body of research demonstrates that the amygdala is involved in emotional experience and emotional learning. Most data is from classical conditioning paradigms. In classical conditioning, an individual is presented with a neutral stimulus followed by a reward or punishment, and, afterwards, the stimulus (i.e. the conditioned stimulus) evokes the same emotional response as the reward or punishment. For example, a neutral tone is followed by electric shock, and, afterwards, the tone alone evokes fear associated with electric shock. The amygdala is active when directly experiencing rewards and punishments, but is more critically involved in learning the stimulus-emotion association, i.e. learning the predictive value of the cue [for reviews see (LaBar & Cabeza 2006, LeDoux 2000, Phelps 2004, Phelps 2006)].

Importantly, emotional learning can occur through direct experience with reward and punishment (as in classical conditioning) or by observing the experience of others, referred to as 'observational' or 'social' learning. Behavioral studies demonstrate that social learning is an effective and efficient avenue for learning about potential dangers and rewards. Children are more likely to avoid an object after observing their mother's fearful response to it and more likely to approach an object after witnessing their mother's joyful response (Campos et al 1994). Monkeys raised in captivity with no exposure to or fear of snakes, develop a fear response to snakes after observing another

monkey's fearful reaction (Mineka & Cook 1993, Mineka et al 1984). Although classical conditioning is one of the most studied phenomena in neuroscience, there is virtually no research on the neural basis of social learning.

In a series of experiments, my colleagues and I used a classical conditioning framework to investigate the neural mechanisms of social learning and how these neural mechanisms contribute to psychopathology. Since emotional learning from direct experience with reward and punishment relies on amygdala function, our hypothesis was that emotional learning from observation also relies on amygdala function.

There were several challenges to testing this hypothesis. The amygdala is active in response to emotional facial expressions during almost any social cognitive task, including passive viewing, emotion matching, and emotion recognition (Sergerie et al 2008). This activity appears to facilitate emotion recognition ability, since degree of amygdala correlates with emotion recognition accuracy and amygdala lesions cause emotion recognition deficits (Adolphs 2010). However, facial expressions communicate information about another person's internal emotional state as well as emotionally-relevant objects or events in the external environment. Thus, amygdala activity could reflect the attempt to learn associations between the observed emotional expression and a stimulus in the environment. Indeed, amygdala response tends to the most robust in response to fearful expressions. One interpretation is that fear communicates a threat in the environment but not what it is or where it is. This ambiguity regarding the

stimulus-emotion association is thought to drive maximal amygdala response which increases arousal and vigilance, and thereby enhances detection and processing of the environmental threat (Whalen 1998, Whalen 2007). However, emotional facial expressions can act as a predictive cue as well as a primary reinforcement. A beautiful woman's smiling face is inherently pleasing and activates reward processing regions (O'Doherty et al 2003, Spreckelmeyer et al 2009); similarly, fear and other negative expressions evoke unpleasant feelings in the observer (Hooker et al 2014, Sergerie et al 2008).

Identifying whether amygdala response to emotional expressions reflects activity related to emotional learning or activity related to emotional experience requires a direct comparison of learning from emotional faces to perceiving those same faces without learning. We developed a novel experiment to examine this comparison (Hooker et al 2006). In the Association Learning (AL) condition, participants saw a woman's neutral face in the center of the screen with an unfamiliar (neutral) object on either side. At the beginning of the trial, a fixation cross appeared underneath one of the objects and the participant predicted whether the woman was going to have a fearful or neutral reaction to that object. Once they made their prediction, the woman turned to look at the object and had either a fearful or neutral reaction. In another block of trials, participants predicted whether the woman was going to have a happy or neutral reaction. Thus, participants learned the threat or reward value of previously neutral object from the emotional expression of someone else. In the Expression Only (EO)

condition, the woman's face appeared on the screen but there were no objects. Participants predicted whether she would have a fearful versus neutral (or happy versus neutral) expression but there was no association to learn. The main analysis compared the AL condition to the EO condition (see Figure 1).

Results showed that the amygdala was significantly more active when learning the emotional value (including both threat and reward value) of an object from another person's facial expression than it was to perceiving the same facial expressions (fearful and happy) when presented alone. These findings suggest that amygdala activity in response to facial expressions reflects an attempt to learn emotionally-relevant (and survival-relevant) information from them.

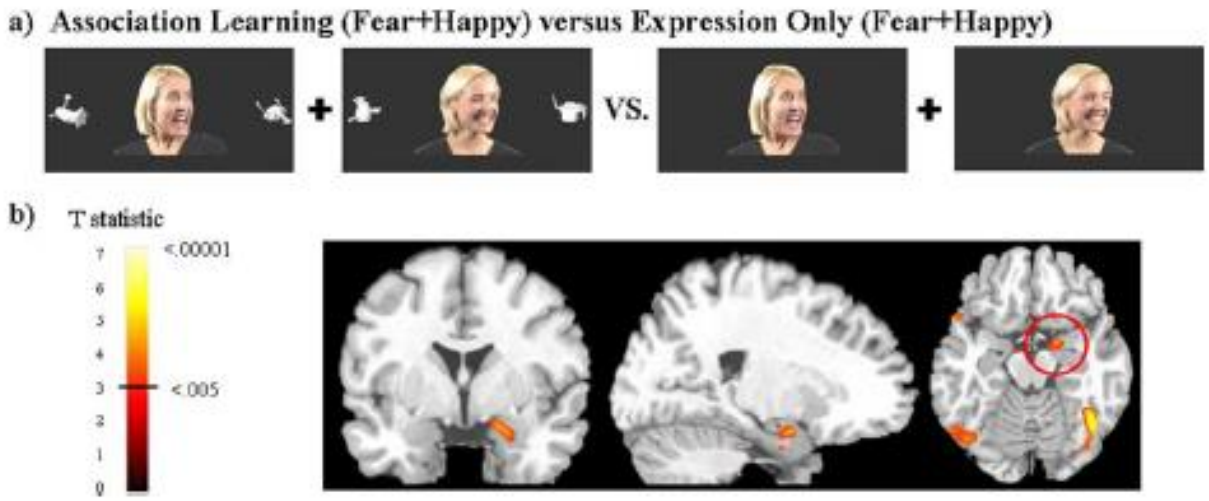

Figure 1 a) An example of the stimuli used in the main analysis. Participants were required to learn whether the woman would respond with a fearful versus neutral or happy versus neutral expression to the novel object; b) shows greater amygdala activity for learning object-emotion associations from facial expressions as compared to emotional faces presented without learning. Reprinted with permission from Hooker et al., (2006) *Journal of Neuroscience*.

These findings highlight an even greater need to understand the influence of social context. What, exactly, do we learn from other people? And, what characteristics of the observer, the communicator, and the environment influence what we learn and how we learn it?

Social Learning and Psychopathology

Although learning to avoid danger and approach reward is crucial for survival, an exaggerated response to perceived danger can lead to maladaptive fear, including anxiety disorders (Mineka & Ohman 2002) and exaggerated response to reward can lead to reward-seeking behaviors, including addiction disorders (LaLumiere & Kalivas 2007). Nonetheless, most neuroscience research on maladaptive learning is conducted within a classical conditioning framework and the social context is rarely considered. It is well known that symptoms of certain psychiatric disorders are influenced by social learning. For example, post-traumatic stress disorder (PTSD) can develop after direct experience of fear or after witnessing the fear of someone else (Mineka & Zinbarg 1996, Ohman & Mineka 2001). Similarly, drug addiction can accelerate (or decelerate) depending on the amount of drug use in the person's immediate social environment (Leshner 1997).

Personality traits, such as neuroticism, are associated with the vulnerability to develop maladaptive stimulus-reinforcement associations, particularly fear

associations. Neuroticism is characterized by an increased sensitivity to punishments and a tendency to feel negative affect (John & Srivastava 1999). Individuals with high levels of neuroticism have greater risk for developing anxiety disorders (Bienvenu et al 2007). Although it has been proposed that increased sensitivity to punishment in people with high neuroticism causes enhanced fear learning (Eysenck 1967, Gray 1982), behavioral studies do not consistently show this pattern (Matthews & Gilliland 1999), and, at the point of this experiment, there was no information about the influence of neuroticism in social learning.

We tested the idea that the effect of neuroticism in maladaptive learning is mediated by exaggerated amygdala response to fear and punishment (Hooker et al 2008b). This hypothesis arose from a neurodevelopmental framework. Prior research indicates that people with the short allele of the 5-HTT polymorphism (serotonin transporter gene), compared to those without the allele, have more amygdala activity to fearful faces (Hariri et al 2005, Hariri et al 2006), higher neuroticism (Lesch et al 1996), and greater risk for mood and anxiety disorders (Lesch 2007). One possibility is that self-reported neuroticism in adolescence or adulthood (which is measured with questions like "I'm worried that the worst will happen") may be the consequence of increased sensitivity of the amygdala in response to negative information. And it is this neural activity, in the context of fearful experiences, which contributes to the development of maladaptive fear.

We tested healthy adult participants with varying levels of neuroticism. Using healthy participants who vary on a personality trait associated with vulnerability to the disorder minimizes research confounds associated with established illness including medication effects, generalized cognitive deficits, internalized stigma, and compensatory neural processes. To best understand the relevance of social learning to anxiety disorders, we investigated each stage of social learning: acquisition of object-emotion associations; subsequent expression of learned emotional value; and enhanced memory for emotion associated objects. We then investigated whether these processes were modulated by neuroticism.

The experiment used a similar paradigm as before (see Figure 2). A woman's face appears on the screen with two unrecognizable objects – one on either side. Participants predict whether she will respond fearfully or neutrally to the object and they learn the emotional value of the object by observing the woman's response. Immediately after learning, participants performed a recognition task in which objects were presented (one at a time), including the just learned fear object and neutral object as well as new objects. Participants were asked "Is this an object that was presented before?" Neural response to the objects presented alone provided the opportunity to test whether the emotion object had acquired neurally represented emotional value from the woman's emotional reaction. After scanning, participants completed a surprise memory post-test in which they viewed objects seen in the experiment and identified whether or not the object had been presented to the woman (Hooker et al 2008b).

As expected, we found that, across all participants, the amygdala–hippocampal complex was more active when learning object-fear associations from someone else's fearful expression than it was to learning object-neutral associations from someone else's neutral expressions. After learning, the amygdala was more active to fear (vs. neutral) associated objects when these objects were presented alone.

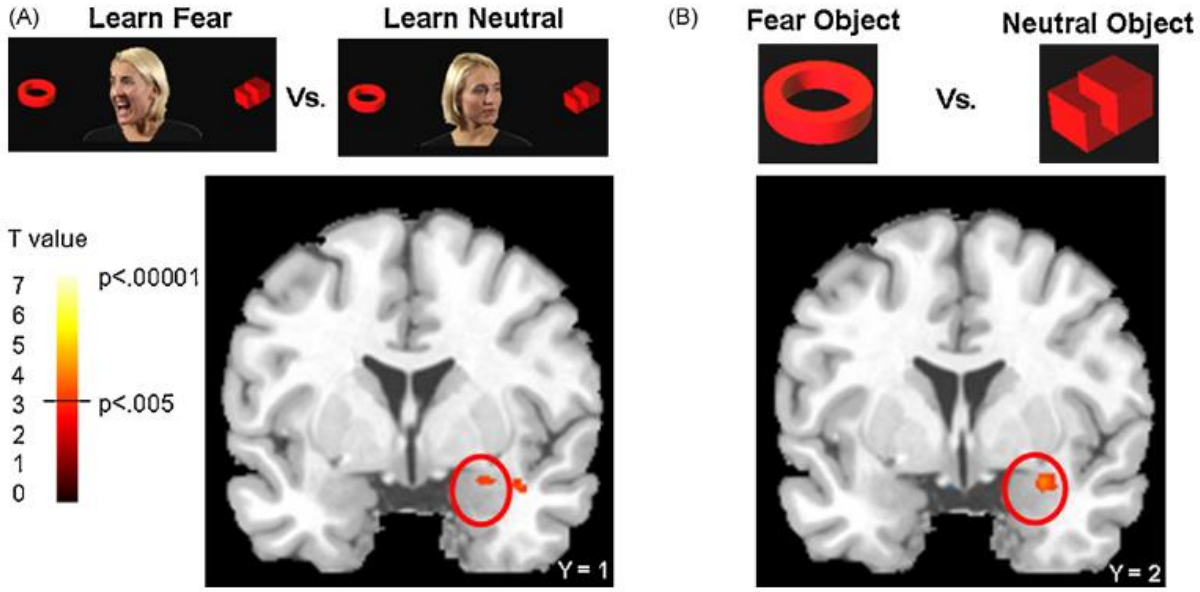

Figure 2. Neural activity during observational fear learning. (A) During learning trials, there was greater right amygdala activity during fear learning relative to neutral learning (Learn Fear vs. Learn Neutral). (B) During recognition trials after learning, there was greater amygdala activity for the fear associated object than the neutral associated object (Fear Object vs. Neutral Object). Reprinted with permission from Hooker et al., (2008) *Neuropsychologia*.

In addition, greater amygdala–hippocampal activity during fear learning predicted better long-term memory for objects with a learned association (i.e. both fear objects and neutral objects from the fear learning experiment). Moreover, higher levels of neuroticism predicted greater neural activity in the amygdala–hippocampal complex during fear (vs. neutral) learning (Hooker et al 2008b) (see Figure 3).

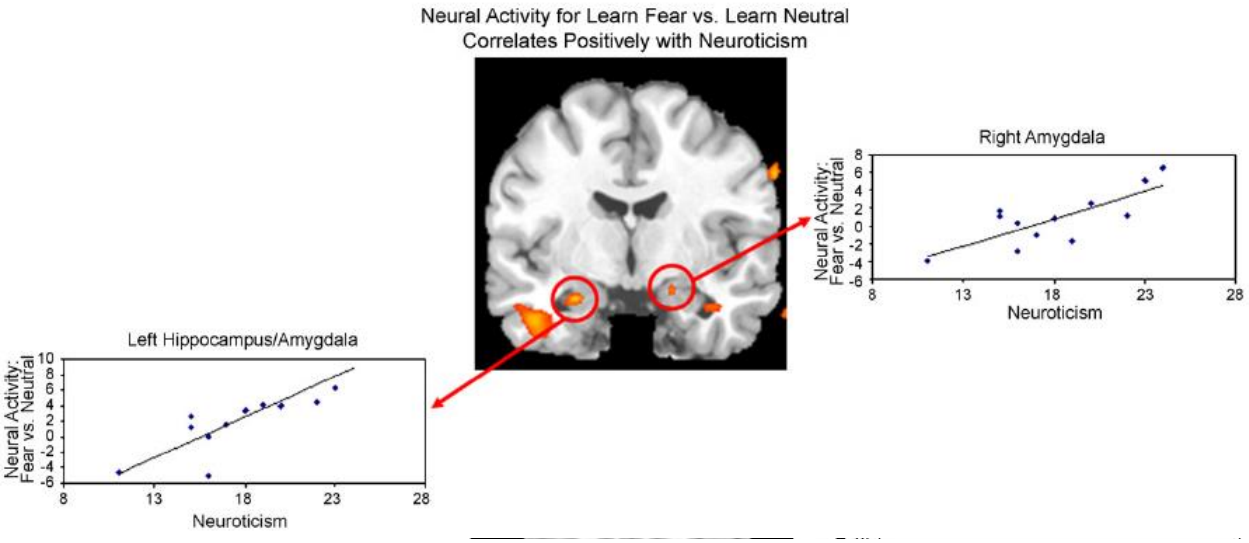

Figure 3. Correlation of amygdala activity during fear learning versus neutral learning with individual neuroticism scores (neuroticism measured with the Big Five Inventory). Reprinted with permission from Hooker et al., (2008) *Neuropsychologia*.

These findings show that social learning has a lasting effect on an individual's response to their environment. Amygdala activity when observing someone else's fearful reaction 'tagged' that object with emotional value, such that the object evoked amygdala response when presented alone after learning. In addition, the degree of amygdala activity during the fear learning experience predicted memory for everything in the environment – i.e. the object associated with threat as well as the object associated with safety. This is consistent with data showing that amygdala activity during encoding of emotional stimuli, such as emotional words or pictures, predicts later memory for those stimuli (Hamann & Canli 2004, Hamann et al 1999) and suggests that amygdala response to emotional arousal modulates encoding and consolidation processes (LaBar & Cabeza 2006, Phelps 2006). Because people with high neuroticism

have a higher degree of amygdala activity during learning, they may be more susceptible to developing problematic fear responses. More specifically, high amygdala activity could assign exaggerated threat value to the learned object, so that future encounters with the learned object would elicit an unnecessarily high level of fear and arousal. The learned object may also be encoded more deeply which could contribute to longer lasting and more intrusive memories. These types of responses after a fear experience are characteristic of anxiety disorder symptoms, including those related to PTSD, simple phobia, and social phobia.

Knowing that the social context is a potential risk factor provides the opportunity for individuals to communicate their needs and vulnerabilities to partners and family members. An emotionally reactive spouse or friend can magnify the risk of maladaptive learning. Fearful reactions to small, arguably inconsequential events, such as a spider on the wall, could cause considerable distress for a person with elevated neuroticism. In extreme circumstances, like an uncontrollable natural disaster, the fearful reactions of others potentiate the fear experience and could contribute to the onset of an anxiety disorder, such as PTSD. If significant others in the social environment can reasonably contain their fear reactions, it could reduce the risk of maladaptive learning.

Self-Regulation

Self-regulation, including the regulation of emotion and behavior, is achieved through a variety of strategies that use cognitive skills, such as attention and inhibition, to control emotional experience and behavioral reactions (Brown et al 2006, Ochsner &

Gross 2005). Stressful events, including interpersonal conflicts and other social stressors, provoke negative affect and require recruitment of regulatory skills to cope effectively. Failure to regulate emotion after a stressful event results in persistent negative mood and potentially self-destructive responses, such as rumination or substance-use, which can trigger a downward spiral and ultimately impair functioning (Ayduk et al 2001, Li & Sinha 2008, Nolen-Hoeksema 2000). Poor self-regulation is not only a common problem in psychiatric disorders, but also a primary cause of symptom exacerbation after stressful event (Hooley 2007, Monroe et al 2001, Muscatell et al 2009).

Effective self-regulation relies on a network of neural regions, including the lateral prefrontal cortex (LPFC), that support cognitive control and related processes (Ochsner & Gross 2005). The LPFC, particularly the ventral portion (VLPFC), facilitates emotion regulation by, automatically or effortfully, engaging strategies that employ cognitive skills, such as attentional control and reappraisal, to control the influence of emotional information on subjective experience (Lieberman 2007 , Ochsner & Gross 2005). The reappraisal task is a common experimental measure of emotion regulation (Ochsner et al 2002), frequently used with psychiatric populations (Modinos et al 2010). While undergoing fMRI, participants view pictures of negative scenes and are instructed to either reappraise (i.e. re-evaluate or re-interpret) the scene to decrease their negative affect or view the scene without attempting to regulate emotional response. The LPFC is more active during reappraisal than passive viewing and greater LPFC is related to less amygdala activity as well as less distress from the negative

picture, suggesting that LPFC activity controls the experience of negative affect by inhibiting amygdala response (Ochsner et al 2002, Ochsner et al 2004).

A limitation of this and similar approaches is that emotion regulation is treated as an isolated experience, removed from social context. In addition, the negative stimuli used to provoke negative affect are used as a proxy for a real-life affective challenge, and it is assumed that behavioral and neural responses observed in the scanner represent what they would do in real-life. This is a shaky assumption, since the experimental context is a highly structured environment in which participants are instructed to regulate their emotion and given a strategy to do it. Just because an individual is capable of employing LPFC-mediated regulatory strategies, does not mean that they will do so in daily life.

To address these limitations, my colleagues and I used a combination of fMRI and experience sampling methods to test whether LPFC-control related functions predicted ability to regulate emotion and behavior after an interpersonal conflict with a romantic partner (Hooker et al 2010a). Couples in a committed relationships participated in an fMRI experiment in which they viewed pictures of their partner displaying interpersonally-relevant positive (e.g. happy, caring), negative (e.g. angry, disappointed) and neutral expressions. Viewing the partner's negative expression was the affective challenge meant to elicit control-related LPFC activity. There were no instructions to regulate emotional response with the idea that a person's natural tendency to regulate in the scanner would be the best predictor of regulation in real-life. After the scan, participants completed an online daily diary in which, each evening for

21-days, they reported whether or not they had a conflict with their partner, and rated the extent to which they felt positive and negative mood, and engaged in rumination, and substance-use.

Measuring mood and behavior each day is more accurate than most social functioning assessments that rely on retrospective accounts over weeks or months. And, the repeated assessments over 21-days provides the opportunity to investigate day-to-day changes – specifically, whether an interpersonal conflict on one day caused an increase in negative mood and maladaptive behaviors the next day.

Results showed that LPFC activity to a partner's negative (vs. neutral) expression predicted ability to recover from an interpersonal conflict with that person. Although everyone had a more negative mood the day of the conflict, LPFC activity significantly predicted mood and behavior the day after the conflict, such that people with low LPFC activity to their partner's negative expression had higher levels of negative mood, destructive thought patterns (rumination), and substance-use (See Figure 4).

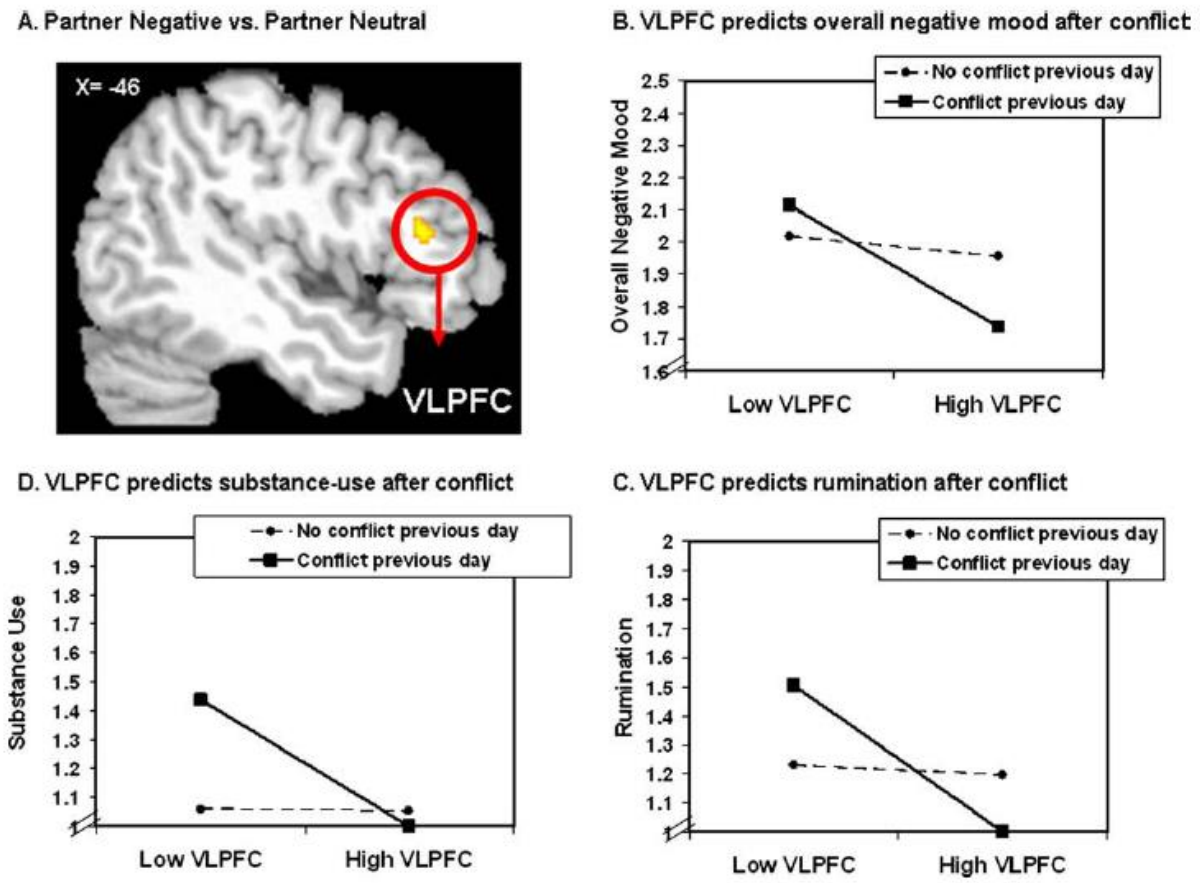

Figure 4. (A) Whole-brain, random-effects analysis across the group of subjects (n = 27) shows significant left VLPFC activity for partner negative versus partner neutral expressions contrast. **(B)** Individual level of VLPFC activity, extracted from this group activation, significantly interacted with interpersonal conflict to predict overall negative mood. Higher scores correspond to more negative mood (graphed on the Y axis). As shown in the figure, when there was no conflict the previous day, VLPFC activity was not related to overall negative mood. However, when a conflict occurred the previous day, lower VLPFC activity was related to more overall negative mood. The same pattern of results can be seen with **(C)** rumination and **(D)** substance use. VLPFC: ventrolateral prefrontal cortex. Reprinted with permission from Hooker et al., (2010) *Biological Psychiatry*.

Interestingly, LPFC activity to positive (versus neutral) expressions also predicted emotion regulation after conflict. Specifically, VLPFC activity to positive expressions was related to up-regulation of positive mood (e.g. happy, accepted, supported) but not down-regulation of negative mood (e.g. sad, disappointed, angry)

after conflict. These findings suggest that LPFC recruitment when processing positive social signals is a valence-specific trait that predicts regulation of positive emotion in interpersonal contexts.

The results, overall, have important implications for psychopathology as they suggest that LPFC deficits could be a vulnerability factor that interacts with social stressors to predict mood and behavior problems (Hooker et al 2010a).

Self-Regulation and Psychopathology

Social stress is a well-known risk factor for the onset and relapse of psychiatric disorders, including major depressive disorder, schizophrenia, borderline personality disorder, and others. Deficits in LPFC regulatory functions are also common to these disorders, and may be a vulnerability factor for the exacerbation of symptoms from interpersonal conflict and other social stressors. (See chapter by Hooley for additional discussion).

Although most emotion regulation research in basic science and psychiatry has focused on the down-regulation of negative emotion, research on the up-regulation of positive emotion is also important. Individuals at-risk for or suffering from schizophrenia-spectrum disorders have behavioral deficits in the experience, expression, and regulation of positive emotion (Kring & Elis 2013). Social anhedonia (SA) defined as diminished pleasure from social relationships, is a personality trait associated with schizophrenia-spectrum pathology. SA is present prior to the onset of

psychosis, persists despite antipsychotic treatment, and contributes to functional disability (Blanchard et al 1998, Horan et al 2008). Abnormally high SA is evident in first-degree relatives of people with schizophrenia (Laurent et al 2000, Schurhoff et al 2003), and, in young adults, prospectively predicts schizophrenia-spectrum disorders 5-10 years later (Gooding et al 2005, Gooding et al 2007, Kwapil 1998). Combined with irrefutable evidence of LPFC dysfunction in schizophrenia liability and illness (Barch 2005, MacDonald et al 2009), the data indicate that SA may be caused by LPFC deficits up-regulating positive emotion from social relationships.

We used fMRI and daily-diary methods (similar to the couples study described above) to test whether healthy adults with high SA had reduced LPFC activity to positive social signals, and if so, whether these LPFC deficits predicted daily ratings of mood and schizophrenia-spectrum symptoms as well as the exacerbation of mood and symptoms after an interpersonal conflict (Hooker et al 2014).

During fMRI, participants viewed videos of interpersonally relevant positive, negative, and neutral facial expressions. After the scan, in an online daily-diary, they rated severity of schizophrenia-spectrum symptoms every evening for 21-days. Results showed that, compared to low SA, high SA participants had less VLPFC activity to positive versus neutral expressions. Analysis with the daily-diary ratings revealed that the interaction of SA and VLPFC activity to positive expressions predicted the daily experience of schizophrenia-spectrum symptoms. Specifically, participants with both high SA and low VLPFC activity had worse cognition, paranoia, psychomotor

retardation, and motivation. In addition, among high SA participants, VLPFC activity predicted the daily relationship between conflict distress and paranoia. High SA participants with low VLPFC activity had worse paranoia on days of high conflict distress compared to days of low conflict distress.

These findings indicate that SA, as measured by behavioral reports of diminished pleasure from social relationships, is related to reduced VLPFC engagement when processing positive social signals, and, among high SA individuals, those with lower VLPFC engagement are especially susceptible to the negative impact of interpersonal conflict. Moreover, even though people can experience high SA for multiple reasons, including social rejection or medication side effects, our results indicate that the combination of high SA and low LPFC function may be specifically related to schizophrenia-spectrum pathology and a possible marker of psychosis-vulnerability.

Theory of Mind, Simulation, and Empathy

'Theory of Mind' (ToM) – also known as 'mental state attribution' or 'mentalizing' - is the ability to infer the mental states of others, including their beliefs, goals, intentions, and emotions, and the understanding of how those mental states motivate behavior (Frith & Frith 2006a, Frith & Frith 2006b, Saxe et al 2004). Mental states can be inferred through 'mental state decoding' – which involves decoding observable non-verbal social cues (e.g. facial expressions, gaze direction, and body posture) as well as 'mental state reasoning' which involves integrating information

from multiple sources and engaging in high-level reasoning about mental states and how they influence a person's actions and reactions (Baron-Cohen 1995, Frith & Frith 2005, Saxe 2005). These ToM skills contribute to empathy, particularly the cognitive component of empathy (Shamay-Tsoory et al 2003, Shamay-Tsoory et al 2005), and help deepen interpersonal relationships. (See chapter by Lee, Horan, and Green for further discussion of mental state attribution and different facets of empathy).

ToM processing, especially mental state reasoning, recruits a network of regions, including both dorsal (D) and ventral (V) MPFC, as well as the TPJ, STS, posterior cingulate, and precuneus. This neural system supports multiple psychological processes that facilitate ToM skills. A main process is *simulation* – which involves using one's own experience as a basis for inferring the experience of others. Simulation includes both automatic and effortful processes. An example of effortful simulation is when an individual tries to understand another person's experience by consciously imagining (or 'simulating') how they would feel or behave in the same situation. This often involves remembering a similar experience of their own and using this as a reference for understanding the other person. Evidence suggests that the MPFC, particularly the VMPFC, supports simulation through self-referential processing which includes integrating information about the self, constructing self-identity, and facilitating the comparison between self and others (Amodio & Frith 2006, Rudebeck et al 2008, van der Meer et al 2010).

'Mirroring' the actions and emotions of others is a form of automatic simulation which is supported by the mirror neuron system. The mirror neuron system includes

the ventral premotor cortex and inferior parietal lobe, and spans both primary and secondary motor and somatosensory cortices (Gallese & Goldman 1998, Gallese et al 2004). Data shows that observing another person's action activates the neural region associated with the execution of that action. For example, observing someone else waving their hand activates the *observer's* hand region of the motor cortex (Iacoboni et al 2005). This mirror neuron activity generates an internal representation of the other person's action which facilitates an understanding of that person's goals and intentions (Gallese 2007, Gallese et al 2004, Hooker et al 2008a, Hooker et al 2010b, Keysers & Gazzola 2007, Keysers et al 2004).

Theory of Mind and Psychopathology

Several neurological and psychological disorders have deficits in ToM, particularly mental state reasoning, as well as structural and functional abnormalities in brain regions supporting ToM. These disorders include autism, schizophrenia and frontotemporal dementia, and for all of these disorders, deficits in ToM skills are related to poor interpersonal relationships and compromised quality of life (Baron-Cohen 1995, Brune 2005, Snowden et al 2003). However, each of these disorders is also associated with severe cognitive deficits, such as attention and memory deficits, making it difficult to identify the specific neural problem associated with ToM deficits and associated social difficulties.

ToM deficits are a major cause of social dysfunction in schizophrenia, so revealing the neurocognitive processing of ToM may help develop functionally

beneficial treatments. We conducted a study to identify the relationship between VMPFC abnormalities and ToM ability (Hooker et al 2011) in schizophrenia. Individuals with schizophrenia have poor behavioral performance on advanced ToM tasks, such as recognizing a social faux pas and other tasks that require mental state reasoning (Bora et al 2009). These impairments are observable prior to illness onset, remain when psychotic symptoms are remitted (Pickup 2006), and predict social functioning, even when controlling for the influence of general cognition (Couture et al 2006, Pijnenborg et al 2009, Roncone et al 2002). VMPFC functions are crucial for mental state reasoning and cognitive empathy (Shamay-Tsoory 2011, Shamay-Tsoory & Aharon-Peretz 2007, Shamay-Tsoory et al 2007). Schizophrenia is associated with both structural and functional abnormalities in the VMPFC (Honea et al 2005, Williams 2008). However, previous research on the relationship between VMPFC dysfunction and ToM ability in schizophrenia has produced conflicting results. Although several ToM studies demonstrate the predicted pattern of less activity in the VMPFC and other ToM regions in schizophrenia versus healthy participants (Brunet et al 2003), other studies report that schizophrenia participants have abnormally high activity in ToM regions or recruit non-ToM regions to complete the ToM task (Benedetti et al 2009, Marjoram et al 2006).

These findings highlight methodological challenges of using fMRI to investigate a social cognitive skill that is difficult for people with schizophrenia. Task-related neural activity is hard to interpret -- hypo-activity can reflect lack of attention and

hyper-activity can reflect additional effort (Callicott et al 2000, Callicott et al 2003). Furthermore, performance-based ToM tasks may not provide the most ecologically valid and clinically useful assessment, since they do not account for the motivation or success in using these skills to enhance social relationships. The day-to-day use of ToM skills may be better evaluated with self-report, experience sampling, observation, or interview-based functional assessments.

We addressed these methodological challenges by investigating the relationship between neural structure, specifically gray matter volume (GMV), and three different behavioral assessments of ToM processing. ToM measures included: 1) behavioral performance on an advanced ToM task in which participants read a short social vignette and identified whether or not a character in the story made a social faux pas; 2) self-reported tendency to engage in perspective-taking (e.g. "Before criticizing somebody, I try to imagine how I would feel if I were in their place"); and 3) an interview-based assessment of the capacity and tendency to consider the perspectives and emotions of other people, such as family and friends, in their real-life relationships. Each measure assesses the ability to integrate both cognitive and affective components of ToM processing in the service of understanding others. Using three different behavioral methods provides converging evidence that the observed relationship between brain structure and behavioral assessment reflects the true relationship between brain structure and ToM processing – i.e. the core construct under investigation - and not an epiphenomenon of the assessment method.

Indeed, we found that among schizophrenia patients, these three different measures of advanced ToM skills were significantly related to VMPFC GMV (see Figure 5).

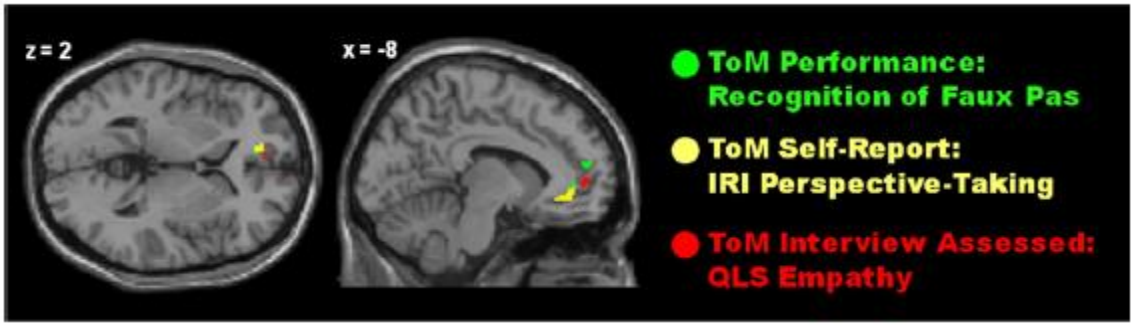

Figure 5. Overlay of three separate regression analyses showing where theory of mind (ToM) skills are significantly related to gray matter volume (GMV) among schizophrenia participants. ToM is assessed by: 1) behavioral performance on the ToM task—The Recognition of Faux Pas Test (green); 2) self-reported ToM skills in daily life as measured by the questionnaire—Interpersonal Reactivity Index (IRI) Perspective-Taking subscale (yellow); and 3) an interview-based rating of the capacity to use ToM skills in the participant's own interpersonal relationships, measured with the Quality of Life Scale (QLS)-Empathy score (red). The data show that, among schizophrenia participants, worse ToM skills are related to less GMV. Data within the bilateral ventromedial prefrontal cortex are displayed at threshold $p < .001$. Regressions are not controlling for global cognition. Reprinted with permission from Hooker et al., (2011) *Biological Psychiatry*.

In addition, when controlling for general cognition among schizophrenia participants, the relationship between ToM task performance (the faux pas task) and VMPFC GMV was reduced slightly, but the relationship between self-reported and interview-rated ToM and VMPFC GMV remained strong. This could be because both the laboratory-based faux pas task and the neuropsychological tasks used to assess cognition require similar test-taking skills, including the ability to sustain attention and/or tolerate explicit performance assessments. However, the fact that self-report and interview-based ToM measures demonstrated a strong and significant relationship with

VMPFC even when controlling for general cognitive abilities suggests that, in schizophrenia, GMV loss in the VMPFC is particularly associated with deficits using ToM skills to enhance social relationships in daily life (Hooker et al 2011).

Given prior evidence that VMPFC facilitates ToM through the processes related to self-reflection, self-monitoring, and comparing the self to others (Rudebeck et al 2008, van der Meer et al), our findings indicate that in schizophrenia, VMPFC structural and functional abnormalities are related to deficits in monitoring and using information relevant to the self in the service of understanding others. If future research verifies this interpretation, it suggests that interventions aimed at improving ToM processing, specifically VMPFC support of ToM, in schizophrenia could employ exercises that encourage self-reflection and the evaluation of one's own experience relative to others.

Conclusion

The purpose of this chapter was not to provide a comprehensive review of the neural mechanisms involved in social behavior. Rather, the goal was to illustrate some of the challenges of social neuroscience research and a few initial methods for addressing them. Capturing the complexity of social behavior will require the continued development of new and creative methods. Ultimately, identifying how specific brain regions support social cognitive skills and the use of those skills in daily life can facilitate the prevention and treatment of mental illness.

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