Adapting Social Neuroscience Measures for Schizophrenia Clinical Trials, Part 1: Ferrying Paradigms Across Perilous Waters

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Social cognitive impairment is prominent in schizophrenia, and it is closely related to functional outcome. Partly for these reasons, it has rapidly become a target for both training and psychopharmacological interventions. However, there is a paucity of reliable and valid social cognitive endpoints that can be used to evaluate treatment response in clinical trials. Also, clinical studies in schizophrenia have benefited rather little from the surge of activity and knowledge in nonclinical social neuroscience. The National Institute of Mental Health-sponsored study, "Social Cognition and Functioning in Schizophrenia" (SCAF), attempted to address this translational challenge by selecting paradigms from social neuroscience that could be adapted for use in schizophrenia. The project also evaluated the psychometric properties and external validity of the tasks to determine their suitability for multisite clinical trials. This first article in the theme section presents the goals, conceptual background, and rationale for the SCAF project.

Key words: social neuroscience/social cognition/schizophrenia/clinical trials

Social Cognition in Schizophrenia

Social cues come at us fast and furious. They change rapidly and are richly contextualized. They occur in multiple sensory modalities simultaneously and can elicit all manner of cognitive, affective, and behavioral responses. For people who have trouble in processing information, the cues can be extremely confusing. In the social environment, we are constantly surrounded by other human minds—social "targets" that require us to make inferences, take perspectives, and hazard guesses. These inferences and guesses are difficult in the best of conditions, and they are more difficult for individuals with schizophrenia.

Social cognition in schizophrenia is a rapidly emerging area of research with clear ties to neuroscience and impressive implications for recovery-oriented treatment.[1,2] Reviews of the literature and meta-analyses reveal consistent differences between schizophrenia patients and healthy controls in many areas of social cognition, including emotion perception and theory of mind (ToM), among others.[3,4] The impairment is large in effect size, persistent across acute and clinically remitted states, and it spans across phase of illness from prodromal to chronic.[5,6] These disturbances have been found to be largely independent of positive symptoms (delusions, hallucinations) but may be more strongly related to disorganized and negative symptoms.[7,8]

Naturally, nonsocial and social cognitive tasks share some cognitive processes (eg, working memory and perception), and therefore are often correlated. Despite these overlapping processes, social cognition is considered to be largely distinct from nonsocial cognition based on evidence from both healthy and clinical samples. Conceptually, social cognition involves the interface of socioemotional and cognitive processing, whereas nonsocial cognition is considered to be affect-neutral.[9,10] This distinction is seen quite clearly in choice of methods, as reflected by the type of stimuli (eg, people or faces vs objects) and the type of judgment being made (eg, attributing a mental state to another person vs basic tests of attention, speed of processing, or memory).

If this distinction between social and nonsocial cognition was only a matter of selecting stimuli, it would be largely superficial. However, growing evidence from neuroscience indicates that the processing of social and nonsocial stimuli rely on semi-independent neural systems (see meta-analysis, Van Overwalle[11]). For example, a neural network composed of the medial prefrontal cortex, fusiform gyrus, superior temporal sulcus (STS),

and amygdala is specialized for processing social information.[10,12] Also, studies that examine the effects of neuropeptides (eg, oxytocin) on behavior can distinguish impact on social vs nonsocial cognition.[13] Further, studies of schizophrenia patients, using both confirmative and exploratory factor analyses, indicate that data are significantly better characterized when models split the 2 domains instead of combine them.[14–16] For all of these reasons, the separation of social from nonsocial cognition is considered to be valid and informative.

Social cognitive deficits are key determinants of daily functioning in schizophrenia, including instrumental activities, interpersonal functioning, and vocational achievement.[17–20] Disturbances in social cognition may be particularly relevant to problems in forming and maintaining social relationships and to interpersonal difficulties at work. These disturbances may lead to social misperceptions that influence how an individual reacts to others, which in turn may lead to maladaptive social patterns and/or social withdrawal.[1,21]

Importantly, we know that social cognition appears to act as a mediator between nonsocial basic cognition and community functioning.[22–25] In a review of 15 studies that assessed whether social cognition is a mediator in functional outcome, 14 found support for this relationship.[26] Specifically, social cognition has significant relationships to nonsocial cognition or perception on the one hand, and to community functioning on the other, and the direct relationships between nonsocial cognition and outcome are reduced or eliminated when social cognition is added to a model. This literature review further found that about 25% of the variance in outcome is explained by mediation models.[26] Similarly, social cognition can explain variance in functioning beyond that provided by nonsocial cognition alone.[22,27,28] Subsequent questions arise about the intervening steps that lie between social cognition and community functioning. Based on statistical modeling, it appears that social cognition's influence on community outcome is mediated by motivational variables, such as the negative symptoms of avolition and anhedonia.[29,30] In other words, the pathways to outcome in schizophrenia appear to run from nonsocial cognition and perception, to social cognition, to motivation, and then finally to community outcome. The term "pathway" in these models is largely developmental; ie, the interpretation is that early and relatively stable impairments in social and nonsocial cognition lead, over time, to motivational problems and ineffective community involvement.

Given that social cognitive impairment is prominent in schizophrenia and so closely related to outcome, it has rapidly become a target for intervention (see following section on intervention). However, the social cognition assessments used in schizophrenia have typically been borrowed from other areas such as developmental psychology or autism research. In fact, clinical studies in schizophrenia have benefited rather little from the surge of activity

and knowledge in social neuroscience. In addition, there is a paucity of reliable and valid endpoints for clinical trials that can be used to evaluate treatment response. The National Institute of Mental Health (NIMH)-sponsored study, "Social Cognition and Functioning in Schizophrenia" (SCAF), attempted to address these challenges by adapting selected paradigms from social neuroscience for use in schizophrenia. The project also assessed the psychometric properties and external validity of the tasks to determine their suitability for multisite clinical trials. The first batch of 3 articles from SCAF comprises this theme section, and this first article presents the conceptual rationale for the SCAF project.

Social Cognition as a Target for Intervention

Intervention efforts in this area include focused training programs, as well as initial attempts at psychopharmacological treatments. The training interventions for social cognition resemble long-standing psychiatric skills training approaches.[31–34] A recent meta-analysis of this literature shows that the results of training interventions are encouraging, but inconsistent, in that the treatments improve some targeted social cognitive domains, but not others.[35] For example, the training effect on facial affect perception was large but the effect on attributional bias was not significant. Notably, the meta-analysis showed that benefits for social cognitive training generalized beyond social cognitive tests to include community functioning outcomes.

Regarding psychopharmacological approaches for social cognition, attempts to show improvements with atypical antipsychotic medications have proved disappointing.[36,37] In recent years, most of the focus has been on oxytocin, based on intriguing results from healthy samples.[38] Across studies, oxytocin appears to increase the salience of social cues in healthy samples, though the results depend on an interaction between the specific task and personality factors.[39] The results in schizophrenia, however, have been mixed[40–43] with benefits seen on some tests for subgroups of patients. A recent study from our laboratory suggests that some of the inconsistency may be because intranasal oxytocin has beneficial effects on some social cognitive processes, but not others.[44] Specifically, the effects are seen in higher level tasks that involve inferences about other people but not lower level tasks that involve identification of social cues. Such conclusions about specific treatment effects necessarily require careful assessment of social cognitive abilities to differentiate levels of processes.

One of the largest obstacles for treatment studies in this area is that there is little guidance or consensus on what measure or measures should be used to document improvement in clinical trials. This problem is prominent, widespread, and it stems from multiple factors. First, many of the tests used in schizophrenia research

have been borrowed from other fields, particularly autism research. As a result, many of the tasks have poor psychometric qualities (including ceiling effects) when applied to higher functioning adults with schizophrenia. Second, many of the existing tests used in schizophrenia research have not been evaluated for their psychometric properties, a problem being addressed in an ongoing NIMH grant, "Social Cognition Psychometric Evaluation."[45] Hence, it is not known if they have the characteristics (eg, test-retest reliability) that are required for clinical trials. Third, many of the existing measures appear far removed from real-world social interaction.[46] Specifically, existing measures tend to be unimodal, whereas social cues in the real world are multimodal (ie, involving visual, semantic, and prosodic information). The stimuli tend to be static, whereas information in the real world is usually dynamic (ie, involving information that occurs serially or simultaneously that needs to be integrated). Also, stimuli in performance measures tend to lack context, whereas social cues in the real world are contextually embedded in a way that constrains their interpretation with regard to others' internal states.[46]

Notably, the existing social cognitive measures used in schizophrenia have not benefited from the surge of activity and knowledge in social neuroscience. Hence, some of the most promising and best characterized measures for social cognitive constructs are not making their way to clinical applications. The goal of the SCAF project was to hitch our clinical wagons to the stellar developments in social neuroscience so that clinical trials in schizophrenia can study treatment effects on measures of more narrowly defined subdomains of social cognition that have the potential to be linked to clearly identified neural circuits. In this respect, the SCAF project is fully consistent with the goals of the NIMH initiative, "Cognitive Neuroscience for Treatment Research to Improve Cognition in Schizophrenia" (CNTRICS),[47] which was to identify and address challenges in adapting measures from cognitive neuroscience for clinical trials of schizophrenia.[48] Although social neuroscience was one of the areas discussed in CNTRICS consensus meetings, it was not included in the data collection component of that project. SCAF aims to fill that gap in the database.

At the time we started SCAF, we knew of no examples of behavioral paradigms that started in social neuroscience and had demonstrated applicability to schizophrenia trials. The question naturally arises: What can go wrong as paradigms move from social neuroscience to clinical trials? And the answer is sobering: *Almost anything*. Activation tasks that work impeccably well in the scanner with college students can fail miserably when used in multisite clinical trials with chronic patients. The list of reasons for failure reads like an introductory text in psychometrics: poor test-retest reliability, scale attenuation (floor or ceiling effects), large and problematic practice effects, excessive missing data, lack of tolerability from subjects (due to duration or difficulty), lack of multisite practicality (due to problems in standardization across clinics), difficulty in subjects understanding complex instructions, and lack of external validity. This last issue of external validity is particularly vexing if the very act of identifying narrow subprocesses inadvertently works against finding correlations with functionally meaningful outcomes.[49] The study of social cognition has focused on 2 different goals—relationship to functional outcome and links to neural substrates. It is possible that the strongest relationships with daily functioning come from tasks that are inherently multidimensional and tap more than 1 cognitive process.[46] So the process of adapting tasks from cognitive and social neuroscience, which tend to focus on specific subprocesses, may work against the goal of finding tasks with external validity that relate to daily functioning.[49] Of course, these problems are not limited to adapting measures from social neuroscience, as they apply equally to adaptation from other fields (eg, cognitive neuroscience) in which the goal is to transition from imaging tasks in college students to behavioral tasks with psychiatric patients.

Things also can go wrong before one even gets to psychometric and validity assessments. Only 2 social neuroscience paradigms were recommended for immediate adaptation for use in schizophrenia from a CNTRICS consensus meeting.[50] One of these involved context-based modulation of emotion identification, based on a study published in the social neuroscience literature.[51] In this task, subjects briefly see a face with a surprised expression and rate it on a scale running from fear to surprised (these emotions are easily confused). Before seeing the face, subjects hear about the situational context for the person in the photo, and these situational "frames" reliably modulate the degree to which someone sees the face as showing more fear or more surprise. The CNTRICS consensus group had high expectations for this task (2 authors, M.F.G. and K.N.O., participated in that discussion). It was noted that this task combines 2 areas in which individuals with schizophrenia have shown impairments: the ability to maintain contextual information in working memory, and the ability to decode the meaning of nonverbal social cues. We thought that a failure to appropriately maintain context would fundamentally limit the way in which contextual information would constrain the meaning of social cues for individuals with schizophrenia.

We learned, however, that contextual information in a social cognition task might not work the same way it does in a cold, basic cognitive working memory task. When we conducted an interim analysis of the SCAF data, we were surprised to see that patients were entirely normal in their degree of situational context modulation.[52] That finding is potentially very important because it suggests ways for interventions that rely on intact processes. For example, training methods for social cognition could be designed

to use richer situational factors. If schizophrenia patients have intact ability to use situational context, they may benefit more from training programs that provide richer situational factors to facilitate social interactions and social learning. While we can celebrate an area of intact functioning in schizophrenia, and the value in identifying it, the results (found in 2 independent samples) deprive a clinical trial of its *raison d'etre*—to improve an area of impairment. Hence, we need to separate what *should* work from what *will* work in schizophrenia clinical trials.

Selecting Relevant Social Cognitive Subprocesses

To identify relevant social cognitive processes that could become targets for intervention in clinical trials, we used a 2-tiered selection process. First, we considered core social cognitive and/or emotional abilities whose neural substrates can be reliability identified, based on a review of the literature.[48] Our understanding of the proposed domains of social cognitive functioning is based primarily on current knowledge from human functional imaging work. As such, the formulation reflects the knowledge at a particular point in time and will surely be modified as new information is gathered based on future imaging, lesion, genetics, and other types of research.

When we refer to neural substrates, the emphasis is on brain systems associated with hypothetical processes that, in turn, underlie social cognitive abilities of interest. In this sense we use the term, "neural substrate," in the way it is typically used in the social and cognitive neuroscience literatures—to indicate a brain region or set of regions whose activation or operation is correlated with—and thought to be necessary for—the operation of specific processes that support the exhibition of specific behaviors.

As noted elsewhere,[48,53] our knowledge of the mechanisms underlying any behavior can be described at multiple levels of analysis. In cognitive neuroscience, 3 levels are highlighted—the levels of behavior and experience, psychological process, and neural substrate. The goal of neuroscience is to describe the connections among them. In schizophrenia research, the levels have typically been divided into higher (eg, clinical symptoms, functioning, and other whole-person variables) and lower (eg, molecules and receptors). However, it is difficult to describe the connections between the macro behaviors and the micro-scale actions of pharmacological agents. What cognitive neuroscience-inspired research adds to this picture is the ability to fill in the missing levels of analysis—connecting macro-level symptoms (eg, poor social functioning) to specific behaviors (eg, an inability to understand specific social cues), specific processes (eg, making mental state attributions), and specific brain systems (eg, medial prefrontal cortex).

The domains initially considered in the SCAF project include: (1) the initial acquisition of the social/emotional value of a stimulus, which includes various forms of learning and conditioning; (2) the perceptual recognition of social/emotional stimuli, which includes face perception and recognition of nonverbal cues; (3) low-level mental state inference, which includes how we identify actions using embodied simulation and the mirror neuron system; (4) high-level mental state inference, which includes ToM and attributions about mental states in general; and (5) context-appropriate regulation, which includes various forms of control over thought, affect, and behavior, such as cognitive reappraisal, and forms of learning that involve updating the social-affective value of a stimulus (eg, extinction). As these domains differ somewhat from those described under the recent NIMH "Research Domain Criteria" (RDoC) project,[54] we list the relevant RDoC domains for each of our constructs in table 1.

Next, for each of the 5 domains, we prioritized the following criteria: (1) the domain provides tasks with performance metrics that could be adapted for use in clinical trials and (2) the domain appears relevant to social functioning in schizophrenia. These criteria prioritized constructs 2 (recognition of stimuli with social-emotional value) and 4 (high-level mental state inference) over the other constructs. The social cognitive tests most frequently used in schizophrenia research map onto these constructs. For example, most tests of emotion perception fit within recognition of social/emotional stimuli, whereas most tests of ToM fit within high-level mental state inference. Notably, these 2 levels are consistent with a current social neuroscience framework that divides processes into lower level social perception (ie, processes to recognize social cues) and higher level social inference (ie, processes that involve making inferences about people's mental states, traits, and preferences).[55]

Low-Level Processes to Recognize Social Cues

For stimuli with innate or acquired social-emotional significance, it is important that an organism is able to recognize them quickly and respond appropriately. Two types of systems are important for this ability (facial expressions and nonverbal social and action cues).

The first system involves recognition of facial expressions of emotion, and to a lesser extent, discrete facial features that have social-emotional significance. Recognition of the affective value of these cues depends on cortical and subcortical systems important for affective learning, including the amygdala, striatum, insula, and orbitofrontal cortex (also, static structural features of faces are encoded by other regions, most prominently, the fusiform face area).[56] Among these, the amygdala's functions with respect to social cue recognition are best understood. Although it is known to respond to arousing stimuli with both positive and negative value,[57] both imaging and lesion work have shown that it plays a special role in quickly recognizing social stimuli that signal the presence

Table 1. Comparison of SCAF to RDoC Domains

SCAF Domain[48]	Relevant RDoC Subdomains[54]	Exemplar Brain Regions	Example Behaviors
1. Acquiring social-emotional values	Reward learning, habit learning, declarative memory, attachment formation	Amygdala, ventral striatum, orbitofrontal cortex, medial temporal lobe	Fear conditioning, reward learning, explicit memory for social stimuli
2. Recognition of stimuli with social-emotional value	Reception of facial communication, reception of nonfacial communication, animacy perception	Amygdala, striatum, insula, orbitofrontal cortex, fusiform face area, extrastriate body area, superior temporal sulcus/gyrus	Perception of nonverbal social cues, including faces and their parts, bodies, tone of voice and perception of biological motion
3. Low-level mental state inference	Action identification	Parietal and prefrontal motor regions (ie, mirror neuron system)	Identify what action someone is performing
4. High-level mental state inference	Understanding mental states, self-knowledge	Medial prefrontal cortex, precuneus, temporal pole, temporal parietal junction	Tests of theory of mind, attributions about mental states or traits for self or other (including judgments of self-reference), judgments about why someone is performing an action
5. Context-appropriate regulation	Any subdomain related to perceiving social cues or exhibiting an affective reaction *plus* the cognitive control domain and all its subdomains	Lateral, medial, and orbital prefrontal cortex	Cognitive reappraisal, extinction, reversal learning

Note: RDoC, Research Domain Criteria; SCAF, Social Cognition and Functioning in Schizophrenia.

of potential threats, such as fearful facial expressions,[58] as well as neutral faces that appear untrustworthy.[59] Other regions associated with social cue recognition include striatal and orbitofrontal systems. These systems have been implicated in recognizing reward-related stimuli, such as attractive faces whose social-affective value is presumably important for social reinforcement and learning.[60]

The second system is important for recognizing nonverbal social and action cues and may convey important intentions on the part of a social agent. In everyday life, the ability to decode the social meaning of others' behavior depends on faces, as well as on nonfacial cues.[61] As such, it is important to know the extent to which patients have problems understanding the meaning of both facial and nonfacial social cues.[62] Compared with the facial affect recognition system described above, this second system has received very little attention in schizophrenia. One example from this system is the perception of biological motion, which can be observed as early as infancy, indicating that specific brain regions may be genetically predisposed to detect biological motion. The regions most clearly associated with this ability include the cortex around the STS. Single-unit recording studies in nonhuman primates and imaging studies in humans have both shown that the STS responds to a variety of nonverbal cues, including images of moving eyes, lips, or mouths, grasping movements, and abstract stimuli that depict biologically plausible motion.[63,64] The latter type of stimulus has been well studied using point-light walkers in which

subjects see dots moving in a characteristic human way, as if attached to someone who is walking, dancing, or engaging in other social actions.[65]

High-Level Inferences About Mental States and Traits

A problem with interpreting the meaning of social stimuli is that they often are ambiguous, especially when presented alone, as they are in most paradigms that assess the simple perception/recognition of social stimuli.[46] The low-level recognition processes described above may be insufficient for representing and interpreting the meaning of complex types of intentional mental states in daily life.[66] For example, if you perceive the smiling face of a man, low-level processing systems might interpret him as being happy and lead you to approach him. But if you are encountering this man on a used car lot, and he is the salesman, then you understand that his apparent smile could be a ruse intended to gain your trust to sell you a car at the highest possible price. Or put simply: he is not happy, he is being deceptively friendly. To understand such complex intentions, we must call upon a network of brain systems capable of taking into account situational/contextual information that constrains the meaning of a social cue or action.[67]

Research indicates that this network—sometimes called the mentalizing or mental state attribution network[68]—centers on the medial prefrontal cortex (mPFC), and may variously involve subregions ranging from the

dorsal to ventral extent, as well as adjacent paracingulate cortices.[69] mPFC is the single most commonly activated region across a wide range of tasks that require the attribution of a mental state, whether an intention, a belief, or an emotion, to a person.[70–72] That person can be either yourself or someone else. Such tasks include paradigms used to assess ToM, empathic connection with or judgments about the emotions of others, and judgments of self-reference in which one must decide whether particular state or trait words describe oneself right now or in general (for reviews, see Denny et al[69] and Spunt and Lieberman[73]).

Aside from the mPFC, other regions that are important for a putative "mentalizing" network include the temporal parietal junction, which may be important for representing false beliefs[74] (but see Mitchell[75]), the precuneus, which may be involved in first-person perspective taking and self-awareness,[76] and the temporal pole, which may represent both gist and episodic social and emotional knowledge.[77] Finally, the STS is thought to represent the simple intentions underlying certain kinds of nonverbal cues (see above and Allison et al[63]). Unpacking the individual contributions of these regions to mental state inference is currently an active basic research area.

Selecting Paradigms for Relevant Social Cognitive Subprocesses

After selecting social cognitive domains and subprocesses that are relevant to clinical trials in schizophrenia, we next considered paradigms. Because the practical goal of this program of research is to evaluate measures for clinical trials, we wanted tasks that detect impairment, so that treatment would move scores in the direction of improvement.

A limitation of this approach is that we did not consider aspects of social cognition that involve biases (eg, attributional bias), or tasks do not yield a clear accuracy score. Our selection of behavioral paradigms was guided by the following considerations: (1) the measure could generate a variety of items that assess a large range of difficulty, (2) potential group differences in response bias would not influence performance (eg, we avoided tasks with subjective judgment responses), (3) the measure can be administered in a tolerable length of time (eg, 25 min or less), (4) the measure does not require complex or time-consuming scoring, (5) equipment is not required that is impractical for a clinical trial (eg, electrophysiology), and (6) stimuli and instructions do not place excessive demands on reading ability and verbal intelligence.

With these criteria, we chose 5 paradigms that are described in more detail in the following article.[78] These 5 paradigms are shown in table 2 with their neuroanatomical regions of interest. In terms of recognizing nonverbal social and action cues, we selected 2 measures: the Basic Biological Motion Task and the Emotion in Biological Motion Task. Both of these tasks draw on processes used to recognize nonverbal social and action cues using point-light walker clips. The Basic Biological Motion Task assesses whether participants can differentiate human motions from random motions and it recruits several brain regions, including the posterior-occipital complex (in particular the STS) and inferior parietal regions.[79,80] The Emotion in Biological Motion Task assesses the ability to perceive emotional cues from point-light walker clips and it appears to recruit the posterior STS and supramarginal cortices.[81,82]

In terms of high-level inferences, we chose 3 paradigms that require participants to combine simple social

Table 2. Brain Regions Associated With SCAF Social Cognitive Paradigms

| Brain Regions Linked to Paradigms | Paradigms | | | | |
| | Recognition of Social/Emotional Value via Nonverbal Social and Action Cues | | Inferences About Mental States and Traits | | |
	Basic Human Biological Motion	Emotional Biological Motion	Facial Affect Recognition (Context Modulated)	Self-Referential Memory	Empathic Accuracy
Amygdala			X		
Insula					X
STS	XX	XX			
TPJ		X		X	X
Temporal pole				XX	
Precuneus/PCC				XX	X
dmPFC/ACC				XX	XX
vmPFC/ACC			X	XXX	X
lPFC			X	XX	X

Note: The number of X's within a column reflects the relative frequency with which a given region has been activated for a given type of task. d, dorsal; v, ventral; m, medial; l, lateral; STS, superior temporal gyrus; TPJ, temporoparietal junction; PFC, prefrontal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex.

cue perception with situational context to draw high-level inferences about mental states and traits. Selected tasks included the Self-Referential Memory Task, the Empathic Accuracy Task, and the Situational Contextual Modulation of Facial Affect Recognition Task. The Self-Referential Memory Task assesses the ability to make inferences about traits applied to oneself and others and is associated with the mPFC.[83] In this task, participants are asked to judge whether trait words describe themselves or others in general, and then perform a recognition memory task of the trait adjectives following a delay period. The Empathic Accuracy Task assesses the ability to accurately infer emotional states of another person using dynamic, multimodal social stimuli and has been associated with the ventral mPFC, anterior insular, and the temporoparietal junction.[68,84] In this task, participants are asked to judge moment-to-moment changes in emotional states of another person while he/she describes a positive or negative autobiographical event. The Situational Contextual Modulation of Facial Affect Recognition Task (mentioned above) assesses the ability to recognize emotional expression of faces within the context of a particular social situation and has been associated with the ventral mPFC and amygdala.[51] In this task, participants are presented with a sentence describing either a fear-inducing or surprise-inducing event, followed by a face, and asked to judge how fearful or surprised the face looks.

All of these tasks have already demonstrated a critical aspect of construct validity: they have neural validity in that they consistently activate a network of brain regions in functional magnetic resonance imaging studies. That feature makes them very appealing for early phase treatment discovery because they can selectively recruit specific neural systems that, in turn, might be targets for intervention. Following their adaptation for use with schizophrenia patients, however, it remains to be determined whether the tasks have psychometric properties that are suitable for large clinical trials that require multiple assessments and occur at multiple sites. In particular, we typically know very little about the reliability of activation tasks that are used in cognitive or social neuroscience. In clinical trials, any reductions in test-retest reliability translate into the need for larger samples to detect treatment effects.[85] Also feasibility is not a major requirement for tasks conducted with young healthy adults at a single site, but it is paramount for multisite clinical trials with chronic psychiatric patients. Beyond such psychometric properties and feasibility issues, it also remains to be determined whether the adapted tasks have any relationship to functionally meaningful outcomes (eg, measures of functional capacity or functional outcome) that would suggest that their improvement could help to reduce the disability of schizophrenia.

The current article reviewed the practical goals and theoretical context for the selection of paradigms from social neuroscience for use in schizophrenia clinical trials. We reviewed the importance of social cognition for schizophrenia, the challenges inherent in adapting measures from basic science, the criteria we used to select measures, and the presumed neuroscientific substrates for the paradigms. The following 2 articles will evaluate the psychometric properties[78] and the external validity[86] of the selected social neuroscience paradigms.

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