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Going From Social Neuroscience to Schizophrenia Clinical Trials

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The goals of the project Social Cognition and Functioning in Schizophrenia (SCAF) were to (1) identify the domains to target from social neuroscience for translation to clinical schizophrenia research, (2) identify the paradigms that represent these domains for which the neural substrates are well documented, (3) adapt these paradigms for use in schizophrenia clinical trials, (4) assess the psychometric properties of these measures, and (5) assess the external validity of these measures. The articles in this theme section present the initial findings from the SCAF project. As more training and psychopharmacological studies evaluate interventions for social cognition, the articles in this theme section are intended to serve as a guide for informed design decisions about possible endpoints in clinical trials.

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

Social cognition has emerged as an area of great interest for schizophrenia research. In fact, a search on PubMed with the terms *social cognition*, *schizophrenia*, and the year *2012* pulls up 303 articles on this topic. Numerous studies in this area have examined topics such as neural correlates of social cognitive activation tasks, patient-control differences on measures from various social cognitive domains, links to daily functioning, and the commonalities and differences in social cognition across different psychiatric illnesses.

Social cognition has also become a treatment target in schizophrenia, as seen in the active development of novel training interventions,[1–3] as well as attempts at pharmacological treatments.[4–6] Treatment studies require critical decisions about endpoints. To demonstrate a treatment effect for social cognition in a clinical trial, What measures should be used to show improvement? Are these measures reliable enough for clinical trials? Can they be repeated without compromising the results? Are they practical for multisite studies? and Are they linked to specific neural systems? For social cognition, these questions are largely unanswered.

An ongoing project funded by the National Institute of Mental Health (NIMH) entitled, Social Cognition and Functioning in Schizophrenia (SCAF) is attempting to address these questions. The goals of this project were to (1) identify the domains that are ripe for extensions from social neuroscience to clinical schizophrenia research, (2) identify the paradigms that tap these domains and for which the neural substrates are well documented, (3) adapt these paradigms for use in schizophrenia clinical trials, (4) assess the psychometric properties of these measures, and (5) assess the external validity of these measures (ie, their relationships to functionally meaningful variables). The SCAF project conceptually grows out of the NIMH Initiative, Cognitive Neuroscience for Treatment Research to Improve Cognition in Schizophrenia (CNTRICS).[7] CNTRICS held a series of consensus meetings to identify the challenges in adapting measures from cognitive neuroscience and social neuroscience for use in clinical trials of schizophrenia.[8] A related project collected data on newly developed paradigms from a subset of the CNTRICS domains, but social cognition and social neuroscience were not represented.[9] Hence, the SCAF project was designed to fill a large gap in the literature, starting with the articles in this theme section.

The paradigms examined in the SCAF project were considered to be novel for psychosis research—there had not been published studies in schizophrenia at the time the study started (see the following articles for complete descriptions of the domains and paradigms). In addition, they assess social cognitive subprocesses not covered by commonly used measures in psychosis research. The investigators on this project were under no illusions about

the difficulty of this translational approach. It is common for measures that work extremely well with college students in the scanner to crash and burn when applied to chronically ill patients with psychotic disorders. There are many ways for such measures to fail, and among the most common are scaling problems (floor or ceiling effects), poor reliability (test-retest or inter-rater), problems with repeated assessments (eg, tasks that have an *aha moment* in which an answer is revealed), or feasibility (too long, too hard, or too dull).

A related project with an overlapping group of investigators, Social Cognition Psychometric Evaluation (SCOPE),[10] is evaluating the suitability of several *existing* social cognitive measures for use in clinical trials. The primary goals of the SCOPE project are to achieve a consensus on the current social cognitive domains studied in schizophrenia and to evaluate psychometric properties of existing measures to determine their suitability for clinical trials. The measures selected through the SCOPE project will differ from those in SCAF in several ways. First, they assess a particular subset of social cognitive domains. Relevant areas of social processing are not covered, such as empathy, self-other processing, nonverbal/nonfacial emotion recognition, and automatic aspects of social processing. Second, the tasks did not come from social neuroscience, such as studies using functional magnetic resonance imaging and electrophysiology. As a result, their neural substrates are typically unclear. Based on the different selection priorities, the SCOPE and SCAF projects are evaluating nonoverlapping sets of measures. With their emphases on existing measures (SCOPE) and adaptations from social neuroscience (SCAF), these 2 projects are complementary.

The 3 articles in this theme are the first batch of publications from the SCAF project. As the project is still ongoing, future articles will capitalize on the larger sample sizes, eg, by using structural equation modeling. The primary psychometric and external validity data, however, are contained in the articles in this theme.

The first article presents the conceptual foundation for the SCAF project, and it describes the process used to guide the selection of the domains and paradigms.[11] This article places these activities and data in the larger context of intervention trials. It also describes the selection criteria that were used to arrive at a small number of experimental paradigms from social neuroscience, and the current knowledge of the neural substrates of those paradigms.

The second article is a detailed psychometric evaluation of the paradigms with samples of patients with schizophrenia and healthy controls.[12] In this article, we present findings for test-retest reliability, between-group effect sizes, utility as a repeated measure (including practice effects), issues of scale attenuation (floor and ceiling effects), practicality, and tolerability. These data indicate the degree to which the measures are suitable for multisite clinical trials on each of these factors.

The third article in this theme examines the external validity of the measures.[13] Specifically, we consider how well the measures relate to functional capacity and community outcome. We also examine the measures' incremental validity—the extent to which they explain variance in functioning beyond that provided by a standard social cognitive measure of facial affect identification and beyond nonsocial cognition. These relationships are important to understand because social cognition may be more proximal (in terms of a causal pathway) to daily functioning than are perceptual and nonsocial cognitive processes.[14]

Taken together, the articles in this theme offer 1 model of how to identify and evaluate paradigms from novel research areas for use with clinical psychiatric disorders. The problems we encountered apply equally well to adapting measures from other areas of basic science; social neuroscience, however, provides a good test case. The articles in this theme provide a summary of the theoretical basis for the paradigms we selected, as well as psychometric and validity data that can be used by clinical trialists when designing clinical trials. As more studies examine social cognition in schizophrenia and other psychotic disorders, and as more studies evaluate training and psychopharmacological interventions for social cognition, the articles in this theme are intended to serve as a guide for informed decisions about relevant social cognitive domains and potential endpoints for treatment studies.

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