The social neuroscience of psychosis: From neurobiology to neurotherapeutics

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ABSTRACT

Psychotic disorders form the core of severe mental illnesses and contribute to substantial disability and health-care costs worldwide. A growing research framework to understand and treat psychotic symptoms using a transdiagnostic paradigm is the social brain perspective of psychoses. The theme of my oration is to highlight how the growing knowledge of evolutionarily preserved social brain networks can help integrate social contextual, psychological, and neurobiological aspects of the genesis of psychotic symptoms and use that knowledge in a translational manner to identify potential therapeutic avenues that extend beyond conventional treatments. The concepts and empirical study of social cognition, social brain (e.g., mirror neuron system), social behaviors (e.g., symptoms and real-world functioning) are illustrated. These give insights into potential newer therapies with brain stimulation, oxytocin, and yoga.

Key words: Evolution, mirror neurons, schizophrenia, social cognition, social connectome

A SOCIAL NEUROSCIENCE PERSPECTIVE OF PSYCHOSIS

Schizophrenia is a chronic and severely disabling[1] brain disorder that has an onset in late adolescence and early adulthood with as yet difficult to understand complex genetic and environmental underpinnings within a neurodevelopmental context.[2] A cardinal expression of schizophrenia and related psychotic disorders is a varying magnitude of aberrant social cognition – mental operations underlying social interactions.[3] This aberration while manifesting as a deficient or deviant process can potentially provide a critical and mechanistic basis for both – the Bleulerian (autistic alienation underlying the persistent negative symptoms) and Schneiderian (ego-boundary disturbances resulting in positive symptoms with a core misattributional phenomenology) philosophies of schizophrenia, respectively. The social neuroscience heuristic framework that conceptualizes psychosis as a costly consequence of social brain evolution in humans,[4] therefore, has the potential to explain psychosis from an evolutionary perspective that the computational demands of living complex social lives have shaped a large social brain that subserves the sophisticated mental operations required for adequate social relationships and behaviors.[5] This "social brain hypothesis" drawing from phylogeny provides an ontogenic foundation of how key genetic and environmental vulnerabilities transact within critical developmental epochs sculpting the hardwiring of socially relevant brain networks that predispose individuals to difficulties in processing social cognition, which manifests

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as abnormal social behaviors of the psychotic syndrome and thereby the devastating social disability.

Given the recent emphasis on the large genetic overlaps across the broader psychiatric phenotype,[6,7] and the shared and rather nonspecific environmental risk factors across disorders,[8] it is important to identify fundamental processes that are deranged transdiagnostically, which can potentially explain symptom manifestation and the resulting dysfunction from a neuroscience-informed perspective. The National Institute of Mental Health (NIMH)-sponsored Research Domain Criteria provides such a template by identifying five fundamental processes to be studied at various levels ranging from genes to behavior, through cells and networks.[9] Social cognition, not surprisingly, is one such fundamental process that has been identified for transdiagnostic study. While disturbances in social behavior and the resulting social disability across a broad range of psychiatric disorders are well described and characterized, the omnipresent nature of social cognition impairments across most psychiatric disorders is only recently emerging.[10] It is in this context that a social neuroscience perspective provides a compelling conceptual framework to study the origins and treatment of severe mental disorders by providing key substrates at the neurobiological (social brain), psychological (social cognition), clinical (social behaviors), and real-world functional (social disability) levels. This essay highlights evidence that pieces together parts of this "social connectome," with a special focus on understanding the pathogenesis, manifestations, and determinants of social dysfunction in psychotic disorders (mostly schizophrenia) from a social neuroscience perspective [Figure 1] and the translational impact of this approach in developing and delivering targeted treatments with the ultimate goal of recovery and reintegrating the affected individual into society.

CLINICAL RELEVANCE OF SOCIAL COGNITION IN PSYCHOSIS

Construct of cognition in schizophrenia

Cognition is a broad set of mental processes that subserves our ability to understand and respond to information in our environment. It is largely hardwired,[11] determined genetically,[12] and acquired during various stages of human development.[13] Cognition can, however, be shaped and pruned by a wide range of environmental influences.[14] Cognitive impairment is ubiquitous to a host of neuropsychiatric disorders ranging from autism and schizophrenia to depression and the dementias.[15]

When cognitive abilities are studied in the context of neuropsychiatric disorders, they are conceptualized as two overlapping yet distinct constructs – general or neurocognition and social cognition. Conceptually, neurocognition involves general information acquiring and processing functions such as attention, concentration, memory, and processing speed and executive functions such as planning and reasoning.[16] It is comparatively free of emotions. These functions are used in both nonsocial (e.g., remembering a shopping list) and social (e.g., responding to an angry friend) situations. In contrast, social cognition embodies the interface between emotional and cognitive processing, with an intersubjective quality, requiring reflective (metacognitive) and social inferential abilities.[17] These include processing biologically relevant motion and detection of eye gaze to understanding perspectives, intentions, and feelings of others that we so often encounter in our daily living. This division was posited by the observation of selective impairment of either of these abilities in specific conditions.[18]

However, in order to demonstrate a more data-driven understanding about this division, we performed a systematic review of empirical data from factor analysis studies that have examined the factor structure of cognition in schizophrenia.[19] Here, we could show consistent evidence for the existence of distinct social and nonsocial cognitive factors, with eight out of nine studies supporting this separateness of the two cognitive dimensions, thus providing construct validity for cognition in schizophrenia. While this does not propose a complete distinction, there are strong correlations between social and nonsocial cognition. Yet, there is a significant nonoverlap resulting in distinct cognitive factors that perhaps reflect different latent structures and neurobiology driving them. While neurocognition has been in the forefront of cognitive neuroscience research over several decades now, social cognition and its neurobiology are being examined only recently.

Measuring social cognition

The measurement of cognition over the last several decades has predominantly focused on quantifying general or neurocognitive abilities. The study of social cognition began in the late 1960s as a purely social-psychological investigation[20] and extended to examining developmental milestones and ontogeny of these processes.[21] At the same time, evolutionary psychology approaches were used to understand the phylogeny of these abilities by identifying comparative processes in social animals like nonhuman primates.[22] The next decade saw its implementation in clinical populations by examining social cognition impairments in children with mental retardation[23] and adults with traumatic brain injuries.[24] However, it was much later that social cognition was seriously examined in disorders such as autism[25] and schizophrenia,[26] which today are considered social brain disorders.[4]

Meetings of the NIMH – Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative[27,28] – recommended a set of subdomains of social cognition to be examined in future studies. These include

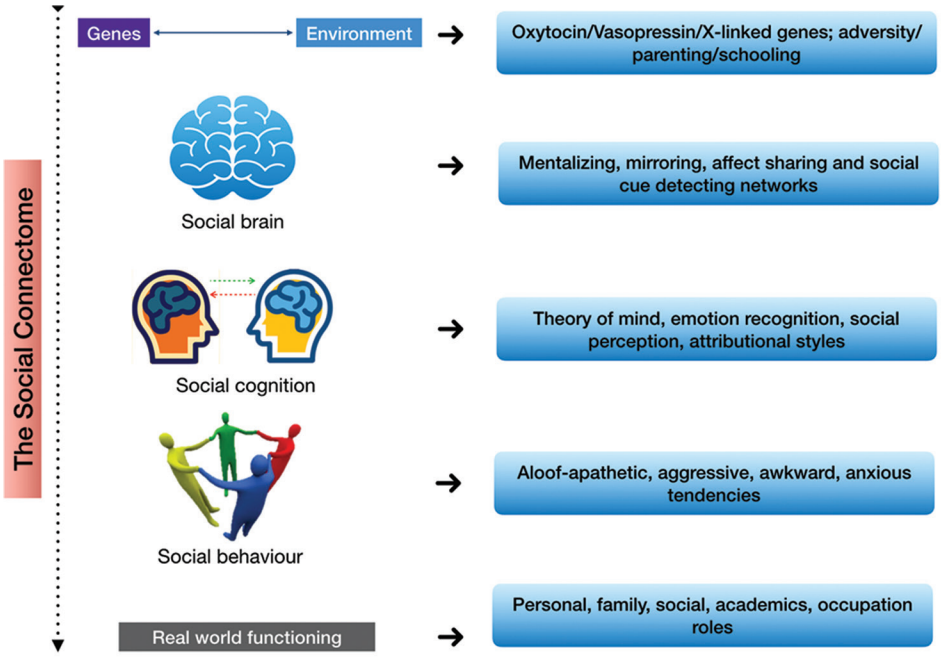

Figure 1: The social connectome from genes to behaviors

theory of mind, emotion processing, social perception, and attributional styles. Theory of mind is the capacity to impute mental states to oneself and to others; the "gold standard" test of comprehending other persons' minds is the ability to understand that others can hold false beliefs that are different from one's own (correct) knowledge.[29] Measures of emotion processing (perceiving and using emotions) include rating of emotions displayed in faces (facial emotion recognition) or voices (affective prosody) or rating from brief vignettes of how individuals manage, regulate, or facilitate emotion.[30] Social perception refers to initial stages in the processing of information of social situations that culminates in the accurate analysis of the dispositions and intentions of other individuals.[31] Attributional style refers to explanations people generate regarding the causes of positive and negative events in their lives. This is assessed using hypothetical positive and negative events for which the participants are asked to draw causal inferences and label them as internal-personal, external-personal, or situational.[32]

The prevailing cultural environment in which the social brain develops and expresses itself can moderate the processing of social cognition. This brought about the need for a culturally appropriate test battery for measuring social cognition within the Indian sociocultural setting. We highlighted this need through sociopsychological, developmental, and neurobiological perspectives – all of which underscore cultural differences in the experience of social interactions and the processing of social cognition.[33] We, therefore, undertook an adaptation and validation process of social cognition measurement across all recommended dimensions listed above. This exercise began with a detailed literature review and discussions with national and international experts in the field of social cognition to identify appropriate tests that could be modified to the Indian context. Next, a thorough process of task adaptation was undertaken – making drawings for picture stories, framing content of social interaction stories and videos, shooting of social perception videos, and performing conceptual rather than translations (to Hindi and Kannada) of original English-version tests with the focus on retaining the construct of assessment but modifying content based on prevailing cultural norms. Tests were adapted to cover domains of theory of mind, social perception, and attributional styles. Finally, we undertook a thorough validation exercise by obtaining content validity from 18 mental health experts and then administering the final shortlisted tests in healthy and schizophrenia populations. Bilingual volunteers were additionally administered English-version tests to compare their performance across both versions. Additional tests of empathy[34] and emotion processing[35] were also administered. Content, concurrent, ecological, and known-groups validity of these tests were satisfactory. The internal consistency of the individual test items was also high.[36,37] Taken together, these tests form the Social Cognition Rating Tools in Indian Setting (SOCRATIS) [Figure 2]. SOCRATIS in conjunction with the existing Tool for Recognition of Emotions in Neuropsychiatric Disorders (TRENDS),[35] forms a comprehensive method of assessing most social cognition in the Indian sociocultural setting. Since 2008, SOCRATIS has been used across various centers in India [Figure 3] to assess social cognition in a broad range of psychiatric disorders. Regular training workshops are

arranged biannually to facilitate administration and scoring skills. A software-based application has been developed that facilitates easy administration and automatic scoring. In summary, the development of SOCRATIS has given impetus to a thus-far neglected research area, and the last decade has witnessed an exponentially higher effort to not just study the clinical and biological correlates of social cognition but also develop specific and unique treatment strategies.

Social cognition deficits across psychiatric disorders

With the availability of a comprehensive test battery to measure social cognition, we examined if social cognition was impaired in patients with schizophrenia who had remitted from their active positive symptoms. This clinical stage was chosen so as to understand the relationship between social cognition and socio-occupational functioning – a clinical need most prominent after resolution of active symptoms. We found that social cognition performance was substantially reduced in remitted schizophrenia patients (n = 60) as compared to matched healthy controls (n = 60), with effect sizes ranging from 0.4–2. These deficits were found to be independent of their general cognition deficits, as assessed using covariate analysis.[38] Next, using both cross-sectional[39] and longitudinal[40] study designs, we demonstrated a state-dependent worsening of social cognition performance in schizophrenia as compared to remitted states, indicating a potential relationship between impaired social cognition and expression of active psychotic symptoms. The magnitude of social cognition deficits was much less in patients with bipolar disorder (during remission, n = 40); in fact, these patients performed better than healthy individuals on second-order theory of mind performance – the same test which was found to have a significant association with social functioning in schizophrenia.[41] Patients with borderline personality also demonstrate social cognition deficits, but these were restricted to social perception deficits – especially for subtle low-emotion cues and attributional styles – higher tendency to attribute negative events to external people than situations.[42]

Social cognition and its functional significance

The above findings paved the way toward heuristic and clinical applications of studying social cognition, especially in psychotic disorders – (a) its potential endophenotypic status since deficits (though state-dependent) were observed even during symptom remission (state-independent) and (b) its potential association with real-world social functioning. In one of these studies, a blind rater assessed the social functioning of patients using the WHO-Disability Assessment Schedule-based Groningen Social Disabilities Schedule.[43] Among a host of social and neurocognitive measures studied, we found that second-order theory of mind was best associated with social functioning. Here, we also demonstrated by means of indirect mediation analyses[44] the role of negative symptoms in mediating the relationship between theory of mind and social functioning.[45] In a larger study of 150 remitted schizophrenia individuals, we not only replicated these observations but also demonstrated a path model to study the interdependent relationship between important determinants of social functioning. This model showed that while the influence of social cognition on social functioning was mediated by negative symptoms, especially amotivation, neurocognition deficits determined social functioning via effects on clinical insight into the illness [Figure 4].[46] In the same sample, we also demonstrated that theory of mind was not just relevant for social functioning but also had an important contribution in predicting parenting role

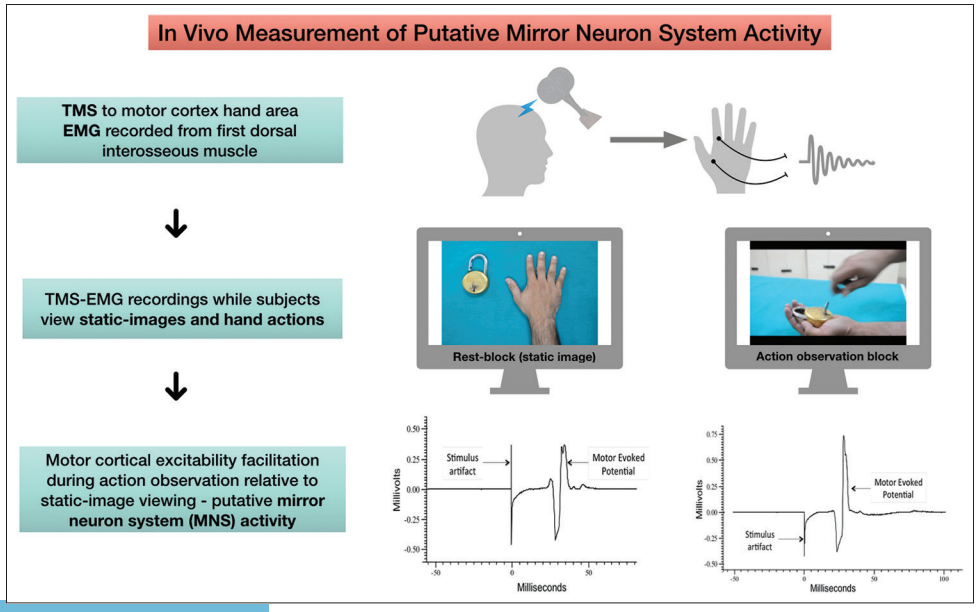

Figure 2: Social Cognition Rating Tools in Indian Setting

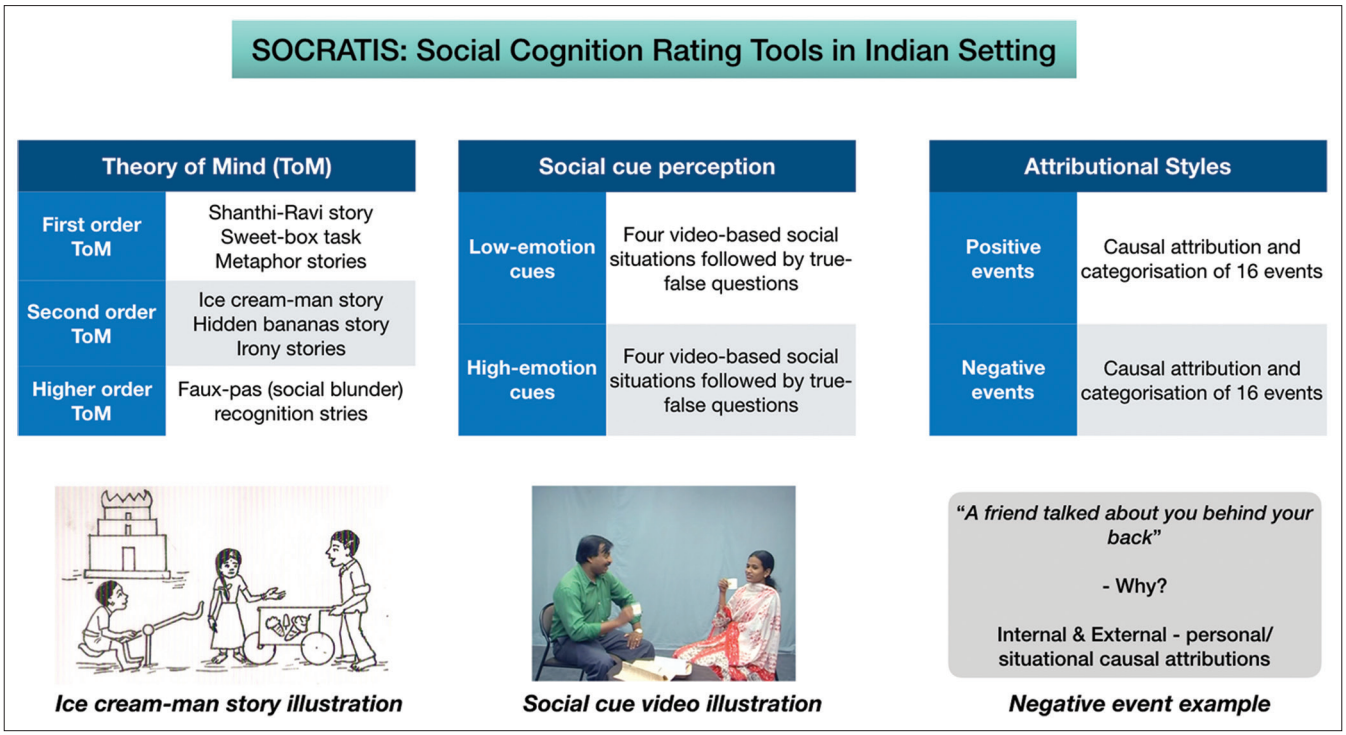

Figure 3: The training and use of the Social Cognition Rating Tools in Indian Setting battery across India

functioning in parents with schizophrenia.[47] However, there was no relationship between social cognition and social functioning in this sample of euthymic bipolar disorder patients,[41] perhaps owing to a ceiling effect in measures of cognition and real-world functioning.

NEUROBIOLOGY OF SOCIAL COGNITION IN PSYCHOTIC DISORDERS

Latent structure of social cognition

In order to understand the latent structure of social cognition, we have conducted a series of factor analytical studies. This is a multivariate statistical approach that identifies patterns in large datasets to segregate the cognitive data into potential latent structures that could potentially have shared origins. First, we studied the distinction of social cognition and metacognition (thinking about thinking) in a sample of 60 schizophrenia patients.[48] A principal components analysis revealed three factors – two social cognitive factors (inferential component – theory of mind and socio-emotive component – emotion processing and social perception) and one metacognitive factor (scores on clinical and cognitive insight that focuses on self-reflective abilities). Next, in a larger sample of 170 schizophrenia patients, a three-factor solution representing socio-emotional processing, social inferential ability, and external attribution components emerged that accounted for 64.43% of the variance. In contrast, a two-factor solution representing socio-emotional processing and social inferential ability was derived in the healthy comparison group (n = 111) that explained 56.5% of the variance,[49] potentially highlighting an illness-specific misattribution component that was absent in the healthy group. There was some external validation of these three components by virtue of their differential association (~4%–40%) with neurocognitive performance in the same dataset. The socio-emotional (30%–40%), social inferential (12%–20%), and misattributional (~4%) component had different grades of association with neurocognition performance as examined using general linear regression models.[50] These are important observations that contribute to our overall understanding of the underlying latent structure of social cognition abilities in schizophrenia and healthy individuals, which were hitherto recommended objectives in expert consensus meetings.[28]

Social brain in schizophrenia

Several lines of investigations have now started to give concerted information regarding neural networks underlying social cognition. This social brain network has been under investigation in patients with schizophrenia and autism since the late 1990s.[5] Recent studies identify four important subsystems operating in a coordinated fashion that represent the social brain, and these include the social cue perception system (amygdala, inferior frontal gyrus, and fusiform gyrus), the affect sharing (insula and anterior cingulate cortex) and motor resonance systems (premotor cortex, inferior frontal gyrus, and inferior parietal lobule), the mentalizing system (medial prefrontal cortex, precuneus, and temporoparietal junction and posterior cingulate cortex), and the emotion regulation system (dorsal and lateral prefrontal cortices).[51,52]

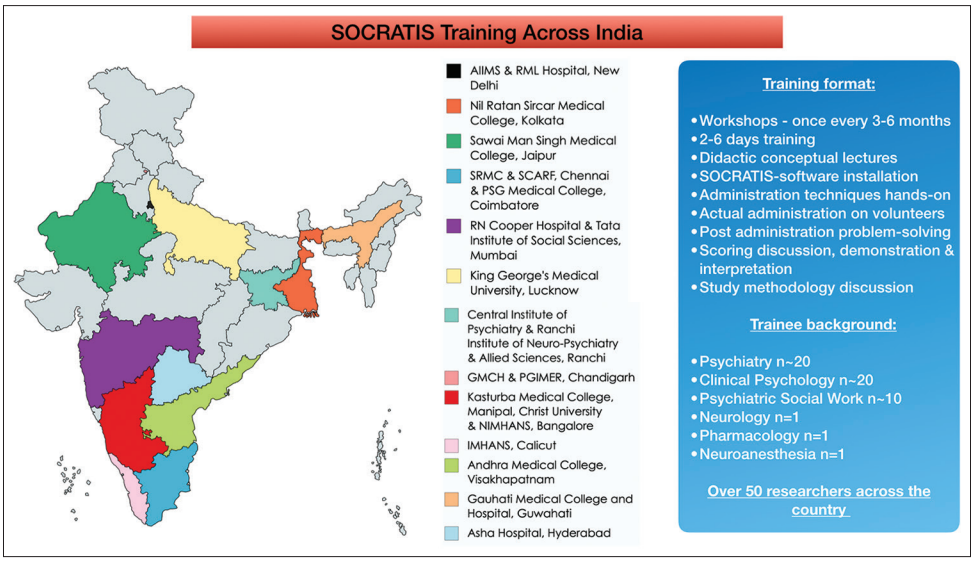

Figure 4: The relationship between cognition and real-world functioning. Note: CFI – Comparative Fit Index; TLI – Tucker-Lewis Index; RMSEA – Root Mean Square Error of Approximation

The prime focus of our approach to studying the neurobiology of social cognition has been to examine the motor resonance system, also referred to as the mirror neuron system (MNS). Mirror neurons are defined as nerve cells that discharge while we perform an action, as well as when we observe someone else perform the same action. Giacomo Rizzolatti's group at Parma, Italy, first discovered mirror neurons (accidentally) in the premotor cortex of the macaque monkey.[53,54] During one such experiment, in which neural responses to food (as an object) were being recorded, the investigators discovered to their surprise that some neurons discharged not when the monkey looked at the food but when the experimenter grasped the food.[53] In humans, the first direct recording and demonstration of mirror neuron activity were done in patients undergoing surgery for refractory epilepsy in 2010.[55] However, indirect measurements of MNS activity are possible by quantifying the change in putative neural response during action observation relative to static image viewing by means of functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), electroencephalography, magnetoencephalography, and optical imaging. A meta-analysis of 125 such fMRI studies has identified an extensive network comprising the ventral premotor cortex, inferior frontal gyrus, inferior parietal lobule, and the insula[56] – several of these regions overlapping with those described as having mirror properties in monkeys. Mirror neuron-driven embodied simulation, captured by the "neural exploitation hypothesis," has been proposed as a physiological substrate of social cognitive abilities in humans.[57] In other words, these are neural circuits that are active when one engages in social situations (e.g., shaking hands or greeting with a *namaste*). Interestingly, parts of these circuits are active even when one observes someone else engaging in the same social behavior, thus providing an internal template to decode intentions underlying gestures, actions, and emotions in an automatic reflexive manner.

This hypothesis was examined in a small sample of schizophrenia patients, where we demonstrated for the first time a relationship between putative MNS activity measured using TMS and social cognition performance in schizophrenia.[58] The TMS experiment [Figure 5] involved recording motor-evoked potentials from the right hand of individuals observing static images and goal-directed actions (e.g., locking/unlocking actions) of the right hand. The degree of facilitation of motor cortical reactivity potentials during action observation relative to static image viewing formed a measure of putative MNS activity. In a larger case–control study implementing the same TMS experiment, we demonstrated reduced MNS activity in untreated drug-naïve schizophrenia patients (n = 33), as compared to medicated (antipsychotics) patients and healthy comparison controls. In the patient group, MNS activity was significantly associated with theory of mind and emotion processing abilities, suggesting that patients with better MNS activity had higher scores on social cognition tests.[39] This not only confirmed our earlier report but also was the first time such findings were being reported in a large sample of schizophrenia and healthy individuals.

Next, we modified the experimental paradigm by incorporating a social context to the action observation sequence. A brief socio-emotive contextual prelude to the same action observation (locking/unlocking) sequence resulted in greater facilitation of motor potentials as compared to neutral action and static image viewing in both – schizophrenia patients and healthy controls. However, the degree of this facilitation was diminished in the patient group. The other difference in this experiment was

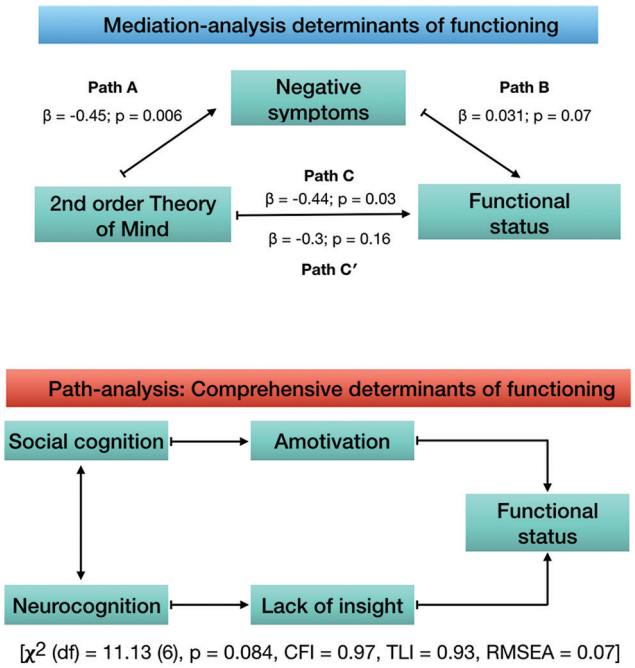

Figure 5: Transcranial magnetic stimulation experiment set-up to measure putative mirror neuron system activity

that all patients had received treatment with antipsychotic medications. With this novel paradigm, we were not only able to show a diminished responsiveness of the MNS in schizophrenia patients when they were treated but also replicate our earlier findings of an association between putative MNS activity and social cognition composite performance.[59]

Social brain in mania

Using TMS, we also examined MNS activity in patients with untreated bipolar mania. In a pilot observation, we demonstrated significant associations between putative MNS activity measured using the neutral action observation paradigm and symptom severity of mania.[60] In a larger case–control study, we were able to demonstrate significantly enhanced MNS activity in patients with mania as compared to healthy controls[61] and an association with manic symptom severity – which did not, however, persist after correcting for multiple comparison testing. Given our earlier observation of heightened MNS activity in a patient with bipolar disorder and echolalia, that reduced following treatment of echolalia with lorazepam,[62] we also measured echo phenomena in the patients with mania recruited in this study.[61] Induced (while being spoken to) and incidental (while not being directly spoken to, but privy to an ambient conversation) echolalia were measured using a modification of the echolalia questionnaire [Figure 6].[63] Echopraxia was measured using the Bush-Francis Catatonia Rating Scale.[64] While none of the patients with mania demonstrated echopraxia, 17 out of the 39 patients demonstrated incidental or ambient echolalia. MNS activity using one of the TMS paradigms had a significant positive association with incidental echolalia scores.[61] In summary, we demonstrated that putative MNS activity was heightened in mania, possibly because of disinhibition, and this was associated with social behavioral abnormalities (incidental echolalia).

Conceptualizing psychosis based on mirror neuron system dysfunction

The rather diametrically opposing findings of MNS activity in drug-naïve patients with schizophrenia (reduced) and mania (elevated) in our experiments prompted us to systematically review evidence from data-driven empirical studies on MNS dysfunction in psychotic disorders. Fourteen datasets were examined; while nine studies demonstrated diminished MNS activity, four reported increased or mixed MNS activity.[65] Interestingly, heightened mirroring responses were associated with auditory hallucinations in one study and depressive symptoms in another study. Diminished mirroring responses were associated with negative symptoms and social cognitive deficits. In this context, we proposed an integrative dynamic model of mirror neuron dysfunction in psychotic disorders, in which an inherent mirror system deficit underlying persistent negative symptoms, social cognition impairments, and self-monitoring deficits triggers a pathological metaplastic reorganization of this system resulting in aberrant excessive mirror system responses and the phasic catatonic, affective, and hallucinatory symptoms.[65] While these are certainly preliminary findings that require replication across centers and in larger samples, they certainly provide exciting avenues to examine the MNS as a potential state-dependent neuromarker, in order to track treatment response and functional recovery.[66]

TRANSLATIONAL APPLICATIONS OF THE SOCIAL BRAIN MODEL OF PSYCHOSIS

While antipsychotic medications are the mainstay for the treatment of psychotic disorders, they are most useful in the treatment of the positive symptoms of hallucinations, delusions, and thought disorders.[2] Despite initial evidence that atypical antipsychotic drugs improved social cognition,[67] subsequent studies have not shown any substantial improvement with antipsychotic medications.[68,69] Cognitive processes are certainly more complex than their rather simplistic mechanistic understanding that we have been able to achieve so far. Nevertheless, there have been several attempts over the last two decades to develop novel treatment strategies that can specifically address social cognition impairments and therefore target social behavior and functioning. This is certainly a cutting-edge research area, with newer strategies being investigated by the day. In this context, we have attempted to target social cognition through a host of novel interventions, and this is certainly

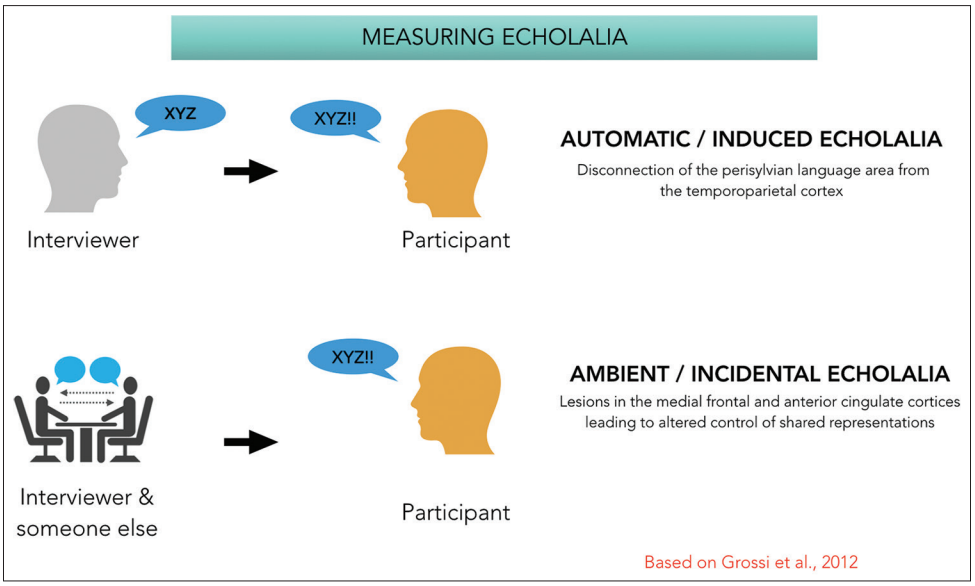

Figure 6: Measurement of echolalia in patients with mania

an ongoing process of learning and adapting in an iterative manner until we finally achieve substantial gains.

Noninvasive brain stimulation

A direct advancement of our evidence suggesting a relationship between MNS activity and social cognition in schizophrenia was to use focal neuromodulation in activating the MNS, with the ultimate hope of achieving cognitive and behavioral change with long-term neuromodulation. A pilot experiment that we conducted using a single individual who received true and sham high-frequency (20-Hz) TMS on different days demonstrated a significant activation of MNS activity as assessed using fMRI.[70] Incidentally, this was the first ever report to show that the MNS can be modulated using externally applied TMS. Next, we conducted a randomized controlled experiment to examine this with a single session of true versus sham repetitive high-frequency (20-Hz) TMS delivered to the left premotor cortex/inferior frontal gyrus in a group of healthy individuals ($n = 30$). MNS activity was measured using single/paired TMS pulses as described earlier. High-frequency TMS is known to enhance activity in the underlying cortical region and its trans-synaptic connections.[71] In keeping with our hypothesis, we found a small but statistically significant enhancement of MNS activity following true TMS as compared to sham TMS, suggesting the malleability and plasticity of this neuronal network.[72] Current experiments are underway to examine similar target engagement in patients with schizophrenia. If found to have similar effects, then subject-specific MRI-guided TMS can be a potential therapeutic avenue for treating social cognition deficits in psychotic disorders.

It is also important to understand that the MNS is but one of the many diverse networks within the social brain, and therefore, we have attempted to engage other social brain networks in bringing about a change in social cognition. In a three-group randomized controlled trial, we examined the potential augmentation of cognitive remediation by delivering 20-Hz TMS to bilateral dorsolateral prefrontal regions, which underlie not just cognitive control but also emotion regulation functions. Schizophrenia patients with cognitive impairments received (a) true TMS and cognitive remediation, $n = 15$; (b) sham TMS and cognitive remediation, $n = 15$; and (c) treatment as usual, $n = 12$. Both active groups demonstrated a significant improvement in not just social and neurocognition performance but also negative symptoms over a period of 3–4 weeks of training.[73] This study suggested that cognitive training was sufficient to produce therapeutic gains in the short term. However, it needs to be seen if similar augmentation strategies could improve the long-term durability of such benefits.

Yet, another hub within the social brain is the cerebellum,[74] which has important functional connections not just with the regulatory lateral prefrontal cortices but also with the mentalizing network comprising the medial prefrontal cortex.[75] In a novel structural MRI-guided intervention, we conducted a randomized controlled trial to examine the benefits of true versus sham intermittent theta-burst stimulation (patterned TMS) over the cerebellar vermis delivered twice daily for 5 days in schizophrenia patients with persistent negative symptoms ($n = 60$). Cognitive, clinical, and functional outcomes were examined at the end of treatment and after 6 weeks. Resting-state fMRI was also performed before and after treatment. While both groups showed improvement in the outcomes assessed, the true TMS group showed a significant enhancement in the connections between the cerebellar

vermis and the right dorsolateral prefrontal cortex, which was associated with the percentage change in negative symptoms.[76] This experiment identifies an important neuronal circuit (cerebellum-prefrontal cortex) that underlies negative symptoms and is likely to be modulated with TMS. Future interventions can be designed to selectively alter connectivity in this neural circuit to bring about long-term clinical gains.

Yoga

Yoga is a multicomponent practice that involves physical postures and exercise, breath regulation techniques, deep relaxation practice, and meditation/mindfulness techniques involving attention control.[77] While earlier studies have demonstrated the utility of yoga therapy in improving social connectedness,[78] depression,[79] and negative symptoms of schizophrenia,[80] recent studies have examined its effect on specific social cognitive processes.[81] A randomized controlled trial of yoga versus treatment as usual in schizophrenia examined domains of social cognition using SOCRATIS and TRENDS. In this study, yoga not only improved all domains of social cognition over a period of 20 sessions delivered over 4–6 weeks but also improved social behavior (negative symptoms) and real-world functional outcomes.[82] Given the effectiveness and feasibility of yoga therapy, this is the most clinically feasible and effective treatment of social cognition deficits in our opinion. Yoga therapy for social cognition deficits is now in the process of being put to regular clinical use at NIMHANS in a graded manner. This is not just for individuals with schizophrenia but also patients with other neuropsychiatric disorders – adults with autism, social deficits following traumatic brain injury, and borderline personality disorder. Possible neurobiological mechanisms through which yoga improves social cognition are discussed in a recent review article.[83] Here, we propose how learning and performing coordinated physical postures (asanas) with a teacher facilitates imitation and the process of being imitated. This two-way process can improve social cognition and empathy through reinforcement of the premotor and parietal mirror neuron system.[84] Oxytocin may play a role in mediating these processes that further lead to better social connectedness and social outcomes.[85,86]

SUMMARY

A social neuroscience perspective of psychosis provides a strong research framework to study the key processes of psychosis from neural systems to real-world functional outcomes via cognition and behavior. Using this model, we have found some consistent findings. First, an association between second-order theory of mind and real-world functional outcomes has been demonstrated – this finding is replicated across different centers in the country. Second, we found associations between MNS activity and social cognition performance, especially in patients with schizophrenia. The role of the mirror neuron system in social cognition (especially theory of mind) and social behavior (echolalia) is a useful heuristic that can be examined in further longitudinal empirical research. While there is understandable skepticism in this line of research, given the overtly exaggerated claims in popular culture, data-driven science is the best way to arrive at logical and firm conclusions based on testable hypotheses.

The results of our experiments in the last decade have not only demonstrated the clinical relevance of social cognition deficits in psychotic disorders but also identified important neurobiological underpinnings of these unique higher-order brain functions. In addition, we are beginning to engage these neural systems in driving therapeutic gains. As the cliché goes, there is no magic pill that is likely to bring about improvement. Utilizing technology to individualize treatments based on one's neurobiology, sociopsychological and cultural milieu will bring about better and perhaps more sustained therapeutic gains. Given the heterogeneous, persistent, and often resistant nature of cognitive and negative symptoms of psychotic disorders, successful treatments will require being multifold, complementary, transdisciplinary, and pragmatic. A combination of social enrichment via building opportunities for social engagement and interactions and the above-described brain stimulation and yoga-based therapies may be examined in future studies. Figure 7 illustrates a therapeutic framework based on this social neuroscience conceptualization that includes the methods described above, and also preventive and early intervention approaches, as well as community integration and policy-level changes to facilitate them. Consistent demonstration of the effectiveness of such concerted biopsychosocial treatment paradigms will then lead to additional efforts for adapting and scaling these treatments for delivery across resource-limited settings in the community.

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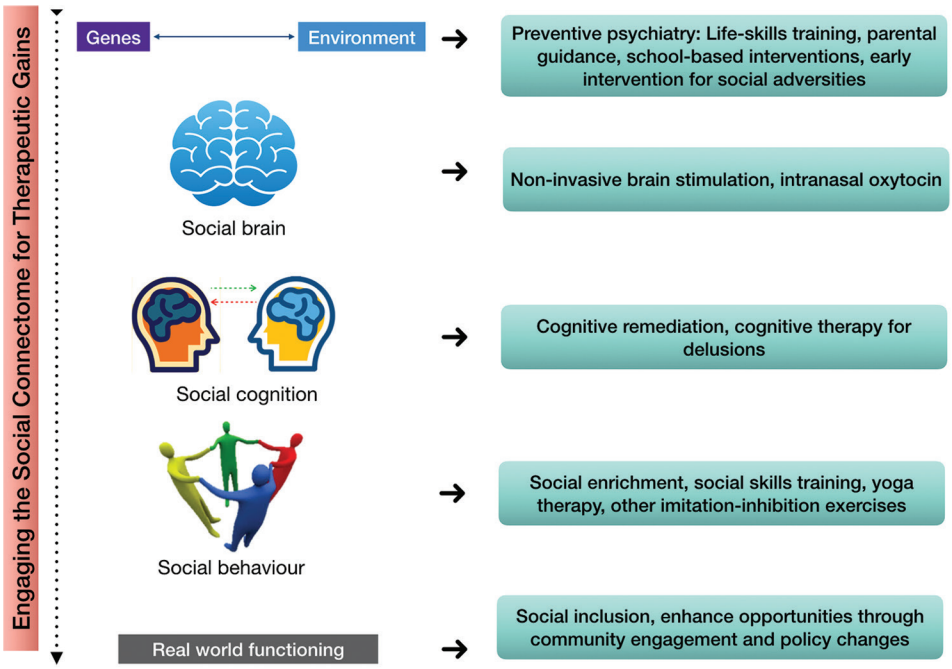

Figure 7: Social neuroscience driven therapeutic framework for interventions

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Salomon JA, Haagsma JA, Davis A, de Noordhout CM, Polinder S, Havelaar AH, *et al*. Disability weights for the Global Burden of Disease 2013 study. Lancet Glob Health 2015;3:e712-23.
2. Mueser KT, McGurk SR. Schizophrenia. Lancet 2004;363:2063-72.
3. Brothers L. The social brain: A project for integrating primate behavior and neurophysiology in a new domain. Concepts Neurosci 1990;1:27-51.
4. Burns J. The social brain hypothesis of schizophrenia. World Psychiatry 2006;5:77-81.
5. Dunbar RI, Shultz S. Evolution in the social brain. Science 2007;317:1344-7.
6. Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. Lancet 2013;381:1371-9.
7. Brainstorm Consortium, Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, *et al*. Analysis of shared heritability in common disorders of the brain. Science 2018;360:eaap8757. doi: 10.1126/science.aap8757.
8. Uher R, Zwicker A. Etiology in psychiatry: Embracing the reality of poly-gene-environmental causation of mental illness. World Psychiatry 2017;16:121-9.
9. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, *et al*. Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. Am J Psychiatry 2010;167:748-51.
10. Cotter J, Granger K, Backx R, Hobbs M, Looi CY, Barnett JH. Social cognitive dysfunction as a clinical marker: A systematic review of meta-analyses across 30 clinical conditions. Neurosci Biobehav Rev 2018;84:92-9.
11. Finn ES, Shen X, Scheinost D, Rosenberg MD, Huang J, Chun MM, *et al*. Functional connectome fingerprinting: Identifying individuals using patterns of brain connectivity. Nat Neurosci 2015;18:1664-71.
12. Davies G, Armstrong N, Bis JC, Bressler J, Chouraki V, Giddaluru S, *et al*. Genetic contributions to variation in general cognitive function: A meta-analysis of genome-wide association studies in the CHARGE consortium (N=53949). Mol Psychiatry 2015;20:183-92.
13. Dekker TM, Karmiloff-Smith A. The dynamics of ontogeny: A neuroconstructivist perspective on genes, brains, cognition and behavior. Prog Brain Res 2011;189:23-33.
14. Dan B, Pelc K, de Meirleir L, Cheron G. Phenotypic plasticity and the perception-action-cognition-environment paradigm in neurodevelopmental genetic disorders. Dev Med Child Neurol 2015;57 Suppl 2:52-4.
15. Millan MJ, Agid Y, Brüne M, Bullmore ET, Carter CS, Clayton NS, *et al*. Cognitive dysfunction in psychiatric disorders: Characteristics, causes and the quest for improved therapy. Nat Rev Drug Discov 2012;11:141-68.
16. Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. Schizophr Res 2004;72:29-39.
17. Dimaggio G, Lysaker PH, Carcione A, Nicolò G, Semerari A. Know yourself and you shall know the other. to a certain extent: Multiple paths of influence of self-reflection on mindreading. Conscious Cogn 2008;17:778-89.
18. Penn DL, Addington J, Pinkham A. American Psychiatric Association Textbook of Schizophrenia. Arlington, VA: American Psychiatric Publishing Press, Inc.; 2006.
19. Mehta UM, Thirthalli J, Subbakrishna DK, Gangadhar BN, Eack SM, Keshavan MS. Social and neuro-cognition as distinct cognitive factors in schizophrenia: A systematic review. Schizophr Res 2013;148:3-11.
20. Heider F. On social cognition. Am Psychol 1967;22:25-31.
21. Chandler MJ. Social cognition and life-span approaches to the study of child development. Adv Child Dev Behav 1976;11:225-39.
22. Premack DG, Woodruff G. Does the chimpanzee have a theory of mind? Behav Brain Sci 1978;1:515-26.
23. Blacher J. Assessing social cognition in young mentally retarded and nonretarded children. Am J Ment Defic 1982;86:473-84.
24. Wais M. Disturbances of the social cognition in right-hemisphere brain-damaged patients. Fortschr Neurol Psychiatr 1982;50:203-6.
25. Dawson G, Fernald M. Perspective-taking ability and its relationship to the social behavior of autistic children. J Autism Dev Disord 1987;17:487-98.
26. Corrigan PW, Green MF. Schizophrenic patients' sensitivity to social cues: The role of abstraction. Am J Psychiatry 1993;150:589-94.
27. Green MF, Olivier B, Crawley JN, Penn DL, Silverstein S. Social cognition in schizophrenia: Recommendations from the measurement and treatment research to improve cognition in schizophrenia new approaches conference. Schizophr Bull 2005;31:882-7.
28. Green MF, Penn DL, Bentall R, Carpenter WT, Gaebel W, Gur RC, *et al*. Social cognition in schizophrenia: An NIMH workshop on definitions, assessment, and research opportunities. Schizophr Bull 2008;34:1211-20.
29. Brüne M. "Theory of mind" in schizophrenia: A review of the literature. Schizophr Bull 2005;31:21-42.
30. Ekman P, Friesen WV. Pictures of Facial Affect. Palo Alto, CA: Consulting Psychologists Press; 1976.
31. Allison T, Puce A, McCarthy G. Social perception from visual cues: Role of the STS region. Trends Cogn Sci 2000;4:267-78.
32. Kinderman P, Bentall RP. A new measure of causal locus: The internal, personal and situational attributions questionnaire. Personal Individ Differ 1996;20:261-4.
33. Mehta UM, Thirthalli J, Gangadhar BN, Keshavan MS. Need for culture specific tools to assess social cognition in schizophrenia. Schizophr Res 2011;133:255-6.
34. Heinrichs DW, Hanlon TE, Carpenter WT Jr. The quality of life scale: An

instrument for rating the schizophrenic deficit syndrome. Schizophr Bull 1984;10:388-98.
35. Behere RV, Raghunandan V, Venkatasubramanian G, Subbakrishna DK, Jayakumar PN, Gangadhar BN. Trends-a tool for recognition of emotions in neuropsychiatric disorders. Indian J Psychol Med 2008;30:32-8.
36. Mehta UM, Thirthalli J, Naveen Kumar C, Mahadevaiah M, Rao K, Subbakrishna DK, *et al*. Validation of social cognition rating tools in Indian setting (SOCRATIS): A new test-battery to assess social cognition. Asian J Psychiatr 2011;4:203-9.
37. Mehta UM, Thirthalli J. External validity of the Social Cognition Rating Tools in Indian Setting. Asian J Psychiatr 2014;8:106-8.
38. Mehta UM, Thirthalli J, Naveen Kumar C, Keshav Kumar J, Keshavan MS, Gangadhar BN. Schizophrenia patients experience substantial social cognition deficits across multiple domains in remission. Asian J Psychiatr 2013;6:324-9.
39. Mehta UM, Thirthalli J, Basavaraju R, Gangadhar BN, Pascual-Leone A. Reduced mirror neuron activity in schizophrenia and its association with theory of mind deficits: Evidence from a transcranial magnetic stimulation study. Schizophr Bull 2014;40:1083-94.
40. Valaparla VL, Nehra R, Mehta UM, Thirthalli J, Grover S. Social cognition of patients with schizophrenia across the phases of illness - A longitudinal study. Schizophr Res 2017;190:150-9.
41. Puneeth M. Social Cognition Deficits in Euthymic Bipolar Disorder and Its Association with their Functioning; 2013.
42. Anupama V, Bhola P, Thirthalli J, Mehta UM. Pattern of social cognition deficits in individuals with borderline personality disorder. Asian J Psychiatr 2018;33:105-12.
43. Wiersma D, DeJong A, Ormel J. The Groningen Social Disabilities Schedule: Development, relationship with I.C.I.D.H., and psychometric properties. Int J Rehabil Res 1988;11:213-24.
44. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods 2008;40:879-91.
45. Mehta UM, Thirthalli J, Kumar CN, Kumar JK, Gangadhar BN. Negative symptoms mediate the influence of theory of mind on functional status in schizophrenia. Soc Psychiatry Psychiatr Epidemiol 2014;49:1151-6.
46. Bhagyavathi HD, Mehta UM, Thirthalli J, Kumar CN, Kumar JK, Subbakrishna DK, *et al*. Cascading and combined effects of cognitive deficits and residual symptoms on functional outcome in schizophrenia A path-analytical approach. Psychiatry Res 2015;229:264-71.
47. Mehta UM, Bhagyavathi HD, Kumar CN, Thirthalli J, Gangadhar BN. Cognitive deconstruction of parenting in schizophrenia: The role of theory of mind. Aust N Z J Psychiatry 2014;48:249-58.
48. Mehta UM, Thirthalli J. Distinctiveness of social and meta-cognition in schizophrenia across cultures. Acta Psychiatr Scand 2013;127:494.
49. Mehta UM, Thirthalli J, Bhagyavathi HD, Keshav Kumar J, Subbakrishna DK, Gangadhar BN, *et al*. Similar and contrasting dimensions of social cognition in schizophrenia and healthy subjects. Schizophr Res 2014;157:70-7.
50. Mehta UM, Bhagyavathi HD, Thirthalli J, Kumar KJ, Gangadhar BN. Neurocognitive predictors of social cognition in remitted schizophrenia. Psychiatry Res 2014;219:268-74.
51. Green MF, Horan WP, Lee J. Social cognition in schizophrenia. Nat Rev Neurosci 2015;16:620-31.
52. Markota M, Mehta U, Solis M. Highlights from the biennial international congress on schizophrenia research (ICOSR), March 28-April 1, 2015. Clin Schizophr Relat Psychoses 2015;9:60-4.
53. di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G. Understanding motor events: A neurophysiological study. Exp Brain Res 1992;91:176-80.
54. Gallese V, Fadiga L, Fogassi L, Rizzolatti G. Action recognition in the premotor cortex. Brain 1996;119(Pt 2):593-609.
55. Mukamel R, Ekstrom AD, Kaplan J, Iacoboni M, Fried I. Single-neuron responses in humans during execution and observation of actions. Curr Biol 2010;20:750-6.
56. Molenberghs P, Cunnington R, Mattingley JB. Brain regions with mirror properties: A meta-analysis of 125 human fMRI studies. Neurosci Biobehav Rev 2012;36:341-9.
57. Gallese V, Sinigaglia C. What is so special about embodied simulation? Trends Cogn Sci 2011;15:512-9.
58. Mehta UM, Basavaraju R, Thirthalli J, Gangadhar BN. Mirror neuron dysfunction-a neuro-marker for social cognition deficits in drug naïve schizophrenia. Schizophr Res 2012;141:281-3.
59. Bagewadi VI, Mehta UM, Naik SS, Govindaraj R, Varambally S, Arumugham SS, *et al*. Diminished modulation of motor cortical reactivity during context-based action observation in schizophrenia. Schizophr Res 2019;204:222-9.
60. Mehta UM, Basavaraju R, Thirthalli J. Mirror neuron activity and symptom severity in drug-naïve mania-a transcranial magnetic stimulation study. Brain Stimul 2014;7:757-9.
61. Basavaraju R, Mehta UM, Pascual-Leone A, Thirthalli J. Elevated mirror neuron system activity in bipolar mania: Evidence from a transcranial magnetic stimulation study. Bipolar Disord 2019;21:259-69.
62. Mehta UM, Basavaraju R, Thirthalli J. Mirror neuron disinhibition may be linked with catatonic echo-phenomena: A single case TMS study. Brain Stimul 2013;6:705-7.
63. Grossi D, Marcone R, Cinquegrana T, Gallucci M. On the differential nature of induced and incidental echolalia in autism. J Intellect Disabil Res 2013;57:903-12.
64. Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia. I. Rating scale and standardized examination. Acta Psychiatr Scand 1996;93:129-36.
65. Mehta UM, Thirthalli J, Aneelraj D, Jadhav P, Gangadhar BN, Keshavan MS. Mirror neuron dysfunction in schizophrenia and its functional implications: A systematic review. Schizophr Res 2014;160:9-19.
66. Mehta UM, Keshavan MS. Can we predict outcome in schizophrenia? The need for prognostic biomarkers. Asian J Psychiatr 2015;14:1-2.
67. Harvey PD, Patterson TL, Potter LS, Zhong K, Brecher M. Improvement in social competence with short-term atypical antipsychotic treatment: A randomized, double-blind comparison of quetiapine versus risperidone for social competence, social cognition, and neuropsychological functioning. Am J Psychiatry 2006;163:1918-25.
68. Kucharska-Pietura K, Mortimer A. Can antipsychotics improve social cognition in patients with schizophrenia? CNS Drugs 2013;27:335-43.
69. Sergi MJ, Green MF, Widmark C, Reist C, Erhart S, Braff DL, *et al*. Social cognition [corrected] and neurocognition: Effects of risperidone, olanzapine, and haloperidol. Am J Psychiatry 2007;164:1585-92.
70. Meherwan Mehta U, Agarwal SM, Kalmady SV, Shivakumar V, Kumar CN, Venkatasubramanian G, *et al*. Enhancing putative mirror neuron activity with magnetic stimulation: A single-case functional neuroimaging study. Biol Psychiatry 2013;74:e1-2.
71. Voineskos D, Rogasch NC, Rajji TK, Fitzgerald PB, Daskalakis ZJ. A review of evidence linking disrupted neural plasticity to schizophrenia. Can J Psychiatry 2013;58:86-92.
72. Mehta UM, Waghmare AV, Thirthalli J, Venkatasubramanian G, Gangadhar BN. Is the human mirror neuron system plastic? Evidence from a transcranial magnetic stimulation study. Asian J Psychiatr 2015;17:71-7.
73. Thirthalli J, Mehta UM, Tyagi V, Dharmappa A, Govindaraj R, Keshav Kumar J, *et al*. Efficacy of Transcranial Magnetic Stimulation Applied Over Bilateral Dorsolateral Prefrontal Cortices Using MRI-Guided Neuronavigation System in Enhancing the Efficacy of Cognitive Remediation. Bangalore: Department of Science & Technology (DST) Technology Interventions for Disabled and Elderly (TIDE) Project Completion Report; 2016.
74. Van Overwalle F, Baetens K, Mariën P, Vandekerckhove M. Social cognition and the cerebellum: A meta-analysis of over 350 fMRI studies. Neuroimage 2014;86:554-72.
75. Buckner RL, Krienen FM, Castellanos A, Diaz JC, Yeo BT. The organization of the human cerebellum estimated by intrinsic functional connectivity. J Neurophysiol 2011;106:2322-45.
76. Basavaraju R, Mehta UM, Ithal D, Gowda A, Thirthalli J, Halko MA, *et al*. Intermittent Theta Burst Stimulation of the Cerebellar Vermis for Persistent Negative Symptoms in Schizophrenia: A Randomized Controlled Trial. Bangalore: Wellcome Trust/DBT India Alliance Research Training Fellowship Project Completion Report; 2018.
77. Khalsa SB. Yoga for psychiatry and mental health: An ancient practice with modern relevance. Indian J Psychiatry 2013;55:S334-6.
78. Kinser PA, Bourguignon C, Taylor AG, Steeves R. "A feeling of connectedness": Perspectives on a gentle yoga intervention for women with major depression. Issues Ment Health Nurs 2013;34:402-11.
79. Cramer H, Lauche R, Langhorst J, Dobos G. Yoga for depression: A systematic review and meta-analysis. Depress Anxiety 2013;30:1068-83.
80. Cramer H, Lauche R, Klose P, Langhorst J, Dobos G. Yoga for schizophrenia: A systematic review and meta-analysis. BMC Psychiatry 2013;13:32.
81. Behere RV, Arasappa R, Jagannathan A, Varambally S, Venkatasubramanian G, Thirthalli J, *et al*. Effect of yoga therapy on facial emotion recognition deficits, symptoms and functioning in patients with schizophrenia. Acta Psychiatr Scand 2011;123:147-53.
82. Naik S. Effect of add-on yoga therapy on social cognition deficits and mirror neuron activity in patients with Schizophrenia - A single blind randomized controlled trial. National Institute of Mental Health and Neurosciences: Bengaluru; 2016.
83. Mehta UM, Keshavan MS, Gangadhar BN. Bridging the schism of schizophrenia through yoga-Review of putative mechanisms. Int Rev Psychiatry 2016;28:254-64.
84. Radhakrishna S. Application of integrated yoga therapy to increase imitation skills in children with autism spectrum disorder. Int J Yoga 2010;3:26-30.
85. Aoki Y, Yahata N, Watanabe T, Takano Y, Kawakubo Y, Kuwabara H, *et al*. Oxytocin improves behavioural and neural deficits in inferring others' social emotions in autism. Brain 2014;137:3073-86.
86. Jayaram N, Varambally S, Behere RV, Venkatasubramanian G, Arasappa R, Christopher R, *et al*. Effect of yoga therapy on plasma oxytocin and facial emotion recognition deficits in patients of schizophrenia. Indian J Psychiatry 2013;55:S409-13.