



Diminished modulation of motor cortical reactivity during context-based action observation in schizophrenia



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ABSTRACT

Background: Deficient mirror neuron system (MNS)-activity is associated with social cognition deficits in schizophrenia. However, it is not known how socio-emotional contexts modulate the MNS-response. In a Transcranial Magnetic Stimulation (TMS)-experiment, we aimed to compare putative MNS-responses to action observation stimuli with and without a context, in patients with schizophrenia and healthy subjects.

Method: TMS-evoked motor cortical reactivity was measured by single and paired [short interval intracortical inhibition (SICI) and facilitation (ICF)] pulse-paradigms in schizophrenia patients (n = 39) and healthy subjects (n = 28) while they observed three experimental-blocks: a static image, a neutral hand action (NA) and a context-based hand action (CA). The degree of cortical reactivity facilitation with the two action observation blocks, relative to the static block provided indirect measures of premotor MNS-activity. A subset of patients (n = 31) also underwent comprehensive social cognition assessments.

Results: RMANOVA demonstrated significantly higher cortical reactivity during the CA-block in both groups (all TMS-paradigms); albeit significantly less pronounced in patients (SICI and ICF paradigms). MNS-activity during the CA-block was significantly higher compared to that during the NA-block in both groups (all TMS-paradigms), but significantly less pronounced in patients (SICI and single-pulse paradigms). MNS-activity during the CA-block measured by the ICF paradigm was positively correlated with social cognition performance.

Conclusion: Providing a context to the action modulates MNS-activity. This modulation is diminished in schizophrenia patients, suggestive of a diminished sensorimotor associative learning process. This novel, ecologically valid paradigm to tap into the MNS may serve as a neuro-marker of social cognition performance in schizophrenia.

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1. Introduction

Schizophrenia is a leading cause of functional disability worldwide (Salomon et al., 2015). Social cognition deficits contribute substantially to this disability (Fett et al., 2011). Social cognition includes a broad range of mental operations applied during social interactions (Brothers, 1990), spanning domains of theory of mind, emotion processing, social perception and attributional styles (Green et al., 2008). Understanding the neurobiology of these social cognition deficits will enable designing neuroscience-informed treatment strategies that can ultimately improve functional outcomes in schizophrenia. Among the various social brain networks implicated in the pathogenesis of schizophrenia and social cognition deficits (Green et al., 2015), the mirror neuron system (MNS) is perhaps the least extensively investigated.

The MNS is a specialized network of neurons which are activated when one performs an action as well as when he/she observes such action (Di Pellegrino et al., 1992; Gallese et al., 1996). This dual property of action perception and action execution that supports a mirroring mechanism provides an internal template to decode intentions underlying actions (Iacoboni et al., 2005). This unique functional property of mirror neurons is thought to drive social cognition abilities in humans via principles of embodied simulation (Gallese and Sinigaglia, 2011). The understandable criticism regarding the causal attributes of the MNS in determining a broad range of higher cognitive abilities (Jarrett, 2012) is also mixed with certain cautiously conducted experiments that indeed demonstrate the role of the MNS in inferring goals underlying actions (Iacoboni et al., 2005) and empathy (Carr et al., 2003). Among clinical groups, schizophrenia patients with lower premotor MNS-activity have been found to have greater deficits in theory of mind and emotion processing (Mehta et al., 2014b). However, the consistency of these findings is not established as another study demonstrated an inverse relationship between frontal MNS-activity and self-reported

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empathy scores (Horan et al., 2014). Nevertheless, experiments examining related processes like motor synchrony (Słowiński et al., 2017) and action imitation (Park et al., 2008) certainly demonstrate impairments in schizophrenia, emphasizing the need for more refined investigations into the motor-cortex neuromarkers of social cognition (e.g., the MNS) and functional outcomes.

In humans, mirror neurons are thought to be distributed across the ventral premotor cortex, inferior frontal gyrus, inferior parietal lobule, and insula. The anterior parts of the MNS (frontal) support interpretation of goals and intentions, while the posterior part (parietal) determines the kinesthetic description of achieving the goal via specific actions (Iacoboni and Dapretto, 2006). Schizophrenia patients demonstrate deficits in activation of both, the frontal (Mehta et al., 2014b), and parietal (Thakkar et al., 2014) components of the MNS in separate experiments. However, the differential impact of each has not been systematically examined. There are different methods of assessing MNS-activity. These include direct methods like single-cell electrode recordings (Mukamel et al., 2010), and indirect methods like functional magnetic resonance imaging (fMRI) (Iacoboni et al., 2005), electroencephalogram (EEG) (Oberman et al., 2005), magnetoencephalography (MEG) (Kato et al., 2011) and transcranial magnetic stimulation (TMS) (Fadiga et al., 1995).

In TMS, single or paired pulses are administered to the primary motor cortex and electromyography recordings of the motor evoked potentials from the contralateral hand muscles are obtained as subjects observe goal-directed actions and static images (Fadiga et al., 1995; Strafella and Paus, 2000). Typically, there is a quantifiable motor cortical reactivity facilitation (increased motor evoked potentials or reduced intracortical inhibition) or motor resonance in the same muscle group that is observed to be in action. This index of motor resonance in the primary motor cortex is likely to be driven by premotor MNS-activity (Avenanti et al., 2007; Mehta et al., 2015) and is used as a putative, indirect marker of premotor mirror neuron system activity (Fadiga et al., 1995; Strafella and Paus, 2000), henceforth referred to as MNS-activity here.

A review of MNS-activity studies in schizophrenia highlighted mixed findings – some studies demonstrating reduced and other reporting heightened MNS-responses (Mehta et al., 2014a). Given the variable findings of MNS-responses in schizophrenia, an integrative model is proposed that hypothesizes diminished MNS-responses contributing to the persistent cognitive and negative symptoms, while an exaggerated MNS-response that may underlie the phasic hallucinations, affective instability and catatonic symptoms (Mehta et al., 2014a). Some studies, nevertheless, demonstrate a normal MNS-response in schizophrenia (Andrews et al., 2015; Horan et al., 2014). While this may be due to underpowered experiments, it might also be a result of normalization with treatment (Mehta et al., 2014b). However, in schizophrenia, social cognition deficits are observed even during symptom remission with antipsychotic medications (Mehta et al., 2013). Given the substantial social cognition deficits in patients with schizophrenia, the difference in MNS-activity between healthy controls and patients can be accentuated when the action observation is perceived within a socio-emotional context. In addition, this method of eliciting putative MNS-activity also has the advantage of possessing better ecological validity (Vaskinn et al., 2009) by virtue of its verisimilitude (test stimuli that resemble social information processing required in everyday life). Most conventional action observation paradigms employed in MNS experiments are neutral goal-directed or intransitive actions. Interestingly, there is emerging evidence that MNS-activity in healthy human subjects can be modulated by coupling the observed action with faces depicting emotions (Enticott et al., 2012; Hill et al., 2013), more so perhaps by negative facial emotions. Observing actions performed in a socio-emotional context results in an increased motor cortical reactivity facilitation, especially under negative valence/high arousal contexts (Lagravinese et al., 2017). This modulation of MNS-activity within a socio-emotional context has not been studied in schizophrenia.

In this TMS experiment, we aimed to compare motor cortical reactivity facilitation with two action observation blocks – a neutral goal-directed action (NA) and goal-directed action embedded within a context (CA), in patients with schizophrenia and healthy comparison subjects. As a secondary aim, we examined the association between social cognition performance and MNS-activity as determined by the CA block.

2. Methods

2.1. Subjects

Data was collated from schizophrenia patients ($n = 45$) and healthy comparison subjects ($n = 30$) recruited as part of two MD dissertations (Bagewadi, 2014; Naik, 2016) conducted at a tertiary care neuropsychiatric hospital in South India. All patients were consulting the hospital for treatment and received a diagnosis of schizophrenia based on DSM-IV TR criteria (American Psychiatric Association et al., 2000) as evaluated by a qualified psychiatrist and confirmed using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). They did not have any comorbid psychiatric or neurological disorders. Healthy comparison subjects were recruited from among the community and were screened to rule out any history of a psychiatric diagnosis using the Mini International Neuropsychiatric Interview – Screening instrument (Sheehan et al., 1998) or a family history of psychosis in a first-degree relative.

All participants were right-handed (Oldfield, 1971), with no contraindications to participating in a TMS study (Keel et al., 2000) and did not have any substance use disorders (except for nicotine) as determined by clinical interview. None of the participants had clinically diagnosable or self-reported visual or auditory impairment, or current pregnant/postpartum state. All participants provided a written informed consent that was approved by the Institute's Ethics Committee. Both the MD dissertation protocols were reviewed and approved by this Ethics Committee. The two groups were matched for gender but not for age. Group-level age matching was ensured by excluding some subjects that were contributing to significantly dissimilar age. Since the dissimilarities were due to higher age in the patient group, we specifically excluded six patients with an age of >38 years and two healthy subjects with an age of 19 years. These cut-offs permitted us to include the maximum number of patients and healthy subjects while ensuring that they were adequately matched at a group level for age. Finally, data from 39 schizophrenia patients and 28 healthy comparison subjects matched for age and gender were taken for the analysis.

2.2. Assessments

Patients were assessed for symptom severity using scales for the assessment of positive (Andreasen, 1984) and negative (Andreasen, 1985) symptoms. Social cognition was assessed using the Social Cognition Rating Tools in Indian Setting (theory of mind, social perception & attributional styles) (Mehta et al., 2011) and the Tool to Recognize Emotions in Neuropsychiatric Disorders (facial emotion recognition) (Behere et al., 2008). Theory of mind tasks included first-order, second-order false belief picture stories, metaphor-irony stories and faux pas recognition stories. Social perception was assessed by posing true/false questions on concrete and abstract (social) cues after subjects viewed brief social interaction videos. Facial emotion recognition was assessed using six basic emotions depicted in static images and dynamic videos. These tools have satisfactory content, construct and external validity (Behere et al., 2008; Mehta et al., 2011; Mehta and Thirthalli, 2014). Each of the theory of mind, social perception and emotion recognition tests provided an index of the respective test performance (range 0 to 1), which was equivalent to the score of an individual on the test divided by the maximum possible score. An average of individual test performance indices was used to calculate the social cognition composite

score that was used in the correlation analyses. Externalizing and personalizing attributional bias scores were calculated based on guidelines given by [Kinderman and Bentall \(1996\)](#).

2.3. TMS experiment to assess MNS-activity

TMS pulses were delivered using a MagPro R30 device, with MagOption, (MagVenture, Farum, Denmark). Motor evoked potentials (MEP) were recorded in the right first dorsal interosseus (FDI) muscle using a One-channel EMG amplifier mounted on the MagPro system. Signal-4 Software (Cambridge Electronic Devices, Cambridge, UK) was used to perform data acquisition and analysis. Subjects were made to sit on a chair at a distance of ~50 cm from the laptop monitor. The scalp region overlying the left motor cortex hand area was identified via trial and error method by observing the contractions in the right FDI muscle. The minimum stimulation intensity (% maximum stimulator output) required, to elicit a $\geq 50 \mu\text{V}$ (Resting Motor Threshold - RMT) and $\geq 1 \text{ mV}$ (stimulation intensity to elicit 1 mV MEP - $SI_{1\text{mV}}$) MEP in the resting, right FDI muscle in at least 6 out of 10 consecutive trials ([Wasserman et al., 2008](#)) was estimated and defined for each subject. Cortical reactivity was recorded in the right FDI muscle with three stimulation paradigms delivered over the left primary motor cortex:

- i. Single-pulse: This was the test pulse delivered with the stimulator intensity required to elicit 1 mV MEPs ($SI_{1\text{mV}}$).
- ii. Short interval intracortical inhibition (SICI): This is a paired-pulse paradigm, reflecting gamma-aminobutyric acid (GABA_A) neurotransmission where a sub-threshold conditioning stimulus (80% of RMT) was applied 3 milliseconds before a supra-threshold test stimulus ($SI_{1\text{mV}}$) to the left primary motor cortex with the right hand at rest ([Kujirai et al., 1993](#)).
- iii. Intracortical facilitation (ICF): This is also a paired-pulse paradigm where a sub-threshold conditioning stimulus (80% of RMT) was applied 10 ms before a supra-threshold test stimulus ($SI_{1\text{mV}}$) to the left primary motor cortex with the right hand at rest ([Kujirai et al., 1993](#)). This paradigm is thought to be mediated by the N-Methyl-D-aspartate (NMDA) glutamatergic receptors ([Ziemann et al., 1998](#)).

Both, SICI and ICF were expressed as a percentage of the ratio between the conditioned MEP and the non-conditioned, test MEP with stimulation intensity of $SI_{1\text{mV}}$ i.e., $[\text{conditioned MEP}/\text{non-conditioned MEP}] \times 100$ ([Patuzzo et al., 2003](#)). A higher value here would mean lesser inhibition for SICI and greater facilitation for ICF. Although single-pulse TMS stimuli are most commonly employed in putative MNS-activity experiments, both SICI ([Patuzzo et al., 2003](#)) and ICF ([Helm et al., 2015](#)) techniques have also been used. In keeping with the greater MEP expected during action observation with single-pulse stimuli, we expected SICI and ICF to reveal lesser inhibition and greater facilitation (respectively) during action observation relative to the rest state.

Fourteen-MEP recordings, using each of these three stimulation paradigms (total of 42 recordings), were elicited in one of three predetermined semi-random sequences with 5-second intervals, while the subjects observed each of the following three experimental observation blocks (see [Fig. 1](#)):

- i. *Rest-block*: The subjects were asked to observe an image of the dorsal aspect of a hand and a lock displayed on the monitor.
- ii. *Neutral action-observation block*: The subjects were asked to observe a video, which depicted the experimenter's hand, holding a key in lateral pinch grip (grasping objects between the side of the index finger and the thumb) to perform repeated locking/unlocking actions. This action requires contraction of the FDI to abduct the index finger.

- iii. *Context-based action-observation block*: In this block, we had subjects observing three consecutive runs of a 170-second video sequence. This sequence though played continuously, had two parts – (a) building up of a context with social and emotional stimuli (first 100 s) and (b) goal-directed actions involving the right FDI muscle similar to the ones observed in the neutral block (last 70 s). In the initial 100 s, a mother and her 4-year daughter are preparing to leave home, when an incoming mobile phone call distracts the mother. While speaking on the phone, she steps out of the house and inadvertently bolts and locks the door with her daughter locked inside the house. There is a small explosion inside the house and smoke starts emanating through the door; the daughter frantically calls her mother to open the door. The latter 70 s of the video depict the mother's panic-stricken efforts to unlock the door, with the key getting stuck in the keyhole, and the video focusing on the right FDI muscle of the mother. The sound of the daughter's frantic calls and the mother's reassurances plays in the background, as the mother tries to open the lock. Fourteen recordings, using the three TMS stimulus paradigms were then obtained in a pseudo-random order, delivered in a time-locked manner to coincide with the last 70 s of the video that depicted goal-directed actions of the FDI muscle. A total of 42 TMS evoked EMG responses were recorded across the three runs in this block.

The sequence of displaying these experimental observation blocks to each subject was also randomized. In order to guarantee optimal attention allocation during the TMS experiments, subjects were instructed to pay attention to all the stimuli throughout the experiment. In addition, to further ensure attention, a second researcher monitored the subjects' behavior as has been done in earlier studies. All subjects who completed the TMS experiment were found to be attentive during the experiment as assessed during behavioral observation.

2.4. Calculation of putative MNS-activity

The % change of cortical reactivity (MEP or cortical inhibition/facilitation) from control condition to goal-directed action observation states formed a measure of motor cortical facilitation or putative MNS-activity. It was calculated using the following formula, where motor cortical reactivity (MCR) refers to MEP (in millivolts) for single-pulse paradigms and SICI or ICF (%) in paired-pulse paradigms:

$$\text{MNS-activity} = \frac{\text{MCR during action observation} - \text{MCR during rest}}{\text{MCR during rest}} * 100$$

2.5. Statistical analyses

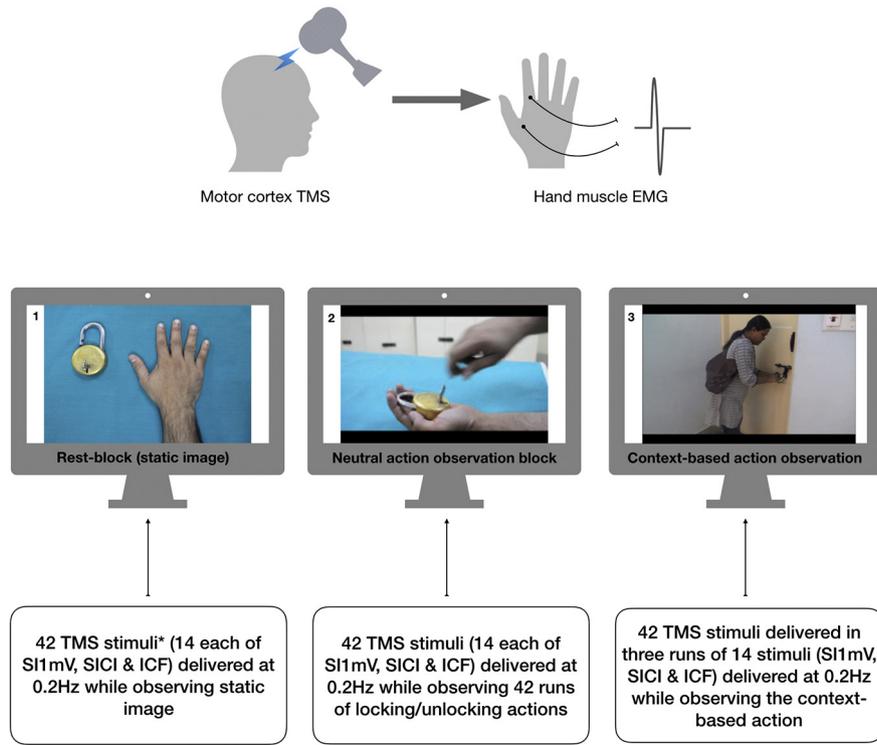
Baseline TMS parameters and socio-demographic characteristics between the two groups were compared using the independent *t*-test and chi-square test. Two-way repeated measures analysis of variance (RMANOVA) was used to examine if motor cortical reactivity was facilitated during action observation relative to static image viewing and if this differed between patients and healthy subjects. Subsequently, two-way RMANOVA was used to compare MNS-activity during neutral and context-based action observation between the patient and healthy groups. Finally, Pearson's correlation analysis was performed to examine the association between motor cortical reactivity facilitation and social cognition composite score.

3. Results

3.1. Clinical details, socio-demographic and baseline cortical reactivity comparisons

Patients had a mean duration of illness of 81.43 (± 57.35) months, the majority had a diagnosis of paranoid schizophrenia ($n = 30$; 76.9%) and were on second-generation antipsychotic medications

TMS-evoked cortical reactivity measured while subjects observe three experimental blocks[#]



Note: Each subject received [#]one of six random orders of experimental blocks and ^{*}one of three pseudorandomly ordered sets of TMS stimuli

Fig. 1. Illustration of the TMS experiment set-up.

with cumulative chlorpromazine equivalents of 482.7 ± 303.2 mg/day. They had moderate intensity symptoms as reflected by their SANS (33.07 ± 17.48) and SAPS (39.58 ± 18.05) composite scores. In terms of socio-demographic characteristics, patients (age 28.6 ± 4.5 years, education 10.6 ± 4.3 years, 38.5% females, 69.2% married) did not differ significantly (all $p > 0.05$) from healthy comparison subjects (age 26.5 ± 4.3 years, education 14.8 ± 4.6 years, 46.4% females, 82.1% married) in all measured variables except education ($t = 3.8, p < 0.05$).

Motor thresholds to elicit $\geq 50 \mu V$ (RMT: $36.74 \pm 9.28\%$ and $35.46 \pm 4.51\%$ in patients and healthy subjects respectively) and $\geq 1000 \mu V$ (SI_{1mV} : $52.71 \pm 12.57\%$ and $49.89 \pm 7.81\%$ in patients and healthy subjects respectively) MEPs were also similar between the two groups (all p values > 0.05). Patients had significantly lower ICF ($t = 2.47, p = 0.025$) but similar SICI ($t = 1.18, p = 0.24$) and MEPs elicited using SI_{1mV} ($t = 1.59, p = 0.11$) as compared to healthy subjects (see Table 1). Since years of education did not

Table 1
Motor cortical reactivity changes with neutral and context-based action observation.

TMS stimuli	Group	Experimental blocks			F statistics ^a		
		Static image (SI)	Neutral action observation (NA)	Context-based action observation (CA)	F ₁	F ₂	F ₃
SI _{1mV} (MEP)	Patients	0.60 (0.32)	0.59 (0.32)	0.69 (0.32)	19.84 ^{***}	6.07 [*]	2.51
	Healthy	0.74 (0.35)	0.77 (0.32)	0.92 (0.26)			
SICI (%)	Patients	45.68 (38.21)	49.25 (42.32)	68.46 (58.04)	22.04 ^{***}	8.06 ^{**}	8.9 ^{**}
	Healthy	55.36 (28.84)	78.11 (61.93)	158.18 (169.82)			
ICF (%)	Patients	99.72 (94.53)	103.53 (105.82)	107.28 (99.27)	8.62 ^{**}	6.13 [*]	4.93 [*]
	Healthy	171.53 (143.21)	194.35 (234.53)	226.11 (257.17)			

Note: SI_{1mV} = stimulation intensity to elicit 1 mV motor evoked potentials (MEP); SICI = short interval intracortical inhibition and ICF = intracortical facilitation; SICI and ICF were expressed as a percentage of the ratio between the conditioned MEP and the non-conditioned, test MEP with stimulus intensity of SI_{1mV} i.e., [conditioned MEP / non-conditioned MEP] × 100.

Post-hoc (Bonferroni) tests demonstrated SI = NA < CA with SI_{1mV} & ICF paradigms; and SI < NA < CA with SICI paradigm.

^a Repeated measures analysis of variance: F₁ = time effect, F₂ = group effect, F₃ = group × time interaction effect.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

demonstrate significant associations with any of the MNS-activity measures (all p values > 0.05), we did not use this variable as a covariate in the RMANOVA.

3.2. Cortical reactivity changes during action observation between the two groups

Cortical reactivity indices during three experimental blocks (static image viewing, neutral, and context-based action observation) were entered as within-subjects factors and group status (patients or healthy subjects) was entered as the between-subjects factor in the RMANOVA. A significant linear time effect was observed suggesting the facilitation of cortical reactivity during action observation blocks as measured using all three TMS paradigms (Table 1). As seen in Fig. 2, the facilitation was the most for the context-based action observation block in all the three TMS stimulation paradigms. This was supported by post-hoc (Bonferroni) tests for the time effect suggesting a significant facilitation during context-based action observation for all three TMS paradigms (footnote Table 1). Next, we found a significant group X time interaction effect suggesting a diminished cortical reactivity facilitation during action observation blocks in patients as compared to healthy subjects in two of the three stimulation paradigms – SICI and ICF, but not with SI_{1mV} (Table 1 and Fig. 2).

3.3. Comparing MNS-activity during neutral and context-based action observation between the two groups

Putative MNS-activity measures derived during the NA and CA blocks (% change of cortical reactivity from static image observation to either neutral or context-based action observation blocks respectively) were entered as the within-subjects factor; group status was entered as the between-subjects factor in the RMANOVA. There was a significant time effect suggesting greater MNS-activity during the CA block compared to the NA block in both groups. In addition, there was a significant group X time interaction effect suggesting greater enhancement of MNS-activity during the CA block (relative to the NA block) in healthy subjects as compared to schizophrenia patients in two of the three stimulation paradigms – SI_{1mV} and SICI, but not with ICF (Table 2 and Fig. 3).

3.4. Association between MNS-activity and social cognition performance

Complete social cognition assessments were possible in only 31 patients due to logistic reasons. The social cognition composite score ($n = 31$) had a significant positive correlation with MNS-activity mediated by ICF during the context-based action observation block ($r = 0.421$, $p = 0.018$; see Fig. S1 in the Supplementary material). None of the other MNS-activity measures had a significant association with the social cognition composite score or any of the attributional bias scores (all p values > 0.05).

4. Discussion

In this TMS experiment, we demonstrated greater cortical reactivity facilitation (relative to rest and neutral action blocks) while observing an action enacted within a socio-emotional context. While this facilitation was observed in both the groups using all three TMS paradigms, it was diminished in schizophrenia patients; significantly so when tested using the SICI and ICF paradigms. We also report significantly stronger MNS-activity (% cortical reactivity facilitation) while observing the context-based action, compared to the neutral action, in both groups, but significantly less pronounced in the schizophrenia group.

These findings convey two important messages. First, we were able to demonstrate a context-based modulation of the MNS during action observation. This is in keeping with emerging findings on how

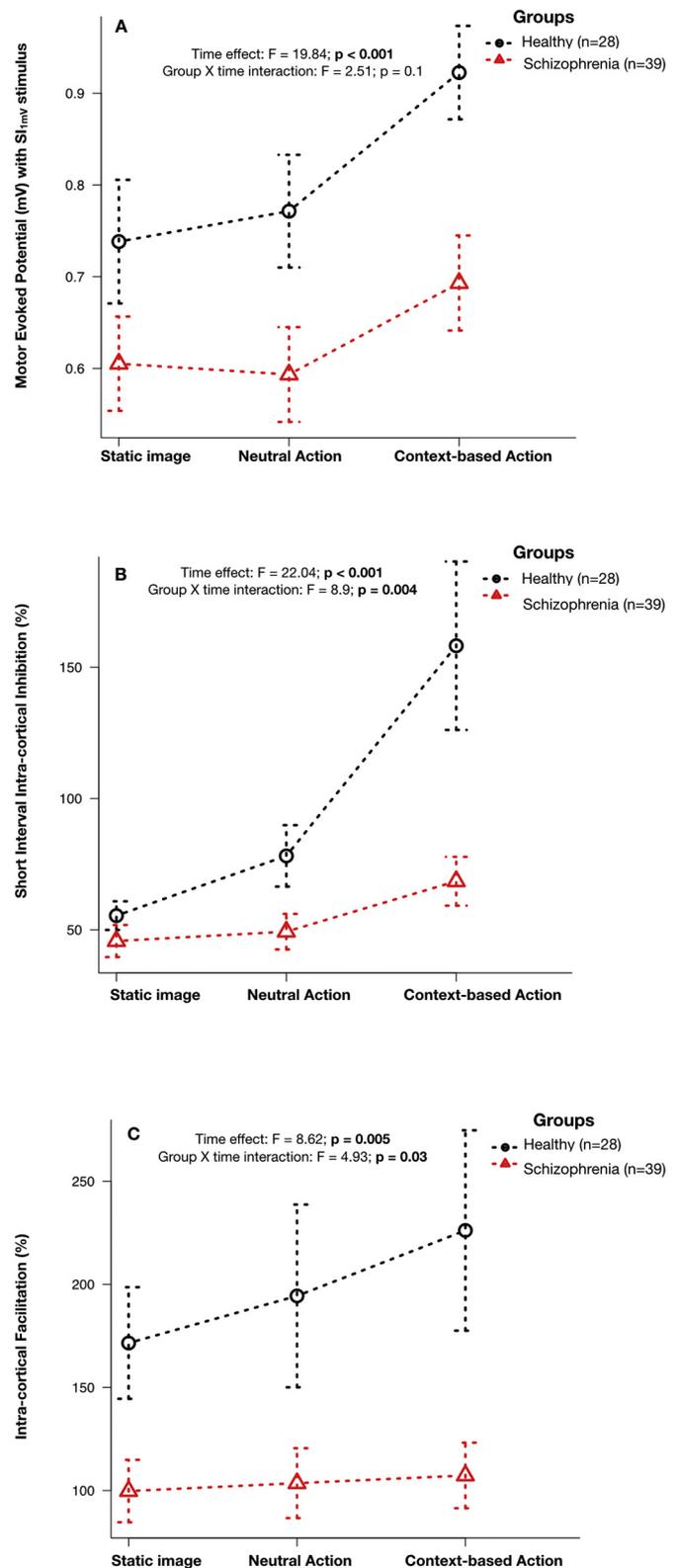


Fig. 2. Line-diagram depiction of motor cortical reactivity facilitation during observation of neutral and context-based actions. Data points represent means and error bars represent standard errors of the means. SI_{1mV} = stimulus intensity to evoke 1-mV motor evoked potentials. SICI and ICF were expressed as a percentage of the ratio between the conditioned MEP and the non-conditioned, test MEP with stimulus intensity of SI_{1mV} i.e., $[\text{conditioned MEP}/\text{non-conditioned MEP}] \times 100$.

processing of actions embedded in emotional contexts directly recruits the supplementary motor areas, emphasizing the malleability of motor cortex as a function of socio-emotional contexts (Mazzola et al., 2013).

Table 2

Putative MNS-activity changes with neutral and context-based action observation.

TMS stimuli	Group	Putative MNS-activity (% cortical reactivity facilitation)		F statistics ^a		
		Neutral action observation (NA)	Context-based action observation (CA)	F ₁	F ₂	F ₃
SI _{1mV}	Patients	4.15 (42.98)	22.63 (37.86)	13.3***	4.02*	4.32*
	Healthy	36.79 (131.23)	104.32 (229.84)			
SICI	Patients	8.15 (38.16)	55.22 (78.94)	36.77***	19.59***	14.04***
	Healthy	42.01 (75.04)	241.4 (253.82)			
ICF	Patients	5.08 (21.03)	15.82 (34.56)	8.48**	0.004	0.170
	Healthy	3.71 (31.72)	17.99 (38.02)			

Note: MNS = mirror neuron system; SI_{1mV} = stimulation intensity to elicit 1 mV motor evoked potentials (MEP); SICI = short interval intracortical inhibition and ICF = intracortical facilitation; SICI and ICF were expressed as a percentage of the ratio between the conditioned MEP and the non-conditioned, test MEP with stimulus intensity of SI_{1mV} i.e., [(conditioned MEP / non-conditioned MEP) × 100].

^a Repeated measures analysis of variance: F₁ = time effect, F₂ = group effect, F₃ = group × time interaction effect.

* p < 0.05.

** p < 0.01.

*** p < 0.001.

Indeed, earlier TMS studies in healthy subjects demonstrate such a modulation of the MNS with positive and negative facial emotion priming of the observed action (Enticott et al., 2012; Hill et al., 2013). The context used in our experiment differed from earlier human experiments by means of its proximity to real-world settings. The target goal-directed action sequence was embedded in a social context that primarily displayed a mix of human emotions ranging from neglect, fear, concern, frustration, urgency, and panic. Similar to earlier studies, we found that the context-based action observation elicited the maximum cortical reactivity facilitation in both the groups. This supports earlier findings that emotion and action processing indeed overlap in the premotor MNS (Lagravinese et al., 2017; Salvia et al., 2016), which forms a neurophysiological substrate for associative sensorimotor learning (Heyes, 2010).

Next, even though the context-based action observation sequence produced the maximum motor cortical facilitation in both groups, it was significantly lower in the patient group when measured using SICI and ICF paradigms. In addition, these findings highlight the diminished modulation of the MNS by a socio-emotional context in patients with schizophrenia, even when they are on antipsychotic medications. Our earlier study with neutral action observation sequence used in this experiment demonstrated a reduced MNS-response only in drug-naïve schizophrenia patients. In this context, it appears that a socially relevant action observation sequence rather than a neutral and non-context based action observation sequence is more likely to differentiate schizophrenia patients from healthy comparison subjects. One possible explanation for these results is from the well-replicated finding that schizophrenia patients have difficulties in appraising and interpreting social cues (Savla et al., 2013). So, when action observation is embedded in a socio-emotional context, patients are likely to show a diminished MNS-response as a function of their poor appraisal of the social cues. Also, the context-based modulation of MNS-activity in the patient group was found to be diminished when measured using the SICI paradigm. Since SICI is thought to be reflective of GABA³³ neurotransmission, our findings emphasize how motor cortical excitation/inhibition imbalance (Yizhar et al., 2011) can result in a muted MNS-response and the associated social deficits in schizophrenia.

In addition, we also report that social cognition performance was significantly associated with MNS-activity mediated by the ICF paradigm during the context-based action observation block. Together, with its better ability to differentiate schizophrenia patients from healthy subjects, the context-based MNS-activity measurement can be studied as a social neuroscience-informed biomarker in schizophrenia. The relationship between MNS-activity and social cognition performance is a replication of our earlier observations (Mehta et al., 2014b, 2012), underscoring the importance of the MNS in social cognitive processes in patients with schizophrenia. Nevertheless, these associations

must be considered preliminary findings coming from a secondary aim of this research.

Important caveats need to be considered while interpreting our findings. It is well known that viewing (Borgomaneri et al., 2017), or listening (Komeilipoor et al., 2013) to emotional stimuli can also alter motor cortical reactivity. In this context, our findings are not conclusive that the motor cortical reactivity facilitation observed with the context-based action observation was a combined effect of emotion and action processing or emotion processing alone. While we devised this novel context-based action observation paradigm to enable better differentiation between schizophrenia patients and healthy subjects, the effect of emotion cues alone on motor cortical reactivity in schizophrenia has not been investigated so far, and may need to be examined in future studies. In addition, the stimuli involved in the context-based action observation are perceptually (auditory and visual) enriched, thus requiring more cognitive effort as compared to the neutral-action observation paradigm. Even though we ensured the kinematics of the action involving the right-hand FDI muscle across both the action observation blocks were similar, the greater cortical reactivity during the context-based action observation in both groups might have been secondary to the general complexity (perceptual and cognitive) of the context-based action observation block, relative to the neutral action block. Nevertheless, this context-based technique of eliciting MNS-response was closer to real-world situations and also differentiated schizophrenia patients from healthy subjects, better than neutral action observation. Similarly, the degree of emotional arousal (subjective reports and autonomic nervous system changes measured using heart rate variability or galvanic skin response) induced by the new paradigm in observers and their appraisal of the social context was not quantified. These are likely to be important determinants of the modulation of MNS-activity observed in this experiment with socio-emotive cues. The broad emotional valence of the context-based action observation sequence was negative. Experiments in healthy individuals also demonstrate positive valence emotions to modulate MNS-responses (Hill et al., 2013). Their effects in schizophrenia may be examined in future studies. The association between MNS-activity and social cognition performance is reported from a cross-sectional correlation analysis. Longitudinal studies with intervention arms are likely to provide more conclusive evidence for the role of MNS-activity in driving social cognition abilities in schizophrenia.

In summary, we report for the first time a significant modulation of MNS-activity by a socio-emotional context in patients with schizophrenia and healthy subjects. This modulation was found to be diminished in the patient group and was associated with a composite social cognition measure in the patient group that encompasses performance on theory of mind, social perception and facial emotion processing. Context-embedded action observation sequences seem to better demonstrate

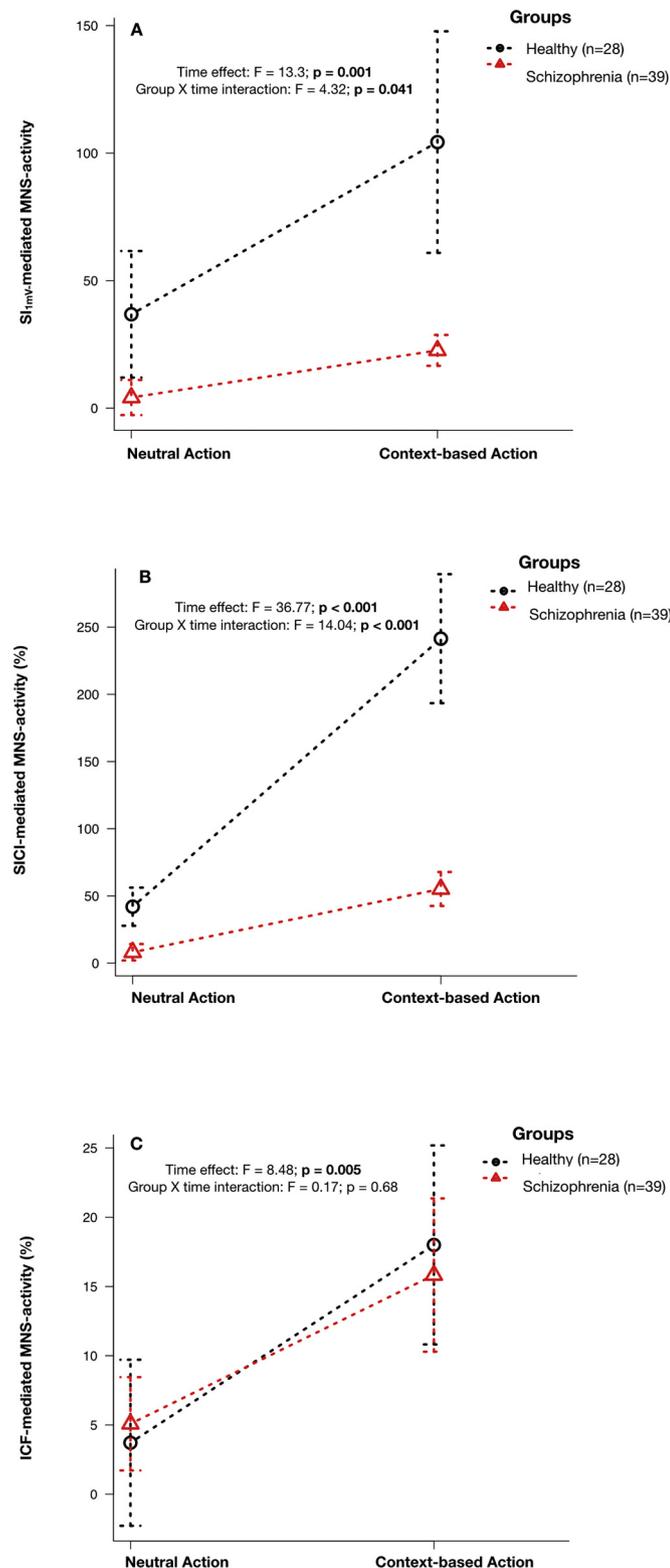


Fig. 3. Line-diagram depiction of putative MNS-activity with neutral and context-based action observation. Data points represent means and error bars represent standard errors of the means. SI_{1mV} = Stimulus intensity to evoke 1-mV motor evoked potentials. MNS = mirror neuron system; SICI = short interval intracortical inhibition; ICF = intracortical facilitation.

the diminished responsiveness of the premotor MNS in medicated schizophrenia patients than neutral action observation sequences used in earlier studies. If replicated, this paradigm has the potential to

reduce the inconsistencies from MNS-experiments that employ diverse experimental tools in distinct clinical and socio-cultural settings. Given the strong impetus towards developing novel treatment strategies that improve social cognition in schizophrenia, this paradigm with better ecological validity may be used as a neuro-marker for social cognition and social skills deficits in monitoring outcomes of such treatment trials.

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Conflict of interest statement

UMM is one of the Associate Editors at Schizophrenia Research and receives honorarium from Elsevier for this service. None of the other authors report any potential conflict of interest.

Contributions

VIB, SSN and RJ recruited study participants and performed the experiments and assessments. UMM conceptualized the study idea, supervised the data collection, performed the analyses and drafted the manuscript. JT also conceptualized the study idea, supervised drafting of protocol, statistical analysis and manuscript writing. SV, SSA and CNK contributed to planning the study methodology, supervised data collection and edited the manuscript.

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