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Schizophrenia Research 102 (2008) 116–121
SCHIZOPHRENIA RESEARCH
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Reduced motor facilitation during action observation in schizophrenia: A mirror neuron deficit?

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Received 20 February 2008; received in revised form 18 March 2008; accepted 2 April 2008
Available online 15 May 2008

Abstract

Impairments in social cognitive functioning are well documented in schizophrenia, however the neural basis of these deficits is unclear. A recent explanatory model of social cognition centers upon the activity of mirror neurons, which are cortical brain cells that become active during both the performance and observation of behavior. Here, we test for the first time whether mirror neuron functioning is reduced in schizophrenia. Fifteen individuals with schizophrenia or schizoaffective disorder and fifteen healthy controls completed a transcranial magnetic stimulation (TMS) experiment designed to assess mirror neuron activation. While patients demonstrated no abnormalities in cortical excitability, motor facilitation during action observation, putatively reflecting mirror neuron activity, was reduced in schizophrenia. Dysfunction within the mirror neuron system may contribute to the pathophysiology of schizophrenia.

Keywords: Schizophrenia; Social cognition; Mirror neurons; Transcranial magnetic stimulation; Primary motor cortex; Premotor cortex

1. Introduction

Individuals with schizophrenia often experience difficulties when processing social information. These social cognitive deficits, including impaired theory of mind and facial emotion processing (Harrington et al., 2005; Shamay-Tsoory et al., 2007), have been linked to functional outcome in schizophrenia (Couture et al., 2006). Despite this, the neural basis of impaired social cognition in schizophrenia is not well understood.

Recent theoretical accounts propose a central role for the mirror neuron system (MNS) in social cognition (Rizzolatti and Craighero, 2004). Mirror neurons are cortical neurons that become active during both the action and observation of a particular motor activity. Comprising a neural network including the superior temporal sulcus, inferior parietal lobe, and inferior frontal gyrus, the MNS was initially thought important for imitation and action understanding. The mirror neuron system, however, also appears to code for the intention of behavior (Iacoboni et al., 2005), and is now

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doi:10.1016/j.schres.2008.04.001

thought to provide the basis for understanding the behavior of a conspecific through an internal "embodied" simulation of their behavior. Accordingly, theoretical perspectives implicate mirror neurons in higher-order social cognitive processes that allow effective social interactions, including empathy, theory of mind, and facial emotion processing (Rizzolatti and Craighero, 2004).

It is therefore reasonable to speculate that schizophrenia could also involve impairment in the MNS; specifically, reduced mirror neuron activation during behavioral observation. Initial imaging evidence indicates that individuals with schizophrenia demonstrate abnormal activation of mirror neuron-related cortical regions whilst viewing emotional stimuli (Quintana et al., 2001), although a recent MEG study reported impaired motor cortical reactivity in schizophrenia (rather than a specific mirror neuron abnormality) (Schurmann et al., 2007).

The current study investigated whether individuals with schizophrenia or schizoaffective disorder demonstrate specific impairment in mirror neuron activation. This was achieved by combining emotionally neutral visual stimuli (demonstrating motor activity) with transcranial magnetic stimulation (TMS) of the primary motor cortex, a method that has been used previously to gauge mirror neuron activity (Fadiga et al., 1995; Maeda et al., 2002). It was hypothesized that schizophrenia would be associated with reduced activity of mirror neurons (i.e., reduced cortical excitability during the observation of motor activity).

2. Method

2.1. Participants

Participants were fifteen individuals diagnosed with either schizophrenia or schizoaffective disorder and fifteen healthy controls (group-matched for age and gender). All clinical participants were medicated (but free of benzodiazepines and anticholingerics for a minimum of four weeks), and had been diagnosed according to DSM-IV criteria. Participants were only included if they demonstrated no significant extra-pyramidal side-effects (i.e., overall score of <10 on the Simpson–Angus Scale and Abnormal Involuntary Movements Scale). Demographic and clinical data are presented in Table 1, while clinical participant data (including diagnosis and medication) is presented in Table 2. This project was approved by the ethics committees of the Alfred and Monash University, and all participants provided informed consent.

2.2. Procedure

Participants completed a transcranial magnetic stimulation (TMS) experiment designed to measure mirror neuron activation. Single pulse TMS (Magstim-200 stimulator; Magstim Company Ltd, UK) was administered to the left primary motor cortex (M1) using a hand-held, 70 mm figure-of-eight coil that was positioned over the scalp. Motor-evoked potentials (MEP) were recorded from the right abductor pollicis brevis (APB) muscle. Resting motor threshold was defined as the minimum stimulation intensity required to evoke a peak-to-peak MEP of >50 μV in at least 3/5 consecutive trials.

Participants were first administered 14 pulses (at 120% RMT) while at rest (baseline MEP). Consistent with Maeda et al. (2002), TMS was then administered during the quasi-random presentation of 10 s video clips that showed right-hand APB activity that was either meaningless (lateral thumb movement to and from index finger), goal-directed (pen grasp), or continuing (hand-writing). Participants were positioned 1.2 m from a 17″ CRT monitor that displayed the visual stimuli. Each of the three videos was presented 14 times, and the TMS pulse was delivered 6 s into each 10 s video clip.

During observation of the movement of the muscle under study, mirror neuron activity is increased in the premotor cortices. Premotor input to the primary motor cortices increases primary motor cortical excitability and results in enhanced MEP amplitude when the corresponding cortical region is stimulated. Accordingly, any increase during action observation (compared with baseline stimulation) represents mirror neuron activation, with goal-directed and meaningful actions often eliciting a further enhanced mirror neuron response.

2.3. Data analyses

TMS trials in which tonic activity (as measured via EMG) was evident were discarded prior to data analysis.

Table 1
Demographic and clinical data

	Schizophrenia	Control
Age	41.80 (8.26)	35.20 (10.13)
Gender (m;f)	12;3	9;6
Years of formal education *	15.00 (3.70)	18.71 (2.56)
PANSS Positive	15.27 (4.46)	–
PANSS Negative	15.00 (4.94)	–
PANSS General Psychopathology	27.47 (3.60)	–
AIMS	1.69 (1.93)	–
Simpson–Angus	4.31 (2.10)	–

* $p<.05$.

Table 2
Clinical participant information

Participant #	Diagnosis	Gender	Age	Medication/dosage
1	Sz	M	42	Amisulpride 400 mg
2	Sz	M	50	Olanzapine 10 mg; Sertraline 50 mg
3	SAD	F	36	Olanzapine 35 mg; Escitalopram 20 mg; Sodium Valproate 1000 mg
4	Sz	M	30	Olanzapine 20 mg; Escitalopram 20 mg
5	SAD	M	52	Risperidone 2 mg; Mirtazipine 35 mg; Venlafaxine 450 mg
6	Sz	M	57	Ziprazidone 80 mg
7	Sz	M	47	Olanzapine 14 mg; Sodium Valproate 1200 mg; Sertraline 1000 mg
8	Sz	M	42	Clozapine 750 mg; Sodium Valproate 300 mg
9	SAD	F	42	Olanzapine 2.5 mg; Ziprazidone 60 mg; Fluoxetine 20 mg
10	Sz	M	40	Clozapine 350 mg; Sodium Valproate 1000 mg; Lithium 450 mg; Aripiprazole 25 mg; Citalopram 10 mg
11	Sz	M	45	Clozapine 325 mg
12	Sz	M	35	Quetiapine 1000 mg
13	Sz	F	27	Quetiapine 300 mg
14	SAD	M	35	Olanzapine 20 mg; Lithium 450 mg; Depot Haloperidol (monthly)
15	Sz	M	47	Olanzapine 10 mg

Tonic activity was evident in very few trials, and there was no difference in the mean number of trials discarded per group (schizophrenia: 1.13; controls: 1.47), $t(28) = -0.20$, $p = .844$. Mean peak-to-peak MEP amplitude was then calculated for each of the four conditions (baseline, and lateral, goal-directed, and continuing APB activity). Of primary interest was each group's level of mirror neuron activation, which was indexed by the MEP amplitude for each of the movement observation conditions relative to the baseline condition:

$$([\text{APB observation mV} - \text{baseline mV}]/\text{baseline mV}) \times 100$$

A greater increase reflects enhanced mirror neuron activation. *T*-tests were used to compare groups on mirror neuron activation. Repeated-measures ANOVA (with simple contrasts) was then used to compare the four TMS conditions (baseline, lateral, goal-directed, and continuing) for each group.

3. Results

There was no difference between the two groups in MEP amplitude for the baseline condition, $t(28) = -1.04$, $p = .305$, indicating comparable cortical excitability when at rest. The MEP percentage increase of each observation condition (relative to the baseline condition) is displayed in Fig. 1. Compared with the schizophrenia group, healthy controls obtained a significantly greater percentage increase for the lateral, $t(28) = -2.56$, $p = .018$, goal-directed, $t(28) = -2.34$, $p = .027$, and continuing, $t(28) = -2.42$, $p = .027$, conditions. This difference is further illustrated by MEP amplitudes following TMS for each of the four conditions (as shown in Fig. 2). Among controls, MEP amplitude was significantly increased (compared with baseline) for the lateral, $F(1,14) = 11.06$, $p = .005$, goal-directed, $F(1,14) = 15.81$, $p = .001$, and continuing, $F(1,14) = 8.90$, $p = .010$, conditions. This facilitatory effect, however, was absent in the schizophrenia group, with no difference in MEP amplitude for the four conditions, $F(3,42) = 1.54$, $p = .236$.

4. Discussion

Individuals with schizophrenia or schizoaffective disorder show reduced MEP facilitation during the observation of action within the stimulated muscle. Action observation is thought to invoke premotor mirror neuron activity and, by consequence, to increase motor cortical excitability. Thus, these results appear to

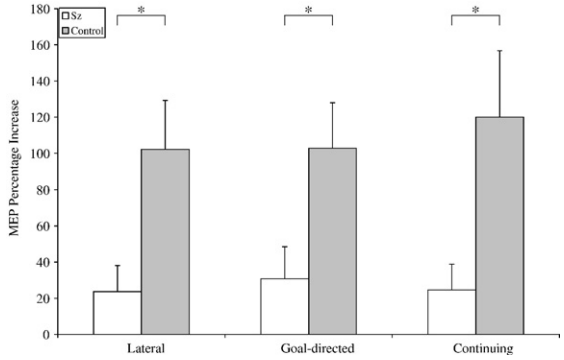

Fig. 1. MEP facilitation (+SEM) during action observation of lateral (thumb movement to and from index finger), goal-directed (pen grasp), and continuing (handwriting) movements. $*p < .05$.

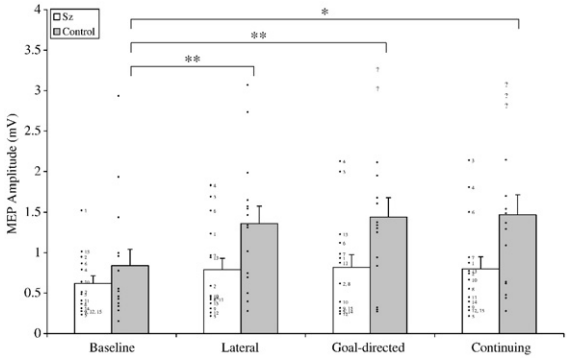

Fig. 2. TMS-induced MEP amplitude (+SEM) during baseline and movement observation conditions (i.e., lateral thumb movement to and from index finger, goal-directed movement [pen grasp], and continuing movement [handwriting]). Individual data points are overlaid (with corresponding participant # from Table 2 for the patient group). $*p<.05$, $**p<.01$.

indicate reduced mirror neuron activity in the premotor cortices of patients with schizophrenia. This is the first demonstration of reduced mirror neuron activation in schizophrenia, although other studies of this population have noted deficits in various aspects of social cognitive processing. Importantly, there was no difference in MEP amplitude for the baseline condition, signaling that this result does not reflect a general dysfunction in cortical excitability.

These novel findings, however, should be interpreted with caution. All patients were medicated, and although the overwhelming majority of research suggests no effect of neuroleptic medication on cortical excitability (e.g., Boroojerdi et al., 1999; Daskalakis et al., 2003; Davey et al., 1997; Fitzgerald et al., 2002, 2003, 2004; Oxley et al., 2004; Ziemann et al., 1997; see Haraldsson et al., 2004 and Stanford et al., in press for reviews), a minority of studies have found that medication is associated with either lower RMT (e.g., Daskalakis et al., 2002) or higher RMT (e.g., Pascual-Leone et al., 2002). If there is a possible effect of medication on cortical excitability, it was not seen in our patients, as there were no differences in our baseline measure of motor cortical excitability. While this suggests that our facilitation results do not reflect medication-induced abnormalities in cortical excitability, the effect of medication on the MNS (in this instance, neuronal activity in the premotor cortex) is not known. Such medication could affect premotor cortical excitability, and the current results may therefore only generalize to medicated patients with schizophrenia and schizoaffective disorder. It is also possible that there are additional factors that influence cortical excitability, such as illness duration and number of psychotic episodes (Eichhammer et al., 2004). Furthermore limitations include a small sample size and the investigation of mirror neurons in only one area of the MNS (i.e., premotor cortex); unfortunately, methods for exploring other regions of the mirror neuron system are somewhat limited.

Nevertheless, on the basis of these results we speculate that reduced function within the mirror neuron system may be a contributory factor to impairments in social cognition observed in schizophrenia. Presumably, reduced mirror neuron activation impairs the ability to experience an internal simulation of other's behavior, and to subsequently infer their likely mental and affective states. It is possible that individuals with schizophrenia instead rely on less-efficient, non-simulation neural networks when engaging in social cognitive processing. Reduced mirror neuron activation has been reported in autism (Dapretto et al., 2006; Theoret et al., 2005), a disorder synonymous with impaired social cognition. The current study, however, indicates that reduced mirror neuron function may not be specific to autism, but also apply to other psychiatric disorders for which social cognitive dysfunction is a defining feature.

While it could be argued that these findings simply reflect reduced attention to the visual stimuli during TMS, this seems unlikely; an experimenter monitored each participant throughout to ensure that visual attention to the stimuli was maintained (i.e., that their gaze was directed toward the screen), and mirror neuron activation has been shown to be a relatively automatic process that is not susceptible to the influence of top-down processes (Iacoboni et al., 2005). Thus, simply watching the visual presentation should be sufficient to induce mirror neuron activation. Despite this, some of the medications taken by the clinical group could affect attention to stimuli, and this possibility should be formally tested in future studies, as should potential visual processing abnormalities in schizophrenia. Given the limitations of the study design, the current findings could also be interpreted as reflecting a more general dysfunction of neural (functional) connectivity (including premotor and primary motor cortex connectivity), which appears common to autism and schizophrenia (Murias et al., 2007; Okugawa et al., 2006), rather than specific dysfunction within mirror neurons. However, even if this were the case, it does not necessarily follow that a mirror neuron explanation of aspects of schizophrenia is irrelevant, but rather that reduced mirror neuron activation in this study is indicative of broader neural deficits. Notwithstanding, reduced mirror neuron activity is likely to have behavioral consequences regardless of whether or not it is the primary deficit. A

connectivity account may go a long way toward explaining the social cognitive similarities in autism and schizophrenia, and a functional imaging study to determine the extent of putative mirror neuron disruption is now warranted. The MNS in schizophrenia should also be examined in the context of aspects of social cognition that might benefit from internal simulation, including theory of mind and facial emotion processing, for which there is substantial evidence of dysfunction in schizophrenia.

Role of Funding Source

Funding for this study was provided by Monash University's Faculty of Medicine, Nursing and Health Sciences. PF was supported by an NHMRC Practitioner Fellowship. PJ was supported by an NHMRC Clinical Training Fellowship. These organisations had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Authors Enticott, Hoy, Herring, and Fitzgerald designed the study, conducted the experiments, undertook statistical analyses and wrote the manuscript. Authors Johnston and Daskalakis contributed to data interpretation of the writing of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

All authors declare that they have no conflicts of interest.

Acknowledgment

The authors wish to thank Ms. Frances Biffin, Ms. Kate Filia, and Ms. Sacha Filia for their assistance with participant recruitment.

References

Boroojerdi, B., Topper, R., Foltys, H., Meincke, U., 1999. Transcallosal inhibition and motor conduction studies in patients with schizophrenia using transcranial magnetic stimulation. Brit. J. Psychiat. 175, 375–379.

Couture, S.M., Penn, D.L., Roberts, D.L., 2006. The functional significance of social cognition in schizophrenia: a review. Schizophrenia Bull. 32, S44–S63.

Dapretto, M., Davies, M.S., Pfeifer, J.H., Scott, A.A., Sigman, M., Bookheimer, S.Y., Iacoboni, M., 2006. Understanding emotions in others: Mirror neuron dysfunction in children with autism spectrum disorders. Nat. Neurosci. 9, 28–30.

Daskalakis, Z.J., Christensen, B.K., Chen, R., Fitzgerald, P.B., Zipursky, R.B., Kapur, S., 2002. Evidence for impaired cortical inhibition in schizophrenia using transcranial magnetic stimulation. Arch. Gen. Psychiatry 59, 347–354.

Daskalakis, Z.J., Christensen, B.K., Chen, R., Fitzgerald, P.B., Zipursky, R.B., Kapur, S., 2003. Effect of antipsychotics on cortical inhibition using transcranial magnetic stimulation. Psychopharmacology 170, 255–262.

Davey, N.J., Puri, B.K., Lewis, S.W., Ellaway, P.H., 1997. Effects of antipsychotic medication on electromyographic responses to transcranial magnetic stimulation of the motor cortex in schizophrenia. J. Neurol. Neurosurg. Psychiatry 63, 468–473.

Eichhammer, P., Wiegand, R., Kharraz, A., Langguth, B., Binder, H., Hajak, G., 2004. Cortical excitability in neuroleptic-naive first-episode schizophrenic patients. Schizophr. Res. 67, 253–259.

Fadiga, L., Fogassi, L., Pavesi, G., Rizzolatti, G., 1995. Motor facilitation during action observation: a magnetic stimulation study. J. Neurophysiol. 73, 2608–2611.

Fitzgerald, P.B., Brown, T.L., Daskalakis, Z.J., Kulkarni, J., 2002. A transcranial magnetic stimulation study of inhibitory deficits in the motor cortex in patients with schizophrenia. Psychiatr. Res. Neuroimmunol. 114, 11–22.

Fitzgerald, P.B., Brown, T.L., Marston, N.A.U., Oxley, T.J., de Castella, A., Daskalakis, Z.J., Kulkarni, J., 2003. A transcranial magnetic stimulation study of abnormal cortical inhibition in schizophrenia. Psychiatr. Res. 118, 197–207.

Fitzgerald, P.B., Brown, T.L., Marston, N.A., Oxley, T., De Castella, A., Daskalakis, Z.J., Kulkarni, J., 2004. Reduced plastic brain responses in schizophrenia: a transcranial magnetic stimulation study. Schizophr. Res. 71, 17–26.

Haraldsson, H.M., Ferrarelli, F., Kalin, N.H., Tononi, G., 2004. Transcranial magnetic stimulation in the investigation and treatment of schizophrenia: a review. Schizophr. Res. 71, 1–16.

Harrington, L., Siegert, R.J., McClure, J., 2005. Theory of mind in schizophrenia: a critical review. Cogn. Neuropsychiatry 10, 249–286.

Iacoboni, M., Molnar-Szakacs, I., Gallese, V., Buccino, G., Mazziotta, J.C., Rizzolatti, G., 2005. Grasping the intentions of others with one's own mirror neuron system. PLoS Biol. 3, e79.

Maeda, F., Kleiner-Fisman, G., Pascual-Leone, A., 2002. Motor facilitation while observing hand actions: Specificity of the effect and role of observer's orientation. J. Neurophysiol. 87, 1329–1335.

Murias, M., Webb, S.J., Greenson, J., Dawson, G., 2007. Resting state cortical connectivity reflected in EEG coherence in individuals with autism. Biol. Psychiatry 62, 270–273.

Okugawa, G., Nobuhara, K., Minami, T., Takase, K., Sugimoto, T., Saito, Y., Yoshimura, M., Kinoshita, T., 2006. Neural disorganization in the superior cerebellar peduncle and cognitive abnormality in patients with schizophrenia: a diffusion tensor imaging study. Prog. Neuro-Psychopharmacol. 30, 1408–1412.

Oxley, T., Fitzgerald, P.B., Brown, T.L., de Castella, A., Daskalakis, Z.J., Kulkarni, J., 2004. Repetitive transcranial magnetic stimulation reveals abnormal plastic response to premotor cortex stimulation in schizophrenia. Biol. Psychiatry 56, 628–633.

Pascual-Leone, A., Manoach, D.S., Birnbaum, R., Goff, D.C., 2002. Motor cortical excitability in schizophrenia. Biol. Psychiatry 52, 24–31.

Quintana, J., Davidson, T., Kovalik, E., Marder, S.R., Mazziotta, J.C., 2001. A compensatory mirror cortical mechanism for facial affect processing in schizophrenia. Neuropsychopharmacology 25, 915–924.

Rizzolatti, G., Craighero, L., 2004. The mirror-neuron system. Annu. Rev. Neurosci. 27, 169–192.

Schurmann, M., Jarvelainen, J., Avikainen, S., Cannon, T.D., Lonnqvist, J., Huttunen, M., Hari, R., 2007. Manifest disease and motor cortex reactivity in twins discordant for schizophrenia. Br. J. Psychiat. 191, 178–179.

Shamay-Tsoory, S.G., Shur, S., Barcai-Goodman, L., Medlovich, S., Harari, H., Levkovitz, Y., 2007. Dissociation of cognitive from affective components of theory of mind in schizophrenia. Psychiat. Res. 149, 11–23.

Stanford, A.D., Sharif, Z., Corcoran, C., Urban, N., Malaspina, D., Lisanby, S.H., in press. rTMS strategies for the study and treatment of schizophrenia: a review. Int. J. Neuropsychopharmacol.

Theoret, H., Halligan, E., Kobayashi, M., Fregni, F., Tager-Flusberg, H., Pascual-Leone, A., 2005. Impaired motor facilitation during action observation in individuals with autism spectrum disorder. Curr. Biol. 15, R84–R85.

Ziemann, U., Tergau, F., Bruns, D., Baudewig, J., Paulus, W., 1997. Changes in human motor cortex excitability induced by dopaminergic and anti-dopaminergic drugs. Electroen. Clin. Neuro. 105, 430–437.