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Mirror neuron deficit in schizophrenia: Evidence from repetition suppression

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ABSTRACT

Background: Schizophrenia is associated with impaired cognition, especially cognition in social contexts. The mirror neuron system (MNS) serves as an important neuronal basis for social cognitive skills; however, previous investigations on the integrity of MNS function in schizophrenia remain approximate.
Methods: We employed a repetition suppression paradigm that allows for measuring neuronal responses to gesture observation and gesture execution. Cross-modal repetition suppression, i.e., adaptation between observe/execute and execute/observe conditions, was defined as the decisive experimental condition characterizing the unique sensori-motor properties of mirror neurons. Event-related potentials (ERPs) were assessed in 15 schizophrenia patients and 15 matched controls.
Results: We isolated an ERP signature of specific adaptation effects to identical hand gestures. Of critical importance, this ERP signature indicated intact intra-modal adaptive pattern, i.e., observe/observe and execute/execute, of comparable magnitude between groups, but deficient cross-modal adaptation, i.e., observe/execute and execute/observe, in schizophrenia patients.
Conclusion: Our data provide robust evidence that pure perception and execution of hand gestures are relatively intact in schizophrenia. In contrast, visuo-motor transformation processes mediated by the MNS seem to be specifically disturbed in schizophrenia. These results unambiguously demonstrate MNS deficits in schizophrenia and extend our understanding of the neuronal bases of social dysfunction in this disorder.

1. Introduction

Impaired social cognition is a common feature of schizophrenia associated with functional outcome (Couture et al., 2006; Smith et al., 2014). Deficits of social interaction have been related to mentalizing/theory-of-mind abilities and empathy, both of which are substantial for social interaction (Corbera et al., 2013; Derntl et al., 2012; Martin et al., 2014). These abilities, in turn, rely on basic social cognitive skills including perception of socially relevant cues like facial expressions and gestures. In contrast to the large literature on face processing in schizophrenia, only few studies focused on processing of gestures and body postures. These studies clearly demonstrate that schizophrenia patients are less accurate in interpreting (Bucci et al., 2008; Thoma et al., 2014) and imitating gestures and body postures (Matthews et al., 2013; Walther et al., 2013a, 2013b).

To successfully process gestures and body postures, the recipient needs to understand both movement and meaning, which neuronally intersect in the mirror neuron system (MNS). Mirror neurons are active during both observing and executing an action (Rizzolatti and Craighero, 2004). Based on this sensori-motor property, an internal motor representation of the observed action (e.g., posture/gesture) is generated, linked with a corresponding affective state, or optionally modulated by higher order cognitive processes. Through this automatic mirroring mechanism, social interaction is facilitated by enabling individuals to understand behavior and intentions of others and thus to imitate or to share emotions (Iacoboni, 2005; Rizzolatti and Sinigaglia, 2007). Following that rationale, it is thought that psychiatric disorders that present with impaired social cognition are likely to exhibit a deficient MNS (Buccino and Amore, 2008; Haker and Rössler, 2009).

Direct evidence of neurons with mirror properties is possible through invasive measurements only (Mukamel et al., 2010). For comprehensible reasons, there are no systematic studies applying invasive methods for assessing the integrity of the MNS in psychiatric disorders. In healthy subjects, mainly functional magnetic resonance imaging (fMRI) was used to show topographically overlapping activations during action observation and imitation tasks (Molenberghs et al., 2012). Using this non-invasive approach, a recent study of Thakkar et al. (2014) found an altered activation pattern in relevant MNS nodes in schizophrenia. Contrarily, Horan et al. (2014a) reported decreased self-reported empathy in correlation with activity of the inferior frontal gyrus (IFG), but failed to show reduced activity within this classical mirror neuron area in schizophrenia patients. Besides these inconsistencies,

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demonstrating overlapping activity, can only provide indirect and preliminary evidence, because this approach cannot exclude spatially overlapping, but distinct neuronal populations (Dinstein et al., 2008). Here, the use of repetition suppression (RS) paradigms constitutes a major advance towards unambiguously and non-invasively characterizing MNS function (Chong et al., 2008; Kilner et al., 2009).

RS describes the reduction of neuronal activity in response to repeated presentation of the same stimulus, e.g., in a paired stimulus design (Grill-Spector et al., 2006). Comparing neuronal response amplitudes to repetitions with non-repetitions then allows for deciding whether the involved neuronal population can be considered sensitive to the repeated stimulus feature. In the mirror neuron context, intra-modal RS effects indicate sensory (observation/observation) or motor (execution/execution) properties, while cross-modal RS (observation/execution; execution/observation) indicates sensori-motor properties that unambiguously characterize mirror neurons (Möhring et al., 2014a), although, as described above, this approach cannot prove the existence of mirror neurons in a strict sense.

So far, the RS paradigm has not been adopted for MNS studies in schizophrenia, which is mainly investigated via transcranial magnetic stimulation to test motor cortex excitability (Enticott et al., 2008; Mehta et al., 2014b) and via mu rhythm suppression in electroencephalography (EEG; Horan et al., 2014b; Mitra et al., 2014; Singh et al., 2011). These studies partially contradict each other, e.g., in terms of decreased (Mitra et al., 2014; Singh et al., 2011) versus increased mu suppression in schizophrenia (Horan et al., 2014b), and, even more important, they investigated surrogates of motor cortex function that is – as an effector organ – associated with, but not part of the MNS (Rizzolatti and Craighero, 2004).

Here, we applied a cross-modal adaptation protocol to investigate MNS activity in schizophrenia for the first time. Adopting the study protocol of Dinstein et al. (2007), our participants observed or executed gestures of the rock–paper–scissors game. According to our previous normative study (Möhring et al., 2014b), we expected to find evidence of reduced mirror neuron activity in mid-latency event-related potentials (ERPs) as expressed by reduced or absent cross-modal RS effects. Specifically, we focused our analysis on the N190 and the P2 components that have been shown to be sensitive to repetitions in our normative study using the same paradigm (Möhring et al., 2014b).

2. Material and methods

2.1. Subjects

Fifteen medicated patients with diagnosis of schizophrenia (11 men, 4 women) and fifteen healthy controls participated in the study. Groups were matched for sex and age (±2 years). Demographic and clinical data of all participants are summarized in Table 1.

Table 1
Demographic and clinical data.

	Schizophrenia (N = 15)	Controls (N = 15)	p
Age (years)	35.60 (7.7)	35.40 (7.9)	.964
Age range (years)	27–57	25–58	–
Education (years)	14.67 (4.6)	17.75 (3.8)	.054
IQ			
Verbal IQ	102.80 (15.1)	102.83 (7.5)	.994
Non-verbal IQ	109.07 (11.4)	112.75 (6.7)	.291
Laterality index	90.67 (14.4)	90.67 (14.4)	1.000
Interpersonal reactivity index			
Perspective taking	17.53 (3.8)	19.46 (3.0)	.136
Fantasizing	16.33 (4.7)	14.77 (3.1)	.295
Empathic concern	20.33 (2.3)	19.85 (3.8)	.706
Personal distress	14.40 (5.4)	11.85 (5.7)	.216

All values are mean values with standard deviation in parenthesis. Between-group differences were assessed by t-tests for independent samples. IQ, intelligence quotient.

All patients were recruited from the outpatient clinic of the Department of Psychiatry, Charité University Medicine Berlin, Campus Benjamin Franklin. They met DSM-IV criteria and had no psychiatric disorder other than schizophrenia and nicotine abuse/dependence. Exclusion criteria were current drug abuse and history of severe medical or neurological disorder including a history of electroconvulsive therapy. Mean duration of illness was 141.23 ± 72.5 months and mean number of episodes was 2.0 ± 1.1. All patients received atypical antipsychotics with a mean chlorpromazine equivalent of 442.04 ± 407.9 mg/d. None of the patients suffered from extrapyramidal motor side effects due to antipsychotic medication within the last 6 months. Clinical symptom severity was assessed with the Positive And Negative Syndrome Scale (PANSS) for schizophrenia: positive symptoms 15.57 (±4.2); negative symptoms 20.43 (±4.9); and general psychopathology 31.29 (±5.5).

Control subjects were recruited via newspaper advertisements. They were screened for mental and physical health by a board certified psychiatrist and were excluded when meeting the criteria of psychiatric disorders according to DSM-IV as determined by semi-structured clinical interviews. Moreover, family history of psychiatric illness, medical or neurological disorders, and current intake of psychotropic drugs led to the exclusion of the study.

All participants completed a multiple choice vocabulary test (MWT; Lehrl et al., 1995) and the German performance testing system (LPS; Horn, 1983) to estimate verbal and non-verbal intelligence, respectively. The Interpersonal Reactivity Inventory (IRI; Davis, 1983) was applied for assessing empathic ability. All participants had normal or corrected-to-normal vision and where right-handed according to the Edinburgh Handedness Inventory (EHI; Oldfield, 1971). The study protocol was approved by the ethics committee of the Charité University Medicine Berlin, and the study was conducted in accordance with the Declaration of Helsinki and its amendments. All subjects gave written informed consent before participating and received monetary reimbursement for their efforts.

2.2. Experimental design

The experiment was carried out in a windowless, dimly lit, electromagnetically shielded, and sound attenuated room. Participants were asked to take a seat in a comfortable chair in front of the screen and to direct their gaze towards the monitor. Standardized instructions were given verbally by the experimenter and visually on the screen. In a training phase comprising 10 trials, participants practiced the task to ensure that they followed instructions correctly. During the whole experimental session, subjects were visually monitored by the experimenter through a window from a neighboring room to control for accurate action execution.

Participants were instructed to passively observe static images of a hand forming gestures of the popular rock–paper–scissors game (observation condition) and to actively execute respective hand gestures as soon as imperative stimuli depicting rock, paper, or scissors were displayed (execution condition). Stimuli were presented on a 24 in. monitor with a viewing distance of approximately 60 cm and a visual angle of approximately 15 × 10° for the outer stimulus contour using Presentation (Neurobehavioral Systems, Albany, CA). On a light gray background, three naturalistic photographs of a right male hand forming rock, paper, or scissors symbols were displayed in the observation condition and three realistic pictures of a rock, paper, or scissors served as imperative stimuli in the execution condition. Stimulus duration was 2000 ms. Stimulus presentation was organized in pairs (S1 = adapter stimulus; S2 = test stimulus) with an inter-stimulus interval (ISI) of 500 ms that was identified as optimal for eliciting maximal RS effects (Harris and Nakayama, 2007; Kuehl et al., 2013). Stimulus pairs were evenly distributed across intra-modal, i.e., purely sensory (observe/observe) or motor (execute/execute) repetitions, and cross-modal trials, i.e., repetitions across modalities (observe/execute or execute/observe). Stimulus pairs showed either identical hand figures/objects (categorized