



Mirror neuron function, psychosis, and empathy in schizophrenia

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ABSTRACT

Processing of social and emotional information has been shown to be disturbed in schizophrenia. The biological underpinnings of these abnormalities may be explained by an abnormally functioning mirror neuron system. Yet the relationship between mirror neuron system activity in schizophrenia, as measured using an electroencephalography (EEG) paradigm, and socio-emotional functioning has not been assessed. The present research measured empathy and mirror neuron activity using an established EEG paradigm assessing the integrity of the Mu rhythm (8–13 Hz) suppression over the sensorimotor cortex during observed and actual hand movement in 16 schizophrenia-spectrum disorder (SSD) participants ($n = 8$ actively psychotic and $n = 8$ in residual illness phase) and 16 age- and gender-matched healthy comparison participants. Actively psychotic SSD participants showed significantly greater mu suppression over the sensorimotor cortex of the left hemisphere than residual phase SSD and healthy comparison individuals. The latter two groups showed similar levels of mu suppression. Greater left-sided mu suppression was positively correlated with psychotic symptoms (i.e., greater mu suppression/mirror neuron activity was highest among subjects with the greater severity of psychotic symptoms). SSD subjects tended to have significantly higher levels of Personal Distress (as measured by the Interpersonal Reactivity Index) than healthy participants. The present study suggests that abnormal mirror neuron activity may exist among patients with schizophrenia during the active (psychotic) phase of the illness, and correlates with severity of psychosis.

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1. Introduction

Social-cognitive and emotion-processing dysfunctions are common features of schizophrenia (Bigelow et al., 2006; Burns, 2006; Shamay-Tsoory et al., 2007; Paradiso et al., 2003; Crespo Facorro et al., 2001) that often appear before the onset of florid psychotic symptoms (Edwards et al., 2001; Brüne, 2005; Bertrand et al., 2008) and that affect functional outcome (Couture et al., 2006). Studies of social cognition in schizophrenia have focused primarily on Theory of Mind (ToM), emotion processing, agency judgment, and empathy (Brunet-Gouet and Decety, 2006; Andreasen et al., 2008; Park et al., 2009). While ToM refers to cognitive aspects of mentalizing or the ability to draw accurate conclusions about others' cognitions and emotions (Frith and Frith, 2003; Keysers and Gazzola, 2006), empathy has both cognitive and affective components and generally refers to the capacity to recognize and share the feelings experienced by another.

One proposed theory for the ability to understand mental states of others is through simulation theory, which is generally hypothesized to be a mechanism for experiencing others' sensory, motor, perceptual, and emotional experiences as if they were one's own (Preston and de Waal, 2002). One proposed mechanism for this simulation approach is through the mirror neuron system, a set of specialized neurons that become active both during motor action and during the observation of another individual's motor action (Rizzolatti and Craighero, 2004; Keysers and Gazzola, 2006). This phenomenon was first described in a series of experiments that used deep brain electrodes in the inferior premotor cortex (F5) of monkeys (di Pellegrino et al., 1992), and was later also shown to include the inferior parietal lobule (IPL) (Keysers and Gazzola, 2006). Numerous functional magnetic resonance imaging (fMRI) studies in humans have since replicated these findings in homologous brain regions such as the posterior inferior frontal gyrus, the rostral inferior parietal lobule, and the precentral gyrus (Rizzolatti and Craighero, 2004; Iacoboni and Mazziotta, 2007). Since its original discovery, studies of mirror neuron system activity have extended to the sensory domains and most recently there have been studies examining the role of the mirror neuron system in the emotional domain. For example, two studies have shown that self-reported empathy is associated with activity in the mirror neuron system (Zaki et al., 2009; Hooker et al., 2010).

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Patients with schizophrenia tend to show dysfunctional empathizing abilities (Brüne, 2005; Montag et al., 2007; Shamay-Tsoory et al., 2007; Benedetti et al., 2009; Derntl et al., 2009; Herold et al., 2009). These may be related to structural and functional deficits in the mirror neuron system and imitation network (Bertrand et al., 2008; Fujiwara et al., 2008; Mier et al., 2010; Park et al., 2011). The mirror neuron system may support appreciation of the self/other boundaries and understanding others' intentions, and its breakdown may originate psychotic symptoms (Frith and Corcoran, 1996; Brüne, 2005; Langdon et al., 2010). For example, people with schizophrenia tend to make false interpretations of other people's intentions, which may result in misperception of benign social cues as threats (paranoid delusions) or hallucinations (Abu-Akel, 2003; Arbib and Mundhenk, 2005; Bentall et al., 2009).

Prior to the discovery of mirror neurons, French epileptologists Gastaut and Bert reported a comparable phenomenon using electroencephalography (EEG) in humans (Gastaut and Bert, 1954). The electrical activity observed was "mu rhythm" (i.e., 8–13 Hz) suppression over bilateral sensorimotor cortices when the person's own hand moved and at about 50% of that by simply watching another person's hand move (Pineda et al., 2000; Muthukumaraswamy et al., 2004; Pfurtscheller et al., 2006). Mu activity is typically highest over the somatosensory cortices during rest and is most strongly suppressed with actual or observed ipsilateral or contralateral hand movements. It is speculated that mu suppression is greatest over the left hemisphere during mimicry of hand and facial movements (Dawson et al., 1985; Cochin et al., 1999). Mu suppression has also been shown to be stronger for watching a live rather than video demonstration of hand movement (Järveläinen et al., 2001). Mu suppression is considered a good estimate of performing and observing hand movement activity in others (Cochin et al., 1998; Babiloni et al., 1999) and is thought to underlie mirror neuron activity (Pineda et al., 2000; Muthukumaraswamy et al., 2004).

This EEG mirror neuron paradigm has been used to examine the functioning of the mirror neuron system in persons with autism (Oberman et al., 2005; Martineau et al., 2008; Oberman et al., 2008). People with autism spectrum disorders exhibit mu suppression during the "self" hand movement condition, but not when watching another person performing this same action (Oberman et al., 2005). This lack of activity in the neural regions engaged during hand moving while viewing others' actions suggests impairment in the functioning of the mirror neuron system. This finding was replicated in children with autism using functional magnetic resonance imaging (fMRI) (Martineau et al., 2010) and in high functioning adults with autism (Bernier et al., 2007).

While people with schizophrenia and autism spectrum disorders tend to exhibit below average performance on cognitive empathy tasks (Baron-Cohen, 2004; Bora et al., 2008), they report on average higher scores on affective empathy questionnaires (as evidenced by high levels of personal distress on the Interpersonal Reactivity Index, IRI) (Lombardo et al., 2007; Montag et al., 2007; Shamay-Tsoory et al., 2007; Dziobek et al., 2008; Lee et al., 2011). This finding is rather notable in light of the fact that in schizophrenia elevated personal distress may actually precede the onset of cognitive empathy deficits (Achim et al., 2011).

Previous studies of mirror neuron function in schizophrenia using various neuroimaging methods have suggested that people with schizophrenia have reduced mirror neuron activity (Enticott et al., 2008) that may relate to lower ability to distinguish between actions of self and others (Schurmann et al., 2007) or empathizing deficits (Varcin et al., 2010). It has also been suggested that the degree of altered empathy and social cognition in schizophrenia may be related to the state of the illness including active psychosis (Andreasen et al., 1986; Frith and Corcoran, 1996; Fahim et al., 2004; Salvatore et al., 2007). The combination of higher than normal self-agency and low self-awareness is then thought to lead to the development of

delusions and psychosis (Frith, 2005). In contrast with this view, other investigators, based on higher than normal empathizing or mirroring abilities found to occur in schizophrenia (Abu-Akel and Bailey, 2000; Quintana et al., 2001), have suggested that intact ToM or ability to empathize is necessary for the development of psychosis (Walston et al., 2000). In a recent fMRI study by Quintana et al. (2001), patients with schizophrenia exhibited greater activation than healthy comparison participants in the face movement areas of the motor and pre-motor cortex when exposed to facial expressions in contrast to color circles.

While people with schizophrenia may show social cognition abnormalities overlapping with autism, it is not clear to what extent the underlying biology in these two conditions also overlaps. Several studies have now shown that people with autism have reduced mirror neuron activity, which may explain the empathy deficits thought to be at the core of social cognition impairment in this disorder (Perkins et al., 2010). To begin to examine the biological basis of empathy in patients with schizophrenia-spectrum disorders (SSD) relative to healthy comparison participants through the measurement of mirror neuron activity, the present research reports on the use of EEG to non-invasively measure mu suppression over the sensorimotor cortices during an observed hand movement paradigm as described by Oberman et al. (2005). Two related but separate hypotheses were tested: (1) whether, as with autism, mu suppression during observed hand movement would be reduced in the SSD group compared to healthy participants; and (2) whether mu suppression during observed hand movement would be atypical only among patients with active psychosis (i.e., a state phenomenon) compared to patients with residual illness and healthy participants. Correlations aimed at determining the extent to which mirror neuron activity covaried with measures of cognitive and affective empathy as well as clinical symptom dimension (i.e., psychotic, disorganized, and negative) scores were also computed.

2. Methods

2.1. Subjects

Initial enrollment included 25 SSD participants, recruited from Dr. Andreasen's longitudinal study or from the inpatient unit at the University of Iowa Hospitals and Clinics; as well as 22 healthy comparison subjects, recruited via local advertisement in the Iowa City community. The diagnosis of SSD (i.e., schizophrenia, schizoaffective disorder, delusional disorder) was made by board certified psychiatrists using criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2000). Exclusionary criteria for SSD subjects included recent use of a long-acting benzodiazepine and self-reported drug or alcohol abuse or dependence within the past three months. Exclusionary criteria for comparison subjects included family history of SSD, other psychotic disorder, or autism; treatment with psychotropic medications, including benzodiazepines, for a psychiatric disorder; substance use within the past three months; and history of seizure, head injury with loss of consciousness greater than five minutes, or other neurological disorder.

Despite specific instruction to remain as still as possible during data acquisition, five SSD datasets and six healthy comparison datasets were eventually excluded due to excessive motion artifact (e.g., eye blinking and jaw movement). Four additional SSD datasets were excluded due to complications related to drowsiness, paranoia, tardive dyskinesia and difficulty focusing/following instructions, respectively. To ensure proper age-matching, we did not enroll healthy comparison participants until we determined that EEG data from the matching SSD dataset was useable. In the end, a total of 16 SSD subjects (including 14 with schizophrenia, one with schizoaffective disorder, and one with delusional disorder) as well as 16 healthy comparison subjects had useable EEG data and were included in our analyses. This study was approved by the Institutional Review Board at the University of Iowa, and written informed consent was obtained from all subjects after the procedures had been fully explained.

2.2. Clinical assessments

All subjects completed clinical interviews using the Scale for the Assessment of Negative and Positive Symptoms (SANS/SAPS) (Andreasen, 1990). Scores from the SANS/SAPS were divided into three dimensions: (1) psychoticism (scale 0–10), based on global ratings of delusions and hallucinations; (2) disorganization (scale 0–15), based on global ratings of bizarre (disorganized) behavior, positive formal thought

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