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Mirror Neuron Dysfunction in Schizophrenia and its Functional Implications: A Systematic Review

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Abstract

Dysfunctional mirror neuron activity (MNA) has been posited to underlie diverse symptoms of schizophrenia (e.g., ego-boundary disturbances, negative symptoms, social cognition impairments and catatonic symptoms). In this paper, we systematically review studies that have empirically compared putative MNA in schizophrenia patients and healthy subjects using different neurophysiological probes. Majority of the studies (n=9) reported reduced MNA in patients. Two each reported either increased MNA or mixed (both increased and decreased) results, while only one study reported normal findings. Reduced MNA was associated with greater negative symptoms and theory of mind deficits. The neurophysiological technique, task paradigms used, specific brain regions studied and laterality did not influence these findings. Further, we propose an overarching model to understand the heterogeneous symptom dimensions of schizophrenia, 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 MNA and the phasic catatonic symptoms, affective instability and hallucinations. Despite being preliminary in nature, evidence of abnormal MNA in schizophrenia reported necessitates more detailed investigation. Future research directions of using this model within the Research Domain Criteria framework of the National Institute of Mental Health are discussed.

Keywords

Mirror neurons; psychosis; neurobiology; social cognition; negative symptoms; self-monitoring

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1 Introduction

Several lines of investigation indicate that schizophrenia is a disorder of the ‘social brain’ (Burns, 2006). These include abnormal cortical activation patterns during social tasks (Abdi and Sharma, 2004; Pinkham et al., 2008), negative symptoms of asociality and avolition (Sergi et al., 2007), and deficits in social cognition (SC) (Mehta et al., 2013d), and social skills (Pinkham and Penn, 2006). These reflect a possible central deficit that expresses in an interpersonal context contributing to substantial deficits in social functioning (Burns, 2006).

Evolutionary theories suggest that schizophrenia exists as a costly trade-off in the evolution of complex social abilities (Burns, 2004). Comparative anatomical studies indicate that hominids evolved complex fronto-temporal and fronto-parietal connections as a result of increasingly complex social selective pressures (Brothers, 1990). This ‘social brain’ is a distributed network of interconnected systems that include both cortical and subcortical structures (Burns, 2004). Rizzolatti and colleagues first discovered mirror neurons in the premotor cortex of macaque monkeys (Di Pellegrino et al., 1992; Gallese et al., 1996). They are collections of neurons that are conceived to be part of this social brain network (Spunt and Lieberman, 2013). These are specialized nerve cells that discharge during both passive observation and active execution, i.e., “mirroring” of goal-directed motor acts (Iacoboni and Dapretto, 2006), thus providing a system for matching observation and execution of motor actions (Gallese et al., 1996) and hence, automatic behavior identification (Spunt and Lieberman, 2013). Functional magnetic resonance imaging (fMRI) studies in humans have demonstrated putative Mirror Neuron Activity (MNA) in the ventral premotor cortex, inferior frontal gyrus, inferior parietal lobule and insula (Molenberghs et al., 2012). These regions receive polysensory inputs through the posterior superior temporal sulcus (Iacoboni and Dapretto, 2006) (figure-1).

This neurophysiological mirror mechanism has generated considerable interest over the past few years, as it is hypothesized to underlie complex cognitive abilities like language, imitation, empathy and understanding goals of observed actions (Corballis, 2004; Gallese, 2003; Iacoboni et al., 1999; Rizzolatti and Sinigaglia, 2010). Concurrently, it has also attracted controversy and sharp criticism as well (Hickok, 2009). Over the years, different methods have been used to quantify MNA in humans. The most definitive and direct method involves single cell recordings from intracranial depth electrodes (Mukamel et al., 2010). However, this procedure is very challenging in humans, more so in those with psychiatric disorders. Various indirect methods of examining putative MNA have been used in clinical populations. These include blood oxygenation level dependent changes measured using fMRI (Iacoboni et al., 2005), blood flow changes using positron emission tomography (PET) (Rizzolatti et al., 1996), mu rhythm suppression using electroencephalography (EEG) (Cochin et al., 1999), alpha band suppression and gamma band amplifications using magnetoencephalography (Kato et al., 2011; Schurmann et al., 2007), motor evoked potential enhancement in transcranial magnetic stimulation (TMS) studies (Fadiga et al., 1995; Maeda et al., 2001) and rapid involuntary facial mimicry in response to facial expressions measured using electromyography (EMG) (Oberman et al., 2009).

In the context of psychiatric disorders, mirror neuron dysfunction has been investigated the most in autism. This is because of the hypothesized ‘broken mirror hypothesis’ and its role in social and language deficits of autism (Iacoboni and Dapretto, 2006; Williams et al., 2004). A systematic review (Hamilton, 2013) of 25 studies examining the integrity of the mirror neuron system in autism overall showed mixed results which were ‘hard to interpret’. It was however reported that these patients showed definite deficits in mirror system activation when specifically assessed using stimuli embedded in an emotional context. Studying mirror neuron dysfunction in schizophrenia is more recent, having evolved only over the past decade. This line of investigation draws motivation from the hypotheses that a dysfunctional mirror neuron system in schizophrenia may underlie specific symptom dimensions across different phases of the illness namely, first-rank symptoms, social cognition deficits and negative symptoms, and catatonic symptoms (Arbib and Mundhenk, 2005; Gallese and Sinigaglia, 2011; Pridmore et al., 2008).

It is crucial, at this juncture, to critically examine the findings available so far from this fairly nascent but evolving field of investigating the neuro-anatomical and neuro-functional abnormalities in schizophrenia. This will help us refine our methods of this investigation, integrate it with existing models of schizophrenia and develop novel treatment targets (Mehta et al., 2013a). In this background, we review existing literature on whether schizophrenia patients have impairments in MNA when compared to healthy comparison subjects, as assessed by experiments using neurophysiological measures.

2 Methods

Two authors (UMM and DA) independently searched published scientific literature in MEDLINE, PsychINFO and GoogleScholar databases with the following search strategy: [(“mirror neuron” OR “mirror system” OR “mirror mechanism”) AND (“schizophrenia” OR “psychosis”)]. This was supplemented by a manual search of bibliographic cross-referencing. Selection criteria were a priori defined to include studies if they: 1. Assessed putative measures of MNA using brain physiology-based investigational techniques, 2. The putative measures of MNA were compared between schizophrenia patients and healthy comparison groups, 3. Patients were diagnosed as schizophrenia or schizoaffective disorder according to the Diagnostic and Statistical Manual of Mental Disorders (American-Psychiatric-Association, 2000) or International Classification of Diseases (World-Health-Organization, 1992). As of May 13th, 2014, we retrieved 65 English language articles published between 2001 and 2014 (figure-2). After their independent searches, both authors who conducted the search arrived at a consensus to incorporate 14 independent data sets that met the selection criteria, in the review. The rest were narrative reviews [e.g., (Arbib and Mundhenk, 2005; Buccino and Amore, 2008)], opinions [e.g., (Arbib, 2007; Pridmore et al., 2008)], studies on healthy populations [e.g., (Leube et al., 2012; Walter et al., 2011)], studies conducted without a control arm of healthy comparison subjects [e.g., (Fahim et al., 2004; Mehta et al., 2012)] and structural brain studies in schizophrenia [e.g., (Bertrand et al., 2008)].

The 14-studies were grouped according to the type of brain-based physiological method used to measure putative MNA (table-1). These included MEG, EEG, EMG TMS, PET and

fMRI. Studies were critically reviewed in terms of subject characteristics, methods and task paradigms, and results in terms of differences in MNA between patients and controls, brain regions of abnormal MNA, effect of medications and the clinical correlates of MNA in patients.

3 Results

3.1 Subject characteristics

Sample sizes ranged from eight (Quintana et al., 2001) to 54 (Mehta et al., 2013c), with a median sample size of 16 subjects each in the patient and control groups. None of the studies reported sample size calculation based on statistical power analysis and the rationale for selecting a particular sample size. The patient group comprised mostly of individuals diagnosed as schizophrenia (DSM-IV). Two studies also included patients with a diagnosis of schizoaffective disorder (Enticott et al., 2008a; Varcin et al., 2010). The proportion of females ranged from 13% (McCormick et al., 2012) to 60% (Varcin et al., 2010), with an average representation of 33% females in the study samples. Mean age of subjects ranged from 32 (Mehta et al., 2013c) to 54 years (Schurmann et al., 2007) and mean duration of illness ranged from ~4 (Mehta et al., 2013c) to ~26-years (Schurmann et al., 2007). Most of the studies reviewed, matched the patients and healthy comparison subjects for age, gender and handedness. Four studies matched the two groups for years of education (Kato et al., 2011; Mehta et al., 2013c; Park et al., 2009; Varcin et al., 2010), two studies each matched them for IQ (Thakkar et al., 2013; Varcin et al., 2010) and parental education (Andreasen et al., 2008; Horan et al., 2014). All except five studies (Andreasen et al., 2008; Horan et al., 2014; Lee et al., 2013; Mitra et al., 2014; Singh et al., 2011), reported analysis of comparing cortical activity during the control condition of their respective tasks between patients and healthy subjects and found no significant differences. Only one study had antipsychotic-naïve schizophrenia patients (Mehta et al., 2013c); two studies recruited antipsychotic-free patients [i.e., off treatment for >6-months (Kato et al., 2011), >3-weeks (Andreasen et al., 2008) or >4 weeks (Mitra et al., 2014)]. The rest examined patients who were on antipsychotic medications. One study had a longitudinal design with putative MNA being assessed at baseline and 1-month after treatment with antipsychotic medications (Mitra et al., 2014).

3.2 Methods and task paradigms

3.2.1 Technique—fMRI (Lee et al., 2013; Park et al., 2009; Quintana et al., 2001; Thakkar et al., 2013) and EEG (Horan et al., 2014; McCormick et al., 2012; Mitra et al., 2014; Singh et al., 2011) were the commonest investigational techniques used. MEG (Kato et al., 2011; Schurmann et al., 2007) and TMS (Enticott et al., 2008a; Mehta et al., 2013c), were each used in two studies. EMG (Varcin et al., 2010) and PET (Andreasen et al., 2008) were employed in one study each. Three studies recorded cortical activity after administering an external stimulation [magnetic (Enticott et al., 2008a; Mehta et al., 2013c) or electrical (Schurmann et al., 2007)]. Rest of the studies recorded cortical activity in the absence of any external stimulation.

3.2.2 Task paradigms—Two types of task-paradigms were used to examine putative MNA:

- (a) *Classical motor tasks:* In these tasks, either a central (e.g., fMRI/EEG/PET) or a peripheral (e.g., TMS/EMG) measure of cortical activity was recorded while subjects observed a goal-directed action (of hands, mouth or facial emotion) relative to control conditions (static images or inanimate motion). The difference in cortical activity across these two conditions gave a measure of MNA. Ten studies (71.42%) used these tasks to obtain measures of MNA (Enticott et al., 2008a; Horan et al., 2014; Kato et al., 2011; McCormick et al., 2012; Mehta et al., 2013c; Mitra et al., 2014; Schurmann et al., 2007; Singh et al., 2011; Thakkar et al., 2013; Varcin et al., 2010).
- (b) *Social tasks:* In these tasks, difference in cortical activity in a priori defined potential mirror neuron regions during a social task (e.g., theory of mind, emotion processing, attributional bias, imitation) and a control task (e.g., reading aloud, visualizing colors, neutral emotions) would give a measure of activity in the mirror neuron system. Four studies employed these tasks in their analysis (Andreasen et al., 2008; Lee et al., 2013; Park et al., 2009; Quintana et al., 2001).

3.3 Mirror neuron activity in schizophrenia

As seen in table-1, all reviewed studies except one (Horan et al., 2014), demonstrated significant differences in putative measures of MNA between schizophrenia patients and healthy controls. Most (n=9) of these studies demonstrated decreased MNA (Enticott et al., 2008a; Kato et al., 2011; Mehta et al., 2013c; Mitra et al., 2014; Park et al., 2009; Schurmann et al., 2007; Singh et al., 2011; Thakkar et al., 2013; Varcin et al., 2010), two each demonstrated either increased MNA (McCormick et al., 2012; Quintana et al., 2001) or mixed results (both increased and decreased) (Andreasen et al., 2008; Lee et al., 2013). Among the studies showing greater MNA in patients, one study demonstrated this in patients having ‘active psychosis’ compared to those with ‘residual psychosis’ or healthy individuals (McCormick et al., 2012). The other study reported this in ‘stable outpatients’ (Quintana et al., 2001).

None of the patient characteristics (e.g., age, gender, education and duration of illness) appeared to specifically influence the findings of decreased or increased MNA. Similarly, none of the methodological aspects (e.g., matching of healthy comparison subjects, technique of investigation and task paradigm used) specifically influenced the findings. Even though two studies demonstrated mixed findings (decreased and increased MNA in patients), these differences were in distinct regions or different voxels in the same anatomical region.

3.3.1 Brain regions of mirror neuron dysfunction

3.3.1.1 Location: Functional MRI, PET and MEG experiments are known to provide good spatial resolution, thus helping in identification of specific brain regions with abnormal activity. In contrast, TMS- and EEG-based techniques have relatively poorer spatial resolution. There were four MNA-specific brain regions in which differences were identified

– inferior frontal gyrus [3-studies (Andreasen et al., 2008; Park et al., 2009; Quintana et al., 2001)], premotor and motor cortices [10-studies (Enticott et al., 2008a; Lee et al., 2013; McCormick et al., 2012; Mehta et al., 2013c; Mitra et al., 2014; Park et al., 2009; Quintana et al., 2001; Schurmann et al., 2007; Singh et al., 2011; Varcin et al., 2010)], inferior parietal lobule [3-studies (Kato et al., 2011; Lee et al., 2013; Thakkar et al., 2013)] and the posterior superior temporal gyrus [2-studies (Lee et al., 2013; Thakkar et al., 2013)]. Across all these regions, more studies demonstrated reduced, rather than greater MNA in the patient group.

3.3.1.2 Laterality: Three studies examined unilateral cortical activity of either the left- (Enticott et al., 2008a; Mehta et al., 2013c) or the right-hemisphere (Varcin et al., 2010) using contralateral peripheral EMG recordings, with or without TMS. All three studies revealed that schizophrenia patients had reduced MNA. Rest of the studies (n= 11) examined bilateral cortical activity. Among these, four studies showed decreased MNA bilaterally (Lee et al., 2013; Mitra et al., 2014; Schurmann et al., 2007; Singh et al., 2011) and in one study there was bilateral increase in MNA (Quintana et al., 2001). The remaining five studies showed significant differences between schizophrenia patients and healthy subjects in right-hemispheric MNA.

3.3.2 Effect of medications—Only one study compared MNA in patients with and without antipsychotic medications and found that the untreated patients had significantly lesser MNA compared to patients on medications, as well as, healthy controls (Mehta et al., 2013c). While most studies did not find any significant association (Horan et al., 2014; Lee et al., 2013; Park et al., 2009; Schurmann et al., 2007; Varcin et al., 2010), one study showed that higher antipsychotic dosages were related to better MNA in the right inferior parietal lobule (Thakkar et al., 2013). The only longitudinal study showed that deficits in putative MNA persist after 1-month treatment with antipsychotic medications, despite there being an improvement in symptoms (Mitra et al., 2014).

3.3.3 Control for attention deficits—It is intuitive to believe that patients may not activate mirror neurons during motor or social tasks because they don't pay attention to the displayed stimuli. Hence, it is imperative that experiments embed the experimental tasks with brief attention tests or use objective methods to ensure sufficient attention. Seven studies reported on methods used to ensure that subjects were adequately attentive during the experimental procedures. Of these, six studies used attention/working-memory tasks embedded in the experimental paradigm, which generated quantifiable responses (Horan et al., 2014; Kato et al., 2011; McCormick et al., 2012; Mitra et al., 2014; Quintana et al., 2001; Singh et al., 2011). Two studies used video-recordings during the experimental procedure, to verify eye-gaze and extraneous movements (Lee et al., 2013; Varcin et al., 2010). Finally, two studies used an experimenter to observe the participants' eye-gaze and behavior during the task (Enticott et al., 2008a; Mehta et al., 2013c). All these studies reported significant differences in MNA in patients after ensuring that subjects attended to the task paradigms.

3.3.4 Functional significance

3.3.4.1 Association with symptoms: These results were mostly part of secondary analyses. Among the eight studies that examined the association between MNA and symptom dimensions, four studies demonstrated that better MNA was associated with lesser negative symptoms (Kato et al., 2011; Lee et al., 2013; Singh et al., 2011; Thakkar et al., 2013), one study showed that greater MNA was associated with more severe auditory hallucinations (McCormick et al., 2012). Three studies found no significant relationship (Horan et al., 2014; Mehta et al., 2013c; Varcin et al., 2010) between measures of MNA and positive/negative symptoms.

3.3.4.2 Association with social cognition: Three studies examined the association between MNA and behavioral performance measures of different social cognition tasks. While three studies reported significant direct associations with social cognition tasks like theory of mind (Mehta et al., 2013c), attributional styles (Park et al., 2009) and perspective taking ability (Horan et al., 2014), one study did not find any significant relationship between MNA and empathy (McCormick et al., 2012). All studies that used SC task paradigms to assess MNA (see above), found significant differences in MNA between patients and controls.

3.3.4.3 Relative comparison of mirror neuron activity and behavioral data between patients and healthy subjects: Eight of the 14 studies analyzed behavioral measures that are posited to be associated with MNA. Most studies showed reduced MNA in patients. They also found the patient group to have greater deficits in social cognition (Mehta et al., 2013c; Park et al., 2009), empathy (Horan et al., 2014) or imitation (Thakkar et al., 2013) tasks. The two studies that showed greater MNA in the patient group, found either better (McCormick et al., 2012) or equal (Quintana et al., 2001) performance on cognitive tasks involving elements of social cognition. Of the two studies that found mixed results, one showed that patients' social cognition was equal to that of controls (Andreasen et al., 2008). The other study showed that patients had impairments in imitating emotions (Lee et al., 2013). However, these studies did not analyze the correlation between behavioral data and putative MNA.

4 Discussion

The concept of mirror neurons in humans, having emerged in the early 1990s has expanded substantially in the late 2000s (Kilner and Lemon, 2013). It would be fair to comment that research examining the mirror neuron system in schizophrenia is still in its infancy. Over the last decade, this inquiry has borrowed from extensive work done in the fields of primatology, developmental psychology, motor cognition, cognitive neuroscience and neurophysiology. The evolutionary significance attached to these neurons, along with their proposed functional roles has unfortunately resulted in many commentaries on the translational utility of these neurons, disproportionate to the evidence for the same. Not surprisingly, some researchers have provocatively attached the sobriquet of “the most hyped concept in neuroscience” to mirror neurons (Jarrett, 2012). Nevertheless, definitive evidence for the presence of mirror neurons in humans through single-cell recording studies (Mukamel et al.,

2010) has provided the necessary fillip to build the foundations of a novel and potentially translational stream of neuropsychiatric research. Moreover, mirror neurons have been identified as the cell type to be examined in relation to social communication and action perception constructs in the Research Domain Criteria (RDoC) initiative of the National Institutes of Mental Health (NIMH-RDoC-Working-Group, 2012).

Given the potential functional implications of this specialized set of neurons in schizophrenia, we examined the available evidence on dysfunction of the mirror neuron system. Two important conclusions could be drawn: First, there is consistent evidence for a dysfunctional mirror neuron system in schizophrenia – most studies showing reduced MNA. It is noteworthy that studies using disparate neuroimaging techniques (MRI, TMS, EEG, MEG and EMG) to study MNA across different cortical regions revealed significant differences between patients and healthy subjects with a fair degree of consistency. Second, there is indication that patients with better MNA have fewer negative symptoms and lesser social cognition deficits (esp. theory of mind). As a corollary, studies that showed reduced MNA in patients also showed greater impairments in social cognition and imitation in them. In contrast, studies that showed greater MNA in patients also showed either normal or greater empathic abilities.

Most studies that found abnormalities in MNA included patients who were on antipsychotic medications. The only study that compared antipsychotic-naïve and medicated patients found that the former had lesser MNA. However, a longitudinal study showed no change in MNA before and after 1-month of treatment with antipsychotic medications. The influence of antipsychotics on MNA may have heuristic and translational implications. It remains to be examined if greater duration of antipsychotic treatment in larger prospective studies has an influence on normalizing MNA deficits. There was no specific influence of age, gender and duration of illness on MNA.

Two types of cell populations seem to be largely specific to primates, with a potential role in social processes – the mirror neurons and the von Economo neurons. Among these ‘social neurons’, the mirror neurons are more amenable to study with contemporary electrophysiological techniques (Brune and Ebert, 2011). The fairly consistent finding of a dysfunctional mirror neuron system in schizophrenia, as reviewed in this paper, is consistent with the social brain hypothesis of schizophrenia (Burns, 2006).

In keeping with Arbib’s proposition (Arbib and Mundhenk, 2005) it was observed that patients with schizophrenia have reduced MNA. This kindles the possibility that schizophrenia patients have an *inherent deficit* in activating their mirror neurons, leading to functional dissociations between action imagination and action enactment, and thus, impairments of self-monitoring and misattribution of agency (Arbib and Mundhenk, 2005; Frith et al., 2000). Preliminary results from a magnetic stimulation study demonstrating poorer MNA in schizophrenia patients with ego-boundary disturbances compared to patients without these symptoms support this hypothesis (Basavaraju et al., 2014).

However, a few studies also reported greater MNA in the patient group, more so, in different voxels of the same anatomical regions. This could be conceptualized as a *compensatory*

mechanism to perform tasks at a satisfactory level (Andreasen et al., 2008; Quintana et al., 2001), or a result of *cortical disinhibition* (Yizhar et al., 2011). The latter proposition draws from emerging evidence on mirror neuron dysfunction in ‘hyper-imitative’ states of autism (Williams et al., 2004). That is to say, imitated/performed actions persist beyond the point of relevance, due to a possible lack of inhibitory control of the anterior frontomedian cortex and the temporoparietal junction over mirror neurons (Brass et al., 2009). Similarly, ‘hyper-empathic’ states could result from absence of inhibitory sensory signals following anesthetic block of an arm, possibly due to MNA reaching the threshold for conscious perception (Case et al., 2010). Preliminary reports suggest that disinhibition of MNA may contribute to catatonic echo-phenomena and affective symptoms (Mehta et al., 2013b; Mehta et al., 2014; Pridmore et al., 2008). Except for the study by Horan et al (Horan et al., 2014), none of the reviewed studies reported associations between MNA and catatonic/affective symptoms. Even though this study (Horan et al., 2014) showed no differences in MNA across patients and controls, one of their MNA measures correlated with greater depression ratings in patients.

The other significant observation in these studies was the association between reduced MNA and negative symptoms of schizophrenia, as well as deficits in theory of mind. This finding partly supports the principles of embodied simulation (Gallese and Sinigaglia, 2011), social projection (Dimaggio et al., 2008) and perception-action coupling (Preston and de Waal, 2002), that are grounded on the premise that mirror neurons become active ‘as if’ we were executing the very same action that we are observing, thus mediating social cognition. Here, the role of mirror mechanisms can be extended from understanding goals underlying motor actions to understanding other key aspects of human social cognition, including empathy and theory of mind. This is reflected in the neural exploitation hypothesis, which suggests that social cognition abilities are produced by the exploitation of brain mechanisms originally evolved for sensory-motor integration (Gallese and Sinigaglia, 2011). Interestingly, *all* studies that used social task paradigms (see above) demonstrated MNA abnormalities in patients. This provides further support for the role of mirror system dysfunction in social cognition deficits. Not surprisingly, studies in normative populations also demonstrate that social cognition abilities are associated with putative mirror neuron activity (MNA) (Baird et al., 2011; Enticott et al., 2008b; Pineda and Hecht, 2009). In addition, structural imaging studies have also reported correlations between social cognitive deficits and reduced gray matter in brain regions with MNA (e.g., inferior parietal lobule, prefrontal and premotor cortices) (Bertrand et al., 2008; Hooker et al., 2011).

A deficit in the ability to produce mental simulations of enjoyable situations or outcomes of one’s own goal-directed actions may also lead to negative symptoms like anhedonia and avolition respectively (Gard et al., 2007; Salvatore et al., 2007; Simpson et al., 2012). In addition, it was demonstrated that schizophrenia patients with affective flattening had greater impairments in emotion recognition than those without (Gur et al., 2006), suggesting common motoric templates (mirror neurons) for expressing one’s own emotions and recognizing emotions in others (Park et al., 2008). Indeed, Lee et al found significant inverse associations between severity of affective flattening and activity in the mirror neuron system in schizophrenia (Lee et al., 2013).

Interestingly, these findings of impaired MNA and its association with negative symptoms and social cognition deficits, aligns equitably with the aberrant frontoparietal networks underlying socio-emotional functioning described in patients with deficit schizophrenia (Rowland et al., 2013). Impairments in this frontoparietal network in deficit schizophrenia have been described using regional cerebral blood flow studies (Lahti et al., 2001), neuropathological studies in postmortem brains (Kirkpatrick et al., 1999; Kirkpatrick et al., 2003) and diffusion tensor imaging studies of white-matter tract (superior and inferior longitudinal fasciculi) abnormalities (Voineskos et al., 2013).

There are several important caveats while interpreting these results. First, intracranial depth electrodes give the most definitive/direct evidence of MNA. Understandably, all the reviewed studies used less direct measures of MNA, and not direct cell recordings. Second, sample size in most of the reviewed studies was rather small (the median sample size was 16). This raises concerns about early positive findings from underpowered studies revealing positive results by chance. This is a crucial caveat especially in the context of this study, which examines a relatively nascent concept in schizophrenia. Indeed, there have been concerns about a publication bias that manifests as an initial wave of studies reporting positive or expected results, followed by a secondary wave of negative results (Button et al., 2013; Ioannidis, 2005). Third, mirror neurons have often been defined as nerve cells that discharge both during active execution of movements, as well as during observation of meaningful movements made by the experimenter (Gallese et al., 1996). Only one study reviewed by us (Schurmann et al., 2007) included analysis of MNA by examining the difference in brain activity during both action observation and execution, relative to rest states. The rest of the studies incorporated only action observation paradigms. It is important to note here that action execution is different from imitation, which includes both action observation as well as execution (Iacoboni et al., 1999). Nevertheless, we have included these studies, as there is satisfactory demonstration on a subject-by-subject basis, of overlapping activation in the human brain during action execution and observation (Gazzola and Keysers, 2009; Rizzolatti et al., 1996). Fourth, most studies that have assessed putative MNA in humans have typically compared brain activity while subjects observe motor actions relative to rest states. We also included studies that assessed brain activity in mirror regions by using paradigms that required subjects to perform social cognition or imitation tasks. The validity of such tasks in detecting MNA is as yet less robustly examined. Fifth, though many studies examined whether subjects were attentive during the action observation tasks, none of the studies have mentioned potential visual processing difficulties that subjects might have faced (e.g., visual acuity and eye-tracking errors). The posterior superior temporal sulcus plays an important role in biological motion perception by transferring visual information from the primary visual cortex to the mirror neuron regions (Allison et al., 2000; Iacoboni and Dapretto, 2006). Two of the studies reviewed also revealed abnormal activations in this region (Lee et al., 2013; Thakkar et al., 2013) during imitation tasks. Thus, while patients had deficits in activating their mirror neurons, whether this deficit was due to abnormalities of mirror neurons *per se* or due to more proximal abnormalities, such as visual perception remains to be elucidated (Enticott et al., 2013). Sixth, the associations between putative MNA and symptom dimensions from these cross-sectional studies should be considered as preliminary, requiring replication from prospective studies. The heterogeneity

of techniques used, task paradigms and differences in reporting results, in terms of statistical tests used, methods to derive a measure of putative MNA, and incomplete provision of mean & standard deviation values of putative MNA measures were some of the constraints that prevented a meta-analysis of these findings. Our inability to get uniform estimate of effect sizes prevented us from examining for publication bias.

Overall, this review suggests a fairly consistent observation of abnormalities of the putative mirror neuron system in schizophrenia. The following questions however need to be investigated in future studies: What mechanism underlies these abnormalities? What is the diagnostic specificity of MNA dysfunction? What specific cognitive processes do they underlie? Will answers to the above questions translate into better treatment for patients?

The variability across studies in our review (reduced and increased MNA) reflects the heterogeneous nature of schizophrenia that cannot be captured by cross-sectional studies with small sample sizes. This provides use with an opportunity to suggest an overarching, integrative model that takes into account diverse symptom manifestations that span the course of the illness. In this model (figure-3), we propose that genetic and environmental factors that contribute to schizophrenia result in an inherent deficit of the mirror neuron system, which contributes to the more *persistent* negative symptoms (e.g., anhedonia, avolition, affective flattening), social cognitive impairments (Kato et al., 2011; Lee et al., 2013; Mehta et al., 2013c; Park et al., 2009; Singh et al., 2011) and self-monitoring (e.g., ego-boundary disturbances and poor insight) deficits (Arbib, 2007; Basavaraju et al., 2014). This deficit state could further trigger a pathological metaplastic reorganization (Keshavan et al., 2014) of the mirror system resulting in an aberrant excessive MNA that contributes to the *phasic* catatonic symptoms (Mehta et al., 2013b; Pridmore et al., 2008), affective instability (Horan et al., 2014; Mehta et al., 2014) and hallucinations (McCormick et al., 2012). This model is potentially verifiable by implementing robust multimodal neuroimaging techniques in concert with novel stimulus paradigms in prospective studies of diverse clinical populations, while taking into consideration the following aspects:

First, combining motor tasks along with social/emotional tasks may yield a stronger MNA signal (Hill et al., 2013; Singer et al., 2004). This method may better differentiate between patients and healthy subjects. Second, use of multiple techniques to derive a putative measure of MNA may be a feasible way ahead. For example, studies combining fMRI with EEG or TMS may provide results with better spatial and temporal resolution. Third, novel stimulus paradigms like cross-modal repetition suppression sequences (Dinstein et al., 2007), can be examined for improved characterization of the nature of MNA abnormalities in schizophrenia. In these sequences, adaptation or repetition suppression of cortical activity is examined. This is done when an action is executed, and then observed, as well as, when an action is observed, and then executed. Since the stimulus feature encoded in mirror neurons is reiterated irrespective of whether the action is observed or executed, this method may help us to attribute the cortical response to a single neuronal population (e.g., mirror neurons) (Dinstein et al., 2007; Grill-Spector et al., 2006; Kilner et al., 2009). Fourth, modulating (enhancing or creating virtual lesions) focal brain activity using repetitive TMS and examining its effects on social information processing will give more definitive evidence (e.g., region specificity, task specificity and chronometry) regarding the role of mirror

neurons in social cognition deficits (Avenanti et al., 2007; Mehta et al., 2013a; Mottaghy et al., 2003). Consistent with this approach, it has been observed that intranasal oxytocin administration also enhances putative MNA measured using EEG (Perry et al., 2010). Fifth, examining MNA in different stages of illness (e.g., symptomatic versus remission) will yield better information regarding specific associations with symptom dimensions. Sixth, examining potential associations between abnormal MNA and specific genome-wide supported psychosis risk variants (e.g., rs1344706 in the gene ZNF804A) in schizophrenia patients will yield novel intermediate phenotypes in understanding its neurobiology (Walter et al., 2011). Seventh, future studies on mirror mechanisms should be supplemented with the investigation of the top-down regulatory mechanisms, which modulate mirror responses (Ganos et al., 2012; Hamilton, 2013). Lastly, in keeping with the proposed RDoC framework (Cuthbert and Insel, 2010; Maj, 2014), mirror neuron dysfunction and its potential cognitive parallels should be examined across diverse psychiatric disorders (e.g., autism, psychotic and affective disorders, and personality disorders) that manifest with stark impairments in social cognition and social functioning.

In conclusion, evidence of mirror neuron system abnormalities provides additional information in identifying critical neuro-anatomical and neuro-functional alterations in schizophrenia. This is a crucial step towards improving our understanding of its neurobiological basis. Future studies examining MNA in schizophrenia may take us closer in improving the diagnostic validity of this complex and heterogeneous disorder, as well as, provide objective targets for treatment research.

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Figure 1.

Representation of the mirror neuron network and its connections

Note: vPMC= Ventral premotor cortex, IFG= Inferior frontal gyrus, pSTS= Posterior superior temporal sulcus, IPL= Inferior parietal lobule. vPMC/IFG, Insula and IPL are regions with mirror neuron activity. The pSTS relays polysensory information to these mirror neuron regions.

Figure 2.
Demonstration of the study-selection process

Figure 3.

Schematic illustration of an overarching model that depicts the role of a dysfunctional mirror neuron system and its metaplastic reorganization to underlie diverse symptom dimensions of schizophrenia

Table 1
Summary of studies examining putative mirror neuron activity in patients with schizophrenia and healthy comparison subjects

Study	Patient characteristics	Healthy comparison subjects	Putative measure of mirror neuron activity	Experimental conditions	Results	MNA	Comments
Magnetoencephalography (MEG)							
Schirmann et al., 2007	11 (~27% ♀) affected siblings from twin pairs discordant for schizophrenia, on antipsychotics; mean (SD) age= 54.4 (4.8) years, illness duration= 25.7 (5.3) years	11 unaffected, same-sex siblings from the same twin pairs	Electrical stimulus-induced rebound suppression in the MEG ~20 Hz rhythm over primary motor cortex during action observation/execution relative to rest states	(a) Rest—resting in a relaxed state (b) Action-observation – manipulation of a small object with the right-hand (c) Action-execution – participants manipulated the small object with their right-hand	Significantly reduced rebound suppression of the ~20 Hz motor cortex rhythm in both hemispheres in patients	✓	No correlation between measure of MNA and antipsychotic doses
Kato et al., 2011	15 (~53% ♀) antipsychotic-free patients (8 never-treated and 7 off-treatment for >6 months); mean (SD) age= 33.4 (6.6) years, illness duration= 68.2 (81.3) months	15 healthy subjects matched for age, gender, education, and handedness	Suppression and amplification of right inferior parietal cortex MEG ~10 Hz (alpha band oscillations) and 25-40 Hz rhythms (gamma band oscillations) respectively during action-observation and rest states	(a) Rest—eyes fixed on a cross (b) Action-observation – mouth opening movements	Patients demonstrated significantly lesser alpha suppression and gamma amplification in right inferior parietal cortex	✓	MNA had a significant inverse association with PANSS total and negative symptom scores
Transcranial Magnetic Stimulation (TMS)							
Enicott et al., 2008	15 (~20% ♀) patients on antipsychotics; mean (SD) age= 41.8 (8.26) years, illness duration not mentioned	15 healthy subjects matched for age and gender	Magnetic stimulation (single-pulse paradigm) induced motor evoked potential (MEP) facilitation during action observation relative to rest states	(a) Rest state – not specified further (b) Action-observation – non-goal directed and goal-directed finger movements	Patients demonstrated significantly lesser MEP facilitation during observation of all actions, relative to the rest state	✓	Group X occasion interaction effect was not reported
Mehta et al., 2013	33 antipsychotic naïve patients (~46% ♀); mean (SD) age= 33.6 (9.74) years, illness duration= 41.12 (44.2) months and 21 patients on antipsychotics (~57% ♀) with mean age= 29.2 (6.6) years, illness duration= 50.4 (42.65) months	45 healthy subjects matched for age, gender, education, and handedness	Magnetic stimulation (two single- and two paired-pulse paradigms) induced motor evoked potential facilitation during action observation relative to rest states	(a) Rest—observing a static image of a hand and lock/key (b) Action-observation – a key held in lateral pinch grasp, performing locking and unlocking movements (video and actual)	Antipsychotic naïve schizophrenia patients had significantly reduced MEP facilitation compared to medicated patients and healthy subjects during action observation relative to the rest state for three	↓*	Significant association of MNA with theory of mind and emotion recognition abilities, but not with positive or negative symptoms

Study	Patient characteristics	Healthy comparison subjects	Putative measure of mirror neuron activity	Experimental conditions	Results	MNA	Comments
Electroencephalography (EEG)							
Singh et al., 2011	20 first episode psychosis patients (~20% ♀), 17 on antipsychotics; mean (SD) age= 19.15 (4.3) years; illness duration not specified	12 healthy subjects matched for age, gender and handedness but not for age	EEG mu rhythm (8-13 Hz) suppression or event related desynchronization over bilateral sensorimotor cortices during action observation, relative to rest states	(a) Rest – inanimate motion (two bouncing balls) (b) Action-observation – hand movements, point light display animation of a jumping human, people playing a game of catch	Patients showed significantly diminished mu wave suppression point light animation condition only. This difference persisted after correcting for the age difference across both groups	↓*	In patients, impaired mu wave suppression correlated with negative symptom severity and poor social adaptation
McCormick et al., 2012	16 patients (~13% ♀), on antipsychotics; mean (SD) age= 37 (9.8) years; illness duration= 15.8 (8.8) years	16 healthy subjects matched for age, gender and handedness	As described in Singh et al., 2011	(a) Rest – watching snow-fall (b) Action-observation – bouncing balls and hand movements (video of own/others' actions, watching actual actions)	Overall, patients and healthy subjects did not differ in mu suppression during any of the action observation conditions relative to rest. Patients with 'active' psychosis (n= 8) had significantly greater mu suppression over the left hemisphere during the 'actual' action observation	↑*	MNA correlated with the SAPS hallucinations score, but not with negative or disorganized symptoms or measures of empathy
Mitra et al., 2014	17 patients (~24% ♀), 16 drug-free (for 4-8 weeks) and 4 drug-naïve, with mean (SD) age= 28.88 (6.7) years; illness duration= 55 (48.32) months	17 healthy subjects matched for age, gender, education and handedness	As described in Singh et al., 201	(a) Rest– White screen on the computer (b) Action-observation –video of handshakes, repeated at one per second	Patients had significantly diminished mu wave suppression during action observation relative to rest. MNA did not change after 1-month of treatment with antipsychotic medications	↓	At 1-month follow-up, MNA deficits persisted despite a significant improvement in psychotic symptoms. Group X occasion interaction effect was not reported
Horan et al., 2014	32 outpatients (~19% ♀), on antipsychotics; mean (SD) age= 47.9 (9.6) years; illness duration= 26.8 (11.5) years	26 healthy subjects matched for age, gender, ethnicity, handedness and parental education, but not for their own education	As described in Singh et al., 201	(a) Rest – inanimate motion (two bouncing balls) (b) Action-observation – hand movements (video of own/others' actions), people playing a game of catch by throwing a ball	Patients and healthy subjects did not differ in mu suppression during any of the action observation	≈	MNA correlated with perspective taking ability and greater depressive symptoms, but not with antipsychotic

Study	Patient characteristics	Healthy comparison subjects	Putative measure of mirror neuron activity	Experimental conditions	Results	MNA	Comments
Electromyography (EMG)							
Varcin et al., 2010	25 patients (~60% 9), on antipsychotics; mean (SD) age= 42.9 (9.43) years; illness duration= 22.7 (10.92) years	25 healthy subjects, matched for age, gender, education and IQ	EMG-measured early (<1 sec) involuntary, rapid, synchronous facial mimicry in facial muscles of emotion expression (corrugator supercilii and zygomaticus major) while observing facial emotion expressions (anger and happiness) in others	Participants observed facial expressions of happiness and anger depicted in four male and four female faces, while EMG was recorded from face muscles corresponding to happiness (zygomaticus major) and anger (corrugator supercilii)	Zygomaticus muscle activity was lower in patients when viewing facial stimuli depicting happiness. Corrugator muscle activity was lower in patients when viewing facial stimuli depicting anger	↓	MNA did not demonstrate any significant associations with SANS/SAPS scores, duration of illness or antipsychotic dose. There was no report of extrapyramidal symptoms that could have influenced the findings
Functional Magnetic Resonance Imaging (fMRI)							
Quintana et al., 2001	8 patients (<25% 9), on antipsychotics; mean (SD) age= 35.22 (10.7), illness duration= 8.5 years	8 healthy subjects matched for gender and handedness, not for age	% BOLD signal changes in specific brain regions while participants <i>correctly</i> performed simple working-memory tasks with facial emotion diagrams or color circles as cues	Block-design paradigms, with four runs – each run comprised of three testing blocks (black visual field) of 24 seconds, interspersed with two sets (colored circles or line drawings of happy/sad face expressions) of six task trials, where in participants were required to match the cues. Each trial consisted of a 0.5 sec cue display, a 7 sec delay (black screen) and then making a choice (2.5 sec) from two given stimuli similar to the cue	Patients showed greater increases in BOLD signal over bilateral premotor cortex (BA6), left motor cortex (BA4) and Broca's area (BA44) while performing working-memory task when the task cues were facial expressions in contrast to color circles	↑	BOLD signal changes during incorrect responses were not included in the analysis. The authors propose that patients may have a compensatory increase in MNA while correctly performing the task
Park et al., 2009	15 patients (socio-demographic details not mentioned), on antipsychotics	16 healthy subjects, matched for age, gender and education	% BOLD signal changes in specific brain regions while perceiving and inferring narrated emotional events compared to neutral conversation	24 blocks: each block comprised of <i>perceiving</i> (30 sec), <i>inferring</i> (20 sec) and selecting appropriate <i>response</i> (10 sec) to ambiguous/certain emotional events narrated by a virtual 'avatar'. Neutral condition was the control condition	While inferring narrated happy events, relative to neutral conversation, patients had reduced activation in the right IFG and right ventral	↓	Deficits in correctly attributing happy events to situational causes were significantly associated with reduced activation of the IFG and VPMC.

Study	Patient characteristics	Healthy comparison subjects	Putative measure of mirror neuron activity	Experimental conditions	Results	MNA	Comments
Lee et al., 2013	15 patients (40% ♀), on antipsychotics; mean (SD) age= 36.7 (8.1), illness duration= 10.9 (7.3) years	16 healthy subjects, matched for age, gender, IQ and handedness	% BOLD signal changes in specific brain regions while expressing happy/sad emotions relative to expressing meaningless emotions	180-trials; each with a <i>watching</i> phase (0.5s) where subjects watched either facial or word stimuli, an <i>expression</i> phase (3.5s), where subjects actively expressed the emotions depicted in the facial/word stimuli and a <i>returning</i> phase (1s) where subjects returned to neutral facial expression after watching a neutral cue on the screen	premotor cortex VPMC	↑↓	Antipsychotic dose did not correlate with MNA in any region SANS affective flattening scores were negatively correlated with activity in the premotor/motor cortex and inferior parietal lobule. Antipsychotic dose did not correlate with MNA in any region. Results for BOLD signal changes during the watching/observation phase of the paradigm were not reported.
Thakkar et al., 2013	16 patients (~44% ♀), on antipsychotics; mean (SD) age= 40.2 (9.1), illness duration= 19.4 (9.9) years	16 healthy subjects matched for age, gender, IQ and handedness, but not for education	% BOLD signal changes in specific brain regions while (a) observing actions and static images and (b) executing imitative and non-imitative actions	Four runs (280s each) of 14 blocks, each block comprising of 3 trials (3 movement conditions in each). The trials required subjects to either <i>observe</i> (a) a hand action of pressing buttons, (b) a static image of a hand and a button box and (c) inanimate X marks, or <i>execute</i> actions (imitative & non-imitative) of pressing buttons while viewing these stimuli	Patients had lesser signal change during imitative relative to non-imitative action in the right inferior parietal lobule and posterior superior temporal sulcus. They also had lesser signal change during action-observation relative to static images in the right inferior parietal lobule	↓	Greater MNA (execution condition) was associated with lesser (especially negative) symptoms. Greater MNA (observation condition) was related to greater socio-occupational dysfunction. Higher antipsychotic dosages were related to MNA in the right inferior parietal lobule. Multiple comparisons were not corrected for
Positron Emission Tomography							
Andreasen et al., 2008	18 patients (~28% ♀); mean (SD) age= 32.5 (11), illness duration= 8.96 (9.3) years. 8 patients were	13 healthy subjects, matched for age, handedness and parental education	Regional cerebral blood flow (rCBF) changes in specific brain regions while	Subjects were asked to compose narrative stories (100s) to explain a given social situation (e.g., make up a story about on why a	Patients had significantly reduced rCBF in the right inferior	↑↓	-

Study	Patient characteristics	Healthy comparison subjects	Putative measure of mirror neuron activity	Experimental conditions	Results	MNA	Comments
	antipsychotic-naïve and the rest were medication-free for 3-weeks before the scan		making theory of mind attributions while composing a story to explain a given social situation, relative to reading aloud a neutral story	lady on the park bench was crying). The control task required subjects to read aloud a neutral story that was presented on the video monitor (40s)	frontal gyrus significantly greater rCBF in the right inferior parietal lobule and right inferior frontal gyrus among other regions		

Note: ↓= reduced in patients, ↓*= reduced in patients when assessed using impoverished stimuli of point light biological motion displays, but comparable to healthy subjects when assessed using tasks with obvious stimuli (Singh et al., 2011) or reduced in antipsychotic-naïve patients (Mehta et al., 2014), but not in patients on medications, ↑= increased in patients, ↑*= increased in a subset of patients with active illness, ≈ = comparable in patients and healthy subjects. All studies used the Diagnostic & Statistical Manual of Mental Disorders (DSM)-IV criteria to diagnose schizophrenia, except Schürmann et al., 2007, which used DSM-III-R. MNA= mirror neuron activity, PANSS= Positive & Negative Syndrome Scale, SAPS= Scale for the Assessment of Positive Symptoms, SANS= Scale for the Assessment of Negative Symptoms, BA= Brodmann area, IFG= inferior frontal gyrus, VPMC= ventral premotor cortex