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Letter to the editor

Motor cortical reactivity to action observation: A biomarker to differentiate mania and schizophrenia?

To the Editor:

Emerging evidence from large-scale genetic (Brainstorm Consortium et al., 2018), brain maturational (Kaufmann et al., 2017) and neurocognitive/neurophysiological (Clementz et al., 2016) investigations highlight shared etiological and pathogenic processes among psychotic and affective disorders. While this is an essential step towards a biological rephrasing of our traditional diagnostic systems, it does not discount the relevance of carefully elicited psychopathology-based clinical assessments. It is here that the relevance of marrying these two approaches – the study of neuroscience-informed, critical biological processes and a systematic transdiagnostic phenomenological characterization of recently-diagnosed patients, not under the influence of psychotropic medications – is likely to maximize true associations between symptoms and their neurobiological underpinnings.

The social brain hypothesis of psychotic disorders, drawing from phylogeny, provides an ontogenic foundation to how key genetic and environmental vulnerabilities transact within critical developmental epochs sculpting the hardwiring of socially relevant brain networks, which manifests as abnormal social behaviors of the psychotic syndrome (Burns, 2006). The mirror neuron system (MNS) is one such social brain network (Di Pellegrino et al., 1992) that has recently gained interest as a neuromarker of social cognition and social behaviors in psychotic and affective disorders (Mehta et al., 2014a; Singh and Feifel, 2013). This network provides a template for matching an observed action to its internal motor representation, thus facilitating not just intention detection, but also imitation – two core processes shaping social behaviors (Gallese et al., 2004; Iacoboni, 1999). Transcranial Magnetic Stimulation (TMS) has been used to study cortical reactivity facilitation during action observation, relative to static image viewing – an indirect measure of putative premotor MNS-activity in humans (Fadiga et al., 1995).

In two earlier experiments, we demonstrated reduced (Mehta et al., 2014b) and elevated (Basavaraju et al., 2018) MNS-activity in untreated patients with schizophrenia and mania respectively. These antithetical state-related variations in putative MNS-activity across psychotic and affective states provide partial empirical support to the dysfunctional MNS model of schizophrenia (Mehta et al., 2014a). However, there are no direct comparisons of MNS-activity across these clinical diagnoses and healthy subjects.

Here, we report a head-to-head comparison of MNS-activity in psychotropic naïve/free patients with a clinical diagnosis of mania ($n = 39$), schizophrenia ($n = 33$) and healthy subjects ($n = 45$) recruited in two experiments (Basavaraju et al., 2018; Mehta et al., 2014b). None of the schizophrenia patients had been treated with psychotropic medications at the time of assessments. In the mania group, 13 were psychotropic naïve, and 27 were psychotropic free (not on psychotropics for ≥two months prior to assessments). Their diagnoses were established according to the Diagnostic and Statistical Manual-IV (American Psychiatric Association, 1994) by a qualified psychiatrist and confirmed using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Healthy subjects were recruited from acquaintances and within the community. All subjects underwent the same TMS-experiment. Left motor cortical reactivity was elicited using TMS and outputs were recorded via electromyography from the right first dorsal interosseous muscle. We obtained recordings while subjects observed three visual cues: (a) static image of a hand and lock/key, (b) video and (c) actual action of locking and unlocking performed by the experimenter using his right FDI muscle (grasping the key in the lateral pinch grip). Ten pulses each of two single-pulse stimuli (excitability) of different intensities [120% of resting motor threshold (120%RMT) and stimulus intensity to evoke 1 mV motor evoked potentials (SI_{1mV})] and two paired-pulse stimuli [short (SICI) and long (LICI) interval intracortical inhibition] were delivered in random sequence according to standard protocols during each of the three visual cues.

The three groups did not vary significantly in terms of their age ($F = 0.89$; $P = 0.4$) and gender ($\chi^2 = 0.24$, $P = 0.8$); however, there were significant group differences for baseline (static image viewing) cortical reactivity measured using 120%RMT ($F = 6.02$; $P = 0.003$), SI_{1mV} ($F = 5.96$; $P = 0.003$), SICI ($F = 4.47$; $P = 0.01$) and LICI ($F = 2.78$; $P = 0.06$ – trend level), perhaps reflecting tonic cortical excitability differences across groups.

We compared MNS-activity across the three groups using two-way RMANOVA, with group-status as the between-subjects factor, cortical reactivity at rest and action-observation states (average of virtual and actual actions) as the within-subjects factor, and baseline cortical reactivity as the covariate. There were significant group × time interaction effects observed across all the four stimulus paradigms, indicating consistently greater facilitation of cortical reactivity during action observation in patients with mania, followed by healthy subjects and then schizophrenia (see Fig. 1).

We report a gradient of putative MNS-activity across mania, healthy and schizophrenia subjects, even after controlling for baseline cortical reactivity differences. The effect sizes (Cohen's *d*) for cortical reactivity facilitation were substantial (0.4 to 0.8) in mania, modest (~0.3) in healthy individuals and nearly absent in schizophrenia (Fig. 1). Given the extensive emerging literature on shared neurophysiological vulnerability between schizophrenia and bipolar disorders (Clementz et al., 2016), the antithetical state-related MNS-responses across these disorders highlights its utility as a biomarker of unique psychopathology. The mechanistic basis for these differences is unclear. It is possible that there is an inherent deficit of MNS-responses in schizophrenia, while the elevated MNS-responses in mania could be a result of prefrontal disinhibition of the MNS. Partial support for this mechanism comes from examining the functional correlates of these opposing neurophysiological brain responses. At a behavioral level, MNS-deficits were associated with social cognition impairments in schizophrenia (Mehta et al.,

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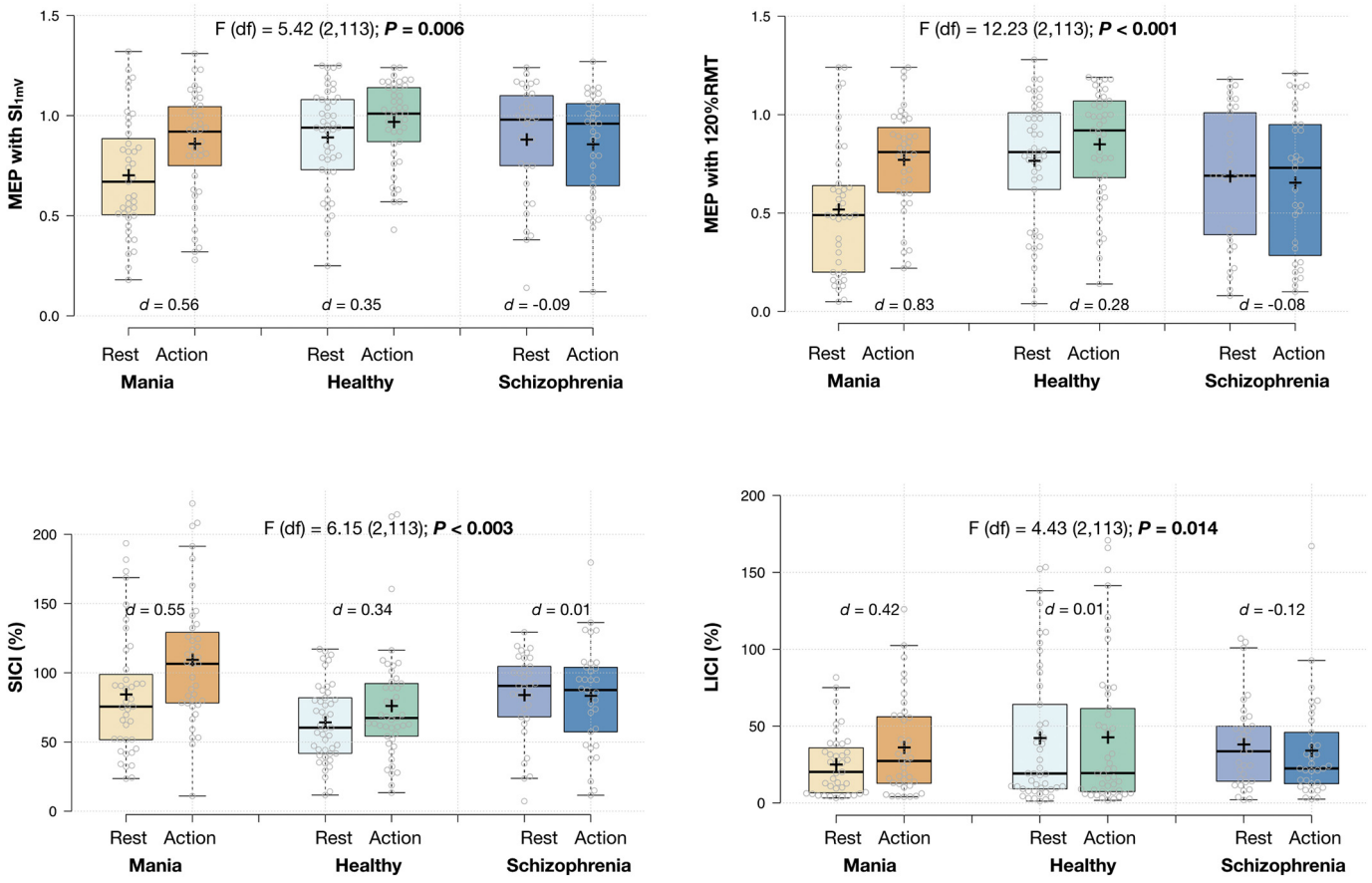

Fig. 1. Box plots demonstrating motor cortical reactivity facilitation during action observation across the three study groups. $S1_{1mV}$ = stimulus intensity to evoked 1 mV motor evoked potential (MEP); 120%RMT = 120% of the resting motor threshold; SICI = short interval intracortical inhibition; LICI = long interval intracortical inhibition; SI_{1mV} and 120%RMT are expressed in millivolts; SICI and LICI are expressed as a percentage of the ratio between the conditioned MEPs and the non-conditioned MEPs with a stimulus intensity of SI_{1mV}; i.e., (conditioned MEP/non-conditioned MEP) × 100. F-statistic reported here is for group × time interaction effects after covarying for baseline (rest) group differences, *df* = degrees of freedom, d = Cohen's d for motor cortical reactivity facilitation from static image viewing (rest) to action observation (action) cues. Center lines show the medians; box limits indicate the 25th and 75th percentiles as determined by R software; whiskers extend to 5th and 95th percentiles, grey circles represent data points; crosses represent sample means.

2014b) and with hyper-imitative echo-phenomena in mania (Basavaraju et al., 2018). The inherent state-related diminution of MNS-activity in schizophrenia could potentially contribute to the impaired attribution of intentions (social cognition), which are building blocks of delusional psychopathology (Bentall et al., 2009). In contrast, mania is associated with impaired prefrontal inhibition of limbic centers (Strakowski et al., 2005) – this might explain their greater MNS-responsiveness and association with behavioral manifestations of disinhibition (echolalia). Replication of these findings in an independent sample, followed by tracking their changes with treatment in longitudinal studies (Mitra et al., 2015), will inform their status as not just diagnostic, but also prognostic biomarkers.

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Declaration of competing interest

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

Contributions

UMM conceptualized the three-way comparison, performed the analyses and drafted the manuscript. UMM and RB collected data and conducted the TMS experiments. JT conceptualized this topic of analysis, supervised data collection and edited the manuscript.

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