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Elevated mirror neuron system activity in bipolar mania: Evidence from a transcranial magnetic stimulation study

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Objectives: The role of the "mirror neuron system" (MNS) in the pathophysiology of mood disorders is not well studied. Given its posited role in the often-impaired socio-emotional processes like intention detection, empathy, and imitation, we compared putative MNS-activity in patients with bipolar mania and healthy comparison subjects. We also examined the association between putative MNS-activity and hyper-imitative behaviors in patients.

Methods: We studied 39 medication-free individuals diagnosed with mania and 45 healthy comparison subjects. TMS-evoked motor cortical reactivity was measured via single- and paired-pulse stimuli (assessing SICI—short and LICI—long interval intracortical inhibition) while subjects viewed a static image and goal-directed actions. Manic symptom severity and imitative behaviors were quantified using the Young's Mania Rating Scale and a modification of the Echolalia Questionnaire.

Results: Two-way repeated measures analysis of variance demonstrated a significant group ×time interaction effect indicating greater facilitation of cortical reactivity during action-observation (putative MNS-activity) in the patient group as compared to the healthy group. While LICI-mediated MNS-activity had a significant association with manic symptom severity (r = 0.35, P = 0.038), SICI-mediated MNS-activity was significantly associated with incidental echolalia scores in a subgroup of 17 patients with incidental echolalia (r = 0.75, P < 0.001).

Conclusions: Our findings demonstrate that putative MNS-activity is heightened in mania, possibly because of disinhibition, and associated with behavioral consequences (incidental echolalia).

KEYWORDS
bipolar disorder, corticospinal facilitation, echolalia, mirror neurons, motor resonance

1 | INTRODUCTION

Bipolar disorder (BD) is a chronic psychiatric disorder with high rates of relapses and recurrences and is among the leading causes of disability worldwide.[1] A sound understanding of its biological substrates will not only help device better treatments but also facilitate identifying a neuroscience-informed and psychopathology-dependent set of biomarkers. The current understanding of brain network disturbances in BD is centered on the theory of diminished prefrontal regulation of anterior limbic emotion processing structures.[2,3] In bipolar mania, this is supported by the observations of a diminished functional connectivity between the prefrontal cortex/anterior cingulate and the amygdala,[3,4] along with an increased functional connectivity of the amygdala with the inferior frontal gyrus[5] and the supplementary motor area.[4] Interestingly, both the inferior frontal gyrus[6] and the supplementary motor area[7] have "mirroring"

properties—the functional attribute of discharging during both action execution and observation. This unique functional property may contribute to human imitation skills based on the direct matching hypothesis,[8,9] which suggests that matching an observed action to its internal motor representation facilitates not just action understanding[10,11] but also imitation. However, there is a top-down regulation of this mirror neuron system (MNS) exerted by the anterior frontomedian and temporoparietal cortices that are critical in controlling automatic mimicry.[12] In fact, it has been proposed that a loss of this prefrontal inhibitory control over the MNS may result in abnormal hyper-imitative[13] or hyper-empathetic[14] behaviors. While there is limited empirical data[15,16] to support the presence of these behaviors in mania, given the shared biological mechanisms (frontal disinhibition), it is possible that these behaviors are relevant to the expression of manic symptoms like increased goal-directed activities, social disinhibition, and overfamiliarity.

Interestingly, the MNS[17,18] is thought to play an important functional role at a neuronal circuit level under the subconstruct of action perception of the "social processes" domain within the Research Domain Criteria (RDoC) framework.[19,20] The behavioral manifestations of this subconstruct include imitation and empathy. Transcranial Magnetic Stimulation (TMS) is a neurophysiological probe that can be used to study motor cortical reactivity facilitation or motor resonance during action-observation, relative to rest states. The degree of this facilitation during action-observation, elicited from the motor cortex, is likely to be influenced by the premotor cortex mirror neuron responses.[21,22] Therefore, TMS-derived motor cortical reactivity facilitation provides a putative, indirect index of premotor MNS-activity.[21,23,24] While this method of quantifying MNS-activity using the degree of motor cortical reactivity facilitation is listed in the RDoC matrix,[20] perhaps owing to its satisfactory millisecond-level temporal resolution,[25] there are important limitations including the inter- and intraindividual variability with TMS-evoked motor potentials,[26,27] the indirect estimate of MNS-activity, and the limited spatial resolution.

Other methods of estimating MNS-activity include electroencephalography (EEG) derived mu-wave suppression and functional magnetic resonance imaging (fMRI). One study employing EEG during an action-observation paradigm demonstrated reduced MNS-activity in euthymic BD patients compared to healthy subjects.[28] Another study using fMRI demonstrated lower activations in the right anterior cingulate, insula, and inferior frontal gyrus—regions that partly overlap with the MNS, when processing emotional compared to neutral control conditions, in euthymic BD compared to healthy subjects.[29] However, MNS-activity has not been studied in patients with BD during the manic state. This will inform specific state-related changes in putative MNS-activity secondary to the frontal disinhibition[3] commonly observed in mania.

In this study, we primarily aimed to compare TMS-measured motor cortical reactivity facilitation during goal-directed action-observation, relative to rest states (a putative measure of MNS-activity), between medication-free/medication-naive patients with mania and healthy comparison subjects. As a secondary aim, we explored

how putative MNS-activity related to manic symptom severity and hyper-imitative echo-phenomena in the patient group. We hypothesized that (a) putative MNS-activity will be high in the manic group compared to healthy subjects and (b) higher putative MNS-activity within the manic group will be positively associated with severity of manic symptoms and hyper-imitative echo-phenomena. We employed two single (of different intensities)- and two paired-pulse TMS paradigms assessing short (SICI) and long (LICI) interval intracortical inhibition, primarily to demonstrate consistency of motor cortical reactivity facilitation during action-observation across diverse physiological mechanisms of cortical excitability—these include cell membrane excitability[30] (single-pulse) and GABA-interneuron effects on pyramidal neuronal output (SICI/LICI).[31,32] Since our primary hypothesis was that the motor cortical reactivity facilitation during action-observation (relative to rest states) would be greater in patients with mania than in healthy subjects, we expected all the four stimulus paradigms to demonstrate this response. That is to say, we anticipated both neuronal membrane-driven and interneuron modulation-driven[33,34] changes in cortical reactivity during action-observation to be higher in patients, indicating a state of disinhibition in mania that overrides different physiological systems of cortical excitability.

2 | MATERIALS AND METHODS

2.1 | Study participants

Forty right-handed,[35] medication-naïve (n = 13; never treated with psychotropics) or medication-free (n = 27; not on any psychotropic medications for ≥2 months prior to assessments) patients diagnosed by a qualified psychiatrist as mania or hypomania according to the Diagnostic and Statistical Manual-IV[36] and confirmed using the Mini-International Neuropsychiatric Interview[37] were recruited for the study from the clinical services of a tertiary care neuropsychiatric hospital in South India. We did not have any symptom severity cut-offs for inclusion of patients. Patients were excluded if they had substance dependence in the last 6 months (other than nicotine), psychoactive substance use in the last 1 week, a clinically diagnosable or self-reported visual or auditory impairment, or need for acute intervention (eg, rescue medications) for severe problem behaviors. The presence of comorbid neurological disorder that predisposed participants for seizures or cognitive impairment, pregnancy, and subjects with metallic implants, cardiac pacemakers, or fulfilling any of the risk factors for TMS procedures as assessed using the TMS Adult Safety Screen[38] were also excluded from the study. All the study participants provided a written informed consent for the study. Patient data were compared to the healthy comparison group recruited from the community for a previous study conducted at the same center with similar methodology.[24] Efforts were made to recruit patients who would match the age, gender, and education profile of the healthy comparison group that was recruited for the earlier study. Of the patients who were screened, ~50% were ineligible as they were not able to consent and cooperate in the
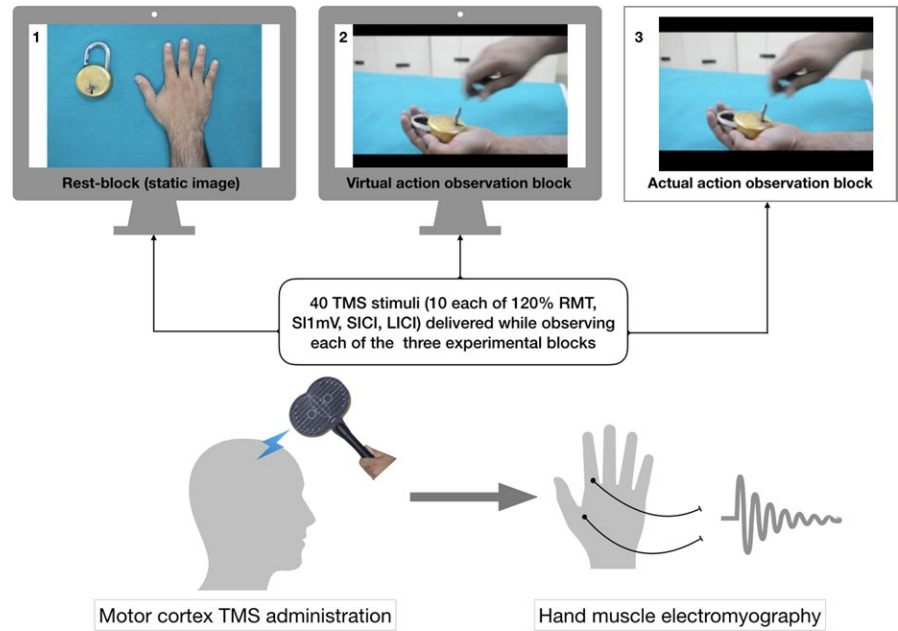
FIGURE 1 Illustration of the TMS experiment. Recording of TMS-evoked motor cortical reactivity while the subject observes three experimental blocks. SI_{1mV} = Stimulus intensity to evoke 1 millivolt motor-evoked potential; RMT = Resting Motor Threshold; SICI and LICI are short and long interval intracortical inhibition [Colour figure can be viewed at wileyonlinelibrary.com]

study. This experiment and the previous experiment (healthy subjects and schizophrenia)[24] were approved by the institutional ethics committee.

2.2 | Assessments

Clinical symptoms were assessed using the Young's Mania Rating Scale (YMRS),[39] an 11-item clinician-rated instrument. *Echo-phenomena* (echolalia and echopraxia) were assessed using a modification of the Echolalia Questionnaire[40] and the echopraxia item from the Bush Francis Catatonia Rating Scale.[41] The echolalia questionnaire (Tables S1 & S2 in supporting information) involves observations for echolalia while the subject is asked a set of 15 questions (automatic or induced echolalia) or when his/her caregiver, sitting nearby, is asked similar 15 questions (ambient or incidental echolalia). Their responses to the 15 questions are rated on a scale from one to six, in an increasing order of severity of echolalia.[40] All patients were rated for manic symptoms and echo-phenomena on the day of the TMS experiment and consenting process by the same clinician. These were assessed either before or after the TMS experiment, based on logistics. Healthy comparison subjects were not rated for manic symptoms and echo-phenomena.

2.3 | TMS experiment to determine Putative MNS-activity

2.3.1 | Setting

The MagPro R30 stimulator with MagOption (MagVenture, Farum, Denmark) was used for the current study as well as the earlier experiment involving the healthy group.[24] Magnetic pulses were delivered with a noncooled figure-of-eight coil (MC-B70); data acquisition and analyses were done using Signal-4 Software (Cambridge Electronic

Devices, Cambridge, UK). The subject was seated on a chair 50 cm away from the observation (13-inch laptop) monitor in a silent room. The area corresponding to the right first dorsal interosseous (FDI) was located in the left motor cortex and motor-evoked potentials (MEP) were recorded by disposable pre-gelled electrodes connected to a 1-channel electromyography amplifier mounted on the MagPro system (MEP-monitor). The minimum stimulation intensity (measured in percentage of maximum machine output) required to evoke a >50 μV (Resting Motor Threshold—RMT) and >1 mV (Stimulation intensity to elicit 1 mV MEP—SI_{1mV}) MEP in the resting right FDI muscle in at least 6 of 10 consecutive trials[42] was defined.

2.3.2 | Cortical reactivity (excitation and inhibition) measurements

Four stimulus paradigms were used in the experimental sessions among which two were single-pulse and two were paired-pulse paradigms:

a 120%RMT: This is a single-pulse parameter. MEPs were recorded using a stimulus intensity of 120% RMT. This stimulus intensity has been most commonly implemented in studying putative MNS activity using TMS.[43,44]

b SI_{1mV}: This is a single-pulse parameter. MEPs were recorded using stimulus intensity to elicit MEPs of approximately 1 mV peak-to-peak amplitude (SI_{1mV}).

c Short Interval Intracortical Inhibition (SICI): This is a dual-pulse TMS paradigm. SICI tests the inhibitory effects of a subthreshold first stimulus at intensity of 80% RMT or the conditioning stimulus (CS) on the amplitude of the test MEP elicited by a suprathreshold second stimulus at SI_{1mV} or the test stimulus (TS), delivered at short interstimulus intervals of 1-5 ms through the same stimulating coil, reflecting inhibitory capacity at the cortical level

.[33,45] SICI at intervals of 2.5-4 ms reflects more purely Gamma Amino Butyric Acid-A (GABA-A) receptor-mediated synaptic inhibition.[46,47]

d Long Interval Intracortical Inhibition (LICI): This is a dual-pulse TMS paradigm. A suprathreshold conditioning stimulus (SI_{1mV}) is given 100 ms before a suprathreshold test stimulus (SI_{1mV}), thus inhibiting the MEP response to the test stimulus (conditioned MEP).[48] It is mediated through the activation of GABA-B receptors.[31]

SICI and LICI were expressed as a percentage of the ratio between the conditioned MEPs and the nonconditioned MEPs with a stimulus intensity of SI_{1mV}; that is, (conditioned MEP/nonconditioned MEP) × 100.[49]

Ten MEP recordings, using SI_{1mV}, 120%RMT, and SICI and LICI stimulus paradigms (total of 40 recordings), were elicited in pseudo-random sequence with 5-second intervals while the subjects observed each of the following three experimental stimulus blocks (Figure 1):

a Actual block: Actual observation of an action being performed involving the FDI. This involved watching, locking, and unlocking of a lock performed by the experimenter with the right hand grasping the key in the lateral pinch grip (holding the key between the side of the index finger and the thumb). This action requires contraction of the FDI to abduct the index finger.[50]

b Virtual block: The subjects observed a video showing the above action.

c Rest block: The subjects observed a still image of a hand and a lock displayed on the monitor.

The sequence of displaying these experimental states to each subject was randomized, with an approximately 5-minute interval between blocks to alter the display logistics. Each of the actual (experimenter performed) and virtual (video display on the laptop monitor) action blocks comprised of 5-second duration goal-directed actions involving the right FDI muscle (locking and unlocking of a lock with a key held in lateral pinch grip) that were looped or repeated 40 times for a total of 200 seconds. The first TMS-pulse was administered to coincide with the first maximum contraction of the right FDI muscle in the above-mentioned action. The preset timing of 5-second pulse-delivery set in the stimulator ensured time locking of the TMS-pulses with the subsequent maximal muscle contractions in the looped (40 times) display of goal-directed actions. The consistency of experimenter-performed actions was ensured by having an experienced experimenter who had performed these actions for our earlier experiment and was trained to maintain the same pace and intensity of the action.

2.3.3 | Ensuring fidelity of the electromyography recordings

In order to guarantee optimal attention allocation during the TMS experiments, subjects were instructed to pay attention to all the stimuli throughout the experiment, also a second experimenter monitored the subjects' behavior. All participants were explicitly asked to remain as relaxed as possible during the TMS experiment. Movements during the recordings were monitored by visual observation; no auditory feedback was used. This was crucial to ensure fidelity of the electromyography recordings. Subjects who moved their hands or any other body parts did not continue the experiment and their data were excluded.

2.4 | Main outcome

The principle used to measure putative MNS-activity is that relative to static image viewing, there is a change in motor cortical reactivity (increased cortical excitability or decreased cortical inhibition) while observing goal-directed actions of the particular muscle from which the electromyography is being recorded. This property of motor cortical reactivity (MCR) facilitation during action-observation (average across virtual and actual action-observation blocks) relative to rest block was the primary outcome measure compared between the two groups (see below under statistical analyses). A percentage of this facilitatory process was calculated for use in correlation analyses with symptom measures[43] as follows:

$$Putative\ MNS - activity = \left\{ \frac{(MCR\ at\ action\text{-}observation - MCR\ at\ rest)}{(MCR\ at\ rest)} \right\} \times 100$$

2.5 | Statistical analyses

To examine cortical reactivity facilitation (putative MNS-activity), we compared the MEP amplitudes (with the four stimulus paradigms described above) during rest and action-observation state using one-way repeated measures analysis of variance (RMANOVA), separately for the two groups. To compare putative MNS-activity between the two groups, we used two-way RMANOVA for each of the four stimulus paradigms. Secondary analyses were performed to examine differences in MNS-activity elicited using virtual- and actual-observation blocks separately. Finally, to examine the association of MNS-activity with YMRS symptom scores and echo-phenomena, we conducted a partial correlation analysis, covarying for baseline differences in cortical reactivity. All statistical tests were two-tailed and significance was set at an error probability of 0.05.

3 | RESULTS

3.1 | Socio-demographic and clinical details

One patient was excluded from the analyses as there were artifacts in the electromyography recordings. The two groups showed no significant difference in age, gender, and marital status, but the healthy comparison group had higher years of education and lower rates of nicotine abuse (Table 1). Two patients of the 39 had hypomania; the rest had mania. Years of education did not have a significant association (Pearson's coefficients ranged from −0.06 to −0.1; all P values >0.3) with any of the measures of putative MNS-activity (percentage of motor cortical reactivity facilitation with action-observation). Therefore, "years of education" was not included as a

TABLE 1 Socio-demographic and clinical characteristics

Variables	Patients (n = 39)	Healthy (n = 45)	t/x^2	P
Age in years	32.82 (11.01)	30.69 (9.58)	0.949	0.345
#Gender				
Male	22 (56)	23 (51)	0.236	0.627
Female	17 (44)	22 (49)		
#Marital status				
Married	25 (64.1)	24 (53)	4.067	0.254
Unmarried	12 (30.8)	21 (47)		
Divorced	1 (2.6)	0		
Widowed	1 (2.6)	0		
Education in years	7.68 (4.82)	13.13 (3.5)	−5.795	**<0.001**
#Nicotine abuse/ dependance	10 (25.6)	2 (4.4)	7.66	**0.006**
YMRS total score	22.36 (7.1)	—	—	—
Duration of current episode (days)	46.13 (48.68)	—	—	—
No. of past episodes				
Any	2.76 (4.12)	—	—	—
Mania	2.32 (3.64)	—	—	—
Depression	0.45 (1.61)	—	—	—
#Drug-naïve patients	13 (30)	—	—	—
#Drug-free patients	27 (70)	—	—	—

Note. All values in mean (SD), except #n(%),YMRS = Young's Mania Rating Scale, drug-naïve = first episode patients who were never treated with medications, drug-free = patients who had a relapse, and were off medications for 2 months or longer. Bold values indicate statistically significant results.

covariate in further analyses to detect group differences in putative MNS-activity.[51]

3.2 | Comparison of baseline TMS parameters between groups

The resting motor threshold (% of maximum machine strength) was not significantly different between the two groups. However, while observing the rest block (static image), patients demonstrated significantly lower MEPs with both the single-pulse stimuli, lower SICI and higher LICI, than healthy subjects (Table 2). Cortical reactivity at baseline for each of the four TMS parameters of interest had a significant correlation (Pearson's coefficients ranged from −0.25 to −0.65; all P values <0.05) with putative MNS-activity, and hence, these baseline parameters were used as covariates in the two-way RMANOVA to explore group differences.

3.3 | Examining motor cortical reactivity facilitation during action-observation (putative MNS-activity) in the two groups

There was a significant facilitation of motor cortical reactivity during action-observation relative to rest states (putative MNS-activity)

as determined by all the four stimulus paradigms in the patient group [one-way RMANOVA (df = 1.38): SI_{1mV} (F = 25.1, P < 0.001); 120%RMT (F = 45.96, P < 0.001); SICI (F = 22.56, P < 0.001); and LICI (F = 10.27, P < 0.001)] even after applying a Bonferroni correction (P < 0.025). Similar facilitation was observed in the healthy comparison group (df = 1.44), [SI_{1mV} (F = 6.54, P = 0.01); 120%RMT (F = 5.72, P = 0.02); SICI (F = 4.16, P = 0.04), and LICI (F = 0.02, P = 0.8)], albeit not significant for the SICI and LICI paradigms after applying a Bonferroni correction (P < 0.025).

3.4 | Comparing motor cortical reactivity facilitation during action-observation (putative MNS-activity) between the two groups

Putative MNS-activity was compared between the two groups using two-way RMANOVA with group status (patients or healthy subjects) as the between-subjects factor, cortical reactivity at rest and action-observation states as the within-subjects factor. This revealed a significant group ×time interaction effect for putative MNS-activity modulated by 120%RMT and LICI stimuli (Table 3) indicating greater putative MNS-activity in the patient group. Since there were baseline (rest block) cortical reactivity differences across all parameters (see Table 2), we controlled for

TABLE 2 Baseline cortical reactivity of patients and healthy comparison subjects

Variables	Patients (n = 39)	Healthy (n = 45)	T	P
SI_{1mV}	53.59 (11.97)	48.4 (11.43)	2.03	**0.046**
RMT	39.36 (8.33)	36.69 (7.23)	1.573	0.12
SICI	84.32 (44.96)	64.12 (27.40)	2.429	**0.018**
LICI	24.99 (20.52)	42.18 (45.38)	−2.285	**0.026**
MEP (SI_{1mV})	0.7 (0.29)	0.89 (0.24)	−3.207	**0.002**
MEP (120%RMT)	0.52 (0.34)	0.77 (0.32)	−3.475	**0.001**

Note. All values are expressed as mean (SD), SI1mV = stimulation intensity in % machine output to elicit 1 millivolt motor-evoked potentials; RMT =Resting Motor Threshold in % machine output to elicit motor-evoked potentials of 50 microvolts, SICI and LICI are short and long interval intracortical inhibition and they were expressed as a percentage of the ratio between the conditioned MEPs and the nonconditioned MEPs with stimulus intensity of SI1mV; that is, (conditioned MEP/noncondi-tioned MEP) × 100; MEP with test pulse (SI1mV) and MEP with 120%RMT =motor-evoked potentials (millivolts) produced by the respective stimulation intensities while viewing the static-block. Bold values indicate statistically significant results.

these differences by including them as covariates in the two-way RMANOVA. A significant group ×time interaction effect was observed indicating higher putative MNS-activity mediation in patients than in healthy subjects by SICI (P = 0.024, partial η^2 = 0.061) and LICI (P = 0.033, partial η^2 = 0.055) paradigms after controlling for these baseline differences. Putative MNS-activity calculated using the SI_{1mV} and 120%RMT paradigms was not significantly different between the two groups after controlling for the baseline differences (Table 3 and Figure 2). Secondary analyses revealed greater putative MNS-activity for both virtual and actual action-observation experimental blocks in the patient group compared to healthy subjects, some of which reached trend-level statistical significance only (table S3 in supporting information).

3.5 | Putative MNS-activity and clinical correlates

Partial correlations were performed to examine how putative MNS-activity related to symptoms, after covarying for the effects of baseline cortical reactivity measurements (rest block). Complete ratings of echo-phenomena were possible in 23 of the 39 patients. In the rest, ratings were not possible because of various pragmatic difficulties including language barriers. While none of the patients demonstrated echopraxia, two patients demonstrated induced echolalia. Incidental echolalia was present in 17 of the 23 patients assessed (~74%). Scores ranged from 20 to 75, with a mean ± SD of 39.65 ± 17.07.

While LICI-mediated putative MNS-activity correlated significantly with the total YMRS score, SICI-mediated putative MNS-activity had a significant association with incidental echo-lalia scores; the latter association persisted even after applying Bonferroni correction (Table 4; scatter plots in Figure S1, supporting information).

Since there was a significantly greater proportion of subjects with nicotine abuse or dependence in the patient group than in the healthy group, we examined if patients with or without nicotine abuse had different putative MNS-activity. None of the single/

TABLE 3 Motor cortical reactivity changes with action-observation in patients and healthy comparison subjects

TMS parameter	Group	Experimental paradigm		F statistics[a]					
		Static	Action-observation	F_1	P	F_2	P	F_3	P
MEP (SI_{1mV})	Patients	0.70 (0.29)	0.86 (0.27)	56.11	**<0.001**	3.14	0.08	0.002	0.96
	Healthy	0.89 (0.25)	0.97 (0.20)						
MEP (120%RMT)	Patients	0.52 (0.34)	0.77 (0.26)	87.65	**<0.001**	10.9	**0.001**	2.132	0.14
	Healthy	0.77 (0.32)	0.85 (0.28)						
SICI (%)	Patients	84.32 (44.96)	110.9 (51.31)	15.25	**<0.001**	3.25	0.075	5.292	**0.02**
	Healthy	64.12 (27.90)	76.01 (41.62)						
LICI (%)	Patients	24.99 (20.52)	36.04 (30.95)	4.237	**0.043**	5.38	**0.023**	4.683	**0.03**
	Healthy	42.19 (45.39)	42.64 (47.98)						

Note. All values in cells are expressed as mean (SD); MEP with test pulse (SI1mV), and MEP with 120%RMT = motor-evoked potentials (in millivolts) produced by the respective stimulation intensities; SICI and LICI are short and long interval intracortical inhibition and they were expressed as a percentage of the ratio between the conditioned MEPs and the nonconditioned MEPs with stimulus intensity of SI1mV; that is, (Conditioned MEP/Nonconditioned MEP) × 100. Bold values indicate statistically significant results.
[a]Two-way repeated measures ANOVA: *F1* = Time effect, *F2* = group ×time interaction effect without covarying for baseline differences with degrees of freedom = (1,82), *F3* = group ×time interaction effect after covarying the effect of baseline cortical reactivity differences with degrees of freedom = (1,81)
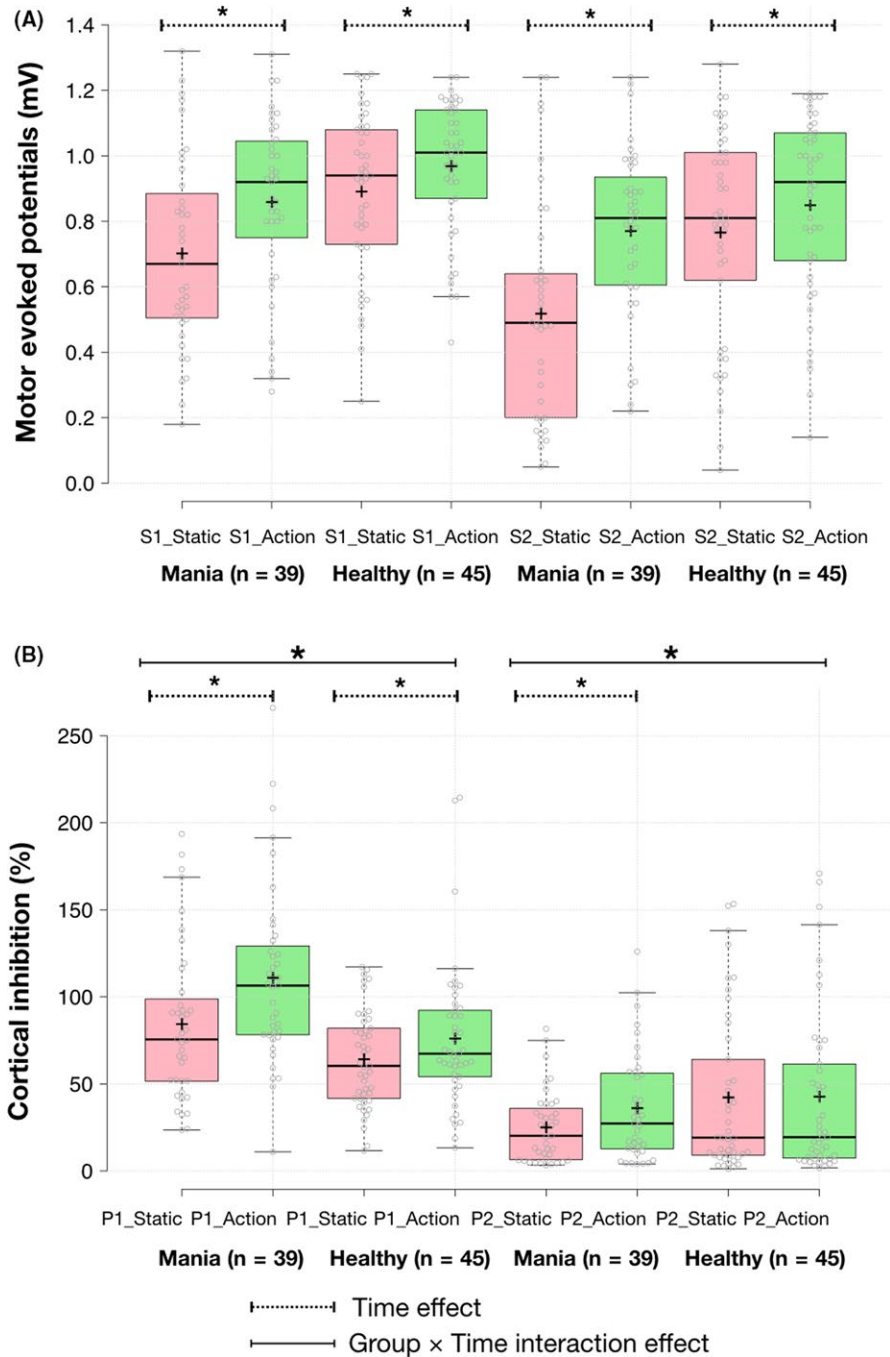
FIGURE 2 Cortical reactivity with action-observation in patients with mania (n = 39) and healthy subjects (n = 45). Boxplots of single (A)- and paired (B)-pulse cortical reactivity measures (S1 = SI_{1mV} or single pulse with stimulus intensity to evoke 1 millivolt motor-evoked potentials, S2 = single pulse with 120% resting motor threshold, P1 = paired pulse using short interval intracortical inhibition and P2 = long interval intracortical inhibition) during static image and goal-directed action-observation stimuli; *$P < 0.05$. Group ×time interaction effects after covarying for baseline differences were significant only for paired pulse TMS measures and not single pulse measures. In the boxplots, the central lines and crosses represent medians and means, respectively; box limits are at 25th and 75th percentiles; whiskers extend 1.5 times the interquartile range from the 25th and 75th percentiles; outliers are represented by black open circles; data points are plotted as gray open circles; pink boxes represent static image observation; and green boxes represent action-observation (average of virtual and actual blocks) [Colour figure can be viewed at wileyonlinelibrary.com]

paired-pulse-mediated putative MNS-activity measures differed between the two patient groups (all T values <0.8; all P values >0.43).

4 | DISCUSSION

The primary finding from this experiment was that patients with mania had significantly greater putative MNS-activity when compared to healthy subjects when measured using paired-pulse TMS paradigms. In addition, in patients with mania, greater putative

MNS-activity was related to more prominent incidental echolalic behavior.

The first inference was made based on the observation of consistent and significantly greater cortical reactivity facilitation during action-observation relative to static image viewing in the patient group. We considered the possibility that this conclusion could be an artifact of a possible overarching hyperexcitable state of mania. However, this is unlikely because generalized hyperexcitability would drive the cortical reactivity during static image viewing as well as during action-observation. Putative MNS-activity is primarily measured as the change in cortical reactivity between

TABLE 4 Relationship of putative MNS-activity with symptom severity of mania and incidental echolalia scores in the patient group

MNS-activity	YMRS score (n = 39)	Incidental echolalia score (n = 17)
MNS-activity_SI$_{1mV}$	−0.15 (−0.444, 0.173)	0.18 (−0.329, 0.608)
MNS-activity_120%RMT	−0.174 (−0.464, 0.149)	0.04 (−0.449, 0.51)
MNS-activity_SICI	0.165 (−0.158, 0.456)	0.751** (0.423, 0.904)
MNS-activity_LICI	0.35* (0.038, 0.599)	-0.013 (−0.491, 0.471)

Note. YMRS, Youngs Mania Rating Scale; MNS, Mirror Neuron System, measured as a percentage of cortical reactivity facilitation from resting to action-observation state; SI1mV = Stimulation intensity to elicit 1 mV motor-evoked potentials, 120%RMT =120% Resting Motor Threshold, SICI, Short Interval Intracortical Inhibition and LICI, Long Interval Intracortical Inhibition, respectively.
*$P < 0.05$.
**$P < 0.001$ (survives Bonferroni correction of $P < 0.006$); all values in cells are Pearson's correlation coefficients (95% confidence intervals), covaried for the respective baseline cortical reactivity measurements.

these two states. This effectively controls for and nullifies the effect of a possible overall hyperexcitable cortical state. Moreover, even after controlling for the baseline cortical reactivity group differences,[52] patients demonstrated greater motor cortical facilitation during action-observation, during the SICI and LICI paradigms. That is to say, despite demonstrating the opposite patterns of baseline abnormalities (low SICI and high LICI), putative MNS-activity in the patient group was higher than that in the healthy subjects. This is a novel finding, which needs to be replicated in future studies. While we expected group differences in putative MNS-activity derived from all four TMS-measures, we found significantly elevated putative MNS-activity in patients when measured using the two paired-pulse paradigms only. Whether this differential between-group putative MNS-response, based on its method of elicitation (single vs paired pulse), is merely reflective of a ceiling effect with single-pulse paradigms or is an indication of a disease-specific frontal disinhibition resulting in GABA-interneuron dysregulation of MNS-activity (as inferred from paired-pulse results) can be examined in future studies.

Two other experiments have reported either reduced[29] or normal[28] activity within the MNS in patients with BD when given emotion attribution and action-observation tasks, respectively. Critically, these prior studies were done in patients with BD studied in euthymic states. Our finding of heightened mirroring response in mania, when put in perspective of these studies in euthymic states,[28,29] suggests a possible state-dependent effect of an exaggerated mirroring response during manic phases of BD. Hence, it is imperative to examine how such neurophysiological measurements of putative MNS-activity relate to various clinical states of bipolar disorder. The relevance of our results is further increased by the fact that our patients were medication naïve or off medications. Therefore, our findings cannot be accounted for by potential medication interactions.

In contrast, our earlier experiment using a similar experimental method in untreated schizophrenia patients demonstrated a deficient MNS response when compared to healthy subjects.[24] If these findings are replicated, TMS-measured putative MNS-activity could potentially be used as a neuromarker to differentiate clinical states

of mania from schizophrenia. Whether this excessive putative MNS-activity is related to the earlier described heightened affective empathy in bipolar disorder patients[15,16] remains to be examined. More importantly, the findings of an exaggerated MNS response in mania add incrementally to the MNS dysfunction model of psychosis[19] which suggests an inherent MNS deficit underlying the persistent negative and cognitive symptoms and a pathological excessive MNS-activity supporting the phasic affective and catatonic symptoms.

Consistent with this hypothesis, we demonstrate enhanced putative MNS-activity in mania compared to healthy subjects. Next, we also demonstrate a positive association between putative MNS-activity mediated by the LICI and SICI stimulus paradigms and global severity of mania and incidental echolalia, respectively; albeit only the latter relationship survived Bonferroni correction. It must be noted that examining clinical correlates of putative MNS-activity was a secondary aim of our study and these associations are to be deemed tentative requiring replication in larger studies. In our earlier analysis of a smaller (n = 20) subsample,[53] we found significant associations between putative MNS-activity measured using all the four stimulus paradigms and symptom severity. We could demonstrate this trend (though not conclusively) only for the LICI paradigm in this larger sample (n = 39). There is a possibility of chance findings from our earlier analysis,[53] owing to a small sample size, reduced power, and hence a potential for poor replicability.[54] Nevertheless, given the heterogeneous nature of mania,[55] it may be worthwhile to examine the relationship between LICI-mediated putative MNS-activity with diverse latent structures of manic symptoms in larger samples.[56,57]

We also observed that putative MNS-activity modulated by SICI, and not baseline SICI was related to incidental echolalia scores in a subset (n = 17) of the patient group. The high (~74%) prevalence of ambient or incidental echolalia, relative to automatic or induced echolalia (~0.08%), is also noteworthy. These two types of echolalia perhaps share distinct mechanisms—while a disconnection of the perisylvian language area from the temporoparietal cortex[58] is associated with induced echolalia, incidental echolalia is associated with lesions in the medial frontal and anterior cingulate cortices leading

to altered control of shared representations (self-other distinctions) and evaluation of outcomes.[59] In addition, treatment of echolalia with lorazepam was associated with a reduction in putative MNS-activity as described in a single case report.[60] Lorazepam primarily acts as a GABA$_A$ receptor facilitator. SICI is thought to be mediated by ionotropic GABA$_A$ receptor neurotransmission[32,61] and was significantly reduced in the patient group. Hence, we surmise that a deficient inhibitory regulation of motor and premotor MNS subsequent to attenuated GABA$_A$-mediated SICI could potentially result in an exaggerated MNS response and the hyper-imitative echo-phenomena thereof. In the context of the manic syndrome, incidental echolalia may be conceptualized as an environmental dependency phenomenon[62] that manifests as a tendency to 'imitate' verbal stimuli in the absence of ongoing control/filtering processes, potentially leading to the more common communicative symptoms of pressured speech and overfamiliarity in an environmentally dependent manner.[63] Such heightened imitative/utilization behaviors have also been described across a range of psychiatric disorders including melancholic depression,[64] mania,[65] schizophrenia,[13] Tourette Syndrome,[66] attention deficit disorder,[67] and autism.[40,68] Together, these findings suggest a need to examine such hyper-imitative behaviors and their relationship to deficient frontal reactive control processes that inhibit MNS-driven imitation after an action is observed[69] within the RDoC initiative using a transdiagnostic approach.[70,71]

Important caveats need to be considered while interpreting our results. First, we employed an indirect measurement of motor cortical reactivity facilitation to infer MNS-activity. Despite providing excellent temporal resolution, TMS does neither provide a direct measurement of MNS-activity nor does it give information from extra-motor areas, many of which are intrinsic to the pathogenesis of mania. Also, since we used four different stimulus paradigms to elicit putative MNS-activity and found group differences in only two of the four paradigms, the influence of a potential type-I error cannot be ruled out. Second, the healthy group data have been taken from an experiment conducted 2 years prior, though from the same center using the same stimulator and by the same experimenters. However, the between-groups baseline cortical reactivity differences have been accounted for statistically, by including them as covariates for detecting MNS-activity group differences. Third, the mean YMRS score in the patient group was 22.36 ± 7.1 indicating mild to moderate symptomatology. This precludes generalizability of our findings to patients with severe mania. Fourth, there was no objective method to ensure attentiveness to the visual stimuli depicted on the monitor. Given the heightened MNS-response in the patient group, poor attentiveness is unlikely to have contributed to this observation. Fifth, an additional visual stimulus of nongoal-directed movement would have improved our inferences by controlling for cortical excitability in response to any movement. Sixth, nicotine use is known to alter cortical reactivity.[72] Even though we have found no difference in putative MNS-activity between patients with and without nicotine abuse, we did not examine the impact of the recency and quantity of nicotine use. Lastly, we report only an association between high putative MNS-activity and incidental echolalia. This does not suggest a causal role for the MNS in hyper-imitative states, as this relationship could reflect an associative learning process[73] that has been unmasked during mania.

A sufficiently large clinical sample, that is not under the influence of psychotropic medications, which can alter TMS cortical reactivity outputs,[74] enhances the validity of our observations. Complementing TMS with functional neuroimaging and electroencephalography will further improve the validity of these findings and enable better temporospatial characterization of responsiveness of the MNS in disease states. The reliability of these findings of diametrically opposite putative MNS-activity across patients with mania and schizophrenia and their extended clinical correlates (eg, relationship to cognition and behavior) may be examined via replication studies. Furthermore, longitudinal studies across the different phases of bipolar disorder (euthymia and depression) and schizophrenia (symptomatic, remission, refractory) will inform how putative MNS-activity varies as a function of symptoms.

In summary, we provide evidence of greater facilitation of motor cortical output during action-observation relative to static image viewing, in drug-free/drug-naïve patients with mania using a TMS experiment. This indicates, albeit in an indirect manner, an aberrant exaggerated responsiveness of the premotor MNS in individuals with mania. These findings were pronounced, even after controlling for baseline cortical reactivity groups differences. Higher putative MNS-activity in the patient group was significantly associated with a greater tendency to verbally imitate parts of a social conversation between two individuals (incidental echolalia). The contribution of a disinhibited MNS to the pathophysiology of manic states is emphasized by demonstrating the first-time link between putative neurophysiological (heightened MNS-activity) and behavioral (incidental echolalia) markers of a disinhibited cortical regulatory state in mania.

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REFERENCES

1. Salomon JA, Haagsma JA, Davis A, et al. Disability weights for the Global Burden of Disease 2013 study. *Lancet Glob Health*. 2015;3:e712-e723.

2. Wegbreit E, Cushman GK, Puzia ME, et al. Developmental meta-analyses of the functional neural correlates of bipolar disorder. *JAMA Psychiatry*. 2014;71:926.

3. Strakowski SM, DelBello MP, Adler CM. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Mol Psychiatry*. 2005;10:105-116.

4. Brady RO, Margolis A, Masters GA, Keshavan M, Öngür D. Bipolar mood state reflected in cortico-amygdala resting state connectivity: A cohort and longitudinal study. *J Affect Disord*. 2017;1:205-209.

5. Cerullo MA, Fleck DE, Eliassen JC, et al. A longitudinal functional connectivity analysis of the amygdala in bipolar I disorder across mood states. *Bipolar Disord*. 2012;14:175-184.

6. Molenberghs P, Cunnington R, Mattingley JB. Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. *Neurosci Biobehav Rev*. 2012;36:341-349.

7. Mukamel R, Ekstrom AD, Kaplan J, Iacoboni M, Fried I. Single-neuron responses in humans during execution and observation of actions. *Curr Biol*. 2010;27:750-756.

8. Iacoboni M. Cortical Mechanisms of Human Imitation. *Science*. 1999;286:2526-2528.

9. Heiser M, Iacoboni M, Maeda F, Marcus J, Mazziotta JC. The essential role of Broca's area in imitation. *Eur J Neurosci*. 2003;17:1123-1128.

10. Gallese V, Keysers C, Rizzolatti G. A unifying view of the basis of social cognition. *Trends Cogn Sci*. 2004;8:396-403.

11. Liepelt R, Cramon D, Brass M. What is matched in direct matching? Intention attribution modulates motor priming. *J Exp Psychol Hum Percept Perform*. 2008;34:578-591.

12. Brass M, Ruby P, Spengler S. Inhibition of imitative behaviour and social cognition. *Philos Trans R Soc B Biol Sci*. 2009;364:2359-2367.

13. Pridmore S, Brune M, Ahmadi J, Dale J. Echopraxia in schizophrenia: possible mechanisms. *Aust N Z J Psychiatry*. 2008;42:565-571.

14. Case LK, Abrams RA, Ramachandran VS. Immediate interpersonal and intermanual referral of sensations following anesthetic block of one arm. *Arch Neurol*. 2010;67:1521-1523.

15. Bodnar A, Rybakowski JK. Increased affective empathy in bipolar patients during a manic episode. *Rev Bras Psiquiatr*. 2017;39:342-345.

16. Shamay-Tsoory S, Harari H, Szepsenwol O, Levkovitz Y. Neuropsychological evidence of impaired cognitive empathy in euthymic bipolar disorder. *J Neuropsychiatry Clin Neurosci*. 2009;21:59-67.

17. Di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G. Understanding motor events: A neurophysiological study. *Exp Brain Res*. 1992;91:176-180.

18. Rizzolatti G, Fadiga L, Matelli M, et al. Localization of grasp representations in humans by PET: 1. Observation versus execution. *Exp Brain Res*. 1996 Sep;111:246-252.

19. Mehta UM, Thirthalli J, Aneelraj D, Jadhav P, Gangadhar BN, Keshavan MS. Mirror neuron dysfunction in schizophrenia and its functional implications: A systematic review. *Schizophr Res*. 2014;160:9-19.

20. NIMH RDoC Working Group. NIMH » Social Processes: Workshop Proceedings [Internet]. 2012. https://www.nimh.nih.gov. https://www.nimh.nih.gov/research-priorities/rdoc/social-processes-workshop-proceedings.shtml. Accessed March 13, 2018.

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

22. Avenanti A, Bolognini N, Maravita A, Aglioti SM. Somatic and motor components of action simulation. *Curr Biol*. 2007;18:2129-2135.

23. Maeda F, Chang VY, Mazziotta J, Iacoboni M. Experience-dependent modulation of motor corticospinal excitability during action-observation. *Exp Brain Res*. 2001;140:241-244.

24. Mehta UM, Thirthalli J, Basavaraju R, Gangadhar BN, Pascual-Leone A. Reduced mirror neuron activity in schizophrenia and its association with theory of mind deficits: evidence from a transcranial magnetic stimulation study. *Schizophr Bull*. 2014;40:1083-1094.

25. Gangitano M, Mottaghy FM, Pascual-Leone A. Modulation of premotor mirror neuron activity during observation of unpredictable grasping movements. *Eur J Neurosci*. 2004;20:2193-2202.

26. Burgess JD, Arnold SL, Fitzgibbon BM, Fitzgerald PB, Enticott PG. A transcranial magnetic stimulation study of the effect of visual orientation on the putative human mirror neuron system. *Front Hum Neurosci*. 2013;7:679.

27. Wilson MT, St GL. Repetitive transcranial magnetic stimulation: a call for better data. *Front Neural Circuits*. 2016;10:57

28. Andrews SC, Enticott PG, Hoy KE, Thomson RH, Fitzgerald PB. Reduced mu suppression and altered motor resonance in euthymic bipolar disorder: Evidence for a dysfunctional mirror system? *Soc Neurosci*. 2016;11:60-71.

29. Kim E, Jung Y-C, Ku J, et al. Reduced activation in the mirror neuron system during a virtual social cognition task in euthymic bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33:1409-1416.

30. Daskalakis ZJ, Christensen BK, Chen R, Fitzgerald PB, Zipursky RB, Kapur S. Evidence for impaired cortical inhibition in schizophrenia using transcranial magnetic stimulation. *Arch Gen Psychiatry*. 2002;59:347-354.

31. McDonnell MN, Orekhov Y, Ziemann U. The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. *Exp Brain Res*. 2006;173:86-93.

32. Ziemann U, Lönnecker S, Steinhoff BJ, Paulus W. The effect of lorazepam on the motor cortical excitability in man. *Exp Brain Res*. 1996;109:127-135.

33. Kujirai T, Caramia MD, Rothwell JC, et al. Corticocortical inhibition in human motor cortex. *J Physiol*. 1993;471:501-519.

34. Strafella AP, Paus T. Modulation of cortical excitability during action-observation: a transcranial magnetic stimulation study. *NeuroReport*. 2000;14:2289-2292.

35. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 1971;9:97-113.

36. American Psychiatric Association. *Diagnostic and statistical Manual of Mental Disorders*, 4th edn. Washington, DC: American Psychiatric Press; 1994.

37. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59 Suppl 20:22–33;quiz 34–57.

38. Keel JC, Smith MJ, Wassermann EM. A safety screening questionnaire for transcranial magnetic stimulation. *Clin Neurophysiol*. 2000;112:720.

39. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133:429-435.

40. Grossi D, Marcone R, Cinquegrana T, Gallucci M. On the differential nature of induced and incidental echolalia in autism. *J Intellect Disabil Res JIDR*. 2013;57:903-912.

41. Bush G, Fink M, Petrides G, Dowling F, Francis A, Catatonia I. Rating scale and standardized examination. *Acta Psychiatr Scand*. 1996;93:129-136.

42. Wasserman E, Ziemann Epstein CM, U, eds. The Oxford handbook of transcranial stimulation (p. 747). Oxford; NY: Oxford University Press; 2008. (Oxford handbooks series).

43. Enticott PG, Hoy KE, Herring SE, Johnston PJ, Daskalakis ZJ, Fitzgerald PB. Reduced motor facilitation during action-observation in schizophrenia: a mirror neuron deficit? *Schizophr Res*. 2008;102:116-121.

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

45. Di Lazzaro V, Restuccia D, Oliviero A, et al. Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits. *Exp Brain Res*. 1998;119:265-268.

46. Fisher RJ, Nakamura Y, Bestmann S, Rothwell JC, Bostock H. Two phases of intracortical inhibition revealed by transcranial magnetic threshold tracking. *Exp Brain Res*. 2002;143:240-248.

47. Hanajima R, Furubayashi T, Iwata NK, et al. Further evidence to support different mechanisms underlying intracortical inhibition of the motor cortex. *Exp Brain Res*. 2003;151:427-434.

48. Valls-Sole J, Pascual-Leone A, Wassermann EM, Hallett M. Human motor evoked responses to paired transcranial magnetic stimuli. *Electroencephalogr Clin Neurophysiol*. 1992;85:355-364.

49. Patuzzo S, Fiaschi A, Manganotti P. Modulation of motor cortex excitability in the left hemisphere during action-observation: a single-and paired-pulse transcranial magnetic stimulation study of self- and non-self-action-observation. *Neuropsychologia*. 2003;41:1272-1278.

50. Geere J, Chester R, Kale S, Jerosch-Herold C. Power grip, pinch grip, manual muscle testing or thenar atrophy - which should be assessed as a motor outcome after carpal tunnel decompression? A systematic review. *BMC Musculoskelet Disord*. 2007;8:114.

51. Kahan BC, Jairath V, Doré CJ, Morris TP. The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. *Trials*. 2014;15:139.

52. Basavaraju R, Sanjay TN, Mehta UM, Muralidharan K, Thirthalli J. Cortical inhibition in symptomatic and remitted mania compared to healthy subjects: A cross-sectional study. *Bipolar Disord*. 2017;19:698-703.

53. Mehta UM, Basavaraju R, Thirthalli J. Mirror neuron activity and symptom severity in drug-naïve mania- A Transcranial Magnetic Stimulation Study. *Brain Stimul*. 2014;7:757-759.

54. Button KS, Ioannidis J, Mokrysz C, et al. Power failure: why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci*. 2013;14:365-376.

55. Post RM, Rubinow DR, Uhde TW, et al. Dysphoric mania. Clinical and biological correlates. *Arch Gen Psychiatry*. 1989;46:353-358.

56. Ruggero CJ, Kotov R, Watson D, Kilmer JN, Perlman G, Liu K. Beyond a single index of mania symptoms: structure and validity of subdimensions. *J Affect Disord*. 2014;161:8-15.

57. Cassidy F, Forest K, Murry E, Carroll BJ. A Factor Analysis of the Signs and Symptoms of Mania. *Arch Gen Psychiatry*. 1998;55:27.

58. Geschwind N, Quadfasel FA, Segarra J. Isolation of the speech area. *Neuropsychologia*. 1968;6:327-340.

59. Berthier ML, Torres-Prioris MJ, López-Barroso D. Thinking on treating echolalia in aphasia: recommendations and caveats for future research directions. *Front Hum Neurosci*. 2017;11:164.

60. Mehta UM, Basavaraju R, Thirthalli J. Mirror neuron disinhibition may be linked with catatonic echo-phenomena: a single case TMS study. *Brain Stimul*. 2013;6:705-707.

61. Di Lazzaro V, Pilato F, Dileone M, et al. GABAA receptor subtype specific enhancement of inhibition in human motor cortex. *J Physiol*. 2006;575(Pt 3):721-726.

62. Human LF. autonomy and the frontal lobes. Part II: Patient behavior in complex and social situations: the "environmental dependency syndrome". *Ann Neurol*. 1986;19:335-343.

63. Raymond LC. Disorders of Thought Are Severe Mood Disorders: the Selective Attention Defect in Mania Challenges the Kraepelinian Dichotomy A Review. *Schizophr Bull*. 2007;34:109-117.

64. Lhermitte F. Imitation and utilization behavior in major depressive states. *Bull Acad Natl Med*. 1993;177:pp. 883-90; discussion 890-892.

65. Abrams R, Catatonia T. A prospective clinical study. *Arch Gen Psychiatry*. 1976;33:579-581.

66. Ganos C, Ogrzal T, Schnitzler A, Münchau A. The pathophysiology of echopraxia/echolalia: Relevance to Gilles De La Tourette syndrome. *Mov Disord*. 2012;27:1222-1229.

67. Archibald S. *Physical Overactivity in Children with ADHD: Utilization Behavior* [Doctoral Dissertation,]. Victoria: BC, Canada; University of Victoria; 2001.

68. Spengler S, Bird G, Brass M. Hyperimitation of Actions Is Related to Reduced Understanding of Others' Minds in Autism Spectrum Conditions. *Biol Psychiatry*. 2010;68:1148-1155.

69. Cross KA, Iacoboni M. Neural systems for preparatory control of imitation. *Philos Trans R Soc B Biol Sci*. 2014;369:20130176-20130176.

70. Insel T, Cuthbert B, Garvey M, et al. Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. *Am J Psychiatry*. 2010;167:748-751.

71. Foss-Feig JH, McPartland JC, Anticevic A, Wolf J. Re-conceptualizing ASD Within a Dimensional Framework: Positive, Negative, and Cognitive Feature Clusters. *J Autism Dev Disord*. 2016 Jan;46:342-351.

72. Strube W, Bunse T, Nitsche MA, et al. Smoking restores impaired LTD-like plasticity in schizophrenia: a transcranial direct current stimulation study. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. 2015;40:822-830.

73. Cook R, Bird G, Catmur C, Press C, Heyes C. Mirror neurons: From origin to function. *Behav Brain Sci*. 2014;37:177-192.

74. Ziemann U, Reis J, Schwenkreis P, et al. TMS and drugs revisited 2014. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol*. 2015;126:1847-1868.

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