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Cortical inhibition in symptomatic and remitted mania compared to healthy subjects: A cross-sectional study

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Abstract

Objectives—Transcranial magnetic stimulation (TMS)-derived cortical reactivity studies provide a unique opportunity to non-invasively study gamma amino butyric acid (GABA)-mediated inhibitory neurotransmission in bipolar disorder (BD). Earlier studies were conducted in smaller samples and on patients who were on medications that can potentially confound the results. We aimed to study short-interval (SICI) and long- interval intracortical inhibition (LICI) in medication-naïve/free symptomatic (manic) BD patients (n=39), first episode mania (FEM) patients who had recently (≤6 months) remitted with treatment (remitted FEM; n = 28) and healthy subjects (HSs; n = 45).

Methods—Resting motor threshold (RMT), stimulation intensity to elicit a 1-mV motor evoked potential (MEP) ($SI_{1\ mV}$), SICI and LICI were measured in three groups using single- and paired-pulse TMS.

Results—Motor thresholds were higher in the manic BD and HS groups compared to the remitted FEM group ($P < .001$). SICI was lower ($P = .026$) but LICI was higher ($P = .044$) in the manic BD and remitted FEM groups compared to the HS group.

Conclusions—Lower motor thresholds in remitted FEM perhaps reflect the effect of treatment, and could be studied as potential prognostic neuromarkers. Inverse findings for SICI (reduced) and LICI (increased) in BD indicate a possible differential involvement of the $GABA_A$ and $GABA_B$ subreceptor systems. These could be trait markers as they are impaired in both mania and euthymia.

Keywords

bipolar disorder; cortical reactivity; $GABA_B$; transcranial magnetic stimulation

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1 Introduction

Inhibitory deficits are noted in individuals with bipolar disorder (BD) when they are assessed using behavioural,[1,2] cognitive,[3,4] neurophysiological[5,6] and brain activation studies.[7] This perhaps reflects impaired activity of the gamma amino butyric acid (GABA) cortical interneurons and their ability to modulate information processing within the corticolimbic system.[8]

Transcranial magnetic stimulation (TMS) is a non-invasive, in vivo method of investigating motor cortical excitability and inhibition in neuropsychiatric disorders.[9] Single- and paired-pulse TMS paradigms applied to the motor cortex have helped to identify neurophysiological substrates underlying cortical reactivity. While single-pulse TMS-derived resting motor threshold (RMT) and cortical silent period (CSP) reflect motor cortical excitability and inhibition, respectively, paired-pulse TMS can elicit cortical inhibition responses measured using short-interval (SICI) and long-interval (LICI) intracortical inhibition.[10] It is hypothesized that SICI and LICI reflect the fast and slow inhibitory post-synaptic potential driven synaptic inhibition mediated by $GABA_A$ [11] and $GABA_B$ [12] subreceptors, respectively, thus serving as proxy measures of GABA-mediated cortical inhibition. Though impairment of GABAergic tone has been documented in BD, there is limited evidence of differential involvement of GABAergic receptor subtypes in BD.[13]

While most cortical reactivity studies in schizophrenia using TMS have identified a fairly consistent deficiency in SICI,[14] very little is known about these processes in BD. Moreover, it is not yet clear how these inhibitory impairments are influenced by the stage of the illness or medications. An earlier study in medicated, remitted BD patients reported significant deficits in SICI compared to healthy subjects (HSs).[5] These subjects also had deficits in other inhibitory processes like interhemispheric inhibition and CSP, thus highlighting their state- independent nature. A more recent study examined cortical inhibition during symptomatic and remitted phases of a manic episode in a prospective study. Manic subjects (n = 19) had significant deficits in SICI and interhemispheric inhibition (but not in CSP and LICI) relative to HSs (n = 28); these differences persisted even during euthymia (n = 15). This reinforced earlier findings that cortical inhibition, especially SICI, was likely to be a trait marker of BD.[6] Both these studies are limited by smaller sample sizes and confounding effects of mood stabilizers and antipsychotics initiated for treatment of mania. These medications are known to have complex effects on GABA receptor- mediated neurotransmission, as inferred predominantly from preclinical animal experiments.[13,15]

In this investigation, we compared cortical reactivity across three groups of subjects – those who were experiencing a manic episode and were not on any medications (manic BD; n = 39), those who had recently remitted from their first episode of mania (remitted FEM; n = 25) and healthy comparison subjects (HS; n = 45) – using single- and paired-pulse TMS. Assuming a trait effect of cortical inhibition impairments, we hypothesized that SICI and LICI would be deficient in the medication-naïve manic BD and treated remitted FEM groups, when compared to HSs. We also hypothesized that the two BD groups would have a lower RMT reflecting a heightened cortical excitability.

2 Methodology

2.1 Subjects

The study subjects were recruited at the National Institute of Mental Health and Neuro Sciences, a tertiary care psychiatry centre in Bangalore, India. For the purpose of this analysis, we combined data from two unpublished studies – one that recruited medication-naïve (never treated; 30% of total sample) or medication-free (off treatment for ≥2 months; 70% of total sample) patients with BD with mania (manic BD; n = 39) to assess mirror neuron system activity using TMS and one that recruited euthymic first episode manic patients (remitted FEM; n = 28) who had recently (≤6 months) remitted with treatment to assess the relationship between cortical reactivity and other putative endophenotypic markers. In addition, the data for HSs (n = 45) were taken from a published study on mirror neuron system activity in schizophrenia.[16] The diagnosis of BD was made clinically based on DSM-IV criteria,[17] by a trained psychiatrist, and confirmed using the Mini International Neuropsychiatric Interview.[18] Euthymic state was determined by scores of <12 and <8 on Young's Mania Rating Scale (YMRS)[19] and the Hamilton Depression Rating Scale,[20] respectively, in the remitted FEM group. Subjects having substance dependence in the last 6 months and any psychoactive substance use in the last 1 week, barring nicotine, were excluded. Given the drug-naïve/ free status of the patients in the manic BD group, those requiring emergency care were excluded from the study. Contraindications to TMS studies were ruled out using the Transcranial Magnetic Stimulation Adult Safety Screen (TASS).[21] The Edinburgh Inventory for Handedness was applied to rule out left-handed and ambidextrous subjects.[22] Subjects recruited for all the three studies were assessed in the same TMS laboratory on the same TMS system by trained experimenters. Independent ethical approvals were obtained for all three studies from the Institute Ethics Committee and all subjects provided written informed consent.

2.2 TMS experiment

A standard TMS unit (MagPro R30 with MagOption; MagVenture, Farum, Denmark) was used to deliver single and paired pulses. Motor evoked potentials (MEPs) were recorded using a one-channel electromyographic (EMG) amplifier mounted on the MagPro system. Electromyogram (EMG) acquisition and analyses were performed using Signal-4 Software (Cambridge Electronic Devices, Cambridge, UK). The subject was seated on a chair with his/her elbows flexed at 90˚ and at rest. An EMG was recorded peripherally from the first dorsal interossues (FDI) muscle using disposable disc electrodes in a belly tendon montage. The cortical area corresponding to the right FDI was located using a 70-mm figure-of-eight coil. Resting motor threshold was defined as the minimum stimulation intensity required to evoke a >50 μV MEP in the resting, right FDI muscle in at least five out of 10 consecutive trials.[23] The stimulation intensity to elicit a 1-mV MEP ($SI_{1\ mV}$) was defined as the minimum stimulation intensity evoking 1-mV peak-to-peak amplitude in the resting, right FDI muscle in at least five out of 10 successive recordings.[23] 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 EMG recordings. Subjects who moved their hands or any other body parts did not continue the experiment and their data were excluded. All

participants underwent the following TMS paradigms in a pre-set pseudorandom sequence, as follows.

2.2.1 Short-interval intracortical inhibition (SICI)—The subthreshold conditioning stimulus was set at 80% RMT and the test stimulus was adjusted to $SI_{1\ mV}$ at an inter-stimulus interval of 3 milliseconds.[11]

2.2.2 Long-interval intracortical inhibition (LICI)—A suprathreshold conditioning stimulus ($SI_{1\ mV}$) was delivered 100 milliseconds before another suprathreshold test stimulus ($SI_{1\ mV}$).[12]

Despite existing literature providing information about the range of inter-stimulus intervals used to obtain SICI (1-6 milliseconds) and LICI (50-200 milliseconds), we used single inter-stimulus intervals of 3 and 100 milliseconds to elicit SICI and LICI, respectively. This was primarily because we wanted to keep the duration of the experiment short so that the drug-naïve or drug-free manic individuals would be able to complete the entire set of assessments. Using multiple inter- stimulus intervals would have made the experiment longer, thus running the risk of higher drop-out rates. Thus, we were required to choose the inter-stimulus interval that was optimal in terms of having been shown to yield satisfactory inhibitory effects that are most likely to be mediated by $GABA_A$ and $GABA_B$ receptor-mediated neurotransmitter activity. Specifically, a 3-millisecond interval reflects the greatest index of inhibition, as opposed to 2- or 4-millisecond inter-stimulus intervals, for SICI.[24] A shorter inter-stimulus interval (1 milliseconds) was not chosen as this might reflect synaptic refractoriness and not activation of inhibitory synapses.[25,26] Similarly, we selected 100 milliseconds as the inter-stimulus interval for LICI, as, among various inter-stimulus intervals tested,[27] this interval has been found to elicit the best inhibition and has also been used in earlier studies.[28]

2.2.3 Single-pulse elicited motor evoked potentials—Unconditioned MEPs were recorded as triggered with the test stimulus of $SI_{1\ mV}$. SICI and LICI were first expressed as percentages of the ratio between the conditioned MEPs and the nonconditioned MEPs; i.e., (conditioned MEP/nonconditioned MEP) × 100. For ease of making inferences, this value was subtracted from 100 to give an effective inhibition value (e.g., 100% − 80% = 20%) that was used in the analysis.

Ten recordings each of SICI, LICI and unconditioned MEPs (a total of 30 recordings) were elicited in pseudorandom sequence with 5-second intervals in all the subjects and the average was considered for comparison between groups.

2.3 Statistical analysis

Clinical and sociodemographic data across the three study groups were compared using one-way analysis of variance (ANOVA) or chi-square tests. The significance of differences across the three groups in RMT, $SI_{1\ mV}$, and effective cortical inhibition elicited using the SICI and LICI paradigms was determined using one-way ANOVA with the post hoc least significant difference (LSD) test.

3 Results

3.1 Sociodemographic and clinical variables

Gender distribution did not differ significantly across the three groups (female gender: manic BD, 43.6%; remitted FEM, 35.7%; HS, 48.9%; $\chi^2 = 1.218$, $P = .54$). However, there were differences in age (mean ± standard deviation [SD]: manic BD, 32.82 ± 11.01 years; remitted FEM, 26.86 ± 7.12 years; HS, 30.68 ± 9.57 years; $F = 3.173$, $P = .046$) and years of formal education (mean ± SD: manic BD, 7.68 ± 4.82 years; remitted FEM, 12.07 ± 3.36 years; HS, 13.13 ± 3.50 years; $F = 20.73$, $P < .01$). The mean (±SD) total YMRS score in the manic BD and remitted FEM groups was 22.36 ± 7.1 and 2.11 ± 2.07, respectively. All remitted FEM subjects scored <8 on YMRS. The mean (±SD) duration of the current episode in the manic BD group was 46.19 ± 49.89 days. The median number of past depressive or manic episodes in the manic BD group was 2. All the remitted FEM subjects had achieved remission from their first manic episode for a median duration of 2 months (range: 1−3 months). Eighteen (64.3%) of them were on antipsychotic medications alone and ten (35.7%) were on a combination of mood stabilizer and antipsychotic medication. None of them were on benzodiazepines. The precise psychotropics and the dose being used by each of the participants are provided in Data S1. None of the subjects in the manic BD group were given benzodiazepines or other rescue medications prior to the TMS experiment.

3.2 Motor thresholds

RMT was significantly different across the three groups (see Table 1). Post hoc analysis showed RMT to be significantly greater in the manic BD ($P = .001$) and HS ($P = .014$) groups than in the remitted FEM group. There was no significant difference between the manic BD and HS groups ($P = .101$). Similarly, $SI_{1\ mV}$ was significantly different across the three groups. In post hoc analysis, $SI_{1\ mV}$ was significantly greater in the manic BD ($P < .001$) and HS ($P = .008$) groups than in the remitted FEM group. $SI_{1\ mV}$ was also significantly greater in the manic BD group than in the HSs ($P = .032$).

3.3 Cortical inhibition measures

SICI was significantly different across the three groups (see Table 1). Post hoc analysis revealed that SICI was significantly reduced in the manic BD ($P = .021$) and remitted FEM ($P = .023$) groups when compared to HSs. There was no significant difference in SICI between the manic BD and remitted FEM groups ($P = .86$). LICI was also significantly different across the three groups. In post hoc analysis, LICI was higher in the manic BD ($P = .021$) and remitted FEM groups ($P = .06$) than in HSs. The differences between the remitted FEM and manic BD groups in LICI were not significant ($P = .81$).

3.4 Analysis of covariance to control for age and education differences

The three subject groups had significant differences in their mean age and years of education. These variables can potentially have independent effects on cortical reactivity.[29] In addition, the differences in test stimuli ($SI_{1\ mV}$) among groups can also potentially impact cortical inhibition.[30] It has been demonstrated in earlier studies that, with increasing test stimulus strength, LICI reduces but SICI improves.[30] We therefore performed analysis of

covariance with each of the cortical inhibition measures as the dependent variable, group status as the fixed factor and age, education and $SI_{1\ mV}$ as covariates. The group difference in cortical inhibition measures (SICI, $F = 6.453$, $P = .002$; LICI, $F = 4.972$, $P = .009$) remained statistically significant even after controlling for age, education and test stimulus differences. Analysis of covariance with each of the motor thresholds as the dependent variable, group status as the fixed factor and age and education as covariates revealed that the group differences in motor thresholds remained significant (RMT, $F = 7.553$, $P = .001$; $SI_{1\ mV}$, $F = 8.151$, $P = .001$).

3.5 Relationship between cortical reactivity and manic symptoms

The total YMRS scores did not have any significant association with LICI ($r = .001$, $P = .9$) or SICI ($r = -.048$, $P = .7$) in the combined patient group (n = 67); however, we observed significant associations between total YMRS scores and measures of motor threshold to elicit 50-μV (resting motor threshold: $r = .37$, $P < .01$) and 1-mV ($SI_{1\ mV}$:$r = .44$, $P < .01$) amplitude motor potentials.

4 Discussion

We demonstrated significantly lower SICI in the manic BD and remitted FEM groups compared to the HSs. This is in keeping with the results of earlier studies, both of which reported reduced SICI in remitted BD/mania compared to HSs.[5,6] Pharmacological probe-guided experiments have suggested that SICI reflects $GABA_A$ receptor-mediated interneuronal synaptic inhibition.[31,32] Interestingly, putative deficits in GABAergic interneurons as measured using the SICI paradigm are also consistently described in schizophrenia.[14] In fact, postmortem studies have also consistently demonstrated deficits in $GABA_A$ receptor- mediated neurotransmission in both schizophrenia and BD patients, perhaps triggered due to the common neurodevelopmental origins of these disorders.[8] As SICI was not different between the manic BD and remitted FEM groups, reduced SICI could be a trait marker of BD. Other criteria for endophenotypic status[33] need to be explored in future studies.

In contrast, and contrary to our hypothesis, LICI was significantly higher in manic BD patients than in HSs. This is also in contrast to the findings of Ruiz-Veguilla et al, where there was no significant difference in LICI between euthymic or symptomatic BD patients and controls. Possible reasons for this difference could be that our manic BD sample was larger and the measurements were not affected by medications like antipsychotics or mood stabilizers. LICI and CSP are two of several TMS-derived cortical reactivity parameters that can be used to assess GABAB-mediated inhibitory neurotransmission.[34,35] A magnetic resonance spectroscopy study demonstrated an elevated GABA:creatine ratio in the anterior cingulate of individuals with euthymic BD when compared to HSs.[36] Our results also indicate the possibility of significantly higher $GABA_B$ neurotransmission in patients with manic BD. $GABA_B$ metabotropic receptors have both post-synaptic inhibitory properties and pre-synaptic autoreceptordriven fatigue of synaptic inhibition that is mediated by different G proteins.[37,38] Despite the complex downstream effects of $GABA_B$ receptor activation, there is evidence that links $GABA_B$ overactivity to mania. There is an increasing

number of reports on the triggering of manic symptoms in patients prescribed baclofen, a $GABA_B$ agonist. A withdrawal of inhibitory control over serotonergic and dopaminergic pathways in the brain is the mechanism proposed.[39,40] This is partly substantiated by experiments demonstrating enhanced growth hormone release in response to baclofen in manic patients compared to healthy controls, suggesting upregulation of hypothalamic $GABA_B$ receptor function in mania.[41] Interestingly, valproate has been shown to attenuate this plasma growth hormone response to baclofen in healthy male subjects, suggesting that valproate may downregulate hypothalamic $GABA_B$ receptors.[42] This finding of enhanced LICI is a unique finding reported for the first time in BD. It could also be investigated as a trait marker for BD in future studies, given that the remitted FEM group also had higher LICI than the HSs, although the difference was not statistically significant ($P = .06$). SICI was reduced but LICI was not different in drug-naïve patients with schizophrenia compared to controls in our earlier study.[16] This also provides scope to study enhanced LICI or LICI:SICI ratio as a differentiating biomarker between schizophrenia and BD in future studies. Neither SICI nor LICI demonstrated any significant associations with symptom severity in the combined patient group. This might suggest that increased LICI and decreased SICI in the patient group are state (symptom) independent.

Motor thresholds for achieving 50 μV (RMT) or 1 mV ($SI_{1\ mV}$) MEPs were higher in the manic BD and HS groups compared to the remitted FEM group. As we did not observe any significant difference between the manic BD and HS groups, we surmise that the decrease in motor thresholds in remitted FEM could be due to the effect of treatment and hence could be a neuromarker of clinical improvement. Our observations of linear associations between motor threshold measures and symptom severity in the combined patient group also suggest a possible state-dependent property. This needs replication and further validation in prospective studies.

The potential distinctiveness of motor thresholds (state dependent) and cortical inhibition paramenets (state independent) in terms of their clinical relatedness can be utilized (a) to better characterize emerging clinically distinct subgroups of BD based on cognitive performance[43,44] and (b) to validate recent brain activation changes following treatment in patients with BD.[45]

Important caveats should be considered when interpreting these results. First, the three subject groups come from three different experiments, although from the same centre. Despite taking maximum precautions to minimize experimenter-driven variations, the group differences could be partly explained by unintended variations in measurements. It is, however, noteworthy that the results remained the same after controlling for confounding variables like age, education and test stimulus. Second, although the manic BD group comprised both first episode patients and patients who had multiple episodes, the average number of past episodes was two, most of which were manic episodes, thus making the two clinical groups fairly comparable in terms of illness duration. Third, manic BD and remitted FEM patients were different groups and not the same individuals followed up longitudinally with treatment. The cross-sectional nature of assessments also limits our conclusions on the endophenotypic status of these biomarkers.

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In conclusion, we demonstrate reduced SICI and enhanced LICI in patients with manic BD and remitted FEM, when compared to HSs. This is a unique demonstration of differential involvement of the two GABA receptor subtypes mediating neurotransmission in BD. Apart from providing important information on the trait-like status of these aberrations, the finding of enhanced LICI may also be used in future as a marker to differentiate BD from schizophrenia. Cortical inhibition has received less attention in BD as compared to schizophrenia and is a potential avenue for furthering our understanding of the pathogenesis of these disorders.

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Table 1
Measures of motor thresholds and cortical inhibition across the three groups

	Manic BD (n = 39)	Remitted FEM (n = 28)	HS (n = 45)	F^a	P^b	Post hoc LSD
RMT	39.36 (8.33)	32.25 (6.08)	36.69 (7.23)	7.582	**<.001**	Manic BD=HS>remitted FEM
$SI_{1\ mV}$	53.59 (11.97)	41.32 (8.04)	48.40 (11.43)	10.332	**<.001**	Manic BD>HS>remitted FEM
SICI (%)	15.68 (44.96)	14.03 (46.51)	35.88 (27.90)	3.790	**.026**	HS>manic BD=remitted FEM
LICI (%)	75.01 (20.52)	72.98 (24.72)	57.81 (45.38)	3.212	**.044**	HS<manic BD=remitted FEM

All values are expressed as mean (standard deviation).

[a]Degrees of freedom 2, 111.

[b]Probability error for the one-way ANOVA omnibus test.

BD, bipolar disorder; FEM, first episode mania; HS, healthy subject; RMT, resting motor threshold (% of maximum machine output); MT1, motor threshold 1 (% of maximum machine output); SICI, % effective inhibition measured using short-interval intracortical inhibition; LICI, % effective inhibition measured using long-interval intracortical inhibition; LSD, least significant difference; $SI_{1\ mV}$, stimulation intensity to elicit a 1-mV motor evoked potential. The bold values indicate that the *P* values are statistically significant. (ie, $P < 0.05$).