Gamma activity model for treatment-resistant bipolar psychotic mania

Shashi Ranjan Kumar, Vinod Kumar Sinha, Sai Krishna Tikka, Nishant Goyal

ABSTRACT

Objectives: The objective was to investigate the effect of clozapine on spontaneous gamma activity in treatment-resistant bipolar psychotic mania.

Methods: Patients with treatment-resistant (TR) bipolar psychotic mania on clozapine monotherapy and nontreatment-resistant bipolar psychotic mania patients receiving lithium were prospectively studied for 6 weeks on severity of psychopathology and 30–49 Hz gamma spectral power.

Results: Spectral power significantly increased in the lithium group and decreased in the clozapine group; no within group significant difference found.

Conclusions: We propose a model highlighting the role of gamma spectral power and modulations of GABAergic neurotransmission in TR bipolar psychotic mania.

KEY WORDS: Bipolar psychotic mania, gamma activity, spectral power, treatment resistance

Introduction

A substantial portion of patients of bipolar disorder with psychotic mania does not respond adequately to traditional lines of drug management. Clozapine monotherapy has been found to be effective in such cases.[1] Perhaps, clozapine treatment in resistant psychotic bipolar mania has been found to be more effective than it is for schizophrenia.[2] Potentiating effects of clozapine on gamma-aminobutyric acid (GABA) have been proposed to underlie its efficacy in the treatment-resistant (TR) schizophrenia.[3] Fewer efforts, however, have been made to understand the mechanism of clozapine action in TR mania.

Electroencephalography (EEG) has been suggested as a useful tool in studying sensory pathways and cognitive processing in patients with bipolar disorder.[4] Particularly, study of gamma band activity could provide more insights into these processes.[5] Dysfunction in the GABAergic neurotransmission, which has been proposed to underlie abnormal gamma activity in schizophrenia,[6] has also been suggested to play a role in bipolar disorders.[7]

With the aim of investigating the effect of clozapine on spontaneous gamma activity in TR bipolar psychotic mania we conducted this 6 weeks prospective study. We also compared change in gamma activity in TR bipolar psychotic mania patients with changes in gamma activity in patients with nontreatment-resistant (NTR) bipolar psychotic mania receiving lithium.

Methods

The study was approved by the Institute Ethics Committee of Central Institute of Psychiatry (CIP), Ranchi, India (Approval no: 302-A [Ethical Committee/CIP/Str.no. 2, dated 23/05/2011). Written informed consent was taken from all the participants (and their legally qualified representatives in case of patients) before enrolling them for the study.

Participants

Patients were recruited by purposive sampling from various in-patient wards of CIP. It is a naturalistic study design. A total of 48 right-handed, male patients in the age group of 18–50 years, having a diagnosis of bipolar affective disorder current episode manic with psychotic symptoms (F31.2) as per International Classification of Disease-10 Diagnostic Criteria for Research[8] were taken up for the study. Eight patients were dropped from the final analysis (4 cases because of side effects; 2 patients were discharged prematurely before the completion of the study; 2 cases had inadequate artefact-free EEG data). Of the final 40, 20 patients among them were TR cases (shown poor response on at least two separate trials of mood stabilizers or one trial of single mood stabilizer with another trial of combination of two mood stabilizers (i.e. TR group). They were started on clozapine monotherapy in the current episode. Other
20 patients (i.e. NTR group) had shown significant improvement on lithium (and an antipsychotic) in the past episodes and the current episode were started on lithium and an antipsychotic drug of the 20 patients, 14 received olanzapine [dose range: 7.5–15]; 4 were on risperidone [dose range: 2–4 mg] and 2 were on haloperidol [both received a dose of 10 mg]. Patients having history of neurological illness, significant head injury, co-morbid substance dependence (excluding nicotine and caffeine), other psychiatric disorder, disruptive behavior (suicidal or homicidal) that warranted immediate intervention, or history of electroconvulsive therapy within previous 6 months were excluded.

Clinical Assessment

Relevant sociodemographic and clinical data were collected from all the participants. Handedness was assessed using the sidedness bias schedule-Hindi version. Baseline and posttreatment (after 6–7 weeks of treatment initiation) severity of psychopathology in patients was evaluated by administering the expanded 24-item Brief Psychiatric Rating Scale (BPRS)[10] and the 11-item Young Mania Rating Scale (YMRS).[11] Blood levels of clozapine and lithium were monitored weekly. Side effects of each drug were assessed with specifically developed screening tool (included all the items from the Udvalg for Kliniske Undersogelser side effect rating scale).[12]

Electroencephalography Recording

All participants underwent an EEG recording at the Centre for Cognitive Neurosciences, CIP. Recording was carried out between 900 h and 1200 h, and participants were advised to avoid the use of tea, coffee, or nicotine for at least 1 h before recording. Ten minutes of spontaneous resting EEG was recorded for each participant, while supine, eyes closed, in a light and sound attenuated room on 32 channels placed according to the international 10–20 system of electrode placement. Eye movement potentials were monitored using right and left electrooculogram channels. Electrode impedance was kept < 5kΩ.

Electroencephalography was filtered (time constant - 0.1 s, high-frequency filter - 70 Hz) and digitized (sampling rate - 256 Hz, 16 bits) using Neurofax EEG-1100K (Nihon-Kohden, Tokyo, Japan). Baseline EEG recording was done within 1st week of treatment initiation and another after 6 weeks of the first recording.

Spectral Power and Coherence Analysis

First 60-s epochs of artifact-free EEG data were visually selected from each recording after carefully excluding segments with eye movement, blink and electromyogram, movement, electrode, and perspiration artifacts or drowsiness changes. Selected EEG epochs were recomputed against common average reference. Spectral power, expressed in μV, (fast Fourier transform routine, Hanning window) was calculated using Welch’s averaged periodogram method. Frequencies between 30 Hz and 49 Hz were analyzed. Spectral power was averaged region-wise (right and left frontal, parietal, temporal and occipital, and central). MATLAB 7 version (The MathWorks, Inc., Massachusetts, USA) was used for EEG analysis.

Statistical Analysis

Group differences on various clinical and sociodemographic variables for the continuous and categorical variables were computed using an independent t-test and the Pearson Chi-square test (the Fisher’s exact test was used where appropriate), respectively. As the spectral power data were not normally distributed (Shapiro–Wilks test), normalization was achieved by log transformation. Repeated measures ANOVA (with Greenhouse–Geisser sphericity correction) was used to compare the groups (both within group and between group) on spectral power data (transformed). The level of significance was kept at 0.05. Statistical analysis was done using Statistical Package for Social Sciences version 16.0 (SPSS, Inc., Illinois, USA).

Results

Comparison of sociodemographic and clinical variables between the two groups is shown in Table 1. Variables-age, education, occupation, marital status, and habitat were not significantly different between the two groups. Age of onset of illness, duration of illness, number of past manic episodes, and positive family history of bipolar illness too were not significantly different across the groups. The TR group, however, had significantly higher total number of past episodes ($t = 6.21; \ P < 0.05$) and total number of previous hospitalizations ($t = 8.98; \ P < 0.05$). Mean clozapine dose was $275.00 \pm 81.92$ mg (range: 150–400 mg) and mean clozapine level was $407.78 \pm 76.59$ ng/ml in the TR group. The mean lithium dose was $1027.50 \pm 111.77$ mg with mean serum lithium level being $0.86 \pm 0.16$ mEq/L in the NTR group.

Between group and within group comparison of scores on BPRS and YMRS as well as of gamma spectral power values in various brain regions is summarized in Table 2. No group differences in the measures of manic and psychotic symptoms as assessed by YMRS and BPRS at baseline. Posttreatment with either lithium or clozapine in the study sample, the YMRS and BPRS scores significantly improved but between the groups there is no significant difference. Change in the gamma spectral power of all the 9 brain areas studied in the clozapine group was significantly different from the change in the lithium group. Spectral power increased in the lithium group and decreased in the clozapine group. However, gamma spectral power in both the groups did not significantly differ across the recordings made at baseline and posttreatment.

Discussion

Except for higher number of previous episodes and number of past hospitalizations in the TR group, no other clinical or demographic variable was significantly different between the two groups. Specifically, when compared to the NTR group, the TR group had more number of episodes in lesser duration of illness. To the best of our knowledge, no previous study has examined power spectrum changes in the gamma band in response to clozapine in TR bipolar psychotic mania and lithium treatment in NTR bipolar psychotic mania patients. Hence, considering the findings on the manic/psychotic symptoms and the findings on EEG gamma band spectral power, we propose a model of treatment resistance in bipolar disorder [Figure 1].

We propose that there is a baseline gamma spectral power in bipolar disorder patients that increases steeply with acute treatment and once maintenance phase of treatment reached; it gradually reduces towards the baseline. However, it does not reach baseline, instead settle down above the baseline.
### Table 1:
Comparison of sociodemographic and clinical variables (continuous variables) in the patients

| Variables                        | TR (n=20)          | NTR (n=20)          | t/χ² | P       |
|----------------------------------|--------------------|--------------------|------|---------|
| Age (in years)                   | 29.15±8.26         | 30.50±6.38         | 0.600| 0.566   |
| Education (in years)             | 8.65±4.32          | 8.55±5.57          | 2.969| 0.095   |
| Total family income (rupees per month) | 4950.00±4795.56   | 6000.00±5638.22   | 0.684| 0.530   |
| Age of onset of illness (in years) | 20.75±5.84         | 23.65±6.84         | 1.287| 0.157   |
| Duration of illness (in years)   | 8.40±6.08          | 7.30±5.69          | 0.101| 0.558   |
| Number of episodes               | 5.7±3.94           | 3.45±1.88          | 6.209| 0.027*  |
| Number of past manic episodes    | 4.35±4.20          | 2.35±1.87          | 6.779| 0.059   |
| Number of past depressive episodes | 0.40±0.88         | 0.15±0.37          | 7.168| 0.249   |
| Number of hospitalizations       | 3.00±2.45          | 1.75±0.64          | 8.978| 0.033*  |
| Occupation                       | 3 (15)             | 6 (30)             | 1.290| 0.225   |
| Employed                         | 17 (85)            | 14 (70)            | 1.012| 0.500   |
| Marital status                   | 11 (55)            | 12 (60)            | 0.102| 0.924   |
| Married                          | 9 (45)             | 8 (40)             | 0.102| 0.500   |
| Unmarried                        | 16 (80)            | 18 (90)            | 0.784| 0.331   |
| Religion                         | 4 (20)             | 2 (10)             | 0.384| 0.539   |
| Hindu                            | 0.40±0.88          | 0.15±0.37          | 7.168| 0.249   |
| Others                           | 3.00±2.45          | 1.75±0.64          | 8.978| 0.033*  |
| Occupation                       | 3 (15)             | 6 (30)             | 1.290| 0.225   |
| Employed                         | 17 (85)            | 14 (70)            | 1.012| 0.500   |
| Marital status                   | 11 (55)            | 12 (60)            | 0.102| 0.924   |
| Married                          | 9 (45)             | 8 (40)             | 0.102| 0.500   |
| Unmarried                        | 16 (80)            | 18 (90)            | 0.784| 0.331   |
| Religion                         | 4 (20)             | 2 (10)             | 0.384| 0.539   |
| Hindu                            | 0.40±0.88          | 0.15±0.37          | 7.168| 0.249   |
| Others                           | 3.00±2.45          | 1.75±0.64          | 8.978| 0.033*  |

Values are expressed as mean±SD or n (%), *P<0.05 as compared to NTR group. TR=Treatment-resistant group, NTR=Nontreatment-resistant group

### Table 2:
Comparison of variables between TR and NTR groups

| Variables                        | Time                      | TR (n=20)          | NTR (n=20)          | Pre- and post-treatment between clozapine and lithium group over time | Pre- and post-treatment interaction within clozapine and lithium groups |
|----------------------------------|---------------------------|--------------------|--------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------|
|                                  |                           | F                  | P                  | Partial 𝜂² | Observed power | F                  | P                  | Partial 𝜂² | Observed power |
| Clinical scales                  |                           |                    |                    |              |                |                    |                    |              |                |
| BPRS                             | Pretreatment              | 34.15±5.68         | 35.75±7.19         | 0.191        | 0.841          | 125.225            | 96.489            | 0.000***    | 0.717          | 1.000         |
|                                  | Posttreatment             | 19.40±3.02         | 20.25±4.24         |              |                |                    |                    |              |                |
| YMRS                             | Pretreatment              | 27.15±5.26         | 28.90±7.48         | 0.342        | 0.753          |                    | 0.000***          | 0.767        | 1.000         |
|                                  | Posttreatment             | 3.40±7.44          | 3.25±6.43          |              |                |                    |                    |              |                |
| Spectral gamma power (in μV²)   |                           |                    |                    |              |                |                    |                    |              |                |
| Right frontal                    | Pretreatment              | 0.93±0.68          | 0.60±0.26          | 11.982       | 0.001**        | 0.240              | 0.921              | 0.621        | 0.436         |
|                                  | Posttreatment             | 0.66±0.34          | 1.04±0.68          |              |                |                    |                    |              |                |
| Left frontal                     | Pretreatment              | 1.01±0.69          | 0.58±0.29          | 21.901       | 0.000***        | 0.366              | 0.995              | 0.001        | 0.976         |
|                                  | Posttreatment             | 0.52±0.29          | 1.06±0.57          |              |                |                    |                    |              |                |
| Right parietal                   | Pretreatment              | 0.82±0.62          | 0.38±0.24          | 10.623       | 0.002**         | 0.218              | 0.888              | 0.686        | 0.413         |
|                                  | Posttreatment             | 0.57±0.38          | 0.92±0.70          |              |                |                    |                    |              |                |
| Left parietal                    | Pretreatment              | 0.93±0.66          | 0.46±0.29          | 22.854       | 0.000***        | 0.376              | 0.996              | 0.263        | 0.611         |
|                                  | Posttreatment             | 0.42±0.32          | 0.87±0.52          |              |                |                    |                    |              |                |
| Right temporal                   | Pretreatment              | 1.33±1.00          | 0.79±0.40          | 11.504       | 0.002**         | 0.232              | 0.911              | 0.982        | 0.328         |
|                                  | Posttreatment             | 0.95±0.53          | 1.49±0.94          |              |                |                    |                    |              |                |
| Left temporal                    | Pretreatment              | 1.33±0.75          | 0.96±0.56          | 22.385       | 0.000***        | 0.371              | 0.996              | 0.000        | 0.986         |
|                                  | Posttreatment             | 0.74±0.53          | 1.56±0.73          |              |                |                    |                    |              |                |
| Right occipital                  | Pretreatment              | 1.04±0.75          | 0.45±0.27          | 14.913       | 0.000***        | 0.282              | 0.964              | 0.514        | 0.478         |
|                                  | Posttreatment             | 0.65±0.45          | 1.02±0.75          |              |                |                    |                    |              |                |
| Left occipital                   | Pretreatment              | 1.01±0.69          | 0.46±0.32          | 27.031       | 0.000***        | 0.416              | 0.999              | 0.039        | 0.845         |
|                                  | Posttreatment             | 0.51±0.41          | 1.00±0.54          |              |                |                    |                    |              |                |
| Central                          | Pretreatment              | 0.83±0.62          | 0.45±0.26          | 18.457       | 0.000***        | 0.327              | 0.987              | 0.120        | 0.730         |
|                                  | Posttreatment             | 0.47±0.31          | 0.88±0.50          |              |                |                    |                    |              |                |

Values are expressed as mean±SD or n (%), **P<0.01, ***P<0.001 as compared to NTR group. TR=Treatment-resistant group, BPRS=Brief Psychiatric Rating Scale, YMRS=Young Mania Rating Scale, NTR=Nontreatment-resistant group
Neurotransmission, which might explain for the reduction in neurotransmission. While clozapine enhances the GABAergic to differential effects of clozapine and lithium on the GABAergic refractory bipolar illness. Interestingly, this finding could be due attempted pharmaceutical agent) is not effective in cases of reducing it, this could explain why lithium (or any other past power. Lithium increases the gamma spectral power rather than psychotic mania is through its reduction of gamma spectral power, lithium, on the other hand, has been found not to exhibit significant change in GABAergic neurotransmission. In addition, we also propose that similar mechanisms through which clozapine act in TR schizophrenia might be underlying its pathophysiology in TR bipolar psychotic mania.

Limitations

Limited sample size, inclusion of only male participants, lack of control for the antipsychotic received along with lithium in the NTR group, and lack of rater blinding are among them. Being the first study to investigate EEG activity in patients of TR bipolar psychotic mania receiving clozapine, it has certain limitations. Longer prospective studies investigation EEG activity across various periods of illness course are suggested to test the hypothesis the study proposes.

Conclusions

Clozapine and lithium have differential effects on the modulation of gamma oscillatory activity in psychotic bipolar patients. This might explain the disparity in efficacy of these two drugs in TR patients. Interestingly, this finding might be extrapolated to differential effects of clozapine and lithium on the GABAergic neurotransmission as well.

References

1. Green AI, Tohen M, Patel JK, Banov M, Durand C, Berman I, et al. Clozapine in the treatment of refractory psychotic mania. Am J Psychiatry 2000;157:982-6.
2. Ciapparelli A, Dell’Osso L, Bandettini di Paggio A, Carmassi C, Cecconi D, Feni M, et al. Clozapine in treatment-resistant patients with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder: A naturalistic 48-month follow-up study, J Clin Psychiatry 2003;64:451-8.
3. Daskalakis ZJ, George TF. Clozapine, GABA (B), and the treatment of resistant schizophrenia. Clin Pharmacol Ther 2009;86:442-6.
4. Degabriele R, Lagopoulos J. A review of EEG and ERP studies in bipolar disorder. Acta Neuropsychiatr 2009;21:59-66.
5. Herrmann CS, Fründ I, Lenz D. Human gamma-band activity: A review on cognitive and behavioral correlates and network models. Neurosci Biobehav Rev 2010;34:981-92.
6. Tikka SK, Nizamie SH, Das B, Katshu MZ, Goyal N. Increased spontaneous gamma power and synchrony in schizophrenia patients having higher minor physical anomalies. Psychiatry Res 2013;207:164-72.
7. Konradi C, Zimmerman EI, Yang CK, Lohmann KM, Gresch P, Pantazopoulos H, et al. Hippocampal interneurons in bipolar disorder. Arch Gen Psychiatry 2011;68:340-50.
8. World Health Organization. The ICD-10 Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research. Geneva: WHO; 1992.
9. Mandal MK, Pandey G, Singh KS, Asthana SH. Hand preference in India. Int J Psychol 1992;27:433-42.
10. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: Reliability, validity and sensitivity. Br J Psychiatry 1978;133:429-35.
11. Lukoff D, Nuechterlein KH, Ventura J. Appendix A: Manual for expanded Brief Psychiatric Rating Scale (BPRS). Schizophr Bull 1986;12:594-602.
12. Langiardo O, Aflittris US, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl 1987;334:1-100.
13. Shibuya-Tayoshi S, Tayoshi S, Sumitani S, Ueno S, Harada M, Ohmori T. Lithium effects on brain glutamatergic and GABAergic systems of healthy volunteers as measured by proton magnetic resonance spectroscopy, Prog Neuropsychopharmacol Biol Psychiatry 2008;32:249-56.