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Impaired frontal synchronization of spontaneous magnetoencephalographic activity in patients with bipolar disorder

Shyan-Shiou Chen[a], Pei-Chi Tu[c], Tung-Ping Su[d,e], Jen-Chuen Hsieh[f,b,c], Ying-Chia Lin[b], Li-Fen Chen[f,b,*]

[a] Department of Mathematics, National Taiwan Normal University, Taipei, Taiwan
[b] Integrated Brain Research Laboratory, Department of Medical Research and Education, Taipei Veterans General Hospital, Taipei, Taiwan
[c] Division of Neuroscience, School of Life Sciences, National Yang-Ming University, Taipei, Taiwan
[d] Division of Psychiatry, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[e] Psychiatric Department, Taipei Veterans General Hospital, Taipei, Taiwan
[f] Institute of Brain Science, School of Medicine, National Yang-Ming University, Taipei, Taiwan

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ABSTRACT

Recent functional imaging studies demonstrated that brain exhibit coherent, synchronized activities during resting state and the dynamics may be impaired in various psychiatric illnesses. In order to investigate the change of neural dynamics in bipolar disorder, we used a new nonlinear measurement “similarity index” to analyze the magnetoencephalography (MEG) recordings and test the hypothesis that there are synchronization changes within different frequency bands in the frontal cortex of patients with bipolar disorder. Ten patients with bipolar I disorder during euthymic phase and ten normal controls underwent 2 min eye-closed resting recording with a whole-head 306-channel MEG system. Eleven channels of MEG data from frontal area were selected for analysis. Synchronization level in the delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–24 Hz) bands was calculated for each subject and compared across group. The results showed that significant dynamic changes in bipolar patients can be characterized by increased synchronization of slow frequency oscillations (delta) and decreased synchronization of fast frequency oscillations (beta). Furthermore, the positive correlation between beta synchronization level and preservative errors in Wisconcin card sorting task was found which would implicate the deficit of executive function in bipolar patients. Our findings indicate that analysis of spontaneous MEG recordings at resting state using nonlinear dynamic approaches may disclose the subtle regional changes of neural dynamics in BD.

Bipolar disorder (BD) is a chronic psychiatric illness characterized by recurrent manic and depressive episodes that are polar opposite on a continuum between elevated mood, grandiose, self importance on one side and depressed mood, feelings of self-loathing, incompetence on the other. Despite lots of molecular, neurobiological and neuroimaging studies, the cause of this pathological mood fluctuation remains unclear. Synchronization among oscillatory networks can be viewed as a mechanism of integration for specific frequency band-associated functions [28]. Investigation of synchronization in spontaneous brain activity at resting state would help to understand impairment of cognitive default network in BD patients.

Recently, chaos theory or nonlinear dynamics has become a potential tool to explain the mechanisms of psychiatric illness [6,19]. The method of nonlinear dynamics is especially attractive to the researchers on BD because the symptoms of each patient oscillate between different mood states such as mania, hypomania, euthymia, dysthymia, and depression. There are two kinds of analytic strategies while applying nonlinear dynamics to the research of bipolar disorder. One is to analyze the time course of self-report mood data. For instance, Glen et al. calculated the approximate entropy of self-reported mood in bipolar patients and found that approximate entropy was significantly greater in the 60 days prior to a manic or depressive episode than the 60 days prior to a month of euthymia [8]. This result implicated that irregularity in mood could be viewed as an indicator of onset of an episode. The other application of nonlinear dynamics is to analyze the biological signals recorded from the BD patients, such as. Electroencenphalographic (EEG) and magnetoencephalographic (MEG), since the signals directly obtained from brains were proposed to be more related to the psychopathology. Bahrami et al. analyzed the EEG recordings of bipolar patients and found that the fractal dimension was significantly augmented in patients during

* Corresponding author at: Institute of Brain Science, School of Medicine, National Yang-Ming University, 155, Section 2, Linong Street, Beitou District, 112 Taipei, Taiwan. Tel.: +886 2 28267384; fax: +886 2 28239113.
E-mail address: lfchen@ym.edu.tw (L.-F. Chen).

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manic phase compared with normal controls [5]. They concluded that the measurement of brain complexity was able to differentiate the EEG data of normal and abnormal mood states. However, their study dealt with the time series recorded at each channel separately. Recent studies suggested that brain function could be characterized by synchronized activities between neural assemblies which motivate us to investigate if synchronized index can be used to detect the neural abnormally in bipolar patients.

In this study, we modified similarity index (SI) proposed by Arnhold et al. [4] as synchronization level to evaluate and detect the impairments of underlying neural dynamics in euthymic bipolar patients. Based on previous functional studies which showed frontal cortical dysfunction in bipolar patients [3,10,12], we hypothesized that in the frontal region of bipolar patients there is a change in the dynamics of neural oscillations during resting state. Since various cognitive and emotional functions are associated with neural oscillations of different frequency bands, similarity indices in different bands were calculated, respectively, and statistically compared between normal subjects and bipolar patients and to reveal the correlation between cognitive dysfunction and brain dynamics.

Ten patients with bipolar I disorder during euthymic phase (five males, mean age = 32.5 ± 10.3 y/o, range = 21:53) were selected from the outpatients of psychiatric department of Taipei Veterans General Hospital. The clinical diagnosis was made by two independent psychiatrists using DSM-IV-TR. The mean illness duration was 9.0 ± 5.2 years. All patients were taking a range of medications, including lithium ($n = 1$), anticonvulsants ($n = 10$), antidepressant ($n = 4$), and antipsychotics ($n = 1$). Ten gender- and age-matched normal controls (five males, mean age = 32.2 ± 11.6 y/o) were recruited through advertisement from the community. All the normal controls underwent Mini International Neuropsychiatric Interview (M.I.N.I.) before the experiments to exclude the possible morbidity of major psychiatric illness. All subjects were without a history of substance misuse or abuse and provided written informed consent to participate in the study according to the guidelines approved by the Institutional Committees of Medical Ethics and Radiation Safety.

At the day before image acquisition, the mood symptoms were rated using Young Mania Rating Scales (YMRS) and 17-item Hamilton Rating Scale for Depression (HAMD17) and the scores were 1.6 ± 2.27 and 4.7 ± 3.9, respectively. The scores posited that our BD patients were not of overt depressive or manic phase. Three kinds of cognitive test batteries, including Wisconcin card sorting test (WCST), wordlist recall, and attention test, were used to test the cognitive impairments of the BD patients. At the time of imaging procedure, the BD patients were all clinically stable and cooperative to follow the requirements of experimental tasks.

For each subject, 2 min eye-closed resting MEG data with 1000 Hz sampling rate and bandpass filtered at 0.03–330 Hz was recorded with a whole-head 306-channel MEG system (Vectorview; Elekta-Neuromag, Helsinki, Finland). Four head-position-indicator (HPI) coils attached on subject's head and three defined anatomical landmarks (nasion and bilateral preauricular points) were used to ensure coverage of the same cortical regions under the selected sensors among all the subjects. The mean translation of all the subjects' heads located within scanner in this study was around 2.2 mm, which were much smaller than the distance between sensor pair (34 mm). After offline artifact rejection, the noise-free MEG data from 11 pairs of planar gradiometers covering frontal regions of individual brains were selected for the calculation of SI. Based on our previous findings from the average power spectrum analysis [27], we specified four frequency bands, delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–24 Hz). For each subject, the similarity index of each pre-specified frequency band was calculated for each combination of 2 channels among 11 frontal channels (i.e. 110 values in total).

We in this work modified the SI method proposed by Arnhold et al. [4], which is described as follows. Let x_n be a scalar filtered time series with delta (theta, alpha or beta) band at time point n. By the time-delay procedure [25], we can construct a d_x-dimensional vector $\mathbf{x}_n$ with the coordinate $(x_n, \ldots, x_{n+(d_x-1)\tau})$, where τ_x is the delay time and d_x is the embedding dimension. A reconstructed trajectory $\mathbf{X}$ denotes the collection of the points, $\mathbf{x}_1^{\mathrm{T}}, \mathbf{x}_2^{\mathrm{T}}, \ldots$, where T denotes transpose. For each $x_n \in R^{d_x}$, the mean Euclidean distance for the set of $\mathbf{x}_n$ and its k nearest neighbors (KNN), $\Gamma_n^k = \{\gamma_{n,j} | j = 1, \ldots, k\}$, is defined as $V_n^{(k)}(\mathbf{X}) = (1/k)\sum_{i=1}^{k} ||\mathbf{x}_{\gamma_n} - \mathbf{x}_{\gamma_{n,i}}||^2$. The conditional mean Euclidean distance is defined by $V_n^{(k)}(\mathbf{X}|\mathbf{Y}) = (1/k)\sum_{j=1}^{k} ||\mathbf{x}_{\omega_n} - \mathbf{x}_{\omega_{n,j}}||^2$, where $\Omega_n^k = \{\omega_{n,j} | j = 1, \ldots, k\}$ is its KNN in $\mathbf{y}_n$. The local interdependences $S_n^{(k)}(\mathbf{X}|\mathbf{Y})$ and global $S^{(k)}(\mathbf{X}|\mathbf{Y})$ are defined as

$$S_n^{(k)}(\mathbf{X}|\mathbf{Y}) = \frac{V_n(\mathbf{X})}{V_n^{(k)}(\mathbf{X}|\mathbf{Y})} \tag{1}$$

and

$$S^{(k)}(\mathbf{X}|\mathbf{Y}) = \frac{1}{N}\sum_{n=1}^{N} S_n^{(k)}(\mathbf{X}|\mathbf{Y}), \tag{2}$$

respectively. The quantity $S_n^{(k)}(\mathbf{X}|\mathbf{Y})$ (resp. $S^{(k)}(\mathbf{X}|\mathbf{Y})$) means the local (resp. global) variation rate of the mean distance influenced by $\mathbf{Y}$, and is called the *local* (resp. global) *similarity index*, LSI (resp. GSI).

To avoid spurious detection of synchronization due to short data, noise, bandpass filtering, and signal complexity, we developed a two-level process of computing GSI in order to get a more significant representation. The univariate difference of GSI between $\mathbf{X}$ and $\mathbf{Y}$ is defined as $S_{\mathrm{uni}}^{(k)}(\mathbf{X}|\mathbf{Y}) := \max\{S^{(k)}(\mathbf{X}|\mathbf{Y}) - \tilde{S}^{(k)}(\mathbf{X}|\mathbf{Y}), 0\}$, where $\tilde{S}^{(k)}(\mathbf{X}|\mathbf{Y})$ is the 95th percentile of distribution for 19 univariate surrogates of $\mathbf{Y}$ [20], generated by the iterative amplitude-adjusted Fourier transform algorithm (IAAFT) [21]. Fig. 1 illustrates signal processing with creation of uni-surrogate and phase reconstruction. Fig. 1(a) is two 68 s time series raw data recorded from two different selected sensors for a subject. Fig. 1(b) illustrates the bandpass filtered signals (delta band) and (c) is their corresponding phase-reconstructed data. Nineteen numbers of uni-surrogate data for each filtered data, F1 [resp. F2], are shown in Fig. 1(d) [resp. (e)], where the spectrums of the filtered data and their responding surrogate data are the same. The bivariate difference of GSI is then defined by

$$S_{\mathrm{bi}}^{(k)}(\mathbf{X}|\mathbf{Y}) := \begin{cases} \max\{S^{(k)}(\mathbf{X}|\mathbf{Y}) - \hat{S}^{(k)}(\mathbf{X}|\mathbf{Y}), 0\}, & \text{if } S_{\mathrm{uni}}^{(k)}(\mathbf{X}|\mathbf{Y}) > 0 \\ 0, & \text{if } S_{\mathrm{uni}}^{(k)}(\mathbf{X}|\mathbf{Y}) < 0 \end{cases}, \tag{3}$$

where $\hat{S}^{(k)}(\mathbf{X}|\mathbf{Y})$ is the 95th percentile of distribution for 19 bivariate surrogates [20], generated by IAAFT algorithm.

For each subject's MEG measurement, the mean bivariate difference of global similarity index (MBDGSI) for each frequency band (i.e., delta, theta, alpha, and beta band) was computed by the average of 110 values (i.e. $S_{\mathrm{bi}}^{(k)}(\mathbf{X}|\mathbf{Y})$) for channel pairs (i, j) where $i \neq j$ and $i, j = 1, \ldots, 11$. We employed in this study a two-way mixed ANOVA (2×2) analysis to investigate the group (patient vs. normal subjects) and gender (male vs. female) effects on MBDGSI values for each frequency band. The MBDGSI values between two groups or two genders were further compared by one-way ANOVA analysis for each frequency band if group or gender effect was found to be significant. A p-value below 0.01 was considered to be significant for both one-way and two-way ANOVA. Two kinds of correlations were provided. One is Kendall's rank correlation, and the other