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Complexity analysis of spontaneous brain activity in mood disorders: A magnetoencephalography study of bipolar disorder and major depression

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ABSTRACT

Background and purpose: The lack of a biomarker for Bipolar Disorder (BD) causes problems in the differential diagnosis with other mood disorders such as major depression (MD), and misdiagnosis frequently occurs. Bearing this in mind, we investigated non-linear magnetoencephalography (MEG) patterns in BD and MD.
Methods: Lempel-Ziv Complexity (*LZC*) was used to evaluate the resting-state MEG activity in a cross-sectional sample of 60 subjects, including 20 patients with MD, 16 patients with BD type-I, and 24 control (CON) subjects. Particular attention was paid to the role of age. The results were aggregated by scalp region.
Results: Overall, MD patients showed significantly higher *LZC* scores than BD patients and CONs. Linear regression analyses demonstrated distinct tendencies of complexity progression as a function of age, with BD patients showing a divergent tendency as compared with MD and CON groups. Logistic regressions confirmed such distinct relationship with age, which allowed the classification of diagnostic groups.
Conclusions: The patterns of neural complexity in BD and MD showed not only quantitative differences in their non-linear MEG characteristics but also divergent trajectories of progression as a function of age. Moreover, neural complexity patterns in BD patients resembled those previously observed in schizophrenia, thus supporting preceding evidence of common neuropathological processes.

1. Introduction

Bipolar disorder (BD) is a chronic and debilitating disease characterized by "abnormal" shifts of mood and energy. The term "bipolar" refers to recurrent episodes that are polar opposite on a continuum between elevated and depressed mood [1]. Currently, there is no objective marker for BD and diagnosis relies on clinical criteria such as the Diagnostic and Statistical Manual of Mental Disorders– DSM-5 [2]. Neurophysiological features are potential candidates for the elucidation of a BD-related biomarker since disturbances in the behavior of the oscillatory patterns may indicate aberrant brain function [3]. Most of the resting state EEG studies of BD revealed a pattern of increased low-frequency and decreased alpha activity [4,5]. The decrease of alpha activity was further highlighted by Basar's group [6,7]. The authors claimed that, although such decrease is shared by schizophrenia (SZ) and BD patients, it is quantitatively greater in the latter, representing a marker of the disease. Additional findings confirmed this pattern of increased low-frequency activity but pointed out abnormally slow beta activity in BD and SZ patients that, according to Narayanan et al.'s [3] point of view, might indicate a common endophenotype for both disorders. However, Venables and coworkers [8] failed to find an abnormal beta or even the typical pattern of increased low-frequency activity in BD.

Investigations using spectral analysis depicted a quite unspecific picture of BD since increased low-frequency and decreased high-frequency activity is a feature not only shared with SZ but also with Alzheimer's disease and mild cognitive impairment [9–12]. Hence, traditional analysis procedures have been challenged by new methods derived from non-linear dynamics analysis and information theory that can reveal features not available to other techniques. Complexity and entropy estimates are good examples of this new arsenal of analysis methods. In particular, parameters of EEG or Magnetoencephalography

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(MEG) complexity usually estimate the predictability of brain oscillations (with more "unpredictable" signals yielding higher complexity scores) and/or the number of independent oscillators underlying the observed signals [13].

With regards to BD investigations, Glenn et al. [14] and Gottschalk et al. [15] used dimensional analysis and approximate entropy to analyze mood variations over time, finding contradictory results of increased or decreased complexity. Thomasson and coworkers [16] analyzed EEG by means of entropy estimates in a 48-hour cyclic BD patient, and found that the signal complexity increased during manic phases and decreased during depressive mood. Bahrami et al. [17] also found that dimensional complexity was increased during manic episodes. Finally, a very recent multiscale entropy analysis of fMRI signals revealed decreased complexity in BD and SZ [18].

The observed contradictory results might be explained by discrepancies in the inner properties of the selected analysis procedure, and also by the diversity of analyzed signals. Some complexity estimators are more sensitive to certain characteristics of brain signals [19]. Therefore, it is convenient to select those estimators that do not require a large amount of data, and stationary or noise-free time series, as it is usually the case for EEG and MEG. It is also important to note that MEG measures direct neural activity as compared with MRI-derived estimates.

Lempel-Ziv Complexity (*LZC*) meets these characteristics and has been successfully used in the investigation of psychiatric disorders. For instance, Li et al. [20] found that *LZC* values were more sensitive than conventional spectral measures to discriminate SZ and psychotic depression patients. Previous studies by our group using MEG technology [21–23] demonstrated that some neuropsychiatric disorders can be characterized by specific patterns of *LZC* variation. Importantly, although variations among diseases existed, they all shared a common characteristic: a rupture of the "normal" increase of complexity scores as a function of age [24,25] that was recovered with clinical improvement [23].

The present study was designed to investigate non-linear MEG patterns in BD, and more precisely, to assess whether BD patients also exhibit the above described rupture of the "normal" increase of complexity scores as a function of age. Contrary to the vast majority of precedent neurophysiological studies that compared BD and SZ, we decided to investigate *LZC* patterns in BD and major depression (MD). Such decision was based on the fact that both diseases share some key characteristics as mood disorders and misdiagnosis frequently occurs. As a consequence, it might be intuitively hypothesized that complexity scores in BD may exhibit a similar behavior as compared with MD patients. Nevertheless, previous studies (see for example [26]) reported quite distinct MEG patterns in both clinical conditions, and therefore such intuitive hypothesis might be questioned.

2. Methods

2.1. Subjects

The sample analyzed in this study included three groups. a) 20 patients who fulfilled the criteria for MD without any diagnosis of comorbid disorders, henceforth called MD group. Patients were moderately to severely symptomatic and remained free of antidepressant treatment for a 3-week period prior to the MEG scan. For a complete description of this group see [23]. b) 16 patients who fulfilled the criteria for bipolar disorder type I (i.e., patients who presented a full manic episode) without any diagnosis of comorbid disorders, henceforth called BD group. BD patients were euthymic at the moment of MEG scans but under pharmacological treatment with lithium salts (70%) or valproate (30%). Notably, BD patients had no previous episodes of psychotic symptoms during the acute phases of the disease. c) 24 Control (CON) subjects.

Patients' inclusion criteria for BD and MD were based on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) [27]. Only patients underwent SCID evaluation. Subjects with a history of head trauma, drug abuse (including alcohol dependence) or neurological diseases were excluded from the study. The average age of the MD group was 47.5 ± 13 (mean ± standard deviation, SD; age range 26 to 66 years) and it was composed of eight males and twelve females. As for the BD group, the average age was 46.4 ± 18.7 years (mean ± SD; age range 21 to 69 years) and it was composed of eight males and eight females. Finally, the 24 control volunteers (12 males and 12 females) had no history of psychiatric disorder. Their average age was 41.25 ± 13.3 years (mean ± SD; age range 24 to 64 years). The differences in age between the MD and CON and the BD and CON groups were not significant (p-value = 0.12 and 0.33, respectively, Student's t-test).

The regional ethics committee for clinical research approved this investigation and all participants gave their informed consent to participate in this study.

2.2. MEG acquisition

In this study, a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) located in a magnetically shielded room at the "Centro de Magnetoencefalografía Dr. Pérez-Modrego," Spain, was used to acquire the MEG recordings. Resting state brain activity was recorded while each volunteer was lying on a patient bed, awake and with eyes closed. For each subject, 5 min of MEG background activity were recorded at 678.19 Hz with a 0.1–200 Hz hardware bandpass filter. The MEG equipment decimated each 5-min recording by a factor of four using a second-order Butterworth IIR anti-aliasing filter, which was applied in both forward and reverse directions with cut-off frequency at 76.30 Hz (45% of the final sampling frequency: f_s = 169.54 Hz). Finally, the recordings were transferred to a computer as ASCII files.

A visual inspection assisted with an amplitude thresholding method [28] was used to select the MEG epochs of 10s with reduced ocular activity for further analysis, blind to the subject's diagnosis. The average number of epochs available for analysis in each group (given as mean ± SD) is 28.8 ± 1.36, 27.7 ± 3.8, 28.6 ± 2.0 for MD, BD and CON, in that order. Finally, a 560th order FIR filter designed with a Hamming window was utilized to digitally filter the MEG epochs between 1.5 Hz and 40 Hz to reduce the impact of muscular, ocular and power line artefacts in the analyses.

2.3. Lempel–Ziv complexity calculation

Formally, *LZC* is a non-parametric metric which counts the number of distinct substrings and their rate of recurrence along a given time series. The higher the number of substrings, the higher the *LZC* value, which is then associated with more complex data [29]. *LZC* requires the signal to be discretized into a small number of symbols (often just two) according to a predefined rule. To do so, in this study, we followed the common practice of binarizing the time signal using its median as threshold due to its robustness to outliers [30,31]. Then, the sequence of symbols is scanned from left to right. A complexity counter $c(N)$ is increased by one unit every time a new subsequence of consecutive symbols appears [31]. However, this would result into a complexity measure dependent on the signal length. To avoid this problem, the value of the counter can be normalized dividing it by $b(N) = N/\log_a(N)$, with a indicating the number of symbols used in the discretization. The normalized *LZC* can be computed as $LZC(N) = c(N)/b(N)$. It is bounded between 0 and 1.

2.4. Data reduction and statistical analyses

In this study, *LZC* features were computed for each 10s epoch, channel and subject in the three groups (MD, BD and CON). For each channel and subject, the results were averaged across epochs. We