Journal of Affective Disorders 243 (2019) 274–279

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Nonlinear dynamics of mood regulation in unaffected first-degree relatives of bipolar disorder patients

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ARTICLE INFO

Keywords:
Nonlinear
Mood regulation
Time-series
Bipolar disorder
Unaffected relatives

ABSTRACT

Background: Mood regulation is a complex and poorly understood process. In this study, we aimed to analyze the underlying dynamics of mood regulation in unaffected first degree relatives of patients diagnosed with bipolar disorder using time-series analysis.

Methods: We recruited 30 unaffected first-degree relatives of bipolar disorder patients. Participants rated their mood, anxiety and energy levels using a paper-based visual analog scale; they recorded their sleep and life events as well. Participants provided information on these variables over a three month period, twice per day. We compared their data using Box-Jenkins time series analysis with data from 30 healthy controls (HC) and 30 euthymic bipolar patients (BD) to obtain information on the autocorrelation and cross-correlation of the series, and calculated entropy for mood, anxiety and energy series.

Results: We analyzed 14,980 data points: 5200 in the healthy control group; 4970 in the bipolar group and 4810 in the unaffected relatives group. There were no significant differences between groups in terms of age, sex or education levels. Using Kolmogorov-Smirnov test, we found that individual measures were normally distributed in the whole sample ($D = 0.23$, $p > 0.1$). Autocorrelation functions for mood in all groups are governed by the ARIMA (1,1,0) model, which means that current values in the series are related to one previous point only. In terms of entropy for the mood series, unaffected relatives and bipolar patients showed lower values [mean (SD) : 1.028 ± 0.679; 1.042 ± 0.680], respectively, compared to healthy controls [(1.476 ± 0.33); F (2,74) = 4.39, $p < 0.01$]. The same case was seen in the energy series, with lower values in the unaffected relatives and bipolar patient groups [mean (SD) : 1.644 ± 0.566; 1.511 ± 0.879], respectively, compared to healthy controls [2.230 ± 0.531; F(2, 75) = 7.89, $p < 0.001$].

Limitations: Low resolution for the visual analog scale.

Conclusions: Using nonlinear analyses, we found that the underlying structure of mood regulation in unaffected relatives is undistinguishable from the one found in bipolar patients. Compared to healthy controls, both bipolar patients and their unaffected relatives showed lower entropy levels, which is in keeping with a more rigid system, not as flexible to cope with the demands of a changing environment.

1. Introduction

Evidence from family, twin and adoption studies indicates a heritable component to bipolar disorder (Craddock and Jones, 1999). Because unaffected relatives share a proportion of the genetic material with the patient, abnormalities found in unaffected relatives may reflect trait-related neurobiological markers of the illness. In this sense, similar structural (Chaddock et al., 2009; McDonald et al., 2004; van der Schot et al., 2009) and functional (Antila et al., 2007; Drapier et al., 2008; Schulze et al., 2011; Surguladze et al., 2010; Thermenos et al., 2010; Zalla et al., 2004) abnormalities in both unaffected relatives and bipolar patients have been described, particularly in relation to neural responses to emotional stimuli (Kruger et al., 2006; Surguladze et al., 2010) and cognitive challenges (Kanske et al., 2015; Thermenos et al.,

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https://doi.org/10.1016/j.jad.2018.09.034
Received 14 May 2018; Received in revised form 14 August 2018; Accepted 15 September 2018
Available online 18 September 2018
0165-0327/

2010; Whalley et al., 2011).

High-risk offspring studies have shown similar concentrations of metabolites in unaffected and affected participants at high genetic risk for bipolar disorder (Hajek et al., 2008). Other studies have shown higher anxious temperament (Mendlowicz et al., 2005); decreased P300 latency delays (Schulze et al., 2008) and resting state EEG oscillatory abnormalities (Narayanan et al., 2014) in both bipolar and unaffected relatives. An aspect of stimulus processing therefore appears to be compromised in both patients and unaffected relatives. More specifically, studies have reported a response bias towards negative stimuli in unaffected siblings of bipolar patients (Brand et al., 2012), as well as the overuse of maladaptive emotion regulation strategies, such as rumination and self-blame (Green et al., 2011). However, in spite of such findings, the question remains how to integrate these to explain mood regulation in this population.

Mood regulation is a complex and poorly understood process. It can be conceived as a system of regulation allowing flexible responses to changing conditions, such as stress and life events. When this system is unable to engage proper responses, depressive or manic episodes can occur.

Mood patterns in bipolar disorder, although aperiodic, may be more organized than those of healthy subjects, which led to the description of mood in bipolar patients in terms of chaotic (nonlinear) dynamics (Gottschalk et al., 1995). In simple terms, a system with two input sequences is nonlinear if their combined effect is different from the sum of the individual sequences. Nonlinear methods offer new tools with which to quantify, model, and attempt to predict the behavior of complex systems (Ehlers, 1995; Pincus, 2001). Entropy is a type of nonlinear method that measures the amount of noise or disorganization in a system. There are different types of entropy-based measures, not all relevant in biology. Here we are using a type called multiscale entropy, which is suitable for measurement of the complexity of a system. Typically, lower entropy levels (corresponding to recognizable patterns in the data), may indicate impaired physiological regulations, as in cardiovascular (Jelinek et al., 2013) and metabolic diseases (Wu et al., 2013), premenstrual dysphoric disorder (Pincus et al., 2008) and bipolar disorder (Ortiz et al., 2015).

A related nonlinear measure is time-series analysis, usually employed to study a collection of observations made sequentially in time (Chatfield, 2016). A special feature of time-series analysis is that successive observations are not independent and that the analysis must take into account the time order of the observations. In other words, time-series analysis is a tool used to study the behavior of variables over time. Time-series data is a type of random variable which is time-ordered. Using time series analysis, findings implicitly associating greater regularity with illness have been found during fatal ventricular tachyarrythmias (Pincus and Goldberger, 1994), and before and after generalized seizures (Chen et al., 2000).

Our primary objective was to analyze the underlying dynamic processes involved in mood regulation in unaffected first-degree relatives of bipolar disorder subjects using time series analyses and entropy calculations. Subsequently, we aimed to compare these results with our prior results in bipolar patients and healthy controls (Ortiz et al., 2015). We hypothesized that: (a) A simple memory stochastic process would underlie mood regulation in all groups and (b) Healthy subjects would present higher variability in their time-series as well as higher entropy values compared to bipolar disorder patients and their first-degree relatives.

2. Methods

2.1. Subject recruitment

Thirty unaffected first-degree relatives (FDR) of bipolar patients aged 18–70 were recruited for this study. Participants who gave consent to participate in the study were interviewed by a psychiatrist to rule out any current or lifetime psychiatric diagnosis. The diagnostic interview followed the Schedule for Affective Disorders and Schizophrenia, Lifetime Version (SADS-L) format (Endicott and Spitzer, 1978). Participants in the unaffected FDR were not necessarily related to those participants in the bipolar (BD) group.

As per our prior paper (Ortiz et al., 2015), we recruited 30 healthy controls and 30 euthymic bipolar I / II patients followed at the Mood Disorders Program at the QEII Health Sciences Center. This sample has been well characterized previously (Ortiz et al., 2011). All study procedures were approved by the Research Ethics Committee at the QEII Health Sciences Centre and by the Research Ethics Committee at the Royal Ottawa Hospital.

2.2. Measurements

As per our prior paper on mood regulation (Ortiz et al., 2015), we used a paper-based visual analog scale to measure mood, anxiety, and energy levels (Folstein and Luria, 1973; Luria, 1975). The scale ranges from '1' to '9', with '5' being 'their usual'; the scale also quantifies total sleep time. Participants provided measurements on these variables over a three month period, on an everyday basis, twice a day. The first rating was completed one hour after waking up, and the second rating one hour before bedtime. For incomplete data in the scale (one day or two days in a row), we used interpolation methods; if more than two days were missing consecutively (usually at the end of the study), the rest of the data was removed from the calculations. Overall, however, time-series analysis is relatively insensitive to small amounts of missing data.

In order to obtain related information that could account for mood changes during the study, we systematically recorded life events experiences through the Interview for Recent Life Events (Paykel et al., 1969), a reliable instrument for assessing stressful life events (Paykel, 2001). Subsequently, we quantified the number and type of life event(s) for each participant and each group.

2.3. Assumptions

As per our prior paper, the analyses performed relied on three assumptions:

We assume that the datapoints S_i (for $i = \{1, 2,\ldots,9\}$) represent an interval scale. This means that we consider the data not only to be a totally ordered set $\{S_i\}$ ($S_i < S_{i+1}$ for all measured quantities) but also that the differences between i and j ($i \neq j$) do have a specific meaning.

The second assumption is about the validity of a model to which we try to fit the data. If our data were noise-free and of high resolution, we could attempt to fit complex models corresponding to sophisticated stochastic processes; however, under the current conditions we will be satisfied with the first-order departure from a completely random process (white noise) - the autoregressive process AR(1).

Finally, given the character of the data, we cannot expect to be able to verify the requirement of strict stationarity, but we may relax this notion and ask the time series to satisfy *weak* stationarity (by the standard procedure of taking first differences and inspecting the resulting autocorrelation functions) (Box, 1976). That is, we require only the first two moments (mean and variance) to be time-invariant. The requirement of at least weak stationarity is crucial for the analysis of the Box-Jenkins style outlined below. In summary, (a) the character of the collected data represents an interval scale, as the processes we are trying to study do not need to be proportional to the scale and most likely are logarithmic, as seen in other human phenomena (Varshney and Sun, 2013); (b) we were careful not to overfit the data, as our series are noisy and (c) we asked the data to satisfy weak stationarity in order to be able to use time-series analysis.

2.4. Data analysis

Auto-correlation and cross-correlation: All distributions (morning