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Illness severity, trait anxiety, cognitive impairment and heart rate variability in bipolar disorder

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ABSTRACT

Numerous studies have documented a significant association between symptom severity and cognitive functioning in bipolar disorder (BD). These findings advanced speculations about a potential link between the physiological stress associated with illness severity and cognitive dysfunction. To explore this hypothesis, the current study employed heart rate variability (HRV) as a physiological measure that is sensitive to the effects of chronic stress, and a scale of trait anxiety for assessing a psychological condition that is correlated with hyper sympathetic arousal. Analyses indicated that BD patients with High Illness Severity reported more symptoms of trait-anxiety (i.e., State Trait Anxiety Inventory), performed more poorly on a computerized neuropsychological battery (i.e., CNS Vital Signs), and exhibited a more constricted HRV profile (i.e., lower SDNN with elevated LF/HF ratio) than patients with Low Illness Severity. Illness severity was determined by a history of psychosis, illness duration, and number of mood episodes. A third group of healthy controls ($n=22$) performed better on the neuropsychological battery and exhibited a healthier HRV profile than the BD groups. This study provides preliminary evidence that illness severity and cognitive impairment in BD may be associated with state anxiety and neuro-cardiac alterations that are sensitive to physiological stress.

1. Introduction

Neuropsychological research in bipolar disorder (BD) revealed the presence of cognitive deficits that linger beyond the resolution of mood disturbance (Martinez-Aran et al., 2004b; Goldberg and Burdick, 2008). Studies suggest that chronic cognitive impairment tends to emerge in patients who suffer from a more severe course of illness (Martinez-Aran et al., 2004a; Robinson et al., 2006; Torres et al., 2007), as indicated by the presence of psychosis (Bora et al., 2007), and increased number of mood episodes and psychiatric hospitalizations (Denicoff et al., 1999; Robinson and Ferrier, 2006). These findings led to speculations about the role of physiological stress associated with illness severity in the development of cognitive dysfunction (Goodwin et al., 2008; Kapczinski et al., 2008; Berk et al., 2011; Vieta et al., 2013).

Previous findings provide preliminary evidence for the ill effects of physiological stress in BD. Physiological stress was implicated by research that revealed disproportionally high stress-related pathology in BD. Studies point to increased medical burden in BD, as indicated by higher rates of cardiovascular disease, diabetes mellitus, and obesity (Kupfer, 2005; McIntyre et al., 2007). On the psychological level, emotional correlates of excessive activation of physiological responses to stress, specifically in the form of anxiety, are also evident in BD.

A large volume of studies has documented extensive comorbidity between BD and anxiety disorders (Freeman et al., 2002; Simon et al., 2004). Co-morbid anxiety disorders predict more frequent mood episodes (McElroy et al., 2001; Baldassano, 2006; Pini et al., 2006) and poor prognosis (Henry et al., 2003; El-Mallakh and Hollifield, 2008; Lee and Dunner, 2008; Azorin et al., 2009; Coryell et al., 2009). In an integrative view, studies have separately linked chronic anxiety and cognitive impairment to greater illness severity in BD. However, these variables have not been examined jointly within a single sample. In addition, there is little data linking signs of chronic physiological stress to cognitive impairment or illness severity in BD.

The current study thus aimed to explore whether the cognitive impairment that develops in more symptomatic BD patients is accompanied by physiological and emotional correlates of chronic physiological stress. For this purpose, the study administered a measure of trait anxiety. This measure assesses an emotional state of chronic worry, which has been previously linked to an over activation of the hypothalamic pituitary adrenal (HPA) axis mediated stress responses (O'Connor et al., 2009; Walker et al., 2011). On the physiological side, the study employed heart rate variability (HRV) as a quantitative measure of neuro-cardiac

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activity that is sensitive to the effects of chronic physiological stress.

HRV refers to the temporal variance in heartbeats, and it is often measured by the standard deviation of the beat-to-beat interval (SDNN). Constriction in HRV is associated with chronic stress and poor cardiac health (Dishman et al., 2000). In psychiatric research, studies have documented a wide range of conditions, such as generalized anxiety disorder (Yeragani et al., 1998) and depression (Yeragani et al., 2002) that are susceptible for both chronic physiological stress and abnormal reduction in HRV. In addition, there is evidence that cardiac data predict physical (Lombardi, 2002; Rugulies, 2002) and mental health (Rottenberg et al., 2002) outcomes in psychiatric patients. In BD research, several studies detected constricted HRV in euthymic patients relative to controls (Cohen et al., 2003; Latalova et al., 2010). The current study explored whether constriction in HRV, elevation in trait anxiety and cognitive impairment co-occur in BD patients with a more severe course of illness.

2. Method

2.1. Overall design

Participants were assigned to three groups: Bipolar I disorder with High Illness Severity (HIS), Bipolar I disorder with Low Illness Severity (LIS), and HC. The HC group ($n=22$) consisted of participants who did not meet diagnostic criteria for a psychiatric disorder. Those who met diagnostic criteria for BD-I disorder were assigned to the High ($n=13$) and Low ($n=17$) Illness Severity groups according to the presence or absence of a previous psychotic episode. To evaluate whether a history of psychosis served as an effective proxy to the larger construct of illness severity, subsequent comparative analysis evaluated group differences in episode recurrence, hospitalizations, and age of onset. The hypothesis was that, relative to the other groups, BD patients with higher illness severity would exhibit lower cognitive test scores, higher scores on a self-report measure of trait anxiety, and a more constricted HRV profile.

2.2. Sample and recruitment

The sample consisted of 30 participants with a BD-I diagnosis and 22 HCs. Potential participants responded to advertisements that were posted in mental health community centers and university campuses around the Boston area. A brief telephone screening assessed for enrollment eligibility, based on a standard protocol that was developed for the study. This procedure excluded people who (1) experienced a mood episode 3 months prior to the interview, (2) carried a diagnosis of a primary psychotic disorder, (3) reported an ongoing serious medical condition, or (4) a history of neurological disorder, (5) participated in substance abuse treatment 6 months prior to the interview, (6) received electroconvulsive therapy (ECT) 12 months prior to the interview, and (7) reported current use of medication with cholinesterase inhibitors/agonists or neuromuscular blocking agents. During the screening interview, on going serious medical conditions referred to life threatening/limiting injury or illness, such as physical trauma, cancer, cardiac illness (with a history of hospitalization), internal organ dysfunction, acute endocrinological dysregulation, emphysema, or any other condition that required recent hospital care or necessitated on going medical monitoring (e.g., serious infection). Neurological disorders referred to a history of brain injury with loss of consciousness, seizure disorders, dementia, stroke, or any reported condition affecting the central nervous system and cognitive functioning. Fifteen participants were excluded during the preliminary screening phase.

The second phase of screening included an in-person interview. Participants enrolled in the study if they met diagnostic criteria for BD-I (or did not meet criteria for any psychiatric disorder in the case of HC) without a co-occurring substance use disorder, scored less than 10 points on both the Beck Depression Inventory – Second Edition (BDI-II) and the Young Mania Rating Scale (YMRS), and signed a written informed consent. During the second screening phase, eight participants were excluded, primarily due to elevated mood symptoms. The enrolled sample consisted of 30 participants with BD-I, and 22 HCs. In the entire sample, there were 25 women. Fourteen participants identified an affiliation with an ethnic minority group. The age range in the sample was 19–59. Participants with BD reported taking on average 2.6 (S.D.=0.9) psychotropic medications (anticonvulsants or mood stabilizers=19, antipsychotics=26 anxiolytics=11, and lithium=21).

2.3. Instruments

2.3.1. Diagnostic measures

A diagnosis of BD-I was established with the Structured Clinical Interview for DSM-IV–P/I (SCID; First et al., 1994). The SCID is a widely used, reliable and valid diagnostic instrument, which includes a semi-structured interview about symptoms for various disorders. This study employed the modules for mood, psychotic and substance use disorders.

2.3.2. Mood and anxiety measures

To evaluate manic symptoms, participants were assessed with the YMRS (Young et al., 1978). YMRS is a clinician-administered assessment instrument, which adheres to a semi-structured interview with defined anchor points. This measure systematically assesses all the symptoms of BD (e.g. mood expansion, sleep, irritability, racing thoughts, etc.). Each item receives a score between 0–4 and 0–8. The YMRS is the most extensively used instrument in BD research, aiming to quantify the degree of manic symptoms in patients who already have a diagnosis of BD.

In order to assess symptom of depression, participants completed the BDI-II (Beck et al., 1996; for psychometric properties, see Dozois et al. (1998). This inventory covers all nine symptoms of depression with 21 questions on an item scale that ranges between 0 and 3. The aggregate score indicates symptom severity, with a cutoff score for mild depression of 13.

Participants further completed the State Trait Anxiety Inventory (STAI; Spielberger et al., 1970). The STAI is a self-report instrument that differentiates between the temporary condition of state anxiety and the longstanding quality of trait anxiety with two distinct scales, each containing 20 items. It is scored on a 4-point Likert scale with a range of raw scores between 20 and 80, and scaled scores with a mean of 50 and a standard deviation of 10.

2.3.3. Measures of substance abuse/dependence

The study applied two highly reliable and valid screening questionnaires for alcohol and substance abuse: the Alcohol Use Disorder Identification Test (AUDIT; for psychometric properties see Reinert and Allen (2002), and the Drug Abuse Screening Test – 20 item (DAST; for review on psychometrics see Yudko et al. (2007). These measures assessed potential problems that resulted from excessive drinking or drug use during the year prior to study enrollment. In the current study, these measures were used to exclude subjects with an active substance use disorder.

2.3.4. IQ

In order to obtain a valid IQ estimate, participants completed two subtests from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) – Vocabulary and Matrix Reasoning, which allow for the calculation of a full-scale IQ score. The Vocabulary subtest assesses verbal fund of knowledge. Subjects provide definitions for words on a scale of increasing difficulty. Matrix Reasoning assesses visual spatial abilities, and non-verbal abstract thinking. The test requires subjects to complete visual patterns according to principles that increase in level of complexity and abstraction. The WASI was developed specifically to ease the client/subject burden of IQ assessment in research settings and clinical practice.

2.3.5. The neuropsychological assessment

Participants completed the CNS Vital Signs (CNS VS) battery (O'Halloran et al., 2008; Gualtieri and Johnson, 2006), which was designed as a valid and reliable computerized equivalent to the paper-and-pencil version of the MATRICS Consensus Cognitive Battery. CNS VS includes verbal and visual memory tests with a recognition paradigm. Participants are presented with 15 words and geometric figures in 2 s. intervals, and an immediate and delay recall tests in a yes/no format. Verbal and visual memory scores aggregate to a memory composite score. In the domains of processing speed, attention, and executive functioning, the battery consists of several subtests. It includes the Symbol Digit Coding (SDC) variant of the Wechsler Digit Symbol substitution test. On this test, subjects are provided with an index of symbols-digit dyads, and they are required to match digits to symbol stems, according to this index, as fast as they can. In the executive domains, the CNS VS also includes an altered version of the Stroop test, which assesses inhibitory control. On this test, subjects are required to name the color of the fonts of color-words, instead of reading the words, under time pressure. The battery further includes a standard Shifting Attention Test (SAT), which measures the subject's ability to respond to alternating sets of rules. On this task, participants receive changing instructions to match between figures according to either shape or color. Working memory was primarily assessed with a Continuous Performance Task (CPT), which progressed from basic to more advanced conditions, such as one and two backward paradigms. Finally, the battery included a social acuity test, which required participants to quickly identify matches/mismatches between facial expressions and verbal labels of emotions. The computer software of CNS VS applies an algorithm, which derives data across subtests, to calculate composite scores (with a mean of 100 and S.D. of 15) of memory, processing speed, reaction

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