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A longitudinal study of cognition in asymptomatic and mildly symptomatic bipolar disorder patients

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ABSTRACT

Bipolar disorder (BD) is characterized by cognitive deficits that impair patients' functioning and quality of life. Most of the earlier studies assessing changes in BD patients' cognitive functioning over time utilized a cross-sectional research design. The few longitudinal studies that were conducted tended to have methodological limitations such as very short follow-up periods, recruitment of acutely ill patients, and lack of assessment of practice effects. The current study aimed to assess changes over time in the cognitive functioning of typical BD outpatients. For this purpose, asymptomatic and mildly symptomatic BD outpatients were assessed at baseline and after two years ($n=31$). At baseline, the cognitive functioning of the BD patients was compared to that of gender- and age-matched healthy controls. Practice effects were estimated by re-assessing the controls one week after their first assessment. Compared to the controls, BD patients had deficits in psychomotor speed, sustained attention, and one domain of executive functioning (cognitive planning). No evidence was found of a decline in their cognitive functioning over the two year time interval. These findings support a developmental model of cognitive impairment in BD. Studies using longer follow-up periods and larger sample sizes, however, are needed before these conclusions can be stated confidently.

1. Introduction

Bipolar disorder (BD) is associated with cognitive impairments that are a major source of functional impairment and disability (Martinez-Aran et al., 2007; Sanchez-Moreno et al., 2009; Wingo et al., 2009). While cognitive impairments were traditionally considered infrequent or limited to affective episodes, more recent studies have stressed the persistence of cognitive deficits during euthymia. Euthymic BD patients were found to be impaired in a variety of cognitive domains, such as psychomotor speed, attention, episodic memory, and executive functioning (Robinson et al., 2006; Torres et al., 2007). These studies stress the chronic nature of cognitive impairment in BD and raise important questions regarding the course of BD patients' cognitive functioning over the life span of the patients. Studies assessing the effects of variables such as illness duration, repeated affective episodes and the passage of time on BD patients' cognitive functioning attempted to address these questions (see review; Goodwin et al., 2008). It has been suggested that their findings, although not fully consistent, tend to support a neurodegenerative model (i.e., decline in functioning) in at least some cognitive domains (Goodwin et al., 2008). For example, Robinson and Ferrier (2006) reviewed cross-sectional studies and concluded that cognitive deficits of BD patients are associated with a worse prior course of illness (reflected in variables such as number of manic episodes and length of illness). It should be noted however that most of these earlier studies used a cross-sectional research design. Such a research design is prone to selection bias (i.e., differences in characteristics between subgroups). A longitudinal approach in this regard may be better suited to provide direct information regarding the course of cognitive functioning over time.

Only a few longitudinal studies however assessed the cognitive functioning of BD patients (as remarked by Goodwin et al. (2008) and Robinson and Ferrier (2006)). Interestingly, these studies tended to support a developmental model of cognitive impairment in BD. For example, Mur et al. (2008) assessed 33

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euthymic BD patients over a two-year time interval and found no evidence for a more rapid decline in their cognitve functioning compared to healthy controls. The findings of these longitudinal studies therefore diverge from that of the earlier reviewed cross-sectional studies. Since cross-sectional studies are prone to biases (as indicated earlier), it may thus be tempting to conclude that longitudinal studies provide a more accurate picture regarding changes over time in BD patients' cognitive functioning. This conclusion however can be stated at present only tentatively. First, the paucity of longitidinal studies limits inferences at present. Second, many previous longitudinal studies have noteworthy limitations that hinder inferences based on their findings, including: (a) very short follow-up period (e.g., three months; Chaves et al., 2011) and small sample sizes (e.g., $n=15$: Balanza-Martinez et al. (2005); $n=15$: Delaloye et al. (2011); $n=18$: Engelsmann et al. (1988); $n=20$: Moorhead et al. (2007)), two factors that might undermine the ability to detect changes over time in cognition. (b) Comparison of patients in an acute affective episode to a later time in which the patients were in a sub-acute or remitted state (e.g., comparing patients at admission and discharge; Liu et al., 2002), and therefore confounding the effect of time with reduction in symptom severity. (c) Failing to thoroughly evaluate practice effects (i.e., not assessing healthy controls or assessing them at only one point in time, for example Balanza-Martinez et al. (2005)). Overall, there is a need for additional longitudinal studies assessing the cognitive functioning of BD patients.

The current study used a naturalistic longitudinal research design (two-year follow-up period) to explore the cognitive functioning of BD patients. We aimed to investigate typical patients treated in outpatient psychiatric clinics, patients who face functional challenges (e.g., in the vocational domain) that are strongly affected by their cognitive functioning (Sanchez-Moreno et al., 2009). Beside asymptomatic patients, mildly symptomatic patents were also included in the study. Their inclusion is in line with studies indicating that a substantial proportion of BD patients continue to show persistent subsyndromal symptoms (Judd et al., 2003, 2002). We hypothesized that the BD patients would be impaired in the domains of psychomotor speed, sustained attention and executive functioning (Bora et al., 2006; Mur et al., 2007; Robinson et al., 2006), but not in visual-spatial memory (in line with Braw et al. (2007)), compared to the healthy controls. Following Mur et al. (2008) and most longitudinal studies of adult BD patients, no decline in the cognitive functioning of the BD patients over the follow-up period was expected. In this regard, it should be noted that several longitudinal studies of older (i.e., geriatric) BD patients did suggest a more rapid cognitive decline among these patients compared to healthy controls (e.g., Gildengers et al., 2009). However, since the current study focused on adult patients, we avoided basing our hypotheses on geriatric patients who may show a different cognitive profile than adult patients.

2. Methods

2.1. Participants

Inclusion criteria were: (a) 18 to 65 years old; (b) diagnosis of BD I or II. Diagnosis was established at baseline (T1 assessment) and at the follow-up assessment (T2) by two senior psychiatrists using the Structured Clinical Interview for DSM-4-TR (SCID-I/P; First et al., 2002b); (c) and clinical stability, as determined by observations of patients in an outpatient setting for at least three months prior to study entry. During these three months no changes were evident in pharmacological treatment, clinical status (i.e., changes in diagnosis or a significant exacerbation of symptoms), or functioning (i.e., changes in vocational or marital status). Exclusion criteria included any one of the following: (a) lifetime axis-I psychopathology other than BD; (b) significant affective symptoms (more than mild affective symptoms), as evidenced by a total score ≥ 15 on the Young Mania Rating Scale (YMRS; Young et al., 1978) and/or the Hamilton Depression Rating Scale 17-items (HDRS; Hamilton, 1960) (based on Martino et al. (2009), Tohen et al. (2009)); (c) any acute, unstable, significant or untreated medical illness (especially neurological disorders such as head trauma); (d) mental retardation or borderline intelligence (<80 full scale I.Q. according to the patients' medical records and/or attendance in a special education program); (e) current drug abuse or substance dependency problem; or (f) recipient of electroconvulsive treatment (ECT) less than six months prior to study entry.

Healthy volunteers were recruited by advertisements posted around the Shalvata Mental Health Center. They were matched in gender and age (± 3 years) to BD patients that completed the study protocol ($n=31$). Inclusion/exclusion criteria for healthy controls were similar to that of the BD patients (except diagnosis). They had no Axis I psychopathology as determined using the non-Patient Edition of the SCID (SCID-I/NP; First et al., 2002a).

The study complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the Institutional Review Board (IRB) committee. All participants gave written informed consent after the nature of the procedures had been fully explained to them.

2.2. Procedure

Participants underwent a clinical interview in which the following aspects were assessed: (a) Affective symptoms: HDRS 17-items and YMRS. (b) General assessment of psychopathology: Clinical Global Impression (CGI; Guy, 1976). (c) Functioning: General Assessment of Functioning (GAF; American Psychiatric Association, 2000). The participants then underwent a cognitive evaluation using the Cambridge Neuropsychological Test Automated Battery (CANTAB). The CANTAB is a reliable and extensively validated computerized assessment battery. It has been used to study a wide range of disorders and age ranges (De Luca et al., 2003; Luciana, 2003; Sahakian and Owen, 1992). The following tasks were presented in a semi-randomized fashion.

Psychomotor speed (Motor Task; MOT): This task was designed to accustom the participant to the CANTAB interface and to assess his/her psychomotor speed. As part of the task, a series of crosses are presented in different locations on the screen. The speed in which the participant touches the crosses is recorded. The selected measure was "response latency" (msec).

Sustained attention (Rapid Visual Processing task; RVP): The task is in essence a Continuous Performance Test (CPT), used as a measure of sustained attention. As part of the task, the participant is required to detect three target sequences (each composed of three digits) among serially appearing digits. The selected measure was "A'" representing the participant's ability to detect the target sequence.

2.2.1. Visual-spatial memory

A. Pattern Recognition Memory (PRM task): This is a task of visual pattern recognition memory. As part of the task, abstract visual stimuli are displayed sequentially on the computer screen. Each stimulus is then presented with a novel stimulus and the participant is asked to choose the one that had been previously shown. The selected measure was "% of correct responses".
B. Spatial Recognition Memory (SRM task): This is a task of spatial recognition memory. As part of the task, five identical squares are presented in series, each at a different location. One square is then presented at each target location along with a square in a new location. The participant is asked to choose the square at the location he recognizes from the initial learning phase. The selected measure was "% of correct responses".

2.2.2. Executive-functions

A. Working memory (Spatial Working Memory task, SWM): The task assesses the ability to retain and manipulate information in spatial working memory. The trial begins with a number of colored squares (boxes) and the goal of the participant is to find a blue "counter" in each of these boxes. The participant must touch each box in turn until opening one that contains a blue counter. Returning to an empty box already sampled on this search constitutes an error. The selected measure was "number of errors".
B. Cognitive shifting and flexibility (Intra/Extra dimensional shift task, ID/ED): The task assesses the ability of the participant to shift between intradimensional (ID) and extradimensional (ED) sets, as well as the capacity for reversal learning. It is considered a computerized analog of the Wisconsin Card Sorting Task (WCST; Eling et al., 2008). Two artificial dimensions are used in the task (color-filled shapes and white lines). During the task, two stimuli (one correct, one incorrect) are displayed and feedback teaches the participant which stimulus is correct. Later, several shifts are introduced to which the participant has to adjust. The selected measure was "number of errors". The number of errors is a measure of the participant's performance, adjusted to the fact that participants completing fewer levels also have fewer chances to make errors.