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Research report

Relationship between neurocognitive functioning and episode recurrences in bipolar disorder

Diego J. Martino [a,*], Sergio A. Strejilevich [a,b,*], Eliana Marengo [a], Ana Igoa [a], Guillermo Fassi [a], Julia Teitelbaum [a], Pablo Caravotta [a]

[a] Bipolar Disorders Program, Neuroscience Institute, Favaloro University, Congreso 2477, Buenos Aires, Argentina
[b] Institute of Cognitive Neurology (INECO), Buenos Aires, Argentina

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ABSTRACT

Background: The relationship between neurocognitive impairment and clinical course in bipolar disorder (BD) is inconclusive. The aim of this study was to compare time to recurrence between patients with and without clinically significant cognitive impairment.
Methods: Seventy euthymic patients with BD were included. Based on baseline neurocognitive performance, patients were divided into those with ($n=49$) and those without ($n=21$) clinically significant cognitive impairment. Both groups of patients were prospectivelly assessed by a modified life chart method during a mean of 16.3 months.
Results: Patients with some cognitive domain compromised had an increased risk of suffering any recurrence (HR: 3.13; CI 95%: 1.64–5.96), hypo/manic episodes (HR: 2.42; CI 95%: 1.13–5.19), or depressive episodes (HR: 3.84, CI 95%: 1.66–8.84) compared with those patients without clinically significant cognitive impairment. These associations remained significant after adjusting for several potential counfounders such as number of previous episodes, time since last episode, clinical subtype of BD, exposure to antipsychotics, and subclinical symptoms.
Limitations: We classified patients as with or without clinically significant cognitive impairment, although deficits in different cognitive domains may not be equivalent in terms of risk of recurrence.
Conclusions: The results did not support the hypothesis that the experience of successive episodes is related to a progressive neurocognitive decline. On the contrary, cognitive impairment could be the cause more than the consequence of poorer clinical course. Alternatively, a specific subgroup of patients with clinically significant cognitive impairment and a progressive illness in terms of counts of recurrence and shortening of wellness intervals might explain the association showed in this study.

1. Introduction

It is now widely acknowledged that patients with bipolar disorder (BD) exhibit neurocognitive impairment in domains of verbal memory, attention, and executive functions even during euthymic periods (Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Kurtz and Gerraty, 2009). Moreover, a positive association between neurocognitive dysfunction and different measures of disability both in cross-sectional (Zubieta et al., 2001; Dickerson et al., 2004; Martinez-Arán et al., 2004) and longitudinal (Jaeger et al., 2007; Tabarés-Seisdedos et al., 2008; Martino et al., 2009) studies have been shown.

Beyond this growing body of evidence, recent studies showed that the percentage of patients with clinically significant neurocognitive impairments fluctuate between 30% and 62% (Martino et al., 2008a; Gualtieri and Morgan, 2008; Reichemberg et al., 2009; Iverson et al., 2011). These findings suggest that studies reporting mean values of neurocognitive functioning in BD might be failing to recognize that a subgroup of patients is demonstrating most of the impairment. In other words, some people with BD might have a neurocognitive functioning within of normal limits while other patients may show poorer cognitive performance than the usually reported in literature. Genetic–environmental interactions might contribute to understanding the differences between patients with BD in neurocognitive functioning. In fact, preliminary evidence showed that several environmental factors such as obstetric complications (Martino et al., 2008a), childhood trauma (Savitz et al., 2008), infection with herpes simplex virus type 1 (Dickerson et al., 2006; Gerber et al., 2012), comorbidities with anxiety disorders (Wu et al., 2011), alcohol abuse (van Gorp et al., 1998; Levy et al., 2008;

* Corresponding authors at: Congreso 2477 PB D, C1428BVK, Capital Federal, Argentina. Tel./fax: +54 11 4833 2424.
E-mail addresses: diejmartino@gmail.com (D.J. Martino), sstrejilevich@ffavaloro.org (S.A. Strejilevich).

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Sanchez-Moreno et al., 2009), and exposure to antipsychotics (Donaldson et al., 2003; Frangou et al., 2005; Torrent et al., 2011) had deleterious effects on cognition in BD and, therefore, might contribute to understanding the heterogeneity on neurocognitive functioning among patients with this disorder.

Another variable that was found to be associated with the degree of cognitive impairment in BD was the number of previous episodes. A review about this topic found a negative association between the number of episodes, especially manic ones, with neurocognitive functioning (Robinson and Ferrier, 2006). This finding led authors to suggest that the experience of successive episodes might be related to a progressive neurocognitive decline (Robinson and Ferrier, 2006). Another recent review summarized the positive evidence that cognitive impairment increase as a function of prior number of episodes in patients with BD (Post et al., 2012). Moreover, this association is now usually referred to as further evidence of illness progression in BD (Berk, 2009; Kapczinski et al., 2009; Post et al., 2012). However, these theories contrast with the few and small longitudinal studies about neurocognitive functioning published to date which found a stable pattern of cognitive impairment over time (Balanzá-Martinez et al., 2005; Mur et al., 2008). A notable exception is a recent study by Torrent et al. (2012) that reported a stable pattern of cognitive impairment across a mean of 9 years follow-up period, although with a slight improvement of attention and worsening of executive functioning. Likewise, studies in elderly patients with ethymic BD tend to find the same pattern of cognitive deficits both in terms of domains affected and magnitude reported in younger patients, suggesting, indirectly, no progression in neurocognitive impairment (Schouws et al., 2007; Gildengers et al., 2007; Martino et al., 2008b; Delaloye et al., 2009). Finally, it is noteworthy that all data about the relationship between number of prior episodes and cognition in BD are based exclusively on cross-sectional studies and, therefore, alternatively might also mean that more severe cognitive impairments are the cause of a poorer course of illness. In fact, there were no longitudinal studies designed specifically to assess the relationship between neurocognitive function and recurrence.

Taking into account the above mentioned issues, we reasoned that comparing prospective time to recurrence in patients with and without clinically significant cognitive impairment may provide clues about the relationship between neurocognitive functioning and clinical course in BD. Using such a design and controlling for several counfounders, the aim of this study was to examine if cognitive impairment is a risk factor for a further recurrence in patients with BD. Clarify this issue is important for a better comprehension of the relationship between clinical and neurocognitive variables in BD. We hypothesized that significant cognitive impairment may have an independent effect on time to any recurrence.

2. Methods

Seventy subjects were consecutively selected from the outpatient population of the Bipolar Disorder Program of the Favaloro University with the following inclusion criteria: age between 18 and 60 years, diagnosis of BD type I (BDI) or BD type II (BDII) according to DSM-IV using Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996), euthymic (defined by Hamilton Depression Rating Scale ≤ 9 and Young Mania Rating Scale ≤ 8) for at least 8 weeks, and more than 12 months of prospective follow up. Exclusion criteria were: antecedent history of substance abuse, history of mental retardation, neurological disease, or any unstable clinical condition (like diabetes or hypothyroidism) that could affect cognitive performance. The study was approved by the Hospital Ethics Committee and all subjects gave written informed consent for their participation after receiving a complete description of the study.

2.1. Clinical assessment

In addition to SCID, all subjects were evaluated with the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), and Young Mania Rating Scale (YMRS) (Young et al., 1978). Additional demographical and clinical information was obtained from clinical charts and direct patients interview (age, gender, years of education, age at illness onset, length of illness, bipolar subtype, previous manic/hypomanic and depressive episodes, and lifetime history of psychosis). When possible, attempts were made to verify these historical data with third-party reports (medical records, family interviews, etc). Exposure to antidepressants, mood stabilizers, antipsychotics, and benzodiazepines at the baseline was assessed by the Clinical Scale of Intensity, Frequency, and Duration of Psychopharmacological Treatment (IFD) (Peralta and Cuesta, 2002). This scale provides a quantitative measure of current exposure to different groups of psychotropic medications in a 0–5 points range (0=no medication, 1=sporadic low dose, 2=continued low dose, 3=middle dose, 4=high dose, and 5=very high dose).

2.2. Neurocognitive assessment

After the complete baseline clinical assessment, patients performed an extensive neuropsychological battery selected to assess the following cognitive domains: (1) attention: Backward Digit SPAN (Wechsler, 1955), and Trail Making Test part A (Reitan, 1958); (2) verbal memory: Memory Battery of Signoret (Signoret and Whiteley, 1979). This test evaluates immediate and delayed recall of a short story, and the serial learning of a 12-word list of different semantic categories (3 trials), free delay recall, and recognition with semantic clues and multiple options of them; (3) language: Boston Naming Test (Kaplan et al., 1983); (4) executive functions: Wisconsin Card Sorting Test (Heaton, 1981), Trail Making Test part B (Reitan, 1958), and Phonological Fluency (Benton et al., 1983); and (5) facial emotion recognition: Ekman-60 (Young et al., 2002). In this test different faces appear in random order for 5 s each in the PC monitor, and subjects have to recognize facial expression of six basic emotions (anger, disgust, fear, surprise, happiness, and sadness). The test yields a score out of a maximum of 60 correct answers for recognition of all six emotions, or scores out of 10, for recognition of each basic emotion.

One experienced psychiatrist (SAS) examined clinically all subjects at study entry. All neuropsychological tests were administered by other physicians (DM) in a quiet testing room according to a standardized order.

2.3. Follow-up assessment

The course of illness was prospectively documented from a modified life charting technique usually rated for each patient treated in our program by his/her psychiatrist in a weekly basis. This life chart technique was used in previous studies by our group (Martino et al., 2009; Strejilevich et al., 2011) and was developed without the knowledge or purpose of the present work. Our mood chart is based on the NIMH life-charting method and anchored by scores from both the Hamilton Depression Rating Scale and the Young Mania Rating Scale (Fig. 1). High inter-rater reliability was obtained for scores in YMRS (interclass correlation coefficient (ICC=0.96)) and HDRS (ICC=0.95). For the purposes of this study we consider 3 types of recurrence: (1) depressive episode: as a period of two or more weeks with mild, moderate, or severe depression; (2) hypomanic episode: a period of at least four days with mild mania; and (3) manic episode: a period of one or more week with moderate or severe mania.