Journal of Affective Disorders 164 (2014) 130–138

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

Longitudinal course of cognitive deficits in bipolar disorder: A meta-analytic study

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ARTICLE INFO

Article history:
Received 27 March 2014
Accepted 11 April 2014
Available online 19 April 2014

Keywords:
Bipolar disorder
Cognitive impairment
Longitudinal
Meta-analysis

ABSTRACT

Objective: Persistent cognitive deficits in bipolar disorder represent a major impediment to functional adjustment, but their static or progressive nature remains to be ascertained. The aim of this study was to synthesize findings from longitudinal research in order to examine the trajectory of cognitive impairment in bipolar disorder.
Method: A literature search was conducted through online databases covering the period between January 1990 and February 2014. Two approaches were undertaken. First, the results of longitudinal studies including neuropsychological assessment of stable bipolar patients at baseline and after a follow-up period of at least one year were meta-analyzed so as to obtain overall test–retest effect sizes for neurocognitive domains. Second, meta-analysis was restricted to longitudinal studies of bipolar patients including a control group. Patients' and controls' overall test–retest effect sizes were compared.
Results: Bipolar patients' performance on 14 cognitive measures remained stable after a mean follow-up period of 4.62 years. When meta-analysis was restricted to controlled studies, no patient-control differences were found regarding longitudinal cognitive outcomes.
Limitations: Test–retest differences for medication variables and mood state could not be controlled. Sufficient data were not available to investigate a wider array of neuropsychological domains. Furthermore, most primary studies included relatively short test–restest intervals.
Conclusion: To date, the available evidence from longitudinal studies is not in accordance with the hypothesis of a progressive nature of cognitive deficits in BD. The implications of this finding for further research are discussed.

1. Introduction

Bipolar disorders (BDs) comprise a heterogeneous group of chronic and recurrent affective illnesses associated with impairments in different aspects of daily living (Gitlin et al., 1995; Huxley and Baldessarini, 2007; Jansen et al., 2012). Several studies have revealed that a considerable number of bipolar patients exhibit persistent cognitive dysfunctions, with medium-to-large effect sizes of impairment noted for attention/processing speed, verbal memory, and executive domains (Robinson et al., 2006; Torres et al., 2007; Mann-Wrobel et al., 2011). Flawed neuropsychological performance has been shown to be a strong predictor of functional maladjustment both in cross-sectional (Dickerson et al., 2004; Martino et al., 2008; Fulford et al., 2014) and longitudinal studies (Tabarés-Seisdedos et al., 2008; Martino et al., 2009; Bonnín et al., 2010). These considerations are particularly relevant to BDs, given that between one and two thirds of bipolar patients do not accomplish functional recovery even when syndromal recovery is evident (Tohen et al., 2000; Strejilevich et al., 2013b). Hence, neurocognitive dysfunctions are increasingly acknowledged as a target area for treatment and research on this group of disorders.

Despite the growing awareness of the critical importance of neurocognitive functioning to BDs' outcome, data on the longitudinal trajectory of cognitive deficits across the course of the illness are scarce and inconsistent. Some studies found a negative association between the number of episodes, particularly manic ones, and neurocognitive functioning (Robinson and Ferrier, 2006; López-Jaramillo et al., 2010; Hellvin et al., 2012). These findings led authors to suggest that the experience of successive episodes might be related to progressive neurocognitive decline. The evidence supporting that cognitive impairments increase as a function of the number of previous episodes in bipolar patients is summarized in a recent review (Post et al., 2012). Moreover, this

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http://dx.doi.org/10.1016/j.jad.2014.04.028
0165-0327/

association is usually considered as further evidence for illness progression in BDs (Robinson and Ferrier, 2006; Berk, 2009; Kapczinski et al., 2009; Post et al., 2012). However, almost all of these hypotheses are primarily based on cross-sectional studies, and the direction of causality is ambiguous (Martino et al., 2013b). As evident, the best approaches to understanding the trajectory of these deficits are longitudinal studies with serial neurocognitive assessments. To date, longitudinal studies have been scant and yielded mixed results: while some of them showed stable cognitive deficits over time (Balanzá-Martínez et al., 2005; Mur et al., 2008a; 2008b; Schouws et al., 2012; Gildengers et al., 2013), others revealed a pattern of progressive deterioration (Moorhead et al., 2007; Gildengers et al., 2009). Furthermore, most of them had high probabilities of type II error owing to small sample size.

Broadening our knowledge on the longitudinal course of cognition in BD is an indispensable step towards having a complete description of these disorders. It would contribute to better understanding of the pathophysiological mechanisms subserving BDs, to identify targets for treatment, to determine possible subtypes of the disorder, and to develop better therapeutic strategies. The aim of the current work was to pool the results of studies including cognitive measures of bipolar patients at different time points in order to overcome sample-size limitations and gain some insight into the longitudinal course of cognition in BDs.

2. Method

2.1. Search strategy

Articles were retrieved from the online databases Pubmed/PsychInfo using combinations of the following keywords: bipolar disorder, manic, cognition, neuropsychology, longitudinal/long term, prospective, follow-up, progression, stability, intelligence, IQ, attention, learning, memory, and executive. The reference lists of the studies identified for inclusion were also reviewed for additional relevant reports.

2.2. Primary study selection criteria

Reports were considered for the current meta-analysis if they met the following criteria: (I) Were published in a peer-reviewed English language journal between January 1990 and February 2014. (II) Included a patient group aged over 18 years, with the diagnosis of BD according to standardized diagnostic criteria (RDC, DSM-III, DSM-IV, ICD-10, etc.). (III) Involved longitudinal study design with neuropsychological assessment at baseline and after a follow-up period of at least one year. (IV) Patients were described as euthymic, stable or mildly symptomatic both at baseline and after the follow-up period. (V) Provided data to estimate effect sizes for patients' differences between test and re-test cognitive scores. (VI) Subjects were not given any specific treatment to enhance cognition. (VII) Included at least one cognitive measure that was examined in a minimum of three studies. (VIII) Included at least ten subjects at both time points.

Additionally, if there were studies with overlapping content based on the same patient sample, we considered the data from the study with the longest follow-up period. Two studies on the same patient group were only included if they reported different cognitive measures.

2.3. Meta-analytic procedure

Meta-analyses were performed using the Comprehensive Meta-Analysis software version 2.0 (Borenstein et al., 2005). Given that only a small number of studies provided data from healthy controls, and in order not to overlook the body of evidence provided by single group longitudinal studies, two different meta-analytic approaches were conducted. First, we included all longitudinal studies, regardless of whether or not they included a healthy control group. Subjects' test–retest effect sizes (d) for each cognitive measure were calculated by subtracting the average score after follow-up from the average score at baseline and dividing the result by the pooled standard deviations of both data sets. Given that correlations between pretest and posttest scores were not available, we used this approach in order to avoid overestimation of the magnitude of effect, as recommended by Dunlap et al. (1996) for the estimation of effect sizes in meta-analysis of repeated measures designs. When studies reported neuropsychological performance at more than two different time points, we only considered the scores reported at baseline and after the longest follow-up period, except in one case in which the subjects included after the longest period were less than ten (Yucel et al., 2007). Effect sizes were weighted using the inverse variance method. Whenever subjects performed better after the follow-up period we reported test–retest differences by positive effect sizes. Second, we performed meta-analyses based only on studies including a healthy control group both at baseline and after follow-up. Hence, we obtained overall test–retest effect sizes for both patients and controls.

The Q-test for heterogeneity was used to test the homogeneity of the resulting mean weighted effect size for each variable and to compare patients' and controls' overall test–retest effect sizes. The I^2 index was calculated to describe the percentage of total variation across reports due to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity respectively. Based on the small sample size and the presence of heterogeneity in some of the analyses, we chose a random effects model. A significance level of $p < 0.05$ was set for the random effects model and homogeneity analyses.

2.4. Cognitive variables

For the purposes of this study, the results of reports utilizing the same test or tapping approximately the same neuropsychological construct were combined into a single summary measure. Fourteen overall neuropsychological measures were obtained. Crystallized Intelligence was explored using the full-scale National Adult Reading Test (Nelson, 1982) and the revised Wechsler Adult Intelligence Scale –WAIS- vocabulary/information scores (Wechsler, 1955; 1997). Two distinct attention summary measures were calculated using results of the Trail Making Test part A – TMT_A – (Reitan, 1958) and variants of the Continuous Performance Test – CPT- (Conners and Staff, 2000). The test parameters considered were 'seconds employed to conclude the task' and 'target detection' respectively. Immediate verbal memory was assessed by means of word list learning (trials 1–5) of the California Verbal Learning Test – CVLT- (Delis et al., 1987) and the Rey Auditory Verbal Learning Test – RAVLT- (Rey, 1964). The results of these tests were combined into a list learning overall score. Delayed list learning was assessed by combining free delayed recall measures of the CVLT and RAVLT. Verbal fluency was assessed by means of tasks requiring either the naming of words corresponding to a common category (animals) or words beginning with a certain letter (Benton et al., 1983). Meta-analyses for categorical and phonemic scores were conducted separately. Processing speed was assessed using latencies (ms) on reaction time tests. Overall measures for digit span were obtained by combining the results of studies utilizing the WAIS Digit Span scores. Forward and backward digit spans were meta-analyzed separately. A measure of cognitive flexibility was obtained by