Verbal memory as a mediator in the relationship between subthreshold depressive symptoms and functional outcome in bipolar disorder

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A B S T R A C T

Background: Most studies on the factors involved in the functional outcome of patients with bipolar disorder have identified subsyndromal depressive symptoms and cognitive impairment as key players. However, most studies are cross-sectional and very few have analyzed the interaction between cognition and subclinical depression. The present study aimed to identify the role of cognition, and particularly verbal memory, and subthreshold depressive symptoms in the functional outcome of patients with bipolar I and II disorder at one year follow-up.

Method: A confirmatory analysis was performed using the path analysis. A total of 111 euthymic patients were included to test the role of verbal memory as a mediator in the relationship of subthreshold depressive symptoms and functional outcome at one year follow-up. Measures of verbal memory, subthreshold depressive symptoms and functioning (at baseline, at 6 months and at one year follow-up) were gathered through the use of a neuropsychological assessment and validated clinical scales.

Results: The hypothesized mediation model displayed a good fit to data (Chi²=0.393, df=2, p=0.625; RMSEA<0.001 with CI: 0.001–0.125 and CFI=1.00). Functional outcome at one year follow-up was predicted by the functional outcome at baseline, which in turn, was related to subthreshold depressive symptoms and verbal composite memory scores as a mediator variable.

Conclusion: The results of this study prospectively confirm previous findings on the disabling role of subthreshold depressive symptoms and verbal memory impairment on psychosocial functioning. However, these results come from a sample with moderate to severe functional impairment; hence, as a limitation, this may hinder the generalization of these results.

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1. Introduction

Bipolar disorder is a highly recurrent and disabling mental illness (Catala-Lopez et al., 2013). Up to two thirds of patients suffering from this illness have difficulties in performing daily-life routines (MacQueen et al., 2001). Poor social relationships, work disability, and impoverished family functioning are the rule rather than the exception, even in patients that have achieved syndromal recovery (Haro et al., 2011; Bonnin et al., 2013; Rosa et al., 2009, 2012; Judd et al., 2008; Stein et al., 2013).

Functional impairment is multiply determined; many variables have already been identified to influence the functional outcome...
in euthymic patients. For a comprehensive review, see Sanchez-Moreno et al. (2009). Among all the studied variables, the presence of depressive symptoms has been reported as the strongest predictor of poor outcome (Judd et al., 2005; Gitlin et al., 2011; Bonnin et al., 2010; Martino et al., 2009; Strejilevich et al., 2013; Gonzalez-Pinto et al., 2010). This symptomatology also affects neurocognitive performance, even at low levels of depressive symptoms (Bonnin et al., 2012; Torrent et al., 2012).

Other investigations also provide empirical evidence related to the role of neuropsychological impairment in the functional outcome. Verbal memory impairment is a neurocognitive function that has been pointed as a core deficit of the illness (Bourne et al., 2013; Arts et al., 2008; Martinez-Aran et al., 2007; Robinson and Ferrier, 2006). Moreover, this particular neurocognitive variable has been linked to functional outcome in many studies (Martinez-Aran et al., 2007; Bonnin et al., 2010; Martino et al., 2009).

On one hand, previous literature links the subthreshold symptomatology with verbal memory (Torrent et al., 2012; Bonnin et al., 2012), on the other hand, previous studies also link memory with functional outcome (Bonnin et al., 2010; Martinez-Aran et al., 2007; Martino et al., 2009). These connections found in the literature suggest that the relationship between the subthreshold depressive symptoms and functional outcome may be accounted for by verbal memory performance, acting as a third variable that mediates this relationship. Hence, the main objective of this report was to explore the role of a verbal memory acting as a mediator in the relationship of subthreshold depressive symptoms and functional outcome at baseline.

To the best of our knowledge, no previous confirmatory analyses have been tested to prospectively prove the role of a neuropsychological variable acting as a mediator in the functional outcome of patients with bipolar I and II disorder.

2. Method

2.1. Participants

The present study is based on a sample of 111 participants from a larger multicentre study conducted in Spain (Torrent et al., 2013) and was registered with the number NCT 01370668 in www.clinicaltrial.gov. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by an independent ethics committee or an institutional review board at each study centre. All patients received extensive information on the study and provided written informed consent prior the inclusion in the study. The main aim of the original study was to assess the efficacy of a novel intervention, named “Functional Remediation” to improve psychosocial functioning measured by means of Functional Assessment Short Test (FAST). However, in the present report, the arm that received the Functional Remediation intervention was excluded for these analyses in order to avoid the confounding effects of the intervention on changes in the functional outcome. Hence, only patients in the psychoeducation group and Treatment As Usual (TAU) group were taken into account for these analyses.

Patients were euthymic at the inclusion of the study and were diagnosed with bipolar I or II according to DSM-IV-TR (American Psychiatric Association (APA), 2000). Exclusion criteria were an IQ < 85, any medical condition that could affect neuropsychological performance (such as neurological diseases), any comorbid psychiatric condition (such as active substance abuse, dependence within the past 3 months, ADHD…), or ECT within the past year. Patients were also excluded if they had participated in any structured psychological intervention, such as psychoeducation or cognitive remediation, within the past 2 years.

2.2. Measures

2.2.1. Clinical and demographic characteristics

Clinical and sociodemographic data were gathered through a clinical interview based on the SCID for DSM-IV-TR (American Psychiatric Association (APA), 2000). Age, gender, education level, diagnosis, number and type of previous episodes, chronicity (illness duration), age at first hospitalization, age at onset, number of hospitalizations, history of psychosis and family history of affective disorders were collected.

2.2.2. Neuropsychological battery and composite score calculation

Patients also underwent a neuropsychological assessment that consisted of a comprehensive battery evaluating four neurocognitive domains: (1) verbal learning and memory; (2) executive functions; (3) processing speed; and (4) working memory. For further details on the neuropsychological assessment, see Torrent and colleagues (2013).

Nevertheless, as the path analysis is a confirmatory analysis, only the measures of verbal memory were used for the present study. We calculated the verbal composite memory score using equally weighted standardized scores (z scores; mean=0, SD=1) for the raw scores in the California Verbal Learning Test (CVLT). Hence, patients’ scores on each measure of the CVLT (free short recall, cued short recall, delayed free recall and delayed cued recall) were converted to z scores and subsequently an average with these variables was performed.

2.2.3. Psychiatric symptoms

The symptomatology was measured by means of the Hamilton Depression Rating Scale (Hamilton, 1960; Ramos-Brieva and Cordero, 1986) to assess the subthreshold depressive symptoms. In the present report, subsyndromal depressive symptoms refer to HAM-D scores = < 8. The Young Mania Rating Scale (Young et al., 1978; Colom et al., 2002) was applied to assess manic symptoms. All patients were euthymic for at least three months at study entry.

2.2.4. Functional outcome

Functional outcome was measured by means of the FAST (Rosa et al., 2007). The FAST comprises 24 items that evaluate disability in the last 15 days in six specific areas of functioning: autonomy, work functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. The total score ranges from 0 to 72 points (Higher score=higher disability).

2.3. Statistical analyses

Data was analyzed using the SPSS v.18 for Windows (Chicago, IL, USA) and with the extension of the SPSS to perform the path analysis, which is the “AMOS graphics”.

The characteristics of the sample were analyzed using frequencies for the categorical variables (bipolar subtype, gender, history of psychotic symptoms, and family history of psychotic disorders). The remaining variables (continuous variables) were explored using the mean and standard deviation.
The next step was to examine the proposed model for the functional outcome using the confirmatory path analyses in a sample of bipolar patients. A total of 111 complete cases were identified, hence, the analyses were performed on these participants.

To test the model, we used three different goodness-of-fit statistics: the model chi-square, the comparative fit index (CFI), and the root mean square error of approximation (RMSEA). A good-fitting model is reflected by nonsignificant chi-square tests, a CFI greater than 0.90 and a RMSEA less than 0.06. The chi-square test is a comparison of the observed covariance matrix to the covariance matrix of the model. The CFI compares the final model with an “independence model” and indicates the percent to which the covariation in the data is replicable. The independence model is a null model that assumes that all variables are uncorrelated with the dependent variable.

Finally, Sobel’s (1982) method was applied to test whether the mediator (the verbal composite memory score) carried the influence of the independent variable (Subthreshold depressive symptoms at baseline) to the dependent variable (functional outcome at baseline).

3. Results

3.1. Clinical, sociodemographic and the verbal composite memory score

The sample consisted of 111 patients diagnosed with Bipolar I Disorder (n=87; 78.4%) and Bipolar II Disorder (n=24; 21.6%). The mean age was around 40 years and patients had a mean of 9 affective episodes in the past. The functional ratings, the demographic and clinical characteristics of the sample are shown in Table 1.

The verbal composite memory score was: mean=−0.005; SD=0.9; minimum=−2.09; maximum=1.62).

3.2. Mediation model

The hypothesized mediation model displayed a good fit to data (chi=0.393, df=2, p=0.625; RMSEA < 0.001 with CI: 0.001–0.125 and CFI=1.00). Subthreshold depressive symptoms and verbal composite memory score explained 19% of the variance in the functional outcome at baseline. As hypothesized, subthreshold depressive symptomatology was positively associated with poor functional outcome at baseline (Beta=0.31; p<0.001), indicating that patients with higher subthreshold depressive symptoms displayed higher levels of disability. Subthreshold depressive symptoms were negatively associated with the verbal composite memory score (Beta=−0.21; p<0.007). Finally, the verbal composite memory score was also negatively associated with functional outcome at baseline (Beta=−2.52; p<0.001) and functional outcome at one year follow-up depended on the functional outcome at baseline (Beta=0.66; p<0.001) explaining 44% of the variance.

Statistical significance of the indirect effect based on Sobel’s (1982) method indicated that the relationship between HAM-D at baseline and FAST baseline scores was mediated by the verbal composite memory score (Indirect effect estimate=2.06; p=0.03) (see Fig. 1).

4. Discussion

This study supports a multivariate path model linking subthreshold depressive symptomatology, verbal memory and functional outcome. Specifically, our model confirms the role of verbal memory as a mediator in the relationship of subthreshold depressive symptoms predicting the functional outcome. Although many studies have evaluated the critical role of neurocognitive impairment in functional outcome, to our knowledge, only one previous study has assessed the direct and indirect effects of neurocognition in bipolar disorder using confirmatory analyses (Bowie et al., 2010). However, our results differ slightly from those reported by Bowie et al., mainly because they modelled the direct and indirect effects of many variables such as neurocognition, symptoms, functional competence and everyday outcomes in patients. They found that the functional outcome was determined by the effect of neurocognition mediated by functional capacity, while in our model the effect of subthreshold depressive symptoms on functional outcome is mediated by verbal memory. Despite the differences in the methodology, the most crucial one being the prospective nature of the present trial, both findings suggest that neurocognition has an important role in predicting functioning, although the effect may not be as stronger and direct as previously expected.
reported (Martinez-Aran et al., 2007; Bonnin et al., 2010). Nevertheless, a recent study has described this variable as a predictor of favourable employment outcomes among individuals with bipolar disorder (Tse et al., 2013).

Even though this path analysis has identified the role of verbal memory as a mediator in the relationship between subthreshold depressive symptoms and functioning, it is worth mentioning that impairments in verbal memory might still be partly a consequence of other neurocognitive deficits. For instance, some authors have suggested that impairments in processing speed could contribute to poorer verbal learning (Antila et al., 2009). Moreover, other authors, such as Deckersbach et al. (2004) found that poor memory performance was secondary to strategic and organizational dysfunction, especially when measured by means of CVLT. This memory test requires the use of semantic clustering which depend on prefrontal regions (Wagner et al., 2001), whereas verbal memory itself relies on the medial and temporal regions of the brain. Hence, it cannot be ruled out that this composite neurocognitive score we have created may also reflect to some extent further impairments in executive functions.

The role of subthreshold depressive symptomatology in predicting functional outcome was quite pronounced and exerted a direct effect on functioning, which is in line with Bowie and colleagues’ study where subthreshold depressive symptoms were directly associated with interpersonal behaviour and work skills. Other studies have also reported a prominent role of depressive symptoms as a predictor of disability in bipolar disorder (Streijievič et al., 2013; Bonnin et al., 2010; Judd et al., 2005; Rosa et al., 2013).

Interestingly, depression symptoms were also associated with verbal memory and its relationship with functional outcome was partially mediated by the latter variable. Thus in bipolar disorder, depressive symptoms are not only negatively associated with the outcome, but also affect verbal memory performance.

In a previous report by our group, patients were divided in “low subthreshold symptomatology” and “high subthreshold symptomatology” according the scores on the HAM-D and the YMRS. It was found that patients in both groups presented low scores in verbal memory measures when compared to the healthy control group (Bonnin et al., 2012). Furthermore, patients with higher scores in the subthreshold symptomatology group had poorer functional outcome measured by means of the World Health Organisation Disability Assessment Schedule (WHODAS-2). That previous study, together with the present results, shed more light on the negative impact of subthreshold symptoms in both functioning and neuropsychological performance.

Despite the clinical and theoretical utility of the present findings, this study has some limitations. First, the sample size was not large enough to present a more complex confirmatory analysis including other variables of illness course (i.e.: chronicity, number of previous episodes …) that might have also exerted some effects on functional impairment (Vieira et al., 2013; Kapczinski et al., 2008; Soeiro-de-Souza et al., 2013; Grande et al., 2013). Second, this is a post-hoc analysis from clinical trial data, which has the advantage of a very careful selection of patients and assessments, but the disadvantage of limited generalizability. Hence, the findings might only hold true for people with moderate to severe levels of functional impairment, which was an eligible criterion to enter the study. Third, all patients were on medication; although there were no statistical differences between groups on that regard, the effects of medications for bipolar disorder on cognition are not totally understood (Dias et al., 2012; Vieira and Valenti, 2013). Finally, to enter the study patients were not required to present any minimal severity of neurocognitive impairment measured by the means of a neuropsychological battery, because the primary outcome was functioning, not cognition.

To sum up, our confirmatory model reaffirms the role of depressive symptoms in functional impairment and also provides prospective evidence on the mediating role of verbal memory. The identification of mediators in the prediction of functional outcome may help to disentangle the complex network of variables that contribute to functional outcome, since many variables with direct and indirect effects might be involved. Finally, further confirmatory analyses including other variables and assessing the remaining neurocognitive domains (executive functions, working memory, processing speed) would also provide valuable information in order to select the best treatments against disability in bipolar disorder.

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Conflict of interest

Professor Eduard Vieta has served as consultant or speaker for the following companies: Alexza, Almirall, AstraZeneca, Bial, Bristol-Myers Squibb, Eli Lilly, Ferrer, Forest Research Institute, Geodon Richter, Glaxo-Smith-Kline, Jansen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck & Co. Inc., Novartis, Organon, Otsuka, Pfizer Inc, Roche, Sanofi-Aventis, Servier, Shering-Plough, Shire, Sunovion, Takeda, United Biosource Corporation, and Wyeth. Dr. Martinez-Aran has served as speaker or advisor for the following companies: Bristol-Myers Squibb, Otsuka, and Pfizer.

Dr. Gonzalez-Pinto has received grants and served as consultant, advisor or CME speaker for the following entities: Almirall, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Glaxo-Smith-Kline, Janssen-Cilag, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Sanofi-Aventis, Shering-Plough, Dr. Crespo has served as consultant or AstraZeneca, Bristol-Myers Squibb, Janssen, Eli Lilly, GlaxoSmithKline, Lundbeck, Novartis, Otsuka, Pfizer, Sanofi-Synthelabo, and Wyatt. The remaining co-authors have no conflict of interest.

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References


