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Research report

Neuropsychological deficits in bipolar depression persist after successful antidepressant treatment

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ABSTRACT

Background: Bipolar disorder is a common disabling illness with a lifetime morbid risk of approximately 4%. Neuropsychological deficits constitute enduring trait-like features in bipolar disorder, are associated with each phase of the illness and persist also in euthymia. Total sleep deprivation (TSD) has been shown to cause rapid and sustained antidepressant effects in bipolar depression and to revert the biased self description and speed of information processing present in these patients. The aim of the study was to assess neuropsychological performances first in a sample of bipolar patients during a depressive episode compared to healthy controls and secondly to investigate if TSD treatment would change cognitive performances.

Methods: One-hundred bipolar patients and 100 healthy controls were evaluated through the Brief Assessment of Cognition in Schizophrenia, 42 patients were assessed before and after TSD treatment.

Results: Bipolar patients obtained significantly lower domain scores across the entire battery compared to healthy subjects. Cognitive deficits persisted in each function despite a clinical improvement of depressive symptomatology.

Limitations: Limitations of the study include issues such as generalizability, possible undetected past comorbidities, population stratification and ongoing medication.

Conclusions: This is the first study of the effect of TSD treatment on cognitive performance. TSD treatment improved clinical symptoms but not cognitive deficits however bipolar patients did not experience the well known worsening of performance observed in healthy controls after sleep loss.

1. Introduction

Bipolar disorder is a common disabling illness with a lifetime morbid risk of approximately 4% (Ketter, 2010). It is estimated that 30–50% of largely remitted bipolar patients fail to attain premorbid levels of psychosocial functioning and much of this disability may be linked to cognitive impairment (Goodwin and Jamison, 1990). Cognitive dysfunction in bipolar disorder is usually not as dramatic as in schizophrenia and can be confused with anxiety or other comorbid features of mood disorder. However analysis of the literature on cognitive performances in bipolar patients indicates that neuropsychological deficits are enduring trait-like features in BD rather than disturbances present only during acute episodes of illness (Burdick et al., 2006; Hill et al., 2009).

Indeed studies comparing various disease states within bipolar disorder reported that each of the mood states or phases (mania, hypomania, depression, and euthymia) of the illness is associated with cognitive impairments. Deficits in sustained attention, inhibitory control, executive functioning, working memory and verbal memory are more pronounced for multiepisode patients and for those with history of psychosis (Albus et al., 1996; Glahn et al., 2007; Martinez-Aran et al., 2008; McGrath et al., 1997; Strauss et al., 1984). Verbal memory has been found to be impaired during both manic and depressive episodes (Gourovitch et al., 1999; Wolfe et al., 1987). Executive function, particularly abstract concept formation, set shifting and planning, was found to be impaired during manic episodes (Ali et al., 2000; Murphy et al., 1999; Sweeney et al., 2000).

Although the euthymic state has been associated with better performances compared to the other states, the cognitive impairment in euthymia is not substantially different from that in manic or depressive state and euthymic bipolar patients are still cognitively impaired in comparison with healthy controls. (Malhi et al., 2004, 2007). Group differences between euthymic bipolar patients and healthy controls have been found for measures of executive function, verbal memory, psychomotor speed, and selective and sustained attention (Bora et al., 2009). Cognitive impairment plays a role in the generally poor social and vocational outcomes in

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bipolar disorder (Martinez-Aran et al., 2007) thus revealing itself more important than it was previously thought. A recent review suggests that impairments in the circadian and sleep systems observed in bipolar patients could play a role in cognitive performances through the neural systems of the prefrontal cortex.

The combination of clinical chronotherapeutic antidepressant techniques such as repeated total sleep deprivation (TSD) and light therapy (LT) has been shown to cause rapid and sustained antidepressant effects in bipolar depression that occur in a matter of hours or days. Besides its clinical efficacy TSD in patients with BD it has been shown to revert the biased self description and speed of information processing present in depressed patients (Baving et al., 1997; Benedetti et al., 2005). However studies investigating the effect of TSD on healthy subjects have shown that cognitive performance deteriorates during TSD already after 24 h of wakefulness (Babkoff et al., 1988; Horowitz et al., 2003).

The aim of the present study was to assess neuropsychological performances first in a sample of bipolar patients during a depressive episode compared to healthy controls and secondly to investigate if TDS treatment would change cognitive performances.

2. Methods

2.1. Sample

The sample included 100 biologically unrelated inpatients with a diagnosis of Bipolar Disorder I (DSM-IV criteria, SCID-I interview) and 100 age matched healthy controls. Twenty five percent patients reported previous psychotic symptoms while 75% never showed psychotic features. Exclusion criteria were: additional diagnoses on axis I, mental retardation on axis II, pregnancy, major medical and neurological disorders, history of drug or alcohol abuse or dependency. Physical examination, laboratory tests and electrocardiograms were performed at admission. No patient received electroconvulsive therapy (ECT) within 6 months prior to study enrollment. After complete description of the study to the participants, written informed consent was obtained. The study was approved by the local ethical committee.

2.2. Treatment

All patients received antidepressant drug treatment upon clinical need. A subsample of 42 patients were administered three consecutive TSD cycles (days 0–7); each cycle was composed of a period of 36 h awake. On days 0, 2, and 4 patients were totally sleep deprived from 07:00 a.m. until 7.00 p.m. of the following day. They were then allowed to sleep during the night of days 1, 3, and 5. Patients were administered LT (exposure for 30 min to a 10000 lux bright white light, color temperature 4600 K) at 03:00 a.m. during the TSD night and in the morning after recovery sleep, half an hour after awakening, between 8 and 9 a.m. Patients were either taking lithium at admission ($n=29$), and continued it, or started lithium ($n=7$) together with the chronotherapeutic procedure to enhance its effect and prevent relapse (Baxter, 1985; Benedetti et al., 1999, 2008). Some of the patients were also taking benzodiazepine, antidepressant and other mood stabilizers.

2.3. Clinical and neuropsychological assessment

Severity of depression was rated (days 0, 1, 2, and 6) on a modified version of the 21-item Hamilton Depression Rating Scale (HDRS).

Cognitive functions have been assessed through the Brief Assessment of Cognition in Schizophrenia (Keefe et al., 2004), a broad battery evaluating several domains of cognition (verbal memory, working memory, psychomotor speed and coordination, selective attention, semantic fluency, letter fluency and executive functions). Normative Italian adjusted scores (Anselmetti et al., 2008) were used for the BACS subtests. In order to investigate executive functions, the BACS battery employs the Tower of London Test. However, while there is substantial agreement across studies upon an impaired performance at the Wisconsin Card Sorting Test (WCST) mixed findings have been reported on the same patients on many measures of the Tower of London task, with some investigators reporting impairments and others not (Glahn and Bearden, 2007). Given these data we decided to replace the Tower of London task with the WCST. WCST normative Italian adjusted scores (Laiacona et al., 2000) were used to evaluate the goodness of executive functions performances. All tests were administered by a trained psychologist. Neuropsychological testing was performed at baseline and repeated in a subsample of 42 patients after TSD treatment.

2.4. Data analysis

To address statistically significant group differences for sex distribution and age in patients and controls, age- and sex-stratified normative data (Anselmetti et al., 2008) were used to compute subtest and global scores for each participant on the BACS. Moreover to provide a standard metric for comparison across neurocognitive domains for each subtest an equivalent score, ranging from 0 to 4, has been obtained. Also a global cognitive index has been calculated as the mean equivalent score of all subtests of the BACS. Standardized domain scores were calculated for symbol coding (selective attention), digit sequencing (working memory), verbal memory, token motor task (psychomotor coordination), verbal fluency and WCST (executive functions). For WCST the number of perseverative errors was used.

Given the number of cognitive outcome measures, we began data analysis with an omnibus test comparing the BD and control groups on the global cognitive index of neurocognitive performance. In the presence of significant group difference on the global neuropsychological measure, step-down domain-wise analyses were undertaken. This was done for baseline data and to test whether a significant change, in cognitive performance, could be observed after TSD treatment. Finally a two-sample t test was performed to investigate if a significant difference could be observed between patients with a history of psychotic symptoms and those who never experienced psychotic features.

3. Results

Clinical and demographic characteristics of the sample are summarized in Table 1. Neuropsychological performances of patients at baseline and controls are summarized in Table 1 and showed in Fig. 1. Neuropsychological performances pre- and post-TSD treatment are summarized in Table 2 and shown in Fig. 2. TSD treatment caused an overall significant decrease in HDRS scores (analysis of variance: $F=305.41$; $P<.001$). Thirty-one patients achieved the strict remission criterion of HDRS score less than 8 at day 7 and could be rated as full responders to treatment.

To establish baseline deficits in subjects with BD, group differences on the mean equivalent score at baseline were tested. Results indicated that the BD group performed significantly more poorly than the HC group ($F=-14.05$, $p<.001$).

Given the significant global deficit at baseline, cognitive performances in each neuropsychological domain have been investigated. Results indicated that bipolar patients, relative to controls, showed impairment on all six domains: verbal memory