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Review

Are major depression and bipolar disorder neuropsychologically distinct? A meta-analysis of comparative studies

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ABSTRACT

Background: Neuropsychological deficits are present in both major depression and bipolar disorder. So far, however, reports directly comparing these mood disorders with regard to cognitive outcomes have been scant and yielded inconsistent results. This work aims to combine the findings of comparative studies of cognition in major depression and bipolar disorder in order to explore whether these neuropsychiatric conditions present with distinct cognitive features.
Methods: The main online databases were extensively searched to retrieve reports assessing neurocognitive functioning in two groups of mood disorder patients, one with major depressive disorder and another with bipolar disorder, both in the same phase of illness. Between-group effect sizes for cognitive variables were obtained from selected studies and pooled by means of meta-analytic procedures.
Results: During euthymia, a significant overall effect size (Hedges'$g = 0.64$, $P < 0.001$) favoring major depressive disorder was found for verbal memory as assessed with list learning tests, whereas no significant between-group differences were found for the remaining variables analyzed. During depressive episodes, similar cognitive outcomes were observed between groups.
Conclusion: At present, it is not possible to postulate specific neuropsychological profiles for major depression and bipolar disorder in light of available evidence. It remains to be ascertained whether the differences found for verbal memory constitute an expression of distinct underlying mechanisms or whether they are best explained by sample characteristics or differential exposure to variables with a negative impact on cognition.

1. Introduction

The current nosological distinction between bipolar disorder (BD) and major depressive disorder (MDD) dates back to the 1960s, when the proposal made by Kleist and Leonhard gained support from the evidence yielded by a number of clinical and epidemiological investigations [1,2]. However, the strongest support for that division may have actually come from the differential response to pharmacological treatment of these disorders. While antidepressants have significant efficacy for the management of acute episodes and prophylaxis in MDD, they may have limited efficacy in the treatment of BD and could even worsen the course of illness [3,4]. Such outcomes not only compel clinicians to make a differential diagnosis in order to prescribe the correct pharmacological treatment but also support the idea that BD and MDD may have their own physiopathology. This division has gained official acceptance in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), which places these entities in different chapters. However, there are no clinical or physiopathological models supporting this division. Furthermore, diagnostic criteria for bipolar and unipolar depression remain unchanged and there is no adequate explanation about why MDD and BD have different evolution and response to treatment. In recent years, a series of studies by means of neuroimaging techniques have found differences in brain structure [5,6] and patterns of neural activity [7,8] between these disorders. It is therefore possible that such differences become evident at a neuropsychological level.

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At present, converging pieces of evidence have revealed that BD subjects display neuropsychological abnormalities that persist during euthymia and involve the domains of memory, attention, and executive functions [9–11]. Similar, though milder, deficits have been found in remitted MDD patients [12,13]. Moreover, cognitive dysfunction has consistently been shown to be a strong predictor of functional outcome in both disorders [14–18].

Currently, however, studies directly comparing MDD and BD with regard to neuropsychological functioning are scant and yield inconsistent results. A number of reports show different cognitive outcomes favoring one or the other disorder [19–22], whereas some investigations suggest that performance on neurocognitive tasks does not differentiate one condition from the other [23–26]. Such discrepancies may be explained, at least partly, by the fact that most studies were conducted on small samples, assessed different neuropsychological domains, and included subjects in different phases of illness. Hence, it is not clear whether the cognitive profiles and magnitude of impairment exhibited by MDD and BD are similar or not. If MDD and BD were found to present with distinct neuropsychological features, this would assist in distinguishing between two diagnostic entities whose boundaries are still fuzzy. Furthermore, ascertaining the existence of neuropsychological differences between BD and MDD could contribute to better understanding the neurobiology of these disorders and to the development of specific interventions targeted at preventing or arresting cognitive impairment and poor functional outcome [27,28].

The aim of the present study was to combine, by means of meta-analytic procedures, the findings of reports comparing neuropsychological functioning between BD and MDD in order to explore whether these mood disorders could be distinguishable by virtue of their neuropsychological features.

2. Material and methods

2.1. Search strategy and study selection criteria

MOOSE guidelines [29] were followed to conduct this study. PubMed/PsycINFO databases were extensively searched, covering the period from January 1980 to April 2016, using combinations of the following keywords: *mood disorders, affective disorders, major depressive disorder, bipolar disorder, mania, depression, affective psychoses, cognition, neuropsychology, memory, executive, and attention*. The same search was performed using Google Scholar in order to identify unpublished material (theses, congress presentations) and reports written in languages other than English or published in journals not indexed in the aforementioned electronic databases. Moreover, the reference lists of retrieved studies and systematic reviews on cognitive aspects of affective disorders were cross-checked for further relevant investigations.

Reports were included in this review if they met the following criteria:

- were available in English, Spanish, Portuguese, French, or Italian;
- assessed neuropsychological domains in two groups of mood disorder patients: one with MDD and another with BD, both in the same phase of illness (euthymia or depression);
- ascertained diagnosis using structured criteria;
- patients within each group were in the same phase of illness;
- ascertained mood state on the basis of standardized measures;
- reported separate behavioral results for each mood disorder group;
- included more than ten subjects in each group;
- provided data to estimate between-group effect sizes for cognitive domains;
- explored a neuropsychological domain assessed in a minimum of three studies.

Additionally, if there were studies with overlapping content based on the same patient sample, only the data from the study with the largest sample were considered.

2.2. Data analysis

Meta-analyses were performed using Comprehensive Meta-Analysis software version 2.0 [30]. Data from depressed and euthymic patients were meta-analyzed separately. Hence, summary measures for both the euthymic and depressive phases of mood disorders were obtained. The effect size for each neuropsychological variable was calculated as the mean difference between groups divided by the pooled standard deviation. Hedges' formula [31] was applied to correct for upwardly biased estimation of the effect size in small samples. Effect sizes were weighted using the inverse variance method. Whenever patients with BD underperformed those with MDD, between-group differences were reported by positive effect sizes. When means and standard deviations of more than one group of euthymic/depressed BD or MDD patients were given, the mean values and standard deviations were combined. The homogeneity of the resulting mean weighted effect sizes for each variable was examined using the *Q*-statistic. The I^2 index [32] 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 sizes and the presence of heterogeneity in most analyses, a random-effects model was chosen. A significance level of $P < 0.05$ was set for the random-effects model and homogeneity analyses.

2.3. Neuropsychological variables

For the purposes of this study, the results of reports utilizing the same test or assessing approximately the same neuropsychological construct were pooled together. Summary measures were obtained for twelve different variables, namely TMT_A, TMT_B, processing speed, forward digit span, backward digit span, digit symbol coding, list learning, spatial span, response inhibition, planning, phonological fluency, and cognitive flexibility, thus reflecting the domains of attention/processing speed, verbal memory, and executive functions (Table 1).

3. Results

The initial search through PubMed and PsycInfo resulted in 1905 potentially relevant abstracts, which were assessed for suitability. Furthermore, a search using Google Scholar enabled the identification of 75 additional records corresponding to studies written in languages other than English, unpublished material, and articles published in journals not indexed in major bibliographic databases. Of this initial pool of 1980 records, only 56 studies assessed neuropsychological functioning in both BD and MDD, and their full texts were retrieved for detailed evaluation. Finally, 23 reports fully met eligibility criteria and were included in the current review (Fig. 1, Table 2). Ten of the selected studies compared the neuropsychological performance of 338 MDD patients with that of 402 BD patients during euthymia (Table 2) and were considered for the meta-analysis of remitted mood disorder subjects. Two studies by Clark et al. [46,47] were included as they explored different cognitive domains. The study by Xu et al. [48], in which the same patients were assessed during depression and remission, was only considered for the analysis of euthymic