Neuropsychological profile of Unipolar Major Depression with psychotic features: protocol for a systematic review and bayesian meta-analysis

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1 Background

1.1 A neuropsychological endophenotype may help differentiate psychotic from non-psychotic individuals

The debate on whether there is a specific neuropsychological endophenotype for unipolar major depressive disorder with psychotic features (PMDD), that is different from both non-psychotic unipolar depression (MDD) and schizophrenia, is not new [1]. The view that PMDD is a more severe kind of MDD, with a profile of impairments that lies in between non-psychotic major depression and schizophrenia, has been consistently put forward in the literature [2].

Much of this rationale is grounded on previous and current PMDD diagnostic criteria. Diagnosis of psychotic unipolar depression has been historically defined by severe impairment, which pushed PMDD to the end of a severity spectrum of major depression. It has also required delusions, hallucinations, or depressive stupor to be present, and has only recently been defined as a specifier that is independent of symptom severity [2,3]. This latter decision is in line with current evidence, which suggests that psychotic features are not necessarily indicative of worse MDD severity from a symptomatology point-of-view, blurring the line between these diagnoses. Individuals with MDD may have equally or even more severe depression than individuals with PMDD [4,5], pointing towards a need of defining PMDD through other markers.

A specific neuropsychological endophenotype, if it exists, may help to better define the boundaries of impairment between PMDD and MDD, and also to guide interventions for distinct mental health services.

1.2 Neuropsychological profiles of PMDD: evidence from meta-analytic studies

Efforts to summarize the available evidence on neuropsychological performance of individuals with PMDD in comparison to MDD are still scarce [6–8]. The study by Fleming et al. (2004) focused on whether neuropsychological tests could help differentiate individuals with PMDD from others with MDD, but due to the small number of studies available at the time (only five), some cognitive functions were compared in a very limited pool of data, sometimes only between two samples. Nonetheless, authors found the largest standardized mean differences in domains of motor speed, verbal memory, and executive functions [6].

The study by Zaninotto et al. (2015) was able to include 12 studies in a systematic review with meta-analysis and meta-regression. Using a random-effects model, they found effect sizes between 0.15 and 0.74 for five cognitive domains: Processing speed, Reasoning, Verbal memory, Visual memory, and Attention/Working memory. Only two of these effects were significant, however, with a standardized mean difference (SMD) of -0.67 [95%CI: -0.82, -0.52] for Verbal memory (n of studies = 6) and SMD of -0.62 [95%%CI: -0.80, -0.44] for Visual memory (n of studies = 4). For a measure of global cognition computed by the study authors, a significant effect of SMD = - 0.38 [95%CI: -0.57, -0.19] was observed. It is important to note that authors excluded two of the studies they found to be outliers, and even then, six out of the ten studies measured for this latter analysis had confidence intervals crossing zero, and an I^2 of 42% was reported. Finally, authors assessed age, gender, education and depressive severity as single moderators, finding an effect for age (β = -1.31, SE = 0.5, p = 0.01) in tasks of working memory, but not for the other moderators.

The latest study to assess neuropsychological performance differences between PMDD and MDD individuals focused on older patients [8]. Authors included a total of 7 studies, and 3 of those had patients with bipolar psychotic depression. They found a Hedge's g of -0.26 for measures of global cognition [95%CI -0.49, -0.02], g = -0.64 [95%CI: -1.24, -0.03] for Attention (n of studies = 5), g = -0.43 [95%CI: -0,69, -0,17] for Executive Function (n of studies = 6), and g = -0.43 [95%CI: -0.70, -0.17] for Memory (n of studies = 5), but no significant effect for Verbal fluency. In this study by Vermeulen et al. (2019), heterogeneity I^2 values ranged from 0 to 69%.

This brief review of the current evidence for, and against a neuropsychological endophenotype that can differentiate PMDD from MDD patients shows that the meta-analytic

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studies conducted so far faced some critical limitations. High heterogeneity and a small number of studies may have precluded researchers from clearly establishing a consistent and robust assessment of the reported effects. More importantly, results vary between meta-analytic studies over which neuropsychological functions are more significantly impaired in individuals with PMDD in comparison with MDD subjects. This means that non-significant p-values were be taken as evidence of an absence of effect, when they may simply be an absence of evidence in face of the above mentioned limitations [9–11].

1.3 Using a bayesian meta-analysis to assess the available evidence

A fully bayesian framework may offer significant advantages over a frequentist method given the previously discussed limitations in the available literature. The small number of studies at the time of these meta-analyses may have ruled out smaller but meaningful effects between PMDD and MDD groups on the basis of a non-significant p-value. In addition, use of the Bayes Factor [12] allows for the assessment of the available evidence both *for* and *against* an effect (i.e., evidence for the null hypothesis) between individuals with PMDD and MDD. These advantages extend to the use of bayesian meta-regression (hierarchical random-effects models) to measure the possible clinical and sociodemographical moderators. In sum, a fully bayesian framework offers a clearer picture of current evidence, and helps establish to which extent results support a neuropsychological endophenotype for individuals with PMDD.

2 Methods

2.1 Systematic Review

This systematic review has been registered at the PROSPERO ....

2.1.1 Inclusion Criteria

2.1.2 Exclusion Criteria

2.1.3 Data Extraction

2.1.3.1 Measures of effect size

2.1.3.2 Moderators

2.2 Bayesian Location-Scale Meta-Analysis

A bayesian location-scale meta-analysis will be conducted using the r package `blsmeta` [13].

2.2.1 Bayesian Meta-Regression: Hierarchical Mixed-Effects Models

Meta-Regression is a statistical tool to assess the effects of pooled study-level factors, such as age, gender and psychiatric comorbidity. In this systematic review, we will focus on possible effects of VARIÁVEIS to be assessed by a Bayesian Hierarchical Model run on the `blsmeta` package.

2.2.2 Between-study variance (τ^2)

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