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

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Abstract

This is a protocol for a systematic review with meta-analysis. This systematic review is focused on summarizing, and critically assessing, the available evidence both *for* and *against* a neuropsychological endophenotype of individuals with psychotic major depressive disorder. To this end, we will conduct a systematic appraisal of the literature, followed by a Bayesian meta-analysis and meta-regression. We follow the PRISMA-P guidelines for meta-analysis protocols [1].

1 Rationale

Unipolar major depression with psychotic features (PMDD) is characterized by the presence of unipolar major depressive disorder (MDD), concomitant with hallucinations and/or delusional beliefs. PMDD is generally seen as a worse kind of MDD, with a profile of symptoms thought to lie between MDD and more severe psychotic disorders such as schizophrenia [2,3]. This is reflected on previous editions of the Diagnostic and Statistical Manual of Mental Disorders [4], where PMDD was classified as an impaired sub-type of depression.

The available evidence, however, has shown that individuals with MDD may exhibit a more severe case of depression than those with PMDD [5,6], suggesting that a "severity approach" to PMDD may not be as precise as previously thought. These findings blur the line between diagnoses from a symptom severity point-of-view, thus, a search for an endophenotype of these disorders, beyond assessing how severe are the depressive symptoms of an individual, may offer a clearer picture that helps define the boundaries and develop interventions tailored to the differences between PMDD and MDD.

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

The debate on whether there is a specific neuropsychological endophenotype for unipolar major depressive disorder with psychotic features, that is different from both non-psychotic unipolar depression (MDD) and schizophrenia, is not new [7]. The number of studies has only recently increased enough to allow a more systematic and robust assessment of the evidence. Thus, efforts to summarize the available evidence on neuropsychological performance of individuals with PMDD are still scarce [8–10]. The study by [8] 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.

The review by Zaninotto et al. (2015) was able to include 12 studies. They found significant effects of standardized mean difference (SMD) = -0.67 [95%CI: -0.82, -0.52] for Verbal memory (n of studies = 6), SMD = -0.62 [95%%CI: -0.80, -0.44] for Visual memory (n of studies = 4), and SMD = -0.74 [95%CI: -0.88, -0.59] for Processing Speed (n of studies = 8), but not for Attention and Reasoning domains. 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 for this latter analysis, and six out of the ten studies had confidence intervals crossing zero. Finally, authors assessed age, gender, education and depressive symptoms severity as single moderators, finding an effect for age (β = -1.31, SE = 0.5, p = 0.01) in working memory tasks, but not for the other moderators.

The latest study to assess neuropsychological performance differences between PMDD and MDD individuals focused on older patients [10]. Authors included a total of 7 studies, and 3 of those had patients with bipolar psychotic depression. They found a SMD of -0.26 for measures of global cognition [95%CI -0.49, -0.02], SMD = -0.64 [95%CI: -1.24, -0.03] for Attention (n of studies = 5), SMD = -0.43 [95%CI: -0,69, -0,17] for Executive Function (n of studies = 6), and SMD = -0.43 [95%CI: -0.70, -0.17] for Memory (n of studies = 5), but no significant effect for Verbal fluency.

This brief review of the current evidence for a neuropsychological endophenotype that can differentiate PMDD from MDD patients shows that the meta-analytic studies conducted so far faced some critical limitations. High heterogeneity and a small number of studies can impede 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 may have been taken as evidence of an absence of effect, when they may simply be an absence of evidence in face of the above mentioned limitations [11–13].

2 Objectives

In this systematic review with meta-analysis, we examine the available literature to answer the following questions:

- Q1: *"**Is there a neuropsychological profile (an endophenotype) for major depressive disorders with psychotic features that is different from that of non-psychotic unipolar depression?**"* For this question, we define a neuropsychological profile as a combination of results that quantify the difference in performance between individuals with PMDD and MDD, and that reflects an established neuropsychological function or domain of interest.
- Q2: *"**What are the moderators that can influence this neuropsychological profile?**"* For this question, we define moderators in three broad categories: within-subject clinical factors (age, acute psychotic episode, psychiatric comorbidities, number of hospitalizations, severity of depressive symptoms, years with diagnosis, family members with psychiatric conditions, and other relevant information); within-subject sociodemographical variables (years of education, household income, marital status, employment status); and between-study factors (study design and setting, type of neuropsychological tests used).

We set out to answer these questions with a Bayesian meta-analysis and meta-regression. New variables of interest may be included if found to help better understand the available evidence. A critical, qualitative appraisal of the literature is also warranted, and should help to identify current gaps, inconsistencies and limitations of relevant studies.

3 Methods

3.1 Eligibility criteria

In this review, we focus on individuals with major depressive disorder with psychotic features, diagnosed by a Diagnostic and Statistical Manual of Mental Disorders or International Classification of Diseases assessment. Eligible studies must include patients with this diagnosis who underwent a cognitive assessment of an established neuropsychological domain.

3.1.1 Types of studies

We include studies with a quantitative approach of all designs, which measure neuropsychological performance with standardized tests and tasks. To allow for an estimation of differences, subjects with PMDD must be compared to a sample of patients with MDD or other psychotic disorders, such as schizophrenia and psychotic bipolar depression. Different study designs will be assessed as possible moderators of study effect size.

3.1.2 Exclusion Criteria

We will exclude studies that: included participants who were given concomitant treatments that may affect neuropsychological performance, such as electroconvulsive therapy and brain stimulation procedures; included participants with co-morbid diagnosis of physical illnesses that may especially impair neuropsychological performance, or studies that included participants

with co-morbid psychiatric conditions that would be classified as axis I or axis II disorders, such as substance abuse or dementia.

3.1.3 Search Strategy

The search for relevant studies will be conducted in the Embase, PsycInfo and PubMed databases. Search strings tailored for the specific thesaurus of each database include terms for *'depression'*, *'psychosis'*, and *'neuropsychology'* or *'cognition'*.

- The following search string will be used in the *Embase* database:
  - 'depression'/exp AND ('depressive psychosis'/exp OR 'psychosis'/exp) AND 'neuropsychological test'/exp;
- For the *PubMed* database, we will use the following search string:
  - ("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms] OR depression[Text Word]) AND ("Cognition"[Mesh] OR "Neuropsychological Tests"[Mesh] OR "Neuropsychology"[Mesh]) AND ("Affective Disorders, Psychotic"[Mesh] OR "Psychotic Disorders"[Mesh]);
- For the *PsycInfo* database, the following search terms will be used:
  - Any Field: Major Depression AND Psychosis AND Cognition.

3.1.4 Study selection

Studies from 1980 onward will be included in the quantitative and qualitative synthesis in three steps. First, articles will be retrieved from each database and organized on a Zotero [14] online group folder so duplicates can be removed and retracted articles excluded. Two researchers then screen all titles and abstracts independently, selecting which studies will be fully screened. At the last selection step, two researchers will screen all of the full manuscripts and determine if a study will or not be included. Any discrepancies will be resolved by consensus, erring on the side of a liberal approach to inclusion up until full manuscript screening.

3.1.5 Data Extraction

Data within included studies will be extracted in two main steps. First, two researchers will extract all study data independently and store in an individual dataset. At this point, we will look for measures of neuropsychological performance that summarize results for each group within included studies. If data that allows transformation to a measure of effect size are not directly available, we will try to extract these effects from F and t statistics [15]. If it is not possible to extract measures of effect size from the manuscripts, we will look to previous meta-analysis and check if these effects are reported. In case no information is available, we will contact the study authors and ask for the data and any necessary additional information they may have stored. As a second step, after data is independently extracted by two researchers, we will resolve any discrepancies by consensus.

3.1.5.1 Moderators Moderating variables to be used in exploratory meta-regression analyses will be coded based on which variables are consistently available. Although it is not

possible to determine which variables will be coded *a priori*, we will at the very least code study variables of study design (*retrospective*, *prospective*), study sample (*community*, *representative*, *outpatient*), and neuropsychological testing strategy (*paper and pencil*, *digital*, *different tests or single battery*). If possible, clinical and sociodemographic moderating variables will be extracted (*age*, *diagnosis of control group*, *education*, and others).

3.1.5.2 Outcome selection We will focus on measures of neuropsychological performance that are present for the PMDD group and the comparison group or groups. It is not possible to predetermine which neuropsychological functions will be extracted, so data will be analyzed following an exploratory process. First, all relevant data will be extracted and coded in neuropsychological domains as reported by study authors. We expect major heterogeneity between studies, so we will attempt to group different, and less common domains, under more common umbrella terms. As an example, if two studies report measures of verbal working memory, two report measures of cognitive flexibility and three of inhibitory control, these variables will be coded as *Executive Functions*. Each test and neuropsychological domain used in the meta-analysis will be fully described in the final manuscript and in the analysis code. If a study reports multiple measures for a single domain, the test or task that is most frequently reported for that specific domain will be included in the meta-analysis. As a minimum, we expect to cluster neuropsychological tests in domains of *Reasoning*, *Attention*, *Executive Functions*, *Memory*, and *Language*.

3.2 Data synthesis

3.2.1 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 [16] 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. In other words, this means that in a Bayesian framework we can directly assess the probability for values of effect (μ) and heterogeneity (τ) that are below or above a given threshold. These advantages extend to the use of bayesian meta-regression to measure the influence of candidate 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. To this end, we will conduct a Bayesian random-effects meta-analysis, or *normal-normal hierarchical model* (NNHM), via the `bayesmeta` **R** package [17].

A Bayesian framework requires that prior beliefs about the data are made explicitly clear. These are presented not as point estimates but as parameters that have probability distributions. In the context of a meta-analysis, we are mostly concerned with three parameters: μ_i, the mean of effects derived from point estimates within included studies i; τ^2, the heterogeneity parameter that quantifies how within-study effects vary from one study to the other; and θ, which represents a distribution of the 'true' effect that is $\sim N(\mu, \sigma)$. Further information on Bayesian meta-analysis and parameters of interest is available elsewhere [17–19].

3.2.2 Prior specification - Effect parameter μ

We will use a ***weakly informative prior*** that is normally distributed, so that the main effect $\sim N(\mu, \sigma^2)$ with a location parameter of **0** and a scale of **.5** (See figure 1). This specification means that 95% of expected values lie between -1 and 1. As a sensitivity analysis, we look for the largest available meta-analysis in the field [9], which gives a mean difference for individuals with PMDD of -0.30 on a 95% confidence interval of -0.57 to -0.19. This gives a standard error of around $SE = 0.2$ [20] which we will use as an ***informative prior*** that is normally distributed $N \sim$ **(-0.3, 0.2)**, so that roughly 80% of expected values lie between -0.5 and 0.5. Finally, estimates from a ***uniform*** prior $\sim (-1, 1)$ will also be used for comparison, which assumes that all possible values between -1 and 1 are equally likely *a priori*. Parameter estimates and model results will be compared analytically and with the aid of Bayes Factors.

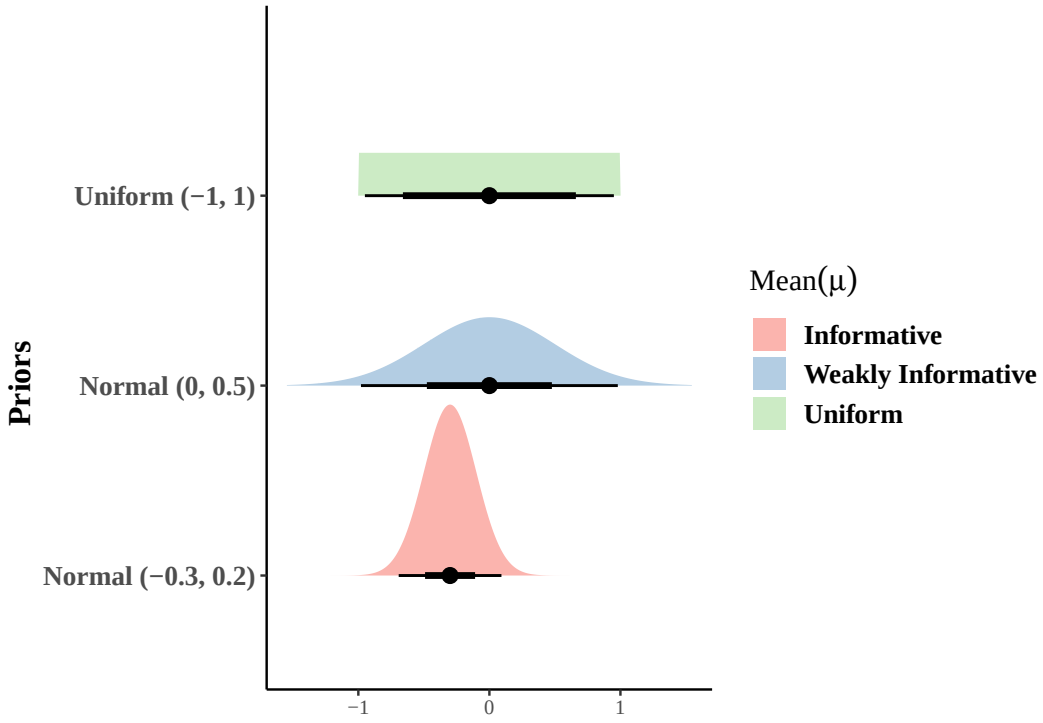

Figure 1: Weakly, Informative and Uniform priors

3.2.3 Prior specification - Heterogeneity parameter τ

We expect heterogeneity values to vary substantially between studies, and thus, we will use a *half-Cauchy* prior for the heterogeneity parameter, such that $\tau \sim$ **half-Cauchy(0.25)** (See figure 2). This is a *Cauchy* distribution truncated at zero (constrained into a positive real value), which has a fatter tail than a half-normal distribution, and offers a ***proper weakly informative prior*** for the heterogeneity parameter with 70% of expected values between 0 and 0.5 [18]. As a sensitivity check, we will rerun the analyses with a less informative prior with scale set to $\tau \sim$ **half-Cauchy(1)**.

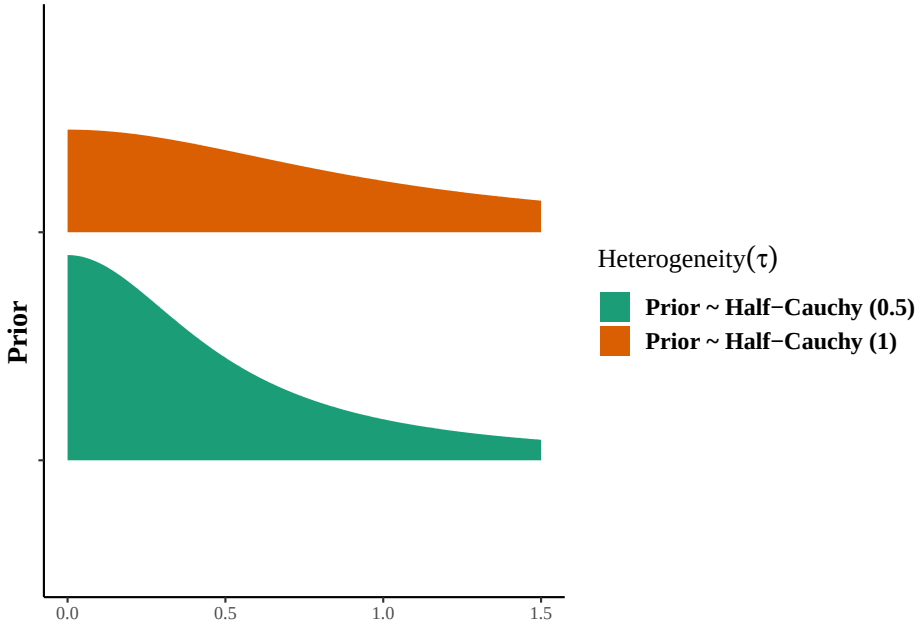

Figure 2: Heterogeneity priors

From the combination of priors for μ and τ, a total of six meta-models will be conducted, two for each of the three priors of for the effect and the two priors for heterogeneity. The values of θ from the combination of the Uniform and Informative priors for the effect with both priors for heterogeneity (four in total), will be considered as exploratory sensitivity analysis for our main model (See 3). The latter consists of the Weakly Informative prior for μ, as was previously described in 3.2.2 of this preregistration protocol. We aim to include all models for the sensitivity analysis as supplemental material to the future manuscript.

3.2.4 Exploratory analysis

We will conduct exploratory analysis to estimate the extent to which moderators of interest to the literature may influence results. We will explore the relationship between clinical factors (such as age and symptom severity), sociodemographical variables (level of education, socioeconomic status), and differences in performance on measures of neuropsychological functioning between individuals with PMDD and comparison groups. The effects of moderators on SMDs will be assessed by bayesian hierarchical models (meta-regression) procedures as implemented in the `bayesmeta` package.

3.3 Publication bias

To assess the possibility of publication bias in the available literature, we will conduct a series of methods in an attempt to quantify meta-biases as possible. Publication bias is still a highly active research area and no method to detect bias seems to outperform the others [21], so we will attempt to provide the most accurate results possible given the amount of information that is available at the time of data synthesis. Both evidences *for* (in case an effect is likely) and *against* (in case effects are unlikely) a moderator effect will be summarized by Bayes Factors.

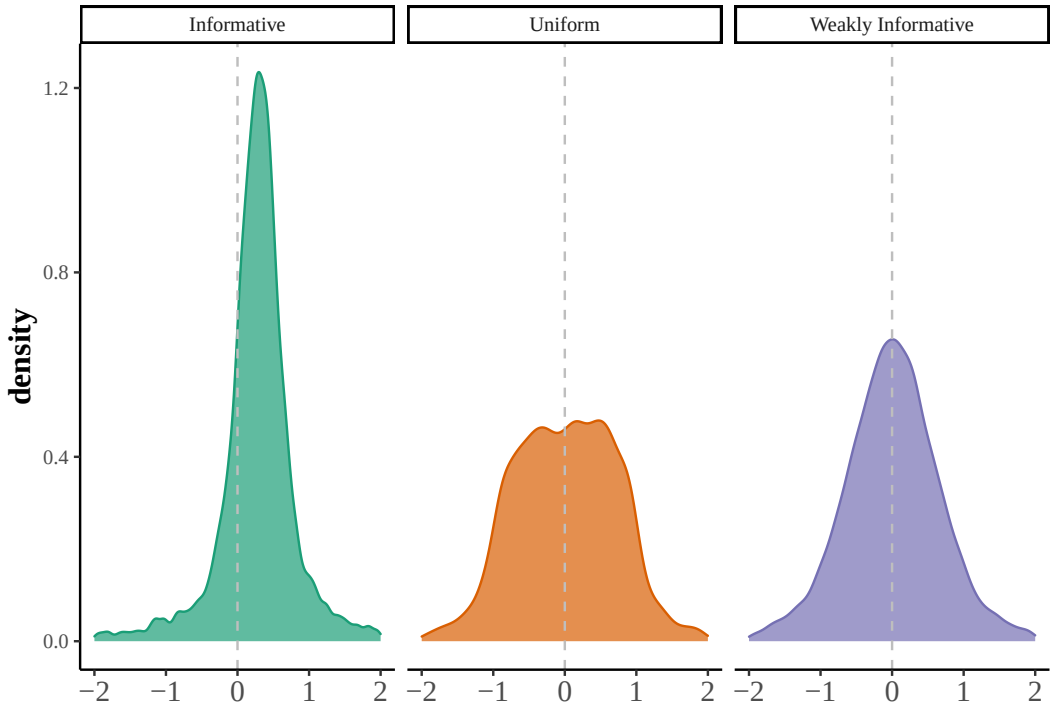

Figure 3: θ prior distributions for $\tau \sim$ half-Cauchy(0.5) and every prior for μ

3.4 Reproducibility and analysis code

This preregistration protocol is publicly available in the Open Science Framework (OSF) repository where this protocol is registered at (https://osf.io/2wp5r/), together with the `R Markdown` file required to reproduce this material. As soon as the data synthesis procedure is concluded, the OSF repository will be updated with the analysis scripts, the dataset, and all of the necessary information to reproduce our methods.

References

[1] Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. BMJ 2015;349:g7647–7. https://doi.org/gcpzzq.

[2] Dubovsky SL, Ghosh BM, Serotte JC, Cranwell V. Psychotic Depression: Diagnosis, Differential Diagnosis, and Treatment. Psychother Psychosom 2021;90:160–77. https://doi.org/gkmr55.

[3] Østergaard SD, Meyers BS, Flint AJ, Mulsant BH, Whyte EM, Ulbricht CM, et al. Measuring psychotic depression. Acta Psychiatr Scand 2014;129:211–20. https://doi.org/gkrbzv.

[4] APA. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washingont, D.C.: American Psychiatric Association; 2013.

[5] Park S-C, Choi J, Kim J-M, Jun T-Y, Lee M-S, Kim J-B, et al. Is the Psychotic Depression Assessment Scale a useful diagnostic tool?: The CRESCEND study. Journal of Affective Disorders 2014;166:79–85. https://doi.org/f583pn.

[6] Østergaard SD, Bille J, Søltoft-Jensen H, Lauge N, Bech P. The validity of the severity–psychosis hypothesis in depression. Journal of Affective Disorders 2012;140:48–56. https://doi.org/gkmr6n.

[7] Jeste DV, Heaton SC, Paulsen JS, Ercoli L, Harris J, Heaton RK. Clinical and neuropsychological comparison of psychotic depression with nonpsychotic depression and schizophrenia. AJP 1996;153:490–6. https://doi.org/gkmr4s.

[8] Fleming SK, Blasey C, Schatzberg AF. Neuropsychological correlates of psychotic features in major depressive disorders: A review and meta-analysis. Journal of Psychiatric Research 2004;38:27–35. https://doi.org/cq7c2z.

[9] Zaninotto L, Guglielmo R, Calati R, Ioime L, Camardese G, Janiri L, et al. Cognitive markers of psychotic unipolar depression: A meta-analytic study. Journal of Affective Disorders 2015;174:580–8. https://doi.org/f62rd8.

[10] Vermeulen T, Lauwers T, Van Diermen L, Sabbe BG, van der Mast RC, Giltay EJ. Cognitive Deficits in Older Adults With Psychotic Depression: A Meta-Analysis. The American Journal of Geriatric Psychiatry 2019;27:1334–44. https://doi.org/gkmr73.

[11] Nickerson RS. Null hypothesis significance testing: A review of an old and continuing controversy. Psychological Methods 2000;5:241–301. https://doi.org/djntrb.

[12] Dienes Z. Using Bayes to get the most out of non-significant results. Front Psychol 2014;5. https://doi.org/f6cmfz.

[13] Altman DG, Bland JM. Statistics notes: Absence of evidence is not evidence of absence. BMJ 1995;311:485–5. https://doi.org/cdvzz9.

[14] Corporation for Digital Scholarship. Zotero 2016. https://www.zotero.org.

[15] Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: A practical primer for t-tests and ANOVAs. Front Psychol 2013;4. https://doi.org/f96zbh.

[16] Wagenmakers E-J, Lodewyckx T, Kuriyal H, Grasman R. Bayesian hypothesis testing for psychologists: A tutorial on the Savage–Dickey method. Cognitive Psychology 2010;60:158–89. https://doi.org/btbnnf.

[17] Röver C. Bayesian Random-Effects Meta-Analysis Using the bayesmeta R Package. Journal of Statistical Software 2020;93. https://doi.org/10.18637/jss.v093.i06.

[18] Röver C, Bender R, Dias S, Schmid CH, Schmidli H, Sturtz S, et al. On weakly informative prior distributions for the heterogeneity parameter in Bayesian random-effects meta-analysis. Res Syn Meth 2021:jrsm.1475. https://doi.org/gjpv9w.

[19] Williams DR, Rast P, Bürkner P-C. Bayesian Meta-Analysis with Weakly Informative Prior Distributions. PsyArXiv; 2018. https://doi.org/10.31234/osf.io/7tbrm.

[20] Green S, Higgins JPT. The Cochrane Collaboration: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 2011. www.handbook.cochrane.org.

[21] Carter EC, Schönbrodt FD, Gervais WM, Hilgard J. Correcting for Bias in Psychology: A Comparison of Meta-Analytic Methods n.d.:30.