

Cognitive Functioning in the First-Episode of Major Depressive Disorder: A Systematic Review and Meta-Analysis

Elayne Ahern and Maria Semkovska
University of Limerick

Objective: Cognitive deficits are frequently observed in major depression. Yet, when these deficits emerge and how they relate to the depressed state is unclear. The aim of this 2-part systematic review and meta-analysis is to determine the pattern and extent of cognitive deficits during a first-episode of depression (FED) and their persistence following FED remission. **Method:** Published, peer-reviewed articles on cognitive function in FED patients through October 2015 were searched. Meta-analyses with random-effects modeling were conducted. Part 1 assessed weighted, mean effect sizes of cognitive function in FED patients relative to healthy controls. Moderator analyses of clinical and demographical variables effects were conducted. Part 2 assessed weighted, mean effect sizes of change in cognitive function at remission compared with acute FED performance in longitudinal studies. **Results:** Thirty-one studies including 994 FED patients were retained in Part 1. Relative to healthy controls, small to large impairments were observed across most cognitive domains. Remission was associated with a normalization of function in processing speed, learning and memory, autobiographical memory, shifting, and IQ. Lower FED age was associated with higher IQ, but more impairment in word-list delayed memory. Four studies including 92 FED patients were retained in Part 2. Following remission, FED patients showed small improvements in processing speed and shifting but persistent impairment in inhibition and verbal fluency. **Conclusion:** Significant cognitive deficits are already identifiable during a FED, with some functions showing persistent impairment upon remission. Clinicians must consider cognitive impairment alongside mood symptoms to ensure functional recovery from the FED.

Keywords: cognitive deficits, first-episode of depression, meta-analysis, remission, systematic review

Supplemental materials: <http://dx.doi.org/10.1037/neu0000319.sup>

Major depressive disorder (MDD) is a mood disorder characterized by a profound state of sadness, or loss of interest in activities, for at least a 2-week duration. This is accompanied by a minimum of five symptoms affecting behavior (disturbed sleep, changes in appetite or weight, fatigue, slowed movement) and/or cognition (feelings of guilt, worthlessness, thoughts of death, difficulty in concentration or indecisiveness; American Psychiatric Association, 2013). Typically, MDD is considered an episodic disorder consisting of one or more depressive episodes; an episode is defined by a minimum 2-week period, accompanied by five of the above-described symptoms, with a distinct onset and offset (Dubovsky & Dubovsky, 2002). MDD is one of the most prevalent of all mental disorders with an estimated 13.5% to 21.2% of the population experiencing at least one episode of depression (Kessler & Walters, 1998). However, recurrent depressive episodes are likely in MDD with up to 80% experiencing more than one episode in their lifetime (Mueller et al., 1999).

Cognitive Deficits in MDD

Although MDD is traditionally recognized as a disturbance of mood, impaired cognitive function has been frequently described as part of the disorder (e.g., Austin, Mitchell, & Goodwin, 2001). Cognitive functions are the mental processes of receiving, using and preserving information, which are divided into domains such as attention or memory (Lezak, Howieson, Bigler, & Tranel, 2012). While difficulties with concentration and making decisions have been included as diagnostic criteria for MDD (American Psychiatric Association, 2013), cognitive deficits in processing speed, attention, learning abilities, long-term memory, autobiographical memory, and executive function have also been demonstrated by numerous studies, reviews and meta-analyses. For example, a meta-analysis of 24 studies, including 784 MDD patients, quantified moderate cognitive deficits in executive function, memory and attention relative to healthy controls (Rock, Roiser, Riedel, & Blackwell, 2014). Moreover, another meta-analysis of 113 studies focusing on executive functioning and including 3396 MDD patients (Snyder, 2013), showed large impairment in inhibition, and moderate impairment in shifting, verbal working memory, visuospatial working memory, and verbal fluency.

Current evidence suggests that cognitive impairment in MDD is a key determinant of individual functional outcomes. It has been shown to persist following depression remission (Hasselbalch, Knorr, & Kessing, 2011), worsen with repeated depressive episodes (Gorwood, Corruble, Falissard, & Goodwin, 2008; Kessing,

This article was published Online First October 10, 2016.

Elayne Ahern and Maria Semkovska, Department of Psychology, University of Limerick.

Correspondence concerning this article should be addressed to Maria Semkovska, Department of Psychology, office E1-033 University of Limerick, Castletroy, Co Limerick Ireland. E-mail: maria.semkovska@ul.ie

1998; Vanderhasselt & De Raedt, 2009), and be a significant predictor of relapse (Peppermund, Ising, Lucae, & Zihl, 2009). Cognitive deficits have been related to difficulties in maintaining job performance which can demand the ability to make decisions or sustain attention (Papazacharias & Nardini, 2012). Moreover, difficulties with social functioning are also linked to cognitive dysfunction in depression (Withall, Harris, & Cumming, 2009).

Lost work productivity has been central to MDD-related societal costs (Evans et al., 2013) alongside the direct health care costs involved in treating MDD (Ekman, Granström, Omérov, Jacob, & Landén, 2013). Even following the remission of mood symptoms, baseline levels of daily functioning are not always restored. Recent accounts have suggested that the persistence of cognitive impairment following depression remission might contribute to compromise a full, functional recovery (Bortolato et al., 2016). Furthermore, it has been suggested that cognitive remission should be now considered as a therapeutic target to restore functioning and prevent relapse (Bortolato et al., 2016; Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Rock et al., 2014; Wekking, Bockting, Koeter, & Schene, 2012).

Relation Between Course of MDD and Cognitive Impairment

Cognitive impairment in MDD has usually been studied in terms of how it relates to the course of the illness, namely during an acute episode, following remission, in chronic depression, or in recurrent depression (Hammar & Ardal, 2009). Remission refers to a period of minimal depressed symptoms experienced by the patient following a depressive episode (Zimmerman et al., 2006). It has been suggested that cognitive impairment is a *state* marker and secondary to depressed mood symptoms, that is, impairment is present only during the depressive episode and normalizes thereafter with remission. However, recent studies have demonstrated its persistence following remission. In a review of 11 studies on 500 remitted MDD patients, Hasselbach and colleagues (2011) documented persistent impairment in attention, memory, and executive function relative to healthy controls. Following from this, a meta-analysis including 27 studies and 895 remitted, MDD patients quantified the impairment as moderate to large with most cognitive domains, but specifically the executive function of inhibition, showing persistent deficits (Bora, Harrison, Yucel, & Pantelis, 2013).

Persistence of deficits following a depressive episode can be indicative of either an impairment present before even a first-episode of depression (FED) or adverse consequence of depression. The *trait* marker hypothesis suggests that cognitive deficits represent a stable, underlying vulnerability for the onset of FED, or subsequent recurrent episodes. Trait markers specifically exist before the FED, and show stable persistence throughout and into remission (Rohde, Lewinsohn, & Seeley, 1990). Population-based studies have suggested that poorer episodic memory is a trait marker which predicts the onset of the FED (Airaksinen, Wahlin, Forsell, & Larsson, 2007). Moreover, a 9-year longitudinal study identified impairment in attention and executive function as trait markers which predicted onset in healthy twins at high-risk to develop an affective disorder (Vinberg, Miskowiak, & Kessing, 2013).

Alternatively, the *scar* hypothesis proposes that cognitive impairment develops during the FED and persists as a consequence or scar of the depressive episode, although the cognitive impairment may only be residual (Lewinsohn, Steinmetz, Larson, & Franklin, 1981). This is related to neural changes that occur during the depressive episode, subsequently affecting cognitive function. Kessing (1998) demonstrated that each depressive episode was associated with greater cognitive impairment in remitted, recurrent MDD patients relative to remitted FED patients, or healthy controls. FED patients were not significantly different from controls. Similarly, in a sample of 1895 MDD tested during an episode and after remission, Gorwood and colleagues (2008) demonstrated that the delayed verbal memory abilities progressively decrease after each consecutive depressive episode, despite patients having achieved remission. Research, however, has been inconsistent, with sometimes no added impairment observed as a result of each depressive episode (e.g., Wekking et al., 2012).

In summary, conclusive profiles characterizing cognitive impairment that is *state*-, *trait*-, or *recurrence*-related have not been determined, yet there is a recognition that cognitive deficits should be addressed conjointly with the mood episode and early in the course of MDD occurrence. Which cognitive functions should be treated early remains debatable.

Heterogeneity in MDD Cognitive Research and FED Cognitive Profile

Much of the inconsistencies in cognitive research in MDD relate to differences in the patients assessed. Individual characteristics are likely to moderate the extent of cognitive impairment, that is, certain characteristics determine whether more or less cognitive impairment is associated with MDD (Hammar & Ardal, 2009). Moderator variables including female gender (Postma, Jager, Kessels, Koppeschaar, & van Honk, 2004), lower premorbid intelligence, educational attainment (Plassman et al., 1995), older age (Deary et al., 2009), medication, inpatient status, younger age of depression-onset, higher depression severity, comorbidity, psychotic features, number of past episodes, and length of these episodes have all been associated with greater cognitive impairment (for review see Porter, Bourke, & Gallagher, 2007).

Notwithstanding the association between the number of episodes and extent of impairment, the majority of research in MDD has focused on samples with recurrent, depressive episodes (Hammar & Ardal, 2009). To disentangle the above-described complexities in cognitive impairment MDD research relative to the *state*, *trait*, and *scar* debate, it would be essential to start with describing the cognitive profile associated with the *state* of FED. To the best of our knowledge, only one meta-analysis of cognitive function in the FED has been conducted, but limited to an adult population. Across 13 studies including 644 FED patients, small to moderate deficits were observed in processing speed, attention, visual learning and memory, shifting, verbal fluency, and cognitive flexibility (Lee et al., 2012). Following moderator analyses, including remission status, the authors concluded that disturbances in psychomotor speed and memory functioning were probably *state*-related, whereas deficits in attention and executive function would be a MDD *trait*-marker.

Lee and colleagues' meta-analysis (2012) was the first to demonstrate cognitive impairment in adult FED, a critical advance in

neuropsychological MDD research. Nevertheless, their conclusions relative to the impairment severity within the different cognitive domains and relative to the *trait/state* debate could be questioned, given the study's methodological limitations in terms of sample selection and choice of assessment for depression severity. First, the meta-analyses included mixed samples with 62% of the reviewed studies having samples containing both FED and recurrent MDD. The inclusion of mixed samples might have led to an overestimation of FED-related cognitive impairment. For example, the meta-analyzed study of [Reppermund and colleagues \(2009\)](#) included 16 patients with FED and 37 with recurrent MDD, while results from the whole sample of 53 were meta-analyzed. Second, [Lee and colleagues \(2012\)](#) excluded samples where the individuals' mean age was "below 18. . .and primarily (greater than 50%) younger than 16," which limits the representativeness of the meta-analyzed samples. Indeed, previous research suggests that about 75% of all MDD patients have had their first FED between the ages of 11 and 15 ([Kovacs et al., 1984](#); [Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993](#)). Also, a recent meta-analysis of 17 studies, including 447 children and adolescents with MDD, showed that moderate impairments are evident in attention, verbal memory, inhibition, and verbal fluency among this population relative to controls ([Wagner, Müller, Helmreich, Huss, & Tadić, 2015](#)). Third, as the authors report, their inclusion of samples with mean age up to 65 probably has increased the risk of having included people with vascular pathologies that also impact on cognitive function ([Lee et al., 2012](#)). Finally, the authors dichotomized the moderator variable of depression severity into "euthymic" (= no symptoms) and "symptomatic" (= mild or greater symptoms). This dichotomization prevents the assessment of the effect of depression severity on the observed outcomes. Indeed, greater depression severity has been associated with larger cognitive impairments ([McDermott & Ebmeier, 2009](#)).

To advance the debate of *state/trait* characteristic of cognitive impairment in depression, an updated meta-analysis to describe the cognitive profile of FED, which addresses the above-described limitations, is needed. Thus, the aims of the present systematic review and meta-analysis are: (a) to determine the pattern and provide a quantitative estimate of the extent of cognitive deficits in FED patients compared with healthy controls; (b) to examine the contribution of moderator variables to the extent of this cognitive impairment; and (c) to explore the persistence of cognitive impairment following FED remission. For the purpose of this review and meta-analysis, cognitive impairment refers to a level of functioning below that of the healthy, normal population that interferes with daily life ([Lezak et al., 2012](#)).

Method

A two-part systematic review and meta-analysis was conducted. Part 1 of the meta-analysis examined cognitive function in FED patients relative to healthy controls. Part 2 reviewed studies that followed FED in remission to further explore the persistence of these cognitive deficits. The repeated assessment of FED patients is considered a more valid measure of persistence as patients are compared with their own baseline performance, eliminating the possibility of individual differences when remitted FED patients are compared with healthy controls ([Douglas & Porter, 2009](#)).

PRISMA guidelines for conducting and reporting systematic reviews and meta-analyses were followed ([Moher, Liberati, Tetzlaff, & Altman, 2009](#)).

Search Strategy

The electronic databases PsycINFO, PsycArticles, MEDLINE, Embase, and PubMed were searched from the year 1980 to October 2015. The year 1980 was selected as this was when the term "major depressive disorder" was introduced to the *Diagnostic and Statistical Manual of Mental Disorders*, third edition (*DSM-III*; [American Psychiatric Association, 1980](#)) and for the most part, diagnostic criteria has remained the same since ([Uher, Payne, Pavlova, & Perlis, 2014](#)). The following search terms were used "first depressive episode" OR ("first episode" OR "single episode" AND ["major depressive disorder" OR "major depressive episode"]) AND (neurocognit* OR cognit* OR neuropsycholog* OR "executive function" OR attention OR memory OR orientation OR perception OR language OR verbal OR visual OR reasoning OR vigilance OR visuospatial OR "problem solving" OR "processing speed" OR intelligence OR impairment). References from relevant reviews and articles returned from the databases were hand-searched to identify additional studies. Only published studies were searched. For the purpose of this systematic review, a study was defined as an article which did not share the same sample and cognitive tests with any other article. In cases of redundancy, the most recent study with the largest sample size was retained to ensure statistical independence of effect sizes ([Lipsey & Wilson, 2001](#)).

Systematic Review and Meta-Analysis I

Selection criteria. For the systematic review, inclusion criteria for studies were as follows: (a) use of sample diagnosed with MDD according to *DSM-III*, *DSM-III-R*, *DSM-IV*, *DSM-IV-TR*, *DSM-5*, ICD-9, or ICD-10 criteria; (b) participants must not have previously been diagnosed with a major depressive episode; (c) inclusion of a healthy, control comparison group; (d) Used at least one objective cognitive test. Furthermore, for the meta-analysis, an additional criterion required that the study reported means and standard deviations of cognitive function in both FED patients and controls, or sufficient statistical data such as *F* or *t* statistics which could be converted into effect sizes. Exclusion criteria were (a) mean age of the study sample ≥ 55 years, (b) redundant reports, that is, separately published studies that have used the same cognitive tests on the same patient sample, (c) case series.

Data extraction and recorded variables. Titles and abstracts returned from the database search were screened for potential inclusion against the selection criteria. Authors EA and MS searched independently the selected databases using the above-described search strategy and identified independently potentially eligible studies. Their interrater agreement for studies' inclusion/exclusion categorization was 0.98. Potentially eligible articles (including the few that *only* EA or *only* MS identified) were retained and full-texts located. The corresponding author was contacted if the full-text of a potentially eligible article could not be located. When sufficient detail was not reported, but articles met the remaining inclusion criteria, a request for the missing information was sent to the corresponding author. Authors who did not initially respond were recontacted twice further.

Cognitive tests were categorized into 12 standard cognitive domains (Lezak et al., 2012) also used in prior meta-analyses of cognitive function in MDD (Lee et al., 2012; Snyder, 2013). A cognitive domain was defined as a class of cognitive functions which could be assessed using one or numerous, different cognitive tests (Lezak et al., 2012). As per standard categorizations, cognitive tests that used a similar methodology to assess cognitive function were pooled together within the cognitive domain, for example, the Rey Auditory Verbal Learning Test and the California Verbal Learning Test both measure verbal learning using a word-list methodology (Lezak et al., 2012). A cognitive test was analyzed separately when two or more studies reported on that test but it could not be pooled with other tests as methodologies were not comparable. All data analyzed were initially extracted and categorized by the first author (E.A.). Second and prior to meta-analyses, the extracted data were cross-checked by the second author (M.S.) against the original publication or communication from authors who provided their data. Disagreements relative to categorization were resolved through discussion between the authors.

Frequently, cognitive tests yield more than a single outcome of performance. For example, the Wisconsin Card Sorting Test provides results including errors and correct responses. It is recommended that cognitive outcomes are assessed separately to provide a more detailed insight into the functions possibly compromised in MDD (Snyder, 2013). Where possible, cognitive outcomes within the same domain were pooled together regardless of the specific cognitive test, for example, test errors, number of categories shifted between, number of trials taken to shift, correct responses, and time variables were formed within the shifting domain. To account for small study numbers, an overall composite score was formed for each domain by pooling all cognitive data categorized within that domain. When necessary, effect sizes were averaged so that each FED sample only contributed to one effect size per analysis. This was done so as to avoid weighting individual studies according to the number of tests or outcomes reported, in addition to ensuring statistical independence of effect sizes (Lipsey & Wilson, 2001). Throughout, cognitive variable will be a general term to refer to all possible categorizations within a cognitive domain, for example, cognitive test or composite score.

The following were coded for each independent sample from each study: (a) number of FED patients and controls; (b) cognitive tests administered; (c) mean (M) and standard deviation (SD) scores of performance by FED patients and controls, or if not available, relevant inferential statistics; and (d) characteristics of patients (gender, depression severity, mean age, medication, patient status, current or remitted depression, premorbid intelligence, age of onset, educational attainment, comorbidity, duration of FED).

Meta-analysis. For each study, effect sizes were calculated as Cohen's d to compare the performance of FED patients to controls on each cognitive variable. Cohen's d effect size was calculated as $M_2 - M_1/SD_{\text{pooled}}$, where M_2 is the mean cognitive performance of the control group, M_1 is the mean cognitive performance of the FED group and SD_{pooled} is the pooled standard deviation of the two groups. When M or SD were not reported, or could not be obtained from the author, effect size was estimated from the F statistic using effect size calculation macros provided by Wilson (2001; $k = 1$), or were estimated from the z standard normal deviate (Rosenthal & DiMatteo, 2001; $k = 1$).

Hedges' g correction for small sample bias (Hedges & Olkin, 1985), $g = d \left[1 - \left(\frac{3}{4} df - 1 \right) \right]$, where df equals the total number of participants, considering the FED patient and control groups combined, minus 2. A positive g indicated a poorer performance by FED patients compared with controls. Therefore, the effect size was inverted for measures where higher scores indicated worse performance, that is, errors, time and overgeneral autobiographical memory. Outliers were omitted only from the analyses in which they were outliers. An outlier was defined as an effect size ≥ 2 or $\pm 3 SDs$ from the mean effect size of each analysis (Snyder, 2013). When data was provided by FED patients at multiple time points, only baseline data were assessed so as to maintain statistical independence of effect sizes. In addition, this eliminated the possibility of practice effects on test performance at follow-up assessments (Lipsey & Wilson, 2001).

Inverse-variance weighted, random-effects modeling was conducted to provide an estimate of the mean effect size across studies for each cognitive variable using Review Manager (v5.3; The Cochrane Collaboration, 2014). The random-effects model assumes that there is more variability between studies than sampling error alone (Borenstein, Hedges, Higgins, & Rothstein, 2009). The studies included in this meta-analysis varied in terms of sample characteristics and the cognitive tests administered which necessitated the use of the random-effects model. Effect sizes were weighted by its inverse variance so that effect sizes with larger samples would be given more weight (Borenstein et al., 2009).

For each analysis, a weighted, mean effect size and 95% confidence intervals were computed. The null hypothesis that the effect size is 0 was tested with z with an alpha level set at .05. Weighted, mean effect sizes were interpreted in accordance with the recommendations of Cohen (1988), ≥ 0.2 = small, ≥ 0.5 = medium, ≥ 0.8 = large. Heterogeneity of effect sizes was assessed using the Q statistic. This tests the null hypothesis that the variability between effect sizes in each study, contributing to the weighted, mean effect size, is attributable to chance. As the Q statistic chi-squared test has low power in a meta-analysis with a small number of studies a p -level of .10 was applied, as recommended by Cochrane (Higgins & Green, 2008); $p \leq .10$ indicated that there was much variability between the study effect sizes in each analysis. The I^2 index quantified the percentage of variability across study effect sizes due to true differences and not chance. This was interpreted in accordance with the recommended cut-offs: 25% = small, 50% = moderate, and 75% = large heterogeneity (Borenstein et al., 2009).

Moderator analyses were conducted using a random-effects model on Comprehensive Meta-Analysis software (v.2.2; Biostat, n.d.; Englewood, NJ) with the moderator variables prespecified. When ≥ 10 samples reported on a continuous moderator variable (depression severity, patient age, and medication), it was entered separately into the metaregression model. Categorical variables, entered for subgroup analysis of variance, included patient status (inpatient vs. outpatient) and remission status (current depression vs. remission). A minimum of two studies in the smaller subgroup category was required for subgroup analysis. The minimum study requirement was to ensure that there was adequate power to predict moderator variables that influenced effect size (Borenstein et al., 2009).

Publication bias was conducted by visual assessment of funnel plots. Funnel plots were only generated when ≥ 10 samples were

included in the analysis, as recommended by Borenstein et al. (2009). Egger's test was used to quantify the amount of publication bias and was chosen as it is considered a more powerful test than the rank correlation method. In cases of bias, trim and fill analyses were conducted to yield an unbiased estimate of the effect size (Lipsey & Wilson, 2001).

Systematic Review and Meta-Analysis II

Selection criteria. For the systematic review, inclusion criteria for studies were as follows: (a) use of sample diagnosed with MDD according to *DSM-III*, *DSM-III-R*, *DSM-IV*, *DSM-IV-TR*, *DSM-5*, ICD-9, or ICD-10 criteria; (b) participants must not have previously been diagnosed with a major depressive episode; (c) participants were followed to remission using a repeated-measures design; (d) used at least one objective cognitive test. The additional criterion for inclusion in the meta-analysis and the exclusion criteria were the same as for the Systematic Review and Meta-Analysis I.

Data extraction and recorded variables. Data extraction followed the same protocol as detailed for Systematic Review and Meta-Analysis I. From each study, the following were coded for each independent sample: (a) number of FED patients, (b) cognitive tests administered, (c) *M* and *SD* of cognitive performance at baseline and follow-up assessments, and (d) patient characteristics (gender, depression severity at baseline and follow-up, length of time to follow-up, mean age, medication, current or remitted depression, premorbid intelligence, age of onset, educational attainment, comorbidity, duration of FED).

Meta-analysis. Standardized mean differences were calculated as Cohen's *d* using the formula $M_2 - M_1/SD_{\text{pooled}}$, where M_2 is the mean, follow-up cognitive performance and M_1 is the mean, baseline cognitive performance in FED patients. SD_{pooled} was given by summing the baseline and follow-up *SDs*, and dividing by 2. To calculate the variance of *d* for each cognitive variable, the correlation between the baseline and follow-up performance is required. As this was not available in any of the included studies, a recommended global estimate of $r = .70$ was applied to calculate the variance of *d*, $\left(\frac{1}{n} + \frac{d^2}{2n}\right)[2(1 - r)]$, where *n* is the number of FED patients (Lipsey & Wilson, 2001). All effect sizes were corrected for small sample bias using Hedges' *g* formula. A positive *g* indicated that cognitive function improved at follow-up compared with baseline.

Inverse-variance weighted, random-effects models were applied for each analysis, considering the variability in cognitive tests pooled under a common domain (Borenstein et al., 2009). The remaining conduct of the meta-analytic process was the same as detailed above for Meta-Analysis I.

Results

Systematic Review I

After deleting duplicates, 389 potentially relevant articles were identified from which 30 were included in the meta-analysis. All articles were published in English. Seventeen authors were contacted for additional cognitive data ($n = 10$) or for subgroup analysis of FED patients from a sample of first-episode, affective

disorders ($n = 7$). Additional information was provided by four authors which allowed the inclusion of those studies in the analysis; authors cited "too busy to prioritize location of data" ($n = 4$) as the main reason for not facilitating data requests. The review process is detailed in Figure 1.

Of the studies included, the majority were published in England ($k = 5$), followed by China or U.S.A. ($k = 4$), then Norway ($k = 3$). France, Finland, Japan, Turkey, and The Netherlands each published two studies ($k = 2$), and Germany, Belgium, Australia, Denmark, and Canada each published one study ($k = 1$). A total of 994 patients (subsample size range 9–49) and 1471 healthy controls (sample size range 11–88) were included in the analysis. The FED group consisted of 356 males (35.81%) and 586 females (58.95%); 52 participants (5.23%) had no gender reported. The weighted, mean patient age was 27.40 years. The healthy control group contained 556 males (37.80%) and 761 females (51.73%); gender was not specified for 154 participants (10.47%). The weighted, mean control age was 29.99 years. For details of reporting on each prespecified moderator variable refer to Table 1.

Eight studies reported data for two FED subsamples. Subsamples included current and remitted FED patients ($k = 4$), or psychotic and nonpsychotic FED patients ($k = 4$). An effect size was calculated for each FED subsample with respect to a single, healthy control group, with the exception of one study that compared each FED subsample to its own geographically matched, healthy control group. One study reported data for three FED subsamples (current, partial remission, and full remission) compared with a single, healthy control group. As the same control group served as a comparison for more than one FED sample, effect sizes were not statistically independent (Reis & Judd, 2014). However, this method was chosen as remission and psychosis were intended to be explored as moderator variables which justified providing a separate effect size for each subsample.

For each study, and relevant subsamples, cognitive performance plus coded variables are outlined in Table 1S in the supplementary online data. Forty-one standardized, cognitive tests were identified; for details of tests and categorization into the relevant cognitive domain refer to Table 2. A separate cognitive domain for reaction time (RT) was formed by pooling RTs from unstandardized tests of sustained attention ($k = 4$). However, not all reported data was meta-analyzable. Five study-level composite scores were excluded, as they pooled tests from different cognitive domains: the "Learning and memory" score from As et al. (2011) included both verbal and visual tests; while the following four composite scores were excluded from Hill, Keshavan, Thase, and Sweeney (2004): "Attention" (pooled tests of processing speed and working memory), "Executive function" (pooled tests of shifting and verbal fluency), "Verbal memory" and "Visual memory" (both pooled tests of learning and delayed).

Only one study reported on reward-based, decision making (Yang et al., 2014) which meant that this cognitive domain could not be meta-analyzed. This study showed motivational deficits in FED patients relative to healthy controls, as well as an abnormal ability to evaluate the probability and magnitude of expected pay-offs. FED patients were not as willing to complete "hard tasks" requiring 20 button-presses within 4 seconds with the non-dominant pinkie finger, for higher monetary rewards, compared with "easy tasks" which required 10 button-presses with the dominant index finger within 4 seconds, but lower rewards.

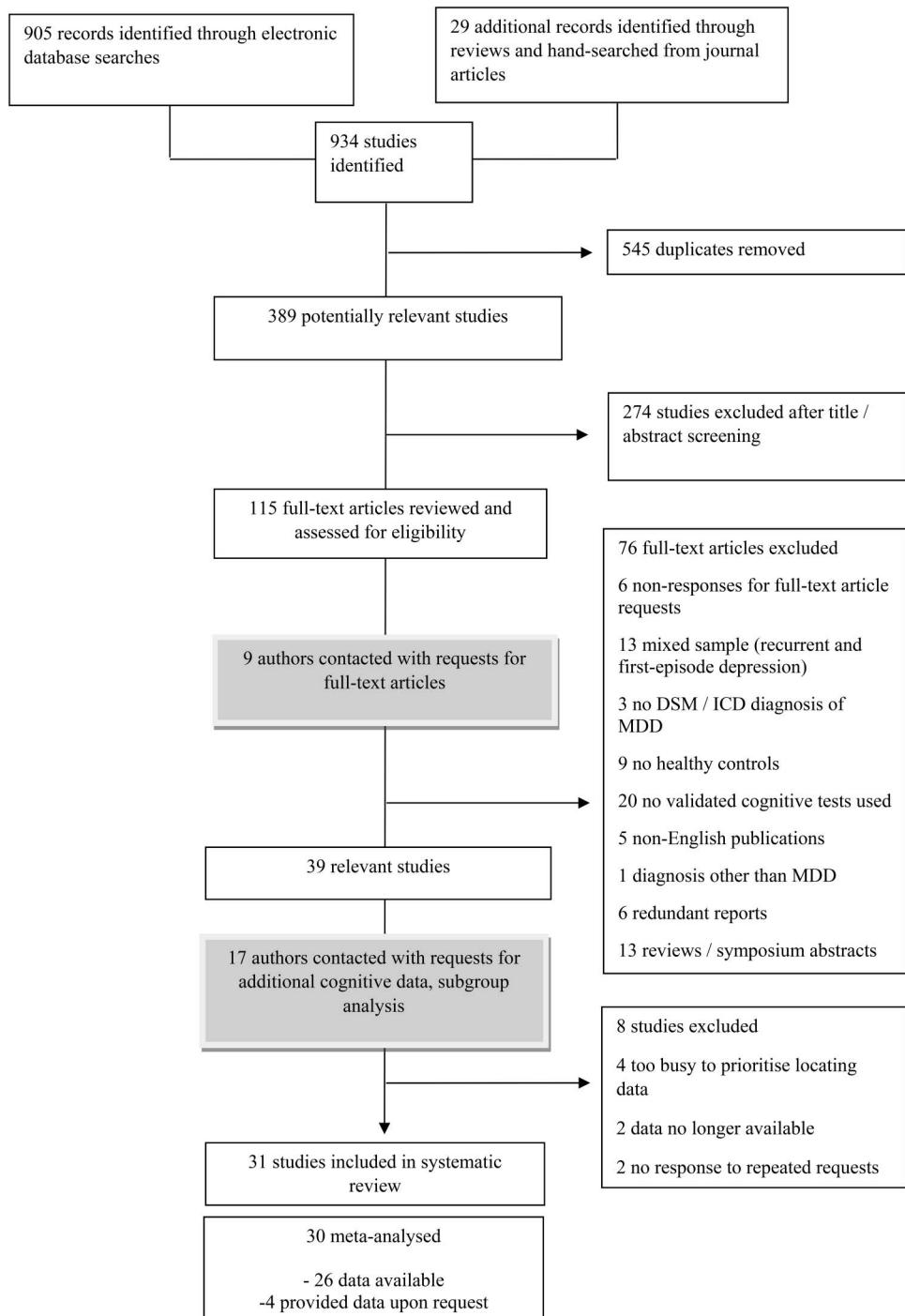


Figure 1. Flowchart for selection of studies relating to pattern and extent of cognitive impairment in first-episode depression (Systematic Review and Meta-analysis I). ICD = International Classification of Diseases; DSM = Diagnostic and Statistical Manual; MDD = major depressive disorder.

In addition, planning ability could not be meta-analyzed as data was only reported by two studies which used different scoring systems (CANTAB Stockings of Cambridge test, Maalouf et al., 2011; Tower of London test, Schmid & Hammar, 2013a). These studies did not obtain fully consistent results. Schmid and Hammar

(2013a) observed no significant differences in planning between FED patients and controls. Similarly, Maalouf et al. (2011) did not find a significant difference in planning between remitted FED patients and controls. However, a group-by-difficulty level interaction was demonstrated where *current* FED patients performed

Table 1
% Studies in Systematic Review I ($k = 31$) Reporting on Each Moderator Variable

Moderator	% Studies
Patient status (outpatient or inpatient)	93.55
Remission status (current or remission)	100.00
Mean age	96.77
Medication (% patients)	87.10
Depression severity	87.10
Age of onset ^a	22.58
Axis I comorbidity ^a	64.52
Duration FED ^a	54.84
Educational attainment ^a	54.84
Premorbid IQ ^a	25.81
Psychotic features (psychotic or non-psychotic) ^b	22.58

Note. FED = first-episode depression; k = number of studies.

^a Moderator analysis could not be conducted (<10 samples reported moderator per cognitive variable). ^b Subgroup analysis of variance could not be conducted (<2 samples in smaller category per cognitive variable).

worse than controls with increasing task difficulty. This indicates that for FED patients, planning may only be minimally impaired, and present only during the depressed state, with deficits emerging as a function of task complexity.

Meta-Analysis I

Table 3 details the weighted, mean effect sizes for cognitive performance in FED patients compared with healthy controls. Outlier screening resulted in the exclusion of three effect sizes which are detailed in the note to Table 3. As a result of outlier screening, cognitive status, assessed by the Mini Mental State Examination, was no longer eligible for meta-analysis ($k = 1$). Nevertheless, results indicated that FED patients were impaired relative to controls (Maeshima et al., 2012).

Processing speed. Data assessing processing speed was derived from four tests and a study-level composite score pooled into four variables (see Table 2). Effect sizes ranged from nonsignificant to large. FED patients did not perform any slower in number-coding tests compared with controls ($g = 0.37, p = .10$), although results between studies were largely heterogeneous, $Q(7) = 36.06, p < .00001, I^2 = 81\%$. Relative to controls, FED patients showed a small impairment in TMT-A ($g = 0.42, p = .004$), a moderate impairment in the processing speed composite score ($g = 0.63, p < .0001$) and a large impairment in the Stroop test color naming and word reading conditions ($g = 0.93, p < .00001$).

Visuospatial attention. Data assessing visuospatial attention was derived from the Spatial Span Forward test reported by three studies. FED patients showed a small impairment in visuospatial attention compared with controls ($g = 0.32, p = .02$).

Auditory attention. Data assessing auditory attention was derived from the Digit Span Forward test reported by three studies. Relative to controls, FED patients showed a small impairment in auditory attention ($g = 0.35, p = .03$).

Sustained visual attention. Data for sustained visual attention was provided by three tests which were pooled into two variables. FED patients showed a small impairment in the sustained attention composite score ($g = 0.43, p = .003$) but did not

produce significantly more errors than controls ($g = 0.34, p = .18$).

RT sustained visual attention. RT for sustained visual attention was derived from unstandardized tests and pooled into three variables. FED patients did not differ from controls in simple RT ($g = 0.11, p = .59$), complex tracking RT ($g = -0.02, p = .92$), or the RT composite score ($g = 0.06, p = .78$).

Visuospatial working memory. Data assessing visuospatial working memory was derived from six tests and a study-level composite score pooled into two variables. Relative to controls, FED patients were moderately impaired on the visuospatial working memory composite score ($g = 0.74, p = .005$) and produced a significantly, larger number of errors ($g = 1.05, p < .00001$).

Auditory working memory. Data assessing auditory working memory was derived from two tests and pooled into two variables. FED patients showed a small impairment in the Digit Span Backwards test ($g = 0.33, p = .02$) and in the auditory working memory composite score ($g = 0.39, p < .0001$) compared with controls.

Autobiographical memory. Data assessing autobiographical memory, measured as the proportion of overgeneral memories, was derived from two studies. Relative to controls, FED patients showed a moderate impairment and produced more overgeneral, autobiographical memories in response to positive or negative words ($g = 0.69, p < .0001$). The results of a third study (Nandrino, Pezard, Poste, Reveillere, & Beaune, 2002) were not meta-analyzable as cognitive data were not available. However, results were partially consistent with that of the meta-analysis as FED patients produced a greater proportion of overgeneral memories for positive, but not for negative cue words, relative to controls.

Visual learning. Data for visual learning was derived from two tests reported by five studies. Relative to controls, FED patients were moderately impaired in the Visual Reproduction I test ($g = 0.65, p = .01$) and in the visual learning composite score ($g = 0.64, p = .001$).

Delayed visual memory. Data for delayed visual memory was derived from four tests and pooled into two variables. FED patients demonstrated a small impairment in the delayed visual memory composite score compared with controls ($g = 0.39, p = .01$) and a moderate impairment in the Visual Reproduction II test ($g = 0.70, p = .03$). However, the overlap in confidence intervals indicates that the true effect sizes may not be substantially different (composite score: 95% CI [0.08, 0.70]; Visual Reproduction II test: 95% CI [0.07, 1.32]).

Verbal memory recognition. Data for verbal memory recognition was pooled from three tests reported by three studies. FED patients did not show any impairment in verbal memory recognition compared with controls ($g = 0.37, p = .15$). Moderate heterogeneity between the studies, $Q(3) = 9.04, p = .03, I^2 = 67\%$, likely explains the nonsignificant findings.

Verbal learning. Data for verbal learning was derived from five tests which provided three variables. Effect sizes ranged from nonsignificant to moderate. FED patients showed a trend toward a small impairment in the verbal learning composite score ($g = 0.31, p = .05$), however, as the confidence interval contained zero, it is assumed that no difference in the composite score exists between FED patients and controls (95% CI [0.00, 0.63]). Relative to controls, FED patients showed no impairment in word-list learning ($g = 0.11, p = .54$) but a moderate impairment in storytelling

Table 2
Cognitive Tests and Domains Included in Meta-Analysis I

Cognitive domain	Cognitive tests/variables	k	n	N
Processing speed	Number-Coding -Pooled from DSST, SDMT TMT-A (time) Stroop Colour Word Test colour naming and word reading conditions (time) Composite -Pooled from cognitive tests outlined, and study-level composite score	5 8 4 11	8 10 4 15	188 212 80 316
Attention				
Visuo-spatial attention	Spatial Span Forward	3	3	82
Auditory attention	Digit Span Forward	3	3	64
Sustained visual attention	Errors -Pooled from RVP, false alarms Visual Detection Task (unstandardised test) Composite -Pooled from CPT, RVP, % hits Visual Detection Task	2 6	3 7	54 149
Reaction time (sustained visual attention)	Simple -Pooled from unstandardised tests Complex Tracking -Pooled from unstandardised tests Composite -Pooled from unstandardised tests outlined	4 2 4	4 2 4	88 45 88
Working memory				
Visuo-spatial working memory	Errors -Pooled from Visual Rotation Task (unstandardised), Cogtest Location Recall, Span of Apprehension Test Composite -Pooled from cognitive tests outlined, Spatial Span Backwards, One Touch Stockings, Clock Drawing and study-level composite score	3 7	3 9	63 212
Auditory working memory	Digit Span Backwards Composite -Pooled from Digit Span (backwards and total) and Mental Control	4 7	5 8	121 186
Autobiographical memory	Composite -Pooled from measures of overgeneral memories	2	4	171
Visual learning and memory				
Learning	Visual Reproduction I Composite -Pooled from Visual Reproduction I, and Penn Face Memory	4 5	4 5	77 98
Delayed memory	Visual Reproduction II Composite -Pooled from Visual Reproduction II, ROCF, Penn Face Memory, and Delayed Matching to Sample	4 7	4 9	77 178
Verbal learning and memory				
Recognition	Composite -Pooled from CVLT, RAVLT and Process Dissociation Task (unstandardised)	3	4	77
Learning	Word list -Pooled from CVLT (free and cued learning), RAVLT, Buschke total recall 1 + 2 Story-telling -Logical Memory - I	6	8	151
Delayed memory	Composite -Pooled from cognitive tests outlined and Paired Associates Learning Test Word list -Pooled from CVLT (total/delayed free and cued recall), RAVLT, Buschke total recall 3, HVLT Story-telling -Logical Memory - II	10 9	12 11	228 225
Reasoning	Composite -Pooled from cognitive tests outlined	12	14	292
Inhibition	Picture Completion Composite -Pooled from Stroop Colour Word Test inhibition and inhibition/switching conditions, Stroop TBAG, and Affective Go/No Go test	2 5	3 5	67 110

(table continues)

Table 2 (continued)

Cognitive domain	Cognitive tests/variables	<i>k</i>	<i>n</i>	<i>N</i>
Shifting	Categories	9	13	285
	-Pooled from WCST, MCST, and D-KEFS switching fluency	9	13	281
	Errors			
	-Pooled from WCST (perseverative, non-perseverative errors, no. errors), Cogtest Set-Shifting errors, ID-ED errors, Stroop Colour Word Test errors, and TMT-B % interference			
	Trials	5	6	172
	-Pooled from WCST (no. trials, no. trials to complete first category), ID-ED trials, and Penn Conditional Exclusion Task trials			
	Correct responses	2	3	77
	-Pooled from WCST (correct responses, % conceptual level responses)			
	Time	6	6	136
	-TMT-B			
Verbal fluency	Composite	16	21	480
	-Pooled from cognitive tests outlined			
	Letter Fluency	6	6	121
	-Pooled from WAIS-R, D-KEFS, COWAT and LPS test			
	Semantic Fluency	5	5	102
Motor skills	-Pooled from WAIS-R, D-KEFS, COWAT and Supermarket test			
	Composite	7	8	147
	-Pooled from cognitive tests outlined and study-level composite score			
Intelligence	Composite	2	3	55
	-Pooled from study-level composite scores, and Cogtest Finger-Tapping			
Intelligence	Composite	10	16	426
	-Pooled from WAIS, WISC, Raven's Standard Progressive Matrices and Raven's Coloured Matrices A, B, AB			

Note. Cognitive variables derived from the following 41 standardized tests: Digit Symbol Substitution Test; Symbol Digit Modalities Test; Trail Making Test-A; Stroop Colour Word Test; Spatial Span; Digit Span; Rapid Visual Processing; Continuous Performance Test; Cogtest Location Recall; Span of Apprehension Test; One Touch Stockings; Clock Drawing Test; Mental Control; Visual Reproduction; Penn Face Memory; Rey-Osterrieth Complex Figure; Delayed Matching to Sample; California Verbal Learning Test; Rey Auditory Verbal Learning Test; Buschke Selective Reminding Test; Logical Memory; Paired Associates Learning; Hopkins Verbal Learning Test; Picture Completion; Affective Go/No Go; Stroop TBAG; Wisconsin Card Sorting Test; Modified Card Sorting Test; Intradimensional-Extradimensional Shift; Trail Making Test-B; Penn Conditional Exclusion Test; Weschler Adult Intelligence Scale-Revised Letter and Category Fluency Tests; Delis Kaplan Executive Function Fluency Test; Controlled Oral Word Association Test; Leistungsprufsystem Fluency Test; Supermarket Fluency Test; Cogtest Finger-Tapping; Weschler Adult Intelligence Scale; Weschler Intelligence Scale for Children; Raven's Standard Progressive Matrices; Raven's Coloured Matrices. COWAT = Controlled Oral Word Association Test; CPT = Continuous Performance Test; CVLT = California Verbal Learning Test; D-KEFS = Delis Kaplan Executive Function System; DSST = Digit Symbol Substitution Test; HVLT = Hopkins' Verbal Learning Test; ID-ED = Intradimensional Extradimensional shift; *k* = number of studies; LPS = Leistungsprufsystem test; MCST = Modified Card Sorting Test; *n* = number of patient samples; *N* = total number of patients; RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure; RVP = Rapid Visual Processing; SDMT = Symbol Digit Modalities Test; TMT = Trail Making Test; WAIS = Weschler Adult Intelligence Scale; WAIS-R = Weschler Adult Intelligence Scale-Revised; WCST = Wisconsin Card Sorting Test; WISC = Weschler Intelligence Scale for Children. Cognitive domains generated from [Lezak et al. \(2012\)](#) and [Snyder \(2013\)](#) meta-analysis of executive function in major depressive disorder.

learning ($g = 0.74, p = .005$). Moderate heterogeneity between the studies likely explains the nonsignificant findings: composite, $Q(11) = 38.08, p < .0001, I^2 = 71\%$; word-list learning, $Q(7) = 19.93, p = .006, I^2 = 65\%$.

Delayed verbal memory. Data for delayed verbal memory was derived from five tests which provided three variables. Effect sizes ranged from small to moderate. Relative to controls, FED patients showed a small impairment in the delayed verbal memory composite score ($g = 0.43, p < .0001$) and in word-list memory ($g = 0.39, p = .002$), but a moderate impairment in storytelling memory ($g = 0.65, p = .004$).

Reasoning. Data assessing reasoning was derived from the Picture Completion test reported by two studies. Relative to controls, FED patients showed a moderate impairment in reasoning ($g = 0.78, p < .00001$).

Inhibition. Data assessing inhibition was derived from three cognitive tests. FED patients reported a moderate impairment in inhibition compared with healthy controls ($g = 0.76, p = .0005$).

Shifting. Data for shifting were derived from eight tests pooled into six cognitive variables. Effect sizes ranged from small to large. Relative to controls, FED patients showed small impairments in shifting between categories ($g = 0.36, p < .0001$), the number of errors made ($g = 0.43, p = .0007$), and trials needed for completion ($g = 0.46, p = .009$). Moderate impairments were observed in the composite score ($g = 0.51, p < .00001$) and in the amount of time required to complete the tasks ($g = 0.57, p < .00001$). The largest impairments were shown in accuracy with FED patients making fewer correct responses relative to controls ($g = 0.82, p = .001$).

Verbal fluency. Data assessing verbal fluency was derived from five tests and a study-level composite score pooled into three variables. Effect sizes ranged from small to moderate. Relative to controls, FED patients showed a small impairment in the letter fluency task ($g = 0.48, p < .0001$), and were moderately impaired in semantic fluency ($g = 0.79, p < .00001$) and in the verbal fluency composite score ($g = 0.64, p < .00001$).

Table 3
Weighted Mean Effect Size Meta-Analysis I

Variable	k	n	N	g	95% CI		p	Homogeneity	
					LL	UL		Q	I ²
Processing speed									
Number-coding	5	8	188	.37	-.07	.81	.10	36.06*	81.00
TMT-A	8	10	212	.42	.13	.70	.004	22.06*	59.00
Stroop color naming and word reading	4	4	80	.93	.63	1.24	<.00001	1.91	.00
Composite	11	15	316	.63	.35	.92	<.0001	51.31*	73.00
Visuo-spatial attention									
Spatial span forward	3	3	67	.32	.04	.60	.02	.59	.00
Auditory attention									
Digit span forward	3	3	64	.35	.04	.65	.03	1.63	.00
Sustained visual attention									
Errors	2	3	54	.34	-.15	.82	.18	3.17	37.00
Composite	6	7	149	.43	.15	.71	.003	9.31	36.00
RT sustained visual attention									
Simple RT	4	4	88	.11	-.28	.50	.59	5.14	42.00
Complex tracking RT	2	2	45	-.02	-.45	.40	.92	1.07	6.00
Composite	4	4	88	.06	-.35	.47	.78	5.66	47.00
Visuo-spatial working memory									
Errors	3	3	63	1.05	.65	1.46	<.00001	2.94	32.00
Composite	7	9	212	.74	.23	1.25	.005	65.67*	88.00
Auditory working memory									
Digit span backwards	4	5	121	.33	.06	.59	.02	5.21	23.00
Composite	7	8	186	.39	.20	.58	<.0001	6.89	.00
Autobiographical memory									
Composite ^a	2	4	171	.69	.36	1.03	<.0001	5.36	44.00
Visual learning									
Visual reproduction I	4	4	77	.65	.13	1.17	.01	9.17*	67.00
Composite	5	5	98	.64	.25	1.03	.001	9.17*	56.00
Delayed visual memory									
Visual reproduction II	4	4	77	.70	.07	1.32	.03	12.92*	77.00
Composite	7	9	178	.39	.08	.70	.01	19.96*	60.00
Verbal memory recognition									
Composite	3	4	77	.37	-.13	.88	.15	9.04*	67.00
Verbal learning									
Word-list learning	6	8	151	.11	-.23	.45	.54	19.93*	65.00
Story-telling learning	4	4	77	.74	.22	1.25	.005	8.74*	66.00
Composite	10	12	228	.31	.00	.62	.05	38.08*	71.00
Delayed verbal memory									
Word-list delayed ^b	9	11	225	.39	.15	.64	.002	20.03*	50.00
Story-telling delayed	4	4	77	.65	.21	1.10	.004	6.60*	55.00
Composite ^b	12	14	292	.43	.22	.64	<.0001	25.82*	50.00
Reasoning									
Picture completion	2	3	82	.78	.45	1.12	<.00001	1.24	.00
Inhibition									
Composite	5	5	110	.76	.33	1.18	.0005	10.74*	63.00
Shifting									
Categories	9	13	285	.36	.19	.54	<.0001	15.16	21.00
Errors	9	13	281	.43	.18	.68	.0007	29.50*	59.00
Trials	5	6	172	.46	.11	.8	.009	13.57*	63.00
Correct responses	2	3	77	.82	.32	1.32	.001	4.42	55.00
Time	6	6	136	.57	.34	.79	<.00001	4.85	.00
Composite	16	21	480	.51	.31	.72	<.00001	56.89*	65.00
Verbal fluency									
Letter fluency	6	6	121	.48	.24	.72	<.0001	1.96	.00
Semantic fluency	5	5	102	.79	.52	1.06	<.00001	2.21	.00
Composite	7	8	147	.64	.43	.85	<.00001	2.33	.00
Motor skills									
Motor skills composite	2	3	55	.39	.06	.72	.02	2.35	15.00
Intelligence									
IQ composite	10	16	426	.26	.08	.44	.005	27.13*	45.00

Note. CI = confidence interval; g = Hedges' g effect size; k = number of studies; n = number of patient samples; N = number of patients; LL = lower limit; p = significance level; Q = heterogeneity statistic; RT = reaction time; TMT-A = Trail Making Test-A; UL = upper limit.

^a One outlier excluded ($g = 2.88$): with this outlier included the weighted mean effect size for autobiographical memory is $g = 1.13$. ^b One outlier excluded ($g = 2.16$): with this outlier included the weighted mean effect size for word-list delayed is $g = .56$, and for the composite score is $g = .57$.

* $p < .10$.

Motor skills. A composite motor skills domain was derived from the Cogtest finger-tapping test and a study-level composite score. FED patients had a small motor impairment in comparison to healthy controls ($g = 0.39, p = .02$).

Intelligence. Data assessing intelligence was derived from four tests. FED patients demonstrated a small impairment in intelligence compared with controls ($g = 0.26, p = .005$).

Moderator analysis. Of the 40 cognitive variables analyzed, 20 showed significant heterogeneity. Because of insufficient number of studies, only five of the prespecified moderators could be meta-analyzed to try and account for this unexplained heterogeneity between studies (see Table 1).

Remission. Subgroup analysis was possible for 17 variables. Remission (see Table 4) was associated with performance comparable to healthy controls on 15 of these variables. Remitted FED patients were less impaired than current FED patients and comparable to controls in number-coding ($p = .007$), TMT-A ($p = .006$), processing speed composite score ($p < .0001$), word-list learning ($p = .03$), word-list delayed ($p = .05$), storytelling delayed ($p = .02$), delayed verbal memory composite score ($p = .09$), and IQ ($p = .05$). Remitted FED patients were not less impaired than current FED patients in autobiographical memory ($p = .47$), visual learning composite ($p = .34$), Visual Reproduction II ($p = .35$), delayed visual memory ($p = .47$), verbal learning composite ($p = .12$), shifting errors ($p = .75$), or shifting composite ($p = .55$). However, remitted FED performed similar to controls as the confidence intervals of effect size for each of these variables crossed zero (Borenstein et al., 2009).

Patient status. Subgroup analysis was possible for 18 variables. Inpatient status was significantly associated with more impairment in number-coding relative to outpatients ($p = .0004$; see Table 5). No significant difference was observed in inpatient performance compared with outpatients in any other variable ($p > .10$). However, as the confidence intervals crossed zero, it can be concluded that inpatient performance was comparable to controls in TMT-A, delayed visual memory composite, word-list learning, verbal learning composite, word-list delayed, delayed verbal memory composite, shifting categories, errors, and IQ. Similarly, outpatient performance was comparable with healthy controls in number-coding, TMT-A, processing speed composite, sustained visual attention composite, visual learning composite, delayed visual memory composite, word-list learning, verbal learning composite, shifting time, and IQ.

Age. Metaregression was possible for nine variables. Higher age at onset significantly predicted larger impairments in IQ ($b = .03, z = 2.77, p = .006$) but smaller impairments in word-list delayed memory relative to controls ($b = -.04, z = -2.06, p = .04$). Age was not significantly associated with any other variable: for TMT-A, processing speed composite, verbal learning composite, delayed verbal memory composite, shifting (categories, errors, and composite), all $p > .20$.

Medication (% patients). Metaregression was possible for six variables: processing speed composite, verbal learning composite, delayed verbal memory composite, shifting (categories, errors, and composite). Medication was not significantly associated with the extent of impairment in any of these cognitive variables (all $p > .36$).

Depression severity. Where possible, depression severity scores were transformed to the Hamilton Rating Scale for

Depression–17 items scale (HRSD-17) using formulae proposed by Heo, Murphy, and Meyers (2007; HRSD-17 = $-1.58 + 0.86$ [MADRS score]) and Vittengl, Clark, Kraft, and Jarrett (2005; HRSD-17 = $0.65 + 0.67$ [BDI-II]). After transformation to HRSD-17 scores, sufficient data were available to perform metaregressions on six variables: processing speed composite, verbal learning composite, delayed verbal memory (word list delayed and composite), and shifting (categories and composite). Depression severity was not significantly associated with the extent of impairment in any cognitive variable (all $p > .18$).

Publication bias. Sufficient sample numbers ($n \geq 10$) meant that it was possible to analyze funnel plots for nine variables. Egger's test indicated a publication bias for studies reporting greater impairment in the shifting composite variable relative to the estimated, mean performance among FED patients (Egger's intercept = 5.58, $p = .008$). For visual presentation of publication bias in the shifting composite variable, a funnel plot (standardized mean difference between FED patients and healthy controls vs. standard error) is presented in Figure 2. Trim and fill analyses revealed that after controlling for publication bias and imputing the effect sizes for six hypothetical, missing studies, the adjusted, weighted mean effect size was significant, although it indicated a smaller impairment in FED patients relative to healthy controls ($g = 0.27$). All other Egger's tests were nonsignificant, p value range .07 to .53.

Systematic Review II

The same articles returned from the database search, as outlined in Part 1 of the review, were screened using the updated inclusion and exclusion criteria. Seven authors were contacted with requests for additional data of which four responded; one provided additional descriptive statistics, two cited "too busy to prioritize locating data," and one author reported "data no longer available." The review process is detailed in Figure 3.

The included studies were published in Japan, France, Spain, and Norway ($k = 1$ published in each country). A total of 92 FED patients (subsample size range 5–30) were included in the review, consisting of 26 males (28.16%) and 32 females (34.78%); 34 participants (36.96%) had no gender reported. The weighted mean patient age was 40.29 years, with a weighted mean follow-up period of 17.68 months. For each study, and relevant subsamples, baseline and follow-up cognitive performance plus coded variables are detailed in Table 2S in the supplementary online data.

Because of insufficient number of studies, it was not possible to meta-analyze the data provided by two studies (Maeshima et al., 2012; Nandrino et al., 2002). Maeshima and colleagues (2012) assessed visual and verbal learning and memory in remitted, FED patients. Results showed that impaired performance on the Logical Memory and Visual Reproduction tests did not persist at follow-up (mean 3.2 years) and were comparable with the performance of healthy controls. Nandrino and colleagues (2002) evaluated the percentage of overgeneral autobiographical memories produced following remission of FED. They observed that, after a 28-day interval, FED patients produced less overgeneral memories, with a complete normalization of function for negative autobiographical memories.

Two studies (Roca et al., 2015; Schmid & Hammar, 2013b) reported comparable data and thus were meta-analyzed. Seven

Table 4
Remission Subgroup Analysis of Variance

Variable	k	n	N	g	95% CI		Q_w	Q_b	p
					LL	UL			
Processing speed									
Number-coding									
Current	5	6	150	.59	-.10	1.08	23.75		
Remission	2	2	38	-.29	-.69	.11	.01	7.39	.007
TMT-A									
Current	8	8	174	.55	.26	.85	14.23		
Remission	2	2	38	-.14	-.54	.26	.00	7.58	.006
Composite									
Current	11	13	278	.76	.49	1.04	33.92		
Remission	2	2	38	-.22	-.62	.18	.00	15.70	<.0001
Autobiographical memory									
Composite									
Current	2	2	124	.84	.53	1.15	.04		
Remission	1	2	47	.54	-.20	1.28	2.85	.52	.47
Visual learning									
Composite									
Current	3	3	51	.82	.41	1.23	2.44		
Remission	2	2	47	.39	-.38	1.17	4.82	.89	.34
Delayed visual memory									
Visual reproduction II									
Current	2	2	30	1.05	-.04	2.15	.48		
Remission	2	2	47	.4	-.42	1.22	5.33	.88	.35
Composite									
Current	5	5	91	.51	.03	.99	11.56		
Remission	4	4	87	.27	-.17	.71	7.98	.52	.47
Verbal learning									
Word-list									
Current	6	6	113	.27	-.12	.66	13.71		
Remission	2	2	38	-.37	-.77	.03	.09	5.00	.03
Story-telling									
Current	2	2	30	1.24	.72	1.77	.66		
Remission	2	2	47	.38	.03	.72	.75	7.34	.007
Composite									
Current	8	8	143	.49	.07	.90	26.21		
Remission	4	4	85	.01	-.43	.46	8.48	2.37	.12
Delayed verbal memory									
Word-list									
Current	9	9	187	.48	.21	.75	15.79		
Remission	2	2	38	.00	-.40	.40	.00	3.86	.05
Story-telling									
Current	2	2	30	1.10	.58	1.61	.16		
Remission	2	2	47	.36	-.01	.74	1.18	5.05	.02
Composite									
Current	10	10	207	.54	.27	.81	19.4		
Remission	4	4	85	.21	-.05	.48	3.08	2.93	.09
Shifting									
Categories									
Current	9	11	247	.36	.15	.56	14.96		
Remission	2	2	38	.42	.01	.82	.12	.07	.79
Errors									
Current	9	11	243	.44	.15	.74	29.43		
Remission	2	2	38	.36	-.04	.77	.03	.10	.75
Composite									
Current	16	19	442	.53	.30	.75	56.70		
Remission	2	2	38	.39	-.01	.79	.07	.35	.55
Intelligence									

(table continues)

Table 4 (continued)

Variable	<i>k</i>	<i>n</i>	<i>N</i>	<i>g</i>	95% CI		<i>Qw</i>	<i>Qb</i>	<i>p</i>
					<i>LL</i>	<i>UL</i>			
IQ composite									
Current	10	12	328	.35	.13	.57	22.43		
Remission	3	4	98	-.01	-.28	.27	.56	3.98	.05

Note. CI = confidence interval; *g* = Hedges' *g* effect size; *k* = number of studies; *n* = number of patient samples; *N* = number of patients; *LL* = lower limit; *p* = significance level; *Qb* = between-group heterogeneity; *Qw* = within-group heterogeneity; TMT-A = Trail Making Test-A; *UL* = upper limit.

cognitive variables were identified (see *Meta-Analysis II* section below).

Meta-Analysis II

The weighted, mean effect sizes and homogeneity statistics for cognitive performance comparing the FED patients (the “remission” subsample from Roca et al., 2015 and the “no relapse” subsample from Schmid & Hammar, 2013b) at baseline and follow-up remission assessments are reported in Table 6.

Processing speed. Data assessing processing speed was derived from two tests pooled into two variables: TMT-A (time) and composite Stroop Color Word Test color naming and word reading conditions (time). At remission, FED patients showed a moderate improvement in TMT-A compared with their baseline acute episode performance, homogenous among the studies. There was no significant improvement observed on the Stroop composite, but large heterogeneity in findings was observed between the studies ($I^2 = 85\%$).

Inhibition. Data were derived from the Stroop inhibition (time) conditions. At remission, FED patients showed a small, nonsignificant improvement in inhibition compared with their baseline acute episode performance.

Shifting. Data assessing shifting were derived from two tests pooled into two variables: TMT-B (time) and Stroop interference/switching (time). At remission, FED patients showed a small improvement in TMT-B compared with their baseline acute episode performance, homogenous among the studies. They also showed a small, non significant improvement in Stroop interference/switching compared with their baseline acute episode performance, an outcome showing a small heterogeneity ($I^2 = 37\%$).

Verbal fluency. Data assessing verbal fluency was derived from two tests pooled into two variables: Letter Fluency and Semantic Fluency. Both showed negligible, nonsignificant improvement following remission of a FED relative to the verbal fluency.

Moderator analysis and publication bias. The TMT-A, TMT-B, and Letter fluency variables showed homogenous outcomes, while the remaining four variables showed small to large heterogeneity. Moderator and publication bias analyses were not conducted due to insufficient number of samples.

Discussion

This systematic review and meta-analysis was conducted to determine the pattern and extent of cognitive impairment in the FED. In addition, we sought to determine how certain moderators influenced the extent of impairment, and finally, to explore

whether the observed impairment persisted, or was present only during the depressive episode.

The Pattern and Extent of Cognitive Impairment

FED patients displayed a broad range of impairment across cognitive domains. Relative to healthy controls, no significant impairment was observed in number-coding speed, errors and RT for sustained visual attention, verbal memory recognition, or word-list learning. In general, small impairments were noted in the composite scores for visuospatial, auditory and sustained visual attention, auditory working memory, delayed visual memory, verbal learning composite, delayed verbal memory, motor skills, and IQ. Moderate impairment was observed in processing speed, visuospatial working memory, autobiographical memory, visual learning, storytelling learning, reasoning, inhibition, shifting, and verbal fluency. Large impairments were shown in the Stroop color naming and word reading speed, visuospatial working memory errors, and shifting correct responses. The extent of impairment was associated with remission, patient status, and age. Remitted FED patients were comparable with controls in processing speed, learning and memory (both verbal and visual), autobiographical memory, shifting, and IQ. Inpatient status did not contribute explaining the heterogeneity in observed results. Increasing mean patient age was associated with more impairment in IQ, but less impairment in word-list delayed memory relative to controls. A very small number of studies (*n* = 4) of cognitive function followed FED patients until remission. They showed moderate improvement in processing speed and a small improvement in shifting between over-learned sequences (TMT-B), but a persistent impairment in Stroop color naming and word reading speed, inhibition, shifting between effortful and automatic processing (Stroop Switching) and verbal fluency (both letter and semantic).

Overall, our findings are fairly consistent with the only meta-analysis of cognitive function in FED to date (Lee, Hermens, Porter, & Redoblado-Hodge, 2012). Similar levels of impairment in processing speed, attention, visual learning and memory, and shifting were shown. Our findings of small to large impairments across working memory and verbal learning and memory, however, were not observed in the Lee et al. (2012) meta-analysis. Although, as only 13 studies were included, it is likely that Lee's meta-analysis might have been underpowered to detect significant differences in performance (Borenstein et al., 2009). Impairment in working memory and verbal learning and memory have been reported in recurrent, MDD patients (Rock et al., 2014; Wagner et al., 2015), with a similar extent of impairment to that observed in the present meta-analysis.

Table 5
Inpatient Status Subgroup Analysis of Variance

Variable	<i>k</i>	<i>n</i>	<i>N</i>	<i>g</i>	95% CI		<i>Qw</i>	<i>Qb</i>	<i>p</i>
					<i>LL</i>	<i>UL</i>			
Processing speed									
Number-coding									
Outpatient	2	4	76	-.18	-.46	.10	.60		
Inpatient	3	4	112	.91	.38	1.44	11.28	12.52	.0004
TMT-A									
Outpatient	4	6	126	.31	-.06	.69	12.79		
Inpatient	3	3	76	.49	-.06	1.04	6.02	.27	.61
Composite									
Outpatient	5	7	147	.42	-.03	.87	24.62		
Inpatient	4	5	133	.70	.23	1.18	16.2	.73	.39
Sustained visual attention									
Composite									
Outpatient	4	5	118	.34	-.04	.71	7.82		
Inpatient	2	2	31	.66	.23	1.09	.29	1.24	.27
Visual learning									
Composite									
Outpatient	3	3	67	.66	-.04	1.36	9.16		
Inpatient	2	2	31	.63	.20	1.06	.00	.00	.95
Delayed visual memory									
Composite									
Outpatient	5	7	147	.39	-.01	.78	19.84		
Inpatient	2	2	31	.41	-.02	.83	.11	.01	.94
Verbal learning									
Word-list									
Outpatient	3	5	97	-.14	-.40	.12	3.29		
Inpatient	2	2	44	.33	-.56	1.22	6.36	.99	.32
Composite									
Outpatient	6	8	164	.16	-.20	.52	22.70		
Inpatient	3	3	54	.51	-.19	1.21	9.10	.76	.38
Delayed verbal memory									
Word-list									
Outpatient	5	7	116	.29	.03	.54	8.96		
Inpatient	3	3	54	.53	-.08	1.14	6.9	.51	.47
Composite									
Outpatient	8	10	183	.36	.14	.59	15.64		
Inpatient	3	3	54	.52	-.08	1.12	6.66	.22	.64
Verbal fluency									
Letter fluency									
Outpatient	4	4	90	.46	.17	.75	1.10		
Inpatient	2	2	31	.51	.09	.94	.83	.03	.85
Semantic fluency									
Outpatient	3	3	71	.85	.50	1.19	1.12		
Inpatient	2	2	31	.70	.27	1.13	.81	.28	.60
Composite									
Outpatient	4	4	116	.63	.34	.92	.79		
Inpatient	2	2	31	.63	.21	1.06	.54	.00	.99
Shifting									
Categories									
Outpatient	5	7	147	.40	.19	.62	.95		
Inpatient	4	6	138	.33	-.05	.71	13.9	.11	.74
Errors									
Outpatient	5	7	145	.44	.12	.75	12.77		
Inpatient	4	6	136	.41	-.02	.85	16.73	.01	.93
Time									

(table continues)

Table 5 (continued)

Variable	<i>k</i>	<i>n</i>	<i>N</i>	<i>g</i>	95% CI		<i>Qw</i>	<i>Qb</i>	<i>p</i>
					<i>LL</i>	<i>UL</i>			
Intelligence									
IQ composite									
Outpatient	2	2	50	.67	-.06	1.39	2.86		
Inpatient	3	3	76	.55	.25	.85	1.96	.09	.77
Composite									
Outpatient	8	10	240	.40	.19	.62	14.46		
Inpatient	6	8	204	.37	.09	.65	15.16	.04	.85
Autobiographical memory									
Outpatient	8	12	343	.12	-.03	.27	6.93		
Inpatient	1	2	57	.72	-.30	1.75	7.45	1.30	.25

Note. CI = confidence interval; *g* = Hedges' *g* effect size; *k* = number of studies; *n* = number of patient samples; *N* = number of patients; *LL* = lower limit; *p* = significance level; *Qb* = between-group heterogeneity; *Qw* = within-group heterogeneity; TMT-A = Trail Making test-A; *UL* = upper limit.

The present meta-analysis did not, however, replicate the association between medication and cognitive performance. Lee et al. (2012) found antidepressants to be associated with poorer verbal learning and memory, but improved shifting in FED patients. Nevertheless, their findings must be interpreted with caution as regression analysis was conducted on fewer than the recommended 10 samples (shifting, *n* = 7; Borenstein et al., 2009), and they used a more liberal alpha level of .10 to determine significance. In line with our findings, Hasselbalch, Knorr, and Kessing (2011) noted that the association between medication and cognitive function is not clearly established. This owes to the fact that it is difficult to parse the direct effects of medication from other clinical, patient characteristics such as depression severity or the number of past episodes. Therefore, independent of past episodes, it is possible that the extent of impairment is not significantly associated with medication in FED patients.

Likewise, our findings showed that inpatient status was not associated with a significantly impaired performance in most cognitive domains relative to healthy controls. This is inconsistent with the results of Porter et al. (2007), who noted larger cognitive impairment in recurrent, MDD inpatients relative to outpatients. However, the authors acknowledged that the length and number of past episodes likely explains why MDD patients are hospitalized and therefore, some extent of the impairment among inpatients. Notwithstanding, Lee et al. (2012) observed greater impairments in FED inpatients relative to outpatients. Yet, their sample were on average older ($M = 39.36$ years) than the sample in the current review ($M = 27.40$ years). Therefore, it is likely that differences in the extent of impairment observed in FED inpatients in each meta-analysis could be attributed to age differences between the patient samples. Taken together, a broad pattern of cognitive impairment is observed from the FED but consideration must be paid to patient characteristics and how this influences the extent of impairment experienced by patients.

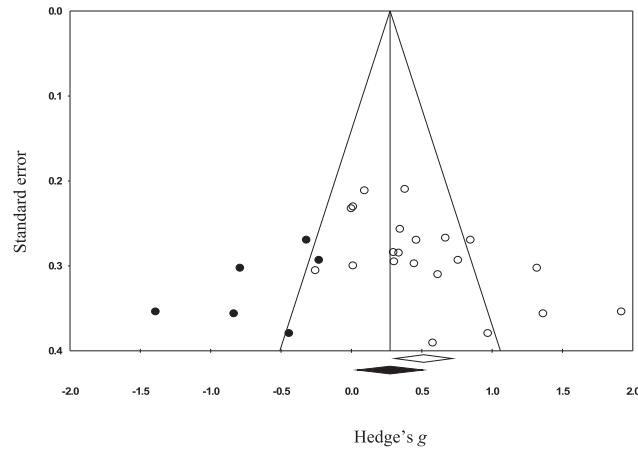


Figure 2. Funnel plot for standardized mean difference (Hedge's *g*) in performance by first-episode depression patients and controls on the shifting domain versus standard error. Vertical line indicates the weighted mean effect size. Clear circles represent actual data points from meta-analyzed studies; black circles represent imputed points of missing studies from the trim and fill analysis. Clear diamond represents unadjusted, weighted mean effect size (*g* = 0.51); black diamond represents the adjusted, weighted mean effect size (*g* = 0.27).

Persistence of Impairment at the FED: State, Scar, or Trait Markers?

Importantly, the persistence of impairment at the FED must be determined, considering that this has been identified as a vulnerability for recurrence, as well as a key determinant of functional recovery (Bortolato et al., 2016). In the present meta-analysis, processing speed and memory showed a normalization of function with remission, consistent with previous reviews (Douglas & Porter, 2009; Lee et al., 2012). Additionally, we demonstrated that learning, autobiographical memory, shifting, and IQ were restored to normal levels of function with remission. Impairment in these domains therefore likely represents state markers.

Moreover, normalization in performance observed in shifting suggests that executive function is somewhat sensitive to the depressive state at the FED. Nevertheless, a caveat of tests measuring executive function is that they are overly reliant on time measures and processing speed (Lezak et al., 2012). As discussed, processing speed normalizes with remission, so it could equally be argued that improvement in executive function is explained by improved processing speed (Nebes et al., 2000). However, FED patients showed a persistent impairment in the Stroop color naming and word reading processing speed condition (*g* = 0.11, *p* =

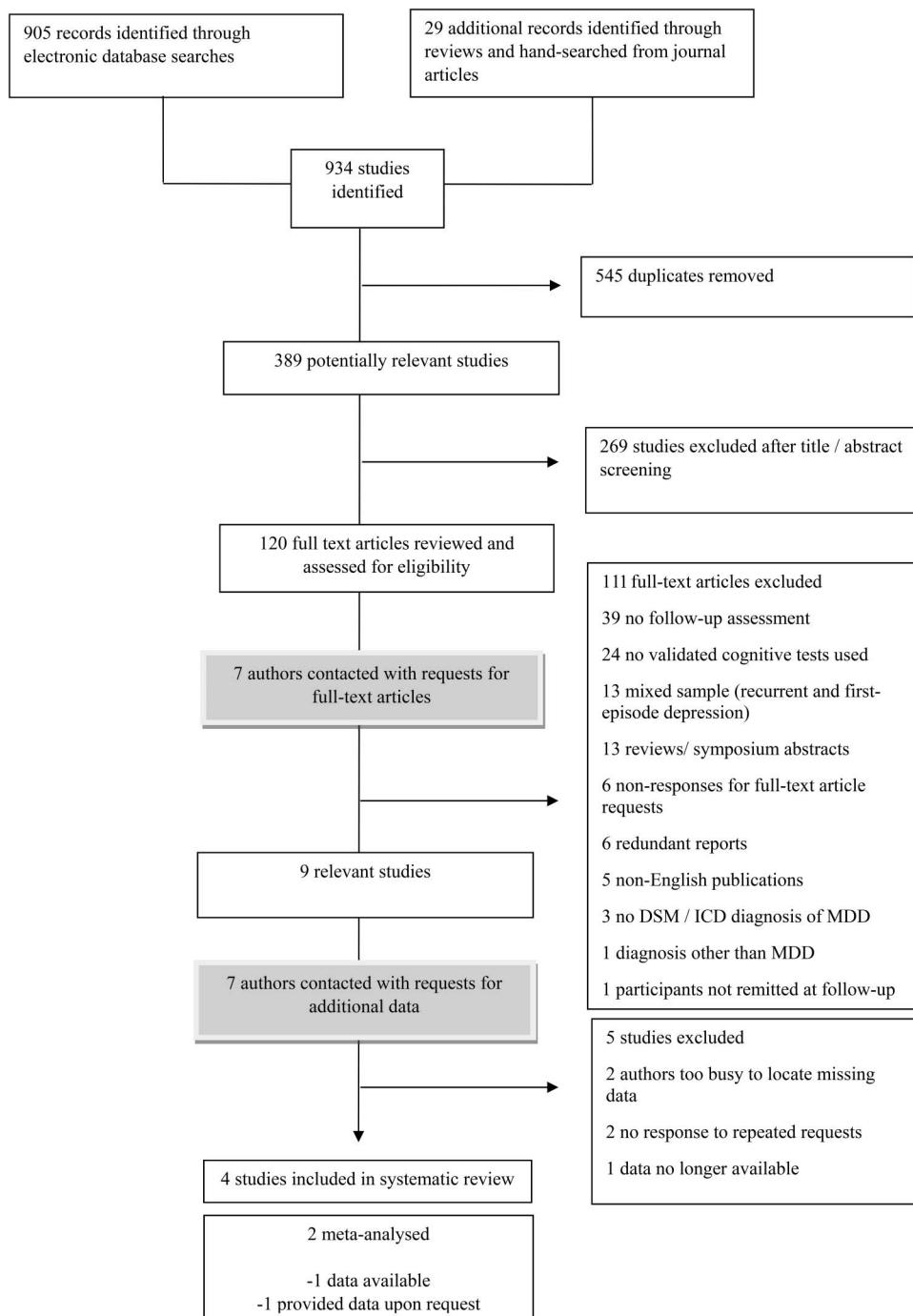


Figure 3. Flowchart for selection of studies relating to persistence of cognitive impairment following remission of FED (Systematic Review and Meta-analysis II). ICD = International Classification of Diseases; DSM = Diagnostic and Statistical Manual; MDD = major depressive disorder.

.82). Thus, processing speed alone could not account for the improvement in shifting. However, larger improvements in the processing speed condition of the Trail Making Test-A ($g = 0.68$) were observed relative to small improvements in the timed, shifting condition of the Trail Making Test-B ($g = 0.45$), suggesting that speed was associated with subsequent shifting improvement. It

is possible to argue, given these results, that the “less effortful” shifting between overlearned sequences (alphabet; counting for TMT-B) is improved following the processing speed normalization observed in remission, whereas the “more effortful” shifting between reading and inhibiting of reading (Stroop Switching) does not benefit from this normalization and stays impaired. How-

Table 6
Weighted Mean Effect Size Meta-Analysis II

Variable	<i>k</i>	<i>n</i>	<i>N</i>	<i>g</i>	95% CI		<i>p</i>	Homogeneity	
					<i>LL</i>	<i>UL</i>		<i>Q</i>	<i>I</i> ²
Processing speed									
TMT-A	2	2	19	.68	.31	1.05	<.001	.79	<.001
Stroop color naming and word reading	2	2	19	.11	-.81	1.02	.82	6.88*	85.46
Inhibition									
Stroop inhibition	2	2	19	.33	-.38	1.05	.36	4.62*	78.34
Shifting									
Stroop switching	2	2	19	.29	-.12	.70	.17	1.59*	37.13
TMT-B	2	2	19	.45	.12	.79	.008	1.01	1.08
Verbal fluency									
Letter fluency	2	2	19	.06	-.26	.38	.70	.92	<.001
Semantic fluency	2	2	19	.03	-.60	.67	.92	3.78*	73.56

Note. CI = confidence interval; *g* = Hedges' *g* effect size; *k* = number of studies; *n* = number of patient samples; *N* = number of patients; *LL* = lower limit; *p* = significance level; *Q* = heterogeneity statistic; TMT-A = Trail Making Test-A; *UL* = upper limit.

* *p* < .10.

ever, this interpretation remains speculative, given the small number of studies available for the Systematic Review and Meta-analysis II.

Nevertheless, previous reviews have tended to identify executive dysfunction, specifically inhibition, as stable and persistent, and therefore a likely trait marker for the onset of MDD (Bora et al., 2013; Snyder, 2013). Yet, as the majority of research has been conducted on recurrent patients, and not determined whether impairment predated the FED, the possibility of scarring effects cannot be ruled out (Hasselbalch et al., 2011). Considering our findings of improvement in shifting upon remission, it is possible that persistence of executive function is a result of recurrent episodes which contribute additional impairment, overall leading to maintenance of the impairment. This assumes the scar hypothesis (Kessing, 1998). However, it remains to be determined whether the FED is sufficient to ensure persistence. Considering small improvements in inhibition were shown in FED patients at remission (*g* = 0.33) relative to moderate impairment during the current state compared with healthy controls (*g* = 0.76), it can be speculated that impaired inhibition remained residually as a scar of the FED. Yet, as it was not possible to compare inhibition in remitted FED patients to healthy controls, the probability of complete normalization of function at the FED cannot be ruled out. Verbal fluency was the only executive function that persisted at a stable level of impairment, consistent with trait-qualities. Again, however, it is inconclusive whether persistence in verbal fluency represents a trait marker, or possibly a scar, unless the impairment was observed to predate the FED.

For the most part, the majority of cognitive domains in the FED appear to have state-like qualities, normalizing with remission. Persistence of deficits in verbal fluency, and likely residual persistence of deficits in inhibition, requires additional research to determine the exact nature as either a trait, or scarring consequence of the FED.

Limitations

This meta-analysis, however, is not without limitations. First, possible bias for any meta-analysis is that a comprehensive search of published material was not completed. Funnel plots revealed

that studies with small patient samples, that reported nonsignificant differences in shifting in FED patients compared with controls, were likely to not be published. As it was not possible to produce funnel plots for all cognitive domains, it cannot be confirmed whether publication bias accounted for some degree of impairment in FED patients, if there is a tendency to not publish studies which show little or no impairment (Borenstein et al., 2009).

Second, considering the significant heterogeneity of 21 cognitive variables included in the two parts of the meta-analysis (see Tables 3 and 6), it is apparent that the studies varied largely in the characteristics of the patients assessed, or the methods used. However, insufficient study numbers meant that possible moderators (e.g., length of depressive episode) could not be assessed to determine how they influenced the extent of cognitive impairment. Moreover, previous reviews have suggested that depression severity is associated with cognitive impairment in MDD (McDermott & Ebmeier, 2009). However, the variance in depression severity scales used in the studies meant that some data could not be translated into a HRSD-17 score to be included in the analysis. Otherwise, this may have allowed for more power to detect a significant effect.

Third, it would be important to determine whether different cognitive profiles are associated with subtypes of depression. Seven psychotic samples were included in the analysis, yet an insufficient number of studies meant that subgroup analysis could not be conducted. Study-level results, however, showed a trend of more severe impairment in executive function (Ilonen et al., 2000; Taiminen et al., 2000), memory and visuospatial attention (Hill, Keshavan, Thase, & Sweeney, 2004) in psychotic, FED patients compared with nonpsychotic, FED patients.

Future Directions and Conclusion

Our findings have shown that cognitive function is impaired at the FED in a broad range of cognitive domains. However, there is little evidence in FED patients for several cognitive domains known to be affected during recurrent episodes, for example, planning (Snyder, 2013). Future studies should look to include an

extensive testing battery to determine the full breadth and pattern of cognitive ability from the FED.

Moreover, the association between medication and cognitive function deserves further research consideration. Rock et al. (2014) demonstrated small to moderate impairment in unmedicated, recurrent MDD patients relative to healthy controls in attention, memory, and executive function. Yet, as only 33.33% of the samples included in this meta-analysis were unmedicated, research on unmedicated patient samples would be necessary to determine the true pattern of impairment at the FED.

Above all, research on cognitive impairment in MDD requires additional, longitudinal assessment of FED patients. This is necessary to better understand the relationship between cognitive impairment and the course of MDD from the FED. The present review showed that only 4 studies followed FED into remission while collecting both acute episode and postepisode cognitive data. Thus the persistence of FED-associated deficits could be assessed only for processing speed and some components of executive function. Specifically, longitudinal assessment would help to establish if persistence, as observed in recurrent patients in domains such as attention and inhibition (Bora et al., 2013), develops as a scar of recurrent, depressive episodes.

The implications of our findings for clinical practice, however, highlight the importance of treating cognitive impairment in FED patients. It is suggested that emphasis must be placed on a “cognitive remission” to achieve a full, functional recovery from MDD (Bortolato et al., 2016). The authors outlined that this involves treating the cognitive impairment, alongside mood symptoms, to negate the likelihood of persistence, even residually, when mood has been restored. As our analysis has evidenced, verbal fluency, and likely inhibition, show already persistent deficits following the FED. Therefore, cognitive interventions that may help to maintain cognitive function, and/or negate the possibility of persistence should be implemented into clinical practice right from onset of the FED. Computerized cognitive remediation, which uses cognitive exercises to activate neural networks within the brain that relate to specific cognitive abilities, has shown much promise in restoring cognitive function (Porter, Bowie, Jordan, & Malhi, 2013). Although research on this intervention is limited, a recent meta-analysis showed moderate to large improvements in attention and working memory, with small to large improvements transferable to global everyday functioning in MDD patients (Motter et al., 2016).

In conclusion, our systematic review and meta-analysis demonstrated that, even from the FED, there are small to large impairments in a range of cognitive abilities. For the most part, cognitive impairment showed state-like qualities, normalizing with remission. However, some persistence was already observed from the FED, with additional persistence in executive function possibly emerging as a scar of subsequent, depressive episodes. Longitudinal assessment of FED patients is required to further explore the relationship between cognitive deficits persistence and the course of MDD. Yet, as the persistence of impairment is of clinical importance for functional recovery, this meta-analysis highlights the need for interventions to treat cognitive impairment, alongside depressed mood symptoms, to promote functional recovery right from the FED.

References

- *Indicates references included in the systematic review and meta-analysis (see supplemental online data).
- *As, M., Dazzan, P., Fisher, H. L., Morgan, C., Morgan, K., Reichenberg, A., . . . Pariante, C. M. (2011). Childhood trauma and cognitive function in first-episode affective and non-affective psychosis. *Schizophrenia Research*, 129, 12–19. <http://dx.doi.org/10.1016/j.schres.2011.03.017>
 - Airaksinen, E., Wahlin, A., Forsell, Y., & Larsson, M. (2007). Low episodic memory performance as a premorbid marker of depression: Evidence from a 3-year follow-up. *Acta Psychiatrica Scandinavica*, 115, 458–465. <http://dx.doi.org/10.1111/j.1600-0447.2006.00932.x>
 - *Albus, M., Hubmann, W., Wahlheim, C., Sobizack, N., Franz, U., & Mohr, F. (1996). Contrasts in neuropsychological test profile between patients with first-episode schizophrenia and first-episode affective disorders. *Acta Psychiatrica Scandinavica*, 94, 87–93. <http://dx.doi.org/10.1111/j.1600-0447.1996.tb09830.x>
 - American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Arlington, VA: American Psychiatric Publishing.
 - American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.
 - Austin, M. P., Mitchell, P., & Goodwin, G. M. (2001). Cognitive deficits in depression: Possible implications for functional neuropathology. *The British Journal of Psychiatry*, 178, 200–206. <http://dx.doi.org/10.1192/bjp.178.3.200>
 - Biostat. (n.d.). Comprehensive meta-analysis (Version 2.2) [Computer software]. Englewood, NJ: Author.
 - Bora, E., Harrison, B. J., Yücel, M., & Pantelis, C. (2013). Cognitive impairment in euthymic major depressive disorder: A meta-analysis. *Psychological Medicine*, 43, 2017–2026. <http://dx.doi.org/10.1017/S0033291712002085>
 - Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2009). *Introduction to meta-analysis*. West Sussex, England: Wiley. <http://dx.doi.org/10.1002/9780470743386>
 - Bortolato, B., Miskowiak, K. W., Köhler, C. A., Maes, M., Fernandes, B. S., Berk, M., & Carvalho, A. F. (2016). Cognitive remission: A novel objective for the treatment of major depression? *BMC Medicine*, 14, 9.
 - *Chantiluke, K., Halari, R., Simic, M., Pariante, C. M., Papadopoulos, A., Giampietro, V., & Rubia, K. (2012). Fronto-striato-cerebellar dysregulation in adolescents with depression during motivated attention. *Biological Psychiatry*, 71, 59–67. <http://dx.doi.org/10.1016/j.biopsych.2011.09.005>
 - *Chen, J., Yang, L. Q., Zhang, Z. J., Ma, W. T., Wu, X. Q., Zhang, X. R., . . . Jia, T. (2013). The association between the disruption of motor imagery and the number of depressive episodes of major depression. *Journal of Affective Disorders*, 150, 337–343. <http://dx.doi.org/10.1016/j.jad.2013.04.015>
 - *Chen, J., Zhang, Y., Wei, D., Wu, X., Fu, Q., Xu, F., . . . Zhang, Z. (2015). Neurophysiological handover from MMN to P3a in first-episode and recurrent major depression. *Journal of Affective Disorders*, 174, 173–179. <http://dx.doi.org/10.1016/j.jad.2014.11.049>
 - Cohen, J. D. (1988). *Statistical power analysis for the behavioural sciences*. Hillsdale, NJ: Erlbaum.
 - Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., . . . Starr, J. M. (2009). Age-associated cognitive decline. *British Medical Bulletin*, 92, 135–152. <http://dx.doi.org/10.1093/bmb/ldp033>
 - *Desseilles, M., Balteau, E., Sterpenich, V., Dang-Vu, T. T., Darsaud, A., Vandewalle, G., . . . Schwartz, S. (2009). Abnormal neural filtering of irrelevant visual information in depression. *The Journal of Neuroscience*, 29, 1395–1403. <http://dx.doi.org/10.1523/JNEUROSCI.3341-08.2009>

- Douglas, K. M., & Porter, R. J. (2009). Longitudinal assessment of neuropsychological function in major depression. *Australian and New Zealand Journal of Psychiatry*, 43, 1105–1117. <http://dx.doi.org/10.3109/0048670903279887>
- Dubovsky, S. L., & Dubovsky, A. N. (2002). *Concise guide to mood disorders*. Washington, DC: American Psychiatric Association.
- Ekman, M., Granström, O., Omérov, S., Jacob, J., & Landén, M. (2013). The societal cost of depression: Evidence from 10,000 Swedish patients in psychiatric care. *Journal of Affective Disorders*, 150, 790–797. <http://dx.doi.org/10.1016/j.jad.2013.03.003>
- Evans, V. C., Chan, S. S., Iverson, G. L., Bond, D. J., Yatham, L. N., & Lam, R. W. (2013). Systematic review of neurocognition and occupational functioning in major depressive disorder. *Neuropsychiatry*, 3, 97–105. <http://dx.doi.org/10.2217/npy.13.3>
- *Fossati, P., Harvey, P. O., Le Bastard, G., Ergis, A. M., Jouvent, R., & Allilaire, J. F. (2004). Verbal memory performance of patients with a first depressive episode and patients with unipolar and bipolar recurrent depression. *Journal of Psychiatric Research*, 38, 137–144. <http://dx.doi.org/10.1016/j.jpsychires.2003.08.002>
- Gorwood, P., Corruble, E., Falissard, B., & Goodwin, G. M. (2008). Toxic effects of depression on brain function: Impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients. *The American Journal of Psychiatry*, 165, 731–739. <http://dx.doi.org/10.1176/appi.ajp.2008.07040574>
- Hammar, A., & Ardal, G. (2009). Cognitive functioning in major depression—A summary. *Frontiers in Human Neuroscience*, 3, 26.
- *Hammar, Å., Kildal, A. B., & Schmid, M. (2012). Information processing in patients with first episode major depression. *Scandinavian Journal of Psychology*, 53, 445–449. <http://dx.doi.org/10.1111/sjop.12012>
- *Hansson, P. B., Murison, R., Lund, A., & Hammar, Å. (2015). Cognitive functioning and cortisol profiles in first episode major depression. *Scandinavian Journal of Psychology*, 56, 379–383. <http://dx.doi.org/10.1111/sjop.12230>
- Hasselbalch, B. J., Knorr, U., & Kessing, L. V. (2011). Cognitive impairment in the remitted state of unipolar depressive disorder: A systematic review. *Journal of Affective Disorders*, 134, 20–31. <http://dx.doi.org/10.1016/j.jad.2010.11.011>
- Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis*. Orlando, FL: Academic Press.
- Heo, M., Murphy, C. F., & Meyers, B. S. (2007). Relationship between the Hamilton Depression Rating Scale and the Montgomery-Asberg Depression Rating Scale in depressed elderly: A meta-analysis. *The American Journal of Geriatric Psychiatry*, 15, 899–905. <http://dx.doi.org/10.1097/JGP.0b013e318098614e>
- Higgins, J. P. T., & Green, S. (Eds.). (2008). *Cochrane handbook for systematic reviews of interventions*. West Sussex, England: Wiley. <http://dx.doi.org/10.1002/9780470712184>
- *Hill, S. K., Keshavan, M. S., Thase, M. E., & Sweeney, J. A. (2004). Neuropsychological dysfunction in antipsychotic-naïve first-episode unipolar psychotic depression. *The American Journal of Psychiatry*, 161, 996–1003. <http://dx.doi.org/10.1176/appi.ajp.161.6.996>
- *Hill, S. K., Reilly, J. L., Harris, M. S. H., Rosen, C., Marvin, R. W., Deleon, O., & Sweeney, J. A. (2009). A comparison of neuropsychological dysfunction in first-episode psychosis patients with unipolar depression, bipolar disorder, and schizophrenia. *Schizophrenia Research*, 113, 167–175. <http://dx.doi.org/10.1016/j.schres.2009.04.020>
- *Ilonen, T., Leinonen, K. M., Wallenius, E., Karlsson, H., Taiminen, T., Salokangas, R. K., . . . Tuimala, P. (2000). Impaired Wisconsin Card Sorting Test performance in first-episode severe depression. *Nordic Journal of Psychiatry*, 54, 275–280. <http://dx.doi.org/10.1080/080394800448156>
- *Inagaki, M., Matsuoka, Y., Sugahara, Y., Nakano, T., Akechi, T., Fujimori, M., . . . Uchitomi, Y. (2004). Hippocampal volume and first major depressive episode after cancer diagnosis in breast cancer survivors. *The American Journal of Psychiatry*, 161, 2263–2270. <http://dx.doi.org/10.1176/appi.ajp.161.12.2263>
- *Karabekiroğlu, A., Topçuoğlu, V., Gimzal Gönençür, A., & Karabekiroğlu, K. (2010). Executive function differences between first episode and recurrent major depression patients. *Turkish Journal of Psychiatry*, 21, 280–288.
- *Kaur, M., Battisti, R. A., Ward, P. B., Ahmed, A., Hickie, I. B., & Hermens, D. F. (2011). MMN/P3a deficits in first episode psychosis: Comparing schizophrenia-spectrum and affective-spectrum subgroups. *Schizophrenia Research*, 130, 203–209. <http://dx.doi.org/10.1016/j.schres.2011.03.025>
- *Kaymak, S. U., Demir, B., Sentürk, S., Tatar, I., Aldur, M. M., & Uluğ, B. (2010). Hippocampus, glucocorticoids and neurocognitive functions in patients with first-episode major depressive disorders. *European Archives of Psychiatry and Clinical Neuroscience*, 260, 217–223. <http://dx.doi.org/10.1007/s00406-009-0045-x>
- Kessing, L. V. (1998). Cognitive impairment in the euthymic phase of affective disorder. *Psychological Medicine*, 28, 1027–1038. <http://dx.doi.org/10.1017/S0033291798006862>
- Kessler, R. C., & Walters, E. E. (1998). Epidemiology of *DSM-III-R* major depression and minor depression among adolescents and young adults in the National Comorbidity Survey. *Depression and Anxiety*, 7, 3–14. [http://dx.doi.org/10.1002/\(SICI\)1520-6394\(1998\)7:1<3::AID-DA2>3.0.CO;2-F](http://dx.doi.org/10.1002/(SICI)1520-6394(1998)7:1<3::AID-DA2>3.0.CO;2-F)
- Kovacs, M., Feinberg, T. L., Crouse-Novak, M., Paulauskas, S. L., Pollock, M., & Finkelstein, R. (1984). Depressive disorders in childhood. II. A longitudinal study of the risk for a subsequent major depression. *Archives of General Psychiatry*, 41, 643–649. <http://dx.doi.org/10.1001/archpsyc.1984.01790180013001>
- *Kyte, Z. A., Goodyer, I. M., & Sahakian, B. J. (2005). Selected executive skills in adolescents with recent first episode major depression. *Journal of Child Psychology and Psychiatry*, 46, 995–1005. <http://dx.doi.org/10.1111/j.1469-7610.2004.00400.x>
- *Ladegaard, N., Larsen, E. R., Videbech, P., & Lysaker, P. H. (2014). Higher-order social cognition in first-episode major depression. *Psychiatry Research*, 216, 37–43. <http://dx.doi.org/10.1016/j.psychres.2013.12.010>
- Lee, R. S., Hermens, D. F., Porter, M. A., & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *Journal of Affective Disorders*, 140, 113–124. <http://dx.doi.org/10.1016/j.jad.2011.10.023>
- Lewinsohn, P. M., Hops, H., Roberts, R. E., Seeley, J. R., & Andrews, J. A. (1993). Adolescent psychopathology: I. Prevalence and incidence of depression and other *DSM-III-R* disorders in high school students. *Journal of Abnormal Psychology*, 102, 133–144. <http://dx.doi.org/10.1037/0021-843X.102.1.133>
- Lewinsohn, P. M., Steinmetz, J. L., Larson, D. W., & Franklin, J. (1981). Depression-related cognitions: Antecedent or consequence? *Journal of Abnormal Psychology*, 90, 213–219. <http://dx.doi.org/10.1037/0021-843X.90.3.213>
- Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological assessment* (5th ed.). New York, NY: Oxford University Press.
- Lipsey, M. W., & Wilson, D. B. (2001). *Practical meta-analysis*. Thousand Oaks, CA: Sage.
- *Maalouf, F. T., Brent, D., Clark, L., Tavitian, L., McHugh, R. M., Sahakian, B. J., & Phillips, M. L. (2011). Neurocognitive impairment in adolescent major depressive disorder: State vs. trait illness markers. *Journal of Affective Disorders*, 133, 625–632. <http://dx.doi.org/10.1016/j.jad.2011.04.041>
- *MacQueen, G. M., Campbell, S., McEwen, B. S., Macdonald, K., Amano, S., Joffe, R. T., . . . Young, L. T. (2003). Course of illness, hippocampal function, and hippocampal volume in major depression. *Proceedings of*

- the National Academy of Sciences of the United States of America*, 100, 1387–1392. <http://dx.doi.org/10.1073/pnas.0337481100>
- *Maeshima, H., Baba, H., Nakano, Y., Satomura, E., Namekawa, Y., Takebayashi, N., . . . Arai, H. (2012). Residual memory dysfunction in recurrent major depressive disorder—A longitudinal study from Juntendo University Mood Disorder Project. *Journal of Affective Disorders*, 143, 84–88. <http://dx.doi.org/10.1016/j.jad.2012.05.033>
- McDermott, L. M., & Ebmeier, K. P. (2009). A meta-analysis of depression severity and cognitive function. *Journal of Affective Disorders*, 119, 1–8. <http://dx.doi.org/10.1016/j.jad.2009.04.022>
- Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G., & the PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Annals of Internal Medicine*, 151, 264–269, W64. <http://dx.doi.org/10.7326/0003-4819-151-4-200908180-00135>
- Motter, J. N., Pimontel, M. A., Rindskopf, D., Devanand, D. P., Doraiswamy, P. M., & Sneid, J. R. (2016). Computerized cognitive training and functional recovery in major depressive disorder: A meta-analysis. *Journal of Affective Disorders*, 189, 184–191. <http://dx.doi.org/10.1016/j.jad.2015.09.022>
- Mueller, T. I., Leon, A. C., Keller, M. B., Solomon, D. A., Endicott, J., Coryell, W., . . . Maser, J. D. (1999). Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *The American Journal of Psychiatry*, 156, 1000–1006.
- *Nandrino, J. L., Pezard, L., Posté, A., Réveillére, C., & Beaune, D. (2002). Autobiographical memory in major depression: A comparison between first-episode and recurrent patients. *Psychopathology*, 35, 335–340. <http://dx.doi.org/10.1159/000068591>
- Nebes, R. D., Butters, M. A., Mulsant, B. H., Pollock, B. G., Zmuda, M. D., Houck, P. R., & Reynolds, C. F., III. (2000). Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. *Psychological Medicine*, 30, 679–691. <http://dx.doi.org/10.1017/S0033291799001968>
- Papazacharias, A., & Nardini, M. (2012). The relationship between depression and cognitive deficits. *Psychiatria Danubina*, 24, S179–S182. Retrieved from http://www.hdbp.org/psychiatria_danubina/pdf/dnb_vol24_sup1/dnb_vol24_sup1_179.pdf
- *Park, R. J., Goodyer, I. M., & Teasdale, J. D. (2002). Categoric overgeneral autobiographical memory in adolescents with major depressive disorder. *Psychological Medicine*, 32, 267–276. <http://dx.doi.org/10.1017/S0033291701005189>
- *Park, R. J., Goodyer, I. M., & Teasdale, J. D. (2004). Effects of induced rumination and distraction on mood and overgeneral autobiographical memory in adolescent Major Depressive Disorder and controls. *Journal of Child Psychology and Psychiatry*, 45, 996–1006. <http://dx.doi.org/10.1111/j.1469-7610.2004.t01-1-00291.x>
- Plassman, B. L., Welsh, K. A., Helms, M., Brandt, J., Page, W. F., & Breitner, J. C. (1995). Intelligence and education as predictors of cognitive state in late life: A 50-year follow-up. *Neurology*, 45, 1446–1450. <http://dx.doi.org/10.1212/WNL.45.8.1446>
- Porter, R. J., Bourke, C., & Gallagher, P. (2007). Neuropsychological impairment in major depression: Its nature, origin and clinical significance. *Australian and New Zealand Journal of Psychiatry*, 41, 115–128. <http://dx.doi.org/10.1080/00048670601109881>
- Porter, R. J., Bowie, C. R., Jordan, J., & Malhi, G. S. (2013). Cognitive remediation as a treatment for major depression: A rationale, review of evidence and recommendations for future research. *Australian and New Zealand Journal of Psychiatry*, 47, 1165–1175. <http://dx.doi.org/10.1177/0004867413502090>
- Postma, A., Jager, G., Kessels, R. P., Koppeleschaar, H. P., & van Honk, J. (2004). Sex differences for selective forms of spatial memory. *Brain and Cognition*, 54, 24–34. [http://dx.doi.org/10.1016/S0278-2626\(03\)00238-0](http://dx.doi.org/10.1016/S0278-2626(03)00238-0)
- Reis, H. T., & Judd, C. M. (2014). *Handbook of research methods in social and personality psychology* (2nd ed.). New York, NY: Cambridge University Press.
- Peppermund, S., Ising, M., Lucae, S., & Zihl, J. (2009). Cognitive impairment in unipolar depression is persistent and non-specific: Further evidence for the final common pathway disorder hypothesis. *Psychological Medicine*, 39, 603–614. <http://dx.doi.org/10.1017/S003329170800411X>
- *Roca, M., López-Navarro, E., Monzón, S., Vives, M., García-Toro, M., García-Campayo, J., . . . Gili, M. (2015). Cognitive impairment in remitted and non-remitted depressive patients: A follow-up comparison between first and recurrent episodes. *European Neuropsychopharmacology*, 25, 1991–1998. <http://dx.doi.org/10.1016/j.euroneuro.2015.07.020>
- Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: A systematic review and meta-analysis. *Psychological Medicine*, 44, 2029–2040. <http://dx.doi.org/10.1017/S0033291713002535>
- Rohde, P., Lewinsohn, P. M., & Seeley, J. R. (1990). Are people changed by the experience of having an episode of depression? A further test of the scar hypothesis. *Journal of Abnormal Psychology*, 99, 264–271. <http://dx.doi.org/10.1037/0021-843X.99.3.264>
- Rosenthal, R., & DiMatteo, M. R. (2001). Meta-analysis: Recent developments in quantitative methods for literature reviews. *Annual Review of Psychology*, 52, 59–82. <http://dx.doi.org/10.1146/annurev.psych.52.1.59>
- *Schmid, M., & Hammar, Å. (2013a). Cognitive function in first episode major depressive disorder: Poor inhibition and semantic fluency performance. *Cognitive Neuropsychiatry*, 18, 515–530. <http://dx.doi.org/10.1080/13546805.2012.754748>
- *Schmid, M., & Hammar, A. (2013b). A follow-up study of first episode major depressive disorder. Impairment in inhibition and semantic fluency—potential predictors for relapse? *Frontiers in Psychology*, 4, 633.
- Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: A meta-analysis and review. *Psychological Bulletin*, 139, 81–132. <http://dx.doi.org/10.1037/a0028727>
- *Taiminen, T., Jääskeläinen, S., Ilonen, T., Meyer, H., Karlsson, H., Lauerma, H., . . . Salokangas, R. K. (2000). Habituation of the blink reflex in first-episode schizophrenia, psychotic depression and non-psychotic depression. *Schizophrenia Research*, 44, 69–79. [http://dx.doi.org/10.1016/S0920-9964\(99\)00140-1](http://dx.doi.org/10.1016/S0920-9964(99)00140-1)
- The Cochrane Collaboration. (2014). Review manager (Version 5.3) [Computer software]. Copenhagen, Denmark: The Nordic Cochrane Centre.
- Uher, R., Payne, J. L., Pavlova, B., & Perlis, R. H. (2014). Major depressive disorder in DSM-5: Implications for clinical practice and research of changes from DSM-IV. *Depression and Anxiety*, 31, 459–471. <http://dx.doi.org/10.1002/da.22217>
- Vanderhasselt, M. A., & De Raedt, R. (2009). Impairments in cognitive control persist during remission from depression and are related to the number of past episodes: An event related potentials study. *Biological Psychology*, 81, 169–176. <http://dx.doi.org/10.1016/j.biopsych.2009.03.009>
- *van der Meere, J., Borger, N. A., Pirila, S., & Sallee, F. (2011). Interference control in children with first episode major depression: A brief report. *Child Neuropsychology: A Journal on Normal and Abnormal Development in Childhood and Adolescence*, 17, 96–104. <http://dx.doi.org/10.1080/09297049.2010.533165>
- *van Eijndhoven, P., van Wingen, G., Katzenbauer, M., Groen, W., Tepest, R., Fernández, G., . . . Tendolkar, I. (2013). Paralimbic cortical thickness in first-episode depression: Evidence for trait-related differences in mood regulation. *The American Journal of Psychiatry*, 170, 1477–1486. <http://dx.doi.org/10.1176/appi.ajp.2013.12121504>
- *van Wingen, G. A., van Eijndhoven, P., Tendolkar, I., Buitelaar, J., Verkes, R. J., & Fernández, G. (2011). Neural basis of emotion recog-

- nition deficits in first-episode major depression. *Psychological Medicine*, 41, 1397–1405. <http://dx.doi.org/10.1017/S0033291710002084>
- Vinberg, M., Miskowiak, K. W., & Kessing, L. V. (2013). Impairment of executive function and attention predicts onset of affective disorder in healthy high-risk twins. *Journal of Clinical Psychiatry*, 74, e747–e753. <http://dx.doi.org/10.4088/JCP.12m08258>
- Vittengl, J. R., Clark, L. A., Kraft, D., & Jarrett, R. B. (2005). Multiple measures, methods, and moments: A factor-analytic investigation of change in depressive symptoms during acute-phase cognitive therapy for depression. *Psychological Medicine*, 35, 693–704. <http://dx.doi.org/10.1017/S0033291704004143>
- Wagner, S., Müller, C., Helmreich, I., Huss, M., & Tadić, A. (2015). A meta-analysis of cognitive functions in children and adolescents with major depressive disorder. *European Child & Adolescent Psychiatry*, 24, 5–19. <http://dx.doi.org/10.1007/s00787-014-0559-2>
- Wekking, E. M., Bockting, C. L., Koeter, M. W., & Schene, A. H. (2012). Cognitive functioning in euthymic recurrently depressed patients: Relationship with future relapses and prior course of disease. *Journal of Affective Disorders*, 141, 300–307. <http://dx.doi.org/10.1016/j.jad.2012.03.034>
- Wilson, D. B. (2001). Meta-analysis macros for SAS, SPSS and Strata [Effect size calculation macros]. Retrieved from <http://mason.gmu.edu/~dwilsonb/ma.html>
- Withall, A., Harris, L. M., & Cumming, S. R. (2009). The relationship between cognitive function and clinical and functional outcomes in major depressive disorder. *Psychological Medicine*, 39, 393–402. <http://dx.doi.org/10.1017/S0033291708003620>
- *Yang, X. H., Huang, J., Zhu, C. Y., Wang, Y. F., Cheung, E. F., Chan, R. C., & Xie, G. R. (2014). Motivational deficits in effort-based decision making in individuals with subsyndromal depression, first-episode and remitted depression patients. *Psychiatry Research*, 220, 874–882. <http://dx.doi.org/10.1016/j.psychres.2014.08.056>
- *Zhu, X., Wang, X., Xiao, J., Liao, J., Zhong, M., Wang, W., & Yao, S. (2012). Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naïve major depression patients. *Biological Psychiatry*, 71, 611–617. <http://dx.doi.org/10.1016/j.biopsych.2011.10.035>
- Zimmerman, M., McGlinchey, J. B., Posternak, M. A., Friedman, M., Attiullah, N., & Boerescu, D. (2006). How should remission from depression be defined? The depressed patient's perspective. *The American Journal of Psychiatry*, 163, 148–150. <http://dx.doi.org/10.1176/appi.ajp.163.1.148>

Received June 28, 2016

Revision received August 23, 2016

Accepted August 25, 2016 ■