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A Meta-Analysis of Executive Dysfunction and Antidepressant Treatment Response in Late-Life Depression

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Abstract

Objective—Depressed older adults with executive dysfunction (ED) may respond poorly to antidepressant treatment. ED is a multifaceted construct and different studies have measured different aspects of ED, making it unclear which aspects predict poor response. Meta-analytic methods were used to determine whether ED predicts poor antidepressant treatment response in late-life depression and to determine which domains of executive functioning are responsible for this relationship.

Methods—A Medline search was conducted to identify regimented treatment trials contrasting executive functioning between elderly responders and nonresponders; only regimented treatment trials for depressed outpatients aged 50 and older were included. Following the most recent PRISMA guidelines, 25 measures of executive functioning were extracted from eight studies. Six domains were identified: cognitive flexibility, planning and organization, response inhibition, selective attention, verbal fluency, and the Dementia Rating Scale Initiation/Perseveration composite score (DRS I/P). Hedge's g was calculated for each measure of executive functioning. A three-level Bayesian hierarchical linear model (HLM) was used to estimate effect sizes for each domain of executive functioning.

Results—The effect of planning and organization was significantly different from zero (Bayesian HLM estimate of domain effect size: 0.91; 95% CI: 0.32–1.58), whereas cognitive flexibility, response inhibition, selective attention, verbal fluency, and the DRS I/P composite score were not.

Conclusion—The domain of planning and organization is meaningfully associated with poor antidepressant treatment response in late-life depression. These findings suggest that therapies that focus on planning and organization may provide effective augmentation strategies for antidepressant nonresponders with late-life depression.

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Keywords

Executive dysfunction; antidepressant treatment; late-life depression; meta-analysis

INTRODUCTION

Depression is a common problem among older adults. Although antidepressant medication is the primary treatment for geriatric depression, response rates range from 25% to 60%. A number of studies have shown that deficits on measures of executive functioning predict poor response to antidepressant treatment in late-life depression.[–] The construct of executive functioning is broad and is composed of numerous domains, including but not limited to response inhibition, cognitive flexibility, working memory, organization, and planning.[–] Because studies that have examined the impact of executive dysfunction (ED) on antidepressant response have relied on different measures, it is unclear which aspects of ED predict poor response to antidepressant treatment. Identifying those features associated with poor response will enable us to focus on identifying the neurobiologic mechanisms by which these specific deficits take place and developing novel interventions that target these mechanisms.

A meta-analysis examined the relationship between antidepressant response and neuropsychological test performance among depressed adults. This study showed that of seven measures of executive function, only the Dementia Rating Scale Initiation/ Perseveration composite score (DRS I/P) predicted poor antidepressant treatment response and concluded that the findings did not provide strong support for the depression–ED model of late-life depression. The findings of this study, however, may be limited with respect to the impact of ED on antidepressant response in geriatric depression. First, the mean age of approximately half the studies in the meta-analysis was less than 50. Second, a number of geriatric depression studies were not included in the meta-analysis.[,] Third, this study did not classify measures as belonging to specific domains of executive functioning. This is potentially important because it may give us insight into the neurobiologic substrates underlying the effects of ED on antidepressant response. Fourth, a number of studies included in this analysis were not regimented treatment trials. Finally, the authors chose to interpret only those effect sizes greater than 0.5 (moderate) as significant. This is potentially problematic because (as already noted) geriatric depression is common and antidepressant nonresponse frequent. Even a small statistical effect can have great clinical value. It makes sense to therefore investigate this problem more closely.

The purpose of this meta-analysis is to determine which components of ED predict poor antidepressant treatment response. We hope to improve on previous research by focusing exclusively on standardized trials of antidepressant medication among depressed older adults, examining the predictive utility of specific executive function domains and not restricting the significance of effect sizes to 0.5 when a small effect could be potentially important.

METHODS

We followed the most recent Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting and reporting the results of this systematic review.

Identification of Studies

A Medline search was conducted to identify regimented antidepressant treatment trials contrasting executive function between elderly responders and nonresponders. The index terms “executive dysfunction,” “executive function,” “executive control,” “working memory,” “verbal fluency,” “response inhibition,” “set switching,” “planning,” “prefrontal dysfunction,” “neuropsychological tests,” “cognitive function,” and “cognitive functioning” were combined using the “or” operator. In addition, the index terms “Depression,” “Depressive Disorder,” and “Depressive Disorder, Major” were combined using the “or” operator. This returned 2,498 results, which were limited to 1) English language articles, 2) age group 50 and older, and 3) publication types, including clinical trials, controlled clinical trials, comparative study, meta-analysis, multicenter study, randomized controlled trials, or review.

The first author (M.A.P.) conducted a review of these articles, sequentially progressing from title to abstract. A study was ruled out if the title did not contain at least one word from each of two categories. The first category contained the key words executive dysfunction, executive function, executive control, working memory, verbal fluency, response inhibition, set switching, planning, prefrontal dysfunction, neuropsychological test, cognitive function, cognitive functioning, neurocognitive, attention network, neuropsychological functioning, psychomotor, neuropsychological, Stroop, trails making, frontal dysfunction, digit span, clock drawing test, exit 25, N-back test, Wisconsin Card Sorting Test, Tower of London, Tower of Hanoi, Word Generation, Color/Word Test, Sorting, DRS-I/P, DRS, Dementia Rating Scale and Initiation/Perseveration. The second category contained the key words depression, major depressive disorder, depressive disorder, late-life depression, late-onset depression, vascular depression, and depressive symptoms. A study was kept if the abstract described an antidepressant treatment trial in which cognitive ability was a variable. This resulted in 40 studies, of which 37 were empirical studies and 3 were reviews or meta-analyses. The three meta-analyses and reviews were searched for additional references, but this search did not yield additional studies.

The remaining 37 articles were reviewed to determine whether they met inclusion criteria: The articles report outcome data from an antidepressant treatment trial for major depressive disorder in outpatient subjects older than 50 years. Ten studies were excluded because the study sample contained subjects younger than age 50.[–] In addition, three of these publications included subjects with bipolar disorder.[,,] One study was excluded because it included subjects with vascular dementia and Alzheimer dementia. Four studies were excluded because they did not measure treatment response as a dependent variable.[–] This resulted in 22 publications.

Two judges (M.A.P. and J.R.S.) reviewed the remaining 22 full paper texts to determine whether the manuscripts reported an acute treatment trial (≤12 weeks) and presented pretreatment scores on a measure of executive functioning separately for responders and nonresponders (or provided sufficient information for this to be derived from the data). Any differences between judges were resolved by discussion. Five studies were excluded because they were not an acute treatment trial,[–] three studies because they included psychotherapy as a treatment modality,[–] two studies because they did not include a specific test of ED,[,] two studies because they did not include sufficient statistical information,[,] two studies because of duplicate reporting,[,] and one study because it included an inpatient sample. This resulted in seven studies that met our inclusion criteria.

To search for unpublished data, we examined the references of our final 40 articles, including reviews and meta-analyses. We also conducted an Internet search. One article that was not identified in our search was included. This article was supplied by one of our authors (J.R.S.) and was not identified in our original search because it had not yet been indexed in Medline. This ultimately resulted in the inclusion of eight articles in our analysis [,,,,–]. Figure 1 provides a schematic representation of our study selection procedures.

Data Extraction

Publication information (author, year of publication), demographic characteristics of the included subjects (sample size, age, clinical characteristics), details of treatment condition (medication name, treatment format), measures of executive functioning used, and outcome data (baseline ED scores, response and remission rates) were extracted from each included trial by one author (M.A.P). Table 1 summarizes the methodologic features of these eight studies. Demographic information of participants in each study is shown in Table 2. Tests of executive functioning were categorized by domain by two authors based on a widely used reference for neuropsychological tests.

Data Analysis

A total of 25 individual measures extracted from eight different studies was included in this analysis as indicators of the six executive function domains (Table 3). Effect sizes (Hedge's g) and standard errors were calculated for each domain using Comprehensive Meta-Analysis version 2. We used the open variant of the **B**ayesian inference **u**sing **G**ibbs **S**ampling software package (OpenBUGS)[,] to estimate a three-level meta-analytic model[,] in which observations are nested within executive function domains, which in turn are nested within study. Table 4 shows the key elements of the structure of this model:

1. The design is an 8 (studies) × 6 (domains) factorial. One dimension (studies) is random, whereas the other (domain) is fixed. Thus, the model is a combination of a fixed and a random effects model and is therefore sometimes called a mixed effects model in meta-analysis.
2. Because some studies report multiple neuropsychological measures. These data are not independent; this dependence has been taken into account in the analysis.

3. Many cells in the design are empty, because not all studies measured all domains of executive function in the analysis. Therefore, care must be used in estimating the effects.

4. A large number of missing cells make it difficult to accurately estimate any potential interactions between studies and domains. The only cells contributing to such an estimate are cells that occur in a pattern of four cells, such that two studies measure the same two domains. We decided not to try to estimate this because of the spareness of the data.

Issues 1 through 3 can be dealt with by using a hierarchical linear model, with effect sizes of different domains nested within studies to take into account the dependence of the outcome data. As such, the statistical model for estimating domain effect sizes represented each observed effect size as a sum of three types of components: 1) an effect due to the specific study (where studies were considered random effects), 2) an effect due to the specific measure used, and 3) measurement error. Because some domains were measured in more studies than other domains and studies had different sample sizes, the accuracy with which we can estimate each effect (i.e., the standard errors) will be different.

The model can be written as

$$g[i] \sim \text{normal}(m[i],\ s[i])$$
$$m[i] = b0[\text{study}[i]] + b1\,D[i] + b2\,P[i] + b3\,R[i] + b4\,V[i] + b5\,S[i] + b6\,C[i]$$

where i indexes the 25 observed effect sizes, g[ ] is the observed Hedge's g, s[ ] is the standard error of g[ ], m[ ] is the true effect size, study[i] is the study in which the effect g[i] is found, and D, P, R, V, S, and C are dummy variables indicating whether the effect measures a particular domain. The parameter values in the vector b0 were assumed to have a normal distribution with mean mu0 and variance var0. All parameters were given vague prior distributions.

We used OpenBUGS, a Bayesian program, to estimate the parameters of this model, both because it can handle the complexities of the design and because Bayesian interpretation is conceptually (though not computationally) simple. A classical (frequentist) interpretation of the results is also possible for those who do not prefer Bayesian results; with vague prior distributions for the parameters, these results are nearly identical. Our interpretation will be made in classical terms, because we presume readers will be more familiar with these interpretations. The OpenBUGS code, data, and results for this procedure are reproduced in Appendix 1.

RESULTS

Eight studies met inclusion and exclusion criteria. All studies included in the current analysis measured at least one of six domains of executive function (response inhibition, verbal fluency, cognitive flexibility, selective attention, planning and organization, and the DRS I/P composite score). The Bayesian hierarchical linear model estimates of effect size for each domain is presented in Table 5, along with the standard error, 95% confidence

interval, and z score for each estimate. Planning and organization was the only executive function domain that emerged with an estimated effect size significantly different from zero. The size of the estimated effect was large, and its confidence interval ranged from small to large (Figure 2). The estimated effect size for verbal fluency, cognitive flexibility, selective attention, response inhibition, and the DRS I/P composite score were not significantly different from zero (Figure 2).

DISCUSSION

The purpose of this meta-analysis was to determine which domains of executive function predict poor antidepressant treatment response. This created a special problem, because the data are nested within studies, studies and executive function domains are crossed, and not all studies measure all domains. To our knowledge, this report represents the first effort to take these features into account in an analysis of ED and poor antidepressant treatment response in late life.

Eight studies meeting inclusion and exclusion criteria were retrieved from the literature. From these eight studies, six domains of executive functioning were extracted (response inhibition, verbal fluency, cognitive flexibility, planning and organization, selective attention, and the DRS I/P composite score). Of these six executive function domains, only planning and organization was significantly associated with antidepressant treatment nonresponse. The estimated effect size was large, whereas its confidence interval ranged from small to large. The width of the confidence interval reflects that the estimate is based on only one study. The effect sizes for response inhibition, verbal fluency, cognitive flexibility, selective attention, and the DRS I/P composite score were small and not significantly different from zero. The current analysis does not provide evidence for an association between these domains and antidepressant treatment response in late life.

It is unclear why patients with poor planning and organization abilities may be less likely to respond to antidepressant medication than patients without planning and organization difficulties. One possibility is that older depressed adults with poor planning and organization abilities may be unable to benefit from the component of medication response that is attributable to patient expectancy. In recent years several studies have documented the influence of expectancy effects on medication response in antidepressant clinical trials, such that higher baseline expectancy has been shown to predict greater depressive symptom improvement.[–] Expectancies involve the organization of cognitions and planning of behaviors related to the various possible outcomes of a future event. Patients with poor planning and organization abilities may therefore be unable to develop and maintain accurate expectancies about the possible outcomes of an antidepressant treatment, thereby lowering the treatment's effectiveness.

The improvement of planning and organization skills in depressed older adults with ED may alleviate depressive symptoms and enhance response to antidepressant medication. Indeed, recent studies have demonstrated the effectiveness of problem-solving therapy in reducing depressive symptoms in older adults with ED.[,] Problem-solving therapy is a behavioral intervention that trains patients to identify problems in daily life and provides a method for

developing, selecting, and implementing solutions for these problems. The improvement of problem-solving skills may alleviate planning and organization deficits, thereby mitigating the behavioral disabilities that may underlie depression in older adults.

Contrary to our hypotheses, response inhibition and verbal fluency were not significantly associated with antidepressant treatment response. Our prediction that response inhibition would be associated with treatment response was based on findings that performance on the Stroop Color and Word Test has been found to predict nonresponse to antidepressant medication.[9,10] Consistent with these results, other tests with a response inhibition component, such as the Attention Network Test, the Wisconsin Card Sorting Test (WCST),[7] and the Go/No-Go Task, have been predictive of treatment response. Several of these studies, however, could not be included in our analysis because they did not meet inclusion criteria. Furthermore, although some measures such as the WCST contain a response inhibition component, they are primarily considered to assess other domains of executive function and were therefore not included in the response inhibition domain in our analysis.

We also predicted that verbal fluency would be associated with antidepressant treatment response. Studies have shown that the Controlled Oral Word Association Test, a measure of verbal fluency, is associated with remission.[7] It has also been demonstrated that only the verbal fluency task of the DRS I/P subtest predicts remission. However, one study found that the use of semantic strategy explained the difference in performance between responders and nonresponders on this subtest. Although this requires replication, these findings appear to be consistent with the current results that planning and organization, and not verbal fluency, are predictive of treatment nonresponse, possibly suggesting a top-down processing effect in which impairment in planning and organization interferes with the generation of words in verbal fluency tasks.

The results of this review highlight the challenges associated with the use and interpretation of executive function measures in geriatric psychiatry. Cognitive abilities need to be well defined to allow reliable and valid neuropsychological measurement. However, executive function remains an ambiguous construct that lacks a clear definition.[7] Measures of executive functioning may require the integration of several cognitive processes. For example, the WCST taps executive processes involving cognitive flexibility, problem solving, and response maintenance. The Trail Making Test part B enlists executive subcomponents such as processing speed and accuracy. As a result, impairment on measures such as the WCST and the Trail Making Test part B may be caused by deficits in several different areas of executive function. Performance on one measure within a domain may not be predictive of performance on another, making it difficult to categorize these measures into domains of executive function.

Limitations

The limitations of this study are balanced by its methodologic strengths. The available data created a methodologic problem because not all studies measured the same domains of executive functioning. As a result, there would inevitably be missing data in the crossing of studies by executive function domains. This required a three-level meta-analytic model to compute estimates for what the average effect size would be in each study, as if the study

had measured all six domains, and estimates of what the average effect size would be for each domain, as if each study had measured that domain.

By including only regimented treatment trials, we were able to decrease the effects of confounding variables. This, however, also restricted the number of available studies. There were differences between studies in treatment duration, type of treatment, definition of treatment response, and type of measure used to quantify depression severity. Because of the number of studies included in this analysis, it was not possible to examine the effect of these variables.

CONCLUSION

Of the six domains of executive functioning (response inhibition, verbal fluency, cognitive flexibility, planning and organization, selective attention, and the DRS I/P composite score) assessed in this review, only planning and organization was significantly associated with treatment nonresponse. This suggests that patients with poor planning and organization abilities may be less likely to respond to antidepressant medication than patients without planning and organization difficulties. The improvement of planning and organization deficits in older depressed adults may mitigate the behavioral disabilities that underlie depression in these individuals. Therapies that focus on increasing planning and organization skills (e.g., problem-solving therapy or an individualized cognitive training protocol) may therefore provide effective augmentation strategies for treatment non-responders with late-life depression. More studies are needed to explain the relationship between planning and organization deficits and poor anti-depressant response in older adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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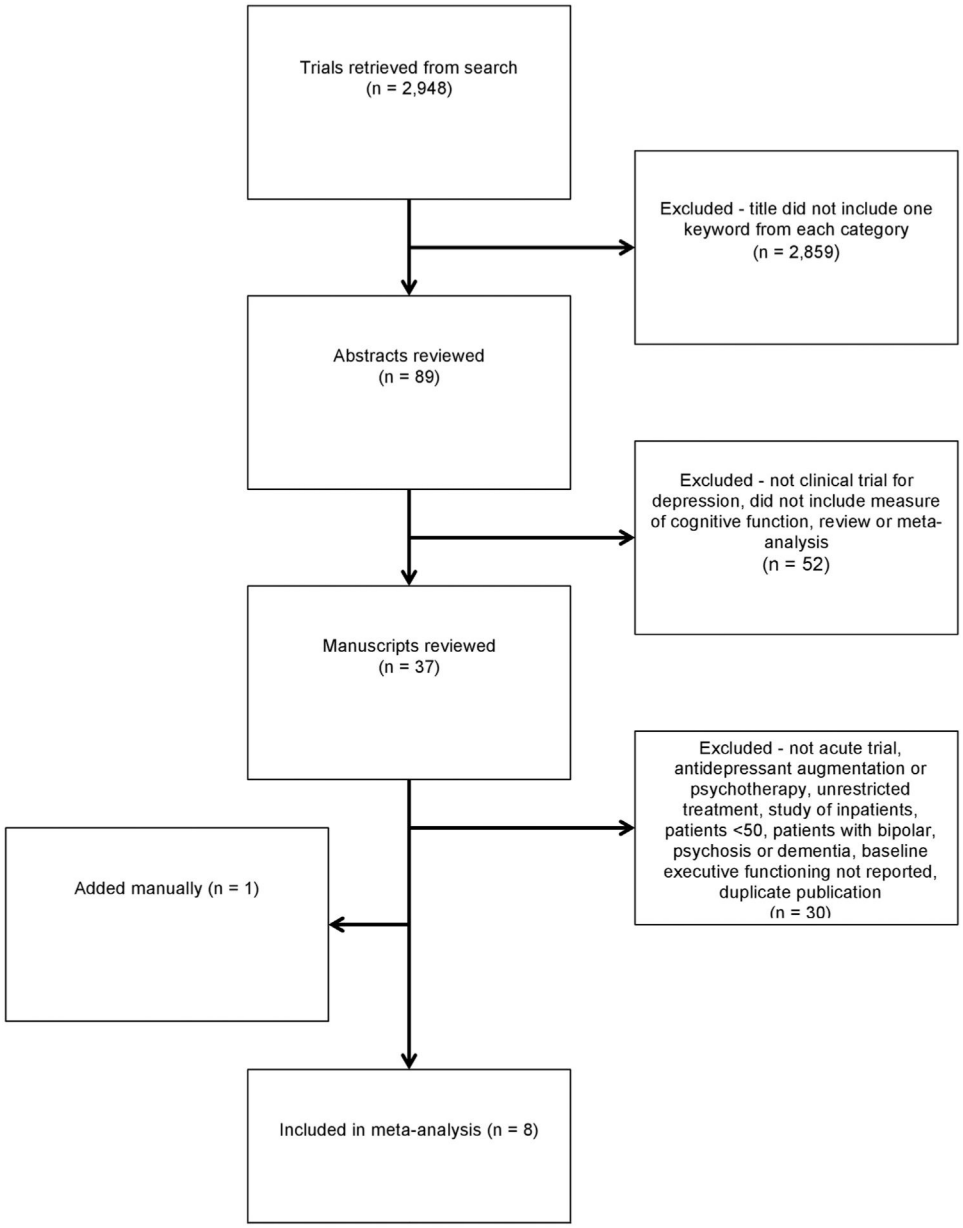

FIGURE 1.
Flow chart of study selection.

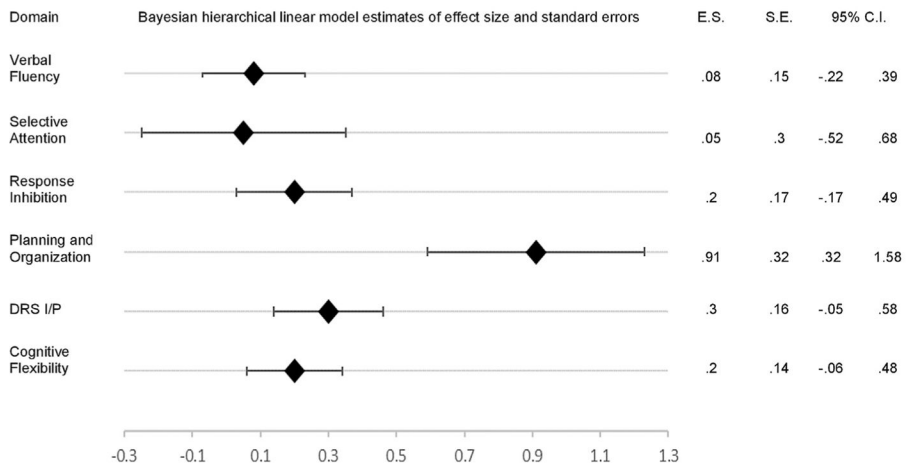

FIGURE 2.

Forest plot of effect sizes (E.S.), standard errors (S.E.), and confidence intervals (95% C.I.).

TABLE 1

Study Characteristics

	Trial Duration (wk)	Treatment Format	Treatment Type	Baseline Depression Scale	Definition of Remission
Alexopoulos et al.	8	Standardized	Citalopram	HAM-D	50% change in HDRS from baseline
Alexopoulos et al.	8	Standardized	Escitalopram	HAM-D	HDRS 10 or lower
Devanand et al.	12	Standardized	Sertraline	HAM-D	50% change in HDRS from baseline
Kalayam & Alexopoulos	6	Standardized	Citalopram	HAM-D	HDRS 10 or lower
Morimoto et al.	12	Standardized	Escitalopram	HAM-D	HDRS 7 or lower
Potter et al.	12	Algorithm	SSRI, venlafaxine, bupropion, TCA, lithium	MADRS	MADRS 7 or lower
Sheline et al.	12	Standardized	Sertraline	MADRS	MADRS 7 or lower
Sneed et al.	8	Standardized	Citalopram	HAM-D	50% change in HDRS from baseline

Note: HDRS: Hamilton Depression Rating Scale; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; MADRS: Montgomery-Asberg Depression Rating Scale.

TABLE 2

Sample Characteristics

	Complete Sample					Nonresponders					Responders				
	N	**Gender (% male)**	**Age (SD)**	**Education (SD)**	**Depression Severity at Baseline (SD)**	**N**	**Gender (% male)**	**Age (SD)**	**Education (SD)**	**Depression Severity at Baseline (SD)**	**N**	**Gender (% male)**	**Age (SD)**	**Education (SD)**	**Depression Severity at Baseline (SD)**
Alexopoulos et al.	112			29.62 (3.30)	24.51 (4.72)	44		75.66 (6.15)	14.36 (3.10)	25.32 (5.08)	68		71.56 (6.25)	15.26 (3.49)	23.69 (4.35)
Alexopoulos et al.	12				20.6 (4.65)	6		68.8 (6.3)		22.0 (6.7)	6		71.2 (5.0)		19.2 (2.6)
Devanand et al.	26	36	72.0 (10.2)	12.0 (4.8)	15.4 (4.5)	9		82.3 (5.0)			17		66.8 (9.4)		
Kalayam & Alexopoulos	22			14 (2.7)	23.55 (6.2)	9		74.9 (8.1)	13.0 (2.8)	25.4 (5.5)	13		70.2 (7.4)	15.0 (2.6)	21.7 (6.9)
Morimoto et al.	70			15.9 (3.55)	22.1 (3.9)	35		70.4 (7.1)	16.1 (3.6)	22.4 (3.7)	35		70.1 (5.8)	15.7 (3.5)	21.8 (4.1)
Potter et al.	110	41	73.78 (0.74)	13.61 (0.85)	24.65 (0.62)	87	41.38	73.76 (0.80)	14.00 (0.38)	24.74 (0.67)	23	39.13	73.87 (1.90)	13.65 (0.94)	24.35 (1.55)
Sheline et al.	190	43.7	68.6 (7.3)	14.4 (3.1)	26.1 (4.4)	118	44.1	69.2 (7.7)	14.2 (2.9)	26.6 (4.5)	72	43.1	67.6 (6.7)	14.7 (3.4)	25.2 (4.1)
Sneed et al.	174	42	79.57 (4.37)	13.74 (3.31)	24.31 (4.21)	47					29				

Note: SD: standard deviation.

TABLE 3

Estimated Effect Sizes for Individual Measures (Hedge's g [Standard Error])

	Cognitive Flexibility	DRS I/P	Planning and Organization	Response Inhibition	Verbal Fluency	Selective Attention
Alexopoulos et al.						
DRS I/P total		0.50 (0.20)				
Stroop Color-Word				0.49 (0.20)		
Alexopoulos et al.						
Go/No-Go commission errors				−0.42 (0.54)		
WCST % perseverative errors	−0.23 (0.54)					
Kalayam & Alexopoulos						
DRS I/P total		1.06 (0.45)				
Stroop accuracy				0.33 (0.42)		
Stroop reaction time				0.64 (0.43)		
Morimoto et al.						
DRS I/P complex verbal clusters			0.79 (0.25)			
DRS I/P verbal perseverations	−0.15 (0.24)					
Potter et al.						
Animal Naming total correct					0.10 (0.23)	
Animal Naming perseverative errors	0.24 (0.23)					
COWAT total correct					−0.09 (0.23)	
COWAT perseverative errors	0.41 (0.24)					
Trails B	−0.22 (0.23)					
Sheline et al.						
COWAT					0.20 (0.16)	
Trails B	0.35 (0.16)					
Stroop Color-Word				0.14 (0.16)		
DRS I/P		0.24 (0.16)				
WCST categories completed	0.27 (0.16)					
Sneed, et al.						
Stroop Color-Word		0.27 (0.24)				
Devanand et al.						

	Cognitive Flexibility	DRS I/P	Planning and Organization	Response Inhibition	Verbal Fluency	Selective Attention
Category fluency					−0.37 (0.41)	
Animal Naming					0.05 (0.41)	
Digit Symbol						0.21 (0.41)
Letter Cancellation time						−0.4 (0.41)
Shape Cancellation time						0.12 (0.41)

Notes: COWAT: Controlled Oral Word Association Test.

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TABLE 4

Estimated Effect Sizes for Domains Within Studies (Hedge's g [Standard Error])

	Cognitive Flexibility	DRS I/P	Planning and Organization	Response Inhibition	Verbal Fluency	Selective Attention
Alexopoulos et al.		0.50 (0.20)		0.49 (0.20)		
Alexopoulos et al.	−0.23 (0.54)			−0.45 (0.59)		
Kalayam & Alexopoulos		1.06 (0.45)		0.33 (0.42) 0.64 (0.43)		
Morimoto et al.	−0.15 (0.24)		0.79 (0.25)			
Potter et al.	0.24 (0.23) 0.41 (0.24) −0.22 (0.23)				0.10 (0.24) −0.09 (0.23)	
Sheline et al.	0.35 (0.16) 0.27 (0.16)	0.24 (0.16)		0.14 (0.16)	0.20 (0.16)	
Sneed et al.		0.27 (0.24)				
Devanand et al.					−0.37 (0.41) 0.05 (0.41)	0.21 (0.41) −0.4 (0.41) 0.12 (0.41)

TABLE 5

Bayesian Hierarchical Linear Model Estimates of Domain Effect Sizes, Standard Errors, and Confidence Intervals

Domain	Studies	Measures	Effect Sizes	Standard Error	95% Confidence Interval	z
Cognitive flexibility	Alexopoulos et al., Morimoto et al., Potter et al., Sheline et al., Devanand et al.	WCST % perseverative errors, DRS I/P verbal perseverations, Animal Naming perseverative errors, COWAT perseverative errors, Trails B, WCST Categories completed	0.20	0.14	−0.06 to 0.48	1.46
DRS I/P	Alexopoulos et al., Kalayam & Alexopoulos, Sheline et al.	DRS I/P total	0.30	0.16	−0.05 to .58	1.87
Planning and organization	Morimoto et al.	DRS I/P Complex verbal clusters	0.91	0.32	.32–1.58	3.08[a]
Response inhibition	Alexopoulos et al., Alexopoulos et al., Kalayam & Alexopoulos, Sheline et al., Sneed et al.	Stroop Color-Word, Go/No-Go commission errors, Stroop accuracy, Stroop reaction time	0.20	0.17	−0.17 to 0.49	0.10
Selective attention	Devanand et al.	Digit Symbol, Letter Cancellation time, Shape Cancellation time	0.05	0.30	−0.52 to 0.68	0.16
Verbal fluency	Potter et al., Sheline et al., Devanand et al.	Animal Naming total correct, COWAT total correct, category fluency test, Animal Naming	0.08	0.15	−0.22 to 0.39	0.53

Notes: COWAT: Controlled Oral Word Association Test.

[a] $p < 0.05$.