The Efficacy of Cognitive Remediation in Depression: A Systematic Literature Review and Meta-Analysis

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Background

Major depressive disorder, is characterized by depressed mood, decreased interest or pleasure in daily activities, weight changes, sleep and psychomotor disturbances, fatigue, feelings of worthlessness, difficulties concentrating, and suicidal ideation (American Psychiatric Association, 2013). Depression represents a major public health concern, with global estimates indicating that 10.8% of individuals are affected by this condition at some point in their lives (Lim et al., 2018). Depression is the leading cause of disability worldwide (World Health Organization, 2017) and accounts for 40.5% of the global burden of disease caused by psychiatric disorders, in terms of years of disability, and years of life lost due to premature mortality (Whiteford et al., 2013). Hence, the development of successful treatment methods for depression is crucial.

Cognitive Deficits in Depression

Prior studies indicate that up to two-thirds of acutely depressed people are affected by cognitive deficits (Rock et al., 2014). These include difficulties in verbal, visuospatial, and working memory, as well as in attention and processing speed, executive functioning, and verbal fluency (Levin et al., 2007; Mattern et al., 2015; Snyder, 2013). Cognitive deficits negatively impact daily functioning and interfere with the ability to contribute actively to society by sustaining employment or schooling (Castaneda et al., 2008; Evans et al., 2013) and consequently aggravate the loss in productivity associated with depression (Murray & Lopez, 1996; Berto et al., 2000; Greenberg & Birnbaum, 2005). Despite the significance of cognitive deficits in depression, traditional psychiatric interventions have exclusively targeted mood and affective symptoms, leaving cognition untreated (Ahern & Semkovska, 2016). Several

studies further indicate that cognitive difficulties tend to persist following remission of affective disturbances (e.g., Bora et al. 2013; Gorwood et al., 2008; Hasselbach et al., 2011; Vanderhasselt & De Raedt, 2009). Therefore, cognitive deficits in depression are an unmet treatment need.

Cognitive Remediation

Cognitive remediation (CR) aims to improve cognitive functioning with drill and practice exercises often supported by strategy coaching (Medalia & Lim, 2004). CR can be delivered in different formats (individually and in groups; Revell et al., 2015), and for different durations (one week to several months; Kim et al., 2018). A substantial body of evidence shows that CR can improve cognitive and functional outcomes in individuals with schizophrenia (Bowie et al., 2012; Cella et al., 2017; Guimond et al., 2018; Mothersill & Donohoe, 2019; Penadés et al., 2013; Wykes et al., 2011), and a growing number of studies have explored its effect in other psychiatric populations, such as affective disorders, attention-deficit/hyperactivity disorder, substance use disorders, and autism spectrum disorder (Kim et al., 2018).

To date, no meta-analysis has investigated the effect of CR in adults with depression on both, global cognition and specific domains, with a focus on protocol characteristics that may moderate its effects. One meta-analysis has summarized aggregated cognitive outcomes across seven randomized and non-randomized studies in affective disorders at large, including participants with depression, bipolar, and schizoaffective disorders, thus precluding any conclusions specific to depression (Anaya et al., 2012). More recently, a second meta-analysis examined nine randomized controlled trials of CR in depression (Motter et al., 2016), focusing solely on computerized training and including a combination of CR with other treatments such as transcranial direct current stimulation (tDCS; Segrave et al., 2014). They

reported the effect of CR on specific cognitive domains, with a relatively small sample size, but did not address CR effects on global cognition. Results indicated that computer-based CR can improve attention and working memory with moderate-to-large effect sizes. Therefore, the effect of CR on global cognition in patients with depression remains unexplored in the context of a meta-analysis. Motter and colleagues (2016) also explored the moderating effect of participant characteristics (age, gender, and medication) on CR. Yet, the moderating effect of protocol characteristics like session format and duration, have not been systematically investigated in depression (Medalia, 2005; Porter et al., 2013). Furthermore, more recent CR studies have been conducted in this clinical population (i.e., Dong et al., 2017; Morimoto et al., 2020; Semkovska et al, 2015; Trapp et al., 2016). Therefore, a novel meta-analysis is warranted in order to 1) estimate the effect of CR on global cognition in depression, 2) identify optimal protocol characteristics, and 3) summarize evidence from the most recently published randomized-controlled trials.

The Present Study

In the present study, we conducted the largest systematic literature review and meta-analysis of published randomized controlled trials investigating the effect of CR on cognitive deficits in adults with depression.

First, we sought to evaluate the effect of CR on global cognition. Then we investigated its specific effect on six specific cognitive domains, namely verbal memory, visuospatial memory, working memory, attention/processing speed, executive functioning, and verbal fluency. Finally, we aimed to explore three potential moderators of the anticipated improvement in global cognition, namely session format (individual or group), duration, and participants' age.

Methods

Literature Search Procedure

Our systematic literature review and meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The literature search and study selection procedure are illustrated in the flowchart in Figure 1.

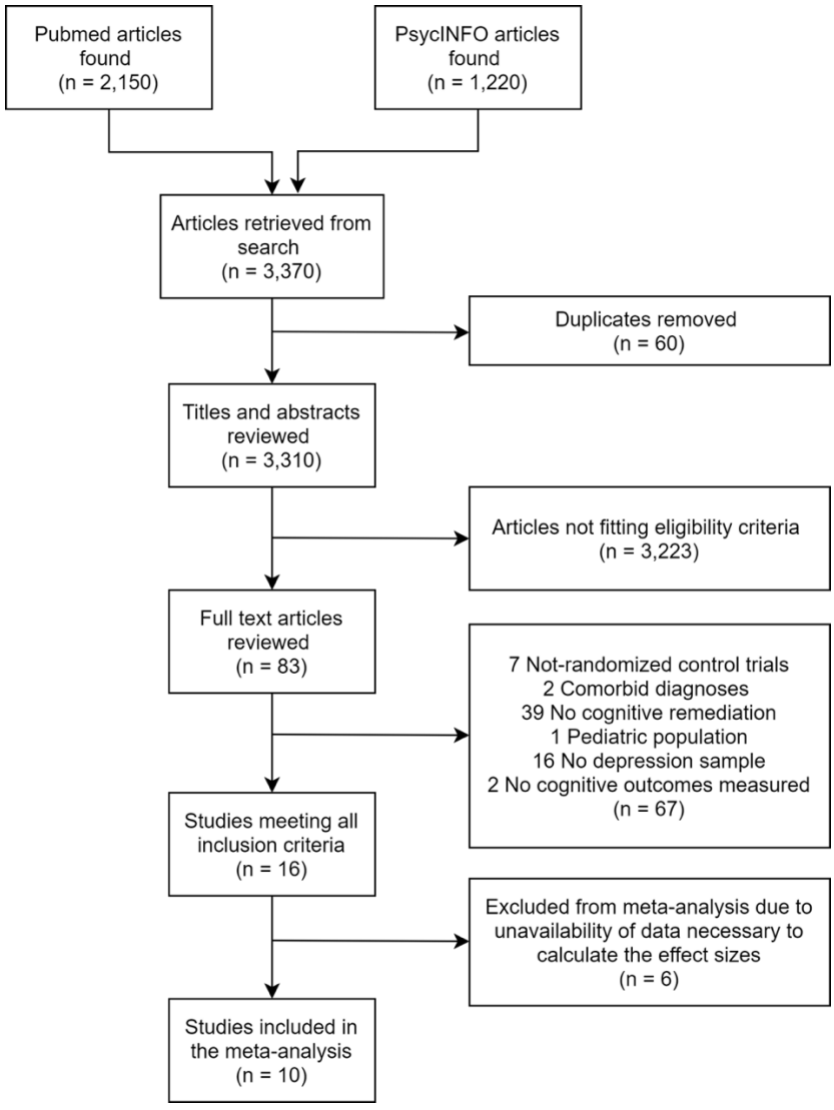

Figure 1. Flow chart illustrating the literature search and study selection procedure.

Eligibility Criteria

Using PubMed and PsycINFO, we selected randomized controlled trials published before September 3, 2020. We conducted a broad and systematic search of the literature using the terms “major depressive disorder” OR “depression” AND “cognitive remediation therapy” OR “cognitive rehabilitation” OR “cognitive training” with filters for randomized controlled trials.

We included studies involving participants 18 years old or older. Participants who received CR were acutely depressed and compared to a control group with the same symptomology. Depression was defined by a score above a validated cut-off on the self-report inventories Beck Depression Inventory II (Beck et al., 1996) or Center for Epidemiological Studies-Depression (CES-D; Ross et al., 1983) or by either the DSM, the Research Diagnostic Criteria (Spitzer et al., 1978), or the International Classification of Diseases (World Health Organization, 1992). Publications had to be written in English.

We also excluded studies that were not randomized controlled trials, that did not include a control group with depression, and/or did not measure cognitive outcomes (see Figure 1). To reduce sample heterogeneity, we further excluded studies involving participants with comorbid neurological illnesses, brain injuries, personality disorders, and substance use disorders.

Study Selection and Data Extraction

The initial search yielded 3,370 scientific articles (PubMed = 2,150 and PsycINFO = 1,220). Sixty duplicates were removed, thus resulting in 3,310 articles. Two authors (AT and MA) conducted a manual screening of all titles and abstracts to identify eligible studies. Disagreements during the selection process were solved with the input of a third author (SG). We excluded 3,223 articles after reading titles and

abstracts, resulting in 83 publications. The totality of these articles was examined, and 67 were removed in compliance with exclusion criteria (see Figure 1). Sixteen articles met the inclusion criteria. However, six of those articles did not report means and standard deviations for the cognitive outcomes. We thus contacted the first and corresponding authors to obtain the missing information. While some authors positively replied to our inquiry, six either refused, did not reply to our emails, or reported no longer having the data (see Appendix 5 in Supplementary Material). Hence, we retained ten eligible articles for the current meta-analysis (i.e., Alvarez et al., 2008; Bowie et al., 2013; Dong et al., 2017; Elgamal et al., 2007; Lohman et al., 2013; Morimoto et al., 2020; Naismith et al., 2011; Owens et al., 2013; Semkovska et al. 2015; Trapp et al., 2016).

Outcome Measures

Global cognition was computed by aggregating scores across all measures for all cognitive domains within each study. Cognitive domain outcomes were grouped into six categories: (1) verbal memory, (2) visuospatial memory, (3) working memory, (4) attention/processing speed, (5) executive functioning and (6) verbal fluency. Please refer to Appendix 2 in the Supplementary Material for a list of cognitive assessments and corresponding cognitive domain categories.

Meta-Analysis Procedure

We used the metaphor R package (Viechtbauer, 2010) to perform our meta-analysis (Morris, 2007). Analysis code used for the current meta-analysis is openly available (github.com/CRANIlab/MetaAnalysis_Depression_Cognitive_Remediation).

Using the means and standard deviations reported in the selected studies, we computed the standardized mean change from pre-test to post-test for both CR treatment and control groups to obtain a measure of effect size (Hedges' *g*; Hedges &

Olkin, 1985). If a decreased mean score from pre-test to post-test implied a positive change, we reverse coded the means and ensured that, in both groups, a positive effect size reflected an improvement in the cognitive outcome at hand.

Specifically, for the treatment group, we computed the standardized mean change, Hedges' g_T, as:

$$g_T = c(n_T - 1)\ \frac{\bar{x}_{post,T} - \bar{x}_{pre,T}}{SD_{pre,T}} \qquad (1)$$

where n_T represents the number of patients in the treatment group, $\bar{x}_{pre,T}$ and $\bar{x}_{post,T}$ are the pre- and post-test means for the treatment group respectively, and $SD_{pre,T}$ is the standard deviation of the pre-test results. The calculation also included a bias correction factor *c* (Becker, 1988) and a correlation factor, reflecting the correlation between pre-test and post-test measures. Since such correlations were not reported in the studies, we set the correlation factor conservatively at 0.5. We also conducted a stability analysis to examine how the random effects estimates varied when the correlation factor ranged from 0.2 to 0.9. Estimates remained relatively consistent and statistically significant, thus confirming the appropriateness of our conservative 0.5 correlation factor (see Appendix 3 in Supplementary Material).

For the control group, we computed the standardized mean change, Hedges' g_C, as:

$$g_C = c(n_C - 1)\ \frac{\bar{x}_{post,C} - \bar{x}_{pre,C}}{SD_{pre,C}} \qquad (2)$$

where all terms are defined as in Equation 1, except that the *C* subscripts referring to the control group.

Next, we computed the effect size difference by calculating the difference in Hedges' *g* for the treatment and the control groups:

$$g = g_T - g_C. \qquad (3)$$

The last calculated Hedges' *g* can be interpreted as the standardized difference between the change observed from pre-test to post-test in a cognitive outcome in the CR treatment group and the change observed in the control group.

Global cognition analysis

As mentioned above, the Hedges' *g* estimates were aggregated within studies for global cognition to address the dependency between observations (Borenstein et al., 2009), resulting in one aggregated Hedges' *g* per study. A meta-analysis was then conducted on these Hedges' *g* values to determine whether CR had significant effect on global cognition relative to the control conditions.

Sub-Group Analysis

We also conducted a sub-group analysis to assess the effect of CR on each cognitive domain (i.e., verbal memory, visuospatial memory, working memory, attention/processing speed, executive functioning, and verbal fluency). Since most studies used more than one outcome measure for each cognitive domain, Hedges' *g* estimates were aggregated by cognitive domain within each study (Borenstein et al., 2009). Please refer to Appendix 1 in the Supplementary Material for a list of cognitive assessments and corresponding cognitive domain categories.

Moderator Analysis

We used a mixed-effects model meta-regression to analyze the influence of three potential moderators on the effect of CR on global cognition compared to control condition. Moderators included one categorical moderator, namely session format, which was coded as whether CR was delivered individually or in groups, and two continuous moderators, namely treatment duration (in hours) and participants' age (in years).

Study Heterogeneity

Since studies were sampled from different populations, we also assessed study heterogeneity, using the Cochran's *Q* test and the I^2 index (Borenstein, 2019). The Cochran's *Q* tests the null hypothesis that the treatment effect is the same across studies, with significant values indicating substantial variation between studies. The I^2 is computed based on the result of Cochran's Q test and reflects the percentage of variation between studies that is due to heterogeneity rather than chance, with values between 40% and 60% being indicative of moderate heterogeneity (Higgins & Cochrane Collaboration, 2020).

Publication Bias

Lastly, we assessed the presence of publication bias by visual inspection of a funnel plot (see Appendix 4 in Supplementary Material).

Results

Our systematic literature review included ten randomized controlled trials with a total of 1,701 adults with depression: 859 individuals who received CR and 842 individuals in control groups. The selected studies examined the effect of CR on six cognitive domains, namely verbal memory (*n* = 8), visuospatial memory (*n* = 4), working memory (*n* = 6), attention/processing speed (*n* = 6), executive functioning (*n* = 6), and verbal fluency (*n* = 4). CR duration ranged from 7 to 30 hours (*M* = 14.95; *SD* = 6.99). Participants were 21 to 82 years old (*M* = 42.50; *SD* = 8.09) and mostly females (75%). Study characteristics are summarized in Table 1.

Table 1. *Characteristics of the ten studies included in the meta-analysis*

Study	Country	Tool to determine depression status (assessor)	Measured cognitive outcome	CR Group			Control Group		Participants					
									N		Age *M* (*SD*)		Gender (% female)	
				Format	Description	Duration (h)	Condition	Description	CR group	Control group	CR group	Control group	CR group	Control group
Alvarez et al., 2008	Mexico	DSM–IV (psychiatrist)	Attention/Processing Speed	Individual	Alcor	16	TAU	Stable dose of antidepressants	20	11	23.0 (3.3)	23.8 (2.7)	55	63.6
Bowie et al., 2013	Canada	DSM–IV (psychiatrist)	Verbal Memory, Working Memory, Attention/Processing Speed, Executive Functioning, Verbal Fluency	Group	Scientific Brain Training Pro (sbtpro.com)	15	Waitlist	N/A	17	16	49.2 (11.8)	42.2 (13.4)	75	65
Dong et al., 2017	U.S.A.	DSM–IV-TR (psychologist)	Verbal Memory	Group	CBT (Beck, 1979) with mnemonic strategies	12	TAU	CBT without mnemonic strategies	25	23	43.9 (9.9)	44.65 (12.2)	48	73.9
Elgamal et al., 2007	Canada	DSM–IV (psychiatrist)	Verbal Memory, Working Memory, Attention/Processing Speed, Executive Functioning, Verbal Fluency	Group	PSSCogReHab (Bracy, 1994)	20	TAU	Stable dose of antidepressants	12	12	50.3 (6.4)	47.4 (6.8)	58.3	58.3
Lohman et al., 2013	U.S.A.	CES-D (self-report)	Verbal Memory	Individual	Mnemonic strategies	10	Waitlist	N/A	703	698	73.5 (6.0)	74 (6.0)	76.4	73.6
Morimoto et al., 2020	U.S.A.	DSM-IV (psychiatrist)	Executive Functioning Working Memory Verbal Memory Verbal Fluency Visuospatial Memory	Individual	Brain HQ	30	Active	Psychoeducation	18	12	74.7 (7.6)	72.2 (9.9)	63.6	63.6
Naismith et al., 2011	Australia	DSM-IV-TR (psychiatrist)	Verbal Memory, Attention/Processing Speed, Executive Functioning, Visuospatial Memory	Individual	Neuropsychological Educational Approach to Remediation (NEAR; Medalia & Mambrino, 2010)	10	Active	Psychoeducation	22	19	64.8 (8.5)	64.8 (8.5)	41.5	41.5

Owens et al., 2013	U.K.	BDI-II (self-report)	Working Memory	Group	Adaptive Dual n-Back task (Jaeggi et al., 2003)	7	Active	Non-Adaptive Dual n-Back with no changes in difficulty level	11	11	22.7 (5.3)	22.6 (3.4)	54.5	72.7
Semkovska et al., 2015	Ireland	DSM–IV (not reported)	Verbal Memory, Working Memory, Attention/Processing Speed, Executive Functioning, Verbal Fluency, Visuospatial Memory	Group	RehaCom (Semkovska et al. 2015)	20	Active	Online games	8	7	42.4 (14.9)	44.4 (13.0)	50	41.6
Trapp et al., 2016	Germany	DSM-IV (psychiatrist)	Verbal Memory, Working Memory, Attention /Processing Speed, Executive Functioning, Verbal Fluency, Visuospatial Memory	Individual	X-Cog (Trapp, 2003)	12	TAU	CBT, Relaxation, Physical Training, Occupational Therapy	23	23	34.3 (11.6)	36.9 (12.1)	60.9	73.9

Note. Results were combined and averaged for both CR groups in Alvarez et al., 2008; *N* = Sample size; *M* = Mean; SD = Standard Deviation; DSM = Diagnostic and Statistical Manual of Mental Disorder; SCID = Structured Clinical Interview for DSM; CES-D = Center for Epidemiological Studies-Depression; BDI = Beck Depression Inventory; CBT = Cognitive Behavioral Therapy; TAU = Treatment as usual.

The Effect of Cognitive Remediation in Depression

The results of our meta-analysis are reported in Table 2. We noted a significant moderate effect size of CR on improved global cognition from pre-test to post-test in adults with depression compared to control conditions (g = 0.38, p = .0003, Figure 2). Sub-group analysis further indicated significant improvements for CR compared to the control condition in verbal memory (g = 0.47, p = .0003), attention/processing speed (g = 0.41, p = .04), working memory (g = 0.40, p = .005), and executive functioning (g = 0.30, p = .02) but no significant improvements in visuospatial memory (g = 0.26, p = .12) and verbal fluency (g = 0.07, p = .72, Figure 3).

Table 2.

Effect of cognitive remediation on cognition in depression.

Cognitive Domain	*N*	Hedges' *g*	95% *CI*	*Z* score	*p*-value
Verbal Memory	8	0.47	0.22, 0.73	3.63	.0003*
Visuospatial Memory	4	0.26	-0.07, 0.58	1.55	.12
Working Memory	6	0.40	0.12, 0.68	2.81	.005*
Attention/Processing Speed	6	0.41	0.03, 0.80	2.10	.04*
Executive Functioning	6	0.30	0.05, 0.55	2.33	.02*
Verbal Fluency	4	0.07	-0.30, 0.43	0.35	0.72

Note. N = number of studies addressing the cognitive domain; Hedges' *g* = effect size difference between CR and control conditions; *CI* = Confidence Intervals; *Z* value = Hedge's g / Standard error. * = Statistically significant at $p < .05$

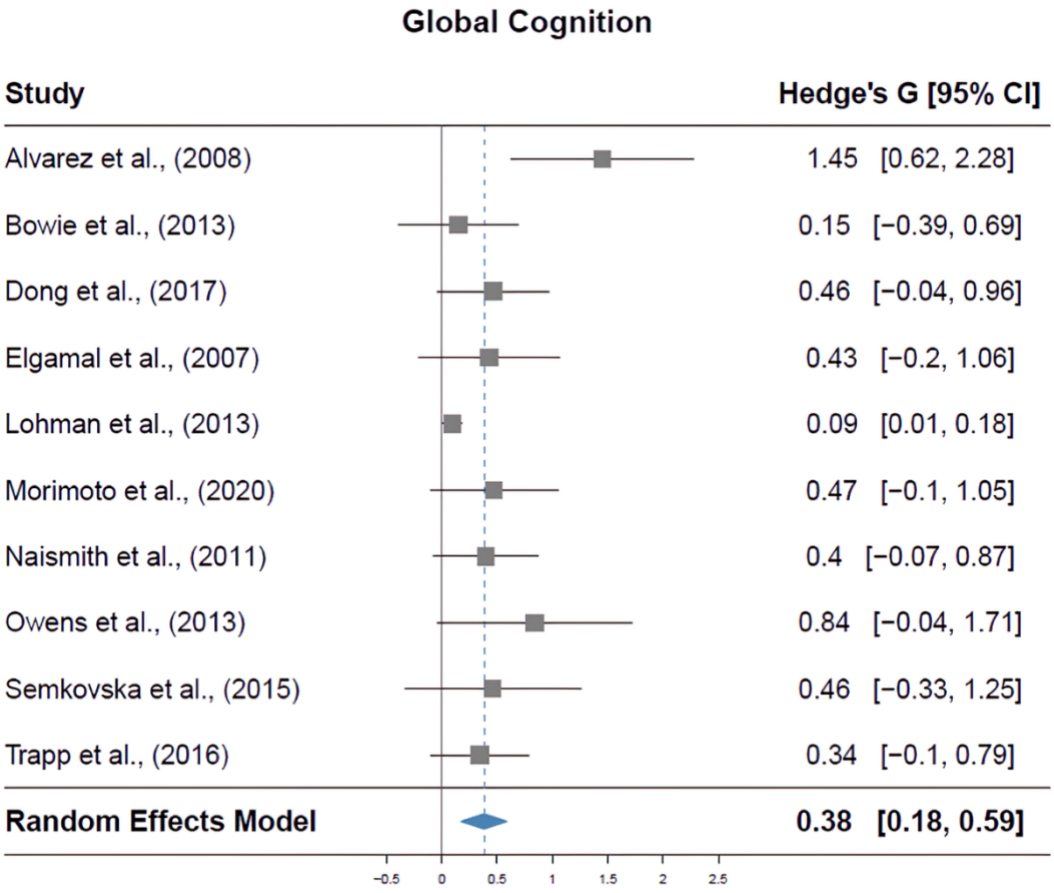

Figure 2: Forest plot displaying the estimated effect size for each study, which describe the effect of cognitive remediation therapy on general cognition in depression

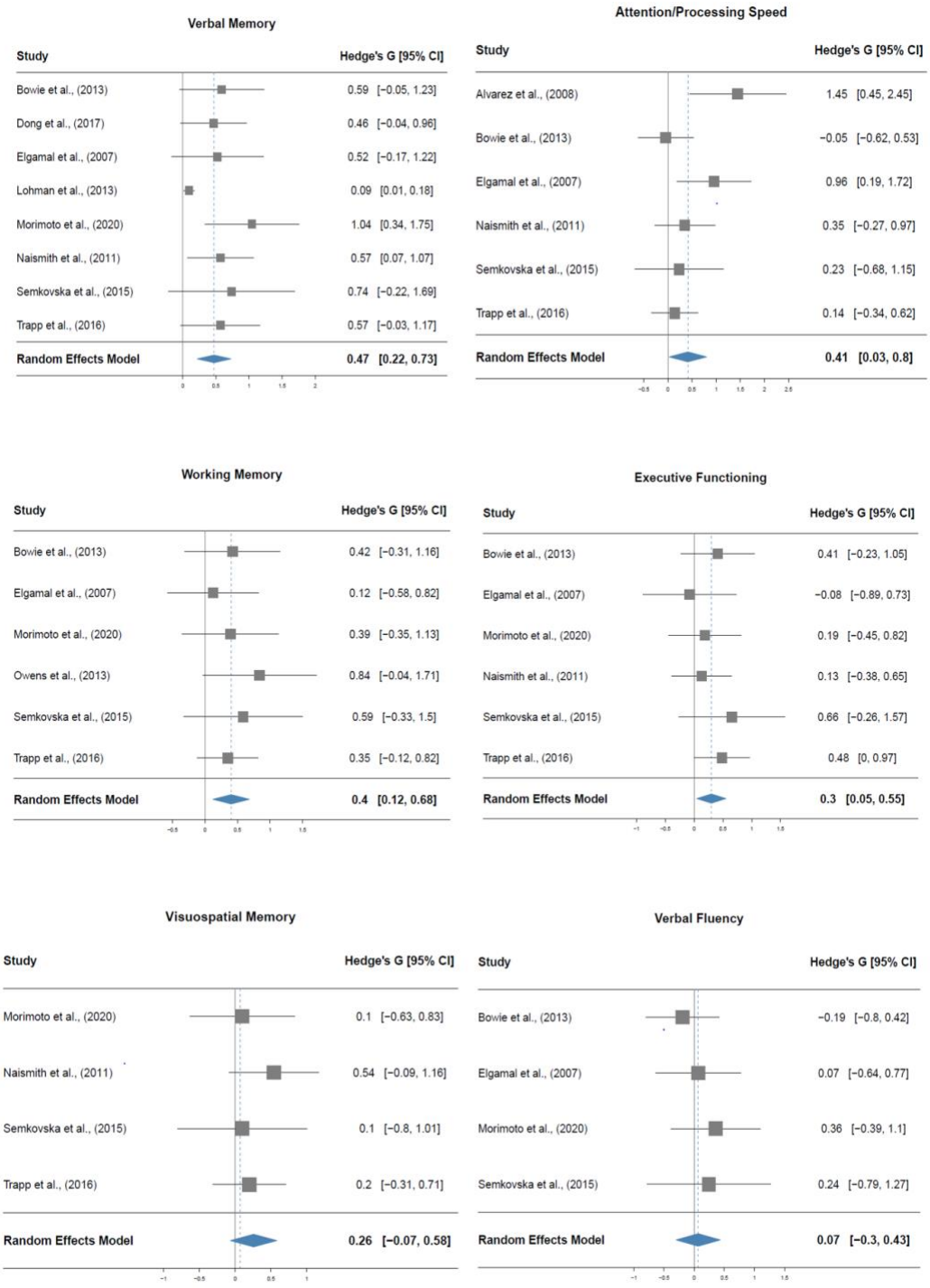

Figure 3: Forest plots displaying the estimated effect size for each study, which describe the effect of cognitive remediation on specific cognitive domains in depression.

Moderators of Cognitive Remediation in Depression

The meta-regression estimates describing the effect of the potential moderators on the effect of CR on global cognition are reported in Table 3. We observed a significant moderating effect of CR session formats (p = .004). A post-hoc subgroup analysis showed that while both individual and group formats significantly improved global cognition in depression (p = <.0001 and p = .04, respectively), the improvement was significantly greater when participants received CR individually rather than in groups. We also found that the effect of CR significantly decreases with participants' age (p = .0005). Lastly, no significant moderating effect of CR duration were observed (p = .29).

Table 3.

Mixed effect model meta-regression estimates for four potential moderators of the effect of CR on global cognition.

	n	*b*	95% CI	Z Score	*p*-value	Post-hoc sub-groups	n	*b*	95% CI	Z Score	*p*-value
Session format	10	0.46	0.15, 0.77	2.90	.004*	Group	4	0.14	0.004, 0.28	2.02	.04*
						Individual	6	0.60	0.33, 0.88	4.28	<.0001*
Duration	10	0.02	-0.01, 0.04	1.05	.29	N/A					
Age	10	-0.01	-0.02, -0.005	-3.47	.0005*	N/A					

Note. N= number of studies; *b* = Meta-regression coefficient; *CI* = Confidence Intervals, NA= not applicable. * = Statistically significant difference at $p < .05$

Study Heterogeneity

The model assessing the effect of CR on global cognition displayed significant and moderate levels of heterogeneity (Q = 19.44, p = .02, I^2 = 45.92%). Heterogeneity was low for the sub-group models addressing the effect of CR on working memory (Q

= 1.78, p = .88, I^2 = 0.00%), executive functioning (Q = 2.61, p = .76, I^2 = 0.00%), visuospatial memory (Q = 1.13, p = .77, I^2 = 0.00%), and verbal fluency (Q = 1.38, p = .71, I^2 = 0.00%), but it was moderate for verbal memory and attention/processing speed (Q = 18.29, p = .01, I^2 = 52.76%, and Q = 9.62, p = .09, I^2 = 47.26%, respectively).

Heterogeneity was also low for the models testing the moderating effect of session format (Q = 7.86, p = .45, I^2 = 7.77%), participants' age (Q = 7.40, p = .49, I^2 = 0.00%), and CR duration (Q = 12.73, p = .12, I^2 = 30.84%).

Publication Bias

We observed a funnel plot asymmetry due to a "tail" of observations pulled to the right of the plot mainly due to the Alvarez and colleagues (2008) study who obtained large effect size in a small sample (see Appendix 4 in the Supplementary Material). The asymmetry suggests the presence of publication bias advantaging the publication of significant over insignificant findings, particularly in small samples.

Discussion

Global and Domain-Specific Effects of Cognitive Remediation in Depression

The current study investigated the effect of CR on global cognition in people with depression. Our results provide evidence that CR can significantly improve global cognition in this population, with a moderate effect size (g = 0.38). The estimated effect size was comparable to the first meta-analysis of studies involving people with various affective disorders (i.e., g =0.44; Anaya et al., 2012) and in line with prior reviews and meta-analysis supporting the overall efficacy of CR in schizophrenia and schizoaffective disorders (Kim et al., 2018; Keshavan et al., 2014; Wykes et al., 2011).

When analyzing cognitive domains separately, we found that CR had a moderate significant effect on verbal memory (g = 0.47), attention/processing speed (g = 0.41),

working memory (g = 0.40), and executive functioning (g = 0.30). No significant effect was observed on visuospatial memory and verbal fluency. Thus, the overall improvement observed in global cognition was likely influenced by domain-specific changes in verbal memory, attention/processing speed, working memory, and executive functioning. However, it is important to note that the small number of studies investigating the other cognitive domains limited our statistical power to identify significant effects. This points to the need for more studies investigating the effect of CR in depression on visuospatial memory and verbal fluency.

Consistent with Motter and colleagues (2016), our findings showed a significant effect of CR on attention/processing speed and working memory in depression. In addition, we observed significant improvements in verbal memory and executive functioning which were not reported in this previous meta-analysis. These findings are likely explained by the inclusion of four recent studies investigating these outcomes (i.e., Dong et al., 2017, Morimoto et al., 2020, Semkovska et al., 2015 and Trapp et al., 2016).

Toward Best Practices for Cognitive Remediation in Depression

The current meta-analysis examined the effect of three potential moderators, namely session format, duration, and participants' age. We observed significantly greater cognitive improvements following individual CR than group CR. It is possible that individually-delivered CR especially facilitates treatment customization by creating a better setting for the development of a therapeutic alliance, for patient-tailored goal setting, and for adapting exercise pace to the individual progress (Dong et al., 2017; Morimoto et al., 2020, Semkovska et al., 2015). This finding is also in line with previous studies reporting that psychological therapies tend to produce greater effects in individuals with depression when delivered individually compared to in groups settings

(Craigie & Paula, 2009; Hauksson et al., 2017; Larøi & Linden, 2013). Nonetheless, it should be noted that while the effect was smaller, significantly improved cognition in group CR was also reported. Hence, CR still appears as a cost-effective option for depression in group settings, when individual CR is not possible (Medalia & Choi, 2009; Revell et al., 2015). It is also important to note that outcomes unavailable in this study, such as everyday functioning and mood symptoms, might be influenced by different session formats and should be further investigated.

We also found that participant's age significantly moderated the effect of CR, which replicates previous findings from Motter et al., (2016). Specifically, in adult individuals with depression, the effect of CR was again found to decrease when participants' age increased. This result highlights the potential importance of addressing cognitive deficits early in the course of depression. Moreover, several factors might be investigated in future work to help understand how CR for older individuals with depression might be more efficacious. Age-related cognitive decline aggravated by the presence of depressive symptoms (Wilson et al., 2014) may possibly underline this decreased efficacy. Longer duration of illness, more episodes, and prolonged avoidance of cognitively challenging activities in daily life (Tran et al., in press) might also affect response to CR in depression.

Interestingly, longer CR treatment was not associated with greater improvements in global cognition. This might imply, as in other disorders such as (Best et al., 2019) schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, or major depressive disorder with psychotic features, that cognitive treatment response in depression can occur early on after CR onset. Nonetheless, CR research in individuals with schizophrenia has indicated that other desired outcomes, such as improved quality of life and everyday functioning, are likely to lag behind cognitive

responses (Bowie et al., 2012). Therefore, more work is needed to clarify the optimal duration for producing and sustaining cognitive improvement and transfer of those improvements to indicators of daily functioning in depression.

Limitations of The Present Study and Areas of Improvement in the Literature

To date, the number of randomized controlled trials investigating the effect of CR on cognition in adults with depression is limited. Our literature search and study selection identified sixteen studies that could be included in the meta-analysis. However, we were unable to directly extract the means and standard deviations for the pre-test and post-test cognitive assessments from numerous articles that initially met our inclusion criteria. Even after contacting the authors, six studies had to be excluded due to a lack of available cognitive outcome data (see Appendix 5 in Supplementary Material). Thus, there is a critical need for greater transparency and accessibility in the field. Additional efforts in that sense should be made not only to facilitate future meta-analyses, but also to improve the rigor and quality of the evidence that is published (Dwan et al., 2013)

The ten studies included in our meta-analysis differed considerably in terms of assessment methods. Specifically, we noted the limited use of standard comprehensive cognitive assessments. The large variation in assessment measures between studies might have contributed to the moderate significant study heterogeneity we observed when testing the effect of CR on global cognition, verbal memory, and attention/processing speed. In light of this, achieving a consensus on a comprehensive yet concise and practical battery of cognitive tests for depression could facilitate comparisons between studies (Russo et al., 2014).

Furthermore, limited information was available on participants' characteristics. Only two studies reported age of onset of depression and mean number of lifetime

depressive episodes (Naismith et al., 2011; Elgamal et al., 2007) and two reported the duration of the depressive episode (Elgamal et al., 2007; Trapp, et al. 2016). Reporting such information could allow for more extensive moderation analyses and could help developing CR protocols tailored to specific patient characteristics.

Lastly, we noted the presence of publication bias in this literature. Studies involving larger samples and reporting significant results were more likely to be published than studies with smaller samples and nonsignificant results. A similar pattern has been observed in the existing literature on other pharmacological and psychological treatments for depression (Driessen et al., 2015) and suggests that the effect of CR might have been overstated as well. In order to contrast publication bias and improve cumulative evidence, we recommend adherence to open science practices like pre-registration and sharing data, code, and negative results on open source repositories (Amrhein, Greenland, & McShane, 2019; Lakens, 2013).

References

***Indicates references included in the meta-analysis.**

Ahern, E., & Semkovska, M. (2016). Cognitive functioning in the first-episode of major depressive disorder: A systematic review and meta-analysis. *Neuropsychology, 31*(1), 52-72. doi: 10.1037/neu0000319.

*Alvarez, L. M., Cortés Sotres, J. F., León, S. O., Estrella, J., & Sánchez Sosa, J. J. (2008). Computer program in the treatment for major depression and cognitive impairment in university students. *Computers in Human Behavior*, 24(3), 816–826. doi:10.1016/j.chb.2007.02.013.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Publishing.

Amrhein, V., Greenland, S., & McShane, B. (2019). Scientists rise up against statistical significance. *Nature*, *567*(7748), 305–307. https://doi.org/10.1038/d41586-019-00857-9

Anaya, C., Martinez Aran, A., Ayuso-Mateos, J. L., Wykes, T., Vieta, E., & Scott, J. (2012). A systematic review of cognitive remediation for schizo-affective and affective disorders. *Journal of Affective Disorders*, 142(1-3), 13–21. doi:10.1016/j.jad.2012.04.020

Beck, A. T. (1979). *Cognitive therapy of depression*. Guilford press.

Beck, A.T., Steer, R.A., & Brown, G.K. (1996). *Manual for the Beck Depression Inventory-II.* San Antonio, TX: Psychological Corporation.

Becker, B. J. (1988). Synthesizing standardized mean-change measures. *British Journal of Mathematical and Statistical Psychology*, 41(2), 257–278. doi:10.1111/j.2044-8317.1988.tb00901.x.

Berto, P., D'Ilario, D., Ruffo, P., Di Virgilio, R., Rizzo, F., 2000. Depression: cost-of-illness studies in the international literature, a Review. *Journal of Mental Health Policy and Economy, 3* (1), 3–10.

Best, M. W., Gale, D., Tran, T., Haque, M. K., & Bowie, C. R. (2019). Brief executive function training for individuals with severe mental illness: effects on EEG synchronization and executive functioning. *Schizophrenia research*, *203*, 32-40.

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. (2019). *Common mistakes in meta-analysis and how to avoid them.* New Jersey, USA: Biostats Incorporated.

Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. (2009). *Introduction to Meta-Analysis.* John Wiley & Sons, Ltd: United Kingdom.

*Bowie, C. R., Gupta, M., Holshausen, K., Jokic, R., Best, M., & Milev, R. (2013). Cognitive remediation for treatment-resistant depression. *The Journal of Nervous and Mental Disease*, 201(8), 680–685. doi:10.1097/nmd.0b013e31829c5030.

Bowie, C. R., McGurk, S. R., Mausbach, B., Patterson, T. L., & Harvey, P. D. (2012). Combined cognitive remediation and functional skills training for schizophrenia: effects on cognition, functional competence, and real-world behavior. *The American journal of psychiatry*, *169*(7), 710–718. https://doi.org/10.1176/appi.ajp.2012.11091337

Bracy, O. L. (1994). *PSSCogReHab Version 95: Technical Manual*. Psychological Software Services: Indianapolis, IA.

Castaneda, A. E., Suvisaari, J., Marttunen, M., Perala, J., Saarni, S. I., Aalto-Setala, T., Tuulio-Henriksson, A. (2008). Cognitive functioning in a population-based sample of young adults with a history of non-psychotic unipolar depressive disorders without psychiatric comorbidity. *Journal of Affective Disorders, 110*(1-2), 36-45. doi:10.1016/j.jad.2007.12.239.

Cella, M., Preti, A., Edwards, C., Dow, T., & Wykes, T. (2017). Cognitive remediation for negative symptoms of schizophrenia: A network meta-analysis. *Clinical psychology review, 52*, 43–51. https://doi.org/10.1016/j.cpr.2016.11.009

Craigie, M. A., & Nathan, P. (2009). A nonrandomized effectiveness comparison of broad-spectrum group CBT to individual CBT for depressed outpatients in a community mental health setting. *Behavior therapy*, *40*(3), 302–314. https://doi.org/10.1016/j.beth.2008.08.002

*Dong, L., Lee, J. Y., & Harvey, A. G. (2017). Memory support strategies and bundles: A pathway to improving cognitive therapy for depression? *Journal of Consulting and Clinical Psychology*, 85(3), 187–199. doi:10.1037/ccp0000167.

Driessen, E., Hollon, S. D., Bockting, C. L. H., Cuijpers, P., & Turner, E. H. (2015). Does Publication Bias Inflate the Apparent Efficacy of Psychological Treatment for Major Depressive Disorder? A Systematic Review and Meta-Analysis of US National Institutes of Health-Funded Trials. *PLOS ONE*, 10(9), e0137864. doi:10.1371/journal.pone.0137864

Dwan, K., Gamble, C., Williamson, P. R., Kirkham, J. J., & Reporting Bias Group (2013). Systematic review of the empirical evidence of study publication bias and outcome reporting bias - an updated review. PloS one, 8(7), e66844. https://doi.org/10.1371/journal.pone.0066844

*Elgamal, S., Mckinnon, M. C., Ramakrishnan, K., Joffe, R. T., & Macqueen, G. (2007). Successful computer-assisted cognitive remediation therapy in patients with unipolar depression: a proof of principle study. *Psychological Medicine*, 37(9), 1229–1238. doi:10.1017/s0033291707001110.

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.

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.

Greenberg, P. E., & Birnbaum, H. G. (2005). The economic burden of depression in the US: societal and patient perspectives. *Expert Opinion on Pharmacotherapy*, 6(3), 369–376. doi:10.1517/14656566.6.3.369.

Guimond, S., Béland, S., & Lepage, M. (2018). Strategy for Semantic Association Memory (SESAME) training: Effects on brain functioning in schizophrenia. Psychiatry Research: *Neuroimaging*, 271, 50–58. doi:10.1016/j.pscychresns.2017.10.010

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.

Hauksson, P., Ingibergsdóttir, S., Gunnarsdóttir, T., & Jónsdóttir, I. H. (2017). Effectiveness of cognitive behaviour therapy for treatment-resistant depression

with psychiatric comorbidity: comparison of individual versus group CBT in an interdisciplinary rehabilitation setting. *Nordic journal of psychiatry*, *71*(6), 465–472. https://doi.org/10.1080/08039488.2017.1331263

Hedges, L. V. & Olkin, I. (1985). *Statistical methods for meta-analysis*. Orlando, FL: Academic Press.

Higgins, J. P. T., & Cochrane Collaboration. (2020). *Cochrane handbook for systematic reviews of interventions (2nd ed.).* Hoboken, NJ: Wiley-Blackwell.

Jaeggi, S. M., Seewer, R., Nirkko, A. C., Eckstein, D., Schroth, G., Groner, R., & Gutbrod, K. (2003). Does excessive memory load attenuate activation in the prefrontal cortex? Load-dependent processing in single and dual tasks: functional magnetic resonance imaging study. *NeuroImage*, 19(2), 210–225. doi:10.1016/s1053-8119(03)00098-3.

Kelly, S. M., & Eack, S. M. (2018). White matter microstructure and cognitive remediation outcomes in schizophrenia. *Schizophrenia Research*, 195, 76–77. doi:10.1016/j.schres.2017.09.037

Keshavan, M. S., Vinogradov, S., Rumsey, J., Sherrill, J., & Wagner, A. (2014). Cognitive Training in Mental Disorders: Update and Future Directions. *American Journal of Psychiatry*, 171(5), 510–522. doi:10.1176/appi.ajp.2013.13081075

Kim, E. J., Bahk, Y. C., Oh, H., Lee, W. H., Lee, J. S., & Choi, K. H. (2018). Current Status of Cognitive Remediation for Psychiatric Disorders: A Review. *Frontiers in psychiatry*, *9*, 461. https://doi.org/10.3389/fpsyt.2018.00461

Lakens D. (2013). Calculating and reporting effect sizes to facilitate cumulative

science: a practical primer for t-tests and ANOVAs. *Frontiers in psychology, 4*, 863. https://doi.org/10.3389/fpsyg.2013.00863

Larøi, F., & Linden, M. V. D. (2013). The need for an individualized, everyday life and integrative approach to cognitive remediation in schizophrenia. *Journal of Psychotherapy Integration*, *23*(3), 290–304. doi: 10.1037/a0032358

Levin, R. L., Heller, W., Mohanty, A., Herrington, J. D., & Miller, G. A. (2007). Cognitive deficits in depression and functional specificity of regional brain activity. *Cognitive Therapy and Research*, 31(2), 211–233. doi:10.1007/s10608-007-9128-z.

Lim, G. Y., Tam, W. W., Lu, Y., Ho, C. S., Zhang, M. W., & Ho, R. C. (2018). Prevalence of Depression in the Community from 30 Countries between 1994 and 2014. *Scientific Reports*, 8(1). doi:10.1038/s41598-018-21243-x

*Lohman, M. C., Rebok, G. W., Spira, A. P., Parisi, J. M., Gross, A. L., & Kueider, A. M. (2013). Depressive Symptoms and Memory Performance Among Older Adults. *Journal of Aging and Health*, 25(8_suppl), 209S–229S. doi:10.1177/0898264312460573

Mattern, M., Walter, H., Hentze, C., Schramm, E., Drost, S., Schoepf, D., Fangmeier, T., Normann, C., Zobel, I., & Schnell, K. (2015). Behavioral evidence for an impairment of affective theory of mind capabilities in chronic depression. *Psychopathology*, *48*(4), 240–250. https://doi.org/10.1159/000430450

Medalia, A. (2005). What predicts a good response to cognitive remediation interventions? *Schizophrenia Bulletin*, 31(4), 942–953. doi:10.1093/schbul/sbi045.

Medalia, A., & Choi, J. (2009). Cognitive Remediation in Schizophrenia. *Neuropsychology Review*, *19*(3), 353–364. https://doi.org/10.1007/s11065-009-9097-y

Medalia, A., & Lim, R. (2004). Treatment of Cognitive Dysfunction in Psychiatric Disorders. *Journal of Psychiatric Practice*, 10(1), 17–25. doi:10.1097/00131746-200401000-00003

Medalia, A., & Mambrino, E. (2010). An Overview of the Neuropsychological and Educational Approach to Remediation. *Key Issues in Mental Health*, 104–117. doi:10.1159/000284382.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Mededcine, 6*(7). doi: 10.1371/journal.pmed.1000097.

Mothersill, D., & Donohoe, G. (2019). Neural Effects of Cognitive Training in Schizophrenia: A Systematic Review and Activation Likelihood Estimation Meta-analysis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 4(8), 688–696. doi:10.1016/j.bpsc.2019.03.005

Motter, J. N., Pimontel, M. A., Rindskopf, D., Devanand, D. P., Doraiswamy, P. M., & Sneed, 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.

*Morimoto, S. S., Altizer, R. A., Gunning, F. M., Hu, W., Liu, J., Cote, S. E., … Alexopoulos, G. S. (2020). Targeting Cognitive Control Deficits With Neuroplasticity-Based Computerized Cognitive Remediation in Patients With Geriatric Major Depression: A Randomized, Double-Blind, Controlled Trial. *The*

American Journal of Geriatric Psychiatry, *28*(9), 971–980. https://doi.org/10.1016/j.jagp.2020.05.023

Morris, S. B. (2007). Estimating effect sizes from pretest-posttest-control group designs. *Organizational Research Methods*, 11(2), 364–386. doi:10.1177/1094428106291059.

Murray, C. J., & Lopez, A. D. (1996). Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *The Lancet*, 349(9063), 1436–1442. doi:10.1016/s0140-6736(96)07495-8

*Naismith, S. L., Diamond, K., Carter, P. E., Norrie, L. M., Redoblado-Hodge, M. A., Lewis, S. J. G., & Hickie, I. B. (2011). Enhancing memory in late-life depression: The effects of a combined psychoeducation and cognitive training program. *The American Journal of Geriatric Psychiatry*, 19(3), 240–248. doi:10.1097/jgp.0b013e3181dba587.

*Owens, M., Koster, E. H. W., & Derakshan, N. (2013). Improving attention control in dysphoria through cognitive training: Transfer effects on working memory capacity and filtering efficiency. *Psychophysiology*, 50(3), 297–307. doi:10.1111/psyp.12010.

Penadés, R., Pujol, N., Catalán, R., Massana, G., Rametti, G., García-Rizo, C., Bargalló, N., Gastó, C., Bernardo, M., & Junqué, C. (2013). Brain effects of cognitive remediation therapy in schizophrenia: a structural and functional neuroimaging study. *Biological psychiatry*, *73*(10), 1015–1023. https://doi.org/10.1016/j.biopsych.2013.01.017

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 & New Zealand Journal of Psychiatry*, 47(12), 1165–1175. doi:10.1177/0004867413502090.

Revell, E. R., Neill, J. C., Harte, M., Khan, Z., & Drake, R. J. (2015). A systematic review and meta-analysis of cognitive remediation in early schizophrenia. *Schizophrenia Research*, 168(1-2), 213–222. doi:10.1016/j.schres.2015.08.017

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.

Ross, C., Mirowsky, J., & Huber, J. (1983). Dividing work, sharing work, and in between : Marriage patterns and depression. *American Sociological Review*, 48,809-823. doi:10.2307/2095327

Russo, M., Mahon, K., & Burdick, K. E. (2014). Measuring cognitive function in MDD: Emerging assessment tools. *Depression and Anxiety, 32*(4), 262-269. doi:10.1002/da.22297.

Segrave, R. A., Arnold, S., Hoy, K., & Fitzgerald, P. B. (2014). Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. *Brain stimulation*, *7*(2), 325–331. https://doi.org/10.1016/j.brs.2013.12.008

Semkovska, M. & Ahern, E. (2017). Online neurocognitive remediation therapy to improve cognition in community-living individuals with a history of depression: A pilot study. *Internet Interventions, 9*, 7-14.

*Semkovska, M., Lambe, S., Lonargáin, D. Ó., & McLoughlin, D. M. (2015). Neurocognitive remediation therapy for depression. *The Journal of Nervous and Mental Disease*, 203(8), 609–616. doi:10.1097/nmd.0000000000000337.

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.

Spitzer, R.L., Endicott, J., and Robins, E. (1978). Research Diagnostic Criteria: Rationale and reliability. *Archives of General Psychiatry, 35*, 773.

Tran T, Hagen AEF, Hollenstein T, Bowie CR. (in press). Physical and cognitive effort-based decision-making in depression: relationships to symptoms and functioning. *Clinical Psychological Science*.

Trapp W. (2003). *X-Cog user manual*. Erlangen: Gruner.

*Trapp, W., Engel, S., Hajak, G., Lautenbacher, S., & Gallhofer, B. (2015). Cognitive remediation for depressed inpatients: Results of a pilot randomized controlled trial. *Australian & New Zealand Journal of Psychiatry, 50*(1), 46-55. doi:10.1177/0004867415622271.

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.biopsycho.2009.03.009.

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metaphor package. *Journal of Statistical Software*, 36(3). doi:10.18637/jss.v036.i03.

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., Charlson, F. J., Norman, R. E., Flaxman, A. D., Johns, N., Burstein, R., Murray, C. J., & Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease

Study 2010. *Lancet (London, England)*, *382*(9904), 1575–1586. https://doi.org/10.1016/S0140-6736(13)61611-6

Wilson, R. S., Capuano, A. W., Boyle, P. A., Hoganson, G. M., Hizel, L. P., Shah, R. C., Nag, S., Schneider, J. A., Arnold, S. E., & Bennett, D. A. (2014). Clinical-pathologic study of depressive symptoms and cognitive decline in old age. *Neurology*, *83*(8), 702–709. https://doi.org/10.1212/WNL.0000000000000715

World Health Organization. (1992). *The ICD-10 classification of mental and behavioral disorders: clinical descriptions and diagnostic guidelines*. World Health Organization. Available at http://www.who.int/iris/handle/10665/37958.

World Health Organization. (2017). *Depression and other common mental disorders: global health estimates*. World Health Organization. Available at https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf

Wykes, T., Huddy, V., Cellard, C., McGurk, S. R., & Czobor, P. (2011). A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *American Journal of Psychiatry, 168*(5), 472-485. doi:10.1176/appi.ajp.2010.10060855