Author/s:
Daglas-Georgiou, R;Bryce, S;Smith, G;Kaur, M;Cheng, N;De Rozario, M;Wood, SJ;Allott, K

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Bryce Shayden (Orcid ID: 0000-0001-6425-9861)

Interventions for objective and subjective cognitive functioning in young people with depression: Systematic review of current evidence

Rothanthi Daglas-Georgiou[1,2#], Shayden Bryce[1,2#], Gabriel Smith[3], Manreena Kaur[4,5,6], Nicholas Cheng[1,2], Magdalene De Rozario[1,2], Stephen J. Wood[1,2,7], & Kelly Allott[1,2*]

[#]Joint first authorship

[1]Orygen, Parkville, Victoria, Australia

[2]Centre for Youth Mental Health, The University of Melbourne, Parkville, Victoria, Australia

[3]Faculty of Science, The University of Melbourne, Parkville, Victoria, Australia

[4]Neuroscience Research Australia (NeuRA), NSW, Australia

[5]School of Psychiatry, University of New South Wales, Australia

[6]Epworth Centre for Innovation in Mental Health, Epworth Healthcare and Department of Psychiatry, Monash University, Melbourne, Australia

[7]School of Psychology, University of Birmingham, Edgbaston UK.

*Corresponding author: Kelly Allott, 35 Poplar Road, Parkville, VIC, 3052, Australia; +3 9966 9423 kelly.allott@orygen.org.au

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Abstract

Aim: Cognitive deficits are recognized features of depressive disorders in youth aged 12-25. These deficits are distressing, predict functional impairment, and limit the effectiveness of psychological therapies. Cognitive enhancement using behavioural, biochemical or physical interventions may be useful in young people with depression, but studies have not been synthesised. The aim was to systematically review the evidence for interventions for objective and subjective cognitive functioning, and their acceptability and functional outcomes in people aged 12-25 with depression. **Method:** Three electronic databases were searched for articles using pre-specified criteria. Pharmacological interventions were not eligible. Risk of bias was rated using the Cochrane Collaboration's revised risk-of-bias tool. Dual full-text article screening, data extraction, and quality ratings were completed. **Results:** Twelve studies were included for review (median participant age: 20.39 years), five of which were randomised-controlled trials (RCTs). Sample sizes were generally small (median=23; range: 9-46). Eight studies investigated behavioural interventions including aerobic exercise, cognitive training, and education or strategy-based methods. Four studies examined repetitive transcranial magnetic brain stimulation (rTMS). Most behavioural interventions revealed preliminary evidence of improved cognitive function in youth depression. Consent rates were greatest for exercise- and education-based approaches, which may indicate higher acceptability levels. Findings from rTMS trials were mixed, with only half showing cognitive improvement. Functional outcomes were reported by three behavioural intervention trials and one rTMS trial, with functional improvement reported only in the former. Some concern of risk of bias was found in each RCT. **Conclusion:** Behavioural interventions, such as exercise, cognitive training, and education/strategy-focused techniques, show encouraging results and appear to be acceptable methods of addressing cognitive deficits in youth depression based on

participation rates. Brain stimulation and biochemical interventions (e.g., nutrient-based treatment) require further investigation.

Key words: MDD, youth, cognition, treatment, rehabilitation

Cognitive impairment is a well-established and central feature of Major Depressive Disorder (MDD; (McIntyre et al., 2015). Empirical studies providing evidence of clinically significant cognitive impairments in MDD relative to healthy controls have steadily increased over recent decades (Bora, Harrison, Yucel, & Pantelis, 2013; Douglas & Porter, 2009; Rock, Roiser, Riedel, & Blackwell, 2014). These cognitive impairments emerge early in the course of MDD (Ahern & Semkovska, 2017; Allott, Fisher, Amminger, Goodall, & Hetrick, 2016; Goodall et al., 2018; R. S. Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Wagner, Muller, Helmreich, Huss, & Tadic, 2015). A recent meta-analysis (*k*=23) found significant moderate-to-large impairments in the domains of attention, verbal memory, visual memory and verbal reasoning in young people aged 12-25 years with MDD compared to healthy controls (standardised mean difference= -0.46 to -0.78; (Goodall et al., 2018). People in remission from MDD continue to experience cognitive impairment, with the number of previous depressive episodes associated with greater levels of impairment (Ahern & Semkovska, 2017; Semkovska et al., 2019). Together, these findings indicate that cognitive impairment is not entirely explained by current depressive symptomatology (i.e., state-related), and that scarring effects on cognitive performance may occur with illness progression (Allott et al., 2016).

Cognitive impairments contribute to the functional disability in MDD (Gore et al., 2011), and negatively impact academic function, vocational achievement and social participation (R. S. Lee et al., 2013; Morey-Nase et al., 2019; Semkovska et al., 2019). Cognitive impairments can also limit the effectiveness of psychological treatment and increase caregiver burden (Hetrick et al., 2015; Morey-Nase et al., 2019). Furthermore, cognitive impairments may increase risk of depression relapse (Buckman et al., 2018). Young people with depression describe cognitive difficulties as highly distressing, poorly treated in standard clinical care, and having negative impacts on role functioning, motivation and self-

esteem (Morey-Nase et al., 2019). Thus, effective interventions specifically targeting cognitive functioning early in the course of MDD may support functional recovery.

Cognitive enhancement interventions can be categorised under three broad modes of delivery: behavioural, biochemical, and physical (Dresler et al., 2019). Behavioural cognitive interventions comprise strategies or actions that an individual must use or perform to experience cognitive enhancement. They can include ensuring optimal duration and quality of sleep, physical exercise, cognitive training, and use of compensatory cognitive strategies, such as mnemonic techniques (Dresler et al., 2019). Biochemical cognitive interventions include pharmaceutical, nutritional or natural agents that alter biochemistry and enhance function. Pharmaceutical agents, such as antidepressants and mood stabilisers, are not a focus of the current review and have been reviewed elsewhere (Prado, Watt, & Crowe, 2018; Wingo, Wingo, Harvey, & Baldessarini, 2009). Examples of non-pharmaceutical agents that might confer cognitive enhancing effects include caffeine, folic acid, omega-3 fatty acids, n-acetyl cysteine and taurine (Pomeroy, Tooley, Probert, Wilson, & Kemps, 2020; Spencer, Korosi, Layé, Shukitt-Hale, & Barrientos, 2017). Physical interventions, such as non-invasive brain stimulation, may also augment cognitive function by directly modulating neural activity (Demirtas-Tatlidede, Vahabzadeh-Hagh, & Pascual-Leone, 2013). Examples include repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS).

There has been no synthesis of the evidence for the usefulness and acceptability of cognitive enhancement interventions on cognitive outcomes in young people with depression. The primary aim of this study was to systematically review and appraise the empirical evidence relating to cognitive enhancement interventions on cognitive functioning (objective and subjective) in young people aged 12-25 with depression, with a focus on behavioural, non-pharmaceutical biochemical and physical modalities. The secondary aim was to evaluate

functional outcomes (global and subjective) and the acceptability of different cognitive enhancement interventions based on the consent and attrition rates across studies.

Methods

This review was conducted in accordance with PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009). Systematic review registries including Cochrane Database of Systematic Reviews, PROSPERO and Open Science Framework were searched prior to commencing this review and did not reveal any similar reviews in progress as of June 2020. The protocol for this review was prospectively registered with Open Science Framework on 17/09/2020 (https://osf.io/xz3he). Note that following peer review, we amended the protocol to include functional outcome (global and subjective) in addition to cognitive outcome and acceptability.

Search strategy

Three electronic databases (Ovid Medline, PsycINFO and Web of Science) were searched for relevant research articles. Title, abstract and keywords were searched in each database using a comprehensive list of search terms (see Supplementary Material for the full list of search terms). These included terms related to depression (i.e., *depress** or *MDD*), young people (e.g., *youth*, *adoles**), cognition (e.g., *cognit**, *neuropsychol*), and treatments with biochemical, behavioural or physical modes of action (e.g., *treat**, *train**, *stimul**, *exercis**, *nutri**). Restrictions to exclude papers containing irrelevant terms (e.g., *CBT*, *rodent*) were applied to each database at the outset to make the search more tenable. Preliminary searches were performed on 13/07/2020 to pilot the search terms, with the finalised systematic search of all databases conducted on 10/08/2020. To increase comprehensiveness, a supplementary search was conducted on 17/11/2020 to add one additional youth-specific term that was not included during the initial searches. Reference lists of all included studies were also screened for relevant articles.

Eligibility criteria

Articles were included for review if they met the following criteria: (1) original peer-reviewed research article published in English; (2) the mean age of participants was 12-25 years, or greater than 50% of the sample fell within this range when the mean age was not reported; (3) participants had a *clinical depressive disorder* such as MDD or clinically elevated symptoms of depression on standardised rating scales; (4) the sample size included a minimum of 5 participants per group; (5) the study examined the impact of an intervention designed to improve cognition as a standalone or adjunctive treatment (randomised and non-randomised intervention studies were permitted); (6) cognition was measured objectively or subjectively using standardised cognitive assessment tasks or rating scales; (7) cognition was measured post-intervention (as either a primary, secondary or exploratory outcome); and (8) relevant statistics related to cognitive outcomes (objective or subjective) were reported. Articles were excluded if participants had an intellectual disability, psychotic disorder, neurodevelopmental disorder (e.g., ASD), neurological illness or insult (e.g., epilepsy), current substance use disorder, or more than 50% of the sample had bipolar disorder.

Studies examining cognitive bias modification were not included for review. Cognitive bias modification represents a group of interventions targeting styles of cognitive response patterns to emotionally salient stimuli (Platt, Waters, Schulte-Koerne, Engelmann, & Salemink, 2017), and therefore distinct from those targeting traditional Cattell-Horn-Carroll (CHC) cognitive domains (Jewsbury, Bowden, & Duff, 2017). The efficacy of these interventions for depression is reviewed elsewhere (Fodor et al., 2020; Platt et al., 2017).

Clinical depressive disorders in this review were defined as either a current full-threshold depressive episode or major depressive disorder (including in partial or full remission), as determined by consensus classification criteria including DSM-V or ICD-10, or subthreshold depression as determined by clinically elevated scores on standardised self-

report or clinician rating scales (e.g., Beck Depression Inventory [BDI], Patient Health Questionnaire [PHQ-9], Hamilton Rating Scale [HAM-D]). The decision to include threshold and subthreshold depression was to increase the review's applicability to youth mental health services focused on prevention and early intervention, and to recognise that cognitive difficulties may partly represent a trait-based feature in youth depression independent from clinical state or symptom severity (Allott et al., 2016; Goodall et al., 2018).

Data screening and extraction

Data screening was managed using the Covidence software program (www.covidence.org). Authors RDG, SB, GS, NC, MDR and KA contributed to data screening. A formalised consensus meeting was conducted prior to screening to ensure interrater reliability. After piloting the review criteria, Phase 1 consisted of the title and abstract screening of each record to identify those meeting inclusion criteria for full-text eligibility. If unclear, full-text articles were retrieved. In Phase 2, two authors independently reviewed each full-text article that was retrieved in Phase 1 using the same review criteria. Disagreements regarding article suitability in Phase 1 or 2 were resolved via discussion with the senior author (KA). Dual data extraction was conducted by authors RDG, SB and GS, with cross-checking of all data to ensure reliability. Variables of interest included year of publication, country, study design, recruitment method, sample size, participant demographics (e.g., age, sex), intervention details, subjective or objective cognitive data at pre- and post-intervention, functioning outcome data, and participant consent/attrition rates. Corresponding authors of each study were contacted when relevant data were unclear or not reported.

Risk of bias

The Cochrane Collaboration risk-of-bias tool version 2 (RoB2) was used to evaluate the risk of bias in the findings of randomised-controlled trials (RCTs) included in this review

(Sterne et al., 2019). The RoB2 evaluates bias according to five domains based on empirical evidence and theoretical considerations that correspond to different stages of trial process (Sterne et al., 2019). Specifically, domains relate to risk of bias in the randomisation process (Domain 1), deviations from the intended intervention (Domain 2), missing outcome data (Domain 3), measurement of the outcome (Domain 4), and selection of the reported results (Domain 5). Each domain contains a series of signalling questions that are rated as either (1) *Yes/Probably Yes*, (2) *No/Probably No* or (3) *No Information*. RoB2 rating guidelines, crib sheet and scoring algorithms were used to judge domain-level and overall risk of bias (Higgins, Savović, Page, Sterne, & RoB2 Development Group, 2019).

Results

Search results

Electronic database searching and review of additional records revealed 29,714 articles, with 17,633 remaining once duplicates (*n*=12,081) were removed. After title and abstract screening, 150 full-text articles were retrieved and screened. Of these, 138 were excluded, with over half (51%) not meeting the age criterion. Twelve articles met the review criteria and were included in the qualitative synthesis. The PRISMA flow chart is presented in Figure 1.

[Insert Figure 1]

Study characteristics

Characteristics of the 12 included studies are presented in Table 1. Over half (*n*=7, 58%) were conducted in North American countries including USA (*n*=4, 33%), Canada (*n*=2, 17%) and Mexico (*n*=1, 8%). Five studies were RCTs, two were non-randomised trials and five were single-arm (open-label) studies. Recruitment settings included community and primary and tertiary mental health settings. The average sample size of the studies was small (median=23; range=9-46). The mean age of participants across the included studies ranged

from 15.35 to 23.84 years (median=20.39). Two-thirds of the studies (*n*=8, 67%) recruited young people with depressive symptoms that were classified as at least *moderately* severe according to standardised rating scales (e.g., Beck Depression Inventory, Hamilton Depression Rating Scale).

[Insert Table 1]

Cognitive outcomes of cognitive enhancing interventions

As shown in Table 2, cognitive interventions were categorized according to mode of delivery: *biochemical* (non-pharmacological), *behavioural,* or *physical* (Dresler et al., 2019). Of the 12 studies included for review, two-thirds (*n*=8, 67%) were classified as behavioural cognitive-enhancing interventions. These included computerised cognitive training (*n*=2), exercise (n=3), or education- or strategy-based techniques (*n*=3). The remaining third of studies (*n*=4, 33%) were classified as physical and specifically involved rTMS brain stimulation to the left dorsolateral prefrontal cortex (L-DLPFC). No study was classified as having a biochemical mode of delivery (i.e., supplements, diet). Cognitive outcome data are presented in Table 3.

[Insert Table 2]

[Insert Table 3]

Behavioural interventions

Cognitive training

Two studies examined the effect of individual computerised cognitive training on cognitive functioning in young people with depression (Alvarez, Corte´s Sotres, Ortiz Leo´n, Estrella, & Sa´nchez Sosa, 2008; Motter, Grinberg, Lieberman, Iqnaibi, & Sneed, 2019). Both interventions were intensive, with the difficulty adapted automatically based on participant performance, and did not include strategy provision. In a non-randomised controlled trial, Alvarez et al. (2008) showed that cognitive training at least twice per week

for 30 minutes produced greater improvements on objective measures of global, verbal and perceptual intellectual functioning with or without antidepressant medication when compared to a non-training control (i.e., antidepressant medication only). Similarly, Motter et al. (2019) demonstrated that cognitive training for at least 15 minutes per day, five days a week for 8 weeks, with a tailored suite of either processing speed/executive exercises or verbal training exercises, produced improved performances on cognitive measures of processing speed and executive function compared to baseline levels. Tailored training protocols targeting processing speed/executive skills specifically, demonstrated a greater degree of improvement on one processing speed task (WAIS-IV Coding, Cohen's d=0.45) and one executive function task (cognitive flexibility; D-KEFS Trail Making Condition 4, Cohen's d=0.40) compared to verbal training exercises. This study highlighted the potential for particular cognitive improvements with personalised domain-specific training protocols.

Education- and strategic instruction-based intervention

Three studies were classified as either education or strategy-based (Bryce, Cooke, Yuen, & Allott, 2020; McFarland, Primosch, Maxson, & Stewart, 2017; Neshat-Doost et al., 2013). Bryce et al. (2020) evaluated a two-page fact sheet on cognitive difficulties in young people with depression: *Thinking about Thinking Skills in Depression*. The cognition fact sheet was delivered by case managers, and contained both psychoeducation material about cognition in depression and compensatory cognitive strategies for attention, memory and problem solving. In addition to high levels of acceptability, fact sheet delivery was associated with significant moderate reductions in subjective cognitive deficits three-weeks after delivery (Cohen's d=0.47).

Two studies examined the impact of memory specificity training on proximal training-related outcomes. McFarland et al. (2017) examined the impact of episodic specificity induction training interviews and control (non-probing) interviews on memory,

imagination and problem solving in young people with depression and non-depressed controls. In young people with depression, episodic specificity induction training produced large improvements in problem-solving skills (i.e., more relevant steps generated on a problem-solving task; Cohen's *d*=1.14), and more internal details on interview-specific measures of memory and imagination (Cohen's *d* = 1.11 and 0.55, respectively). Neshat-Doost et al. (2013) examined the impact of a five-week Memory Specificity Training (MEST) group intervention relative to a non-treatment control in an RCT involving young people with at least mild depression. These authors also demonstrated large improvements in memory specificity (i.e., significantly greater recall of specific memories on the Autobiographical Memory Test) relative to intervention-naive participants.

Exercise

Three studies investigated the impact of exercise on objective cognitive function, including aerobic exercise programs (Keating et al., 2019; Olson, Brush, Ehmann, & Alderman, 2017) and high-intensity interval training (J. S. Lee, Boafo, Greenham, & Longmuir, 2019). A single-arm trial showed that a 12-week structured running group, *Team Unbreakable*, which occurred twice per week and gradually increased to a distance of 5km, produced significant improvement in two tasks of processing speed and attention capacity, out of 18 cognitive tasks in total (Keating et al., 2019). A second RCT showed that an eight-week aerobic exercise intervention, consisting of three 30-45-minute training sessions per week maintained at moderate intensity, produced significantly large improvements in reaction time (η=0.13), and an increase in N2 amplitude (η=0.13) reflecting greater cognitive control processes, compared to placebo exercise (i.e., stretching; (Olson et al., 2017). Finally, another RCT showed that a 12-minute high-intensity interval training produced large improvements in cognitive control (interference cost) immediately post-intervention and 30-

minutes post-intervention when compared to non-exercise controls (η=0.34;(J. S. Lee et al., 2019).

Physical interventions

Repetitive Transcranial Magnetic Stimulation

Four studies examining the impact of rTMS treatment on objective cognitive outcomes in young people with depression were identified (Bloch et al., 2008; Kaur et al., 2019; Pan et al., 2020; Wall et al., 2013). All four studies administered high-frequency rTMS targeted to the L-DLPFC. These studies revealed somewhat mixed findings. Two open-label treatment studies demonstrated improvements in cognitive test performance in young people with severe and mild depression, respectively (Bloch et al., 2008; Wall et al., 2013). Bloch et al. (2008) delivered 14 rTMS sessions (i.e., 10Hz at 80% of resting motor threshold; RMT) once daily over consecutive working days to adolescents with severe, resistant depression. This study showed increased reaction times immediately post-treatment and greater planning skills at one-month post-treatment relative to baseline levels. No changes in other domains, including attention/working memory, memory, or set-shifting were observed. Wall et al. (2013) delivered 30 rTMS sessions (i.e., 10Hz at 120% RMT) provided once daily for 5 days a week over 6-8 weeks to adolescents with resistant depression. Subtle improvements in cognitive function were detected, but were isolated to immediate and delayed verbal memory tasks. No change was found on other objective measures of verbal memory, motor processing speed or cognitive flexibility. Subjective cognition did not improve following rTMS.

The remaining two studies demonstrated no evidence of cognitive improvement following rTMS (Kaur et al., 2019; Pan et al., 2020). In an open-label study, Kaur et al. (2019) delivered 20 rTMS sessions (i.e., 10Hz at 110% RMT) provided once daily for 5 days a week over four weeks to young adults with moderate-to-severe resistant depression. No change on objective measures of verbal learning or memory or executive function (cognitive

flexibility) were found with treatment. Lastly, Pan et al. (2020) conducted a double-blind sham-controlled RCT of rTMS adjunctive with 10mg/day of escitalopram treatment for severe depression, with active rTMS involving daily sessions over seven consecutive days (i.e., 10Hz at 100% RMT). The sham rTMS protocol was identical to the active rTMS protocol with the TMS coil angled away from the scalp at 90°. Escitalopram was commenced on the same day as active or sham rTMS. There was no difference between groups in performance on various executive functioning tasks after one week of treatment.

Acceptability based on consent and attrition rates

Participant consent and attrition rates are presented in Table 4. Only 50% (6/12) of studies reported the total number of participants who were approached and consented for the study. The consent rates varied widely, ranging from 19%-89%. Consent rates were highest for exercise-based interventions (62%-89%) and psychoeducation (81%), when compared with cognitive training (19%) or strategic instruction interventions (33%). None of the rTMS studies reported on consent rates.

[Insert Table 4]

Ten of the 12 studies reported attrition rates during the interventions (i.e., after consent, but prior to end-assessment). When classified according to mode of delivery, attrition during these intervals in behavioural interventions ranged from 0%-38% (median: 8%). Two of the three exercise trials demonstrated the highest rates of attrition (20%-38%). In contrast, attrition from physical interventions (i.e., rTMS) ranged from 11%-22% (median: 16%). Participants who completed the intervention generally completed the final assessment.

Functional outcomes of cognitive enhancing interventions

Of the 12 studies reviewed, only four (33.3%) reported on functional outcomes (Supplementary Table 1). Three of these studies investigated a behavioural intervention (Bryce et al., 2020; Keating et al., 2019; Motter et al., 2019), each revealing moderate

improvements in functioning over the intervention period. Specifically, individuals who undertook 8 weeks of executive functioning/processing speed or verbal training exercises showed moderate improvements in global functioning (Cohen's d = 0.78) measured by the Sheehan Disability Scale (Motter et al., 2019). Subjective social functioning, as measured by the 36-item Short Form Survey (SF-36) improved over a 12-week structured running program (Keating et al., 2019). A medium effect size increase in subjective functioning (Cohen's d = 0.67) was observed over three weeks after receiving a psychoeducational fact sheet on cognitive self-management strategies (Bryce et al., 2020). One study investigating a physical intervention (rTMS) showed no significant changes in clinician-rated (objective) global functioning over the four-week intervention period (Kaur et al., 2019).

Risk of bias

Risk of bias was rated using the RoB2 for the five RCTs only (J. S. Lee et al., 2019; Motter et al., 2019; Neshat-Doost et al., 2013; Olson et al., 2017; Pan et al., 2020). Non-RCT trials were not rated as they were automatically rated as high risk. The final ratings are presented in Figure 2. Overall, while there was no indication of *High Risk* of bias in any domain, all five studies received at least one rating indicating *Some Concern* of bias. Risk was most common in domains related to the randomisation process (n=3, 60%), deviations from the intended intervention (n=2, 40%), and missing outcome data (n=2, 40%). In contrast, there were no concerns in the measurement of the outcome, while bias regarding selection of the reported results was only apparent in one study (20%).

[Insert Figure 2]

Discussion

The aim was to systematically review, synthesise and appraise the evidence regarding the effects and acceptability of cognitive enhancement interventions in young people with depression. Of the 12 studies included, eight were behavioural interventions and four were

physical interventions. No studies examined biochemical interventions. Only five of the included studies were RCTs and most studies involved small samples (all $N<50$), suggesting that cognitive enhancement research in youth depression is relatively new and findings should be considered as preliminary.

In general, behavioural interventions, which included cognitive training, education and strategy-based interventions, and exercise demonstrated enhancement in domains of objective and, in one case subjective, cognitive function. These positive findings were not only limited to single-arm studies; more rigorous RCTs also showed superiority of behavioural cognitive enhancement interventions relative to control conditions (J. S. Lee et al., 2019; Motter et al., 2019; Neshat-Doost et al., 2013; Olson et al., 2017).

Preliminary evidence from two studies showed that intensive computerised cognitive training protocols involving multiple training sessions per week may produce improved cognitive test performance in young people with moderate depression (Alvarez et al., 2008; Motter et al., 2019). Motter et al. (2019) further showed that training in tasks focused on processing speed and executive functioning produced more potent effects on cognition outcomes than verbal skill-based training. Nevertheless, neither study examined the impact of cognitive training relative to an active non-training control. Therefore, it is not possible to delineate training-specific effects from non-specific elements (e.g., general computer stimulation, routine), which contribute significantly to intervention change (Radhakrishnan, Kiluk, & Tsai, 2016). Furthermore, neither study employed a therapist to assist with strategy coaching, which is known to further enhance functional outcomes in adults (Bowie et al., 2020; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). A meta-analysis of nine RCTs involving adults with depression showed moderate-to-large effects of cognitive training on attention, working memory and global cognition (Motter et al., 2016), providing encouragement for further RCTs in youth specifically.

The acceptability of cognitive training in youth with depression remains unclear. While Alvarez et al. (2008) did not report consent rates in their study, the consent rates in Motter et al. (2019) were only 19%, which may suggest that cognitive training is only appealing to a subgroup of young people with depression. Retention rates once enrolled, however, were over 75% in both studies, suggesting cognitive training was acceptable to consenting participants. Focussed attention spent on psychoeducation and motivational enhancement prior to study enrolment might enhance consent rates in studies of cognitive training for depression. Motivational interviewing prior to cognitive training has been shown to increase adherence in adults with schizophrenia, and therefore these techniques may be useful in promoting early engagement in cognitive treatment (Fiszdon, Kurtz, Choi, Bell, & Martino, 2016).

In this review, young people with depression benefited from psychoeducation and strategy-based cognitive interventions involving a therapist (Bryce et al., 2020; McFarland et al., 2017; Neshat-Doost et al., 2013). Bryce et al. (2020) showed that increasing a young person's knowledge about cognitive difficulties in depression and offering simple management strategies in a single-session may be associated with reduced subjective impairment and improved subjective functioning. Addressing perceived deficits is important given that these are related to depression severity (Allott et al., 2020) and may contribute to the avoidance of cognitively effortful tasks, including cognitive training (Bowie, Milanovic, Tran, & Cassidy, 2017; Morey-Nase et al., 2019). The other two RCTs showed that training in strategies for increasing the specificity of episodic recall can improve autobiographical memory and problem-solving in young people with depression (McFarland et al., 2017; Neshat-Doost et al., 2013). These findings are promising given that memory and problem-solving are among the most impaired cognitive domains in youth depression (Goodall et al., 2018). When an individual is able to accurately recall and integrate their past experiences,

they may be more able to develop novel, adaptive solutions to current problems (McFarland et al., 2017), and thus, be more responsive to psychological interventions such as cognitive-behavioural therapy. Importantly, retention in all three psychoeducation and strategy-based studies was high (>90%), suggesting young people may find them relatively more acceptable than more intensive interventions such as cognitive training. Together, these studies show that strategies for addressing specific cognitive difficulties in depression have the potential to benefit people beyond objective cognitive enhancement and may facilitate clinical and functional recovery.

While aerobic exercise (and other physical activity) has been shown to reduce depression symptomatology (Schuch et al., 2016), including in adolescents and young adults (Bailey, Hetrick, Rosenbaum, Purcell, & Parker, 2018), the evidence for an effect of exercise on cognitive functioning in depression has been equivocal. Our review identified three studies that have investigated moderate-to-high intensity aerobic exercise as a cognitive enhancement intervention in youth depression (Keating et al., 2019; J. S. Lee et al., 2019; Olson et al., 2017), and one was associated with improvement in social functioning (Keating et al., 2019). Findings from the two RCTs showed that, compared with control conditions, aerobic exercise produced short-term selective improvements on objective measures of reaction time and executive control in young people with depression (J. S. Lee et al., 2019; Olson et al., 2017). Consent rates to the exercise studies ranged from 62%-89% and retention rates were 62%-100%, suggesting that exercise is generally an acceptable intervention to young people with depression (also see Bailey et al., 2018). While these findings are promising, it remains unclear whether cognitive gains can be achieved with other forms of physical activity (e.g., yoga, dance, resistance-training), a specific 'dose' of activity is required to achieve cognitive gains, or if effects differ between supervised and unsupervised exercise.

Regarding physical interventions, four studies examining the effect of high-frequency rTMS treatment applied to the L-DLPFC on cognitive functioning in youth depression were identified (Bloch et al., 2008; Kaur et al., 2019; Pan et al., 2020; Wall et al., 2013). This literature revealed mixed findings. Two open-label rTMS studies reported improved reaction time and planning skills (but not attention, working memory or cognitive flexibility; Bloch et al., 2008) and, immediate and delayed verbal memory (Wall et al., 2013). These studies are consistent with the adult treatment-resistant depression literature, with numerous RCTs and open-label studies demonstrating improvements in cognitive functions with rTMS treatment (for reviews, see Demirtas-Tatlidede et al., 2013; Serafini et al., 2015). Another open-label study by Kaur and colleagues (2019) found no significant improvement in cognition (i.e., verbal learning/memory or cognitive flexibility, and executive functioning) with rTMS treatment. Similarly, the RCT of active or sham rTMS adjunctive with escitalopram treatment showed no difference in cognitive outcomes (Pan et al., 2020).

Notably, the literature on rTMS treatment for young people with depression is in its infancy, consisting of mostly open-label studies and modest sample sizes. Further, while all the studies utilised high-frequency rTMS, there are considerable differences across other treatment parameters (particularly, intensity, number of sessions, number of pulses), making it difficult to draw conclusions on the effects of rTMS on cognition. In the only RCT identified in this literature by Pan and colleagues (2020), treatment with selective serotonin reuptake inhibitors (SSRIs) was commenced concurrently with rTMS, and thus the unique effects of each treatment on cognition cannot be dissociated. Critically, SSRIs may worsen cognition in the acute phase of treatment (Sayyah, Eslami, AlaiShehni, & Kouti, 2016). This provides one possible explanation for the null finding, together with the low number of rTMS sessions delivered (7 sessions) and short duration of treatment (1 week) compared with a standard rTMS treatment course of 20 sessions over four weeks. Future research using

randomised, sham-controlled designs that are adequately powered are required to elucidate the therapeutic cognitive effects of rTMS treatment in youth with depression.

There were no included studies that could be classified as biochemical in their mode of delivery. There is a vast literature on the benefits of nutrient supplements such as polyunsaturated fatty acids, vitamins, minerals and antioxidants in the treatment of mental disorders (Firth et al., 2019). Improvements in depression have been observed following treatment with omega-3, folate, vitamin D and n-acetyl cysteine (Firth et al., 2019). Nutrients and healthy diets are known to positively impact cognitive performance in healthy people, including adolescents (Kim & Kang, 2017; Spencer et al., 2017), while Western-style high-fat diets have been associated with reduced memory performances in healthy young adults (Attuquayefio, Stevenson, Oaten, & Francis, 2017). Thus, studies investigating the effects of nutrient-based interventions on cognition in young people with depression are encouraged.

Limitations

To keep the size of our search and screening feasible, we excluded cognitive behavioural therapy (CBT), a first-line treatment for depression, from the included interventions. This could have resulted in missing some relevant studies where they measured cognition as a secondary outcome. A recent review has examined the impact of psychotherapies such as CBT on cognitive outcomes in adults with mood disorders (Groves, Douglas, Milanovic, Bowie, & Porter, 2021), but future research should extend this investigation to adolescents. Our age inclusion criterion aimed to comprehensively capture any study that included primarily youth with depression, but this also meant that there were two included studies that had a substantial minority of participants who were much older than 25 years of age (McFarland et al., 2017; Pan et al., 2020). The studies included generally involved small sample sizes, therefore the findings should be considered preliminary only, with larger studies required in future. Finally, potential publication bias must be

acknowledged**,** which may have contributed to the strong preliminary evidence for behavioural interventions (i.e., all eight included studies reported evidence of cognitive improvement). Registration of research protocols and conduct of larger, well-powered and controlled studies may assist in reducing bias (Joober, Schmitz, Annable, & Boksa, 2012).

Future directions

Douglas, Milanovic, Porter, and Bowie (2020) have recently outlined several clinical and methodological considerations for future psychological treatment studies for cognitive impairment in depression. Many of these recommendations could be applied to behavioural, biochemical and physical cognitive-enhancing interventions. One key recommendation is to pre-screen participants to ensure they have objective or subjective cognitive difficulties prior to enrolment. Cognitive impairment was not an inclusion criterion for any of the reviewed studies. This is potentially problematic as including large proportions of young people without cognitive deficits may underestimate the impact of cognitive treatment. Screening for impairment may also increase participant 'buy-in' and optimise consent and retention rates.

Another recommendation is to enrol participants when their mood is stable and relatively euthymic (Douglas et al., 2020). This suggestion may be more specific to cognitively-demanding training-based interventions. Other intervention types may be suitable during acute illness phases. For example, exercise has been proposed as an appropriate behavioural activation intervention in depression (Hetrick et al., 2015), while rTMS is frequently administered to people with persistent depression (Fitzgerald, 2020).

Further, the effects of medication on intervention impact (e.g., effects of SSRIs or benzodiazepines) should be considered (Douglas et al., 2020; Sayyah et al., 2016). With the exception of Olsen et al. (2017) and Alvarez et al. (2008), most studies that recruited young people using psychotropic medication did not account for their potential cognitive effects. Since cognitive deficits in depression predict poorer functioning, it is also recommended that

more studies addressing cognition include functional outcome measures (i.e., activity/participation; (Douglas et al., 2020). We also suggest that subjective cognitive difficulties should be an outcome of focus given the relationship between perceived impairment and depression symptoms, self-esteem/efficacy and functioning in young people (Allott et al., 2020; Morey-Nase et al., 2019). Adequate 'doses' for each type of cognitive enhancement intervention in youth depression, and the extent to which cognitive effects are durable over time, are also poorly understood and warrant further investigation. Regarding brain stimulation techniques, there were no studies identified on youth depression that investigated other forms of non-invasive brain stimulation which have shown promise for cognitive enhancement (Hoy & Fitzgerald, 2010). Exploring the shared or unique mechanisms of cognitive enhancement action is needed to better personalise interventions and maximise their potential benefit.

Conclusion

This is the first systematic review to examine the acceptability and impact of cognitive enhancement interventions on cognitive functioning and functional outcomes for youth aged 12-25 with depression. Only five RCTs using mixed modes of cognitive enhancement were retrieved, precluding meta-analysis to report overall effect sizes. As this review was only able to qualitatively synthesise data from 12 studies, the findings of this review should be interpreted with caution and be used to design well-controlled studies. Nevertheless, in this preliminary field of research, behavioural interventions, including cognitive training, psychoeducation, cognitive strategies and aerobic exercise showed promise as methods of enhancing cognitive function and functional outcomes in young people with depression and appear acceptable based on retention rates. rTMS was the only physical intervention studied, with mixed findings. Further investigation of behavioural,

biochemical (e.g., nutrient-based treatments) and physical cognitively enhancing interventions in youth depression are worthy of research investigation.

Conflict of Interest

None

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Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure 1. PRISMA flow diagram

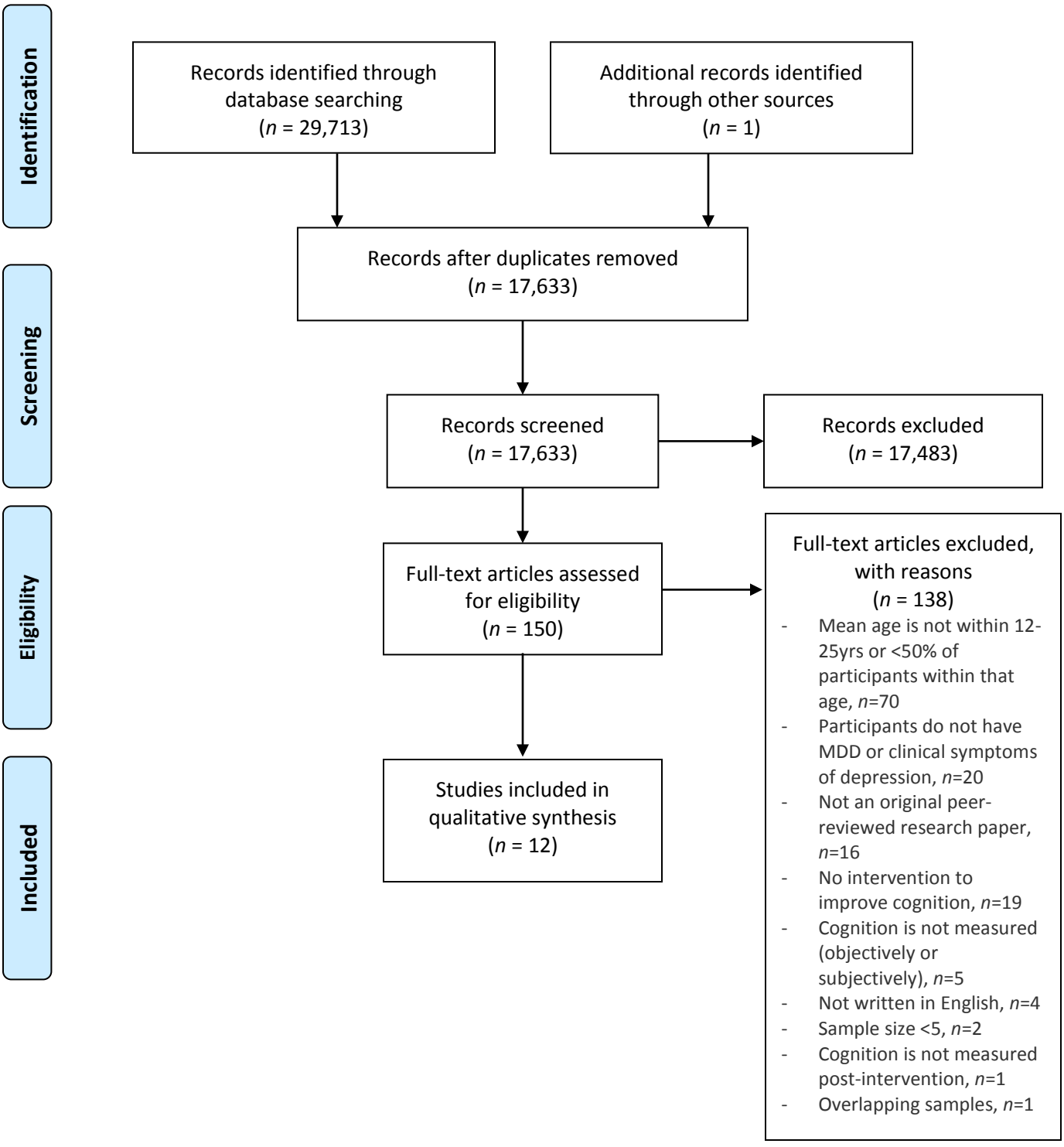

Figure 2. Risk of bias ratings of randomised-controlled trials based on the Cochrane RoB2 tool

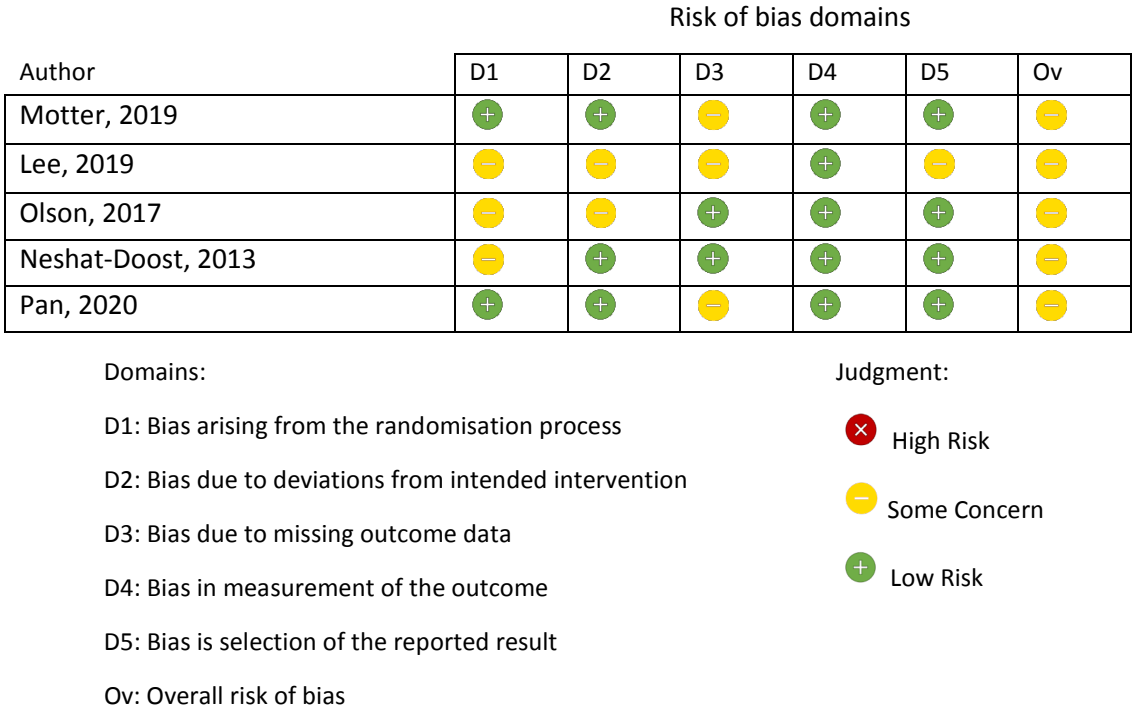

Table 1.

Characteristics of studies included in the systematic review (N=12)

First author, year (country)	Study design	Setting	Sample size, analyzed †	Group (*G*): Mean age, years (SD) §	Age range	Sex, % male	Depression scale: *M* (*SD*)	Depression severity
Behavioural: Cognitive Training								
Alvarez, 2008 (Mexico)	NRT	University students	31	G1: 21.0 (2.9) G2: 23.3 (3.7) G3: 23.8 (2.7)	NR	G1: 40% G2: 50% G3: 36%	G1 BDI: 23.8 (9.4) G2 BDI: 25.8 (10.6) G3 BDI: 23.4 (4.7)	Moderate
Motter, 2019 (USA)	RCT	Community	46	G1: 20.3 (2.8) G2: 21.7 (4.5)	18-29	G1: 28% G2: 29%	G1 BDI: 20.1 (9.3) G1 HDRS: 15.4 (4.9) G2 BDI: 26.4 (13.2) G2 HDRS: 17.2 (6.2)	Moderate
Behavioural: Exercise								
Keating, 2019 (Canada)	Single-arm	Community	18	21.2 (2.4) ∫	16+	17% ∫	BDI: 21.2 (2.4)	Moderate
Lee, 2019 (Canada)	RCT	Inpatient hospital unit	28	15.5 (0.92)	14-17	29%	N/A	N/A
Olsen, 2017 (USA)	RCT	Community	30	G1: 21.0 (1.9) G2: 21.2 (2.2)	18-30	G1: 27% G2: 13%	G1 BDI: 24.5 (11.5) G2 BDI: 24.3 (11.9)	Moderate
Behavioural: Psychoeducation								
Bryce, 2020 (Australia)	Single-arm	Specialised youth mental health clinic	23	19.6 (2.3)	15-25	65%	PHQ-9: 16.1 (6.4)	Moderate-severe
Behavioral: Strategy-based								
McFarland, 2017 (USA)	NRT	Community	22	23.84 (8.75) ¶	18-50	43%	N/A	N/A
Neshat-Doos, 2013 (Iran)	RCT	Charity school students	23	G1: 15.25 (1.66) G2: 15.45 (2.07)	NR	G1: 50% G2: 55%	G1 MFQ: 27.42 (13.63) G2 MFQ: 30.64 (15.47)	Mild
Physical: Brain stimulation								
Bloch, 2008 (Israel)	Single-arm	Inpatient hospital unit and outpatient clinic	9	17.3 (0.83)	16-18	22%	BDI: 40.1 (8.3), CDRS: 71.8 (6.3)	Severe
Kaur, 2019 (Australia)	Single-arm	Specialised youth mental health clinic	16	22.0 (3.9)	18-29	6%	HDRS: 18.9 (6.9)	Moderate-severe
Pan, 2020 (China)	RCT	Hospital	42	G1: 18.14 (3.94) G2: 21.43 (6.79)	13-45	G1: 10% G2: 24%	G1 HAMD: 38.33 (7.93) G1 MADRS: 37.14 (7.18)	Severe

							G2 HAMD: 35.76 (8.85) G2 MADRS: 36.43 (4.87)	
Wall, 2013 (USA)	Single-arm	NR	14	16.2 (1.1) ‡	13.9-17.8	39% ‡	CDRS: NR	Mild

Note: BDI=Beck Depression Inventory (I/II); CDRS=Children's Depression Rating Scale; G*n*=Group number (only reported in studies ≥ experimental/control condition); HDRS=Hamilton Depression Rating Scale; M=Mean; MADRS=Montgomery-Asberg Depression Rating Scale; MFQ=Mood and Feelings Questionnaire; N/A=Not applicable; NR=Not reported; NRT=Non-randomised controlled trial; PHQ-9=Patient Health Questionnaire-9; RCT=Randomised controlled trial; SD=Standard deviation; † Sample size = total number of young people with depression analysed (i.e., healthy controls excluded); §Where possible, data are presented according to individual experimental groups (total sample data only reported when individual group data were not available/applicable); ʃData reported for youth group aged 16-25 presented only (i.e., *n*=12), which represented over 50% of the sample (i.e., *N*=18, Mean age=30.2, *SD*=15.4); ¶ Mean age for total sample of depressed/non-depressed young people (i.e., *N*=47) as depressed only not reported; ǂData from total sample only (*N*=18).

Table 2

Overview of cognitive enhancement interventions and comparison groups used in young people with depression

First author, year	Intervention classification	Experimental intervention(s)	Comparison group (if applicable)
Alvarez, 2008	Behavioural: Cognitive training	**G1:** Cognitive training and antidepressant treatment. **G2:** Cognitive training without antidepressant treatment. Computerised training in both conditions used the "Alcor" training program. Training was conducted for at least 30 minutes, twice per week, for 3 months.	**G3:** Antidepressant treatment only
Motter, 2019	Behavioural: Cognitive training	**G1:** Cognitive training (processing speed and executive domains). **G2:** Cognitive training (verbal domains). Training in both groups was conducted using Peak; a commercially available program). The application consisted of five processing speed/executive function modules or five non-fluency verbal modules, depending on group assignment. All modules scaled in difficulty and provided immediate feedback on performance. Participants could choose which modules they wanted to play and were requested to train for a minimum of 15 minutes per day, five days a week, over the course of eight weeks (i.e., at least 10 hours of training).	N/A
Keating, 2019	Behavioural: Exercise	**G1:** Aerobic exercise. Participants met twice per week in a group, alternating between walking and running. Participants increased their total distance by ~0.5 km per run and increased running intervals by 30–60s per week. The goal was to run 5km by week 12 and then complete a local 5km run as a group. Sessions were facilitated by running coaches and included weekly motivational talks and support from volunteers.	N/A
Lee, 2019	Behavioural: Exercise	**G1:** High intensity interval training. Participants performed 12-minutes of circuit training consisting of 4 full body exercises: jumping jacks, modified burpees, side jumps, and high knees. Exercises were repeated 3 times using a 1:1 work-to-rest ratio (i.e., 30s work, 30s rest). Participant heart rate was monitored throughout the exercise. Participants were encouraged to keep their heart rate ≥80% of their predicted maximum.	**G2:** Non-exercise control (i.e., read magazines)

Olsen, 2017	Behavioural: Exercise	**G1:** Aerobic exercise. Participants attended three 30-45-minute aerobic training sessions for 8 weeks. Exercise consisted of up to 45 min of continuous steady-state exercise performed on a treadmill or cycle ergometer at a prescribed moderate-intensity corresponding to 40–65% of heart rate reserve, which was determined from heart rate recorded during the initial baseline fitness test.	**G2:** Placebo exercise. Participants attended three 30-45-minute light intensity stretching sessions for 8 weeks. Stretching targeted major muscle groups and was performed while sitting and standing with a rest period.
Bryce, 2020	Behavioural: Psychoeducation	**G1:** Cognition fact sheet. Participants were presented with a two-page fact sheet about cognitive difficulties in depression and simple compensatory strategies. The fact sheet was delivered by their case manager who directed them to key sections as part of a regular therapy appointment.	N/A
McFarland, 2017	Behavioural: Episodic specificity induction interview	**G1:** Episodic specificity induction interview. Participants watched a video and were asked specific probing questions, which required participants to retrieve and discuss specific episodic details about the material.	**G2:** Control interview. Participants watched a video and asked questions about their impressions or general aspects of the material.
Neshat-Doos, 2013	Behavioural: Memory specificity training	**G1:** Memory Specificity Training (MEST). Training package conducted by senior clinical psychologists, which consisted of five weekly 80-minute group sessions. Words used in the training were different from those used in assessment measures. No further information was reported.	**G2:** No-treatment control.
Bloch, 2008	Physical: Brain stimulation	**G1:** High-frequency rTMS to the L-DLPFC. Treatment involved 14 sessions provided once daily over consecutive working days. Site of stimulation was located using the 5cm method. At each session, 10 Hz rTMS was provided at 80% RMT for 20 trains of 2s with an inter-train interval of 58s.	N/A
Kaur, 2019	Physical: Brain stimulation	**G1:** High-frequency rTMS to the L-DLPFC. Treatment involved 20 stimulation sessions provided once daily for 5 days a week over four weeks. Site of stimulation was located using structural MRI-guided neuronavigation. At each session, 10 Hz rTMS was provided at 110% RMT for 50 trains of 5 secs with an inter-train interval of 25s.	N/A
Pan, 2020	Physical: Brain stimulation	**G1:** High-frequency rTMS to the L-DLPFC and escitalopram. rTMS treatment involved 7 sessions over consecutive days. Site of stimulation was located using structural MRI-guided neuronavigation. At each	**G2**: Sham rTMS and escitalopram. Subjects received the same number of stimuli with parameters identical

		session, 10Hz rTMS was provided at 100% RMT for 120 trains of 5s with an inter-train interval of 15s (i.e. 6000 pulses). An escitalopram dose of 10mg/day was commenced on the first day of active rTMS.	to those in the active group, with the coil angled 90° away from the participant, as per standard sham procedure. An escitalopram dose of 10mg/day was commenced on the first day of active rTMS.
Wall, 2013	Physical: Brain stimulation	**G1:** High-frequency rTMS to the L-DLPFC. Treatment involved 30 sessions provided once daily for 5 days a week over 6-8 weeks. Site of stimulation was located using either structural MRI-guided neuronavigation or the 5cm method. At each session, 10Hz rTMS was provided at 120% RMT for 3000 pulses over 4s trains with an inter-train interval of 26s.	N/A

Note: G*n*=Group number (only reported in studies ≥ experimental/control condition); Hz=Hertz; Km=Kilometre; L-DLPFC=Left dorsal lateral prefrontal cortex; MRI=Magnetic reasoning imaging; N/A=Not applicable; rTMS=Repetitive transcranial magnetic stimulation; RMT = resting motor threshold; s=Seconds.

Table 3

Overview of cognitive outcome data for each study

First author, year	**Cognitive outcome**	**Baseline**			**Post-intervention**			**Summary of main findings**
Alvarez, 2008		CT+AD	CT only	AD only	CT+AD	CT only	AD only	
	WAIS Verbal IQ, Mean (*SD*)	101.9 (8.2)	98.1 (6.3)	97.8 (9.7)	116.5 (11.5)	110.0 (6.5)	96.5 (9.2)	CT+AD and CT, but not AD alone, were associated with significant improvements in WAIS Verbal IQ, Performance IQ and Total IQ. CT+AD and CT produced comparable cognitive improvements.
	WAIS Performance IQ, Mean (*SD*)	95.3 (14.5)	97.7 (12.1)	103.4 (11.4)	109.5 (12.8)	110.0 (13.7)	101.1 (10.3)	
	WAIS Total IQ, Mean (*SD*)	98.2 (9.8)	97.7 (8.9)	100.3 (10.5)	111.4 (9.4)	111.0 (8.2)	98.4 (9.6)	
Motter, 2019		PS/EF CT	Verbal CT		PS/EF CT	Verbal CT		
	WAIS-IV Coding, Mean (*SD*)	78.0 (16.6)	74.9 (13.0)		NR	NR		EF/PS CT produced significantly greater improvement in WAIS-IV Coding and D-KEFS Trails 4 compared to the Verbal CT (*d*=0.45 and 0.40, respectively). Mean change in all primary outcomes measure significantly improved over time (except CWI CNR and Inhibition). The effect sizes for WAIS-IV Coding and D-KEFS Letter fluency, Trails 2 and Trails 4 were large (i.e., *d*=0.71-0.97). When models were re-run with one group selected at a time, EF/PS CT produced significant improvement in all cognitive outcome measures over time including CWI CNR and Inhibition (i.e., *d*=0.41-0.95).
	D-KEFS Trails 2 Number sequencing, Mean (*SD*)	30.0 (9.6)	28.8 (9.5)		NR	NR		
	D-KEFS CWI CNR, Mean (*SD*)	12.0 (1.7)	12.02 (2.1)		NR	NR		
	D-KEFS Letter Fluency, Mean (*SD*)	38.0 (10.4)	38.9 (10.7)		NR	NR		
	D-KEFS Trails 4 Number/Letter Sequencing, Mean (*SD*)	69.1 (23.5)	68.3 (25.8)		NR	NR		
	D-KEFS CWI Inhibition, Mean (*SD*)	47.7 (10.4)	46.8 (10.8)		NR	NR		
Keating, 2019		Running Group						
	Recall trials 1–5, Mean (*SD*)	53.2 (7.6)			50.3 (9.4)			The *Team Unbreakable group* (a twelve-week structured running group) was

	CVLT-II Short delay free recall, Mean (*SD*)	11.6 (3.2)	12.1 (2.8)	associated with significant improvement on 2 (of 18) cognitive tests (i.e. WAIS-IV Digit Span Forward and Stroop Colour). This data was used to conclude that aerobic exercises was associated with improved processing speed and working memory.
	CVLT-II Short delay cued recall, Mean (*SD*)	12.2 (2.2)	12.6 (2.5)	
	CVLT-II Long delay free recall, Mean *(SD*)	12.2 (3.4)	11.6 (4.0)	
	CVLT-II Long delay cued recall, Mean (*SD*)	12.5 (2.8)	12.6 (2.5)	
	CVLT-II Total repetitions, Mean (*SD*)	3.0 (3.5)	1.4 (1.6)	
	CVLT-II Total intrusions, Mean (*SD*)	1.0 (1.9)	0.7 (1.7)	
	WAIS-IV Digit Span Total score, Mean (*SD*)	28.6 (5.2)	29.8 (6.0)	
	WAIS-IV Digit Span Forward, Mean (*SD*)	10.7 (2.6)	11.8 (2.7)	
	WAIS-IV Digit Span Backward, Mean (*SD*)	8.7 (2.4)	8.6 (2.3)	
	WAIS-IV Digit Span Sequential, Mean (*SD*)	8.4 (2.0)	8.6 (2.5)	
	Stroop Word, Mean (*SD*)	90.2 (10.3)	90.5 (12.2)	
	Stroop Colour, Mean (*SD*)	67.2 (10.7)	71.9 (10.8)	
	Stroop CWI, Mean (SD)	44.9 (8.2)	46.3 (10.4)	

	CANTAB Motor screening test (% similar correct), Mean (*SD*)	40.5 (20.5)		44.9 (20.1)		
	CANTAB Delayed match to sample (% matches correct), Mean (*SD*)	86.0 (5.4)		85.4 (11.7)		
	CANTAB Spatial recognition memory (% matches correct), Mean (*SD*)	66.4 (17.8)		68.2 (14.7)		
	CANTAB Paired associate learning (number of trials), Mean (*SD*)	10.6 (2.8)		10.3 (2.7)		
	CANTAB Rapid visual processing (% correct), Mean (*SD*)	88.4 (13.2)		89.3 (8.6)		
Lee, 2019		HIIT (exercise)	Control (magazines)	HIIT (exercise)	Control (magazines)	
	SCWT Congruent reaction time ms, Mean (*SD*)	756 (146)	772 (111)	757 (134)	762 (127)	There was a significant interaction between condition and time for the SCWT interference cost measure (p< .001, η^2=.34). Interference Cost=Reaction time of incongruent task−reaction time of neutral task. The 12-minute HIIT exercise intervention produced significantly reduced interference cost immediately after 12-minute HIIT exercise (Mean difference=78.8±14.91, p<.001) and 30-
	SCWT Incongruent reaction time ms, Mean (*SD*)	994 (146)	983 (134)	895 (119)	990 (94)	
	SCWT Neutral reaction time ms, Mean (*SD*)	796 (139)	797 (114)	783 (106)	802 (79)	

	SCWT Interference cost ms, Mean (*SD*)	198 (60)	185 (54)	112 (73)	187 (66)	min post-exercise (Mean difference= 59.6±15.14, *p*=.001) when compared to control. Accuracy did not differ by time or condition. This data was used to conclude that HIIT exercise was associated with increased inhibitory control (via response efficiency rather than overall ability to response).
	SCWT Accuracy ms, Mean (*SD*)	93 (5.4)	93 (5.5)	92 (4.8)	94 (4.0)	
Olsen, 2017		Aerobic exercise	Placebo exercise	Aerobic exercise	Placebo exercise	
	Modified Flanker Task: % congruent response accuracy, Mean (95% CI)	93.3 (90.2-96.5)	92.8 (89.6-95.9)	94.6 (91.3-97.8)	92.5 (89.3-95.8)	The 8-week AE treatment was associated reduction in reaction time from pre-to-post treatment when compared to placebo exercise. This was driven by lowered response times to challenging incongruent trials. Examination of the Time x Condition interaction revealed a significant reduction in RT for the AE group (73.45ms) relative to an increase in the PE group (13.76ms). A parallel increase in N2 amplitude to incongruent flanker task trials was also observed, reflecting an increase in cognitive control processes. No significant Time x Condition interactions was observed for response accuracy.
	Modified Flanker Task: % incongruent response accuracy, Mean (95% CI)	89.4 (82.8-95.9)	91.6 (85.1-98.2)	90.9 (84.2-97.6)	87.8 (81.1-94.5)	
	Modified Flanker Task: % congruent reaction time, Mean (95% CI)	598.5 (529.0-667.9)	556.4 (486.9-625.8)	554.5 (447.7-661.3)	596.9 (490.1-703.7)	
	Modified Flanker Task: % incongruent reaction time, Mean (95% CI)	752.1 (619.6-884.6)	694.6 (562.1-827.2)	649.2 (510.9-787.4)	681.7 (543.4-819.9)	
Bryce, 2020		Psychoeducation (fact sheet)				
	PDQ-D, Mean (*SD*)	44.6 (12.1)		41.3 (11.0)		Cognition fact sheet delivery produced a significant reduction in perceived cognitive difficulties over time (*d*=0.47)
McFarland, 2017		Episodic specificity induction interview	General interview (control)	Episodic specificity induction interview	General interview (control)	

	MEPS: Relevant steps, Mean (*SD*)	-	-	12.4 (4.0)	8.6 (2.5)	Participants with depression receiving the episodic specificity induction interviews generated significantly more relevant steps (*M*=12.4; *SD*=4.0) compared to the general impressions interview (*M*=8.6; *SD*=2.5), *p*<.001, *d*=1.14. Participants also generated significantly more internal memory details following the episodic specificity induction (*M*=23.0; *SD*=10.4) compared to the general impressions interview (*M*=13.6; *SD*=6.01), *p*<.001, *d*=1.11. Participants also generated significantly more internal details following the episodic specificity induction (*M*=21.9; *SD*=8.8) compared to the general impressions interview (*M*=17.3; *SD*=7.8), *p*<.001, *d*=0.55.
	Memory task Internal details, Mean (*SD*)	-	-	23.0 (10.4)	13.6 (6.01)	
	Imagination task: Internal details, Mean (*SD*)	-	-	21.9 (8.8)	17.3 (7.8)	
Neshat-Doos, 2013		MEST	No-treatment control	MEST	No-treatment control	
	AMT Specific, Mean (*SD*)	0.63 (0.15)	0.61 (0.51)	0.95 (0.07)	0.65 (0.15)	There was a significant Group × Time interaction for AMI Specific outcome, *p*<.01, η_p^2=.32. Further analysis revealed that MEST retrieved a significantly greater proportion of specific memories than the control group (*d*=2.56). In addition, MEST provided a significantly greater proportion of specific memories at post-training than at pre-training, *p*<.001, *d*=2.14. These findings were not related to changes in depression symptoms. The findings were used to conclude that MEST can improve auto-biographical memory performance in people with depression symptoms.
	AMT Categoric, Mean (*SD*)	0.23 (0.61)	0.29 (0.20)	0.03 (0.05)	0.23 (0.17)	
	AMT Extended, Mean (*SD*)	0.14 (0.10)	0.10 (0.09)	0.02 (0.03)	0.12 (0.19)	
Bloch, 2008		Active rTMS				
	CANTAB Memory	NR		NR		Active TMS treatment produced improvement on CANTAB reaction time
	CANTAB Attention	NR		NR		

	CANTAB Set-shifting	NR		NR		immediately after treatment cessation and more so at one-month post-treatment, relative to baseline (p<.01). Planning was improved at one-month post treatment only relative to baseline (p<.05). There was no change on CANTAB measures of memory, attention, set-shifting or working memory (i.e. p>0.05)
	CANTAB Planning	NR		NR		
	CANTAB Working memory	NR		NR		
	CANTAB Reaction time	NR		NR		
Kaur, 2019		Active rTMS				
	TMT-B z-score, Mean (*SD*)	-0.4 (1.8)		-0.2 (1.0)		Active rTMS treatment was not associated with any improvement in executive function (TMTB) or learning and memory (RAVLT) from pre-post treatment (i.e. all p>0.05).
	RAVLT total z-score, Mean (*SD*)	0.3 (1.3)		0.2 (1.2)		
	RAVLT delay z-score, Mean (*SD*)	0.2 (1.0)		0.2 (1.2)		
Pan, 2020		Active rTMS	Sham rTMS	Active rTMS	Sham rTMS	
	WCST Total number of trials, Mean (*SD*)	47.33 (1.39)	47.15 (2.54)	-1.53 (3.47) †	-1.38 (2.63) †	Active rTMS treatment did not produce any change on neuropsychological assessment compared to sham rTMS after 1 week of treatment (all p>0.05).
	WCST Number of correct trials, Mean (*SD*)	31.86 (7.76)	30.60 (7.55)	2.18 (4.49) †	4.75 (7.44) †	
	WCST Total number of errors, Mean (*SD*)	15.48 (8.32)	16.05 (8.87)	-3.71 (5.28) †	-4.81 (9.47) †	
	WSCT Number of perseverative errors, Mean (*SD*)	9.57 (5.39)	10.70 (5.67)	-1.47 (4.16) †	-3.31 (6.32) †	
	WSCT Number of random errors, Mean (*SD*)	5.90 (3.43)	5.55 (4.58)	-2.24 (2.44) †	-1.50 (4.38) †	
	WSCT categories, Mean (*SD*)	4.24 (1.64)	3.95 (1.73)	0.59 (1.12) †	0.44 (2.10) †	
	CPT 1, Mean (*SD*)	10.19 (1.72)	10.95 (0.22)	0.76 (2.05) †	-0.94 (3.23) †	
	CPT 2, Mean (*SD*)	8.29 (2.03)	9.05 (2.33)	0.47 (2.63) †	0.56 (2.50) †	
	CPT 3, Mean (*SD*)	10.85 (1.49)	10.55 (2.09)	0.47 (1.55) †	0.50 (2.92) †	

	SCWT A, Mean (*SD*)	42.52 (7.46)	42.90 (8.52)	-1.76 (4.80) †	0.31 (11.46) †	
	SCWT B, Mean (*SD*)	72.86 (11.26)	68.70 (14.12)	-5.29 (23.60) †	0.13 (13.91) †	
	SCWT C, Mean (*SD*)	120.00 (23.45)	115.25 (21.87)	-17.17 (23.60) †	-8.63 (13.91) †	
	SCWT Interference, Mean (*SD*)	47.05 (17.72)	47.83 (17.25)	-12.13 (20.57) †	-9.64 (12.07) †	
Wall, 2013		Active rTMS				
	CAVLT Immediate memory scale (all participants), Mean (*SD*)	98.6 (NR)		113.1 (NR)		Active rTMS produced subtle but statistically significant improvement in CAVLT immediate memory and delayed recall when including all participants (p <.001, d=0.81; p=.03, d=0.33 respectively). All other learning and memory indices remained stable. No significant changes were noted on the D-KEFS Trail Making Test indices from baseline to treatment completion. No subjective changes in memory, cognitive functioning, or attention were reported by any participant or their families.
	CAVLT Level of learning (all participants), Mean (*SD*)	98.4 (NR)		106.2 (NR)		
	CAVLT Interference (all participants), Mean (*SD*)	104.4 (NR)		109.2 (NR)		
	CAVLT Immediate recall (all participants), Mean (*SD*)	98.5 (NR)		100.2 (NR)		
	CAVLT Delayed recall (all participants), Mean (*SD*)	94.7 (NR)		102.3 (NR)		
	D-KEFS TMT Number sequencing (all participants), Mean (*SD*)	10.1 (NR)		11.1 (NR)		

	D-KEFS TMT Letter sequencing (all participants), Mean (*SD*)	10.3 (NR)	11.3 (NR)	
	D-KEFS Composite score (all participants), Mean (*SD*)	10.7 (NR)	11.8 (NR)	

Note: Alvarez et al. provided intermediate data (i.e. cognitive outcome data collected between baseline and post-intervention) however this is not presented here. Lee et al. provided follow up data (i.e. 30-minutes post intervention) however this is not presented here. AD=Antidepressant medication; AE=Aerobic exercise; AMT=Autobiographical Memory Test; CANTAB=Cambridge Neuropsychological Test Automated Battery; CI=Confidence interval; CNR=Combined Naming Reading; CPT=Continuous Performance Test; CT=Computerised training; CVLT-II=California Verbal Leaning Test, Second Edition; CWI=Colour Word Interference; *d*=Cohen's *d;* D-KEFS=Delis-Kaplan Executive Function System; HIIT=High intensity interval training; IQ=Intellectual Quotient; M=Mean; MEST=Memory Specificity Training; RAVLT=Rey Auditory Verbal Learning Test; ms=Millisecond; NR=Not reported; PDQ-D=Perceived Deficits Questionnaire-Depression; PS/EF=Processing speed/executive function; rTMS=repetitive transcranial magnetic stimulation; s=Seconds; SCWT=Stroop Colour Word Test; MEPS=Means-Ends Problem Solving Task; SD=Standard deviation; CAVLT=Children's Auditory Verbal Learning Test; TMT=Trail Making Test Part; WAIS-IV=Wechsler Adult Intelligence Scale, Fourth Edition; WCST=Wisconsin Card Sorting Test; η^2=Eta square; η_p^2=Partial eta square. † Pan et al. (2020) post-intervention data represents 'change from mean' (i.e., not M and SD).

Table 4

Summary of attrition rates for reviewed studies

First author, year	Experimental intervention	Approached, *n*	Consented, *n*	Enrolment (i.e., consented /approached), %	Pre-intervention attrition *n* (% of total consented remaining)	During intervention attrition, *n* (% of total consented remaining)	Post-intervention attrition, *n* (% of total consented remaining)
Alvarez, 2008	Behavioural: Cognitive training	NR	34	NR	31 (91)	31 (91)	31 (91)
Motter, 2019	Behavioural: Cognitive training	248	46	19	46 (100)	NR	35 (76)
Keating, 2019	Behavioural: Exercise	42	26	62	26 (100)	26 (100)	18 (69)
Lee, 2019	Behavioural: Exercise	42	35	83	30 (86)	28 (80)	28 (80)
Olsen, 2017	Behavioural: Exercise	56	50	89	40 (80)	31 (62)	30 (60)
Bryce, 2020	Behavioural: Psychoeducation	31	25	81	23 (92)	23 (92)	23 (92)
McFarland, 2017	Behavioural: Episodic specificity induction interview	NR	23	NR	22 (96)	22 (96)	22 (96)
Neshat-Doos, 2013	Behavioural: Memory specificity training	70	23	33	23 (100)	23 (100)	23 (100)
Bloch, 2008	Physical: Brain stimulation	NR	9	NR	9 (100)	8 (89) †	9 (100) †
Kaur, 2019	Physical: Brain stimulation	NR	21	NR	17 (81)	NR	16 (76)
Pan, 2020	Physical: Brain stimulation	NR	50	NR	44 (88)	42 (84)	33 (66)
Wall, 2013	Physical: Brain stimulation	18	18	NR	18 (100)	14 (78)	14 (78)

Note: *n*=participant number. NR=Not reported. †One participant in Bloch et al. (2013) ceased rTMS treatment after 10 sessions (33% of planned treatment), but was included in the final analysis.