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Cognitive boosting interventions for impulsivity in addiction: a systematic review and meta-analysis of cognitive training, remediation and pharmacological enhancement

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ABSTRACT

Aims To evaluate and compare the effects of three cognitive boosting intervention approaches (computerised cognitive training, cognitive remediation and pharmacological cognitive enhancers) on measures of impulsive action and impulsive choice. **Design** Systematic review and meta-analysis of publications that reported original controlled trials of cognitive boosting interventions. **Setting** Studies conducted anywhere in the world. No language restrictions were applied. **Participants** Treatment-seeking adults with substance use disorder or gambling disorder. **Measurements** Our primary outcome was a reduction in impulsive action or choice on a validated cognitive measure post-intervention. We assessed risk of bias using the Cochrane Collaboration tool and determined pooled estimates from published reports. We performed random-effects analyses for impulsive action and impulsive choice outcomes and planned moderator analyses. **Findings** Of 2204 unique studies identified, 60 were included in the full-text review. Twenty-three articles were considered eligible for inclusion in the qualitative synthesis and 16 articles were included in our meta-analysis. Articles eligible for pooled analyses included five working memory training (computerised cognitive training) studies with 236 participants, three goal management training (cognitive remediation) studies with 99 participants, four modafinil (cognitive enhancer) studies with 160 participants and four galantamine (cognitive enhancer) studies with 131 participants. Study duration ranged from 5 days to 13 weeks, with immediate follow-up assessments. There were no studies identified that specifically targeted gambling disorder. We only found evidence for a benefit on impulsive choice of goal management training, although only in two studies involving 66 participants (standardised mean difference (SMD) = 0.86; 95% CI = 0.49–1.23; $P = 0.02$; $I^2 = 0\%$, $P = 0.95$). **Conclusion** Cognitive remediation, and specifically goal management training, may be an effective treatment for addressing impulsive choice in addiction. Preliminary evidence does not support the use of computerised cognitive training or pharmacological enhancers to boost impulse control in addiction.

Keywords Cognitive remediation, cognitive training, gambling disorder, impulsivity, meta-analysis, pharmacological enhancers, substance use disorder, systematic review, treatment.

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INTRODUCTION

Impulsivity, the tendency to act without sufficient consideration of potential consequences, is a cardinal feature of substance and gambling addictions [1,2]. Poor impulse control is a strong predictor of both the development and escalation of addictive behaviours [3]. Further, heightened impulsivity is related to clinical outcomes including poor treatment retention, higher relapse rates and poor quality of life [4–7]. There is, therefore, a key need to compile

evidence of interventions that effectively improve impulse control in the context of addiction treatment.

Cognitive neuroscience categorises impulsivity into two processes: action and choice [2]. Impulsive action is the ability to inhibit a prepotent motor response; it is frequently measured using go/no-go and stop-signal test (SST) paradigms. Impulsive choice is the preference for smaller immediate rewards over larger delayed rewards; it is frequently assessed with delay discounting tasks, the Iowa gambling task and the balloon analogue risk task.

Neurocognitive models propose that drug and gambling rewards drive impulsive behaviours via dysregulation of monoaminergic, glutamatergic and orexin systems in prefrontal-striatal circuits [8,9]. However, there is accumulating evidence to suggest that impulsivity can be counteracted by treatments that focus on enhancing deliberative behavioural control, which in turn, may help to reverse the addiction process and improve clinical outcomes [10,11]. Three promising avenues for cognitive improvement as a component of addiction treatment include computerised cognitive training (CCT), cognitive remediation (CR) and pharmacological enhancement (cognitive enhancers [CEs]).

CCT uses software to train specific cognitive processes, with the goal of enhancing their functioning [10,12]. A popular modality is working memory training (WMT), which involves practise with tasks where participants have to hold 'on line' series of numbers or shapes with increasing difficulty [13]. Other modalities include approach avoidance training and inhibitory control training, where the goal is to retrain automatic response biases [11]. Although CCT has demonstrated success in improving performance on the training tasks themselves, there is inconsistency around treatment-related gains (i.e. ability to transfer skills to other tasks.) [12]

CR focuses on training higher-order cognitive processes through meta-cognitive principles and practise of cognitive strategies in real-life scenarios to enhance generalisation [14]. A promising modality is goal management training (GMT), which aims to strengthen executive (i.e. deliberative) control [15]. The goal-based nature of this intervention appears to be effective at remediating impulsive choice [16] and has demonstrated cognitive benefits across a number of studies in non-addiction populations [17]. Other CR modalities include a mixture of cognitive rehabilitation techniques, typically derived from programs applied in brain injury recovery [18].

CEs are pharmacological drugs shown to be beneficial for cognition [19]. CEs include stimulants that act on the dopamine, noradrenaline and orexin systems and acetylcholine-esterase inhibitors. Prefrontal control of impulsivity relies on the function of these neuromodulators [20], but their availability and turnover rates are disrupted in addiction [21]. Findings from translational research suggest that CEs may be effective in rescuing prefrontal control over impulsive actions and choices [22,23].

Previous reviews have assessed the effectiveness of neuropsychological interventions for decision-making in substance and behavioural addiction [24], evaluated potential benefits of CEs [20] and reviewed the general cognitive benefits of CR in gambling disorder [25]. However, no previous studies have systematically reviewed and compared the efficacy of different cognitive boosting intervention approaches for impulse control, nor included trials from both the substance use and gambling fields. By reviewing multiple approaches and addictions, we can also gain a better understanding of key moderators, such as intervention modality and intensity, primary drug/behaviour of concern and treatment settings.

In this systematic review and meta-analysis, we aimed to:

1 Compare the effects of cognitive-boosting interventions (i.e. CCT, CR and CEs), relative to control interventions, on measures of impulsive action and choice.
2 Compare the effects of each of the cognitive-boosting intervention modalities, relative to control, on measures of impulsive action and choice.
3 Determine if intervention intensity, type of addiction and treatment setting moderate the effects of cognitive-boosting interventions on measures of impulsive action and choice.
4 Quantify the risk of bias in the studies selected in the meta-analyses.

METHODS

We performed a systematic review and meta-analysis in accordance with the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [26]. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO ID 140788) before commencement.

Search strategy and selection criteria

Studies were assessed for eligibility according to pre-determined population, intervention, comparison, outcomes and study design criteria (PICOS). Participants were adults, age 18 years and over, who were seeking treatment for substance use disorder or gambling disorder and did not have a current or past history of a co-morbid psychotic disorder, bipolar disorder, acquired brain injury, other neurological disorder or intellectual disability. Interventions included CR, CCT or CEs, applied in an addiction treatment context. Studies examining the acute effects of treatment (i.e. single intervention and testing session) were excluded. Comparisons included treatment as usual, placebo and

interventions without an active training component. Outcome variables were cognitive measures of impulsivity, with pre- and post-intervention assessments. Although randomised clinical trials provide the most reliable estimates of effect, because of the small number of anticipated studies, we also included pilot studies, which included non-randomised and yoked designs. If data were missing, we contacted the corresponding author twice within a 3-week period.

References for this review were identified through searches of PubMed, Scopus and PsycINFO for articles published before 31 December 2019. An example search term was 'alcohol use AND cognitive training (or specific trainings, e.g. cognitive bias modification, working memory training) AND impulsivity (or specific tasks e.g. go-no-go/information sampling/delay discounting)'. Details of all search terms are included in the Supporting information (Table S1). Studies retrieved from these searches and relevant references identified in review articles were considered for inclusion. Studies were not restricted to those published in English.

Two authors (A.C.A. and A.H.R.) screened the articles for inclusion using an unblinded, standardised, systematic approach, using the online software Covidence. Disagreements between these reviewers were resolved by consultations with a senior author (A.V.G.).

Data analysis

We completed a data extraction form developed by the investigators for eligible studies. Extracted information included country, number of participants, baseline characteristics, study design, type of addictive disorder, treatment modality and specific intervention (e.g. CR, CCT or CE and then treatment/drug name), treatment intensity (including number of active intervention days, duration of CR or CCT sessions [in minutes] and CE dose), category of impulsivity (impulsive action or impulsive choice), assessment outcomes and effect sizes. All included articles reported unique data that had not been reported in another eligible study.

All analyses were conducted using R v3.6.2 [27]. Hedges' g effect sizes were used as the primary effect size of interest. We calculated the mean gain (pre-post) between active (experimental) and comparator groups using the 'esc' package [28]. In three CE studies that included multiple assessment points following the baseline assessment [29–31] we used the baseline and the last assessment before medication 'wash-out' to calculate the effect size. Where means and standard deviations were not provided, we calculated the effect size through t statistics, if reported. For studies that reported different pre- and post-intervention sample sizes, the smaller n was used to calculate the effect. A positive Hedges' g value reflected a greater improvement in impulsivity (less impulsive) for the experimental relative to the comparator group. When multiple impulsivity outcomes were provided by authors for either impulsive action or impulsive choice, we aggregated effects using the 'MAd' package [32] (see Supporting information Table S3). When aggregating effects, we used an assumed correlation of 0.5 between aggregated outcomes, but sensitivity analyses using different assumed correlations (0.5, 0.8 and 1.0) found this decision had no influence on the aggregated estimate for each study. All meta-analyses were conducted using the 'dmetar' package [33]. Specifically, we used a random effects meta-analysis model and we pooled effects when there were at least two studies that could be grouped. If a treatment group for a particular study received secondary aspects of another intervention modality (e.g. WMT and attentional bias modification), we conducted a sensitivity analysis to rule out the possibility that mean effects were driven by this particular multifaceted intervention (i.e. replicated the meta-analysis of WMT after removing the WMT and attentional bias modification study). Separate analyses were conducted for impulsive action and impulsive choice. The I^2 statistic and its associated Cochrane's Q test P value were reported to evaluate heterogeneity. Publication bias was assessed using Egger's test of the intercept, using 'dmetar' and through visual assessment of funnel plots, using 'meta', to determine the presence of asymmetry (Supporting information Fig. S1).

We used meta-regression to assess the effects of moderators that were selected a priori, including intervention modality, type of addiction (primary substance), treatment setting (inpatient or outpatient) and the intensity of treatment (including session duration for CCT and CR, CE medication dose and the number of active intervention days). We performed mixed effects meta-regressions using 'dmetar' (for categorical moderators) and 'meta' (for continuous moderators) [33,34]; and tested any overall moderator effects using χ^2 statistic (for categorical moderators) or t statistic (continuous moderators). Any significant categorical moderators were explored using pairwise comparisons.

Each article was assessed for risk of bias by two authors (A.C.A. and A.H.R.) using the Cochrane Collaboration's tool for assessing risk of bias (RoB2) [35]. Risk of bias was assessed across five domains, including bias arising from the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Where trials were pre-registered on a clinical trials registry, they were assessed for data analysis intentions. Of the contacted authors, three responded providing further pre-specified analysis plans [18,36,37]. Each study was assessed as

having low risk, unclear risk or high risk across the five domains.

RESULTS

Screening and study characteristics

The literature search yielded 3340 articles. Following the removal of duplicates, 2204 articles were retained for title and abstract screening. Of these articles, 23 were identified as eligible and included in the review (Fig. 1). All eligible full-text papers were published in English. Full-text inter-rater reliability between the two investigators (A.C.A. and A.H.R.) was .90. Three articles did not provide sufficient information for effect size calculations and authors could either not be reached or did not respond to requests for further information. Sixteen full-text studies are included in the meta-analysis. Two of these studies included more than one intervention type (e.g. CR and CCT). Group analyses were able to be performed for four interventions; GMT, WMT, modafinil and galantamine.

Summary of included studies

Table 1 displays a summary of the study methodologies. Participants comprised individuals seeking treatment for alcohol, stimulants, opioids, cannabis and polysubstance use disorders. Intervention modalities varied within each category. Five of the CCT studies delivered WMT, one used cognitive function training and one used Serious Games (e.g. gamified supermarket shopping). Two of the CR studies used GMT, one developed a unique CR program and a fourth used a mixture of brain injury rehabilitation interventions, including GMT. Of the CE interventions, four administered modafinil, four administered galantamine and single studies trialled N-acetylcysteine, minocycline, guanfacine and rivastigmine. Control groups were largely equivalent within GMT (CR), with all studies including 'treatment as usual' (i.e. counselling and relapse

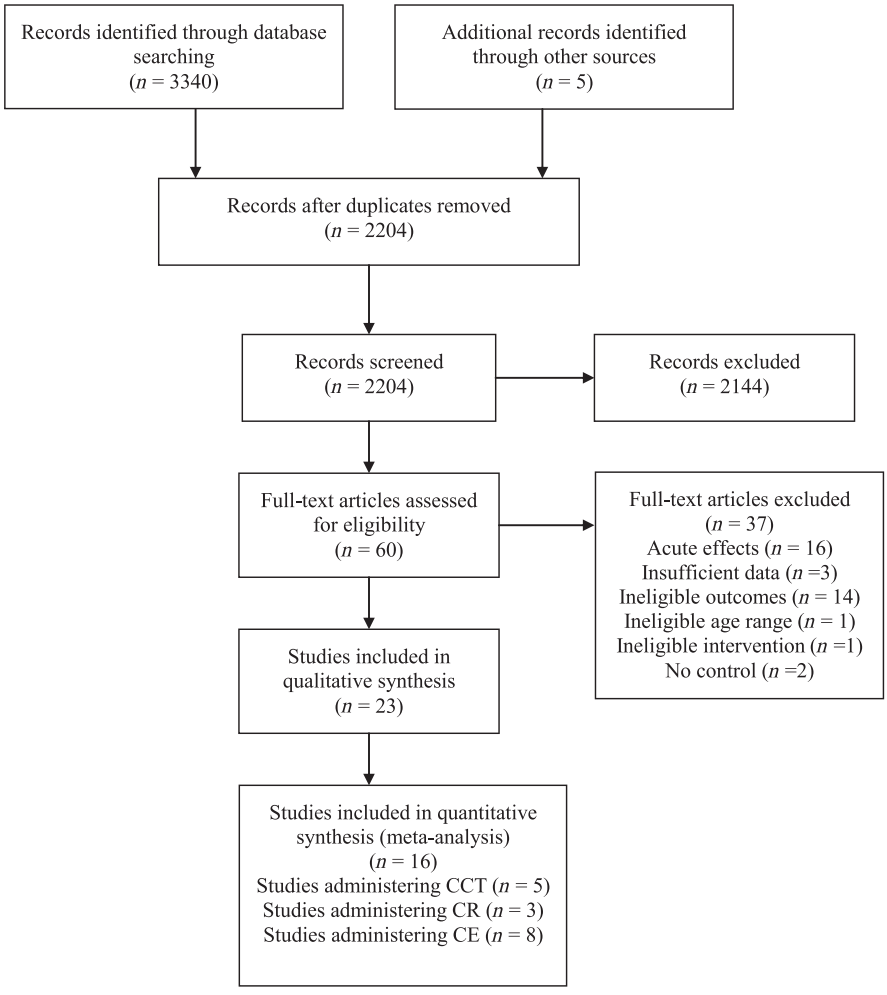

Figure 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

Table 1 Summary of methodologies.

Author	*Country*	*Study design*	*Active (A) and control (C) interventions*	*Participants: N (male/age) (SD)*	*Intensity: number of active intervention days, duration/dose*	*Addiction/setting*	*Impulsivity*	*Outcome*
Computerised cognitive training								
Kumar *et al.* [36]	India	Randomised matched case control design	A: Computerised cognitive function training C: TAU (pharmacotherapy, yoga, relapse prevention sessions)	A: 25 (25 M), 34.28 (5.33) C: 25 (25 M), 34.08 (5.78)	18 sessions/days (time not specified)	Alcohol/inpatient therapeutic community	Impulsive action Impulsive choice	Stroop inhibition time Game of dice task: net score
Gamito *et al.* [38]	Portugal	Randomised pilot study	A: Serious games to train executive functions, C: TAU (methadone maintenance)	A: 11 (11 M) C: 3 (3 M) Total sample age: 37 (4.48)	10 (60 min) 4–6 weeks	Heroin/inpatient therapeutic community	Impulsive choice	IGT: net score
Rass *et al.* [39]	USA	Randomised controlled trial	A: WMT (Cogmed) including performance feedback C: WMT with static difficulty + no feedback All participants received methadone maintenance	A: 28 (14 M), 43.3 (8.8) C: 28 (12 M), 43.5 (7.1)	25 (45 min) Mean: 45 days	Heroin, cocaine, alcohol/outpatient methadone treatment	Impulsive action Impulsive choice	CPT: error rate DDT: hypothetical area under the curve QDOT: area under the curve IGT: net difference
Zhu *et al.* [40]	China	Randomised controlled trial	A: WMT + ABM C: TAU (health education, judicial education, sports activities, vocational training)	A: 20 (20 M), 32.70 (5.27) C: 20 (20 M), 33.05 (8.02)	20 (60 min) 4 weeks	Methamphetamine/ inpatient compulsory rehabilitation centre	Impulsive choice	BART: total balloon inflations/ total unexploded balloons IGT: net score
Bickel *et al.* [41]	USA	Yoked experimental design (matched gender + memory)	A: WMT with monetary reinforcement C: Memory training with correct answers provided. Progression and reinforcement was yoked to performance of a participant in the active intervention	A: 14 (10 M), 35.7 (8.26) C: 13 (10 M), 41.6 (7.91)	4–15 sessions 9–44 days dependent on progress mean: 25 days	Stimulants/ inpatient treatment facility	Impulsive choice	BART: number of pumps DDT: k parameters
Hendershot *et al.* [42]	Canada	Double-blind randomised controlled trial	A: WMT (adaptive) C: WMT (non-adaptive; static difficulty level). All participants received group-based psychosocial treatment	A: 55 (37 M), 39.4 (11.42) C: 55 (39 M) 40.00 (11.19)*	25 (45 min) 5 weeks	Polysubstance/ inpatient therapeutic community	Impulsive choice	DDT: *k* parameter

(***Continues***)

Table 1. (Continued)

Author	*Country*	*Study design*	*Active (A) and control (C) interventions*	*Participants: N (male/age) (SD)*	*Intensity: number of active intervention days, duration/dose*	*Addiction/setting*	*Impulsivity*	*Outcome*
Khemiri *et al.* [43]	Sweden	Randomised controlled trial	A: WMT with adaptive difficulty C: WMT (non-adaptive; static difficulty level)	A: 25 (13 M) 49.6 (6.1) C: 25 (12 M) 49.8 (8.7)*	20 (45 min) 5 weeks	Alcohol/outpatient research clinic	Impulsive action Impulsive choice	RVP: errors SST: SSRT, proportion successful stops DDT: k parameters CGT: risk taking, deliberation time
Cognitive remediation								
Alfonso *et al.* [44]	Spain	Non-randomised pilot	A: GMT + mindfulness C: TAU (psychotherapeutic interventions, family sessions, relapse prevention, skills training)	A: 18 (17 M) 41 (7.62) C: 16 (15 M) 34.89 (10.26)	14 sessions (90 min) 7 weeks	Polysubstance/ outpatient community treatment centres	Impulsive action Impulsive choice	Stroop inhibition time IGT net score
Valls-Serrano *et al.* [16]	Spain	Randomised proof of concept trial	A: GMT + mindfulness C: TAU (therapeutic community: involvement in daily living activities, individual and group therapy; psychoeducation focus)	A: 16 (9 M) 35.19 (5.39) C: 16 (12 M), 30.94 (7.29)	8 sessions (120 min) 8 weeks	Polysubstance/ inpatient therapeutic community	Impulsive action Impulsive choice	Stroop inhibition time, inhibition errors IST: boxes per trial/sampling errors
Marceau *et al.* [18]	Australia	Controlled sequential groups design	A: Mixed CR and CCT (executive function training) C: TAU (therapeutic community model of care; skills-based psychoeducation; therapy, family-support)	A: 16 (0 M), 33.6 (10.1) C: 17 (0 M), 32.9 (7.6)	12 sessions (60 min CR; 60 min CCT) 4 weeks	Polysubstance/ inpatient therapeutic community	Impulsive action	Colour-word interference Test: time
Rezapour *et al.* [45]	Iran	Randomised controlled trial	A: NECOREDA pencil-and-paper tasks C: Group painting sessions plus TAU (methadone maintenance; counselling)	A: 57 (57 M), 32.26 (5.68) C: 60 (60 M), 32.30 (5.37)*	16 sessions (60 min CR) 8 weeks	Opioid/inpatient therapeutic community	Impulsive action	Stroop: time
Cognitive enhancers								
Nuijten *et al.* [46]	Netherlands	Randomised feasibility trial	A: Modafinil C: TAU: Weekly CBT sessions	A: 30 (25 M), 47.1 (7.8)	400 mg daily (84 days) 12 weeks	Cocaine/outpatient research setting	Impulsive action	SST: SSRT Stroop: time

(*Continues*)

Table 1. (Continued)

Author	*Country*	*Study design*	*Active (A) and control (C) interventions*	*Participants: N (male/age) (SD)*	*Intensity: number of active intervention days, duration/dose*	*Addiction/setting*	*Impulsivity*	*Outcome*
				C: 35 (27 M), 45.3 (8.3)*				
Kalechstein *et al.* [47]	USA	Randomised double-blind, placebo-controlled trial	A: Modafinil C: Placebo No other treatments specified	A: 16 (13 M), 42.3 (6.5) C: 14 (12 M), 46.3(5.1)	200 mg daily (5 days)	Cocaine/inpatient research setting	Impulsive action	CPT: commissions, response style
Hester *et al.* [48]	Australia	Randomised double-blind, placebo-controlled pilot trial	A: Modafinil C: Placebo All participants received general support as usual from the nursing and medical staff	Total sample: 20 (14 M) 34.3 (12.07)*	100–200 mg daily (7 days)	Methamphetamine/ inpatient withdrawal unit	Impulsive action	Stroop: time
Joos *et al.* [30]	Netherlands	Randomised placebo-controlled trial	A: Modafinil C: Placebo All participants received a behaviourally orientated treatment program within a residential and/or a day care setting	A: 41 (35 M), 42.0 (9.8) C: 42 (36 M), 41.6 (9.2)*	100–300 mg daily (10 weeks, testing at 42 days)	Alcohol/inpatient and outpatient treatment centres	Impulsive action Impulsive choice	Stroop: time, SSRT, RVP errors DDT: area under the curve
Carroll *et al.* [49]	USA	Randomised placebo-controlled trial	A: Galantamine C: Placebo All participants received standard methadone treatment, consisting of daily methadone and weekly individual or group counselling	A: 27 (16 M), 38.7 (10.8) C: 27 (20 M), 36.3 (9.4)*	8 mg daily (12 weeks)	Cocaine/outpatient methadone maintenance centres	Impulsive action	SST: SSRT
Sugarman *et al.* [37]	USA	Randomised double-blind, placebo-controlled trial	A: Galantamine C: Placebo No other treatments specified	A: 18 (15 M), 30.2 (8.0) C: 16 (10 M), 29.8 (9.7)*	8 mg daily (10 days)	Cannabis/outpatient research clinic	Impulsive action	SST: direction errors, proportion of successful stops CPT: response style
Sofuoglu *et al.* [50]	USA	Randomised double-blind, placebo-controlled trial	A: Galantamine C: Placebo No other treatments specified	A: 14 (10 M), 40.2 (7.1) C: 14 (9 M), 42.3 (6.7)	8 mg daily (10 days)	Cocaine/outpatient research clinic	Impulsive action	SART/go/no-go: commissions, RVP response style
DeVito *et al.* [51]	USA	Randomised double-blind,	A: Galantamine C: Placebo and	A: 31 (22 M), 47.4 (6.8)	8 mg daily (13 weeks)	Cocaine/outpatient research clinic	Impulsive action	SST: SSRT

(*Continues*)

Table 1. (Continued)

Author	*Country*	*Study design*	*Active (A) and control (C) interventions*	*Participants: N (male/age) (SD)*	*Intensity: number of active intervention days, duration/dose*	*Addiction/setting*	*Impulsivity*	*Outcome*
		placebo-controlled trial	TAU: contingency management and weekly 1-h individual psychotherapy sessions	C: 32 (20 M), 48.1 (7.2)*				RVP: response style errors
Schulte *et al.* [31]	Netherlands	Randomised double-blind, placebo-controlled trial	A: N-acetylcysteine + WMT C: Placebo + WMT	A: 9 (9 M), 44.78 (8.72) C: 15 (15 M), 32.40 (7.74)	2400 mg daily (25 days) Daily WMT	Cocaine/outpatient university research clinic	Impulsive action	SST: SSRT
Arout *et al.* [29]	USA	Randomised double-blind, placebo-controlled trial	A: Minocycline C: Placebo All participants were currently enrolled in an opioid agonist treatment program (methadone or buprenorphine/naloxone)	A: 10 (7 M), 46.5 (4.53) C: 10 (8 M), 47.9 (10.00)	200 mg daily (15 days)	Opioids/outpatient opioid substitution programs	Impulsive action	Go/no-go: commissions
Fox *et al.* [52]	USA	Randomised double-blind, placebo-preliminary study	A: Guanfacine C: Placebo All participants received weekly individual and twice weekly group therapy sessions (inpatient) or twice weekly individual drug counselling and contingency management (outpatient)	A: 12, 44.1 (5.9) C: 13, 40.6 (8.3) Sex all: 22 M	200–300 mg daily (up to 8 weeks)	Cocaine/inpatient and outpatient psychiatric research unit	Impulsive action	SST: directional errors
Mahoney *et al.* [53]	USA	Randomised double-blind placebo-controlled trial	A: Rivastigmine C: Placebo No other treatments specified	A: 13 (10 M), 43.9 (5.77) C: 14 M, 40.4 (8.0)	3 mg/6 mg twice daily (7 days)	Cocaine/inpatient research medical centre	Impulsive action	CPT: commissions

A = active intervention; C = control intervention; GMT = goal management training; TAU = treatment as usual; IGT = Iowa gambling task; IST = information sampling task; WMT = working memory training; DDT = delay discounting task; CPT = continuous performance task; ABM = attentional bias modification; SST = stop signal task; SSRT = stop-signal reaction time; CGT = Cambridge gambling task; RVP = rapid visual information processing; QDOT = quick discounting operant task; BART = balloon analogue risk. task; SART = sustained. attention to response task. *Smaller sample was included in the cognitive analyses.

prevention) as a comparator. Most WMT (CCT) studies (4/5) used a standardised active control (i.e. practising a simple working memory task, without the active training component, which involves progressive difficulty). The majority of CEs trials were placebo-controlled (11/12). However, there was greater variability in the behavioural interventions running in the background of the active and placebo conditions, with four studies having no behavioural interventions and eight studies describing interventions of varying intensity (e.g. general nursing support, drug counselling, CBT). Similarly, of the five WMT studies, three studies offered no additional behavioural interventions, and two described interventions of varying intensity (e.g. psychosocial treatment, vocational training).

Studies eligible for group analyses

We examined the combined effect of specific interventions on impulsive action and choice outcomes. An adequate number of studies ($n \geq 2$) were available to calculate pooled intervention effects for WMT on impulsive action and choice, GMT on impulsive action and choice, modafinil on impulsive action and galantamine on impulsive action. See Figs. 2 and 3 for pooled effects of interventions on impulsive action and choice respectively. It is noted that only a small number of studies were included in each analysis.

Meta-analyses

Meta-analysis of the effect of all studies

We combined 13 studies with 485 participants across intervention categories for impulsive action. The combined studies showed no significant effect of CCT, CR and CE interventions over control interventions for decreasing impulsive action (Fig. 2; $P = 0.11$). A meta-analysis of 7 studies with 302 participants showed no significant effect of combined CCT, CR and CE interventions over control interventions at decreasing impulsive choice (Fig. 3; $P = 0.07$). There was a group moderation effect for both impulsive action and choice and therefore, we present results that are stratified by treatment modality. Note that the formal tests of moderation and pairwise comparisons are presented in a later section.

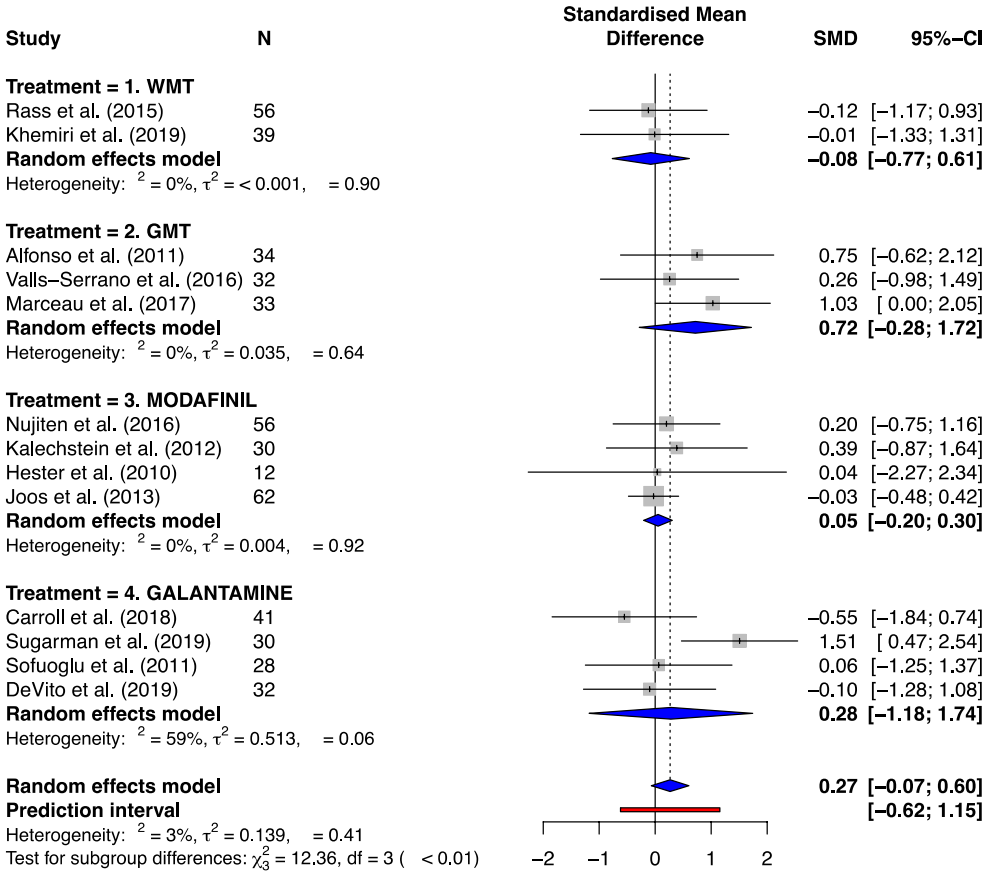

Figure 2 Pre-post intervention effects on impulsive action in addiction. Each subgroup represents a separate meta-analysis. The overall effect and test for subgroup differences are included at the bottom of the figure. GMT = goal management training, WMT = working memory training [Colour figure can be viewed at wileyonlinelibrary.com]

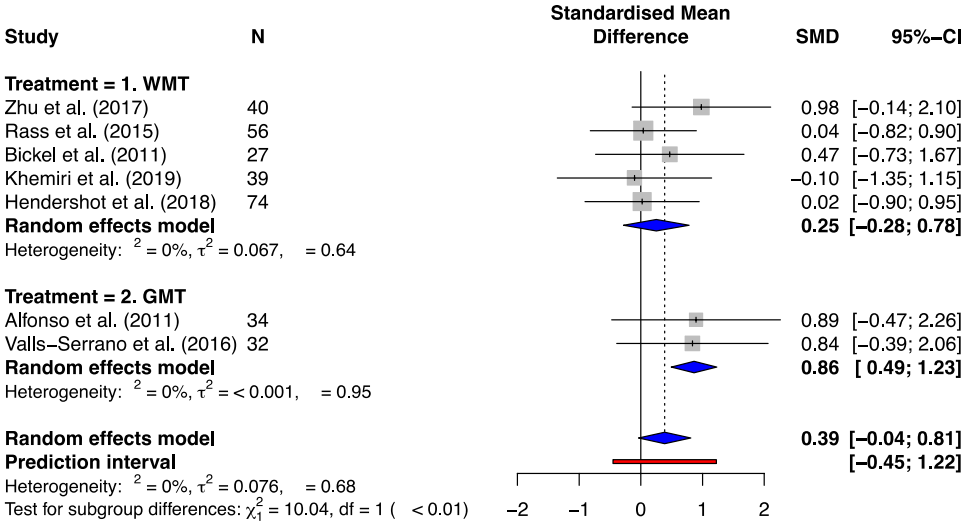

Figure 3 Pre-post intervention effects on impulsive choice in addiction. Each subgroup represents a separate meta-analysis. The overall effect and test for subgroup differences are included at the bottom of the figure. GMT = goal management training, WMT = working memory training [Colour figure can be viewed at wileyonlinelibrary.com]

Meta-analysis of the effect of WMT

A meta-analysis of two studies with 95 participants showed no significant effect for WMT over control interventions at decreasing impulsive action (Fig. 2; P = 0.38). A meta-analysis of five studies with 236 participants showed no significant effect for WMT over control interventions at decreasing impulsive choice (Fig. 3; P = 0.26). As Zhu and colleagues [42] also included Attentional Bias Modification (ABM), we performed a sensitivity analysis to examine whether removing this study from analysis influenced the pooled effects. Once removed, the pooled effect was lower (standardised mean difference; SMD = 0.09, 95% CI = −0.25–0.43; P = 0·47; I^2 = 0%, P = 0.92), but well within the confidence interval of the original result, therefore not altering the interpretation of the effect size. Consequently, it was retained in the group analysis.

Meta-analysis of the effect of GMT

A meta-analysis of three studies with 99 participants showed no significant improvement in GMT compared to the control intervention for impulsive action (Fig. 2; P = 0.09). As Marceau and colleagues [18] included a combination of GMT and CCT interventions, we performed a sensitivity analysis. Excluding this study did not alter the interpretation of the result, although the magnitude of the pooled effect was attenuated (SMD = 0.48; 95% CI = −2.64–3.59, P = 0.30). A meta-analysis of two studies with 66 participants showed significant improvement in GMT compared to the control intervention for impulsive choice (Fig. 3; P = 0.02).

Meta-analysis of the effect of modafinil

A meta-analysis of four studies with 160 participants showed no significant effect for modafinil over control interventions for impulsive action (Fig. 2; P = 0.58).

Meta-analysis of the effect of galantamine

A meta-analysis of four studies with 131 participants showed no significant effect for galantamine over control interventions for impulsive action (Fig. 2; P = 0.58). Whereas three of the four studies appeared to have consistent results, one study appeared to be driving some heterogeneity in effect sizes [37], which we note was the only study with cannabis as type of addiction whereas the others included cocaine. Our a priori moderators did not significantly explain this heterogeneity (Supporting information Table S4).

Moderation analyses

Although several moderation analyses were planned a priori for specific intervention groups, because of the small number of available studies in each category, formal testing of the moderators was not possible for all planned analyses. As shown in Fig. 2, there was a significant moderation by intervention modality. Pairwise comparisons revealed that GMT had a significantly larger SMD than WMT (P < 0.001) and modafinil (P = 0.018). Modafinil had a larger SMD than WMT, with this difference approaching significance (P = 0.051). GMT also had a larger SMD than WMT for impulsive choice (Fig. 3; P = 0.002). Notably, treatment setting did not moderate the meta-analytic effect for impulsive action (Supporting information, Fig. S2) or

choice (Supporting information Fig. S3). Treatment setting and treatment intensity (dose, session duration or number of intervention days) were also not significant moderators of pooled separate intervention effects for impulsive action or choice (see Supporting information Table S4).

Heterogeneity and risk of bias

We did not find evidence of substantial heterogeneity in any of the other pooled results. Neither Egger's test, nor visual inspection of the funnel plots indicated possible publication bias. However, we caution interpretation of heterogeneity and publication bias because of the low number of studies in many of the analyses.

The qualitative risk of bias assessments is visually summarised in Fig. 4. The results of the bias assessment for each intervention are included in the Supporting information, Table S5. The largest source of bias was the lack of pre-specified data analysis intentions, resulting in some concerns about the selection of reported results. Other major sources of bias were participant attrition, without adequate analysis methods to minimise bias in the outcome measure and low adherence to assigned intervention. Most studies used adequate outcome measurement (81%) and most had an appropriate randomisation process (75%). These domains of risk were largely comparable between intervention modalities, although we observed higher risk of bias for randomisation in WMT and GMT studies than in modafinil and galantamine studies.

Systematic review

Systematically reviewed studies are included in the Supporting information.

DISCUSSION

There were 23 studies in our systematic review and 16 studies in our meta-analyses. We were able to perform meta-analyses on CR (GMT), CCT (WMT) and CEs (modafinil and galantamine). We found that only CR yielded significant benefits on impulsivity, with a large effect on impulsive choice. Although not significant, CR also had a moderate effect on impulsive action. Only a small number of studies were eligible for inclusion in our meta-analyses and there only were a small number of interventions for each pooled analysis ($n = 2$–$n = 5$). This prevented the assessment of key moderators of interest (e.g. addiction type and parameters of intervention delivery) in some analyses, and those that were able to be tested contained <10 studies and were likely underpowered to detect potential effects.

Our analysis provides initial evidence that CR may be effective for improving impulsivity in addiction. CR interventions act on higher-order cognitive functions, including executive functions and problem-solving [54], and metacognitive strategies to regulate internal thoughts and feelings [55]. These broad-spectrum effects tap into key neuropsychological mechanisms of impulsive choice [56]. GMT encompasses these key CR trainings as well as an explicit focus on goal-related decisions. Participants are taught to stop and mindfully reflect on whether their attention is focused on a planned goal or if they are acting on autopilot (impulse). Although the program may more actively target impulsive choice, the absence of a significant pooled effect on impulsive action may also reflect the small number of available studies rather than true non-significance, because GMT strategies are theoretically relevant for stopping motor responses [57]. Further, GMT was associated with a larger effect at reducing impulsive

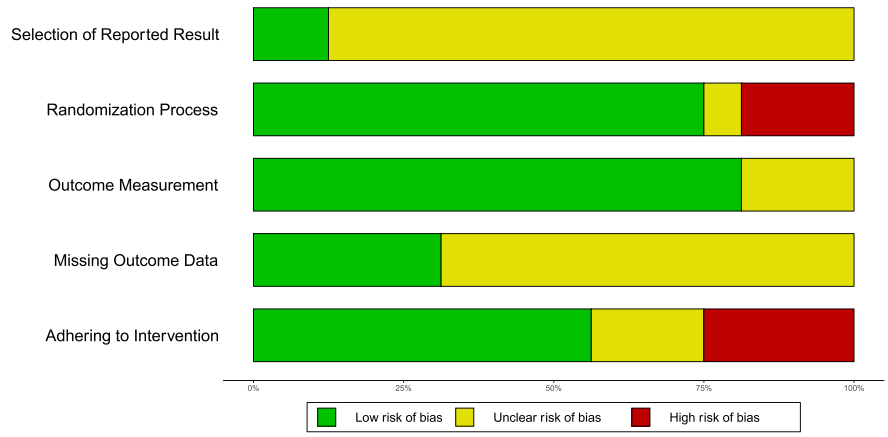

Figure 4 Risk of bias summary revealing the percentage of studies with low, unclear, or high risk of bias across five domains. The summary plot includes the 16 that were eligible for meta-analysis. The risk of bias is highest for selection of reported results as nearly all studies did not publish pre-data analysis plans. The risk of bias because of missing outcome data is high if adequate reasons for drop out, unrelated to the intervention type or outcome (i.e. impulsivity) were not clearly specified [Colour figure can be viewed at wileyonlinelibrary.com]

action than another CR program without the goal-based and mindfulness components [45]. Direct comparisons between the pooled treatment modalities in our meta-analyses suggest that GMT is superior to the CCT, WMT, at improving impulsive choice. Although GMT did not result in a significant pooled effect for impulsive action, it was superior to WMT and modafinil. These results indicate promise for the CR approach and GMT and point to the need for further high-quality clinical trials.

In the context of CCT, we take particular interest in the absence of a group effect of WMT on impulsive choice. Although our results are in the predicted direction, they contradict previous assumptions that WMT may be well suited to decreasing impulsivity in addiction treatment [58] and add support to the ongoing controversy surrounding the generalisability of CCT [12]. Meta-analytic research has revealed a neurobiological overlap in the posterior portion of the left lateral prefrontal cortex for both WM and impulsive choice [59]. Yet, WMT does not appear to be sufficient to consistently improve impulsive choices [39,43], see Supporting information Table S3. It is possible that the training strategies ('drill and practise') [54]; context (computerised stimuli that are not relevant to addiction) [60]; and format (typically individual participation) are not adequate to reinforce control strategies over heightened impulsivity in addiction.

The lack of a significant group effect of modafinil or galantamine may reflect an ability of CEs to preferentially enhance control over impulsivity in patients with greater baseline deficits. Indeed, neuroimaging studies have shown that modafinil can transiently ameliorate neural functions in regions relevant to impulse control in individuals with poorer baseline cognitive functioning [61–63]. In two of these studies, changes in neural functioning or connectivity were related to an improvement in impulsive action [62,63]. Research reporting a longer-term effect of modafinil for substance use disorder treatment; have also revealed both modafinil-induced improvements in cognitive tasks and clinical outcomes in those with greater impairments [30, 64]. Notably, those with better baseline impulsivity performance showed poorer alcohol use outcomes when administered modafinil [30]. A similar pattern of optimal galantamine response in those with greater deficits should also be considered [65].

Limitations

Variations in treatment approaches place some limitations on the generalisability of our findings. Although this reflects the specific questions we were interested in, and the relatively novel treatment area within addiction, we acknowledge that the findings are tentative. Further, variations in control interventions content and the background context of trials need to be factored in when interpreting the effect sizes. Differences between control groups mean that there is no standardised comparison group, limiting the interpretability of the effect of the active compared to the control intervention both within and across different treatment modalities. Detailed description of the contents of comparators is an important area of improvement in this field, as variations in the content and intensity of 'treatment as usual' and/or behavioural interventions used in the background of select trials can affect comparability of main intervention effects [66].

The small number of pooled studies limits interpretability of publication bias and heterogeneity. We found greater risk of bias for randomisation in CCT and CR studies than pharmacological CE studies, which is a limitation of the emerging literature on behavioural interventions [67]. This finding suggests the need for more structured pathways for the design of behavioural trials (e.g. the NIH stage model) [68], to increase the rigour of future trials. Although we found a greater number of eligible CE studies (n = 12), the pharmacological agents are diverse and only a small number could be pooled for the meta-analyses. Further, CE studies have typically assessed clinical outcomes (e.g. abstinence, time to relapse), without capturing change in impulsivity and the potential link with these clinical outcomes. Conversely, only two CR studies assessed for clinical outcomes, preventing assessment of clinical benefits.

Future research

Our review points to the need for further high-quality trials in substance use and gambling disorder populations with an active control group (including an alternative task or placebo medication), prespecified methodological and data analysis plans (to reduce a risk of bias), comprehensive reporting of active and control intervention content [69] and the inclusion of both impulsivity and clinical outcome measures. Although our findings on cholinesterase inhibitors do not support beneficial effects of galantamine, rivastigmine has shown large effects on impulsive action in a single study [53], and hence more studies are needed to assess its potential benefit. Other CEs that may be effective interventions for reducing impulsivity in addiction include n-acetylcysteine and guanfacine; however, as only singular studies were found for each CE, further clinical trials are needed. Other CCT tasks such as approach avoidance training or serious games may have greater real-world relevance than WMT [70,71]. However, we did not find sufficient evidence relating to the impact of these interventions on impulsivity. There was some inconsistency in the effect of galantamine on impulsive action, and further studies are needed to see whether this variation is driven by type of addiction. Finally, we did not identify any studies that

met our criteria for gambling disorder, consistent with a recent review article reporting zero articles assessing cognitive training as a gambling intervention [72]. Further research on cognitive boosting interventions for gambling disorder are therefore required.

Conclusions

The CR approach, GMT, was the only cognitive boosting intervention that showed evidence of improving impulsive choice in addiction treatment. The CEs modafinil and galantamine did not significantly modulate impulsivity and require further research. WMT does not appear to be effective in reducing impulsivity, although other categories of CCT may offer alternative findings. We have highlighted a need for replicated findings and future areas of research to extend the clinical utility of these interventions in an addiction context.

Declarations of interest

A.V.G. has received honoraria for preparation of literature reviews from Servier and for editing work from Elsevier. A.V.G. is part of the scientific advisory board of Monclarity/Brainwell, which produces computerised cognitive training games, but do not receive any honorarium. D.I.L. has provided consultancy advice to Lundbeck and Indivior and has received travel support and speaker honoraria from Camurus, Indivior, Janssen, Lundbeck, Shire and Servier. These organisations do not stand to benefit from this project. D.I.L. has been an investigator on an untied education grant from Sequirus, as well as an investigator-led grant from Camurus, both unrelated to the current work.

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Author contributions

Alexandra Anderson: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; visualization. **George Youssef:** Data curation; formal analysis; visualization. **Alex Robinson:** Investigation; project administration. **Dan Lubman:** Conceptualization; supervision. **Antonio Verdejo-García:** Conceptualization; methodology; supervision.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 List of search terms.
Table S2 Classification of impulsivity tasks.
Table S3 Hedges g effect sizes per outcome and aggregated effect sizes for multiple test outcomes.
Table S4 Meta-regression analyses for moderators on pooled intervention effects.
Table S5 Risk of bias assessment for included studies.
Table S6 Key components of the cognitive boosting interventions in the meta-analyses.
Figure S1 Funnel plots of studies reporting on impulsive action and impulsive choice for GMT, WMT, modafinil and

galantamine interventions. The studies for each intervention lie symmetrically around the dotted line (pooled effect size), suggesting that there is no publication bias.

Figure S2 Meta-analysis of treatment setting on impulsive action in addiction.

Figure S3 Meta-analysis of treatment setting on impulsive choice in addiction.

Figure S4 Risk of bias summary revealing the percentage of studies with low, unclear, or high risk of bias across five domains. The summary plot includes the 23 that were eligible for inclusion in the review. The risk of bias is highest for selection of reported results as nearly all studies did not publish pre-data analysis plans. The risk of bias because of missing outcome data is high if adequate reasons for drop out, unrelated to the intervention type or outcome (i.e. impulsivity) were not clearly specified.