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REVIEW

How effective are pharmaceuticals for cognitive enhancement in healthy adults? A series of meta-analyses of cognitive performance during acute administration of modafinil, methylphenidate and D-amphetamine

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Abstract
Modafinil, methyphenidate (MPH) and D-amphetamine (D-amph) are putative cognitive enhancers. However, efficacy of cognitive enhancement has yet to be fully established. We examined cognitive performance in healthy non-sleep-deprived adults following modafinil, MPH, or D-amph vs placebo in 3 meta-analyses, using subgroup analysis by cognitive domain; executive functions (updating, switching, inhibitory control, access to semantic/long term memory), spatial working memory, recall, selective attention, and sustained attention. We adhered to PRISMA. We identified $k = 47$ studies for analysis; $k = 14$ studies (64 effect sizes) for modafinil, $k = 24$ studies (47 effect sizes) for Methylphenidate, and $k = 10$ (27 effect sizes) for D-amph. There was an overall effect of modafinil (SMD=0.12, p=.01). Modafinil improved memory updating (SMD=0.28, p=.03). There was an overall effect of MPH (SMD=0.21, p=.0004) driven by improvements in recall (SMD=0.43, p=.0002), sustained attention (SMD=0.42, p=.0004), and

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inhibitory control (SMD=0.27, p=.03). There were no effects for D-amph. MPH and modafinil show enhancing effects in specific sub-domains of cognition. However, data with these stimulants is far from positive if we consider that effects are small, in experiments that do not accurately reflect their actual use in the wider population. There is a user perception that these drugs are effective cognitive enhancers, but this is not supported by the evidence so far.

1. Introduction

Cognitive enhancement strategies refer to techniques intended to improve cognitive capabilities of cognitively healthy individuals, usually by administration of psychoactive drugs, particularly in cognitively demanding education and employment settings (Battleday and Brem, 2015; Bellebaum et al., 2017; Repantis et al., 2010). Popular interest in cognitive enhancement has increased recently (Advokat and Scheithauer 2013; Maier and Schaub, 2015) and there are high user expectations and perceptions of efficacy (e.g. Bagot and Kaminer (2014); Battleday and Brem (2015); Linssen et al. (2014)). This may partly be driven by media coverage, which suggests that use is widespread among university students (Partridge et al., 2011). Prevalence studies are often methodologically limited and depending on target drug definition, available data suggests lifetime use of between 5 and 55% in the USA and Europe (McCabe et al., 2014; Smith and Farah, 2011; Singh et al., 2014; Schelle et al., 2015; Micoulaud-Franchi et al., 2014). Nevertheless, it is has been suggested that the use of pharmacological cognitive enhancers in competitive academic settings is likely to increase (Vargo and Petróczi, 2016). Similarly, in the wider context of the adult workforce, there is evidence of increasing willingness to experiment with cognitive enhancers, in line with increased job-market competition, and preoccupation with job stability (Vargo et al., 2014).

There are three main drugs which are most likely to be used as cognitive enhancers, to improve performance; modafinil, methylphenidate (MPH) and D-amphetamine (D-amph) (Ragan et al., 2013). This is a pharmacologically diverse group of drugs, used to treat the medical conditions of ADHD (methylphenidate in UK and USA, D-amph in USA only), or narcolepsy (modafinil in UK and USA, D-amph in USA). Amphetamine and MPH are Schedule II substances under UN Conventions, and all three are subject to national illicit drug and medicines controls.

D-amph and other amphetamine enantiomers (including MPH) are psychostimulants that are structurally related to, and stimulate the release of, the catecholamine neurotransmitters norepinephrine and dopamine (Iverson, 2008). MPH (trade name Ritalin) is another psychostimulant similar to amphetamine which increases monoaminergic activity and is prescribed for ADHD (Ragan et al., 2013). Modafinil (Provigil), is a wakefulness promoting agent used in the treatment of narcolepsy. Like MPH and D-amph, modafinil is a psychostimulant (Battleday and Brem, 2015) but is a weak dopamine transporter inhibitor (Avelar et al., 2017; Cao et al., 2016). Modafinil is considered to have lower abuse potential than D-amph and MPH (Jasinski, 2000), and is currently being studied as a candidate for pharmacotherapy treatment in cocaine addiction, due to its atypical action at the dopamine transporter (Zhang et al., 2017). The exact cognitive enhancement mechanisms of all three drugs are currently unknown.

Whilst there are extensive experimental data assessing neurocognition after clinical administration of cognitive enhancers in healthy volunteers, there is considerable heterogeneity in the findings which make interpretation of their overall efficacy difficult. For example, in the domain of set-shifting alone, several studies suggest no benefit of modafinil (Randall et al., 2003, 2005), others show improvements (Marchant et al., 2009), and others still show a decrease in performance (Randall et al., 2004). Battleday and Brem (2015) concluded that overall it is likely that modafinil improves executive functioning, but the evidence for attention and learning is less convincing, and cognitive enhancement was more robust with increased task complexity.

A meta-analysis from 2010 on cognitive enhancement after administration of modafinil and MPH in healthy volunteers (Repantis et al., 2010) studied the efficacy of these two cognitive enhancers on 1) mood, 2) motivation, 3) wakefulness, 4) attention and vigilance, 5) memory and learning 6) executive functions and information processing. The authors found that MPH improved memory, whereas modafinil only improved attention in non-sleep deprived individuals (but had a greater effect on wakefulness, memory and executive function in the sleep deprived relative to placebo). Repantis and colleagues (2010), concluded that these drugs may lead to overestimation of subjective cognitive performance. However, this analysis was limited as it did not effectively differentiate between cognitive domains and there has been considerable data published since. Other more recent meta-analyses have studied stimulants as a broad drug class, on working memory, inhibitory control, immediate and delayed episodic memory (Ilieva et al., 2015) and processing speed, planning, decision making, and cognitive perseveration (Marraccini et al., 2016) by pooling data from MPH and amphetamine. Illieva et al. (2015) report that stimulants (methylphenidate and amphetamine results pooled) produced a small (Hedge's $g = 0.20$) but significant improvement in inhibitory control, and short term episodic memory, and a significant medium sized (Hedge's $g = 0.45$) in delayed episodic memory. The same analysis showed non-significant effects on working memory. Marraccini et al. (2016) report a small but significant effect of stimulants on processing speed accuracy, but not on planning time, planning accuracy, decision making, or cognitive perseveration. However, no meta-analysis to date has assessed the separate effects of the 3 drugs included in the current analysis, over numerous domains.

Consequently, the aim of the current study was to assess the nature and extent of modafinil, MPH or D-amph cognitive enhancement on separable components of executive function (updating, switching, inhibitory control, access to semantic/long term memory based on theoretical frameworks of executive function e,g. Miyake et al. 2000; Fisk and Sharp 2004), spatial working memory, recall, selective attention, and sustained attention. This is important due to differential patterns of task performance based on cognitive domain and underpinning psychopharmacological mechanism of action.

2. Methods

2.1. Information source and search strategy

Literature searches were guided by Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA). The formal search strategy comprised searching three electronic databases (PubMed, Scopus and Web of Science) in November 2019. We searched the 3 databases using the following string: (eugeroics OR modafinil OR armodafinil OR methylphenidate OR amphetamines OR adderall OR dextroamphetamine OR lisdexamfetamine OR racetams OR piracetam OR oxiracetam OR aniracetam) AND cogniti* AND healthy. Electronic searches were supplemented with manual searches of the reference lists of previously published systematic reviews (Bagot and Kaminer, 2014; Battleday & Brem, 2014). The additional searches yielded a further 7 studies for the final analyses. During the review process, it was suggested that the search term 'Ritalin' ought to be included in the search string. We ran the searches using Ritalin AND cogniti* AND healthy. This did not lead to the inclusion of any additional data.

2.3. Eligibility criteria

2.3.1. Studies

Studies comparing cognitive performance following acute administration of a pharmaceutical cognitive enhancer (modafinil, methylphenidate, D-amphetamine) relative to placebo in a repeated measures or between subject's design were included. The following domains were included in this meta-analysis: executive functions; updating, switching, inhibitory control, access to sematic/long-term memory, spatial working memory, recall, selective attention, and sustained attention. Tasks eligible for inclusion and the cognitive domain that they assess are detailed in Table 1. There was no early date limitation, but the final date limitation was November 2019.

2.3.2. StudiesParticipants

We included studies assessing cognitive function (inhibitory control, switching, access to semantic/long-term memory, updating, spatial working memory, recall selective attention, and sustained attention) following acute administration of modafinil, MPH, and D-amph or placebo in healthy adults (18+ years) who reported having no history of psychiatric of neurological disorder. We initially also wanted to include racetams, however we found only one study which met this eligibility criteria (Meador et al., 2011) and so this was subsequently excluded from the final analysis

2.3.3. StudiesOutcome measures

As each cognitive function can be assessed using several tasks, there are a number of outcome measures. Outcome measures were chosen based on discussion between CAR and CM about which measures reflect the best performance indicator, and reflect those used in previously published meta-analyses (e.g. Roberts et al., 2016). Thus each task contributes one outcome measure to the analysis only. Tasks and outcome measures are described in Table 1.

2.4. Data search and extraction

2.4.1. Article selection and data extraction

Initial and supplementary searches were conducted by CAR and SG. CAR, SG and CM extracted the data. Several studies that met the eligibility criteria did not report necessary information to compute effect size; in each case, data requests were submitted to the corresponding authors of the manuscript via email. Data requests were not met for 23 studies.

2.4.2. Additional handling of data

In cases where varying doses of a drug were administered (e.g. Batistela et al., 2016), we included data from the highest dose only. This was decided due to previous reports suggesting varying optimum doses for different cognitive domains e.g. (Linssen et al., 2014). Most of the data included in this analysis would be described as medium or high by Linsenn's definition for MPH (see Table 2 for dose data) which is optimum for the domains that most closely resemble the domains included in our analysis. Optimum performance by dose and domain is also likely to differ for D-amph and modafinil as well, and so difficulties arise for synthesising varying doses in a meaningful way. Highest doses were chosen in the individual studies due to them being representative of putative 'enhancing' doses. There was heterogeneity in the amount of time elapsed post administration to commence cognitive testing across studies (see Table 2). If a paper reported cognitive testing at several time points post administration data were taken from the time point that most accurately reflected peak plasma concentration for each drug (Modafinil = 3.5 h, Methylphenidate = 120 min, D-amphetamine = 3 h, FDA medication guides). In cases where performance data was reported for several levels of difficulty of a task, we included performance scores for the most difficult (e.g. Studer et al., 2010) whereby correct responses are reported for condition with the highest working memory load). In Batistela et al. (2016), there were a number of outcome measures for each task, it was decided upon discussion between authors to include the measures listed in Table 1. In cases where there was a prolonged dosing regimen (e.g. Chevassus et al., 2013) we included results from testing at day 1 of dosing, so to be comparable with the other studies included in the meta-analysis.

A number of studies employed more than one task to measure one cognitive function (Batistela et al., 2016; Randall et al., 2003, 2005; Turner et al., 2003; Müller et al., 2013; Franke et al., 2017; Ilieva et al., 2013; Lees et al., 2017; Kollins et al., 2015; Müller et al., 2004; Oken et al., 1995; Silber et al., 2006; Chevassus et al., 2013; Unrug et al., 1997). In these cases, means and SDs were entered for each task, however the total n was divided by the number of tasks included for that domain (as per Roberts et al., 2016). In Oken et al. (1995) they report three tasks which assessed selective attention (Covert orienting to spatial attention, parallel search task, and serial search task), however only 14 out of the total sample (n = 22) completed the covert orienting to spatial attention task. As such, it was decided to exclude this task, as there were already two tasks in this paper with the full sample which assessed selective attention. Means and SDs for delayed and immediate recall were estimated from the figure presented in Linssen et al. (2012), using Web Plot Digitizer 3.8 (Rohatgi, 2015). In two studies that used the Stroop task (Barch and Carter, 2005; Fernandez et al., 2015), Stroop interference cost was not presented in the paper. In these instances, we extracted reaction time on incongruent trials as the measure of inhibitory control. In the Flankers's task inhibition cost was the extracted outcome measure except in the case of

Table 1 Tasks and outcome measures for each cognitive domain assessed in the series of meta-analyses.

Executive Function	Task	Outcome measure
Inhibitory control	Stroop	Stroop interference reaction time cost*; Reaction time on incongruous trials*
	Random Number Generation	Errors*
	Eriksen Flankers	Interference reaction time cost*, Errors on Incongruous Trials*
	Go/no-go	Commission errors*; probability of inhibition
	Conners Continuous Perfromance Test	Commission errors*
	Stop Signal Reaction Time (SSRT)	SSRT*;% correct on stop trials
	Tower of London	% correct on level 5; mean attempts (all moves)*; time*
	Tower of Hanoi	Time to completion (seconds)*
	Sustained Attention to Response	Commission errors*
Switching	Trail Making Test - B	Items Correct, time to complete*
	Wisconsin Card Sorting Task	Perseverative Errors*
	CANTAB Intra-Extra Dimension set-shifting test	Errors*
	CANTAB OTS	Errors*
	Stockings of Cambridge	Number correct
Updating	Backwards Digit Span	Number correct
	Operation Span Sums	Number correct
	Corsi Blocks Backwards	Items correctly recalled
	n-back task	Omission errors*
	n-back task	% correct
	Number updating	Error rate*
Access	Verbal Fluency	Number correct
	Controlled Oral Word Associaton Test	Number correct
Spatial Working Memory	Spatial Working Memory task	Immediate reaction time*; Delayed reaction time*; errors*,
	Digit Symbol Substitution Test	Number correct;% correct
	CANTAB Spatial Working Memory	Number correct; strategy score
	Object relocation	% correct
	Modified Sternberg item recognition task	Accuracy
	Visuospatial Delayed match-to-sample task	8-second error rate*
	Serial visual working memory task	Number correct
Verbal Working Memory	Verbal working memory task	Total score
Planning/Decision Making	Logical Episodic Recall	Delayed recall score
	Zoo Test	Score of correct planning
	Matrics Consensus Cognitive Battery – Reasoning	Number correct
	Group Embedded Figures Task	Number correct
Selective Attention	Selective Attention Reaction Time Task	Reaction time change from baseline*
	Eriksen response competition task	Accuracy on incompatible condition
	Trail Making Test - A	Reaction time*
	Visual Attention Test (selective)	Reaction time*
	Parallel search task	Errors*
	Serial search task	Errors*
	Alertness Task	Phasic alertness reaction time*
	Attention Network Task	Alerting effect reaction time*
	Matrics Consensus Cognitive Battery	Vigilance reaction time*
Sustained Attention	Digit vigilance	Reaction time*
	Mackworth clock test	Accuracy
	Conners Continuous Perfromance Test	Reaction time*, Omission errors*, Reaction time standard error*
	Visual Attention Test (sustained)	Reaction time*
	Continuous Temporal Expectancy	Proportion of correct responses
	5-choice Continuous Performance Task	D-prime
	Rapid Visual Information Processing	Latency*

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Table 1 (*continued*)

Executive Function	Task	Outcome measure
	Sustained Attention to Response Test	Reaction time*
	Modified letter e regulation task	Reaction time variability*
Recall	Feedback Learning Task	Learning Accuracy
	Kendrick Object Learning Task	Objects correctly recalled
	Forwards Digit Span	Number correct
	Picture Recall	Number correct
	Face memory	Number correct
	Word recall	Number correct
	Matrics Consensus Cognitive Battery	Verbal learning correct, visual learning correct
	CANTAB Paired Associates Learning	Total adjusted errors*; mean trials to success*
	CANTAB Verbal Recognition Memory	Immediate recall score
	Immediate Recall	Number correct;% correct
	Delayed Recall	Number correct;% correct
	Delayed word Recognition	% correct
	Spatial Span	Span
	Pattern Recognition	Number Correct
	Woodcock Johnson Story Recall	Scaled score

*Higher score reflects worse performance.

De Bruijn et al. (2004), where inhibition cost was not available, therefore errors on incongruent trials was extracted. In addition to this Servan-Schreiber et al. (1998) use a modified Eriksen flanker's task to measure selective attention, in this instance accuracy on that task is included in the selective attention subgroup. Two studies used the sustained attention task (SART); Batistela et al. (2016) report reaction time, therefore this is included in the sustained attention subgroup, however Sofuoglu et al. (2008) report commission errors, as such this is included in the inhibitory control subgroup. Finally the inclusion of the Tower of Hanoi, and Tower of London tasks in the inhibitory control domain is based on work by Miyake et al. (2000) which suggest that these tasks should be conceptualised as inhibitory control tasks, rather than planning tasks.

2.4.3. Data extracted

The following information was extracted for each study: number of participants; gender; age; drug administered; dose; time to testing; cognitive function; task; outcome measure (Table 2) and means and SD's for each outcome measure.

2.5. Statistical and subgroup analysis

Standardised Mean Difference (SMD) and standard error (S.E) of the mean were calculated between experimental conditions (Durlak 2009), and separately for each cognitive task outcome in each study. SMDs were used to control for the variation in outcome measures from cognitive tasks included in analysis (SMD = ^{mean}Cognitive enhancer - ^{mean}Placebo / pooled within-group S.D.). SMD magnitude can be interpreted; 0.2 = small, 0.5 = moderate and 0.8 = *a* large effect (Higgins and Green, 2011). SMD quantifies the size of intervention effect in each study relative to the variability in that study. In our analysis we included data from studies which used both repeated measures/crossover trials, and between groups/parallel groups trials; as such the within-subject correlations were taken into account when calculating the standard error of the SMD for studies which included within-group contrasts (following recommendations by Elbourne et al., 2002). If the within-group correlation was not reported in the paper, and could not be acquired by other means, we used a conservative estimate ($r = 0.70$), as per Khoury et al. (2015), and the recommendation by Rosenthal (1991).

As SMD provides an estimate of the differences between experimental conditions on a given outcome variable, subgroup analyses were conducted by cognitive function (inhibitory control, access, switching, updating, spatial working memory, recall, selective attention, and sustained attention). We separated our analysis into three meta-analyses, one for each drug (modafinil, MPH, and D-amph). Meta-analyses were conducted using the software package RevMan 5.3 (Cochrane Informatics & Knowledge Management Department, UK, 2014).

Analytic Strategy: Each meta-analysis was conducted by separating effect sizes from tasks reported in each study into distinct cognitive functions. The main effects, and formal subgroup analyses were examined, wherein each cognitive function was considered a subgroup. We reviewed the outcome measures of each task included in our analyses, so that a positive SMD reflected better performance in the cognitive enhancer condition, and a negative SMD reflected better performance under placebo. This meant that outcome measures were negatively coded where appropriate. For example, greater number of perseveration errors on Wisconsin Card Sorting Task (WCST) would be indicative of impaired performance, yet would contribute a positive SMD, if it were not recoded (in cases where participants in the cognitive enhancer condition had made more errors). We used random effects models for meta-analysis due to the high heterogeneity in the data across studies. Studies considered outliers if their contributing SMD had a z-score > 3.30, or confidence intervals that don't overlap with any other contributing experiment in that domain. We also conducted Two One-Sided T-test (TOST) equivalence tests (Lakens, 2017) to examine whether any non-significant comparisons had an effect size which was equivalent to a *small* effect (our smallest effect size of interest: Lower bound $d = -0.20$, Upper bound $d = 0.20$). This would allow us to provide support that our pooled effect sizes were statistically equivalent to a small effect, and allow us to infer the absence of a meaningful effect.

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Table 2 Summary of studies included in the series of meta-analyses of cognitive performance during acute administration of modafinil, methylphenidate and D-amphetamine.

Authors and study	Drug, dose, time post-admin	participants, design	Tasks(s) used	Results
AdelhÖfer et al. (2018)	MPH (0.25 mg/kg)	$n = 24$ (50% female, mean age 23.38±2.4) Double blind placebo controlled crossover design	focused-attention dichotic listening task	MPH improved accurace
Asghar et al. (2003)	D-amph, 90 min	$n = 25$ (0% female, mean age 27, 18-45 years) Double blind placebo controlled crossover design	Selective Attention Task	D-amph improved reaction time
Barch & Carter (2005)	D-Amph (0.25 mg/kg), 150 min	$n = 22$ (10% female, age 36.6 ± 8.7 years) placebo controlled crossover design	Stroop, Spatial working memory	D-amph reduced reaction time on both tasks
Batistela et al. (2016)	MPH (40 mg) 90 min	double blind placebo controlled between groups design MPH $n = 9$ (mean age 22.56±2.6), placebo $n = 9$ (mean age 22.22±2.59)	Stroop, Random Number Generation, Backwards Digit Span, operation span, spatial updating, Trail Making Test-B, Zoo test, Visual Attention Task	No differences were observed on any task
Bellebaum et al. (2017)	Modafinil (200 mg) 120 min	double blind placebo controlled between groups design Modafinil $n = 18$, placebo $n = 22$	Alertness task, feedback learning task	No effect of modafinil on these tasks
Bensmann et al. (2018)	MPH (0.5 mg/kg) 120 min	$n = 25$ (60% female, age 23.92±2.88) Double blind placebo controlled crossover design	Flankers task	MPH decreased flanker conflicts
Bennsman et al. (2019)	MPH (0.5 mg/kg) 120 min	$n = 28$ (57.14% female, mean age 23.89±2.79) Double blind placebo controlled crossover design	Go NoGo	No overall effect on inhibitory control
Brignell et al. (2007)	MPH (40 mg) 60 min	placebo controlled between groups design MPH $n = 16$ (56.3% female, mean age 23.44±4.13), placebo $n = 16$ (43.8% F, mean age 23.56±5.82)	Kendrick object learning test	Information processing performance not reported in the paper - data provided by author
Chevassus et al. (2013)	MPH (10 mg) 150 min	$n = 12$ (0% female, age 16, 21-35 years) Double blind placebo controlled crossover design	Stroop, forwards digit span, picture recall	No significant differences reported on any measure

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Table 2 (*continued*)

Authors and study	Drug, dose, time post-admin	participants, design	Tasks(s) used	Results
Cope et al. (2017)	Modafinil (400 mg)	placebo controlled between groups design Modafinil $n = 15$ (41.7% female, mean age 25.54±5.3), placebo $n = 33$ (45.5% F, mean age 23.4 ± 4.2)	5 choice Continuous Perfromance Test, Wisconsin Card Sorting Task	Modafinil significantly improved attention, but not mental set switching performance
De Bruijn et al. (2004)	D-Amph (15 mg) 270 min	$n = 12$ (41.7% female, age 22.58±5.7) Double blind placebo controlled crossover design	Eriksen Flankers	No between condition differences observed
Dockree et al. (2017)	MPH (30 mg) 90 min	$n = 40$ (0% female, age 24.3 ± 5.6) Double blind placebo controlled crossover design	Continuous temporal expectancy	Significantly improved performance with MPH relative to placebo
Dolder et al. (2018)	D-Amph (40 mg) 225min	$n = 24$ (50% female, age 25.3 ± 3.0) Double blind placebo controlled crossover design	Digit symbol substitution, digit span, Stop signal task.	D-amph improved accuracy on Stop signal task, accuracy of mackworth clock test, and processing speed on digit symbol substitution. D-amph had no effect on digit span
Fernández et al. (2015)	Modafinil (200 mg) 120 min	$n = 128$ (59.4% female, age 21.3 ± 2.68) Double blind placebo controlled crossover design	Stroop, forwards digit span, backwards digit span	Modafinil improved Stroop performance. No differences between groups on digit span measures.
Franke et al. (2017)	MPH (2 × 20 mg) 150 min, modafinil (2 × 200 mg) 150 min	$n = 39$ (age 37.3 ± 12.5) Double blind placebo controlled crossover design	Psychomotor vigilance, Trail Making Test-A, Trail Making Test-B, Stroop, Wisconsin Card Sorting Task, Tower of Hanoi	Stroop performance improved in MPH condition relative to placebo. No other between groups differences observed
Froböse et al. (2018)	MPH (20 mg)	$n = 100$ (50% female, age 21.5 ± 2.31) Double blind placebo controlled crossover design	Demand selection task	No between condition differences observed.
Gvirts et al. (2017)	MPH (20 mg) 45 min	$n = 39$ (52.63% female, age 25.36±3.88) Double blind placebo controlled crossover design	Verbal fluency	No differences found
Hamidovic et al. (2010)	D-Amph (20 mg) 180 min	$n = 157$ Double blind placebo controlled crossover design	Digit symbol substitution task	Improved performance after D-amphetamine administration in val/val and val/met carriers, but not met/met carriers.

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Table 2 (*continued*)

Authors and study	Drug, dose, time post-admin	participants, design	Tasks(s) used	Results
ter Huurne et al. (2015)	MPH (20 mg) 180 min	$n = 20$ (60% female, age 21.6, 19-28.4 years) Double blind placebo controlled crossover design	Visuospatial attention task	Improved task performance with MPH
Ikeda et al. (2017)	Modafinil (200 mg) 150 min	$n = 23$ (39.13% female, age 29.5 ± 5.0) Double blind placebo controlled crossover design	Attention network task	Modafinil improved performance in attention network task
Ilieva et al. (2013)	D-Amph (20 mg) 75 min	$n = 42$-45 Double blind placebo controlled crossover design	Face memory, word recall, forwards digit span, backwards digit span, n-back, Go-NoGo, flankers task	No between group differences observed
Kollins et al. (2015)	MPH (40 mg) 150 min	$n = 16$ (37.5% female, age 24.6) Double blind placebo controlled crossover design	N-back, Conners Continuous Performance Test (inhibitory control, vigilance, psychomotor function, attentional lapse)	Direct comparison between MPH and placebo not reported in manuscript
Kulendran et al. (2016)	Modafinil (200 mg)	Between subjects placebo compared RCT. Modafinil $n = 20$ (0% female), placebo $n = 40$ (0% female)	Stop signal task	Modafinil improved Stop signal task performance
Lees et al. (2017)	Modafinil (200 mg) 120 min	$n = 21$ (29% female, age 25.81±4.82) Double blind placebo controlled crossover design	MATRICS Consensus Cognitive Battery (verbal working memory, vigilance, reasoning and problem solving, verbal learning, visual learning) CANTAB (Spatial working memory, Rapid visual processing, Verbal Recognition Memory, Paired Associates Learning)	In healthy volunteers, there were no performance differences between modafinil and placebo on our included measures from MATRICS Consensus Cognitive Battery. However modafinil did improve Rapid Visual Processing and verbal recall accuracy on CANTAB.
Linssen et al. (2012)	MPH (40 mg) 150-270min	$n = 19$ (0% female, age 23.4 ± 5.4) Double blind placebo controlled crossover design	Immediate recall, delayed recall, object relocation, Stop signal task, Tower of London	MPH improved delayed recall, and stop signal performance. No other differences were observed at 40 mg dose.

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Table 2 (*continued*)

Authors and study	Drug, dose, time post-admin	participants, design	Tasks(s) used	Results
Mattay et al. (2000)	D-Amph (0.25 mg/kg) 120min	$n = 10$ (20% female, age 30) Double blind placebo controlled crossover design	n-back	d-amph improved performance in participants with low working memory capacity, but impaired performance of participants with high baseline working memory capacity.
Moeller et al. (2012)	MPH (20 mg) 90 min	$n = 15$ (6.67% female, age 38.9 ± 7.1) within subjects placebo controlled study	Stroop	No performance differences observed
Müller et al. (2004)	Modafinil (200 mg) 90–180 min	$n = 16$ (37.5% female, age 24.1 ± 1.9) Double blind placebo controlled crossover design	Number updating, visuospatial delayed matching to sample task, Trail Masking Test-A	Modafinil reduced error rates in the long-delay condition of the visuospatial task, but not in the maintenance condition of the numeric task. Attentional control tasks were not affected by modafinil
Müller et al. (2013)	Modafinil (200 mg) 120 min	Double blind placebo controlled parallel groups design. Modafinil $n = 32$ (age 26.2 ± 4.2), placebo $n = 32$ (age 24.6 ± 3.6)	Backwards digit span, Spatial working memory, Stockings of Cambridge, immediate recall, delayed recall, PAL	Modafinil improved performance on spatial working memory, planning and decision making (at most difficult level) and visual pattern recognition memory tasks
Nandam et al. (2014)	MPH (30 mg) 90–150 min	$n = 27$ (0% female, age 18–35) Double blind placebo controlled crossover design	Go-NoGo	MPH improved inhibition performance compared to placebo, atomoxetine or citalopram
Nandam et al. (2011)	MPH (30 mg) 150–180 min	$n = 24$ (0% female, age 18–35) Double blind placebo controlled crossover design	Stop signal task	MPH improved Stop signal performance
Oken et al. (1995)	MPH (0.2 mg/kg) 60 min	$n = 23$ - although not all completed each task (52.17% female, age 25, 21–39). Double blind placebo controlled crossover design	Backwards digit span, parallel search, serial search	MPH improved performance on covert orienting to spatial attention. It did not impact on the other tasks
Pauls et al. (2012)	MPH (40 mg) 90 min	$n = 16$ (0% female, age 23.6 ± 3.6) Double blind placebo controlled crossover design	Stop signal task	Stop signal reaction time was reduced following MPH compared to placebo.

(*continued on next page*)

Table 2 (*continued*)

Authors and study	Drug, dose, time post-admin	participants, design	Tasks(s) used	Results
Ramasubbu et al. (2012)	MPH (20 mg) 60 min	$n = 13$ (61.54% female, age 28±3.5) Double blind placebo controlled crossover design	n-back	MP improved performance on the n-back in relation to correct responses and missed responses
Randall et al. (2003)	Modafinil (200 mg) 180 min	Placebo controlled between groups design. Modafinil $n = 10$ (age 20.7 ± 0.3), placebo $n = 10$ (age 20.7 ± 0.4)	Delayed matching to sample, Intra-Extra Dimensions set shifting task, Stockings of Cambridge, Rapid visual information processing, Stroop, Trail Making Test-A, Trail Making Test-B, Controlled oral word association task	Modafinil did not influence performance on any of the tasks
Randall et al. (2005)	Modafinil (200 mg) 120 min	Placebo controlled between groups design. Modafinil $n = 20$ (age 19-22), placebo $n = 20$ (age 19-22)	Trail Making Test-A, digit symbol substitution, Rapid visual information processing, backwards digit span, Spatial working memory, immediate recall, delayed recall, Trail Making Test-B, Stockings of Cambridge, Stroop, Controlled oral word association task, Intra-Extra Dimensions set shifting task	Modafinil improved performance on backward and forward digit span (at 100 mg), although latency was slower at higher dose (200 mg). There was no effect of modafinil on the other cognitive tasks presented
Schmidt et al. (2017)	MPH (60 mg), Modafinil (600 mg) 90-150min	$n = 21$ Double blind placebo controlled crossover design	Go NoGo	Relative to placebo, methylphenidate and modafinil improved inhibitory controlk
Servan-Schreiber et al. (1998)	D-Amph (0.25 mg/kg)	$n = 8$ (age 24-39) Double blind placebo controlled crossover design	Eriksen response competition task	D-amph improved reaction times only in the task condition requiring selective attention
Silber et al. (2006)	D-Amph (0.42 mg/kg) 180-240 min	$n = 20$ (0% female, age 23.6 ± 3.6) Double blind placebo controlled crossover design	Backwards digit span, digit symbol substitution, digit vigilance, tracking task, Trail Making Test-A, Trail Making Test-B	D-amph improved digit vigilance, digit symbol substitution and movement estimation performance

(*continued on next page*)

Table 2 (*continued*)

Authors and study	Drug, dose, time post-admin	participants, design	Tasks(s) used	Results
Sofuoglu et al. (2008)	D-Amph (20 mg) 120 min	$n = 12$ (41.67% female, age 27.7 ± 6.9) Double blind placebo controlled crossover design	Selective Attention Reaction time Task	d-amph improved reaction time on the Selective Attention Reaction time Task, but also increased the number of errors to commission
Sripada et al. (2014)	MPH, 60 min	Placebo controlled between groups design. MPH $n = 27$, placebo $n = 27$	Modified letter e regulation task	There was weak evidence that MPH reduced reaction time during incongruent trials, and improved mean accuracy, compared to placebo
Studer et al. (2010)	MPH (20 mg) 120 min	$n = 11$ (54.54% female, age 29.7 ± 4.8) Double blind placebo controlled crossover design	Serial visual working memory task	MPH did not improve performance on the task
Turner et al. (2003)	Modafinil (200 mg) 120–240 min	Placebo controlled between groups design. Modafinil $n = 20$ (0% female, age 25.1 ± 4.61), placebo $n = 20$ (0% female, age 25.3 ± 5.09)	Backwards digit span, pattern recognition, Paired Associates Learning, delayed matching to sample, Spatial working memory, spatial span, Tower of London, Rapid Visual Information Processing, Intra-Extra Dimensions set shifting task, Stop Signal Task	Modafinil enhanced performance on digit span, visual pattern recognition memory, spatial planning and SSRT. It slowed latency on delayed matching to sample, a decision-making task, and a spatial planning task
Unrug et al. (1997)	MPH (20 mg) 60 min	$n = 12$ (52.63% female, age 24, 19-27) Double blind placebo controlled crossover design	Immediate recall, delayed recall	MPH did not impact performance on these memory tasks
van der Schaaf et al. (2013)	MPH (20 mg) 185 min	$n = 19$ (50% female, age 20.9, 19-24.4) Double blind placebo controlled crossover design	Backwards digit span	MPH did not impact performance on digit span
Weyandt et al. (2018).	D-Amph (30 mg) 90 min	$n = 13$, Double blind placebo controlled crossover design	Conners Continuous Performance Test, forwards digit span, backwards digit span, Woodcock Johnson story recall	D-amph had little impact on cognitive performance
Winder-Rhodes et al. (2010)	Modafinil (300 mg) 120 min	$n = 12$ (0% female, age 26.3 ± 6.6) Double blind placebo controlled crossover design	Pattern recognition, Stop Signal Task, backwards digit span, Rapid Visual Information Processing, Stockings of Cambridge	Modafinil improved performance only at the difficult levels of the Stockings of Cambridge

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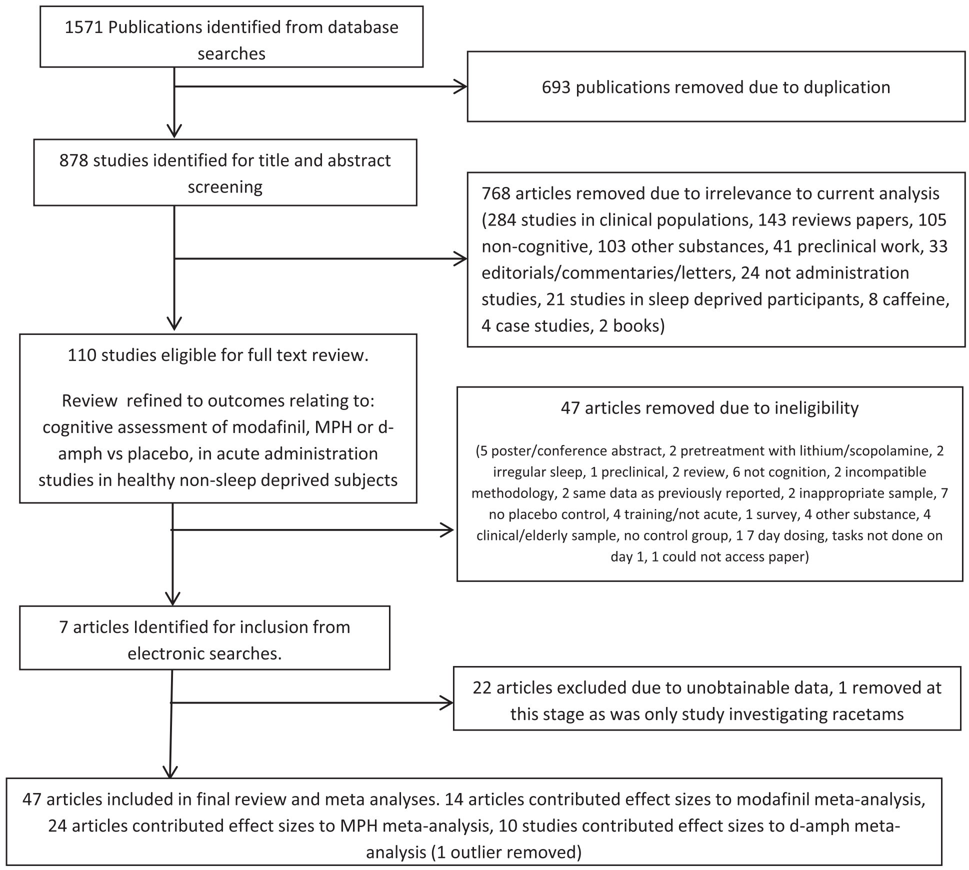

Fig. 1 PRISMA diagram to show the process of inclusion and exclusion of studies in the series of meta-analyses of cognitive performance during acute administration of modafinil, methylphenidate and D-amphetamine.

3. Results

3.1. Study selection (Figure 1)

Literature searches were conducted in November 2019. Our search strategy identified 595 studies using web of science, 585 using Scopus, and 391 using PubMed. After removing 693 duplicated papers 878 remained for initial review. After initial screening of titles and abstracts for relevance 110 articles remained for full text review. Review of titles of articles and abstracts led to the exclusion of a further 47 papers (see Figure 1, for reasons for exclusion). A further 22 papers were excluded for not reporting required statistics in the articles or supplementary material, and necessary data were not available upon request. Seven additional paper was included following supplementary searches, and one paper (Meador et al., 2011) was excluded prior to final analysis due to this being the only paper which studied effects of racetams on cognition. A total of 47 articles were included in the final analysis.

3.2. Overview

Individual study information from all studies included in our analyses, including sample sizes, dose and participant characteristics are included in Table 2. The majority of studies carried out cognitive testing after 90–150 mins post drug administration. The mean age of participants in the D-amph studies was 27.54 The mean age of participants in the crossover trials with MPH was 23.64, in the between groups designs MPH participants had a mean age of 24.33, and placebo participants had a mean age of 24.26. The mean age of the participants in the modafinil crossover trials was 25.40, and in the between groups designs modafinil participants had a mean age of 24.39, and placebo participants had a mean age of 23.5. Of the D-amph studies, 2 had 0% females in the sample, a further 4 studies had no gender distribution information, of the remaining 5 studies a mean of 32.67% were female participants. Six MPH studies were all male samples, a further 3 did not report gender distribution, in the remaining 14 studies there was a mean of 51.50% females in these samples. Three modafinil studies had all male samples, a further 4 report no gender distribution, of the remaining 5 studies a mean of 41.73% were female.

3.3. Meta-analysis of cognitive function after modafinil vs placebo

Data from 14 published studies, contributing 64 effect sizes were included in analysis. The sample consisted of 260 par-

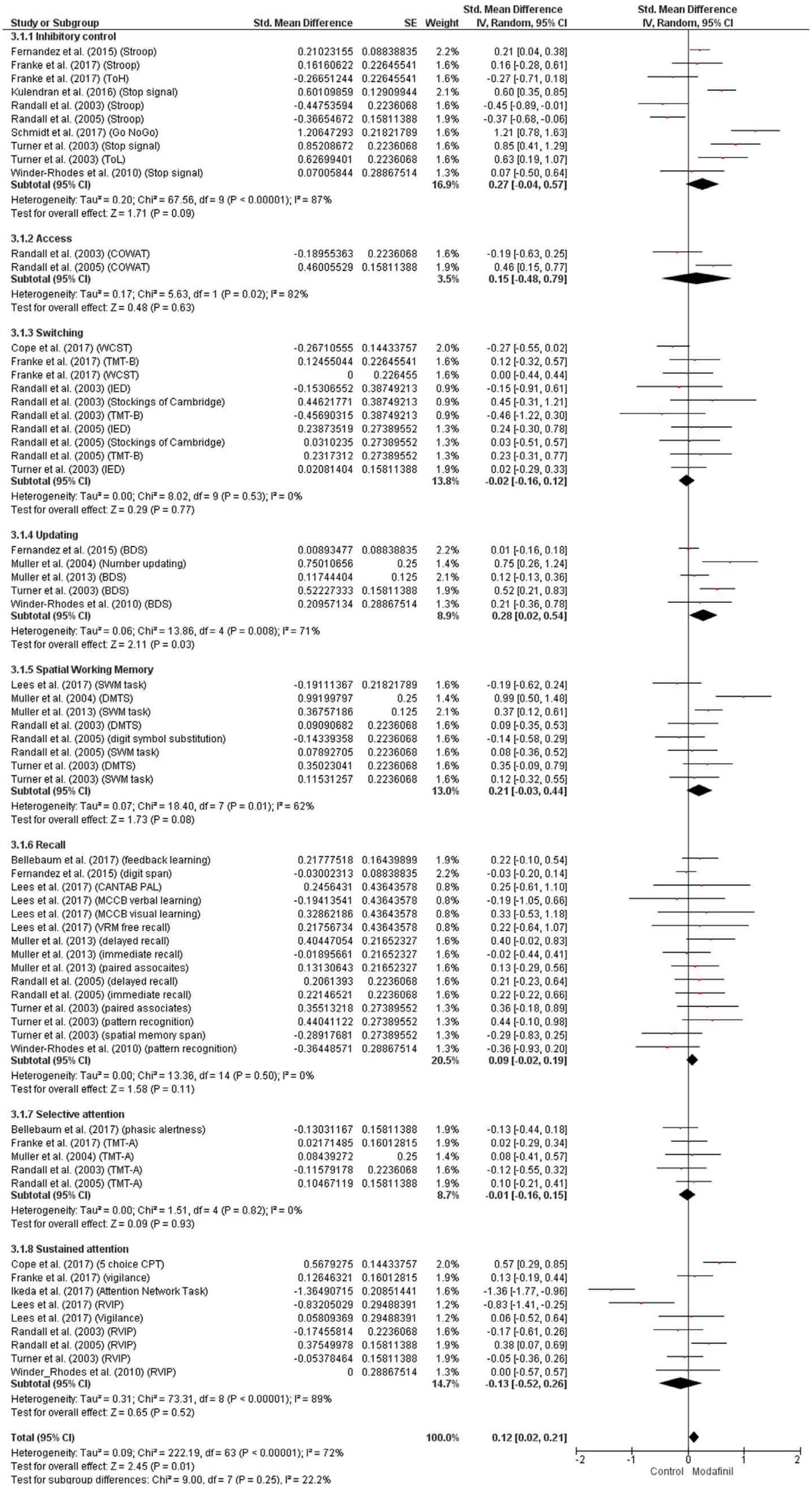

Fig. 2 Forest plot and funnel plot for the meta-analysis of cognitive performance during acute administration of modafinil vs placebo. I 2 is an indicator of heterogeneity between comparisons. Inverse variance (IV) meta-analysis using standardized (Std.) mean differences. SE, Standard error; CI, confidence interval; df, degrees of freedom.

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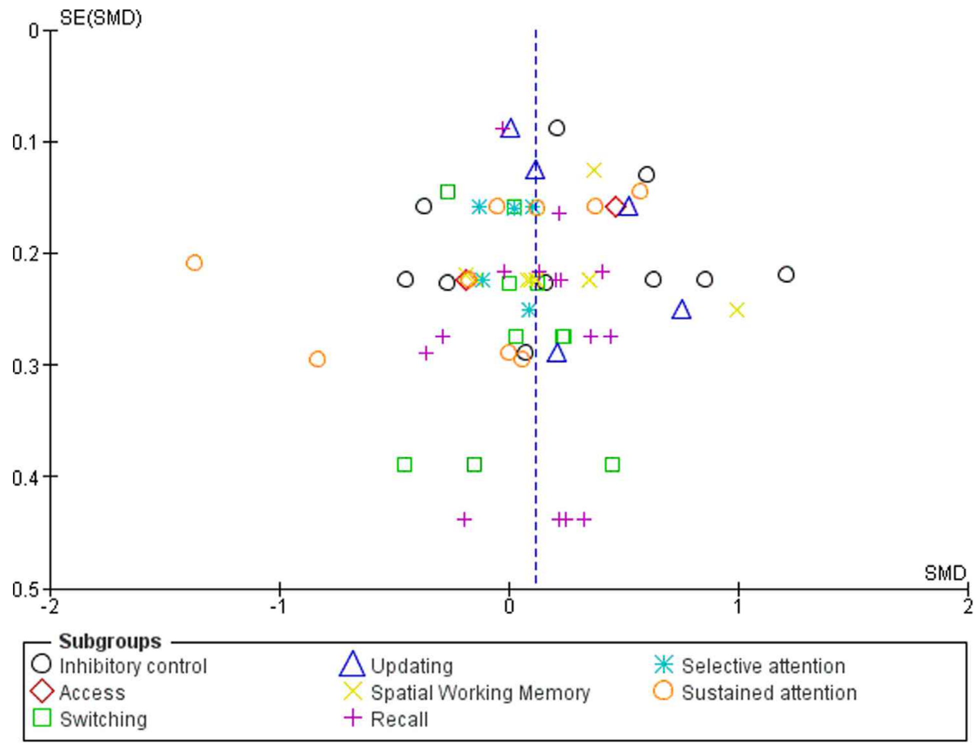

Fig. 2 (continued)

ticipants from repeated measures designs and 312 from between groups designs (135 modafinil, 177 placebo). For study descriptions please refer to Table 2.

3.4. Meta-analysis (Figure 2)

There was evidence of a small overall effect of modafinil vs placebo [SMD = 0.12, 95% confidence interval (CI) 0.02 to 0.21, $Z = 2.45$, p= .01, $I^2 = 72\%$], although the TOST procedure indicated that the observed effect size ($d = 0.12$) was significantly within the equivalent bounds of $d = -0.2$ and $d = 0.2$, $Z = -1.65$, $p = .05$. There was no evidence of a subgroup effect ($\chi^2 = 9.00$, df = 7, $p = .25$, $I^2 = 22.2\%$). Individual analyses are reported below. The pattern of results did not change with removal of outliers.

3.4.1. Inhibitory control

A total of 8 studies, contributing 10 effect sizes assessed inhibitory control. Performance on this function did not differ between groups (SMD = 0.27, 95% CI −0.04 to 0.57, $Z = 1.71$, $p = .09$, $I^2 = 87\%$), TOST ($Z = 0.45$, p=.97)

3.4.2. Access

Only two studies assessed access to long term/semantic memory with modafinil. There was no evidence of an effect in this function (SMD = 0.15, 95% CI −0.48 to 0.79, $Z = 0.48$, $p = .63$, $I^2 = 82\%$), TOST ($Z = -0.15$, $p = .44$).

3.4.3. Switching

Five studies assessed switching performance between modafinil and placebo conditions, contributing 10 effect sizes. No statistical evidence of an effect was observed here (SMD = −0.02, 95% CI −0.16 to 0.12, $Z = 0.29$, $p = .77$, $I^2 = 0\%$). TOST procedure indicated that the observed effect size ($d = 0.02$) was significantly within the equivalent bounds of $d = -0.2$ and $d = 0.2$, $Z = -2.35$, $p = .01$.

3.4.4. Updating

There were 5 studies assessing updating, contributing 5 effect sizes. Modafinil enhanced updating performance relative to placebo. (SMD = 0.28, 95% CI 0.02 to 0.54, $Z = 2.11$, $p = .03$, $I^2 = 71\%$), TOST ($Z = 0.6$, $p = .73$).

3.4.5. Spatial WM

Six studies assessed spatial WM, contributing 8 effect sizes. There was no evidence of between group effects in spatial WM (SMD = 0.21, 95% CI −0.03 to 0.44, $Z = 1.73$, $p = .08$, $I^2 = 62\%$), TOST ($Z = 0.08$, $p = .53$)

3.4.6. Recall

Seven studies reported recall performance after modafinil and placebo, contributing 15 effect sizes. We report no evidence of a between groups effect here (SMD = 0.09, 95% CI −0.02 to 0.19, $Z = 1.58$, $p = .11$, $I^2 = 0\%$), TOST ($Z = -2.05$, $p = .02$).

3.4.7. Selective attention

A total of 5 studies investigated simple attention, contributing 5 effect sizes. There was no statistical evidence of a between group effect in this domain (SMD = −0.01, 95% CI −0.16 to 0.15, $Z = 0.09$, $p = .93$, $I^2 = 0\%$), TOST ($Z = -2.4$, $p = .01$).

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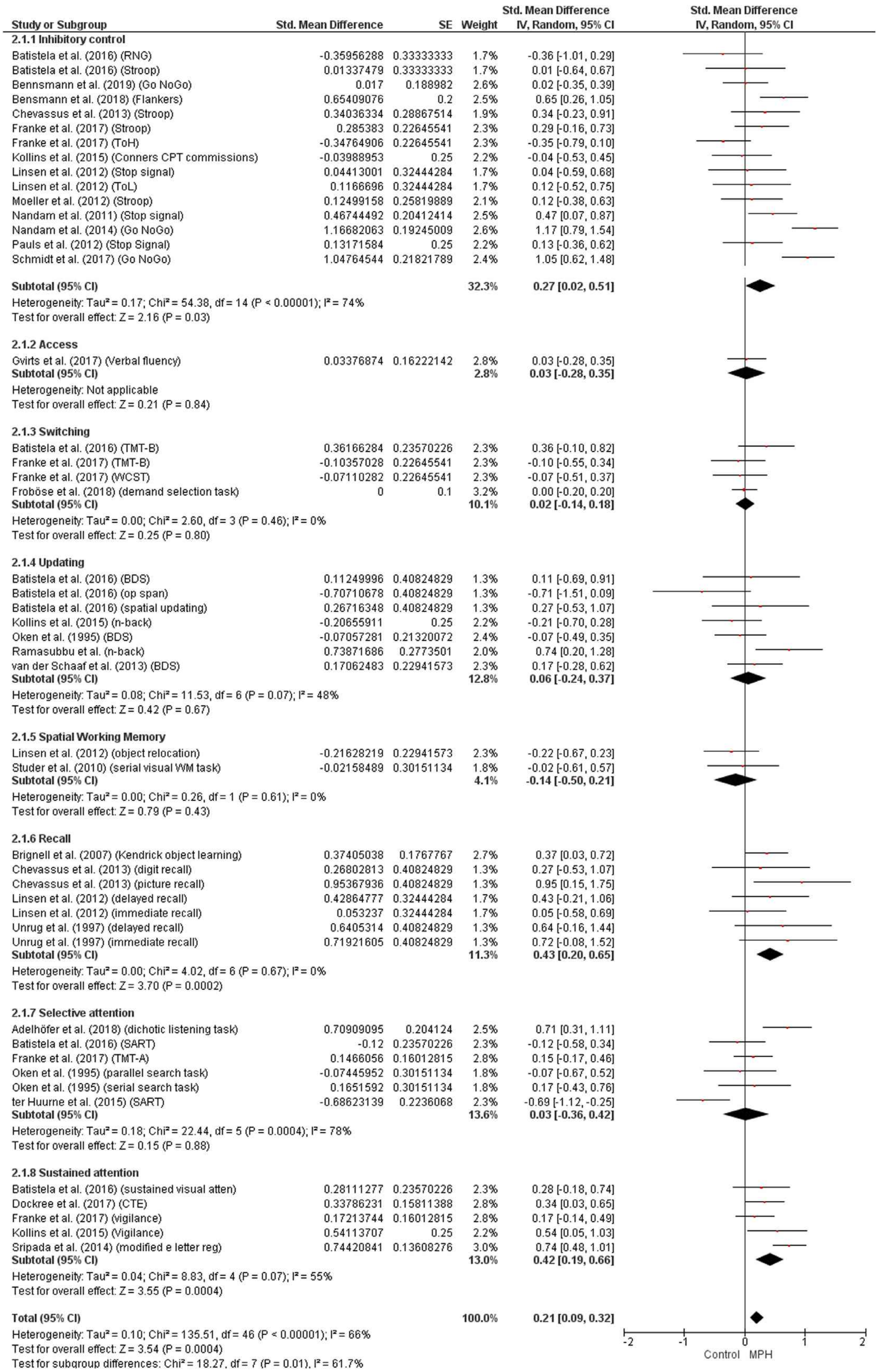

Fig. 3 Forest plot and funnel plot for the meta-analysis of cognitive performance during acute administration of MPH vs placebo. I 2 is an indicator of heterogeneity between comparisons. Inverse variance (IV) meta-analysis using standardized (Std.) mean differences. SE, Standard error; CI, confidence interval; df, degrees of freedom.

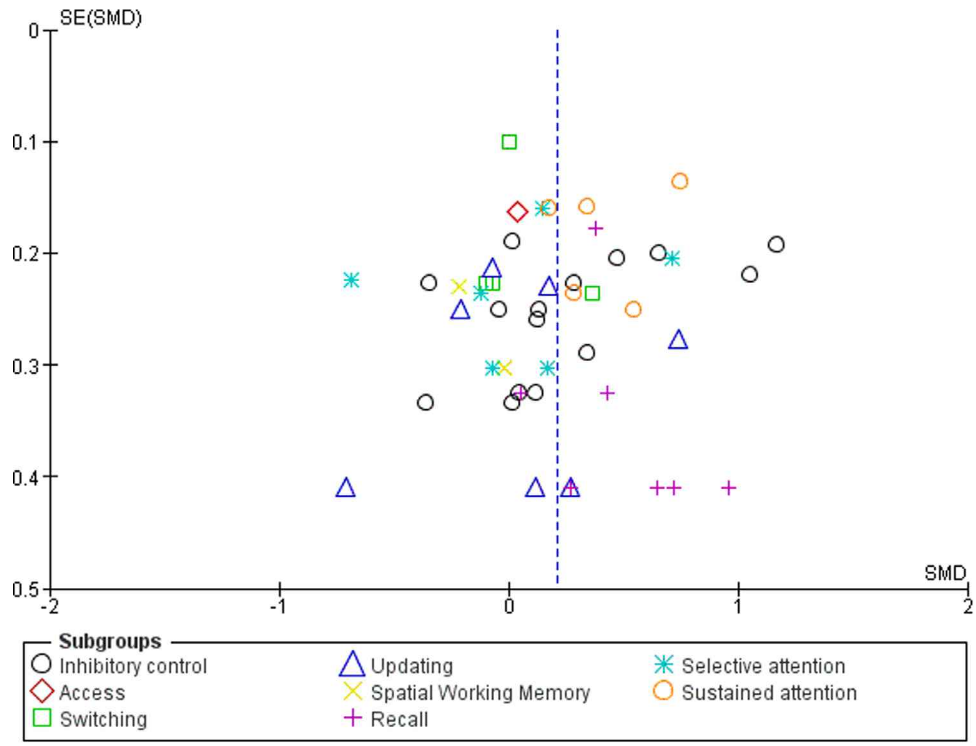

Fig. 3 (continued)

3.4.8. Sustained attention

A total of 8 studies investigated simple attention, contributing 9 effect sizes. There was no evidence of a between group effect in this domain (SMD = −0.13, 95% CI −0.52 to 0.26, $Z = 0.65$, $p = .52$, $I^2 = 89\%$), TOST ($Z = 0.35$, $p = .36$).

3.5. Meta-analysis of cognitive function after MPH vs placebo

Data from 24 published studies, contributing 47 effect sizes were included in the methylphenidate vs placebo analysis. The sample consisted of 501 participants from repeated measures designs and 144 from between-groups designs (92 MPH, 92 placebo). For descriptive information see Table 2.

3.6. Meta-analysis (Figure 3)

Our analyses indicated that MPH improved overall cognitive performance relative to controls (small effect) (SMD = 0.21, 95% CI 0.09 to 0.32, $Z = 3.54$, $p = .0004$, $I^2 = 66\%$), TOST ($Z = 0.17$, $p = .56$). The test for subgroup differences showed statistical evidence of an effect ($\chi^2 = 18.27$, df = 7, $p = .01$, $I^2 = 61.7\%$). Individual analyses are reported below. The pattern of results do not change with removal of outliers.

3.6.1. Inhibitory control

There were 12 studies assessing inhibitory control under MPH and placebo conditions, contributing 15 effect sizes to our analysis. Inhibitory control performance was enhanced in the MPH condition relative to placebo, and this was a small effect (SMD = 0.27, 95% CI 0.02 to 0.51, $Z = 2.16$, $p = .03$, $I^2 = 74\%$). TOST ($Z = 0.56$, $p = .71$).

3.6.2. Access

There was only one study which assessed access, for completeness this remains included to contribute to the overall effect size, however the subgroup effects are not reported here.

3.6.3. Switching

Three studies investigated switching, contributing a total of 4 effect sizes. There was no evidence of an effect in this cognitive function (SMD = 0.02, 95% CI −0.14 to 0.18, $Z = 0.25$, $p = .80$, $I^2 = 0\%$), TOST suggests equivalence ($Z = 2.21$, $p = .01$).

3.6.4. Updating

Five studies, contributing 7 effect sizes assessed updating. There was no evidence of an effect in this domain (SMD = 0.06, 95% CI −0.24 to 0.37, $Z = 0.42$, $p = .67$, $I^2 = 48\%$). TOST ($Z = -0.9$, $p = .18$).

3.6.5. Spatial working memory

There were only 2 studies, which contributed an effect size each to the spatial working memory analysis. There was no statistical evidence of an effect in this domain (SMD = −0.14, 95% CI −0.50 to 0.21, $Z = 0.79$, $p = .43$, $I^2 = 0\%$). TOST ($Z = 0.33$, $p = .37$).

3.6.6. Recall

Four studies contributing 7 effect sizes were included for the recall analysis. MPH enhances recall relative to placebo, and this is a small to medium sized effect. (SMD = 0.43, 95% CI 0.20 to 0.65, $Z = 3.70$, $p = .0002$, $I^2 = 0\%$). TOST ($Z = 1.06$, $p = .86$).

3.6.7. Selective attention

A total of 5 studies, contributing 6 effect sizes assessed selective attention. There was no evidence of an effect in this domain (SMD = 0.03, 95% CI −0.36 to 0.42, $Z = 0.15$, $p = .88$, $I^2 = 78\%$). TOST ($Z = -0.85$, $p = .20$).

3.6.8. Sustained attention

A total of 5 studies, contributing 5 effect sizes assessed sustained attention. There was a small to medium, statistically significant effect in this domain (SMD = 0.42, 95% CI −0.36 to 0.42, $Z = 3.55$, $p = .0004$, $I^2 = 55\%$), whereby sustained attention performance was improved with MPH relative to placebo. TOST ($Z = 1.11$, $p = .87$).

3.7. Meta-analysis of cognitive function after d-amph vs placebo

After removal of one effect size (Servan-Schriber et al., 1998) due to their contributing effect size having z-score > 3.30, data from 10 published studies, contributing 27 effect sizes were included in the D-amph vs placebo analysis. The sample consisted of 337 participants from repeated measures designs. For descriptive information see Table 2.

3.8. Meta-analysis (Figure 4)

There was no evidence of an effect of D-amph vs placebo (SMD = 0.21, 95% CI −0.06 to 0.47, $Z = 1.52$, $p = .13$, $I^2 = 91$), TOST ($Z = 0.07$, $p = .53$). There was also no evidence of an effect of subgroups ($\chi^2 = 7.09$, df = 6, $p = .31$, $I^2 = 15.3\%$). Individual analyses are reported below.

3.8.1. Inhibitory control

There were 5 studies assessing inhibitory control, contributing 6 effect sizes. There was no evidence of between group differences (SMD = 0.21, 95% CI −0.15 to 0.57, $Z = 1.15$, $p = .25$, $I^2 = 65\%$), TOST ($Z = 0.05$, $p = .52$).

3.8.2. Switching

There was only one study which assessed switching, for completeness this is included in the analysis for the overall effect size, however the subgroup effects are not reported here.

3.8.3. Updating

Four studies, contributing 5 effect sizes assessed updating. There was no statistical between group difference in this domain (SMD = 0.03, 95% CI −0.19 to 0.24, $Z = 0.23$, $p = .82$, $I^2 = 0\%$), TOST ($Z = -1.55$, $p = .06$).

3.8.4. Spatial working memory

There were 4 studies which contributed to the spatial working memory analysis. There was no evidence of an effect in this domain (SMD = −0.01, 95% CI −0.50 to 0.48, $Z = 0.03$, $p = .97$, $I^2 = 88\%$), TOST ($Z = 0.76$, $p = .22$).

3.8.5. Recall

Three studies contributing 6 effect sizes were included for the recall analysis. There were no statistical differences between groups (SMD = −0.10, 95% CI −0.32 to 0.11, $Z = 0.94$, $p = .35$, $I^2 = 0\%$), TOST ($Z = 0.91$, $p = .18$).

3.8.6. Selective attention

A total of 2 studies, contributing 2 effect sizes assessed selective attention (after the removal of one outlier Servan-Scrieber et al. 1998 – however inclusion of this study does not change the overall result). There was no evidence of effects in this domain (SMD = 0.98, 95% CI −1.15 to 3.11, $Z = 0.90$, $p = .37$, $I^2 = 98\%$), TOST ($Z = 0.72$, $p = .76$).

3.8.7. Sustained attention

A total of 3 studies, contributing 3 effect sizes assessed sustained attention. There was no evidence of effects in this domain (SMD = 1.08, 95% CI −0.40 to 2.55, $Z = 1.43$, $p = .15$, $I^2 = 97\%$), TOST ($Z = 1.17$, $p = .88$).

3.9. Leave-one-out jack-knife analysis

We conducted leave-one-out jack-knife analyses to examine whether any results were particularly sensitive to individual effect sizes . For each primary meta-analysis, we assessed how the overall effect, and domain specific effects, change following the removal of each contributing effect size (in domains with 3 or more contributing effect sizes), one at a time (See supplementary Table 1). The overall effects of each primary analysis (modafinil, MPH, D-amph) were robust to removal of individual effect sizes, showing minimal change in overall effect size. However, due to fewer studies contributing to domain specific effects, some of these are susceptible to change following removal on individual contributing effect sizes. For example, inhibitory control, updating, spatial WM and recall show changes that are sensitive to this analysis in the modafinil analysis. MPH domain specific results are robust to this sensitivity analysis, with the exception of inhibitory control which becomes non-significant after removal of Bennsamn et al. (2018), Nandam et al. (2011), Nandam et al. (2014) and Schmidt et al. (2017). D-amph analyses are also robust to ssensitivity analysis with the exception of sustained attention, following removal of Dolder et al. (2018).

3.10. Evidence of publication bias

As there was asymmetry in the funnel plots for modafinil and MPH, we conducted Egger's tests of publication bias (Egger et al., 1997) on the 64 effect sizes contributing to the modafinil meta-analysis, and the 47 contributing to the MPH analysis. We based evidence of asymmetry on $p < .1$. The same significance level has been used in previous analyses of heterogeneity in meta-analysis. Egger's test was not significant for modafinil (t (63) = 1.32, $p = .19$), or MPH (t (46) = 1.62, $p = .11$), suggesting no evidence of publication bias.

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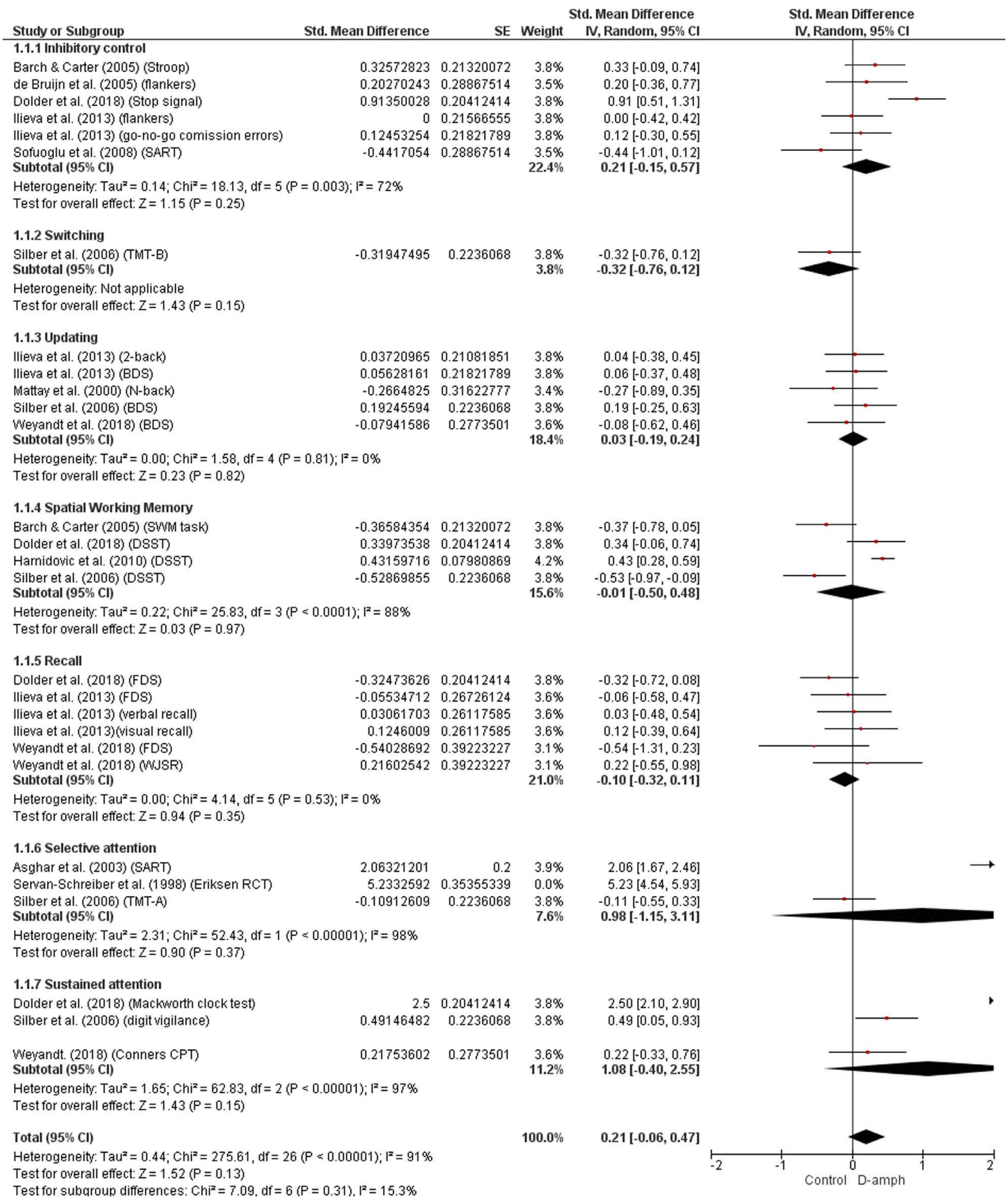

Fig. 4 Forest plot and funnel plot for the meta-analysis of cognitive performance during acute administration of D-amph vs placebo. I 2 is an indicator of heterogeneity between comparisons. Inverse variance (IV) meta-analysis using standardized (Std.) mean differences. SE, Standard error; CI, confidence interval; df, degrees of freedom.

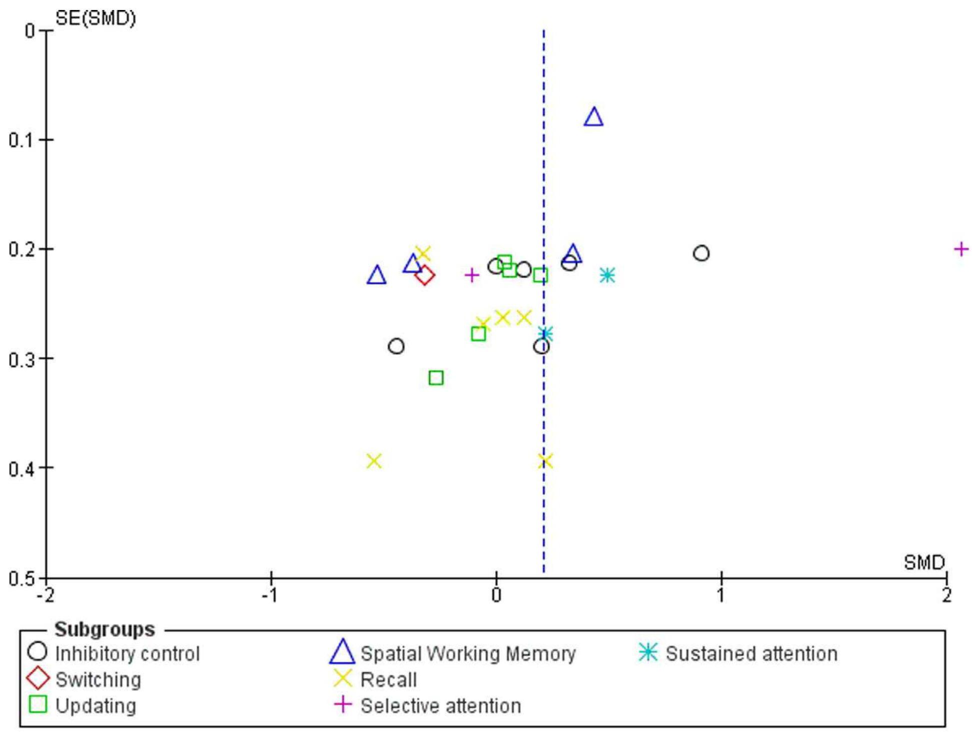

Fig. 4 (continued)

4. Discussion

We undertook a series of meta-analyses assessing the cognitive enhancing effects of acute administration of D-amph, modafinil, and MPH or placebo in healthy non-sleep deprived adults. We found a differential pattern of cognitive enhancement based on drug administered and cognitive domain assessed. In terms of overall effects on a broad range of cognitive functions, modafinil and MPH produced a small improvement in cognitive performance, and D-amph showed no evidence of an overall effect. D-amph also showed no evidence of cognitive enhancement in subgroup analysis by cognitive domain. There was evidence of a small effect of modafinil on the updating component of working memory in subgroup analyses. The overall effect of MPH on cognition was produced by improvements in recall (small to medium effect), inhibitory control (small effect) and sustained attention (small to medium effect).

4.1. Methylphenidate

A previous meta-analysis reported no consistent effects, other than a small positive effect on memory, relative to placebo (Repantis et al., 2010). However, meta-analyses combining methylphenidate studies with other stimulants suggest effects on inhibitory control, episodic memory, and processing speed accuracy (Illieva et al., 2015; Marraccini et al., 2016). Our data suggest that it is the specific cognitive component of “recall” which is most likely to account for the greatest enhancement in memory.

In addition, our analysis showed evidence of an effect of MPH on inhibitory control in healthy adults. The effects of MPH on inhibitory control are perhaps not surprising given the licensed indication of MPH in the treatment of ADHD; a disorder characterised by high impulsivity, and low inhibitory control (American Psychiatric Association, 2013). However, previous findings on the effects of prescription stimulants on this domain in healthy participants have only shown small effects (Ilieva et al., 2013; Smith and Farah, 2011). This is consistent with evidence that MPH improved inhibitory control in healthy people (as per Nandam et al., 2011; Schmidt et al., 2017, 2014). However, whether this translates to increased productivity/performance in the workplace or academic achievement is speculative. Perhaps the suggested improvement in recall and sustained attention would be more valuable for students in the run up to exams. However, effects are small to moderate, and probably transient (Sahakian and Morein-Zamir, 2007) and experimental studies do not accurately reflect the pattern of use in students in the run up to exams.

4.2. Modafinil

Previous studies of the efficacy of modafinil on executive functions have been mixed (Battleday and Brem, 2015). However, separating out executive functions, showed that modafinil had a positive effect on the updating component of executive function. The mechanism underlying this effect is likely to stem from increases in cortical activation in the prefrontal cortex following modafinil administration (Minzenberg et al., 2008; Minzenberg et al., 2014). Like other psychostimulant cognitive enhancers, which preferentially increase catecholamine neurotransmission in the PFC (e.g. MPH, as observed in Berridge et al., 2006), modafinil has been shown to potentiate dopamine and norepinephrine neurotransmission (Minzenberg and Carter, 2008). However, unlike typical psychostimulants, modafinil only shows weak affinity for the DA transporter, and has an atypical neurochemical profile. The reduced affinity for the DA transporter underlies its reduced potential for abuse relative to typical psychostimulants. In addition to this, modafinil has a reduced risk of producing adverse cardiovascular effects relative to MPH and D-amph (although this does not mean 'no' or 'low' risk, hence restricted indications of modafinil by the EMA), which may contribute to its popularity for cognitive enhancement in healthy individuals (Rasetti et al., 2010; Minzberg & Carter, 2008).

4.3. Strengths and limitations

The main strength of this analysis is that it is the most comprehensive to date in terms of conducting an analysis for each of the three most frequently used cognitive enhancers. Similarly, the inclusion of subgroup analysis has afforded comprehensive analysis of cognitive enhancement by cognitive domain. We also have a large sample of contributing experiments, despite employing stringent inclusion/exclusion criteria, and the large number of studies for which no data was available. Our formal analysis of publication bias suggested no evidence of publication bias. However, there were 22 published papers which did not have extractable data, which does mean that the current analysis does necessarily omit data that could potentially affect the results. However, many of these omitted papers report null effects (for summary of findings of these studies see supplementary Table 2), which suggests that many overall effects reported in our analysis, may in fact, be smaller if inclusion of these data were permitted.

Meta-analyses are conducted to produce a quantitative analysis of all available data in order to avoid interpretation generalisations from individual studies. It is therefore essential that research reporting conforms to consistent and transparent data reporting, and improved data sharing practises (Munafò et al., 2017).

Despite having a large sample of contributing experiments, results suggesting there are no statistical differences between groups need to be treated with caution. In order to better determine whether non-significant results support evidence of a null effect, we also employed equivalence testing (as per Quintana, 2018). Although for modafinil the overall effect is of statistical equivalence, as is switching, recall, and selective attention, there was no other evidence of statistical equivalence in other domains for modafinil, or any domains for MPH and D-amph. Thus it could be that as yet the data are not substantial enough to show a drug effect in these areas, as opposed to them not having an effect per se.

In meta-analyses such as this it is also difficult to incorporate varying doses of each drug across studies in a meaningful way. It has been suggested previously that there is an inverted U-shape for cognitive effects of catecholaminergic drugs, and that to achieve an optimum level of catecholamines, first it is necessary to consider baseline levels (Cools & D'Esposito, 2011). Alternatively, it has been suggested that for MPH there are differing optimum doses for different cognitive domains, with medium or high doses appearing to be best for domains of "working memory" and "attention" (Linnsen et al., 2014) which are the domains that most closely resemble the domains we investigated. Optimum performance by dose and domain is likely to differ again for D-amph and modafinil, so dose effects needs to be considered when interpreting our results. Nevertheless, our data are representative of studied putative 'enhancing' doses, and provide the most comprehensive analysis to date of effects in several cognitive domains.

On a similar note, it is perhaps the individual differences in baseline levels of catecholamine's which contribute to the heterogeneity of results, and thus small effect sizes. For example therapeutic effects of D-amph and MPH on cognition and behavior in ADHD patients is driven by a mechanism of action whereby the stimulant increases catecholamine levels in the PFC, and related cortical and subcortical regions. This is due to individuals with ADHD having consistently low levels of catecholamines (Smith and Farah, 2011; Volkow et al., 2007). If we assume that non-clinical populations have baseline catecholamine levels that fall within a range that is higher than the range observed in ADHD populations, then this is a potential neurobiological mechanism underpinning positive effects seen in clinical populations.

Finally, there were only data available to conduct meta-analyses on acute short-term administration studies. Moreover, although many experimental assessments of cognition provide important information about the underlying mechanisms for many day-to-day functions, they do not necessarily reflect utilization outside the laboratory. For example, students report use of pharmacological cognitive enhancers for diverse reasons including improving assessment and revision performance, the regulation of emotions in study settings, and to provide distinction between social and study activities (Schelle et al., 2014; Vargo et al., 2016). Future research in this area needs to explore the pattern of use and type of cognitive performance that users are seeking to enhance. This information should then be used to inform the design of experimental studies that can assess the efficacy of cognitive enhancement in the real world.

5. Conclusions

MPH has the strongest effects on cognition of the three stimulants observed. However, the positive effects are small to moderate, and limited to recall, inhibitory control and sustained attention. Clinical studies also suggest that MPH also has high abuse potential, and high toxicity through excessive extracellular dopamine and norepinephrine, whereby in overdose patients show delirium, hallucinations, agitation, paranoia and seizures, as well as cardiovascular effects (Spiller et al., 2013). Modafinil has a lower abuse potential and toxicity problems (although doses of up to 8 g i.e. 20 times recommended daily dose, can cause overdose which presents as mainly neurological effects such as anxiety, agitation headache, insomnia, and tremor - Spiller et al., 2013) and has a small positive effect on memory updating. D-amphetamine produces no improvements in cognition, and so can probably be ruled out of future investigation for safe, effective cognitive enhancement. The data with these stimulants is far from positive if we consider that effects are

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small and likely transient, in experiments that do not accurately reflect their actual use in the wider population.

Author disclosures

All authors declare that they have no conflict of interest.

Contributors

CAR designed the study, managed the literature searches, extracted data, undertook the statistical analysis, and wrote the first draft of the study. AJ advised on statistical analysis. SG consulted on study design, confirmed literature searches, extracted data, and cross-checked data extraction. CM consulted on study design, extracted data, and cross checked data extraction. All authors: reviewed and edited the manuscript and read and approved the final manuscript.

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All other authors declare that they have no conflicts of interest.

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Supplementary materials

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