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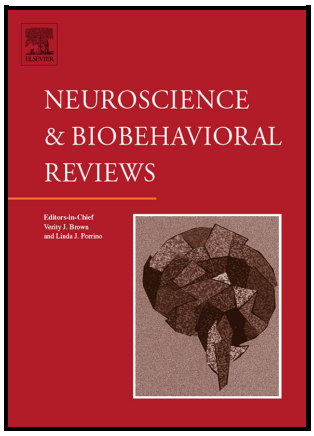

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The Effects of Chronic Administration of Stimulant and Non-stimulant Medications on Executive Functions in ADHD: A Systematic Review and Meta-Analysis

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Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) is associated with executive function deficits that are improved with medications. However, meta-analyses of stimulant effects on cognition have mostly tested single-dose effects, while there is no meta-analysis of non-stimulant effects. This systematic review and meta-analysis tested the clinically more relevant longer-term effects of Methylphenidate (20 studies; minimum 1 week) and Atomoxetine (8 studies; minimum 3 weeks) on reaction time, attention, inhibition, and working memory, searching papers on PubMed, Embase, Ovid MEDLINE, and PsycINFO.

The meta-analysis of 18 studies in 1667 subjects showed that methylphenidate was superior to placebo in all cognitive domains with small to medium effect sizes (Hedges g of 0.34-0.59). The meta-analysis of atomoxetine included 7 studies in 829 subjects and showed no effects in working memory, but superior effects in the other domains with medium to large effect sizes (Hedge's g of 0.36-0.64). Meta-regression analysis showed no drug differences on cognitive effects.

The meta-analyses show for the first time that chronic Methylphenidate and Atomoxetine have comparable effects of improving executive functions in people with ADHD.

Keywords: ADHD; stimulant medication; non-stimulant medication; methylphenidate; atomoxetine; cognitive function; executive functions; attention; working memory; inhibition; reaction time, reaction time variability, meta-analysis; systematic review

1. Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most prevalent neurodevelopmental disorders (4-7% prevalence) (Polanczyk et al., 2014). ADHD is defined in the DSM-5 as persistent, age-inappropriate and impairing symptoms of inattention and/or hyperactivity/impulsiveness (APA, 2022). ADHD persists into adulthood in the majority of cases (Faraone et al., 2021, Faraone et al., 2023 [Nature,]). ADHD is associated with deficits in cognitive functions, most consistently in executive functions such as motor and interference inhibition, sustained attention, working memory, timing, psychomotor speed, reaction time variability (RTV), and switching (Kofler et al., 2013; Pievsky and McGrath, 2017; Faraone et al, 2021, 2023; Noreika et al., 2013; Senkowski et al., 2023). However, evidence for cognitive deficits is more consistent in children than in adolescents or adults with ADHD (Groen et al., 2013; Pievsky and McGrath, 2018) Functional magnetic resonance imaging studies (fMRI) have shown that this is underpinned by reduced activation in several domain-specific inferior and dorsolateral fronto-striatal, fronto-parietal and fronto-cerebellar regions and networks (Hart et al., 2012, 2013; Norman et al., 2016; Lukito et al., 2021, Sutcubasi et al., 2020) and there is evidence for a delay in functional maturation in particular in ventral and dorsal attention and executive control networks (Sripada et al., 2014). Several of these regions are also smaller in structure, in particular frontal, temporal, basal ganglia, and limbic regions (Hoogman et al., 2013, 2017). There is furthermore evidence for neurotransmitter abnormalities, most prominently in dopaminergic and noradrenergic systems (Faraone, 2018; Fusar-Poli et al., 2012).

First line treatment for ADHD is with stimulant medication (most commonly Methylphenidate, followed by Amphetamine, Dexamphetamine, Lisdexamfetamine), shown to block dopamine transporters and to enhance dopamine and noradrenaline (Faraone et al., 2018), while second-line treatment (for stimulant non-responders, or poor tolerability) is with non-

stimulant noradrenergic agonist medication (most commonly Atomoxetine, followed by Guanfacine and Clonidine) which enhance noradrenaline but also dopamine in frontal and cortical regions (Groom & Cortese, 2022). A recent network meta-analysis on drug efficacy and safety/tolerability closest to 12 weeks including 133 randomized double-blind controlled studies (RCTs) showed highest efficacy based on clinician's ratings for amphetamines (Standardized mean difference [SMD] = 1), followed by methylphenidate (SMD = –0.78) and atomoxetine (SMD = – 0.56) in children and adolescents, with similar findings in adults with highest efficacy for amphetamines (SMD = –0.79), followed by methylphenidate (SMD = – 0.49,), bupropion (SMD = – 0.46,), and atomoxetine (SMD = 0.45). Guanfacine was efficacious for children and adolescents based on clinician's ratings (SMD = 0.67), while no sufficient data was available for adults (Cortese et al., 2018). However, taking into account both efficacy and safety/tolerability, methylphenidate in children and adolescents, and amphetamines in adults were considered as preferred first-choice medications for the short-term treatment of ADHD (Cortese et al., 2018).

There is evidence that acute or longer-term pharmacological treatments do not only alleviate ADHD related behaviors, but also improve cognitive performance (Coghill et al., 2018). However, it has been shown that cognitive deficits are not closely or causally associated with behavioral symptoms (Coghill et al., 2013; van Lieshaut 2013), and there is large cognitive heterogeneity, with a substantial proportion of people with ADHD not showing cognitive deficits (Nigg et al., 2005; Sonuga-Barke, 2003; Sonuga-Barke et al., 2010). Behavioral and cognitive effects of stimulants are hence not strongly associated, which makes it important to understand the specific effects of ADHD medications on cognitive functions (Coghill 2014).

Four meta-analyses tested the effects of ADHD medications on cognition in ADHD (Coghill et al., 2014; Tamminga et al., 2016; Pievsky & McGrath et al., 2018; Vertessen et al., 2022). Two of them included only children and adolescents with ADHD (Coghill et al., 2013;

Vertessen et al., 2022), one included both children/adolescents and adults with ADHD (Tamminga et al., 2016) and one included only adults with ADHD (Pievsky & McGrath et al., 2018).

The first comprehensive meta-analysis included 36 parallel group and counterbalanced crossover studies with 31 studies testing acute doses and 5 studies testing chronic doses of methylphenidate compared to placebo in children and adolescents with ADHD (Coghill et al., 2014). Methylphenidate compared to placebo improved all cognitive functions. Specifically, there were medium effect sizes in non-executive memory (0.60), and RTV (0.62), and small effect sizes in executive memory (0.26), reaction time (RT) (0.21), and inhibition (including motor and interference inhibition) (0.41).

The most recent meta-analysis, which also only included children and adolescents with ADHD, meta-analyzed 31 within subject and counterbalanced crossover studies of both single dose (N = 22) and chronic dose stimulant effects (N = 9) on several neurocognitive functions (Vertessen et al., 2022). The meta-analysis found significant positive effects of methylphenidate across all dose ranges in all measures with similar results as Coghill et al., 2014 in overlapping domains with medium effect size in RTV (0.73) and cognitive flexibility (0.67), and small effect size in RT (0.29), non-executive memory (0.33), executive memory (0.20), and inhibition (0.32) (including motor, interference inhibition, premature and commission errors in the continuous performance test (CPT)).

A study that included pediatric (N = 39) and adult studies (N = 11) meta-analyzed the effects of methylphenidate versus placebo on cognition in 50 parallel group and crossover studies, of which 31 tested acute and 19 tested chronic dosages (Tamminga et al., 2016). Significant superior effects were found for Methylphenidate versus placebo in sustained attention with an effect size of 0.42, and in motor inhibition with an effect size of 0.40, similar to the effect size of 0.41 found in the meta-analysis of Coghill et al. (2014) and 0.32 for

inhibition in the meta-analysis of Vertessen et al. (2022). However, unlike in the other 2 meta-analyses, the effect on working memory was not significant with a small effect size of 0.24 (Tamminga et al., 2016).

One meta-analysis tested the effects of methylphenidate versus placebo on performance of only adults with ADHD including 21 parallel group and crossover studies consisting of 12 studies measuring effects of acute dosages, and 9 studies measuring effects of chronic dosages (Pievsky and McGrath, 2018). Adults with ADHD showed significant performance improvements with stimulants compared to placebo with small effect sizes in memory (0.25), working memory (0.13), RTV (0.16), vigilance (0.22), and inhibition (including motor and interference inhibition, and commission errors in the CPT) (0.23). No significant improvements were found in the domains of memory, RT, and set–shifting. The meta-analysis that included only adults with ADHD (Pievsky and McGrath, 2018) thus reported the lowest effect sizes, which is parallel to meta-analytic findings of larger effect sizes for stimulants improving behavioral symptoms of children/adolescents than those for adults with ADHD (Cortese et al., 2019). The inferior stimulant effects on cognition in adults with ADHD (Tamminga et al., 2016) (compared to the other 3 meta-analyses) may also be related to the fact that cognitive functions are less impaired in adults than children with ADHD and may be less susceptible to improvement (Groen et al., 2013; Pievsky and McGrath, 2018).

So far there are no meta-analyses on the chronic effects of non-stimulants on cognitive functions in ADHD. There are only 8 studies that tested the effects of chronic administration of non-stimulants compared to placebo on cognition in ADHD patients, of which 5 studies are in children and adolescents with ADHD (4 studies tested atomoxetine, 1 tested guanfacine) and 3 studies in adults with ADHD (testing atomoxetine).

In children and adolescents with ADHD, improvements with atomoxetine versus placebo were found on inhibitory control in 2 studies using commission errors in the CPT and the

Go/No-go task (GNG) after 8 weeks and 6 weeks, respectively (Wehmeier et al., 2012; Griffiths et al., 2018) but not in Stop task measures after 4 weeks (de Jong et al., 2009). Furthermore, Wehmeier et al. (2012) found improvement in RT and sustained attention after 8 weeks but neither de Jong et al. (2009) (4 weeks) nor Griffiths et al. (2018) (6 weeks) found a RT improvement measured in the Stop task. Working memory performance was not improved after 4 weeks (de Jong et al., 2009) or 16 weeks of atomoxetine versus placebo (Wietecha et al., 2013).

In adults with ADHD, improvements were found with atomoxetine versus placebo in performance on interference inhibition in the Stroop task after 3 weeks (Spencer et al., 1998) but not in another study after 10 weeks of treatment (Faraone, et al. 2005) and in inhibitory control, sustained attention, and RT after 8 weeks of treatment (visual information processing task), but not on visual processing (Fan et al., 2017).

Only one (pediatric) study tested the chronic effects of guanfacine against placebo and found no effects after 45 days of treatment on any cognitive tasks measured, including sustained attention, spatial working memory, and visual-motor processing (Kollins et al., 2011). In conclusion, findings of the effects of non-stimulants on cognition in ADHD are inconsistent, and so far, there is no systematic review or meta-analysis.

While for the effects of stimulant medication on cognition in ADHD there are 4 meta-analyses (Coghill et al., 2014; Pievsky and McGrath, 2018; Tamminga et al., 2016; Vertessen et al., 2022), the studies did not focus specifically on the effects of chronic dose administration on cognitive functions in people with ADHD. Effects of chronic dose, however, are clinically more relevant as they reflect the typical use of stimulants in patients with ADHD. Furthermore, chronic dose effects of stimulants on cognition can be better compared to the effects of non-stimulants on cognition, which are rarely tested after an acute dose, given that non-stimulants

like atomoxetine take several weeks to show a behavioral improvement of ADHD symptoms (Montoya et al., 2009).

The aim of this study was therefore to conduct a systematic review and meta-analyses on the chronic effects of stimulants and non-stimulants on the key domains of cognition that are typically impaired in ADHD, i.e., RT, attention (including sustained attention, response variability), inhibition (including motor and interference inhibition and switching) and working memory. Based on the literature reviewed above, we hypothesize that chronic stimulants versus placebo will significantly improve performance in all executive function domains, while chronic non-stimulants versus placebo will improve performance in inhibition and attention domains with only minor or no effects on RT and working memory. We furthermore hypothesize based on the above reviewed meta-analyses (Coghill et al., 2014; Pievsky and McGrath, 2018; Tamminga et al., 2016; Vertessen et al., 2022), that the effects of chronic stimulant medication on cognition will be stronger for children than for adults with ADHD. We furthermore hypothesize that studies that were individually titrated will show stronger effects than those that tested fixed dosages.

2. Methods

A systematic literature search was conducted on common search engines to identify studies that evaluated the chronic effects of stimulant and non-stimulant medication on various neuropsychological domains. This systematic review/meta-analysis was pre-registered on Open Science Framework (Center for Open Science): https://doi.org/10.17605/OSF.IO/N8MXP.

2.1. Search strategy

A literature search was conducted on PubMed, Embase, Ovid MEDLINE, and PsycINFO until the end of June 2023. Additional papers were hand searched from existing systematic reviews or meta-analyses, or from references of relevant papers. The search terms contained the following common and specific words to identify studies that measured the effects of stimulants and non-stimulants on cognitive performance in children and adults with ADHD ((Attention Deficit Hyperactivity Disorder or ADHD or hyperkinetic disorder or Attention Deficit Disorder or ADD) AND (stimulants or stimulant medication or non-stimulants or non-stimulant medication) AND/OR (methylphenidate or dexamphetamine or lisdexamfetamine or atomoxetine or guanfacine) AND (reaction time or reaction time variability or attention or selective attention or sustained attention or inhibition or motor inhibition or interference inhibition or working memory or time estimation or timing or decision making or temporal discounting) AND/OR (cognitive function or cognitive functions or executive functions). Studies with sufficient measures in the following cognitive domains were included in this systematic review and meta-analysis: speed of response (i.e., reaction time), attention (i.e., omission errors in vigilance/sustained attention tasks; interindividual reaction time variability), inhibition (measures of motor and interference inhibition, commission errors in vigilance/sustained attention tasks), and working memory (scores, errors, or correct responses). Some studies that did not include sufficient data for meta-analysis were excluded from the meta-analysis but were included in the systematic review.

2.2. Inclusion and Exclusion Criteria

2.2.1. Participants

Participants with either a DSM–5 or earlier clinical diagnosis of ADHD and its presentations (DSM-5)/subtypes (DSM-IV and older), or those above the cut-off point for ADHD on validated research diagnostic instruments were included. Comorbid psychiatric or

neurological conditions were included only if ADHD was the primary disorder. Studies were required to have 10 or more participants. Studies with less than 10 participants may be underpowered and insufficient to provide reasonable evidence (Brysbaert, 2019). Studies must have had participants with a minimum score of 70 or more on Intellectual Quotient (IQ) tests to rule out the possibility of intellectual impairment.

2.2.2. Study designs

Included were double-blind, placebo-controlled, randomized studies, either parallel or cross-over, that tested the effects of chronic (minimum of 3 days) dosage of stimulant or non-stimulant medications on the above-mentioned executive function measures in ADHD. Included licensed stimulant medications were methylphenidate, dexamphetamine, and lisdexamfetamine, and licensed non-stimulant medications were atomoxetine and guanfacine. All other interventions were not included in this review. Studies that compared one medication to another or compared results of baseline/off-medication scores to follow-up results were excluded from this review. Studies were included regardless of the settings, i.e., where the intervention took place such as school, home, or clinic. Due to the possibility of situational confounds, studies that included cognitive testing during functional magnetic resonance imaging, event related potentials or any other imaging devices were not included in this review.

2.3. Study Selection

All studies were double-coded and were first screened based on the title and abstract using the web-tool Rayyan (Ouzzani et al., 2016). The raters (FI, SEM) then analyzed relevant papers thoroughly through full text based on the inclusion and exclusion criteria for potential analysis. Any uncertainty or difference of opinion on studies was resolved by the senior reviewer (KR) who screened the full text of the selected papers and made the final decision on whether data in studies were relevant and matched the inclusion/exclusion criteria. Raters were blinded to

each other's results but were not blinded to author information, affiliations, or publication journals during screening.

2.4. Data Extraction

One of the first authors (FI) extracted the information which was checked for validity by the other first author (SEM) and the senior author (KR). All relevant study details were extracted and contained the following information: author, year of publication, study title, country of study, study design, sample size, participant information (i.e., male-to-female ratio, age, IQ), cognitive domains, cognitive tasks and measures at each timepoint, clinical diagnosis, comorbidities, medication status, medication type and dose, duration of drug treatment, and findings of the study on the relevant cognitive outcomes and statistical results. For studies that measured several dosages of methylphenidate, we adopted the same approach described in the meta-analysis of Coghill et al., 2014 and meta-analyzed only the highest dosage, as this dosage was closer to the typical clinical dosage. This approach is further supported by the systematic review on stimulant effects on cognition in ADHD from Pietzrak et al. (2006) that found that high dosages of methylphenidate improved cognition in children and adolescents with ADHD more than low or moderate dosages in 7 cognitive outcomes across 12 studies. The meta-analysis from Vertessen et al. (2022) found no dosing effects on inhibitory control, executive memory or cognitive flexibility, but higher effect sizes with higher dosages on reaction time, reaction time variability and non-executive memory. Last, the statistical rationale was that including lower dosages from the same individuals would not increase the sample size but reduce the overall effect (due to the likely smaller effects from lower dosages), ultimately decreasing the statistical power of the meta-analyses.

For the meta-analyses on the studies testing effects of methylphenidate and atomoxetine studies, relevant data from studies with sufficient information for analysis were extracted into

2 separate tables. We recorded the change scores between baseline and follow-up for every outcome we found suitable with enough relevant data for analysis. We did not manually calculate any missing data; we recorded any available data for the review and meta-analysis.

2.5. Quality assessment and risk of bias

2.5.1. Cochrane Risk of Bias 2.0. Tool for RCTs

To guarantee that only high-quality datasets were included, we used Cochrane Risk of Bias 2.0. Tool for RCTs (Sterne et al., 2019).

2.5.2. Quality of the evidence (GRADE)

To evaluate the certainty of evidence of our meta-analyses, we used Cochrane Handbook for systematic reviews and interventions (Higgins et al., 2023) and included the GRADE approach, assessing the data quality based on evidence that is separated into 5 different domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (Schünemann et al., 2023). Criteria were used as described by Schünemann et al. (2013); however, the ranges (I^2) for assessing inconsistency were slightly adapted (I < 40% not relevant H; 40-60% moderate; I = 60-90% substantial), as the categories described in Schünemann et al. (2013), are overlapping. We used the Cochrane Risk of Bias 2.0. Tool for RCTs described above to evaluate the risk of bias. Indirect evidence refers to evidence from trials conducted in special population groups (e.g., due to strict exclusion criteria) or that have not measured the outcomes but surrogates (e.g., cognitive tests to infer cognitive functioning, as was the case here). Finally, as in previous studies (Solanes et al., 2021; Radua et al., 2023), we rated serious imprecision if the confidence interval included both null and large effects or if the overall number of individuals in each arm was inferior to 394. This number corresponds to the sample size required to detect small effects (g = 0.2) with 80% statistical power according to a standard formula (R function “power.t.test”). We rated very serious imprecision if the overall number

of individuals in each arm was inferior to 394 and the confidence interval included both null and large effects or if the overall number of individuals in each arm was smaller than 64. This number corresponds to the sample size required to detect medium effects (g = 0.5) with 80% statistical power. The results of the GRADE approach are summarized in Table 1.

2.6. Synthesis/Statistical Analysis

The random effects meta-analyses were conducted in R's metansue and metafor software packages (v2.5 and v4.2-0, respectively; Viechtbauer, 2010, Radua et al., 2015, Albajes-Eizagirre et al., 2019). Specifically, we used metansue to convert the various statistics reported in the studies into Hedges' g (i.e., SMD corrected for small sample size) of the difference between the drug conditions (placebo, medication) for the differences in the performance measures pre-post within each drug condition. When studies reported means and standard deviations for each group separately for pre- and post- measures under the placebo and under the medication conditions, we first calculated the pre-post change for each medication condition (in within-group cross-over designs) or for each medication group (for parallel between-group designs), considering a r=0.5 correlation between them, and then the within-group medication condition differences (for cross-over designs) or the between-medication group differences (for parallel designs) in the pre-post changes. If this information was not reported, we converted the available statistics (e.g., F-values, t-values, or p-values) into SMDs. Therefore, effect sizes are standardized mean differences (SMD) (between-medication group/within-medication condition) in the pre-post changes. We synthesized and assembled studies that measured similar cognitive domains to have a valid and reliable meta-analysis for each cognitive domain if there were more than 3 studies with relevant outcome variables available. The following cognitive domains were meta-analyzed: speed of response (reaction time measured in different tasks), attention (including omission errors in the CPT and other

sustained attention tasks; intra-individual reaction time variability), inhibition (stop signal reaction time or probability of inhibition in stop tasks, probability of inhibition or commission errors in Go/No-go tasks, Stroop/Simon interference inhibition scores in Stroop/Simon/Flanker tasks, commission errors in CPT), and working memory (accuracy or errors in working memory tasks). Studies with insufficient data, such as missing standard deviation (SD) or standard error values, were excluded from the meta-analysis. Studies were pooled using metafor random-effects multilevel models, which allow the inclusion of more than one effect size per study. We assessed the effects of heterogeneity with the I^2 statistic; for multilevel models, we calculated I2 as recommended by the creator of the metafor package at https://www.metafor-project.org/doku.php/tips. Finally, we used the metansue's metabias function (conceptually analog to Egger's test) to detect potential publication/reporting bias.

2.6.1. Sensitivity Sub-Meta-Analyses

Depending on the number of studies, we also aimed to conduct sensitivity or subgroup meta-analyses on studies testing stimulant effects on cognition only in children/adolescents and in adults with ADHD given evidence for stronger effects of medications in children/adolescents than adults with ADHD on symptoms (Cortese et al., 2018) and given evidence for larger cognitive impairments in children than adults with ADHD which may be more susceptible to medication improvements (Groen et al., 2013; Pievsky and McGrath, 2018).

We also conducted subgroup meta-analyses on studies using titrated and fixed dosages in order to test whether meta-analytical findings on studies using individually titrated dosages would achieve superior effect sizes than those that used fixed dosages.

2.6.2. Meta-regression analyses: statistical comparison between the effects of atomoxetine and the effects of methylphenidate on cognitive functions and between the effects of methylphenidate on cognitive functions in children/adolescents and those on adults.

In addition, to statistically compare the effects of methylphenidate and those of atomoxetine on cognition, a meta-regression analysis was conducted for each cognitive domain to assess whether the type of medication (methylphenidate versus atomoxetine) moderated the effects (i.e., testing whether the effects of methylphenidate were different from the effects of atomoxetine). Meta-regression analyses were also conducted to compare statistically the effects of methylphenidate in children versus the effects in adults for each cognitive domain. This was only conducted in the methylphenidate meta-analysis as there were not sufficient data available for atomoxetine.

3. Results

A total of 28 studies (N = 1384 on medication, N = 1269 on placebo) were included in the review. Figure 1 shows a complete outlined PRISMA flow diagram. The primary reasons for exclusion of studies were related to study participants not meeting inclusion criteria (i.e., IQ<70, non-ADHD, animal studies, major neurological conditions), the study not meeting criteria for study design and comparators (i.e., comparing atomoxetine with methylphenidate but not with a placebo condition, comparing medication with off medication/baseline instead against a placebo condition, studies being single dose studies; naturalistic studies, pilot studies, case reports or reviews), or studies providing different outcomes than cognition (rating scales, nonrelevant outcomes).

The meta-analysis and the systematic review on the effects of stimulant medication versus placebo only included studies testing methylphenidate, as there were no studies testing the chronic effects of other types of stimulant medications that met inclusion criteria. Eighteen studies on chronic effects of methylphenidate that provided sufficient data for the meta-analysis were included (Boonstra et al., 2005; Bron et al., 2014; Campez et al., 2022; Coghill et al., 2007; Epstein et al., 2011; Goodman et al., 2017; Hadar et al., 2021; Kortekaas – Rijlaarsdam

et al., 2020; Luman et al., 2015; Merrill et al., 2022; Murray et al., 2011; Nigg et al.,1996; Rhodes et al., 2004; Schachar et al., 2008; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011; and Zeiner et al., 1999), while 2 additional studies were included in the systematic review (Blum et al., 2011; Kupietz et al., 1998).

Twenty studies measured the effects of stimulants and 8 studies measured the effects of non-stimulants on cognitive functions of reaction time, attention, inhibition, and working memory in people with ADHD.

Of the 8 studies testing chronic effects of non-stimulants on cognitive functions, 7 studies measured the effects of atomoxetine (de Jong et al., 2009; Fan et al., 2017; Faraone et al., 2005; Griffiths et al., 2018; Spencer et al., 1998; Wehmeier et al., 2012, Wietecha et al., 2013), and one study (Kollins et al., 2011) tested the effects of guanfacine. Given that only one study testing guanfacine met inclusion criteria (Kollins et al., 2011), we only meta-analyzed the effects of (chronic) atomoxetine versus placebo.

3.1. Cochrane Risk of Bias 2.0 Tool for RCTs: results

All 28 studies were assessed for their quality and risk of bias using Cochrane Risk of Bias 2.0 tool for crossover and parallel RCT studies (Sterne et al., 2019). Twenty studies (Boonstra et al., 2011; Bron et al., 2014; Campez et al., 2022; de Jong et al., 2009; Fan et al., 2017, Faraone et al., 2005; Goodman et al., 2017; Kortekaas–Rijlaarsdam et al., 2020; Kupietz et al., 1988; Merrill et al., 2022; Murray et al., 2011; Nigg et al., 1996; Rhodes et al., 2004; Solanto et al., 2009; Spencer et al., 1998; Tamminga et al., 2021; Wehmeier et al., 2012; Wietecha et al., 2013; Wigal et al., 2011; Zeiner et al., 1999) were rated as “low” risk of bias, 7 studies (Blum et al., 2011; Coghill et al., 2007; Epstein et al., 2011; Griffiths et al., 2018; Hadar et al., 2021; Luman et al., 2015; Schachar et al., 2008) were rated as having “some concerns” due to missing outcome data, selection of reported outcome or measurement of the outcome,

differences in baseline values and missing measures of adherence and one study (Kollins et al., 2011) was rated as "high" risk because of missing outcome data for some participants.

3.2. Systematic review: stimulant medication

Table 2 outlines all the details of each eligible study. Of the 20 studies testing the effects of Methylphenidate against placebo, 16 studies were cross-over (Blum et al., 2011; Boonstra et al., 2005; Bron et al., 2014; Campez et al., 2022; Coghill et al., 2007; Epstein et al., 2011; Hadar et al., 2021; Kortekaas-Rijlaarsdam et al., 2020; Luman et al., 2015; Merrill et al., 2022; Murray et al., 2011; Rhodes et al., 2004; Schachar et al., 2008; Solanto et al, 2009; Wigal et al., 2011; Zeiner et al., 1999), while 4 were parallel designed (Goodman et al., 2017; Kupietz et al., 1988; Nigg et al.1996; Tamminga et al., 2021). Sixteen studies tested children with ADHD (Blum et al., 2011; Campez et al., 2022; Coghill et al., 2007, Epstein et al., 2011; Hadar et al., 2021; Kortekaas – Rijlaarsdam et al., 2020; Kupietz et al., 1998; Luman et al., 2015; Merrill et al., 2022; Murray et al., 2011; Nigg et al., 1996; Rhodes et al., 2004; Schachar et al., 2008; Solanto et al., 2009; Wigal et al., 2011; Zeiner et al., 1999), 3 tested adults with ADHD (Boonstra et al., 2005; Bron et al., 2014; Goodman et al., 2017), and one study (Tamminga et al., 2021) tested both children and adults with ADHD.

3.2.1. Reaction Time

Eleven studies measured the chronic effects of methylphenidate on measures of reaction time (Boonstra et al., 2005; Bron et al., 2014; Coghill et al., 2007; Epstein et al., 2011; Kortekaas-Rijlaarsdam et al., 2020; Murray et al., 2011; Nigg et al., 1996; Schachar et al., 2008; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011). Four studies found improvements on RT, of which 2 were in the Test of Variables of Attention Test (TOVA) in 67 (Murray et al., 2011) and 71 children with ADHD (Wigal et al., 2011) and one in 50 children and adolescents, but not in 48 adults with ADHD in median RT on the Simple RT task (Tamminga et al., 2021), and one on the RT to targets in the GNG task in 75 children and

adolescents with ADHD (Coghill et al., 2007), but not on the 5-Choice RT task. Seven studies failed to show any improvements on measures of RT. Three of these studies were in children, specifically 93 children with ADHD (Epstein et al., 2011), 23 children with ADHD (Nigg et al., 1996) and 25 children with ADHD (Solanto et al., 2009); 2 of these studies were in children and adolescents, specifically 17 children and adolescents with ADHD (Kortekaas – Rijlaarsdam et al., 2020) and 63 children and adolescents with ADHD (Schachar et al., 2008); and 2 studies were in adults, specifically 22 adults with ADHD (Bron et al., 2014) and 43 adults with ADHD (Boonstra et al., 2005).

3.2.2. Attention

Sixteen studies tested the chronic effects of methylphenidate versus placebo on measures of attention (Blum et al., 2011); Boonstra et al., 2005; Bron et al., 2014; Campez et al., 2022; Epstein et al., 2011; Goodman et al., 2017; Hadar et al., 2021; Luman et al., 2015; Merrill et al., 2022; Murray et al., 2011; Nigg et al.,1996; Schachar et al., 2018; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011; Zeiner et al., 1999). Seven studies showed significant performance improvements in all their measurements of attention in 22 to 78 children with ADHD (Hadar et al., 2011; Merrill et al, 2022; Nigg et al., 1996; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011), 17 children and adolescents (Schachar et al., 2018), and 48 adults with ADHD (Tamminga et al., 2021) on the number of interruptions in the Visuomotor Attention Test (VMAT) (Hadar et al., 2011), on the number of omission errors (Nigg et al., 1996, Solanto et al., 2009), on RTV and Hit Reaction Time Standard Error/Reaction time consistency (HIT RT SE) (Solanto et al., 2009) on the CPT, on RTV on the Sustained Attention to Response Task (SART) (Merrill et al., 2022), on the simple RT task (Tamminga et al., 2011) and on omission errors and RTV (Wigal et al., 2011). Another 7 studies found improvements in some, but not all measures of attention in children with ADHD (Blum et al., 2011; Epstein et al., 2011; Luman et al., 2015; Murray et al., 2011; Zeiner et al.,

1999), and adults with ADHD (Boonstra et al, 2005; Bron et al., 2014). There were no medication effects on omission errors in the CPT, and in the sky search dual, creature counting, map mission, and sky search, in The Test of Everyday Attention for Children (TEA-Ch) in 25 children with ADHD; however, the score of the dual task in the TEA-Ch and attentional control of the Opposite World task performance showed improvements (Blum et al., 2011). The performance of 93 children with ADHD in the RTV on the choice task SST, and n-back, in attention was not improved, but in the attentional network task (ANT) and GNG tasks, as well as on the percent accuracy in ANT (Epstein et al., 2011). Significant improvements were found in the RTV on the Time Production Task (TPT) but not the percent accuracy in 23 children with ADHD on the TPT (Luman et al., 2015). RTV but not omission errors were improved in the TOVA in 68 children with ADHD (Murray et al., 2011). Omission errors in 36 boys with ADHD were only improved in the children's checking task but not in the CPT (Zeiner et al., 1999). Forty-three adults with ADHD had reduced RTV and increased attentiveness in the CPT; however, no difference between methylphenidate and placebo was found on the RTV in the change task (Boonstra et al., 2005). There was a significant reduction of RTV in the Computerized CPT (C – CPT) but not in the TOVA, nor in omission errors in both tasks (C-CPT, TOVA) in 22 adults with ADHD (Bron et al., 2014). Two studies did not find any performance improvements in the tapping task (fast and slow coefficient of variations) in 35 children with ADHD (Campez et al., 2022), nor in omission errors in the CPT in 222 adults with ADHD (Goodman et al., 2017).

3.2.3. Inhibition

Fourteen studies measured the chronic effects of methylphenidate on measures of inhibition (Blum et al., 2011; Boonstra et al., 2005; Bron et al., 2014; Campez et al., 2022; Coghill et al., 2007; Epstein et al., 2011; Kortekaas – Rijlaarsdam et al., 2020; Murray et al., 2011; Nigg et al.,1996; Schachar et al., 2008; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011;

Zeiner et al., 1999). Four studies (Campez et al., 2022; Coghill et al., 2007; Murray et al., 2011; Nigg et al., 1996) found improvements in all measures of inhibition. The total points earned in the Choice Impulsivity Task were significantly improved in 35 children with ADHD (Campez et al., 2022). Seventy-five children and adolescents with ADHD showed significant improvements in errors of distractors on the GNG task (Coghill et al., 2007). Commission errors in the TOVA were significantly reduced in 68 children with ADHD (Murray et al., 2011). There was a significant effect of methylphenidate in 22 boys with ADHD on commission error reductions in the CPT (Nigg et al., 1996). Five studies (Blum et al., 2011; Boonstra et al., 2005; Epstein et al., 2011; Schachar et al., 2008; Zeiner et al., 1999) found improvements in some but not other measures of inhibition in children with ADHD. In 30 children with ADHD, there were significant reductions in commission errors in the Gordon Diagnostic System – CPT, but not in a response inhibition parameter of the Walk don't Walk task. While commission errors were improved, there were no effects in SSRT on the change task in 43 adults with ADHD (Boonstra et al., 2005). Accuracy in the GNG task was improved but not accuracy or SSRT in the SST in 93 children with ADHD (Epstein et al., 2011). Seventeen children with ADHD improved in the SSRT in the SST, but not in commission errors in the CPT (Schachar et al., 2008). Commission errors in the CPT were reduced but not on the children's checking task in 36 boys with ADHD (Zeiner et al., 1999). Five studies found no performance improvements in adults with ADHD (Bron et al., 2014; Tamminga et al., 2021) nor in children with ADHD (Kortekaas – Rijlaarsdam et al., 2020; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011) on any measures of inhibition, including in commission errors in the C – CPT and in the TOVA in 22 adults with ADHD (Bron et al., 2014), nor in the GNG task in 48 adult men with ADHD (Tamminga et al., 2021) nor in interference scores in the flanker task in 63 children and adolescents with ADHD (Kortekaas-Rijlaarsdam et al., 2020) nor in commission errors in the CPT nor in interference scores in the Stroop task in 25 children with ADHD (Solanto et al.,

2009) nor commission errors in the GNG task in 50 boys with ADHD (Tamminga et al., 2021) and 78 children with ADHD in the TOVA (Wigal et al., 2011).

3.2.4. Working Memory

Eleven studies (Blum et al., 2011; Campez et al., 2022; Coghill et al., 2007; Epstein et al., 2011; Kortekaas – Rijlaarsdam et al., 2020; Kupietz et al., 1988; Murray et al., 2011; Rhodes et al., 2005; Tamminga et al., 2021; Wigal et al., 2011; Zeiner et al., 1999) measured the effects of chronic methylphenidate versus placebo on working memory. Campez et al. (2022) found improvements in 35 children with ADHD in the number of correct responses in the Working Memory Task (WMT). Seven studies found significant improvements in some but not all measures of working memory in children (Murray et al., 2011; Wigal et al., 2011), and children and adolescents with ADHD (Coghill et al., 2007; Kupietz et al., 1988; Rhodes et al., 2005; Tamminga et al., 2021; Zeiner et al., 1999). Thus, accuracy in the DMS was significantly improved, but not on the spatial working memory task in 75 children and adolescents with ADHD (Coghill et al., 2007). Errors were reduced in the paired associate learning task, whereas number of correct responses performance in the short-term memory task showed no improvements after methylphenidate in 21 children and adolescents with ADHD (Kupietz et al., 1998). The score on the finger window backwards was improved; however, the score on the digit span backwards was not improved in 68 children with ADHD (Murray et al., 2011). Significant improvements were found in the immediate and delay accuracy performance in the DMS but not in errors in the spatial working memory task in 75 children and adolescents with ADHD (Rhodes et al., 2005). In 50 children and adolescents with ADHD, significant performance improvements on scores in the n-back test were found at 8 weeks but not after the entire treatment duration (16 weeks) (Tamminga et al., 2021). Moreover, no significant improvements on immediate or delayed recall performance on the RAVLT was found in boys with ADHD (Tamminga et al., 2021). Forty-eight adult men with ADHD did not improve in

their scores in the n-back, nor on the immediate and delayed recall in Rey's Auditory Verbal Learning Test (RAVLT) (Tamminga et al., 2021). Significant performance improvements on the finger windows backward in the Wide Range Achievement Test (WRAT) were found, with no performance improvements on the digit span backward of the WISC in 78 children with ADHD (Wigal et al., 2011). Improvements were found in the A version of the Paced Auditory Serial-Addition task (PA-SAT) but not in the R version of the task in 36 boys with ADHD (Zeiner et al., 1999).

Four studies found no improvements in any measure of working memory in children with ADHD (Blum et al., 2011.; Epstein et al., 2011; Kortekaas – Rijlaarsdam et al., 2020) and adult men with ADHD (Tamminga et al., 2021). The accuracy in the n-back task was not improved in 93 children with ADHD (Epstein et al., 2011). No effects were found on the digit span backward in the third version of the WISC, nor on the correct responses in the Visuospatial Working Memory Task (VsWMT) in 63 children and adolescents with ADHD (Kortekaas – Rijlaarsdam et al., 2020).

In conclusion, most studies found improvements in attention, inhibition, and working memory, with the most consistent results in attention, followed by inhibition and working memory, while for reaction only one third of the studies found improvements.

3.3. Systematic Review: Non-stimulant medication

Eight studies were included. A detailed description of each eligible study included can be seen in Table 3. Four studies were crossover studies (de Jong et al., 2009; Fan et al., 2017; Griffiths et al., 2018; Spencer et al., 1998;), and 4 studies were parallel design studies (Faraone et al., 2005; Kollins et al., 2011; Wehmeier et al., 2012; Wietecha et al., 2013). Dosages of atomoxetine used typically began with 0.5 mg/kg/day in the first week and were titrated to 1.4

mg/kg/day by the second week depending on the study's protocol. Kollins et al. (2011) used 1 – 3 mg of guanfacine in children and adolescents with ADHD.

3.3.1. Reaction Time

Four randomized placebo-controlled studies (de Jong et al., 2009; Fan et al., 2017; Griffiths et al., 2018; Wehmeier et al., 2012) measured the chronic effects of atomoxetine versus placebo, and one study measured the chronic effects of guanfacine versus placebo on measures of reaction time (Kollins et al., 2011). Wehmeier et al. (2012) found significant improvements with atomoxetine versus placebo on RT in the CPT in 125 children with ADHD. Fan et al. (2017) found improvements on mean reaction time in the Delayed Matching to Sample Task (DMS) but no improvements on RT in the Rapid Visual Information Processing (RVIP) task in 48 adults with ADHD. RT was not found to be improved in the go trials of the Stop Signal Task (SST) in 16 children with ADHD (De Jong et al., 2009) and in the CPT in 116 children and adolescents with ADHD (Griffiths et al., 2018).

No effects of guanfacine were found on mean RT in the choice reaction time task in 178 children and adolescents with ADHD (Kollins et al., 2011)

3.3.2. Attention

Chronic atomoxetine versus placebo effects were measured in 3 studies (Fan et al., 2017; Griffiths et al., 2018; Wehmeier et al., 2012), and chronic guanfacine versus placebo was measured in one study (Kollins et al., 2011). Atomoxetine improved RTV and omission errors in the CPT in 125 children with ADHD (Wehmeier et al., 2012), but had no effects on omission errors and RTV in the CPT in 116 children and adolescents with ADHD (Griffiths et al., 2018). Atomoxetine improved the probability of hits in the RVIP task of attention in 48 adults with ADHD (Fan et al., 2017).

Guanfacine relative to placebo did not improve performance in The Permanent Product Measure of Performance task (PERMP) in 178 children and adolescents (Kollins et al., 2011).

3.3.3. Inhibition

Six studies tested the chronic effects of atomoxetine versus placebo on measures of inhibition (de Jong et al., 2009; Fan et al., 2017; Faraone et al., 2005; Griffiths et al., 2018; Spencer et al., 1998; Wehmeier et al., 2012). Four studies found significant improvements in inhibition in 116 children and adolescents with ADHD on commission errors in the Go/No-go task (GNG) (Griffiths et al., 2018) and in 125 children with ADHD on commission errors in the CPT (Wehmeier et al., 2012), as well as in 48 adults with ADHD in the probability of false alarm in the RVIP task (Fan et al., 2017) and in 21 adults with ADHD in the interference t-test score in the RVIP task (Spencer et al., 1998). However, no effects were found in 16 children with ADHD in the Stop Signal Reaction Time (SSRT) in the SST (de Jong et al., 2009), nor in 424 adults with ADHD on the interference score in the Stroop task (Faraone et al., 2005).

3.3.4. Working Memory

Three studies measured the chronic effects of atomoxetine versus placebo (de Jong et al., 2009; Fan et al., 2017; Wietecha et al., 2013), and one study (Kollins et al., 2011) measured the effects of guanfacine versus placebo on measures of working memory. No significant performance improvements were observed in 16 children with ADHD in the number of correct sequences completing the Corsi Block Tapping Task (de Jong et al., 2009), nor in 27 children and adolescents with ADHD in the central executive component score in the Working Memory Test Battery for Children (WMTB-C) (Wietecha et al., 2013), nor in percent accuracy in the DMS task in 48 adults with ADHD (Fan et al., 2017). Guanfacine relative to placebo did not improve performance in a working memory task (CANTAB) in 178 children and adolescents (Kollins et al., 2011).

In conclusion, the majority of studies found improvements in attention, inhibition, and reaction time, which were, however, inconsistent. No effects were observed in working memory.

3.4. Quality of the evidence (GRADE): results

All data of the 10 meta-analyses were assessed with the GRADE approach. Three meta-analyses on the atomoxetine studies were assessed as being of very low quality (inhibition, attention and working memory), while one was assessed as being of low quality (reaction time). For the methylphenidate meta-analyses, one was assessed to be of very low quality (attention), 2 were assessed to be of low quality (reaction time and inhibition), and the remaining one was assessed to be of moderate quality (working memory). All detailed results are shown in Table 1.

3.5. Meta-Analysis: Studies testing effects of methylphenidate on cognition

Eighteen studies testing the effects of stimulants on cognition in ADHD were meta-analyzed (Boonstra et al., 2005; Bron et al., 2014; Campez et al., 2022; Coghill et al., 2007; Epstein et al., 2011; Goodman et al., 2017; Hadar et al., 2021; Kortekaas – Rijlaarsdam et al., 2020; Luman et al., 2015; Merrill et al., 2022; Murray et al., 2011; Nigg et al.,1996; Rhodes et al., 2004; Schachar et al., 2008; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011; and Zeiner et al., 1999). All 18 studies tested the effects of Methylphenidate. Fifteen of the 18 studies (Campez et al., 2022; Coghill et al., 2007; Epstein et al., 2011; Hadar et al., 2021; Kortekaas-Rijlaarsdam et al., 2020; Luman et al., 2015; Merrill et al., 2022; Murray et al., 2011; Nigg et al.1996; Rhodes et al., 2004; Schachar et al., 2008; Solanto et al, 2009; Tamminga et al., 2021; Wigal et al., 2011; Zeiner et al., 1999) tested the effects of methylphenidate in children/adolescents with ADHD, 3 studies in adults with ADHD (Boonstra et al., 2005; Bron et al., 2014; Goodman et al., 2011), and 1 study in both children/adolescents and adults with ADHD (Tamminga et al., 2021). Therefore, 2 separate sensitivity meta-analyses, one on the 16 studies that included children/adolescents with ADHD

and a second one on the 4 studies that included adults with ADHD, were conducted to test whether the effect size would be larger than the effect size of the meta-analysis that included both children/adolescents and adults. In addition, a meta-regression analysis was conducted to statistically compare the meta-analytic effects of methylphenidate in children/adolescents and those in adults with ADHD on the cognitive domains.

Eleven of the 18 studies used individual titrated dosages, while 7 studies used fixed clinical dosages, either one dosage or a low and high dosage (of which the high dose was meta-analyzed). The 11 studies that tested the effects of methylphenidate on cognition using titrated dosages only (Boonstra et al., 2005; Bron et al., 2014; Campez et al., 2022; Epstein et al., 2011; Goodman et al., 2017; Kortekaas – Rijlaarsdam et al., 2020; Merrill et al., 2022; Murray et al., 2011; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011) were meta-analyzed to test if the effect size would be larger than the effect sizes in the analyses that included only fixed dosages.

3.5.1. Main Meta-Analysis of effects of Methylphenidate on Reaction Time

Eleven studies (Boonstra et al., 2005; Bron et al., 2014; Coghill et al., 2007; Epstein et al., 2011; Kortekaas-Rijlaarsdam et al., 2020; Murray et al., 2011; Nigg et al., 1996; Schachar et al., 2008; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011) tested the effects of chronic methylphenidate on measures of reaction time on a total of 467 participants with ADHD taking methylphenidate and 458 participants with ADHD taking placebo. The forest plot (Figure 2A) showed statistically significant small to medium effect size (Hedges' g = 0.34; 95% CI = [0.11 to 0.57]; p = 0.004; z = 2.9). Heterogeneity was substantial (I^2 = 71%). Imprecision of studies was not serious and publication bias was undetected (metabias p = 0.58).

3.5.1.1.Sensitivity Sub-Meta-Analysis on the effects of Methylphenidate on reaction time in pediatric studies only

Nine studies tested the effects of methylphenidate (N=405) versus placebo (N = 405) on reaction time in children/adolescents with ADHD (Coghill et al., 2007; Epstein et al., 2011; Kortekaas – Rijlaarsdam et al., 2020; Murray et al., 2011; Nigg et al., 1996; Schachar et al., 2008; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011). The sensitivity analysis in children/adolescents only found a medium effect size (Hedges' g = 0.45; 95% CI = [0.21, 0.7]; $p < 0.001$; z = 3.6). There was substantial heterogeneity ($I^2 = 72\%$), and no evidence of a publication bias (metabias p = 0.68).

3.5.1.2.Sensitivity Sub-Meta-Analysis of the effects of Methylphenidate on reaction time in adult studies only

Three studies tested the effects of methylphenidate (N=60) versus placebo (N=53) in adults with ADHD (Broonsta et al., 2005; Bron et al., 2024; Tamminga et al., 2021). The sensitivity sub-meta-analysis in adults only showed no effect (95% CI = [-0.36, 0.34]; z = 0.0).

3.5.1.3.Statistical Comparison between effects of methylphenidate in pediatric and adult studies on reaction time

Meta-regression analysis showed that there was no statistically significant difference between effects of methylphenidate and those of atomoxetine on reaction time (b = 0.00 [95% CI -0.46, 0.45]; p = 0.996; z = 0.0) between children/adolescents and adults. Heterogeneity was substantial ($I^2 = 67\%$).

3.5.1.4.Sensitivity Sub-Meta-Analysis on effects of Methylphenidate on reaction time with titrated studies only

Eight studies tested the effects of titrated dosages of methylphenidate versus placebo on reaction time in children/adolescents and adults with ADHD (Boonstra et al., 2005; Bron et al.,

2014; Epstein et al., 2011; Kortekaas – Rijlaarsdam et al., 2020; Murray et al., 2011; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011). The sensitivity analysis on the titrated dosages only showed a small to medium effect size (Hedges' g = 0.32; 95% CI = [0.02, 0.62]; p = 0.035; z = 2.1). There was substantial heterogeneity (I^2 = 80%), but no evidence of a publication bias (metabias p = 0.42).

3.5.1.5.Sensitivity Sub-Meta-Analysis on the effects of Methylphenidate on reaction time in fixed dosage studies only

Three studies tested the effects of fixed doses of methylphenidate (N = 64) versus placebo (N = 64) on reaction time in children and adolescents with ADHD (Coghill et al., 2007; Nigg et al., 1996; Schachar et al., 2008). The sensitivity analysis on the fixed dosages only found a medium effect size (Hedges' g = 0.44; 95% CI = [0.14, 0.73]; p = 0.004; z = 2.9). There was no evidence of heterogeneity (I^2 = 0%), and no evidence of publication bias (metabias p = 0.58).

3.5.2. Main Meta-Analysis on effects of Methylphenidate on Attention

Sixteen studies (Boonstra et al., 2005; Bron et al., 2014; Campez et al., 2022; Epstein et al., 2011; Godman et al., 2017; Hadar et al., 2021; Luman et al., 2015; Merrill et al., 2022; Murray et al., 2022; Nigg et al., 1996; Schachar et al., 2008; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011; Zeiner et al., 1999) provided sufficient data for meta-analysis on effects of chronic methylphenidate on measures of attention in a total of 665 participants with ADHD taking methylphenidate and 657 participants with ADHD taking placebo. The forest plot (Figure 2B) shows a statistically significant medium effect size (Hedges' g = 0.59; 95% CI = [0.44 to 0.74]; p < 0.001; z = 7.8). There was moderate heterogeneity (I^2 = 53%). Imprecision of studies were not serious, whereas publication bias was suspected (metabias p = 0.025).

3.5.2.1.Sensitivity Sub-Meta-Analysis the effects of Methylphenidate on Attention in pediatric studies only

Twelve studies tested the effects of methylphenidate (n = 504) versus placebo (n = 501) in attention in children and adolescents with ADHD (Campez et al., 2022; Epstein et al., 2011; Hadar et al., 2021; Luman et al., 2015; Merrill et al., 2022; Murray et al., 2011; Nigg et al., 1996; Schachar et al., 2008; Solanto et al., 2009; Taminga et al., 2021; Wigal et al., 2011; Zeiner et al., 1999). The sensitivity analysis in children/adolescents only showed a medium to large effect size (Hedges' g = 0.63; 95% CI = [0.46, 0.8]; $p < 0.001$; z = 7.3). There was moderate heterogeneity ($I^2 = 56\%$) and potential publication bias (meta bias p = 0.038).

3.5.2.2.Sensitivity Sub-Meta-Analysis on effects of Methylphenidate on Attention in adult studies only

Four studies tested the effects of methylphenidate (N=161) versus placebo (N=156) in adults with ADHD (Broonsta et al., 2005; Bron et al., 2024; Goodman et al., 2017; Tamminga et al., 2021). The sensitivity analysis on adults only found a medium effect (Hedge's g = 0.46, 95% CI = [0.13, 0.79]; z = -1.4). There was moderate heterogeneity ($I^2 = 42\%$) and no evidence of a publication bias (metabias p = 0.007).

3.5.2.3.Statistical Comparison between effects of Methylphenidate in pediatric and adult studies on Attention

Meta-regression analysis showed that there was no statistically significant difference between effects of methylphenidate and those of atomoxetine on attention (b = 0.03 [95% CI -0.37, 0.43]; p = 0.872; z = 0.2) between children/adolescents and adults. Heterogeneity was moderate ($I^2 = 58\%$).

3.5.2.4.Sensitivity Sub-Meta-Analysis on effects of Methylphenidate on Attention in titrated studies only

Ten studies tested the effects of titrated dosages of methylphenidate versus placebo on attention functions in children and adolescents with ADHD (Boonstra et al., 2005; Bron et al., 2014; Campez et al., 2022; Epstein et al., 2011; Goodman et al., 2011; Merrill et al., 2022; Murray et al., 2011; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011). The sensitivity sub-meta-analysis on the titrated dosages only showed a medium effect size (Hedges' g = 0.55; 95% CI = [0.38, 0.73]; $p < 0.001$; z = 6.1). There was moderate heterogeneity ($I^2 = 58\%$), and potential publication bias (meta bias p = 0.064).

3.5.2.5.Sensitivity Sub-Meta-Analysis on effects of Methylphenidate on Attention with fixed studies only

Five studies tested the effects of fixed doses of methylphenidate (N = 134) versus placebo (N = 134) on attention in children/adolescents with ADHD (Hadar et al., 2021; Luman et al., 2015; Nigg et al., 1996; Schachar et al., 2008; Zeiner et al., 1999). The sensitivity analysis on the fixed dosages only found a large effect size (Hedges' g = 0.71; 95% CI = [0.42, 1]; $p < 0.001$; z = 4.8). There was no relevant heterogeneity ($I^2 = 33\%$), and no evidence of a publication bias (metabias p = 0.27).

3.5.3. Main Meta-Analysis on effects of Methylphenidate on Inhibition

Thirteen studies **(**Boonstra et al., 2005; Bron et al., 2014; Campez et al., 2022; Coghill et al., 2007; Epstein et al., 2011; Kortekaas – Rijlaarsdam et al., 2020; Murray et al., 2011; Nigg et al.,1996; Schachar et al., 2008; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011; Zeiner et al.,1999) provided sufficient data to meta – analyze the effects of chronic methylphenidate on measures of inhibition in a total of 604 participants with ADHD taking methylphenidate and 597 participants with ADHD taking placebo. Evidence from the forest plot (Figure 2C) shows statistically significant small to medium methylphenidate effect size

(Hedges' g = 0.37; 95% CI = [0.23 to 0.51]; p < 0.001; z = 5.3). The heterogeneity was not relevant (I^2 = 32%). Imprecision of studies was not serious, whereas publication bias was suspected (metabias p = 0.094).

3.5.3.1.Sensitivity Sub-Meta-Analysis on effects of Methylphenidate on Inhibition in pediatric studies only

Ten studies tested the effects of methylphenidate (N = 443) versus placebo (N = 441) in children/adolescents with ADHD in inhibition (Coghill et al., 2007; Epstein et al., 2011; Kortekaas – Rijlaarsdam et al., 2020; Murray et al., 2011; Nigg et al., 1996; Schachar et al., 2008; Solanto et al., 2011; Tamminga et al., 2021; Wigal et al., 2011; Zeiner et al., 1999). The sensitivity analysis in children/adolescents only found a small to medium effect size (Hedges' g = 0.35; 95% CI = [0.19, 0.51]; p < 0.001; z = 4.3). There was no relevant heterogeneity (I^2 = 35%), and no indication of a publication bias (meta bias p = 0.55).

3.5.3.2.Sensitivity Sub-Meta-Analysis on effects of Methylphenidate on Inhibition in adult studies only

Four studies tested the effects of methylphenidate (N=161) versus placebo (N=156) in adults with ADHD (Broonsta et al., 2005; Bron et al., 2024; Goodman et al., 2017; Tamminga et al., 2021). The sensitivity analysis in adults only found a medium effect size (Hedge's g = 0.44, 95% CI = [0.13, 0.74]; Z = -1.4). There was no relevant heterogeneity (I^2 = 34%) and no evidence of a publication bias (metabias p = 0.041).

3.5.3.3.Statistical Comparison between effects of Methylphenidate in pediatric and adult studies on Inhibition

The meta-regression analysis showed that there was no statistically significant difference between effects of methylphenidate and atomoxetine on inhibition (b = 0.07 [95% CI -0.29, 0.44]; p = 0.688; z = 0.4) between children/adolescents and adults. Heterogeneity was substantial (I^2 = 63%).

3.5.3.4.Sensitivity Sub-Meta-Analysis on effects of Methylphenidate on Inhibition in titrated studies only

Nine studies tested the effects of titrated doses of methylphenidate versus placebo on inhibition in children, adolescents, and adults with ADHD (Boonstra et al., 2005; Bron et al., 2014; Epstein et al., 2011; Goodman et al., 2017; Kortekaas – Rijlaarsdam et al., 2020; Murray et al., 2011; Solanto et al., 2009; Tamminga et al., 2021; Wigal et al., 2011). The sensitivity analysis on the titrated dosages only found a small to medium effect size (Hedges' g = 0.33; 95% CI = [0.17, 0.48]; p < 0.001; z = 4.0). There was no relevant heterogeneity (I2 = 37%), and no evidence of a publication bias (metabias p = 0.11).

3.5.3.5.Sensitivity Sub-Meta-Analysis on effects of Methylphenidate on Inhibition with fixed studies only

Four studies tested the effects of fixed doses of methylphenidate (N = 100) versus placebo (N= 100) on inhibition in children and adolescents with ADHD (Coghill et al., 2007; Nigg et al., 1996; Schachar et al., 2008; Zeiner et al., 1999). The sensitivity analysis on the fixed dosages only found a medium effect size (Hedges' g = 0.51; 95% CI = [0.28, 0.74]; p < 0.001; z = 4.4). There was no evidence of heterogeneity (I^2 = 0%), and publication bias was undetected (metabias p = 0.5).

3.5.4. Main Meta-Analysis on the effects of Methylphenidate on Working Memory

Nine studies (Campez et al., 2022; Coghill et al., 2007; Epstein et al., 2011; Kortekaas – Rijlaarsdam et al., 2020; Murray et al., 2011; Rhodes et al., 2004; Tamminga et al., 2021; Wigal et al., 2011; Zeiner et al., 1999) analyzed the effects of chronic methylphenidate versus placebo on measures of working memory in 514 participants with ADHD taking methylphenidate and 511 participants with ADHD taking placebo, which had sufficient data to meta–analyze. The forest plot (Figure 2D) shows statistically significant results with a small to medium effect size (Hedges' g = 0.36; 95% CI = [0.20 to 0.52]; p < 0.001; z = 4.4). There was moderate

heterogeneity (I^2 = 48%), and no evidence of a publication bias (metabias p = 0.28). Nine studies tested the effects of methylphenidate (N = 490) versus placebo (N = 487) in children/adolescents with ADHD on placebo in working memory (Campez et al., 2022; Coghill et al., 2007; Epstein et al., 2011; Kortekaas – Rijlaarsdam et al., 2020; Murray et al., 2011; Rhodes et al., 2004; Tamminga et al., 2021; Wigal et al., 2011; Zeiner et al., 1999).

3.5.4.1.Sensitivity Sub-Meta-Analysis on effects of Methylphenidate on Working Memory in pediatric studies only

The sensitivity analysis in children/adolescents only found a small to medium effect size (Hedges' g = 0.38; 95% CI = [0.25, 0.51]; p < 0.001; z = 5.9). There was no relevant heterogeneity (I^2 = 25%), but there was a potential publication bias (metabias p = 0.03). There was only one study on working memory in adults, hence we could not conduct a separate sensitivity analysis in adults only, nor a statistical comparison between pediatric and adult studies.

3.5.4.2.Sensitivity Sub-Meta-Analysis on effects of Methylphenidate on Working Memory in titrated studies only

Six studies tested the effects of titrated doses of methylphenidate versus placebo on working memory in children, adolescents, and adults with ADHD (Campez et al., 2022; Epstein et al., 2011; Kortekaas – Rijlaarsdam et al., 2020; Murray et al., 2011; Tamminga et al., 2021; Wigal et al., 2011). The sensitivity analysis on the titrated dosages only found a small to medium effect size (Hedges' g = 0.38; 95% CI = [0.09, 0.66]; p = 0.009; z = 2.6). There was substantial heterogeneity (I^2 = 75%), and no evidence of a publication bias (metabias p = 0.56).

3.5.4.3.Sensitivity Sub-Meta-Analysis on effects of Methylphenidate on Working Memory in fixed dosage studies only

Three studies tested the effects of fixed doses of methylphenidate (N = 136) versus placebo (N = 136) on working memory in children and adolescents with ADHD (Coghill et al., 2007;

Rhodes et al., 2004; Zeiner et al., 1999). The sensitivity analysis in the fixed dosages only found a small to medium effect size (Hedges' g = 0.33; 95% CI = [0.15, 0.5]; p < 0.001; z = 3.7). There was no evidence of heterogeneity (I^2 = 0%), and no evidence of a publication bias (metabias p = 0.38).

In conclusion, the main meta-analysis on the effects of methylphenidate on cognitive functions in ADHD showed that methylphenidate was superior to placebo in improving performance in all cognitive domains with small to medium effect sizes (Hedges g of 0.34-0.59). The effect sizes for the meta-analyses including only children/adolescents were somewhat larger than the ones for children and adults in reaction time (Hedges' g = 0.45 for children/adolescents versus g = -0.36 for adults) and for attention (Hedges' g = 0.63 for children/adolescents versus g = 0.46 for adults), while for inhibition the effect in adults was larger (Hedges' g = 0.44 for adults versus g = 0.35 for children/adolescents). For working memory there was only one study in adults, hence we could not conduct a separate sensitivity analysis in adults only, nor a statistical comparison between pediatric and adult studies. The statistical comparison between children/adolescents and adults on the effects of methylphenidate on reaction time, attention and inhibition showed no differences. The meta-analyses for fixed dose studies had larger effect sizes than the meta-analysis for titrated dosage studies in reaction time (Hedges' g = 0.44 for fixed versus g = 0.32 for titrated dosages), attention (Hedges' g = 0.71 for fixed versus g = 55 for titrated dosages), and inhibition (Hedges' g = 0.51 for fixed versus g = 0.32 for titrated dosages), except for larger effect size in working memory in titrated dosage studies (Hedges' g = 0.38 for titrated versus g = 0.33 for fixed dosage). Fixed dose studies had smaller sample sizes (N = 434) in both methylphenidate and placebo groups compared to the sample sizes in titrated studies in methylphenidate (N = 1,816) and placebo (N = 1,789). However, there was no relevant heterogeneity between fixed dose

studies on any of the cognitive domains, compared to titrated dose studies that mostly had substantial heterogeneity in reaction time (I^2 = 80%) and working memory (I^2 =75%), moderate heterogeneity in attention (I^2 =58%), and no relevant heterogeneity in inhibition (I^2 =37%).

3.6. Meta-Analysis: Atomoxetine studies

3.6.1. Reaction Time

Four studies (de Jong et al., 2009; Fan et al., 2017; Griffiths et al., 2018; Wehmeier et al., 2012) that tested the effects of chronic atomoxetine versus placebo had sufficient information on reaction time data for inclusion in the meta-analysis. The total number of participants with ADHD on atomoxetine was 147 and 139 on placebo. Forest plot of the effects of atomoxetine versus placebo (Figure 3A) shows a statistically significant small to medium effect size (Hedges' g = 0.36; 95% CI = [0.04 to 0.68]; z = 2.2; p = 0.027). The heterogeneity was moderate (I^2 = 38%). The sample size of the studies was small overall which resulted in serious imprecision. Publication bias was undetected (metabias p was 0.82).

3.6.2. Attention

Three studies (Fan et al., 2017; Griffiths et al., 2018; Wehmeier et al., 2012) had sufficient data for inclusion in the meta–analysis on the effects of atomoxetine versus placebo on attention. The forest plot (Figure 3B) shows a statistically significant medium to large effect size favoring atomoxetine (Hedges' g = 0.64; 95% CI = [0.16 to 1.12]; p = 0.009; z = 2.6) in 131 participants with ADHD taking atomoxetine, and 123 participants with ADHD taking placebo. There was substantial heterogeneity (I^2 = 74%) with a small overall sample size resulting in serious imprecision. Publication bias was not detected (metabias p = 0.67).

3.6.3. Inhibition

Six studies (de Jong et al., 2009; Fan et al. 2017; Faraone et al., 2005; Griffiths et al., 2018; Spencer et al., 1998; Wehmeier et al., 2012) tested the effects of atomoxetine versus placebo on measures of inhibition in a total of 380 participants with ADHD in the atomoxetine group

and 373 participants with ADHD in the placebo group. The forest plot (Figure 3C) shows a statistically significant medium effect size favoring atomoxetine in children and adults with ADHD (Hedges' g = 0.47; 95% CI = [0.02 to 0 .92]; p = 0.041; z = 2.0). Heterogeneity was substantial (I^2 = 84%) with a small overall sample size resulting in serious imprecision. Publication bias was not detected (metabias p = 0.89).

3.6.4. Working Memory

Three studies (de Jong et al., 2009; Fan et al., 2017; Wietecha et al., 2013) had sufficient data to include in the meta-analysis on the working memory domain of atomoxetine in a total of 66 participants in the atomoxetine group and 66 participants in the placebo group, shown on the forest plot (Figure 3D). The findings were non-significant with a small effect size (Hedges' g = 0.30; 95% CI = [- 0.30 to 0.90]; p = 0.334; z = 1.0). Heterogeneity was moderate (I^2 = 60%) with a small overall sample size and a large effect size that was not excluded, resulting in very serious imprecision. Publication bias was not detected (metabias p = 0.4).

3.7. Meta-regression analysis for statistical comparison between the effects of methylphenidate and atomoxetine on cognitive functions

The meta-regression analysis did not detect any statistically significant differences between the effects of methylphenidate and atomoxetine on any of the cognitive functions. There was moderate to substantial heterogeneity (see Table 4).

4. Discussion

This is the first systematic review and meta-analysis on the chronic effects of stimulant and non-stimulant medications on the cognitive functions of children, adolescents, and adults with ADHD. The systematic review of stimulant medication effects on 20 studies shows improvement effects on all cognitive domains in the majority of studies with mixed results only in reaction time measures. For atomoxetine, the systematic review of a smaller number of 8

studies showed improvements in attention and inhibition measures in most studies, but no effects on working memory and mixed effects on reaction time.

For methylphenidate, the meta-analysis showed significant beneficial effects on all neurocognitive domains with Hedges' g between 0.34 and 0.59, with the largest effect size for attention and the lowest for reaction time. The meta-analysis for atomoxetine showed significant beneficial effects on all neurocognitive domains (i.e., reaction time, attention, inhibition), except for working memory, with Hedges' g between 0.36 and 0.64, with the largest effect size also for attention and the lowest for reaction time. The effect sizes of improvements were similar for all cognitive domains, including working memory (i.e., 0.30 for atomoxetine, 0.36 for methylphenidate), although it did not reach significance for atomoxetine, which could be due to the small number of only 3 studies versus 11 studies for methylphenidate. In fact, the meta-regression analyses showed no significant differences between the 2 drugs on any cognitive domains, including working memory.

The effect sizes for the meta-analyses including only children and adolescents were somewhat larger than the ones for adults in reaction time and attention, while for inhibition the opposite was the case. The statistical comparison, however, showed no significant differences between pediatric and adult studies. The findings of these meta-analyses show for the first time that atomoxetine is efficient and furthermore, comparable in efficiency to methylphenidate in improving cognitive functions that are relevant to ADHD. We also extend previous findings of meta-analyses of predominantly acute dosages of Methylphenidate by showing that chronic Methylphenidate use is also associated with significant benefits in executive functions in ADHD.

The key novel findings of this meta-analysis are the comparable beneficial effects of chronic administrations of atomoxetine and of methylphenidate on attention, inhibition, processing speed and working memory in ADHD with very similar effect sizes and no

significant differences between them. The non-significant effects of atomoxetine on working memory were based on a very small number of only 3 studies and may have been underpowered when compared to the meta-analysis of stimulant effects which was based on a much larger sample of 11 studies. This is further supported by the lack of statistical comparison between the 2 drugs in the direct comparison.

The findings of comparable beneficial effects on cognition are interesting in view of superior effects of methylphenidate over atomoxetine on ADHD behaviours (Cortese et al., 2019). However, they may be related to chemical imaging findings that show that both drugs have relatively similar effects on frontal and other cortical regions where they enhance both dopamine and noradrenaline (Bymaster et al. 2002, Hannestad 2010). Methylphenidate, however, has in addition more prominent effects on basal ganglia dopamine (Volkow et al., 1998). They are also parallel to fMRI findings of shared upregulation/normalization of inferior frontal as well as fronto-parieto-striatal and fronto-cingulo-parietal regions during tasks of inhibition and attention as well as during rest (Cubillo et al., 2014a, Kowalczyk 2019, Fu et al., 2022), all of which are key areas of dysfunctions in ADHD (Faraone et al., 2022, 2023, Rubia, 2018). Furthermore, the meta-regression findings of no differences between the drugs in working memory are parallel to our findings of a fMRI study during working memory that showed shared improved performance and fronto-temporo-striatal brain activation effects with atomoxetine and methylphenidate relative to placebo, although we found a drug-specific effect of atomoxetine of upregulation of right dorsolateral prefrontal cortex compared to placebo and methylphenidate (Cubillo et al., 2014b).

Our meta-analysis findings of beneficial effects of chronic Methylphenidate on all cognitive domains tested extends the previous meta-analytic findings which included predominantly acute stimulant effects. The here reported effect sizes are relatively similar to those of previous meta-analyses which included predominantly acute dosages (Coghill et al.

2014, Vertessen et al. 2022, Tamminga et al. 2016 and Pievsky & McGrath et al. 2018), suggesting that chronic effects are as beneficial as acute stimulant effects on ADHD cognition. Thus, the small effect size of stimulant effects on inhibition (0.37) in this meta-analysis was similar to the effect size of all 4 meta-analyses on effects of methylphenidate on the domain of inhibition: 0.41 (Coghill et al., 2014), 0.40 (Tamminga et al., 2016), 0.23 (Pievsky and McGrath,2018), and 0.32 (Vertessen et al., 2022). The effect size of 0.34 of chronic effects of methylphenidate on reaction time in this MA was somewhat larger than the previous reported effect sizes of mostly acute stimulant effects of 0.24 (Coghill et al., 2014), 0.29 (Vertessen et al., 2022), and 0.08 in Pievsky and McGrath (2018) who found non-significant results. The meta-analysis of chronic stimulant effects on attention showed a medium effect size (0.59), close to the effect size of Coghill et al. (2014) (0.62) and Vertessen et al. (2022) (0.73) and larger than those of Tamminga et al. (2016) (0.42) and Pievsky and McGrath (2018) (0.23). The effect size of stimulant medication effects on working memory (0.36) in this meta-analysis was larger than the effect sizes of the other meta-analyses with 0.26 in Coghill et al. (2014), 0.20 in Vertessen et al. (2022), 0.13 in Pievsky and McGrath (2018) and 0.24 in the meta-analysis that found no significant effects (Tamminga et al., 2016). Overall, it thus appears that the effects of longer-term stimulant use are similar if not somewhat larger to the predominantly acute effects of previous meta-analyses.

It has been argued that stimulants can produce tolerance based on findings of striatal dopamine transporter upregulation with long-term use (Fusar-Poli et al., 2013, Wang et al., 2013). Behaviourally, longer-term beneficial effects have been questioned based on epidemiological and meta-analytical data (Cortese et al., 2019, Swanson et al., 2019). Here, however, we show beneficial effects of chronic stimulant use on cognition. However, it needs to be considered that chronic stimulant use in this meta-analysis refers to a range between 1

week and a maximum of 8 weeks. Therefore, it is currently unknown whether treatment longer than 8 weeks or even years will still elicit cognitive benefits.

The 2 separate sensitivity sub-meta-analyses for effects of methylphenidate in children/adolescents and adults showed larger effect sizes for children/adolescents in reaction time and attention, while for inhibition the effect sizes for adults were larger. Statistically, however, the effects of methylphenidate on cognitive functions were not different between children/adolescents and adults. This does not support the hypothesis that stimulant effects are larger in children and adolescents than in adults with ADHD. However, there were only 4 studies testing effects of methylphenidate on cognitive functions in adults with ADHD that met criteria for meta-analysis, hence the findings are inconclusive. Sub-meta-analyses comparing studies of titrated versus fixed dosages showed very similar effect sizes, which is not in line with our hypothesis of larger effects when drugs are individually titrated. However, this could be due to the more homogenous and smaller sample size of the fixed dosage studies compared to the titration dosage studies. Another explanation could be the inclusion of the largest dosage only for all fixed dosage studies, which may have been more effective for cognition than the individually titrated dosage, given that the dosage was titrated based on ADHD behaviours, and not cognitive performance. This would be in line with both the findings of the meta-analysis from Vertessen et al. (2022) and the systematic review from Pietzrak et al. (2006), that found that higher dosages improve attention, vigilance, and working memory more than lower dosages.

The findings of positive and comparable effects of stimulants and non-stimulants on typically impaired cognitive domains in ADHD of attention, inhibition, speed of processing and working memory are relevant in view of the difficulties people with ADHD face in academic and occupational settings because of cognitive deficits (Bhullar et al., 2023). It has been shown that improvements in clinical symptoms are independent of improvements in

cognitive functions, with clinical improvements not necessarily improving cognition (Coghill et al., 2014). It is hence reassuring to show with meta-analytic findings that both stimulant and non-stimulant medications for ADHD not only improve ADHD symptoms but also key cognitive functions that are typically impaired in ADHD (Faraone et al., 2022; Kofler et al., 2013; Pievsky and McGrath, 2017; Faraone et al, 2021, 2023; Senkowski et al., 2023).

Cognitive performance has been shown to be related to real life academic performance, which is lower in ADHD than in healthy classroom peers based on a meta-analysis (Prasad et al., 2013) and has been shown to be improved by methylphenidate (Kofler et al., 2018; Kortekaas-Rijlaarsdam, 2019). The findings of our meta-analysis are therefore important as executive function deficits impact patients with ADHD on many other domains at all life stages such as in academic performance, education, occupation and in later life.

Thus, executive functions measured behaviorally or cognitively have shown to impact school performance. For example in school-class environment, working memory problems assessed through behavioral rating scales have shown to impair attainment of children with ADHD (Alloway et al., 2010); also, performance in auditory-verbal and visual-spatial working memory tasks can be predicted by in-class behaviour such as classroom inattention, mainly reading (Rogers et al. (2011), while performance in other cognitive tasks like vigilance, planning and organization, selective attention, visual scanning and verbal learning can be risk factors for grade retention, lower academic achievement and learning disability (Biederman et al, 2004). Moreover, children with ADHD who experience executive functioning problems not only show problematic classroom behaviour or negative performance in cognitive tasks, but also deficits in social cognition including theory of mind ability and affective recognition (Miranda et al., 2017).

Likewise, clinical symptoms in adults with ADHD have shown to be related to cognitive impairments in several contexts. For example, self-reports on experiencing behavioural

executive functioning deficits were correlated with occupational performance, everyday life satisfaction and life quality (Stern et al., 2014) and performance in the Continuous Performance task, Colour Word Stroop Test and memory can significantly predict occupational impairments (Barkley et al., 2010). In older adults with ADHD, behavioural self-ratings of executive function, especially working memory was associated with quality of life, comparable to the associations in younger people with ADHD (Thorell et al., 2019). The findings of our meta-analysis of positive effects of chronic administration of methylphenidate and atomoxetine on cognition are therefore encouraging as they may likely have an impact on real-life achievements such as school and academic performance in ADHD, as well as occupational performance and overall quality of life.

5. Limitations

This study has several limitations. First, the number of studies on the chronic effects of atomoxetine versus placebo was very small compared to the number of studies on chronic effects of methylphenidate. Hence, the results of the meta-analysis on non-stimulants are based on less than ten studies which limit the generalizability of findings, as well as making it underpowered. As discussed above, this could potentially have affected the small effect size for the working memory meta-analysis which was based on 3 studies and needs to be corroborated in future meta-analyses of larger number of studies. This may also have affected the statistical comparison between the 2 drugs. Second, the results of the random effects (RE) model show that 3 meta-analyzed domains had serious heterogeneity. There was significant heterogeneity in the meta-analysis results for the inhibition domain of the atomoxetine studies (I^2 =74%), in the meta-analysis results for the inhibition domain of the atomoxetine studies (I^2 = 84%), and in the meta-analysis results for the reaction time domain of the methylphenidate studies (I^2 = 71%). The higher heterogeneity could also explain the wider confidence intervals in the meta-analysis results of these 3 domains when compared to the meta-analytic results of

the reaction time and working memory domains that showed no serious heterogeneity. It is possible that the heterogeneity was large in some of the meta-analytic findings, because we clustered outcomes from different task under the same cognitive domain, which applies in particular to the domains of inhibition and attention (i.e., omission errors and reaction time variability under the domain of attention or commission errors from sustained attention tasks and outcomes of different tasks of motor and interference inhibition under the inhibition domain). There was also large heterogeneity in the clinical populations with different patterns of comorbid conditions and different age ranges. Third, the duration of medication intake varied between studies, with a range of 3 weeks to 4 weeks for atomoxetine and of 1 week and 8 weeks for methylphenidate. which could have affected the heterogeneity in findings. Fourth, the studies on titrated dosages and fixed dosages differed in sample size and heterogeneity which could have affected the findings. Fifth, the meta-regression analyses were affected by differences in sample size between the studies on effects of methylphenidate and atomoxetine and those on pediatric and adult studies. Also the meta-analysis in adult studies only for effects of methylphenidate was based on very small samples. Sixth, there was only a sufficient number of studies to meta-analyze the effects of methylphenidate and atomoxetine and we could not test for effects of other stimulant and non-stimulant ADHD medications. Future research should therefore test the effects of other stimulants such as dexamfetamine or the newer lisdexamfetamine and non-stimulants such as guanfacine or clonidine on cognition in people with ADHD. Seventh, the majority of participants in the studies were male with a 30.34% of females in the non-stimulant studies, and 18.6% of females in methylphenidate studies. As a result, we may not be able to generalize the findings of this meta-analysis to the entire ADHD population.

6. Conclusion

In conclusion, these meta-analyses of chronic effects of stimulants and non-stimulants on executive functions in ADHD showed significant improvements with both methylphenidate and with atomoxetine in all cognitive domains tested with relatively similar effect sizes, and no statistical differences between them. The findings hence suggest comparable positive effects of both ADHD medication types on the most relevant executive functions in ADHD, suggesting for the first time that stimulant and non-stimulant ADHD medications, when taking longer-term, do not only improve behavioural symptoms of ADHD, but also executive function performance, and to a similar degree. The findings are clinically relevant and encourage the use of these medications to improve academic performance.

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Contribution of authorship

SEM and FI contributed equally to the publication: defining search terms (SEM) and inclusion criteria (FI, SEM), searching for literature (FI, SEM), extracting (FI), double checking study data (SEM), quality assessments of selected studies (FI, JR, SEM). SEM did the revisions. KR checked all selected papers for inclusion and helped with data extraction. JR meta-analysed the data. FI, SEM, and KR drafted the publication, and all authors edited the content. SEM, KR and JR implemented the revisions after peer review.

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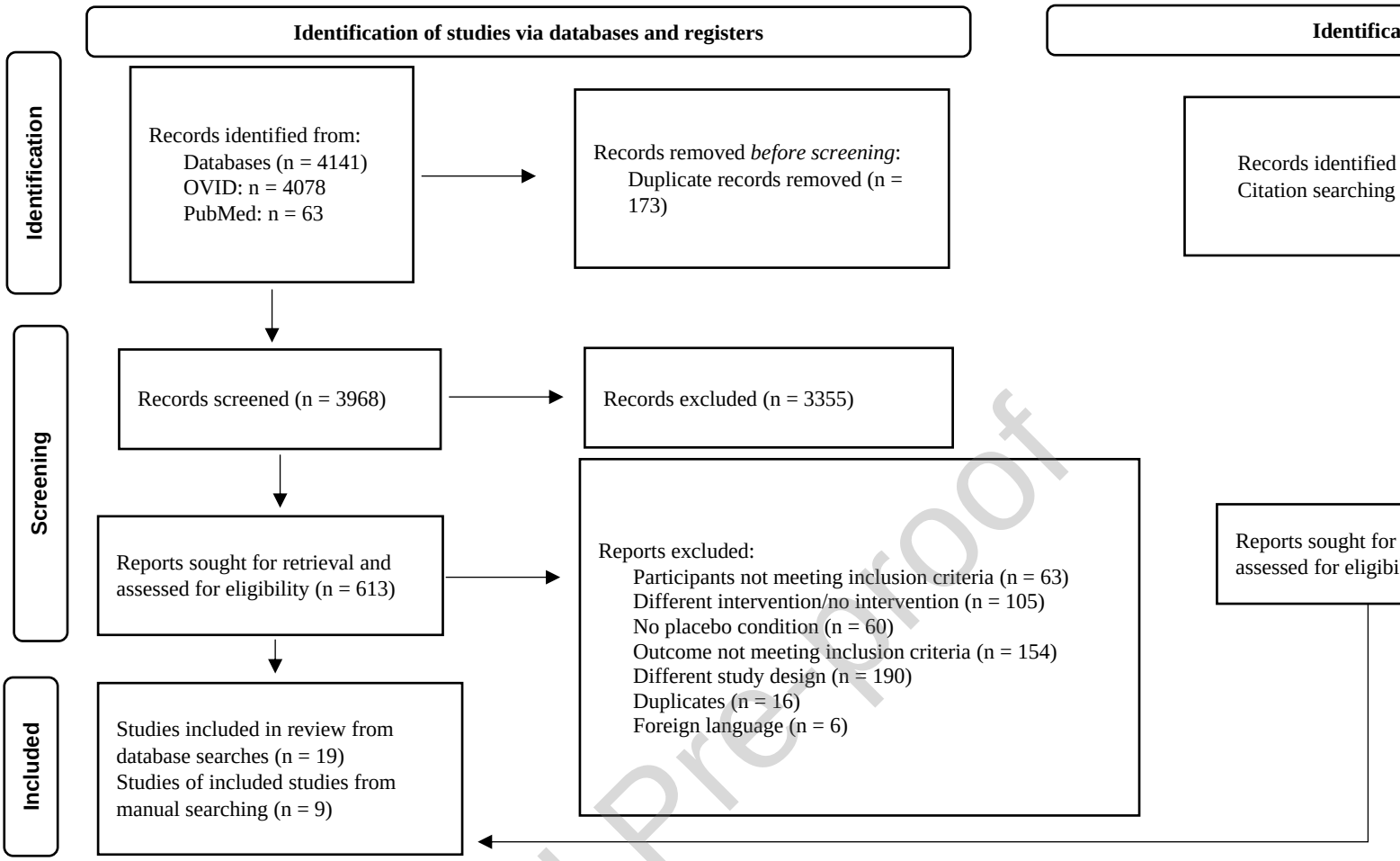

Figure 1: PRISMA Flow Chart of the systematic literature search on the effectiveness of stimulants and non-stimulants on people with ADHD.

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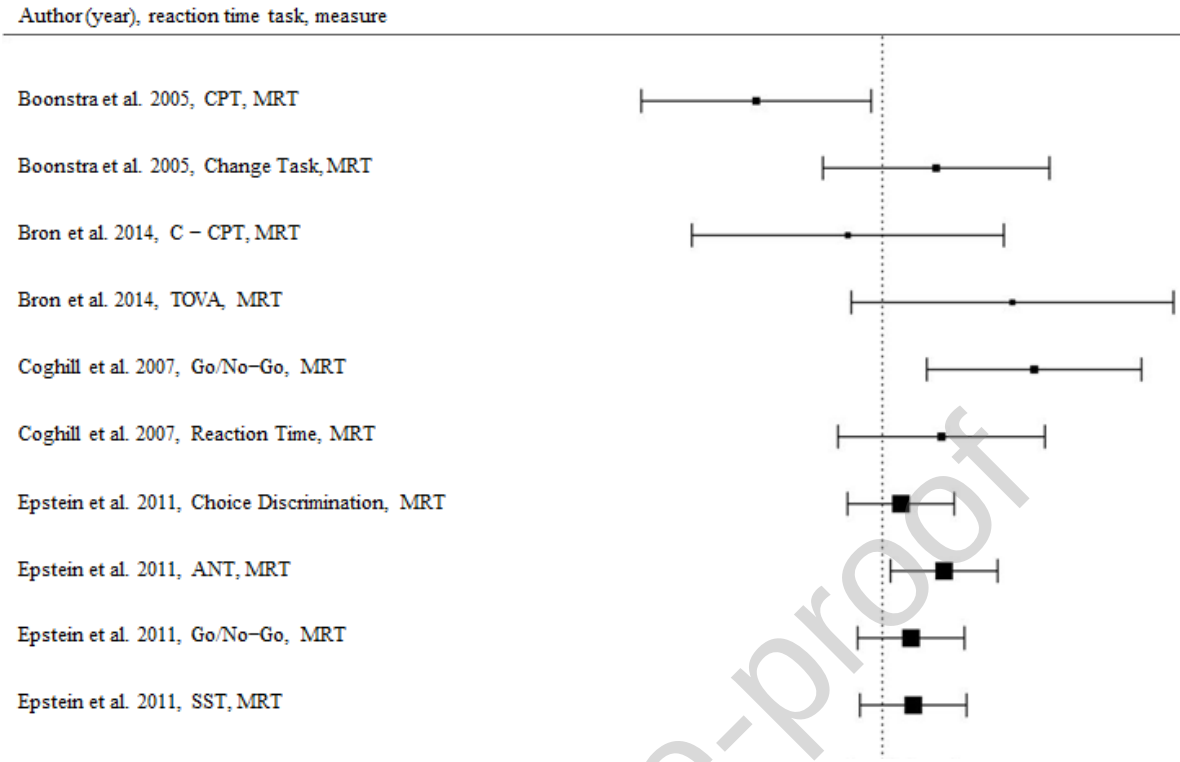

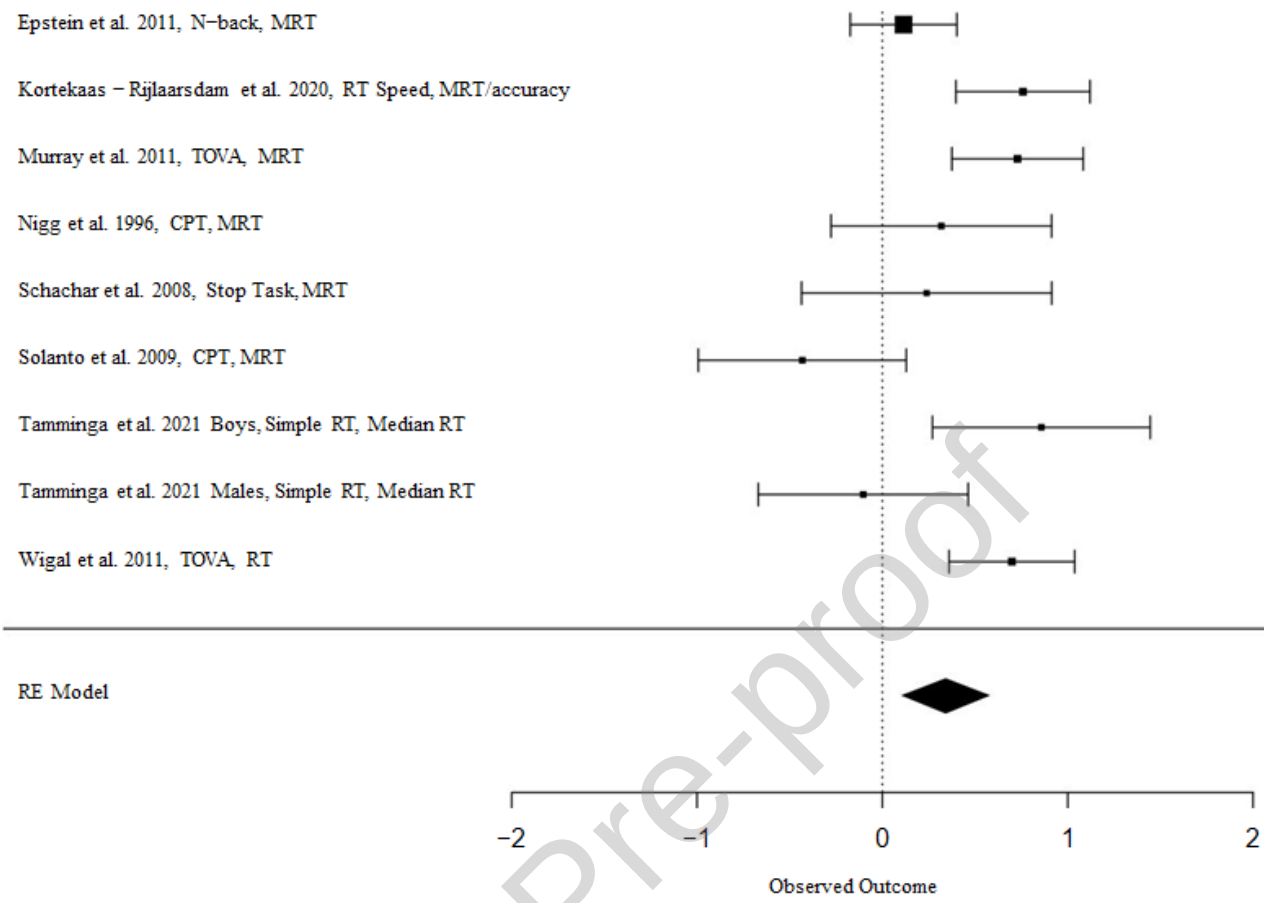

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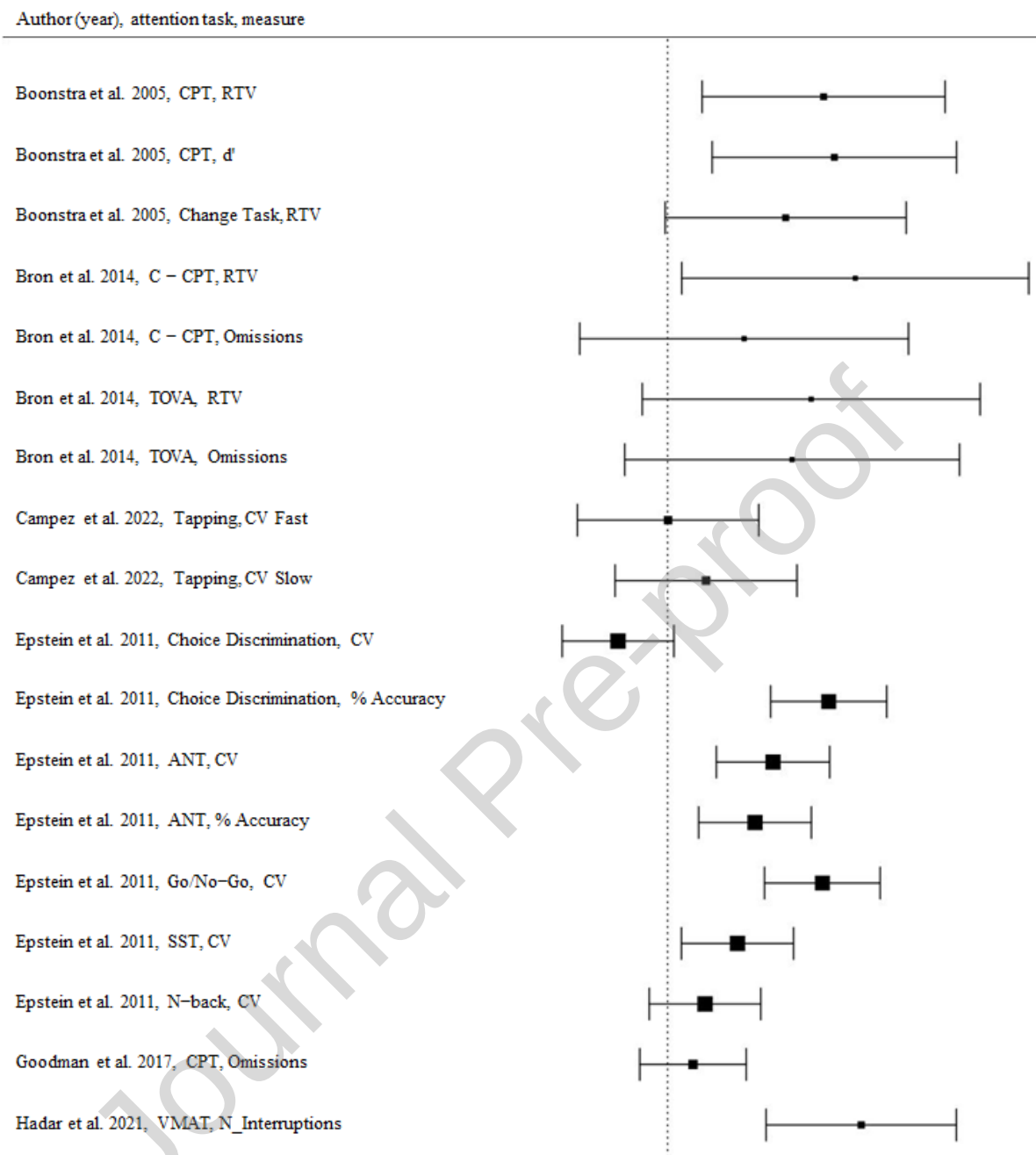

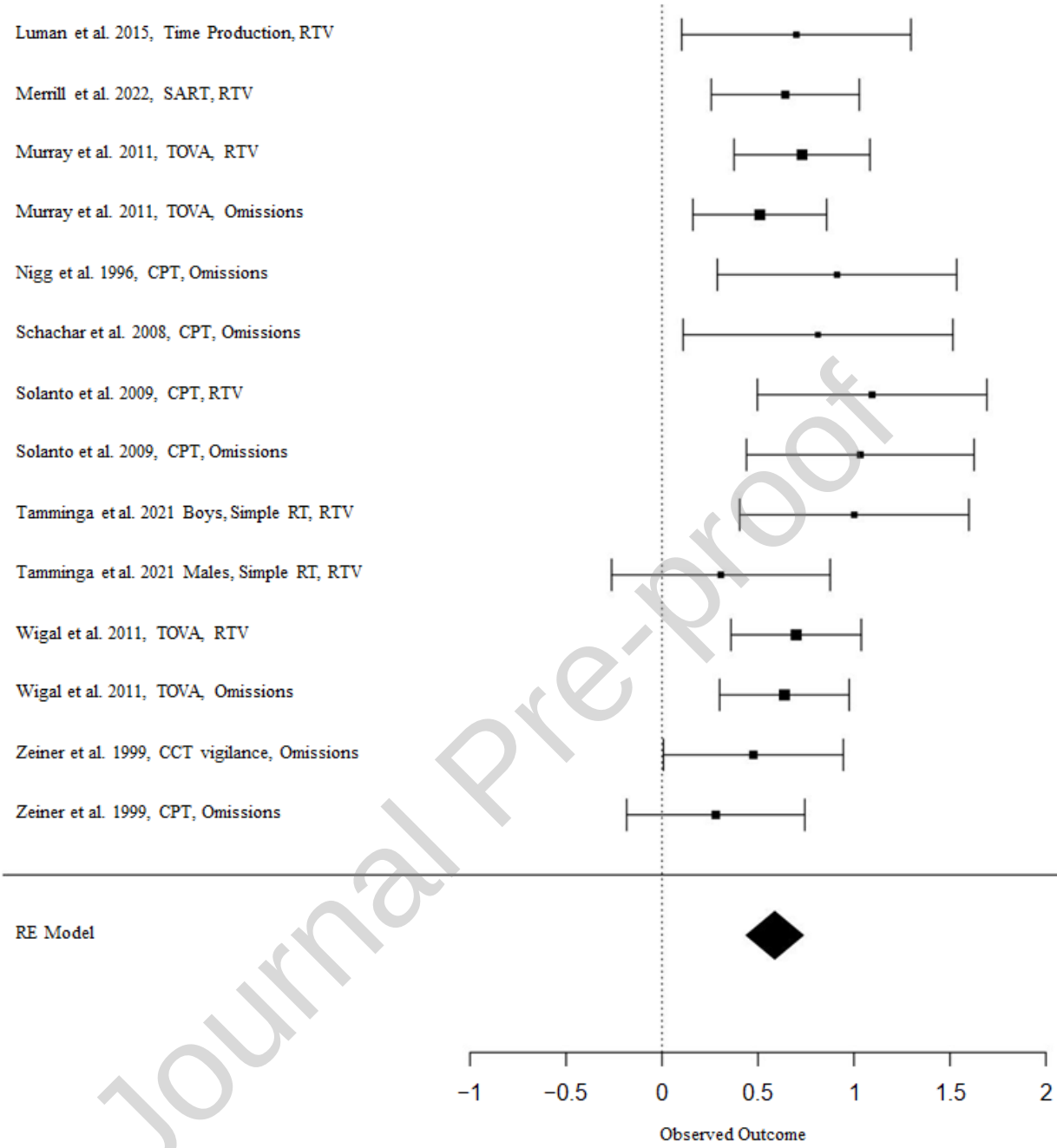

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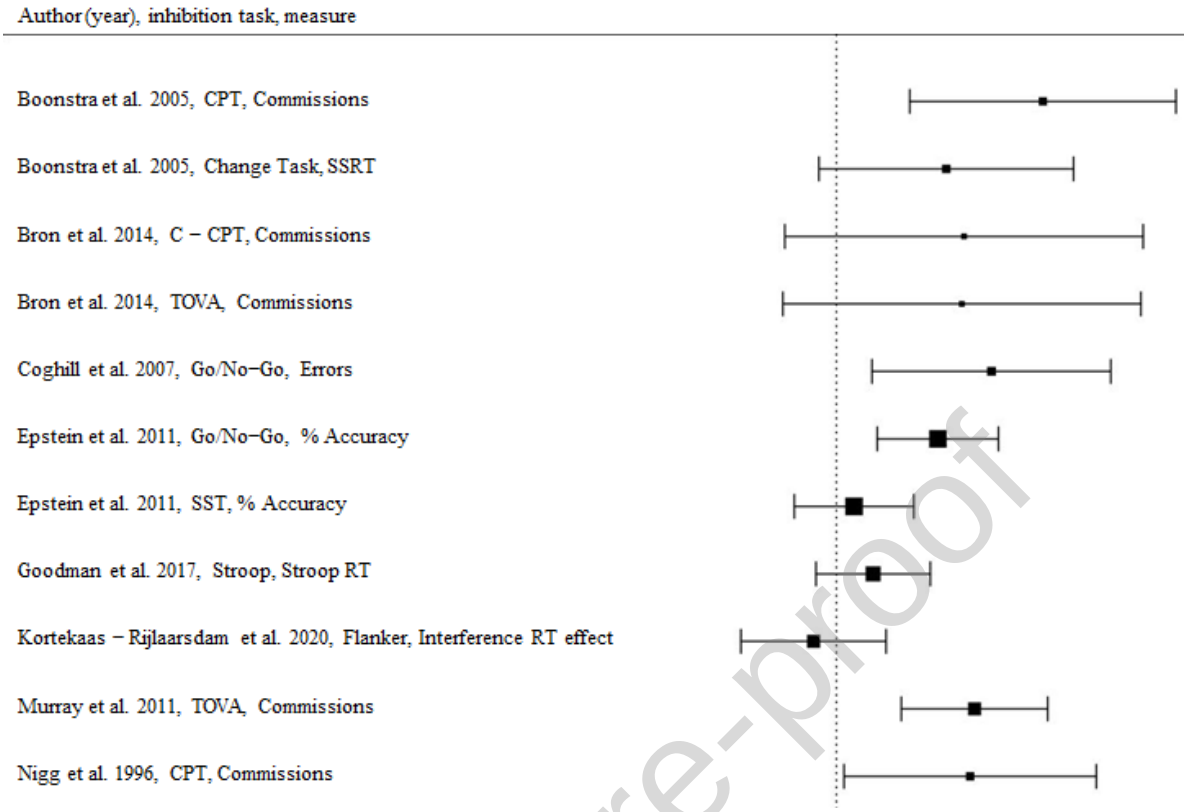

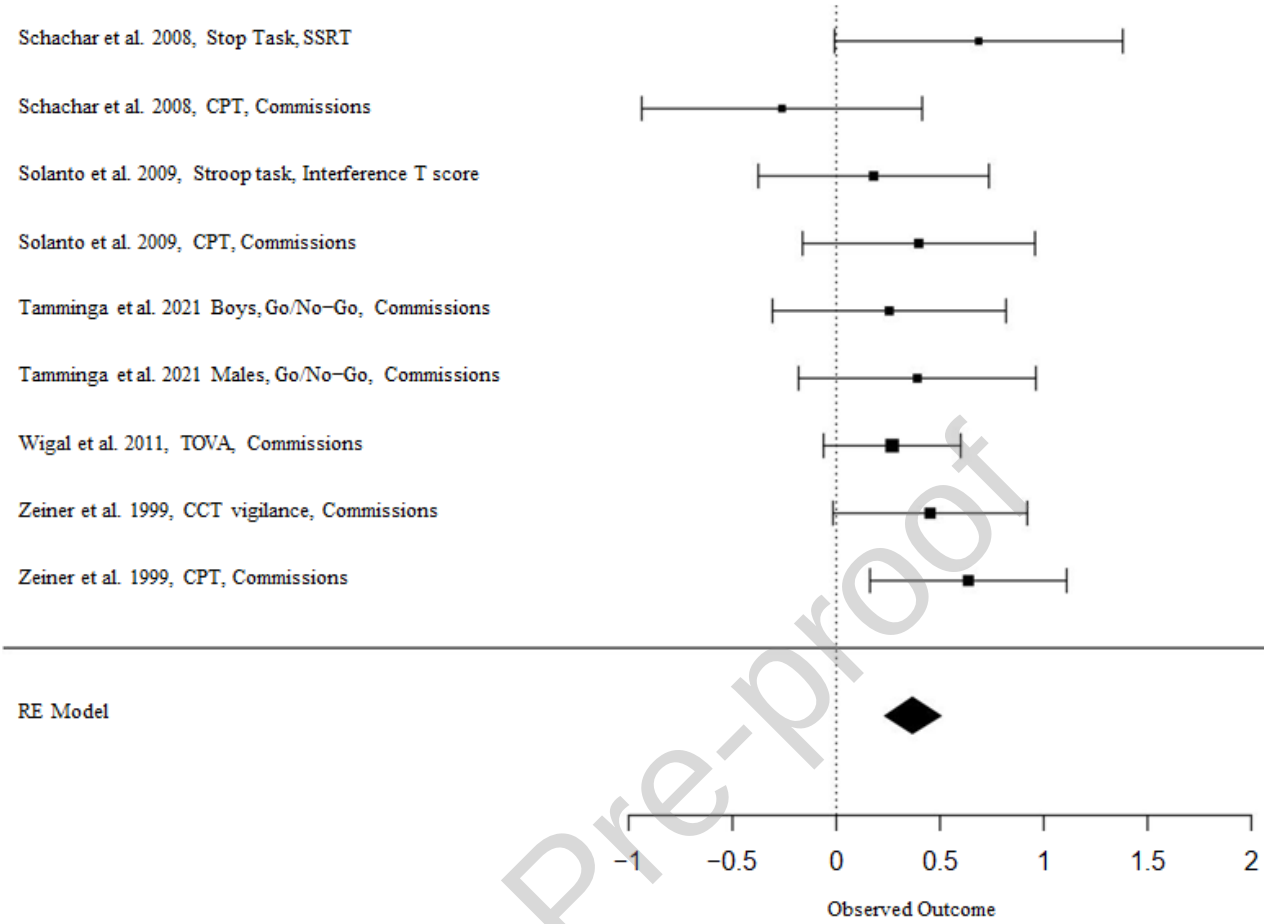

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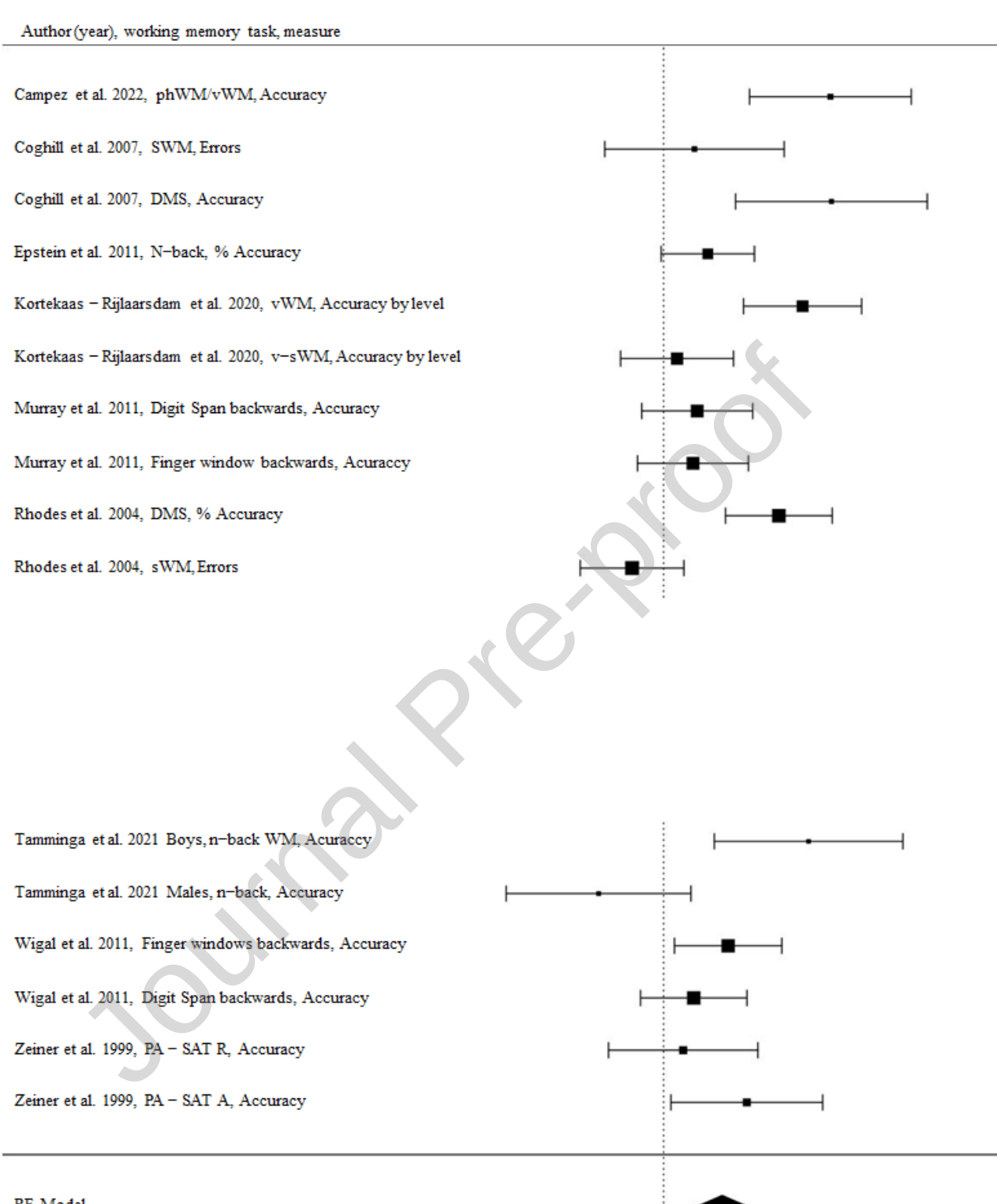
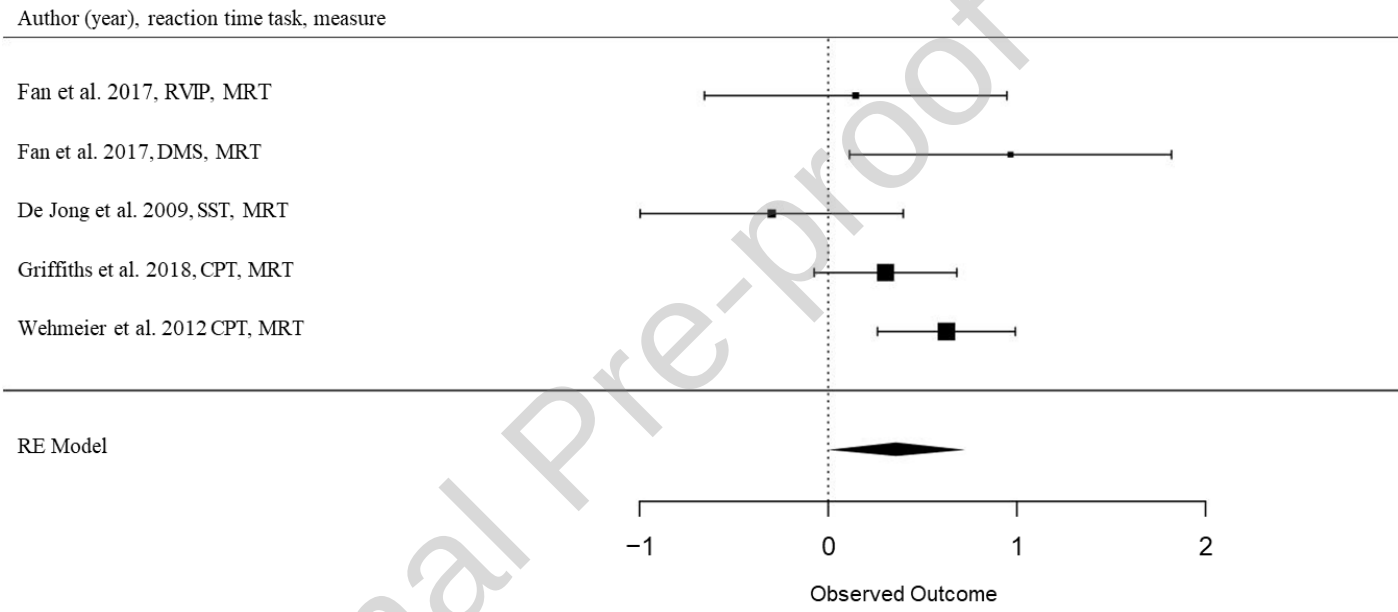


Figure 2: ~~on the~~ Eeffects of methylphenidate versus placebo on measures of reaction time (A), attention (
memory (D).

CI, confidence interval; RE model, random effects model; ANT, Attention Network Test; CI, Confide
Performance Task; C - CPT, computerized continuous performance task; MRT, mean reaction time; SST, St
Variables of Attention; CV, coefficient of variation; d', measure of attention; RTV, reaction time varia
processing; SART, sustained attention to response task; VMAT, visuomotor attention; CCT, children's check

(A)



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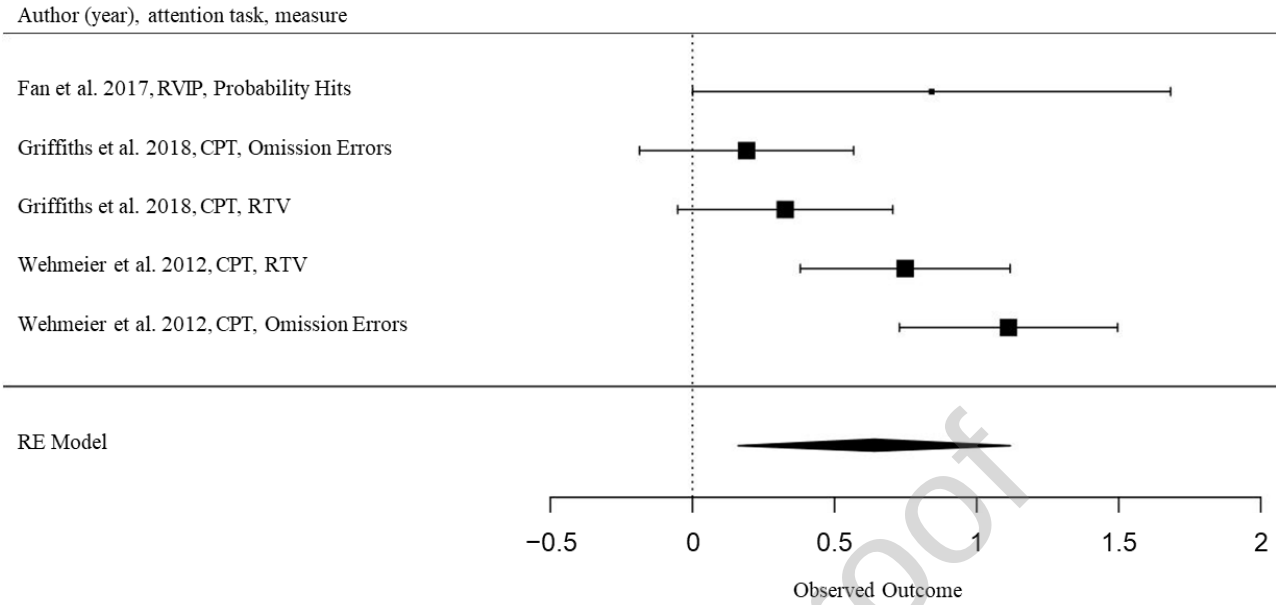

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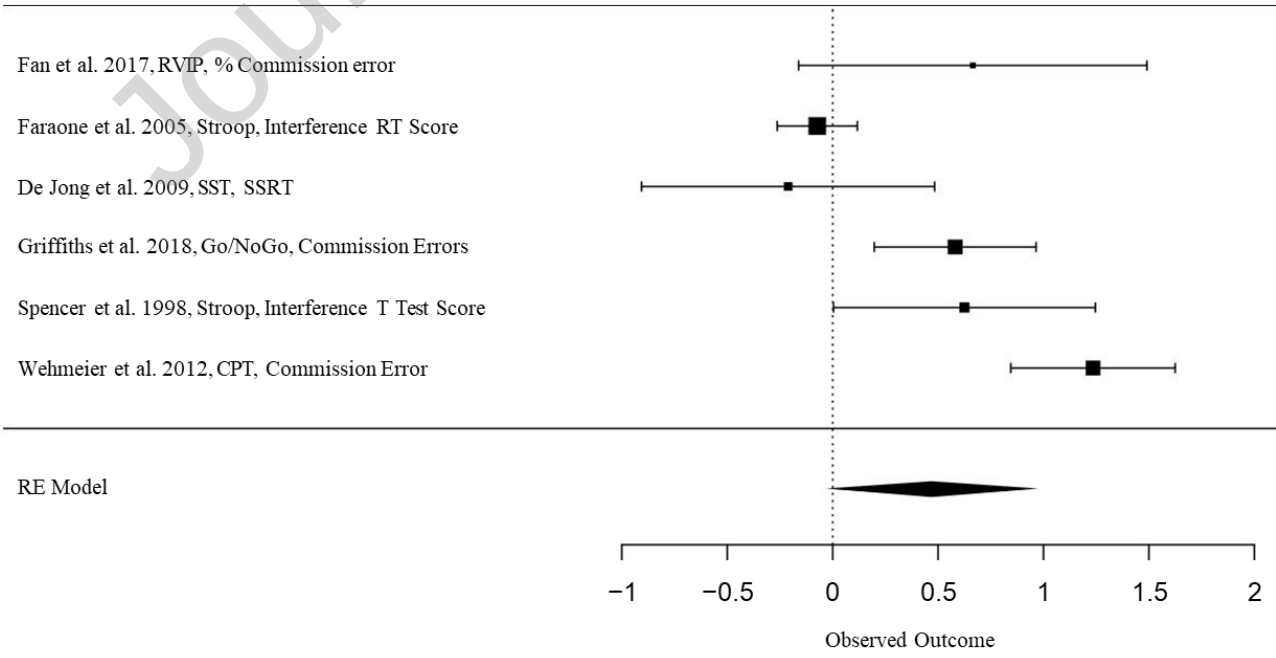

(D)

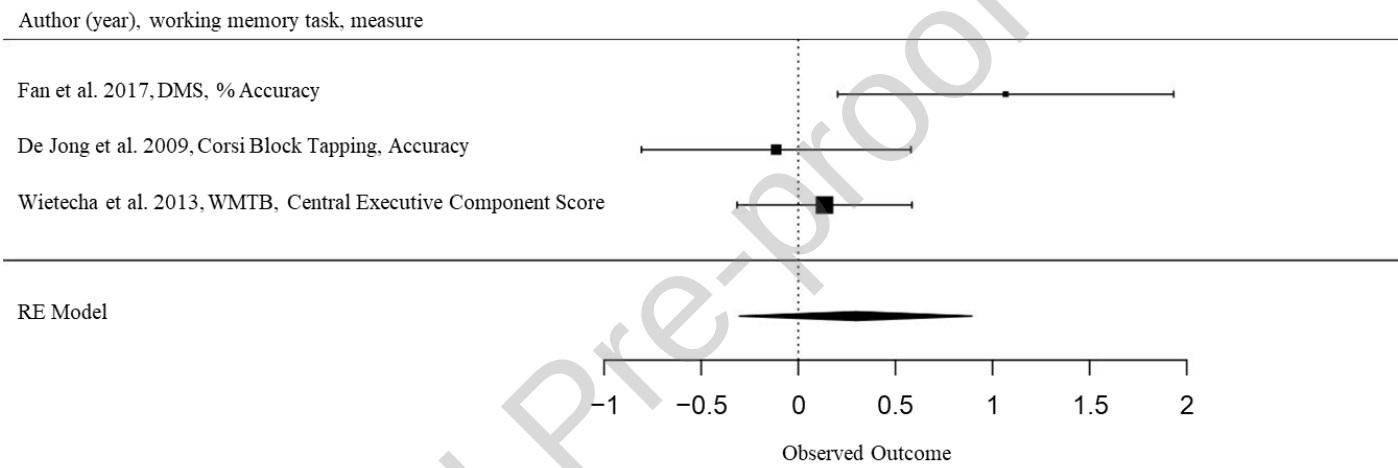

Figure 3: Effects of atomoxetine versus placebo on measures of reaction time (A), attention (B), inhibition (C) and workin

CI, confidence interval; RE model, random effects model; CPT, Continuous Performance Test; DMS, Delayed Matching t mean reaction time; RVIP, Rapid Visual Information Processing; SST, stop signal. task; RTV, reaction time variability; Matching to Sample Task; WMTB, Working Memory Test Battery; %, percent.

Table 1 GRADE evidence profile for the effects of methylphenidate and atomoxetine on cognition

	Quality assessment					Summary of findings			
						N		Hedges' g (95% CI)	Quality
Methylphenidate	**Limitations**	**Inconsistency**	**Indirect-ness**	**Imprecision**	**Publication bias**	**Drug**	**Placebo**		

(Number of studies)								
Reaction Time (N = 11)	No intention to treat (N = 2)	Substantial (I2=71%)	Not serious	Undetected (p=0.58)	467	458	0.34 (0.11, 0.57)	⊕⊕◯◯ Low
Attention (N = 16)	No intention to treat (N = 4)	Moderate (I2=53%)	Not serious	Suspected (p=0.025)	665	657	0.59 (0.44, 0.74)	⊕◯◯◯ Very low
Inhibition (N = 13)	No intention to treat (N = 3)	Not relevant(I2=32%)	Not serious	Suspected (p=0.094)	604	597	0.37 (0.23, 0.51)	⊕⊕◯◯ Low
Working Memory (N = 9)	No intention to treat (N = 1)	Moderate (I2=48%)	Not serious	Undetected (p=0.28)	514	511	0.36 (0.2, 0.52)	⊕⊕⊕◯ Moderate
Atomoxetine (Number of studies)								
Reaction Time (N = 4)	No intention to treat (N = 1)	Not relevant (I2=38%)	Serious (small sample size)	Undetected (p=0.82)	147	139	0.36 (0.04, 0.68)	⊕⊕◯◯ Low
Attention (N = 3)	No intention to treat (N = 1)	Substantial (I2=74%)	Serious (small sample size)	Undetected (p=0.67)	131	123	0.64 (0.16, 1.12)	⊕◯◯◯ Very low
Inhibition (N = 6)	No intention to treat (N = 2)	Substantial (I2=84%) (33% Hedges' g<0)	Serious (small sample size)	Undetected (p=0.89)	380	373	0.47 (0.02, 0.92)	⊕◯◯◯ Very low

Serious (surrogate outcomes)

Working Memory (N = 3)	No intention to treat (N = 1)	Moderate (I2=60%)	Very serious (small sample size) (large effect not excluded)	Undetected (p=0.4)	66	66	n.s. (-0.3, 0.9)	⊕◯◯◯ Very low

Table 2 Characteristics of all included studies on methylphenidate

Author (Year)	**Sample Size (M:F)**	**Mean age in years (SD)**	**Mean IQ**	**Comorbidities**	**Study Design**	**Drug type (Dose)**	**Duration of drug treatment**	**Cognitive Domain**	**Task**	**Measure**

Blum et al. (2011)	30 (24:6)	8.6 (1.11)	97.8 (12.4)	ODD = 12 LD = 10 ANX = 2 Dysthymia = 1	Double blind, randomized, placebo-controlled, crossover trial	OROS-MPH (first week: 18 mg 2nd week: 36 mg)	1 week (1 week MPH, 1 week placebo)	Attention	The Gordon Diagnostic System-CPT	Omission Errors
									The Test of Everyday Attention for Children TEA – Ch: Sky Search	Time per target score Dual task decrement score
								Working Memory	Sky Search Dual Task Score	No correct responses
									Dual Task	Nº correct responses
								Inhibition	Creature Counting	Nº correct recalled sequences
									Map Mission	Nº correct recalled sequences
									WISC – IV: Digit Span Backwards	Commission errors
									Finger Windows Backwards	*
									GDS-CPT	*
									TEA – Ch: Walk don't walk	
									Opposite Worlds	

Boonstra et al. (2005)	43 (21:22)	38.4 (10.1)	100.3 (17.9)	ANX = 51% mood disorders = 53% ASPD = 9.3% BPD 16.3%	Double blind, randomized, placebo-controlled, crossover trial	MPH (Week 1 = 0.5 mg/kg, Week 2 = 0.75 mg/kg, Week 3 = up to 1.0 mg/kg)	3 weeks (3 weeks MPH, 3 weeks placebo)	Reaction Time Attention Inhibition	CPT Change Task CPT Change Task CPT Change Task	MRT MRT RTV d' RTV Commission errors, SSRT
Bron et al. (2014)	22 (17:5)	30.5 (7.4)	*	Mood disorder = 11 ANX = 11 Substance Abuse Disorder = 9 ED: 1	Double blind, randomized, placebo-controlled, crossover trial	OROS-MPH (week 1: 36 mg, week 2 and 3: 72 mg)	3 weeks (3 weeks MPH, 3 weeks placebo)	Reaction Time Attention Inhibition	C – CPT, TOVA C – CPT, TOVA C – CPT, TOVA	MRT RTV, Omission Errors Commission Errors
Campez et al. (2022)	35 (28:7)	9.56 (1.44)	97.86 (12.05)	ODD = 22 CD = 3 Separation ANX = 1	Double blind, randomized, placebo-controlled, crossover trial	OROS-MPH (18 mg, 27 mg, or 36 mg)	3 weeks (3 weeks MPH, 3 weeks placebo)	Attention Inhibition Working Memory	Tapping Task Choice Impulsivity Task WM Tasks	Fast CV Slow CV Total points Accuracy

Coghill et al. (2007)	75 (75:0)	ages 7 - 15	*	ODD = 31 CD = 21 MDD = 3 GAD = 2 Separation ANX = 3 Tics = 2 Social Phobia = 1	Double blind, randomized, placebo-controlled, parallel trial	MPH (0.6 mg/kg)	28 days (28 days low dose MPH, 28 days high dose MPH, 28 days placebo)	Reaction Time Inhibition Working Memory	GNG Reaction Time Task GNG Spatial WM DMS Pattern Recognition Spatial Recognition Paired Associate Learning	MRT RT 5 choice Errors of distractions Span score, between search errors, score N° correct responses Accuracy Accuracy N° trials, total errors
Epstein et al. (2011)	93 (68:25)	8.11 (1.22)	105.58 (12.94)	ODD = 34 CD = 4 ANX = 31 Mood disorders = 2	Double blind, randomized, placebo-controlled, crossover trial	OROS-MPH (18, 27, and 36 mg for children <25 kg; 18, 36 or 54 mg for children >=25 kg)	1 week (1 week each for low, middle and high dose of MPH, 1 week Placebo)	Reaction Time Attention Working Memory Inhibition	Choice, ANT, GNG, SST, N-back Choice, ANT, GNG, SST, N-back ANT n-back N-back, GNG, SST SST	MRT CV Accuracy Accuracy Accuracy SSRT
Goodman et al. (2017)	222 (*)	MPH: 36.8 (11.95) Placebo: 34.7 (11.60)	*	*	Double blind, randomized, placebo-controlled, parallel-trial	OROS-MPH (titrated: 18 - 72 mg/day)	6 weeks (6 weeks MPH, 6 weeks placebo)	Inhibition Attention	Stroop CPT	Stroop RT Omission errors

Hadar et al. (2021)	36 (36:0)	8.3 to 9.7 years	*	*	Double blind, randomized, placebo-controlled, crossover trial	IR-MPH: 0.3 mg/kg	1 week (1 week MPH, 1 week placebo)	Attention	Visuomotor Attention Test	Nº interruptions
Kortekaas-Rijlaarsdam et al.(2020)	63 (43:20)	10.49 (1.24)	97.68 (13.82)	parent and teacher rated ODD, CD scores	Double blind, randomized, placebo-controlled, crossover trial	Equasym-XL MPH (titrated 10 - 40 mg/day)	1 week (1 week MPH, 1 week placebo)	Reaction Time Attention Inhibition Working Memory	Flanker Task Flanker Task Flanker Task Verbal WM task Visuospatial WM task	MRT, Accuracy Lapses of attention Interference RT Accuracy by level Accuracy by level
Kupietz et al. (1988)	21 (*)	MPH: 9 Placebo: 9.6	MPH: 92.6 (10.6) Placebo: 93.2 (10.5)	*	Double blind, randomized, placebo-controlled, parallel trial	MPH (0.3, o.5 or 0.7 mg/kg twice daily)	1 month (1 month of each of 3 dosages of MPH, 1 month placebo)	Working Memory	Paired Associate Learning Short term memory task	Nº errors Nº correct responses
Luman et al. (2015)	23 (15:8)	119 (17) months	98 (15)	parent and teacher rated ODD scores	Triple blind, randomized, placebo-controlled, crossover trial	IR-MPH (5, 10 or 15/20 mg depending on weight)	1 week (1 week each of the 3 dosages of MPH, 1 week placebo)	Attention	Time Production Task	RTV, Accuracy

Merrill et al. (2022)	59 (47:12)	8.7 (1.44)	96.47 (12.47)	ODD = 63% CD = 5%	Double blind, randomized, placebo-controlled, crossover trial	MPH (lowest effective dose)	3 weeks (3 weeks MPH, 3 weeks placebo)	Attention	Sustained Attention to Response Task	RTV
Murray et al. (2011)	68 (45:23)	10.3	*	ANX = 6 MDD= 1 LD = 26	Double blind, randomized, placebo-controlled, crossover trial	OROS-MPH (54 mg/day or maximum tolerated dose)	1 week (1 week MPH, 1 week placebo)	Reaction Time Attention Inhibition Working Memory	TOVA TOVA TOVA Digit Span Backwards Finger windows backwards	MRT RTV, Omission errors Commission errors Accuracy Accuracy
Nigg et al. (1996)	22 (22:0)	103.6 (20.9) months	Verbal IQ: 110.2 (20.5)	ODD = 12 CD = 7	Double blind, randomized, placebo-controlled, parallel trial	MPH (low: 0.3mg/kg, moderate: 0.6 mg/kg)	1 week (1 week each of low and high dose MPH, 1 week placebo)	Reaction Time Attention Inhibition	CPT CPT CPT	MRT Omission errors Commission errors
Rhodes et al. (2004)	75 (75:0)	10.85 (2.46)	*	ODD = 31 CD = 21 MDD = 3 GAD = 2 Separation ANX = 3 Tic disorder = 2 Social phobia = 1	Double blind, randomized, placebo-controlled, crossover trial	MPH (0.3mg/kg, 0.6 mg/kg)	28 days (28 days each for low dose, high dose and placebo)	Working Memory	Delayed Matching to Sample Spatial Working Memory Task Pattern Recognition	Simultaneous % correct, Delay % correct Between search errors Nº correct responses

Schachar et al. (2008)	17 (15:2)	11.3 (2.2)	*	No comorbid conditions	Double blind, randomized, placebo-controlled, three-way crossover trial	MPH-MLR (1.2 mg/kg/day or IR MPH 0.6mg/kg)	1 week (1 week MPH-MLR, 1 week IR MPH, 1 week placebo)	Reaction Time Attention Inhibition	Stop Task CPT Stop Task CPT	MRT Omission errors SSRT Commission error
Solanto et al. (2009)	25 (11:14)	8.86 (1.45)	111 (15.98)	ODD = 3 LD = 8 ANX = 1	Double blind, randomized, placebo-controlled, crossover trial	IR-MPH (0.6 mg/kg)	1 week (low, medium and high dose each 1 week, placebo 1 week)	Reaction Time Attention Inhibition	CPT CPT CPT Stroop Task	MRT RTV Omission errors d' Commission errors Interference
Tamminga et al. (2021)	Boys: 50 (50:0) Men: 48(48:0)	MPH: 11.35 (0.83) Placebo: 11.24 (0.93) MPH: 28.01 (4.45) Placebo: 28.90 (4.97)	MPH 105.68(19.98) Placebo: 103.35 (15.05) MPH: 107.86 (8.75) Placebo: 107.30 (6.81)	MPH M(SD): ODD = 6.48 (5.68) CD = 1.28 (1.57) Placebo M(SD): ODD = 7.36 (5.52) CD = 3.20 (4.50) Men: *	Double blind, randomized, placebo-controlled, parallel, multicenter trial	MPH (40 mg maximum)	8 weeks (8 weeks MPH, 8 weeks placebo)	Reaction Time Attention Working Memory	Simple RT task Simple RT Task n-back Rey's auditory verbal learning test	Median RT RTV Accuracy Immediate Recall Delayed Recall

Wigal et al. (2011)	78 (55:23)	10.1 (1.08)	IQ ≤ 80	LD = 25	Double blind, randomized, placebo-controlled, crossover trial	OROS-MPH (18 mg: n = 10 36 mg: n = 34 54 mg: n = 27)	1 week (1 week MPH, 1 week placebo)	Reaction Time Attention Inhibition Working Memory	TOVA TOVA TOVA Finger windows backward Digit Span backwards	RT RTV Omission errors Commission errors Accuracy Accuracy
Zeiner et al. (1999)	36 (36:0)	8.7 (1.2)	102 (15)	Parent and teacher ratings of conduct problems	Double blind, randomized, placebo-controlled, crossover trial	MPH (0.5 mg/kg)	3 weeks (MPH 3 weeks, placebo 3 weeks)	Attention Inhibition Working Memory	Children's Checking Task CPT Children's Checking Task CPT Paced Auditory Serial-Addition Task (PA-SAT) R & A Version	Omission errors Omission errors Commission errors Commission errors Accuracy

Note: *information unavailable; ADHD, Attention Deficit/Hyperactivity Disorder; ADD Attention Deficit Disorder; ANT Attention Network Test; ANX, anxiety disorder; ASPD: Antisocial Personality Disorder; BD, Bipolar Disorder; BPD, Borderline Personality Disorder; C – CPT, Computerized Continuous Performance Task; CCT, Children's Checking Test; CD, Conduct Disorder; CDRS, Children's Depression Rating Scale; CI, Confidence Interval; CNS, Central Nervous System; CPT, Continuous Performance Task; CTOPP, Comprehensive Test of Phonological Processing; CV, Coefficient of Variation; d', Measure of Attentiveness; DMS, Delayed Matching to Sample Test; DSM-5, Diagnostic and Statistical Manual for Mental Disorders – Fifth edition; DSM –IV, Diagnostic and Statistical Manual for Mental Disorders – Fourth Edition; DSM-3, Diagnostic and Statistical Manual for Mental Disorders – Third Edition; GAD, Generalized Anxiety Disorder; GDS – CPT, Gordon Diagnostic System – Continuous Performance Task; GNG, Go/No-go task; GORT, Gray Oral Reading Test; IQ, Intellectual Quotient; I2, percentage of variation; mg/kg, milligram per kilogram; LD, Learning Disability; MDD, Major Depression disorder; MDT, Multi-disciplinary Team; mg, Milligram; MPH, Methylphenidate; MPH (IR), immediate release MPH; MPH-MLR, Multilayer release MPH; MRT, Mean Reaction Time; Nº, number; N_Interruptions, Number of interruptions measure; OCD, Obsessive-Compulsive Disorder; ODD, Oppositional Defiant Disorder; OROS MPH, The Osmotic-Release Oral System Formulation of Methylphenidate; p value, value of significance; PDD, Pervasive Developmental Disorder; PTSD, Post-traumatic stress disorder; RT, Reaction Time; RTV, Reaction Time Variability; RVIP, Rapid Visual Information Processing; SAD, Substance use disorder; SART, Sustained Attention to Response Task; SD, Standard Deviation; SSRT, Stop Signal Reaction Time; SST, Stop Signal Task; TEA – Ch, Test of Everyday Attention for Children; TOVA, Test of Variables of Attention; WIAT-2, Wechsler Individual Achievement Test - Second Edition; WISC / WISC-IV, Weschler Intelligence Scale for Children / Weschler Intelligence Scale for Children – Fourth edition.

Table 3 Characteristics of all included studies on atomoxetine

Author (Year)	Sample Size (M:F)	Mean age in years (SD)	Mean IQ	Comorbidities	Study Design	Drug type (Dose)	Duration of drug treatment	Cognitive Domain	Task	Measure
Fan et al. (2017)	ATX: 12 (5:7) Placebo: 12 (5:7)	ATX: 28.9 (7.8) Placebo: 32.5 (9.8)	ATX: 115.8 (13.5) Placebo: 119.9 (13.8)	*	Randomized, placebo controlled, crossover trial	ATX (1st week: 0.5 mg/kg, 2nd week to 8th weeks: 1.2 mg/kg)	8 weeks (8 weeks ATX, 8 weeks placebo)	Reaction Time Attention Inhibition Working memory	Rapid Visual Processing Delayed Matching to Sample Rapid Visual Processing Delayed Matching to Sample Delayed Matching to Sample	MRT MRT Probability of Hits Probability of false alarm Number of correct responses

Faraone et al. (2005)	ATX: 212 (*) Placebo: 213 (*)	41.2 (11.2)	*	*	Double blind, randomized, placebo-controlled, parallel trial	ATX (14 days: 60 mg – those with residual symptoms got after 14 days 90 mg after that: 120 mg/day)	10 weeks (10 weeks ATX, 10 weeks placebo)	Inhibition	Stroop Task	Interference RT score
De Jong et al. (2009)	16 (14:2)	8.8 (1.3)	99.3 (14.0)	*	Double blind, randomized, placebo-controlled, crossover trial	ATX (First 7 days: 0.6 mg/kg, 8- 21 days: 1.2 mg/kg)	28 days (28 days ATX, 28 placebo)	Reaction Time Inhibition Working memory	SST SST Corsi Block Tapping Task	MRT SSRT Number of correct sequences
Griffiths et al. (2018)	116 (91:25)	11.29 (2.5)	*	ANX = 43 CD = 14 MD = 3 OCD = 10 ODD = 46 PTSD = 7	Double blind, randomized, placebo-controlled, crossover trial	ATX (Mean dose: 1.35 mg/kg)	6 weeks (6 weeks ATX, 6 weeks placebo)	Reaction time Attention Inhibition	CPT CPT GNG	RT Omission errors, RTV Commission Errors
Kollins et al. (2011)	Total: 178 (124:54) Guanfacine: 121 (80:41) Placebo: 57 (44:13)	Total: 12.6 (2.81) Guanfacine: 12.6 (2.83) Placebo: 12.8 (2.77)	*	No comorbidities	Double blind, randomized, placebo-controlled, parallel trial	Guanfacine (1-3 mg)	45 days (45 days ATX, 45 days placebo)	Reaction Time Attention Working Memory	Choice RT Choice RT PERMP CANTAB: Spatial working memory	MRT Accuracy Accuracy Number of errors

Spencer et al. (1998)	21 (10:11)	34 (9)	*	Comorbid psychiatric disorder = 13	Double blind, randomized, placebo-controlled, crossover trial	ATX (Week 1: 40mg, week 2: 80 mg, week 3: 80 mg)	3 weeks (3 weeks ATX, 3 weeks placebo)	Inhibition	Stroop Task	Interference T Test score
Wehmeier et al. (2012)	Total: 125 (97:28) ATX: 63 (47:16) Placebo: 62 (50:12)	Total: 9 (1.78) ATX 9.1 (1.93) Placebo: 8.9 (1.64)	*	ATX: ODD = 20 CD = 9 ODD+CD = 25 Tic disorder = 1 Placebo: ODD= 19 CD = 12 ODD+ CD = 25 Mood disorder = 1	Double-blind, randomized, placebo-controlled parallel trial	ATX (1 week: 0.5 mg/kg, 7 weeks: 1.2 mg/kg)	8 weeks (8 weeks ATX, 8 weeks placebo)	Reaction time Attention Inhibition	CPT CPT CPT	RT RTV, Omission Errors Commission Errors
Wietecha et al. (2013)	27 (*)	12.3 (*)	*	*	Double-blind, randomized, placebo-controlled, parallel, multicenter study	ATX (3 days: 0.5 mg/kg/day, after that 1.0 - 1.4 mg/kg)	16 weeks (16 weeks ATX, 16 weeks placebo)	Working Memory	Working Memory Test Battery for Children	Central Executive Component Score

Note: *information unavailable; ADHD, Attention Deficit/Hyperactivity Disorder; ADD Attention Deficit Disorder; ANT Attention Network Test; ANX, anxiety disorder; ASPD: Antisocial Personality Disorder; ATX: Atomoxetine; BD, Bipolar Disorder; BPD, Borderline Personality Disorder; C – CPT, Computerized Continuous Performance Task; CCT, Children's Checking Test; CD, Conduct Disorder; CDRS, Children's Depression Rating Scale; CI, Confidence Interval; CNS, Central Nervous System; CPT, Continuous Performance Task; CTOPP, Comprehensive Test of Phonological Processing; CV, Coefficient of Variation; d', Measure of Attentiveness; DMS, Delayed Matching to Sample Test; DSM-5, Diagnostic and Statistical Manual for Mental Disorders – Fifth edition; DSM –IV, Diagnostic and Statistical Manual for Mental Disorders – Fourth Edition; DSM-3, Diagnostic and Statistical Manual for Mental Disorders – Third Edition; GAD, Generalized Anxiety Disorder; GDS – CPT, Gordon Diagnostic System – Continuous Performance Task; GNG, Go/No-go task; GORT, Gray Oral Reading Test; IQ, Intellectual Quotient; I2, percentage of variation; mg/kg, milligram per kilogram; LD, Learning Disability; MDD, Major Depression disorder; MDT, Multi-disciplinary Team; mg, Milligram; MRT, Mean Reaction Time; N_Interruptions, Number of interruptions measure; OCD, Obsessive-Compulsive Disorder; ODD, Oppositional Defiant Disorder; OROS MPH, The Osmotic-Release Oral System Formulation of Methylphenidate; p value, value of significance; PDD, Pervasive Developmental Disorder; PTSD, Post-traumatic stress disorder; RT, Reaction Time; RTV, Reaction Time Variability; RVIP, Rapid Visual Information Processing; SAD, Substance use disorder; SART, Sustained Attention to Response Task; SD, Standard Deviation; SSRT, Stop Signal Reaction Time; SST, Stop Signal Task; TEA – Ch, Test of Everyday Attention for Children; TOVA, Test of Variables of Attention; WIAT-2, Wechsler Individual Achievement Test - Second Edition; WISC / WISC-IV, Weschler Intelligence Scale for Children / Weschler Intelligence Scale for Children – Fourth edition.

Table 4 Results of the meta-regression analysis statistically comparing the effects of methylphenidate and atomoxetine on cognitive functions in ADHD

Cognitive domain	Differences in Hedges' g (95% CI)	z	p
Reaction time	0.00 (-0.46; + 0.45)	0.0	0.966
Attention	0.03 (-0.37; +0.43)	0.2	0.872
Inhibition	0.07 (-0.29; + 0.44)	0.4	0.688
Working memory	-0.11 (-0.58; +0.36)	-0.5	0.644

Note: CI, confidence interval; z, z-score; p, p-value.

HIGHLIGHTS

- First meta-analysis of chronic medication effects on cognition in ADHD
- Cognitive domains included attention, inhibition, reaction time and working memory
- Chronic methylphenidate improved performance on all cognitive domains
- Chronic Atomoxetine improved performance on all domains except working memory
- Methylphenidate and Atomoxetine did not differ in their effects
- Methylphenidate and Atomoxetine have comparable effects on improving cognition in ADHD