Human Psychopharmacology: Clinical and Experimental

WILEY

RESEARCH ARTICLE OPEN ACCESS

Acute Administration of 10 mg Methylphenidate on Cognitive Performance and Visual Scanning in Healthy Adults: Randomised, Double-Blind, Placebo-Controlled Study

Blair Aitken[1] | Luke A. Downey[1,2] | Serah Rose[1] | Brooke Manning[1] | Thomas R. Arkell[1] | Brook Shiferaw[1,3] | Amie C. Hayley[1,2]

[1]Centre for Mental Health and Brain Sciences, Swinburne University of Technology, Hawthorn, Australia | [2]Institute for Breathing and Sleep (IBAS), Austin Health, Heidelberg, Australia | [3]Human Factors, Seeing Machines, Fyshwick, Australia

Correspondence: Amie C. Hayley (ahayley@swin.edu.au)

Received: 13 November 2024 | **Revised:** 27 January 2025 | **Accepted:** 5 February 2025

Funding: The authors received no specific funding for this work.

ABSTRACT

Objective: To examine the effect of a low dose (10 mg) of methylphenidate on cognitive performance, visuospatial working memory (VSWM) and gaze behaviour capabilities in healthy adults.

Methods: This randomised, double-blind, placebo-controlled and crossover study examined the effects of 10 mg methylphenidate on cognitive performance, VSWM and gaze behaviour. Fixation duration and rate, gaze transition entropy, and stationary gaze entropy were used to quantify visual scanning efficiency in 25 healthy adults (36% female, mean ± SD age = 33.5 ± 7.8 years, BMI = 24.1 ± 2.9 kg/m^2). Attention, memory, and reaction time were assessed using the E-CogPro test battery.

Results: Methylphenidate significantly enhanced performance in numeric working memory tasks, reflected by reduced errors and increased accuracy relative to placebo. No significant changes were observed in other cognitive or visual scanning metrics.

Conclusions: A low dose of methylphenidate improves limited domains of psychomotor speed and accuracy but does not affect visual scanning efficiency. This suggests limited usefulness as a general pro-cognitive aid and raises the possibility of a lower threshold of effect for measurable psychostimulant-induced changes to visual scanning behaviour. Further research is needed to explore these potential dose-response relationships and effects across diverse populations.

Trial Registration: ACTRN12620000499987

1 | Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent psychiatric condition, diagnosed in approximately 2.6% of adults and 7.6% of children globally (Salari et al. 2023; Song et al. 2021). It is characterised by pervasive, developmentally inappropriate and impairing levels of hyperactivity, inattention, and impulsivity (Biederman 2005). Neuroimaging studies have revealed an association between ADHD and hypofunction in several brain regions, particularly the prefrontal cortex (PFC) and striatum, which are linked to the cognitive deficits typically observed (Bush, Valera, and Seidman 2005). Since the initial use of amphetamine sulphate, also known by brand name Benzedrine, stimulant-based medications such as methylphenidate

have been considered the 'gold standard' for ADHD treatment (Chan et al. 2023; Strohl 2011). Methylphenidate works by inhibiting the reuptake of dopamine and noradrenaline, thereby increasing their extracellular concentrations in key brain regions such as the PFC, striatum, and hippocampus (Faraone et al. 2004). This biochemical mechanism is believed to stabilise cognitive functions, including working memory, processing speed, and attentional control (Faraone et al. 2004). These improvements, which enhance skills crucial for social functioning, emotional regulation, and academic success (Shellenberg et al. 2020), underly the therapeutic efficacy of methylphenidate for ADHD.

Given the well-documented therapeutic benefits of stimulant-based medications for individuals with ADHD (Shellenberg et al. 2020), these same medications are often used non-medically, particularly among college students (Sharif et al. 2021). Recently, certain centrally stimulating medications have been colloquially referred to as 'smart drugs'. This labelling has fostered a potentially dangerous misconception that these drugs enhance focus and productivity, with little-to-no side effects or risks (Partridge et al. 2011). It is estimated that around 17% of college students in the United States misuse stimulant medication (Benson et al. 2015). An online poll conducted by *Nature* magazine in 2008 further revealed that 12.4% of its readership had used methylphenidate for non-medical purposes, seeking off-label effects such as euphoria, prolonged wakefulness, or enhanced cognitive performance (Maher 2008). This phenomenon raises important questions about the extent of methylphenidate's objective cognitive enhancement capabilities in the absence of underlying pathology. Moreover, using methylphenidate without a prescription poses several risks, including potential interactions with other medications and undiagnosed cardiovascular issues, which may remain unnoticed in the absence of medical supervision (Kapur 2020). Similarly, purchasing methylphenidate from online or non-pharmaceutical vendors raises concerns about its authenticity, the accuracy of the stated dosage, and the presence of harmful contaminants.

Methylphenidate produces dose- and task-dependent effects on numerous core cognitive domains in healthy adults, including working memory and processing speed (Linssen et al. 2014). By comparison, data outlining the scope and magnitude of alterations to visual information processing capabilities produced due to acute methylphenidate use, and the methods best suited to quantify these changes, are lacking. Established pharmaco-behavioural models outline how psychostimulant use critically alters key chemical (predominantly dopamine) and neuroanatomical pathways implicated in visual-attentional processing capabilities (Hayley, Shiferaw, and Downey 2021). Specifically, drug-induced alterations to brain regions and functions that similarly govern oculomotor control are proposed to produce measurable changes in both static (e.g. saccadic and fixational) and dynamic eye movements (e.g. gaze). These changes can be quantified by examining the continuity and accuracy of visuomotor movement and performance, highlighting the close pathophysiological relationship between oculomotor control and higher-order, visually driven, cognitive processes. Thus, measurement of movement related to the motion of the eye reflects a potential direct measure of quantifying neurocognitive capabilities under the influence of these centrally stimulating drugs. Of interest, past work similarly proposes a potential 'optimal range' for psychostimulants, whereby low to moderate doses produce some limited beneficial pro-cognitive effects, yet this becomes maladaptive at high doses, particularly for principally visual-based tasks (Hayley et al. 2024; Narayan et al. 2021). As much of the existing experimental work on methylphenidate has exclusively examined higher doses (Kasparbauer et al. 2016; Roberts et al. 2020), it remains unclear whether this effect on neurobehaviour and cognition is similarly observed under the acute effects of methylphenidate at this lower dose. The current study therefore addresses these limitations by utilising a placebo-controlled design to directly compare visual attention and cognitive performance changes attributable to low, therapeutic doses of methylphenidate in healthy adults. Specifically, it aims to examine the effects of a 10 mg dose of methylphenidate on visual attention, visual scanning, memory, and reaction time in a single cohort of healthy adults, relative to placebo.

2 | Method

2.1 | Participants

Participants were healthy adults aged 21–45 years, recruited in Melbourne, Australia, from May 2022 to November 2023 via physical flyers and online advertisements. Inclusion criteria required participants to be fluent in written and spoken English, possess normal or corrected-to-normal vision and have a blood pressure below 160/100 mmHg. Participants were excluded if they reported a history or current diagnosis of psychiatric disorders, as assessed by the Beck Depression Inventory [BDI (Beck, Steer, and Brown 1996)] score of $\geq$ 20 and the Beck Anxiety Inventory [BAI (Beck, Steer, and Brown 1996)] score of $\geq$ 16. The presence of mood disorders, substance abuse or dependence, or any significant psychological or neurological/neurodevelopmental conditions, including ADHD, were assessed by clinical interview. Participants taking psychoactive medications with known or potential interactions with methylphenidate, as well as those who were pregnant, potentially pregnant, or lactating, were also excluded.

2.2 | Design

In this randomised, double-blind, placebo-controlled and crossover trial, participants received either 10 mg of methylphenidate (Ritalin) or a placebo during the first session and the alternate treatment in the subsequent session, separated by a 1-week washout period. Randomisation was performed using a computer-generated sequence [Research Randomiser Software Version 4.0 (Urbaniak and Plous 2013)]. To reduce potential learning and practice effects, participants completed cognitive assessments twice before enrolment. Participants were instructed to abstain from consuming food and drinks (excluding water) for 2 hours, caffeine for 12 h, and alcohol and nicotine for 24 h prior to testing sessions. Participants were requested to refrain from using psychoactive medicines or illicit drugs for the duration of the study, unless already approved by the study

physician. All participants provided written informed consent prior to their enrolment in the study. Upon study completion, participants were debriefed and compensated for their time and travel (AUD$100 total; AUD$50/session) and informed about potential side effects. Ethical approval was granted by Swinburne University's Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Human Research (2018) (National Health and Medical Research Council, 2018), approval number 20202839-411. All study procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983. The study protocol was prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR; ACTRN12620000499987).

2.3 | Procedure

On testing days, participants underwent a breathalyser test (Lion Alcolmeter SD-400PA) to confirm a zero-blood alcohol concentration (BAC). They also provided an oral fluid sample which was screened for recent use of substances including delta-9-tetrahydrocannabinol (THC), opiates, cocaine, amphetamines, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA) using the Securetec DrugWipe 6s device. After confirming a negative drug screening, participants received their assigned treatment (10 mg methylphenidate or placebo) and underwent a 20-min absorption period before engaging in study assessments. Cognitive performance and visuospatial working memory (VSWM) were assessed at 20 min post-dosing (T1), with this initial assessment timed to capture the early effects of methylphenidate as it began to take effect. Subsequently, a 40-min driving simulator task was conducted, though the results of this task are not reported in this paper. A second, identical cognitive and VSWM assessment were completed at 130-min post-dosing (T2), closely aligning with the known peak plasma concentration times for methylphenidate, which typically occurs between 1 and 3 h after administration (Kimko, Cross, and Abernethy 1999). The duration of each testing visit was approximately 3 hours.

2.4 | Materials

2.4.1 | Cognitive Performance

Attention, memory and reaction time were assessed using the online computerised test battery ECogPro (Ecog Pro Ltd., United Kingdom). Five distinct tasks to evaluate cognitive performance were administered in a standardised form to participants on a study computer in a quiet environment.

- *Simple reaction time*: Participants were asked to respond to the word YES when it appears on the screen by pressing their right forefinger on the RIGHT arrow key. The word appeared unpredictably, with 50 stimuli presented at random intervals ranging from 1 to 3.5 s. Participants were instructed to keep their forefinger on the key to prioritise speed. The task measured reaction time in milliseconds (ms) for all responses.
- *Choice reaction time*: Participants were asked to place their forefingers on the arrow keys and respond to 50 unpredictable stimuli presented in the centre of the screen. They were instructed to press the appropriate key (left or right) based on the direction indicated by the stimulus as quickly and accurately as possible. The task stimuli consisted of 50 items appearing at random intervals ranging from 1 to 3.5 s. The task measured reaction time (ms) and accuracy (% correct) for all responses.
- *Digit vigilance*: Participants were asked to monitor a stream of digits presented one at a time on the left side of the screen, while a randomly selected target digit was displayed separately on the right side. Participants were instructed to press the RIGHT arrow key whenever the target digit on the right appeared in the stream on the left. The task measured the number (no.) and speed (ms) of correct detections and false alarms, with digits presented at a rate of 150 per minute.
- *Spatial working memory*: Participants are asked to memorise a 3×3 lit bulb pattern that was displayed on the screen for 10 s. Afterwards, they were shown 36 randomised variations of a 3×3 array, each with a single bulb illuminated. Participants were instructed to press the RIGHT arrow key if the illuminated bulb matched the position of one of the original lit bulbs and the LEFT arrow key for non-target positions. The task measured reaction time (ms) and accuracy (% correct).
- *Numeric working memory*: Participants were shown a series of five digits (ranging from 0 to 9) to memorise. Later, they were presented with 30 probe digits, which included the original five digits mixed with other numbers. Participants were instructed to press the RIGHT arrow key when they saw one of the original target digits and the LEFT arrow key for any non-target digits. The task measured reaction time (ms) and accuracy (% correct).

2.4.2 | Visuospatial Working Memory (VSWM)

VSWM was evaluated using a Python-based task (Python Software Foundation, Beaverton, OR) developed by Shiferaw et al. (Shiferaw et al. 2019). The task involves 80 trials, each starting with a cue period of 500 ms where four empty squares are presented at cardinal points. Subsequently, an array of coloured squares appears for 500 ms, followed by a 1000-ms delay. The array size varies randomly from 1 to 5 squares to minimise predictability. After the delay, a square reappears in an adjacent cardinal position. Participants ask instructed to identify the square's movement direction using arrow keys, with a 3000 ms response time window. A 30 ms flash signals the end of each task trial. Reaction time (ms) and accuracy (% correct) are recorded for each trial. Figure 1 illustrates an example of the VSWM trial as seen by participants.

Eye movements were recorded with an EyeLink 1000 (SR-Research, Mississauga, Ontario, Canada) at a sampling frequency of 1000 Hz. The task was presented on a 1920 by 1080 (32-bit colour) display monitor with a 60 Hz refresh rate, located 60 cm from the headrest used to secure participants in position.

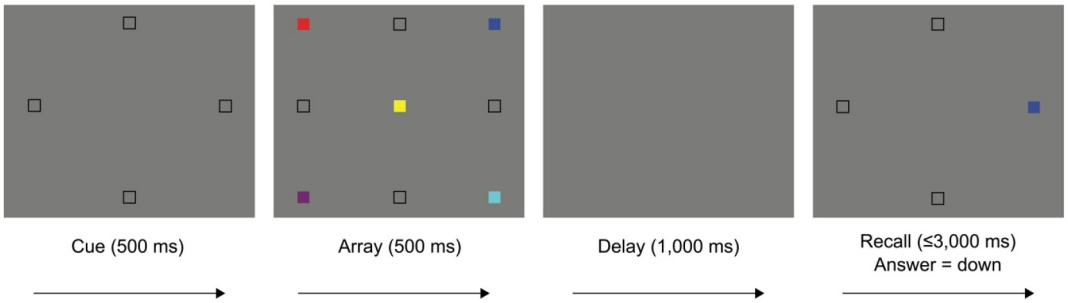

FIGURE 1 | Example of trial presentation with a set size of 5 (B. Shiferaw et al. 2019).

The ioHub event monitoring framework (Python package by iSolver Software Solutions, Osgoode, Ontario, Canada) was used to automatically initiate the 9-point calibration and validation process before commencing with the task and enable real-time recording of ocular events during trial presentation. The following parameters assessed during the VSWM task:

- *SGE*: SGE was calculated using Shannon's entropy equation to determine the probability distribution of fixation locations within the valid area of interest to calculate the level of uncertainty in the spatial distribution of a sequence of fixations. Higher values indicate that the subject distributes their visual attention more equally within the area of interest (greater dispersion), whereas lower values reflect a more narrowed (focussed) distribution of gaze (Krejtz et al. 2014). SGE was calculated for each participant, condition, and trial period.
- *GTE*: GTE applies the conditional entropy equation to first-order Markov matrices of fixation transitions to calculate an overall measure of the predictability of visual scanning patterns (Ellis and Stark 1986). Higher values indicate a less structured, or more random, pattern of scanning behaviour (Krejtz et al. 2014). Per existing frameworks (Shiferaw et al. 2018), entropy values (measured in bits) were normalised by dividing by the maximum possible entropy, with the normalised 0 values reflecting minimum entropy, and 1 reflecting maximum entropy. GTE was calculated for each participant, condition, and trial period.
- *Fixation duration*: Measured in milliseconds, this reflects the average (mean) time per minute that a participant held their gaze at a specific location. Longer fixation duration reflects greater visual and mental processing demands during tasks of high cognitive load (Walter and Bex 2021).
- *Saccadic amplitude*: Measured in degrees (°), refers to the distance travelled by the eye between two points of fixation.
- Fixation rate: Measured as rate (count) per trial and reflects the number of times a driver gazed at a specific location.

2.5 | Data Processing

To calculate SGE and GTE, the valid area of interest was segmented into 280 equal state spaces, resulting in a maximum entropy of $\log_2(280) = 2.79$, which was used to normalise scores. This grid was designed to capture the critical visual area needed for a driver to maintain a steady lane position and speed, while excluding non-pertinent values in GTE calculations. Entropy values (measured in bits) were normalised by dividing by the maximum possible entropy, with 0 being minimal entropy and 1 representing maximum entropy, as recommended by Shiferaw et al. (2018).

2.6 | Statistical Analysis

Prior to analyses, data were screened for missing values and potential outliers. Outliers on neurocognitive tasks were flagged using boxplot and z-score analysis. Potential outliers were identified across all cognitive measures, except for spatial working memory accuracy and VSWM reaction time and accuracy. Upon examination, these cases were retained in the dataset as genuine anomalies rather than errors, as sensitivity analyses confirmed that their inclusion did not affect the statistical significance of the results. One participant was missing choice reaction time data due to equipment failure, and seven participants had incomplete VSWM performance data (displayed in Supporting Information S1: Table A1).

Generalised linear mixed models (GLMMs) were used to analyse both accuracy and error outcomes, modelled with a binomial distribution and logit link function to account for the proportion of correct and incorrect responses out of the total trials for each outcome. This approach was chosen to address potential floor and ceiling effects, as these outcomes were not normally distributed. Results for accuracy are reported as mean percentages for interpretability, although the statistical analysis was conducted on the proportion of correct responses. An autoregressive covariance structure (AR1) was selected based on lower AIC and BIC values to account for temporal dependencies among repeated measures. Fixed effects included condition, time, and their interaction, while random intercepts were specified for subjects. For normally distributed continuous outcomes, linear mixed-effects models with restricted maximum likelihood (REML) were applied, with condition, time, and their interaction as fixed effects, and random intercepts for subjects. Likelihood ratio tests identified compound symmetry as the optimal variance structure for most cognitive outcomes and a diagonal structure for VSWM measures. Significant interactions were further explored using stratified one-way analyses by timepoint, while main effects were investigated in the absence of interactions. Bonferroni-corrected pairwise comparisons were applied for significant main effects. All analyses were conducted using SPSS v29 (SPSS Inc., Chicago, IL), with two-tailed tests and a significance threshold of $p < 0.05$.

3 | Results

3.1 | Demographic Characteristics

Figure 2 presents a Consolidated Standards of Reporting Trials (CONSORT) diagram illustrating the participant recruitment flow.

Of the 33 individuals screened for eligibility, four were excluded due to being outside the range for BMI criterion, two were excluded due to the use of prescription medications not permitted in the study, one was excluded due to having clinically relevant anxiety scores on the BAI, and one withdrew after post-enrolment due to time constraints. Each of the remaining 25 participants successfully completed both treatment conditions.

Participants had a mean age of 33.5 years (SD ± 7.8, range 23–47) and BMI of 24.1 kg/m^2 (SD ± 2.9). The study sample demographic composition was predominantly Caucasian (88%), and a significant majority (92%) had achieved at least a tertiary level of education. Regarding substance use, more than half of participants (52%) reported previous use of a psychostimulant, with amphetamines/speed used by 36%, MDMA/ecstasy by 40%, and cocaine by 44% of participants. Only one participant reported monthly amphetamine use, with all other participants reporting their use of amphetamines/speed, MDMA/ecstasy, or cocaine as less frequent (i.e., less than once a month). All participants reported previously consuming alcohol, with 88% having previously used cannabis, and one individual (4%) having used inhalants.

3.2 | Cognitive Performance

Mean scores for cognitive performance outcomes are presented in Table 1. A significant main effect of treatment was observed for numeric working memory accuracy, whereby accuracy improved (better performance: $F(1,96) = 8.76$, $p = 0.004$) following methylphenidate ($M = 96.47$, SD ± 2.83) administration relative to placebo ($M = 94.45$, SD ± 4.43, with an odds ratio of 1.67 (95%CI: 1.09–2.57).). No significant main effects of treatment, time, or their interaction were observed for any other cognitive performance outcomes (all $p > 0.05$).

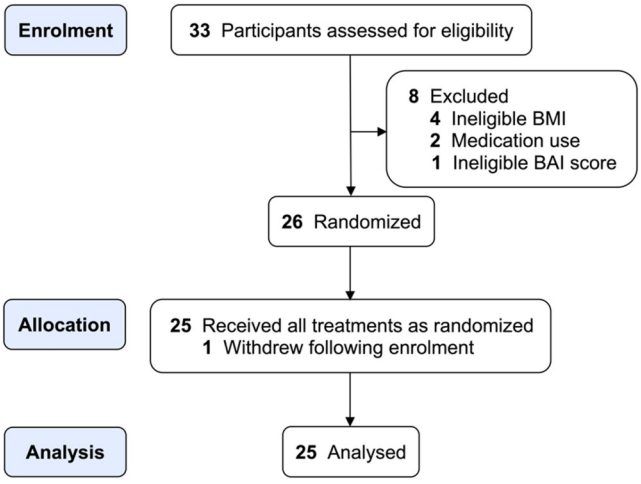

FIGURE 2 | CONSORT diagram illustrating the flow of participant recruitment.

3.3 | Visuospatial Working Memory

Mean scores for VSWM ocular and performance-based outcomes are presented in Table 2. There was no main effect of treatment, time, or their interaction for any ocular or performance outcomes (all $p > 0.05$).

4 | Discussion

This study investigated the acute effects of 10 mg methylphenidate relative to placebo on cognitive performance in healthy adults. Consistent with prior research, we observed select, modest improvements in tasks that assess numeric working memory. Considering the absence of improvement across other cognitive domains, these findings suggest that the effects produced by low-dose methylphenidate are more dose-limited and task-specific (i.e. behaviourally driven psychomotor performance) than previously theorised. This suggests that cognitive effects of methylphenidate are not universally distributed but may instead be contingent on the specific cognitive demands examined and reflect task composition or complexity.

Methylphenidate primarily exerts its neurocognitive and behavioural effects by inhibiting the re-uptake of dopamine and noradrenaline, thereby increasing availability in the synaptic cleft (Swanson and Volkow 2003). The observed improvements in specific tasks assessing numeric working memory emphasise the role of neurotransmitter enhancement in the PFC which is essential for the manipulation and retention of information (Linssen et al. 2014; Spencer, Devilbiss, and Berridge 2015). Even at relatively low introductory dose of 10 mg, significant improvements in sustained attention task performance were observed relative to placebo, reflected by greater accuracy and subsequent reductions in errors, supporting very limited previous work in this space (Koelega 1993). Such enhancements in sustained attention could arguably be useful in contexts requiring prolonged focus, such as academic settings or during functional behavioural tasks such as driving which require extended visual attention. Nonetheless, these findings have not yet been reliably replicated (Batistela et al. 2016), and thus further investigation is needed to evaluate the scope and magnitude of these potential enhancing effects.

Methylphenidate exhibits a potentially dose-limited impact on cognitive function that is similar to other therapeutic and illicit catecholaminergic drugs. Previous work cites a likely dose, inter-individual and task-dependent inverted-U effect, characterised by select improvement, a 'ceiling effect' and potentially diminishing performance (Cools and D'Esposito 2011). Higher doses can induce unintentional (and typically unwanted) adverse cognitive outcomes during principally visually based tasks, including decreased attentional control, and heightened distractibility (Dolder et al. 2018; Narayan et al. 2021). The dose examined in the present study (10 mg) reflects an introductory

TABLE 1 | Mean scores (±SD) for cognitive performance outcomes across condition (placebo and methylphenidate) and time (T1 and T2) ($N = 25$).

	Placebo			Methylphenidate 10 mg		
Outcome measure	**T1**	**T2**	**Overall**	**T1**	**T2**	**Overall**
Simple reaction time						
Reaction time (ms)	310.24 (36.0)	313.34 (46.09)	311.84 (40.96)	306.94 (41.41)	302.58 (38.19)	304.76 (39.49)
Choice reaction time						
Reaction time (ms)	454.06 (52.90)	456.26 (56.53)	455.16 (54.19)	467.58 (52.01)	460.14 (55.93)	463.79 (53.62)
Accuracy (% correct)	96.48 (3.28)	96.48 (3.80)	96.48 (3.51)	97.50 (2.52)	96.48 (2.33)	96.98 (2.45)
Digit vigilance						
Reaction time (ms)	453.92 (49.75)	459.50 (51.64)	456.71 (50.26)	453.20 (56.67)	452.13 (63.03)	452.67 (59.32)
Accuracy (% correct)	97.14 (3.67)	97.51 (2.82)	97.32 (3.25)	97.68 (3.11)	97.51 (3.87)	97.60 (3.48)
Errors (no.)	0.20 (0.50)	0.12 (0.33)	0.16 (0.42)	0.04 (0.20)	0	0.02 (0.14)*
Spatial working memory						
Reaction time (ms)	691.38 (173.96)	667.72 (190.01)	679.55 (180.69)	696.10 (186.22)	662.32 (143.56)	679.21 (165.44)
Accuracy (%)	95.80 (5.30)	95.80 (5.15)	95.80 (5.17)	94.78 (5.40)	95.73 (4.32)	95.25 (4.86)
Numeric working memory						
Reaction time (ms)	689.24 (141.01)	710.04 (158.01)	699.64 (148.58	736.21 (194.84)	701.28 (166.65)	718.74 (180.30)
Accuracy (%)	94.98 (4.50)	93.91 (4.38)	94.45 (4.43)	96.53 (2.93)	96.40 (2.78)	96.47 (2.83)**

Note: Missing data for $n = 1$ were present at T1 in the methylphenidate condition for choice reaction time.
* Symbol indicates a significant difference from placebo based on post-hoc paired *t*-test analyses with Bonferroni adjustment at *$p < 0.05$ or **$p < 0.01$.

TABLE 2 | Mean scores (±SD) for visuospatial working memory performance and ocular outcomes across condition (placebo and methylphenidate) and time (T1 and T2) ($N = 22$).

	Placebo			Methylphenidate 10 mg		
Outcome measure	**T1**	**T2**	**Overall**	**T1**	**T2**	**Overall**
Reaction time (ms)	502.99 (41.69)	488.85 (29.09)	495.92 (36.22)	494.23 (27.49)	500.51 (20.53)	497.45 (24.06)
Accuracy (% correct)	93.45 (4.59)	95.11 (3.16)	94.29 (3.98)	93.49 (6.79)	95.25 (4.58)	94.39 (5.76)
Fixation duration (ms)	265.27 (26.07)	263.0 (28.02)	264.14 (26.70)	264.79 (25.73)	268.81 (26.65)	266.80 (25.94)
Fixation rate (count per trial)	3.24 (1.47)	3.22 (1.31)	3.23 (1.37)	2.89 (1.45)	3.11 (1.51)	3.0 (1.46)
Saccade amplitude (°)	5.03 (1.94)	4.65 (1.87)	4.84 (1.89)	4.63 (2.15)	4.50 (2.12)	4.56 (2.11)
SGE (bits)	0.35 (0.08)	0.30 (0.12)	0.33 (0.11)	0.30 (0.15)	0.30 (0.14)	0.30 (0.15)
GTE (bits)	0.30 (0.08)	0.30 (0.08)	0.30 (0.08)	0.27 (0.11)	0.28 (0.11)	0.27 (0.11)

Note: missing data were present for $n = 1$ at T1 in the methylphenidate condition for reaction time and accuracy; $n = 3$ at T1 and T2 in the placebo condition for saccade amplitude; and $n = 1$ at T1 and T2 in the placebo condition for fixation duration, fixation rate, SGE and GTE.
Abbreviations: SGE, stationary gaze entropy; GTE, gaze transition entropy.

therapeutic dose. We report no measurable change to oculomotor control or function during the VSWM task, and no changes in rapid visual tracking skills in the cognitive testing suite. This is largely in agreement with lack of clear effect to neurocognitive measured aspects of visual tracking capabilities at this low dose (Klinge et al. 2018). Of note, compound visual tracking skills (smooth pursuit performance) is observed to improve at marginally higher doses (20 mg) (Allman et al. 2012). It is thus possible that there exists an 'optimal' pro-cognitive effect range for visual scanning and processing capabilities which may, in part, be proportional to task composition, difficulty and/or complexity at the dose concentrations provided (Naylor, Halliday, and Callaway 1985) and more closely reflect underlying pharmacokinetic and pharmacodynamic properties of the (stimulant) drug examined. Indeed, low-moderate oral doses (0.42 mg/kg) of a pharmacologically similar agent (methamphetamine) did not significantly alter sustained visual attention during a cognitive testing suite (Hayley et al. 2023), yet produced marked and sustained alterations in gaze behaviour during a dynamic visual task (driving simulation) (Hayley et al. 2024), suggesting an upper limit to select psychostimulant-derived cognitive enhancing effects which can be effectively measured and indexed through direct monitoring of the eye. Understanding the optimal dose-response relationship is essential for maximising therapeutic benefit whilst minimising side effects, adverse reactions, and safety concerns—particularly on tasks that are principally visually-dependent, such as driving. This novel insight warrants a re-evaluation of the standard

practice in pharmacokinetic studies of stimulants, which often assess performance only after peak plasma concentrations have been reached.

4.1 | Limitations

Firstly, while select cognitive enhancements were observed, these findings could be further elucidated with larger sample sizes or by exploring a broader spectrum of cognitive tasks. Second, our sample predominantly consisted of highly educated healthy young adults (92% with at least tertiary education), which may influence baseline cognitive scores and the magnitude of observed effects. This demographic homogeneity limits the generalisability of our findings to other populations, including those with different cognitive baselines or individuals experiencing cognitive decline. Additionally, while our study comprehensively assessed visual and attentional metrics relevant to safety-sensitive tasks, it did not encompass all cognitive domains potentially impacted by methylphenidate. Future research would benefit from including assessments of additional domains such as long-term memory, creative thinking, and emotional processing, which could offer further insights into the cognitive effects of methylphenidate.

4.2 | Conclusions

The present study affirms the somewhat limited efficacy of methylphenidate in enhancing certain cognitive functions in healthy adults, specifically in areas requiring working memory capabilities. Although some individuals may experience improvements in select cognitive functions, our study confirms that methylphenidate does not universally enhance cognitive performance. This limited efficacy highlights the need for additional exploration of the cognitive effects of methylphenidate across a broader spectrum of dosages and in varied populations, including those with different baseline cognitive abilities. As the non-medical use of methylphenidate continues to rise, particularly among college students seeking academic advantages (Sharif et al. 2021), understanding the drug's cognitive impacts will be crucial in informing public health policies and educational strategies aimed at mitigating misuse and ensuring safe usage.

Author Contributions

Conceptualization: A.C.H., L.A.D. Data acquisition: A.C.H., T.R.A., B. M., S.R. Statistical analysis: A.C.H., B.A., T.R.A., B.M. Drafting of the manuscript: B.A., T.R.A., B.M., S.R., B.M., L.A.D., A.C.H. Reviewing and editing: B.A., T.R.A., B.M., S.R., B.M., L.A.D., A.C.H. All authors reviewed the manuscript, revised it critically for important intellectual content, have read and approved the final submitted manuscript, and agree to be accountable for the work contained within.

Acknowledgements

Open access publishing facilitated by Swinburne University of Technology, as part of the Wiley - Swinburne University of Technology agreement via the Council of Australian University Librarians.

Conflicts of Interest

ACH is supported by a Rebecca L Cooper Al and Val Rosenstrauss Fellowship (GNT: F2021894) and held an NHMRC Early Career Fellowship (GNT: 1119960). L.A.D. received a R.D Wright Career Development Fellowship with no conflicts of interest. B.A., S.R., B.M., T.R.A. and B.S. declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

References

Allman, A. A., U. Ettinger, R. Joober, and G. A. O'Driscoll. 2012. "Effects of Methylphenidate on Basic and Higher-Order Oculomotor Functions." *Journal of Psychopharmacology* 26, no. 11: 1471–1479. https://doi.org/10.1177/0269881112446531.

Batistela, S., O. F. A. Bueno, L. J. Vaz, and J. C. F. Galduróz. 2016. "Methylphenidate as a Cognitive Enhancer in Healthy Young People." *Dementia & Neuropsychologia* 10, no. 02: 134–142. https://doi.org/10.1590/s1980-5764-2016dn1002009.

Beck, A. T., R. A. Steer, and G. Brown. 1996. "Beck Depression Inventory–II." *Psychological Assessment*.

Benson, K., K. Flory, K. L. Humphreys, and S. S. Lee. 2015. "Misuse of Stimulant Medication Among College Students: A Comprehensive Review and Meta-Analysis." *Clinical Child and Family Psychology Review* 18, no. 1: 50–76. https://doi.org/10.1007/s10567-014-0177-z.

Biederman, J. 2005. "Attention-Deficit/Hyperactivity Disorder: A Selective Overview." *Biological Psychiatry* 57, no. 11: 1215–1220. https://doi.org/10.1016/j.biopsych.2004.10.020.

Bush, G., E. M. Valera, and L. J. Seidman. 2005. "Functional Neuroimaging of Attention-Deficit/Hyperactivity Disorder: A Review and Suggested Future Directions." *Biological Psychiatry* 57, no. 11: 1273–1284. https://doi.org/10.1016/j.biopsych.2005.01.034.

Chan, A. Y., T.-T. Ma, W. C. Lau, et al. 2023. "Attention-Deficit/Hyperactivity Disorder Medication Consumption in 64 Countries and Regions From 2015 to 2019: A Longitudinal Study." *EClinicalMedicine* 58: 101780. https://doi.org/10.1016/j.eclinm.2022.101780.

Cools, R., and M. D'Esposito. 2011. "Inverted-U–shaped Dopamine Actions on Human Working Memory and Cognitive Control." *Biological Psychiatry* 69, no. 12: e113–e125. https://doi.org/10.1016/j.biopsych.2011.03.028.

Dolder, P. C., P. Strajhar, P. Vizeli, A. Odermatt, and M. E. Liechti. 2018. "Acute Effects of Lisdexamfetamine and D-Amphetamine on Social Cognition and Cognitive Performance in a Placebo-Controlled Study in Healthy Subjects." *Psychopharmacology* 235, no. 5: 1389–1402. https://doi.org/10.1007/s00213-018-4849-0.

Ellis, S. R., and L. Stark. 1986. "Statistical Dependency in Visual Scanning." *Human factors* 28, no. 4: 421–438. https://doi.org/10.1177/001872088602800405.

Faraone, S. V., T. Spencer, M. Aleardi, C. Pagano, and J. Biederman. 2004. "Meta-Analysis of the Efficacy of Methylphenidate for Treating Adult Attention-Deficit/Hyperactivity Disorder." *Journal of Clinical Psychopharmacology* 24, no. 1: 24–29. https://doi.org/10.1097/01.jcp.0000108984.11879.95.

Hayley, A. C., B. Shiferaw, B. Aitken, J. Rositano, and L. A. Downey. 2024. "Acute Methamphetamine and Alcohol Usage Alters Gaze Behaviour During Driving: A Randomised, Double-Blind, Placebo-Controlled Study." *Journal of Psychopharmacology* 38, no. 7: 636–646. https://doi.org/10.1177/02698811241261024.

Hayley, A. C., B. Shiferaw, and L. A. Downey 2021. "Amphetamine-induced Alteration to Gaze Parameters: A Novel Conceptual Pathway and Implications for Naturalistic Behavior." *Progress in Neurobiology* 199: 101929. https://doi.org/10.1016/j.pneurobio.2020.101929

Hayley, A. C., B. Shiferaw, J. Rositano, and L. A. Downey. 2023. "Acute Neurocognitive and Subjective Effects of Oral Methamphetamine With Low Doses of Alcohol: A Randomised Controlled Trial." *Journal of Psychopharmacology* 37, no. 9: 928–936. https://doi.org/10.1177/02698811231179805.

Kapur, A. 2020. "Is Methylphenidate Beneficial and Safe in Pharmacological Cognitive Enhancement?" *CNS Drugs* 34, no. 10: 1045–1062. https://doi.org/10.1007/s40263-020-00758-w.

Kasparbauer, A.-M., I. Meyhöfer, M. Steffens, et al. 2016. "Neural Effects of Methylphenidate and Nicotine During Smooth Pursuit Eye Movements." *NeuroImage* 141: 52–59. https://doi.org/10.1016/j.neuroimage.2016.07.012.

Kimko, H. C., J. T. Cross, and D. R. Abernethy. 1999. "Pharmacokinetics and Clinical Effectiveness of Methylphenidate." *Clinical Pharmacokinetics* 37, no. 6: 457–470. https://doi.org/10.2165/00003088-199937060-00002.

Klinge, C., C. Shuttleworth, P. Muglia, A. C. Nobre, C. J. Harmer, and S. E. Murphy. 2018. "Methylphenidate Enhances Implicit Learning in Healthy Adults." *Journal of Psychopharmacology* 32, no. 1: 70–80. https://doi.org/10.1177/0269881117731472.

Koelega, H. S. 1993. "Stimulant Drugs and Vigilance Performance: A Review." *Psychopharmacology* 111: 1–16. https://doi.org/10.1007/bf02257400.

Krejtz, K., T. Szmidt, A. T. Duchowski, and I. Krejtz. 2014. "Entropy-based Statistical Analysis of Eye Movement Transitions." In *Proceedings of the Symposium on Eye Tracking Research and Applications*. New York, NY: Association for Computing Machinery.

Linssen, A. M., A. Sambeth, E. F. Vuurman, and W. Riedel. 2014. "Cognitive Effects of Methylphenidate in Healthy Volunteers: A Review of Single Dose Studies." *International Journal of Neuropsychopharmacology* 17, no. 6: 961–977. https://doi.org/10.1017/s1461145713001594.

Maher, B. 2008. "Poll Results: Look Who's Doping: In January, Nature Launched an Informal Survey Into Readers' Use of Cognition-Enhancing Drugs. Brendan Maher Has Waded Through the Results and Found Large-Scale Use and a Mix of Attitudes Towards the Drugs." *Nature* 452, no. 7188: 674–676.

Narayan, A. J., B. Aitken, L. A. Downey, and A. C. Hayley. 2021. "The Effects of Amphetamines Alone and in Combination With Alcohol on Functional Neurocognition: A Systematic Review." *Neuroscience & Biobehavioral Reviews* 131: 865–881. https://doi.org/10.1016/j.neubiorev.2021.10.003.

Naylor, H., R. Halliday, and E. Callaway. 1985. "The Effect of Methylphenidate on Information Processing." *Psychopharmacology* 86, no. 1-2: 90–95. https://doi.org/10.1007/bf00431690.

Partridge, B. J., S. K. Bell, J. C. Lucke, S. Yeates, and W. D. Hall. 2011. "Smart Drugs 'As Common as Coffee': Media Hype About Neuroenhancement." *PLoS One* 6, no. 11: e28416. https://doi.org/10.1371/journal.pone.0028416.

Roberts, C. A., A. Jones, H. Sumnall, S. H. Gage, and C. Montgomery. 2020. "How Effective Are Pharmaceuticals for Cognitive Enhancement in Healthy Adults? A Series of Meta-Analyses of Cognitive Performance During Acute Administration of Modafinil, Methylphenidate and D-Amphetamine." *European Neuropsychopharmacology* 38: 40–62. https://doi.org/10.1016/j.euroneuro.2020.07.002.

Salari, N., H. Ghasemi, N. Abdoli, et al. 2023. "The Global Prevalence of ADHD in Children and Adolescents: A Systematic Review and Meta-Analysis." *Italian journal of pediatrics* 49, no. 1: 48. https://doi.org/10.1186/s13052-023-01456-1.

Sharif, S., A. Guirguis, S. Fergus, and F. Schifano. 2021. "The Use and Impact of Cognitive Enhancers Among University Students: A Systematic Review." *Brain Sciences* 11, no. 3: 355. https://doi.org/10.3390/brainsci11030355.

Shellenberg, T. P., W. W. Stoops, J. A. Lile, and C. R. Rush. 2020. "An Update on the Clinical Pharmacology of Methylphenidate: Therapeutic Efficacy, Abuse Potential and Future Considerations." *Expert Review of Clinical Pharmacology* 13, no. 8: 825–833. https://doi.org/10.1080/17512433.2020.1796636.

Shiferaw, B., D. Crewther, and L. A. Downey. 2019. "Gaze Entropy Measures Reveal Alcohol-Induced Visual Scanning Impairment During Ascending and Descending Phases of Intoxication." *Journal of Studies on Alcohol and Drugs* 80, no. 2: 236–244. https://doi.org/10.15288/jsad.2019.80.236.

Shiferaw, B. A., L. A. Downey, J. Westlake, et al. 2018. "Stationary Gaze Entropy Predicts Lane Departure Events in Sleep-Deprived Drivers." *Scientific Reports* 8, no. 1: 2220. https://doi.org/10.1038/s41598-018-20588-7.

Song, P., M. Zha, Q. Yang, Y. Zhang, X. Li, and I. Rudan. 2021. "The Prevalence of Adult Attention-Deficit Hyperactivity Disorder: A Global Systematic Review and Meta-Analysis." *Journal of global health* 11: 04009. https://doi.org/10.7189/jogh.11.04009.

Spencer, R. C., D. M. Devilbiss, and C. W. Berridge. 2015. "The Cognition-Enhancing Effects of Psychostimulants Involve Direct Action in the Prefrontal Cortex." *Biological Psychiatry* 77, no. 11: 940–950. https://doi.org/10.1016/j.biopsych.2014.09.013.

Strohl, M. P. 2011. "Bradley's Benzedrine Studies on Children With Behavioral Disorders." *Yale Journal of Biology & Medicine* 84, no. 1: 27.

Swanson, J., and N. Volkow. 2003. "Serum and Brain Concentrations of Methylphenidate: Implications for Use and Abuse." *Neuroscience & Biobehavioral Reviews* 27, no. 7: 615–621. https://doi.org/10.1016/j.neubiorev.2003.08.013.

Urbaniak, G. C., and S. Plous. 2013. Research Randomizer (Version 4.0) [Computer Software].". http://www.randomizer.org/.

Walter, K., and P. Bex. 2021. "Cognitive Load Influences Oculomotor Behavior in Natural Scenes." *Scientific Reports* 11, no. 1: 12405. https://doi.org/10.1038/s41598-021-91845-5.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.