Examensarbete

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Methylphenidate as a Cognitive Enhancement for Working Memory: A Systematic Review

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Abstract

The term cognitive enhancers are substances that increase cognitive performance. The stimulant methylphenidate is commonly used as a medication for attention deficit hyperactive disorder and is highly popular as a cognitive enhancer. One of its theorized mechanisms of action is to enhance working memory. This systematic review aims to examine literature that tests the effect of methylphenidate on cognitive performance, specifically working memory, in healthy subjects. Following the PRISMA guidelines, a systematic search was conducted on Web of Science, Scopus, and Medline Ebsco on 1st March 2022. Articles were selected based on the predetermined eligibility criteria. Of the ten selected articles, three found a significant effect of methylphenidate on working memory, and one found a significant effect on spatial working memory. *The studies produced varied results due to differential use of working memory tasks and methylphenidate dosage. Further studies on how methylphenidate affects working memory are needed.*

Keywords: methylphenidate, working memory, spatial working memory, cognitive performance.

Methylphenidate as a Cognitive Enhancer for Working Memory: A Systematic Review

A cognitive enhancer is a substance that increases the cognitive ability of individuals using it, whether the user is cognitively impaired or not. Cognitive enhancers can be divided into two groups; activities and stimulants that improve cognitive abilities. Eating healthy and exercising positively affect cognitive abilities, such as improving memory (Meeusen, 2014). Stimulant refers to drugs affecting the central nervous system used for medical purposes, recreational purposes (for pleasure or enjoyment), and performance enhancement (Advokat & Scheithauer, 2013). These stimulants can be divided into non-prescription stimulants and prescription stimulants. Most people use non-prescription cognitive enhancers daily. For example, the most popular non-prescription cognitive enhancers include caffeine, vitamin B6, vitamin B12, and guarana, while the most popular prescription cognitive enhancers include amphetamine, modafinil, piracetam, and methylphenidate (Sharif et al., 2021). The stimulant medication methylphenidate (tradename ritalin) is mainly prescribed to treat attention-deficit/hyperactivity disorder (AD/HD) (Challman & Lipsky, 2000). Additionally, methylphenidate can also treat patients with traumatic brain injury and stroke (Challman & Lipsky, 2000). This thesis will focus on methylphenidate.

Methylphenidate works by increasing catecholamine concentration in the brain (Gazzaniga et al., 2014). Catecholamine is a category of neurotransmitters, including dopamine, norepinephrine, and epinephrine (Gazzaniga et al., 2014). The increase in catecholamine concentration is caused by blocking their reuptake between synapses. Methylphenidate has improved typical performance in executive functions (Farah, 2005). These executive functions include working memory (Mehta et al., 2000), spatial working memory, and planning (Elliott et al., 1997).

Working memory was previously used to describe short-term memory, a temporary storage of limited material over a short period of time (Baddeley, 2010). The term ‘working memory’ was initially coined in 1960 in the book *Plans and the Structure of Behaviour* by Miller, Galanter, and Pribram. Later, the model for working memory was introduced in 1974 by Baddeley and Hitch. They termed it *The multicomponent model*, which describes working memory as a system in the brain that involves functions such as temporary storage and management of information needed to perform complex cognitive tasks (Baddeley, 2010). Working memory plays a role in many everyday cognitive tasks, from reading and studying, to comparing and contrasting. For the brain to process working memory, Baddeley suggests that working memory involves three components (Manktelow et al., 2017). These three components include one for manipulating information and two different storage systems. One of the storage systems, specific for language, is called the phonological loop, and the

second storage system is specialized for spatial information (Manktelow et al., 2017). Within the working memory system, a secondary system where spatial information is stored and remains readily available for some time is called spatial working memory (Asselen et al., 2006).

Brain areas involved during working memory tasks are the bilateral frontal areas, bilateral parietal areas, and parts of the superior temporal lobe (Manktelow et al., 2017). Depending on what type of working memory task is being performed, different networks in the brain are active. For example, the Broca's area and inferior supramarginal gyrus are active during verbal working memory tasks. During visual or spatial working memory tasks, the superior occipital gyrus, right calcarine, and bilateral fusiform gyrus are active (Manktelow et al., 2017). Pharmacologically improved working memory is associated with reductions in regional cerebral blood flow in the dorsolateral prefrontal cortex and posterior parietal cortex related to tasks performed (Mehta et al., 2000). Furthermore, spatial working memory is connected to the right posterior parietal and right dorsolateral prefrontal cortex (Asselen et al., 2006), and verbal working memory is connected to activation in the left ventrolateral prefrontal cortex (Gazzaniga et al., 2014).

Stimulants for cognitive enhancement are increasingly being used among healthy people to enhance performance related to either work or school situations (Smith & Farah, 2011). Methylphenidate is increasingly being sold, with higher sales each year in the US (Farah, 2005). Furthermore, surveys from 2005 estimate that 20% of college students have used stimulants illegally (Farah, 2005), and methylphenidate is one of the most popular stimulants (Sharif et al., 2021). The high use of stimulants among healthy people gives rise to ethical issues. These issues involve, for example, whether or not to use cognitive enhancers to improve their cognitive ability (Farah et al., 2004). Additionally, it causes the question of whether or not to give stimulants to their children to get ahead in education. There is also the issue concerning safety since there is potential for long-term or rare side effects (Farah et al., 2004). Given the previous research on its effect on performance, specifically working memory (Mehta et al., 2000), knowing to what extent it causes improvement is relevant to the ethical debate surrounding brain enhancement. Since there is a lack of data, long-term studies, and the long-term side effects of methylphenidate in daily use (Krinzinger et al., 2019), any gathered data is valuable. For methylphenidate to be used as a cognitive enhancer for healthy living participants, a careful risk versus reward analysis is needed to minimize the risk of adverse effects.

The purpose of this systematic review is to summarize the literature on methylphenidate's role as a cognitive enhancer for working memory. It aims to collect and analyze available evidence of the effect of methylphenidate in healthy individuals, which

brain regions and pathways are affected, and if it has shown positive effects in healthy individuals, then discuss its ethical implications.

Methods

The methods were formatted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

Search Strategy

For the systematic review, a systematic search using the PRISMA 2009 flow diagram (Fig. 1) was conducted on Web of Science, Scopus, and Medline Ebsco the 1th March 2022. The search terms used were: (Methylphenidate AND "working memory" AND placebo AND healthy).

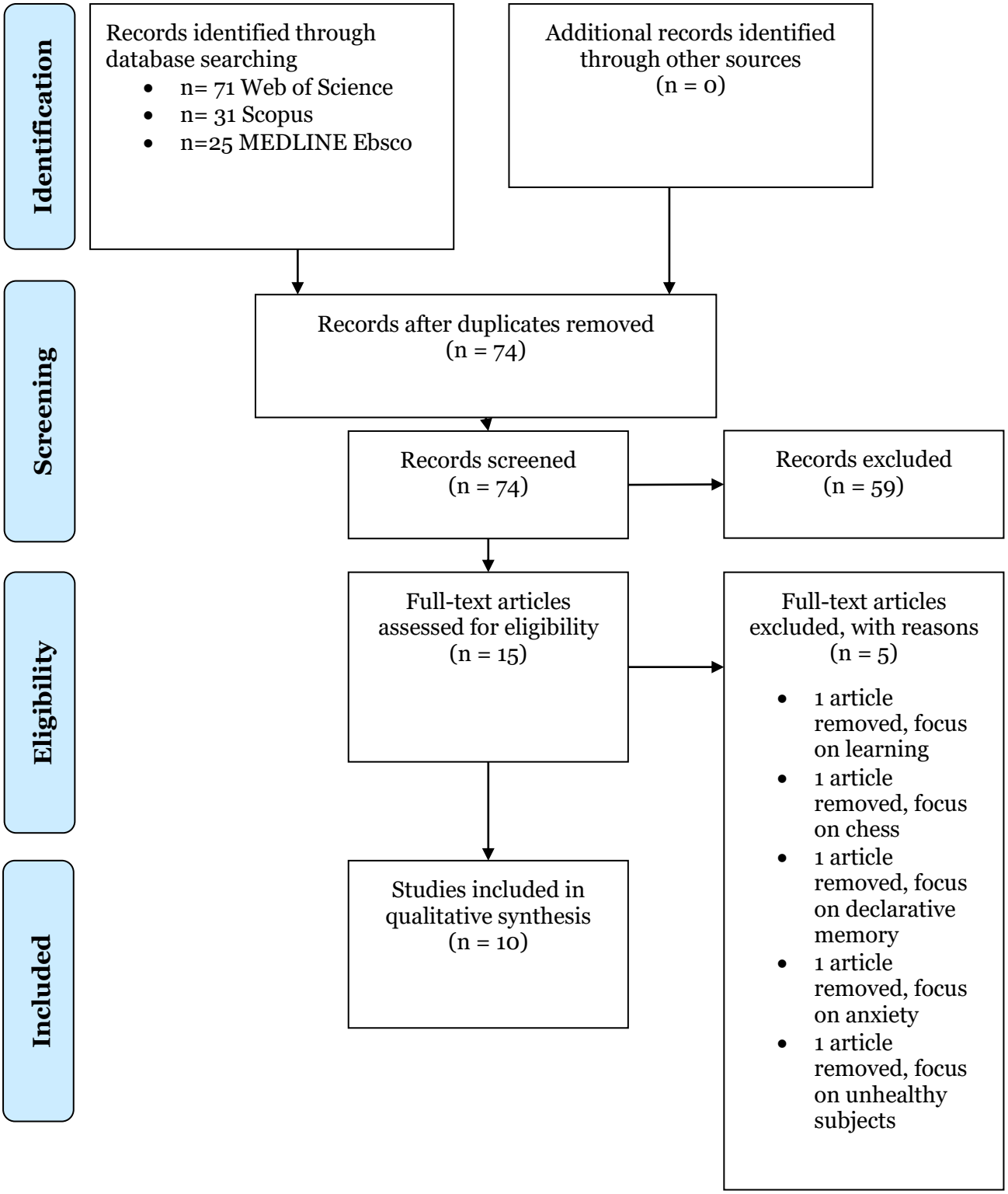
Inclusion and Exclusion Criteria

Following the PICO model, inclusion criteria were: 1) population-based on healthy adults; 2) exposure to methylphenidate and placebo; 3) comparing the stimulant to placebo; 4) outcome being how the stimulant affects working memory in different ways in healthy participants; 5) published between years 1990-2022. Studies were excluded if they: 1) were not written in English; 2) focused on participants with diagnoses or addictions; 3) were not original research studies published in peer-reviewed journals; 4) lacked DOI number; 5) did not have full-text availability; 6) did not pass the PICO model criteria. Duplicates were removed. Titles and abstracts were screened for the relevance of each publication and then saved full-text in folders.

Data Extraction

A data extraction form was used to include relevant data: (1) Author and year of publication, (2) Country region, (3) Sample size, (4) Sample characteristics, (5) Task, (6) Method, (7) Outcome measure.

Figure 1



Note: Standard flow diagram used to document the literature search process (Moher et al., 2009)

Results

Search Results

In total, 127 published articles were identified throughout three database searches (Figure 1). A total of 50 were removed for duplications. Of those remaining, 59 were excluded based on screening titles and abstracts. The remaining articles were assessed for eligibility in full-text, and five were excluded. One excluded for focusing on learning, one excluded for focusing on chess play, one excluded for focusing on declarative memory, one excluded for focusing on anxiety, and the last excluded for focusing on different participant criteria. Followed by the full-text screening, ten articles met the inclusion criteria.

Study Sample Characteristics

In the total of ten analyzed articles, the total numbers of participants were 286 (Table 1). Participants were predominantly male (male n=257, female n=29), with three studies having a mix of male and female participants (Ramasubbu et al., 2012; Studer et al., 2010; Van der Schaaf et al., 2013). In total, four studies reported that the participants were right-handed (n=99).

All studies reported that their subjects were healthy (i.e., absence of psychiatric or neurological diseases and substance abuse), as it was a criterion across all selected studies. However, one study focused specifically on elderly healthy participants to compare any age difference between previous studies on the same topic. The ten studies were conducted in six different countries, which include Australia (n=1), Brazil (n=1), Canada (n=1), Germany (n=2), The Netherlands (n=2), and The United Kingdom (n=3).

Tasks and Methods

Across the ten studies, one or multiple experimental tasks were conducted to test either working memory (Batistela et al., 2016; Cooper et al., 2005; Marquand et al., 2011; Ramasubbu et al., 2012; Repantis et al., 2021; Studer et al., 2010; Van der Schaaf et al., 2013) or spatial working memory (Elliott et al., 1997; Linssen et al., 2012) (WM=7, SWM=3). There was an exception of one study testing both WM and SWM (Turner et al., 2003). The variety of tests included *0-Back* test, where subjects had to press a button when a prespecified number appeared. Further, *2-Back* test where the subjects had to press a button when a presented number was identical to the number presented two steps earlier. *Object Relocation* test, a two-part test where subjects had to relocate visual stimuli to their original locations. In the first part, the subjects had to memorize the locations for a set time and afterward had to place the objects in the correct positions, cued with black dots. In the second part, the subjects had an increased time to memorize the locations. They then placed the objects in the

original position as accurately as possible without cues. *Digit Span Forward/Backward* test, where the subject has to repeat a sequence of numbers after being presented, either forward in the correct order or backward in reverse order. The *Digit Span Backward* test is sometimes named the *Reverse Digit Span* test. *Continuous Performance* test, where the subject is presented with a series of letters, and if the same letter appears twice in succession, the subject has to press a button. Lastly, in the *Delayed Match-To-Sample* test, the subject is presented with stimuli and has to identify the stimuli among different stimuli after a set time. Tasks from the battery CANTAB were used for SWM, where the subject has to find hidden tokens without returning to where one has been previously found. These tasks from CANTAB appeared in two studies and did not specify the task's name (Elliott et al., 1997; Turner et al., 2003). All studies used a substance vs. placebo design, with the substance being methylphenidate in different doses. Doses varied between studies, with 5mg methylphenidate being the lowest tested dose and 45mg the highest (Cooper et al., 2005). All studies used a double-blind design, with the majority including either a within-subject design or crossover design.

Table 1.

Basic information and summarized results.

Lead author and year	Country	Sample Size	Sample Characteristics	Memory Task	Method	Results
Batistela et al. 2016	Brazil	36	Male. Healthy subjects. Aged between 18 and 30	WM task (Digit Span Test, Forward/Backward)	10, 20 and 40mg oral dose of MP. Methylphenidate vs. placebo. Double-blind design	Forward - p-value 0.07. Backward - p-value 0.25
Cooper et al. 2005	Australia	32	Male. Healthy subjects. Mean age 22.26	WM task (Continuous Performance Test)	5, 15 or 45mg oral dose of MP. Double-blind, within-subject design	Dosage = Omission Errors $F=43.99$, $p<0.001$. Reaction Time $F=22.71$, $p<0.001$
Elliott et al. 1997	The United Kingdom	28	Male. Healthy subjects. Mean age 21,25	SWM task (CANTAB)	20mg or 40mg oral dose of MP. Methylphenidate vs. placebo. Double-blind, counterbalance design	CANTAB - Session order - $F(1,26)=4.4$, $p<0.05$ $F(1,45)=8.4$,$p<0.01$. Score - $F(1,45)=8.4$,$p<0.01$
Linssen et al. 2012	The Netherlands	19	Male. Right-handed. Healthy subjects. Mean age 23,4	SWM task (Object Relocation Test)	10, 20 or 40mg oral dose of MP. Methylphenidate vs. placebo. Double-blind crossover design	$p>0.05$
Marquand et al. 2011	The United Kingdom	15	Male. Healthy subjects. Aged between 20 and 39	WM task (Variant of Object Relocation Test)	30mg oral dose of MP. FMRI. Randomized, double-blind design	Accuracy during encoding, delay, retrieval. Rewarded - $p<0.05$ Accuracy during encoding. Non-rewarded - $p<0.05$
Ramasubbu et al. 2012	Canada	13	Right-handed. Healthy subjects. 5 Male, 8 Female. Mean age 28	WM task (0-back and 2-back task)	20mg oral dose of MP. fNIRS. Methylphenidate vs. placebo. Double-blind crossover design	0-back task - Reaction time ($t=2.55$, $df=12$, $p=0.025$) 2-back task - Correct responses ($t = 2.40$, $df = 12$, $p = 0.033$). Missed responses ($t =3.49$, $df = 12$, $p = 0.005$)
Repantis	Germany	48	Male. Right-	WM task (Reverse	20mg oral	Reverse digit

et al. 2021			handed. Healthy subjects. Mean age 26,27	Digit Span Test)	dose of MP. Methylphenidate vs. placebo. Randomized double-blind, within-subject design	span test - p-value 0.718
Studer et al. 2010	Germany	16	Healthy subjects. 5 Male, 6 Female. Mean age 29,7	WM task (Delayed Match-To-Sample Test)	20mg dose of MP. Methylphenidate vs. placebo. Double-blind, crossover design	WM load - F(2,18), p-value 0.24
Turner et al. 2003	The United Kingdom	60	Male. Healthy subjects. Mean age 61	WM task (Digit Span Test, Forwards/Backward). SWM task (CANTAB)	20 or 40mg oral dose of MP. Methylphenidate vs. placebo. Randomized double-blind, between-subjects design	Forward digit span - p-value 0.616. Backward digit span - p-value 0.481 CANTAB - p-value 0.658
Van der Schaaf et al. 2013	The Netherlands	19	Right-handed. Healthy subjects. 9 Male, 10 Female. Mean age 20,9	WM task (Digit Span Test, Forward/Backward)	20mg oral dose of MP. Methylphenidate vs. placebo. Double-blind, within-subject crossover design	Digit Span Test - p-value 0.3

Working Memory

Eight studies tested the performance and effect methylphenidate had on working memory, using a placebo as a control group. Throughout these eight, only three found a significant effect of methylphenidate on working memory (Cooper et al., 2005; Marquand et al., 2011; Ramasubbu et al., 2012). Cooper et al. (2005) hypothesized that there would be a dose-dependent relationship between methylphenidate and WM. They found that increasing the dosage decreased omission errors ($F=43.99$, $p<0.001$). Additionally, Cooper et al. (2005) found that there was a significant dosage effect on reaction time ($F=22.71$, $p<0.001$). However, there is no difference in commission errors between the dosages of methylphenidate. Marquand et al. (2011) conducted a study on combining event-related fMRI with whole-brain network communication to characterize the effects of methylphenidate during the WM task. They used a variant of *the Object Relocation* test with rewarded and non-rewarded trials. Their results showed improvements in accuracy for encoding, delay, and retrieval during the rewarded trials of the WM task ($p<0.05$). In contrast, during non-rewarded trials, there was only an improvement in accuracy during encoding ($p<0.05$). Ramasubbu et al. (2012) hypothesized that methylphenidate would improve working memory performance. Their results showed during the *2-Back* task, a significant improvement in correct responses ($t = 2.40$, $df = 12$, $p = 0.033$) and for missed responses ($t =3.49$, $df = 12$, $p = 0.005$) compared to placebo. During the *0-back* task, the reaction time was significantly less than the placebo ($t=2.55$, $df=12$, $p=0.025$).

Batistela et al. (2016) tested if methylphenidate would affect memory, including attention and executive functions. They used the *Digit Span Forward/Backward* test to test WM performance and found no significant effect on WM in either the forward version (p-value 0.07) or backward version (p-value 0.25). Repantis et al. (2021) tested the cognitive effect of methylphenidate and two other stimulants, comparing each with a placebo. They hypothesized that there would be different effects in different areas of cognition for each stimulus. Methylphenidate had no significant effect on working memory during a *Reverse Digit Span* test (p-value 0.718). Van der Schaaf et al. (2013) tested if there was a relationship between methylphenidate and reward and punishment learning. They tested the working memory capacity using the *Digit Span* test and compared it with placebo and methylphenidate. They found no significant effect from methylphenidate on the *Digit Span* itself (p-value 0.3). Studer et al. (2010) aimed to investigate the neuronal processing phases during encoding, retention, and retrieval of a WM task named the *Delayed Match-To-Sample* test. Additionally, they looked at the effect of methylphenidate on WM processes, and they did not find any significant effect between methylphenidate and WM load ($F (2,18)$, p-value 0.24). Turner et al. (2003) investigated if there was a relationship between aging,

dopaminergic neurotransmission, and cognitive functions depending on the dosage of methylphenidate among elderly healthy volunteers. They tested for WM and SWM and used the *Digit Span Forward* test. Backward tests found no significant effect of methylphenidate on WM compared to placebo (Forward digit span - p-value 0.616, Backward digit span - p-value 0.481).

Spatial Working Memory

Three studies tested the effect of methylphenidate on performance in SWM. Among the three studies, one found a significant effect of methylphenidate on performance (Elliott et al., 1997). The study aimed to test the effect of methylphenidate on cognitive performance, specifically SWM, along with a few others (Elliott et al., 1997). The subjects conduct the same test in two different sessions using the CANTAB battery to have appropriate tests for measuring performance. The sessions were divided into either subjected to methylphenidate first session and placebo the next or vice versa. There was a significant main effect in the session order ($F(1,26) = 4.4$, $p < 0.05$), with the session with methylphenidate first making fewer errors in the test ($F(1,45) = 8.4$, $p < 0.01$). The second study, Linssen et al. (2012) aimed to see if there was a possible enhancing effect of three different doses of methylphenidate on WM, specifically SWM, among other cognitive functions. Linssen et al. (2012) used the *Object Relocation* task to measure SWM performance, finding no significant results among all parameters ($p > 0.05$). In the third study, Turner et al. (2003) measured both WM and SWM in elderly subjects. Using a test from the CANTAB battery, there was no significant difference between any of the dosages of methylphenidate and placebo on the test score (p-value 0.658).

Involved Brain Areas

Tools used for information on brain activity during testing were minimal, with one study using functional near-infrared spectroscopy (fNIRS) (Ramasubbu et al., 2012), and one using functional magnetic resonance imaging (fMRI) (Marquand et al., 2011). Ramasubbu et al. (2012) hypothesized that the treatment of methylphenidate would decrease WM task depending on changes in oxy-Hb in the lateral prefrontal regions. Their fNIRS study found an oxy-Hb decrease from methylphenidate, significantly correlated with increased correct responses and decreased missed responses in the 2-back task (p-value 0.036) located in the right prefrontal cortex. In addition, Marquand et al. (2011) combined event-related fMRI with pattern recognition (PR) methods to characterize the effects of methylphenidate on reward vs. non-reward WM tasks. They expected to find a reduction in activity in the prefrontal cortex caused by methylphenidate. They found that methylphenidate affected the ability to encode information and correlated this significant effect with higher activation in

the cerebellum and lateral prefrontal cortex. At the same time, methylphenidate caused higher activation in WM networks during rewarding trials, while in non-rewarding trials, methylphenidate activated a similar brain pattern as if receiving a reward.

Discussion

Previous studies have found that methylphenidate significantly affects performance when conducting WM and SWM tasks (Elliott et al., 1997; Mehta et al., 2000). The stimulant can affect the capacity to store information available for use at a specific time and the reaction time in which the information is applicable (Ramasubbu et al., 2012). However, Studer et al. (2010) specifically focused on whether methylphenidate would affect the amount of time a subject could hold information stored, with no significant results. Studer et al. (2010) argue that this could be because their participants were highly motivated at the start. Compared to other studies, the difference in performance could be caused by a motivational effect of methylphenidate on cognitive performance. The argument is further backed by Linssen et al. (2012), who did not find a significant result on three different dosage levels on the SWM effect by methylphenidate. Linssen et al. (2012) state that since dopamine is involved in SWM specifically, it could cause difficulties encoding information due to overarousal. The argument for overarousal could explain why subjects perform better in trials involving reward than non-reward (Marquand et al., 2011). Most noteworthy is that when ruling out a reward factor, the only noticeable effect of methylphenidate on WM is the accuracy of encoding (Marquand et al., 2011), which can be interpreted as an increased effect of analyzing and storing stimuli. Batistela et al. (2016) argue that methylphenidate enhances cognitive performance by improving personal well-being, which might explain its popularity and increased use, as previously stated.

The differing results could be affected by sample size, and the significant study only had n=13 subjects (Ramasubbu et al., 2012). Their results are not in line with most of the findings in this review compared to similar studies that did not find a significant effect of methylphenidate in versions of the *Digit Span* task (Batistela et al., 2016; Repantis et al., 2021; Van der Schaaf et al., 2013). However, the difference could be task-related since every study utilizing the Digit Span task found no significant results.

Ramasubbu et al. (2012), using fNIRS, correlated the increase in performance with a decrease in oxy-Hb and neural activity in the right lateral prefrontal region. This is consistent with previous studies that associate improved working memory with regional cerebral blood flow reductions in the dorsolateral prefrontal cortex (Mehta et al., 2000). Additionally, Marquand et al. (2011) expected a reduction in prefrontal cortex activity. They gathered from their study using fMRI that they found that during the encoding in a non-rewarded context,

methylphenidate enhanced activity in the cerebellum and lateral prefrontal cortex when compared to placebo.

Ethical and Societal Aspects

Given the results gathered from this systematic review, data regarding its actual effectiveness is based on the previous statement that methylphenidate is a highly popular prescription stimulant (Sharif et al., 2021; Smith & Farah, 2011) is essential information. Since there could be high pressure for excellent cognitive performance at either work or in studies, the effectiveness of popular prescription stimulants is significant. If the stimulant positively affects healthy individuals, the questions arise about their societal and ethical implications. From an accessibility standpoint, the stimulant would need to be equally accessible by everyone and will face the problem of cost. Another issue is if it minimizes the value of working hard, where stimulants for improvement will be normalized instead of experience and dedication. Lastly, there is the possibility of hidden costs or long-term implications, which can be unpredictable (Farah et al., 2004).

Limitations

This systematic review faced certain limitations. There were not multiple studies that conducted highly similar methods, making it difficult to compare their results. Additionally, there was high variation in both used dosage levels and tasks for measuring working memory or spatial working memory. These differences in dosage are hard to rule out since only one study specifically focused on the significance of dosage dependence (Cooper et al., 2005). Furthermore, there was a lack of in-depth analysis tools (i.e., PET, fMRI) to give a more neurological view of the gathered results. Two studies used event-related potentials measured in their study, which was not relevant for the aim of this review (Cooper et al., 2005; Studer et al., 2010). All in all, this concludes that the results from this review are rather lackluster.

Conclusion

This systematic review aimed to collect and analyse available evidence of the effect of methylphenidate in healthy individuals and on brain areas, its positive effects, and discuss ethical implications.

The outcome was that most studies did not find a significant effect of methylphenidate on working memory and spatial working memory. This might be because of the stimulant effect on arousal, which could affect the performance when the tasks themselves involve any reward, as seen from fMRI. There was an effect from methylphenidate on the right prefrontal cortex, lateral prefrontal cortex, and cerebellum.

Based on gathered data, methylphenidate should not be used as a cognitive enhancer because of its lack of effectiveness for healthy individuals.

In other words, the information gathered from this systematic review suggests that further research on the topic needs to be done. The main focus of future research should be to use larger sample sizes and increasing the amount of analysis tools for gathering data on the neurological effect of methylphenidate.

References

Advokat, C. D., & Scheithauer, M. (2013). Attention-deficit hyperactivity disorder (ADHD) stimulant medications as cognitive enhancers. *Frontiers in Neuroscience*, *7*. https://doi.org/10.3389/fnins.2013.00082

Asselen, M., Kessels, R. P., Neggers, S. F., Kappelle, L. J., Frijns, C. J., & Postma, A. (2006). Brain areas involved in spatial working memory. *Neuropsychologia*, *44*(7), 1185-1194. https://doi.org/10.1016/j.neuropsychologia.2005.10.005

Baddeley, A. (2010). Working memory. *Current Biology*, *20*(4), 136-140. https://doi.org/10.1016/j.cub.2009.12.014

Batistela, S., Bueno, O. F. A., Vaz, L. J., & Galduróz, J. C. F. (2016). Methylphenidate as acognitive enhancer in healthy young people. *Dementia & Neuropsychologia*, *10*(2), 134-142. https://doi.org/10.1590/S1980-5764-2016DN1002009

Challman, T. D., & Lipsky, J. J. (2000). Methylphenidate: Its pharmacology and uses. *Mayo Clinic Proceedings, 75*(7), 711-721. https://doi.org/10.4065/75.7.7.711

Cooper, N. J., Keage, H., Hermens, D., Williams, L. M., Debrota, D., Richard Clark, C., & Gordon, E. (2005). The dose-dependent effect of methylphenidate on performance, cognition and psychophysiology. *Journal of integrative neuroscience*, *4*(01), 123-144. https://doi.org/10.1142/S0219635205000744

Elliott, R., Sahakian, B. J., Matthews, K., Bannerjea, A., Rimmer, J., & Robbins, T. W. (1997). Effects of methylphenidate on spatial working memory and planning in healthy young adults. *Psychopharmacology*, *131*(2), 196-206. https://doi.org/10.1007/s002130050284

Farah, M. J. (2005). Neuroethics: the practical and the philosophical. *Trends in Cognitive Sciences*, *9*(1), 34-40. https://doi.org/10.1016/j.tics.2004.12.001

Farah, M. J., Illes, J., Cook-Deegan, R., Gardner, H., Kandel, E., King, P., Parens, E., Sahakian, B., & Wolpe, P. R. (2004). Neurocognitive enhancement: what can we do

and what should we do? *Nature Reviews Neuroscience*, *5*(5), 421-425. https://doi.org/10.1038/nrn1390

Gazzaniga, M. S., Ivry, R. B., & Mangun, G. R. (2014). *Cognitive Neuroscience: The biology of the mind* (4th ed.). New York: Norton.

Krinzinger, H., Hall, C. L., Groom, M. J., Ansari, M. T., Banaschewski, T., Buitelaar, J. K., Carucci, S., Coghill, D., Danckaerts, M., Dittman, R. W., Falissard, B., Garas, P.,Inglis, S. K., Kovshoff, H., Kochhar, P., McCarthy, S., Nagy, P., Neubert, A., Roberts, S., … Liddle, E. B. (2019). Neurological and psychiatric adverse effects of long-term methylphenidate treatment in ADHD: A map of the current evidence. *Neuroscience & Biobehavioral Reviews*, *107*, 945-968. https://doi.org/10.1016/j.neubiorev.2019.09.023

Linssen, A. M. W., Vuurman, E. F. P. M., Sambeth, A., & Riedel, W. J. (2012). Methylphenidate produces selective enhancement of declarative memory consolidation in healthy volunteers. *Psychopharmacology*, *221*(4), 611-619. https://doi.org/10.1007/s00213-011-2605-9

Manktelow, A. E., Menon, D. K., Sahakian, B. J., & Stamatakis, E. A. (2017). Working memory after traumatic brain injury: the neural basis of improved performance with methylphenidate. *Frontiers in Behavioral Neuroscience*, *11*(58) https://doi.org/10.3389/fnbeh.2017.00058

Marquand, A. F., De Simoni, S., O'daly, O. G., Williams, S. C., Mourao-Miranda, J., & Mehta, M. A. (2011). Pattern classification of working memory networks reveals differential effects of methylphenidate, atomoxetine, and placebo in healthy volunteers. *Neuropsychopharmacology*, *36*(6), 1237-1247. https://doi.org/10.1038/npp.2011.9

Meeusen, R. (2014). Exercise, nutrition and the brain. *Sports Medicine*, *44*(1), 47-56. https://doi.org/10.1007/s40279-014-0150-5

Mehta, M. A., Owen, A. M., Sahakian, B. J., Mavaddat, N., Pickard, J. D., & Robbins, T. W. (2000). Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. *Journal of Neuroscience*, *20*(6), RC65-RC65. https://doi.org/10.1523/JNEUROSCI.20-06-j0004.2000

Moher, D., Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PloS Med *6*(7): e1000097. https://doi.org/10.1371/journal.pmed.1000097

Ramasubbu, R., Singh, H., Zhu, H., & Dunn, J. F. (2012). Methylphenidate-mediated reduction in prefrontal hemodynamic responses to working memory task: A functional near-infrared spectroscopy study. *Human Psychopharmacology: Clinical and Experimental*, *27*(6), 615-621. https://doi.org/10.1002/hup.2258

Repantis, D., Bovy, L., Ohla, K., Kühn, S., & Dresler, M. (2021). Cognitive enhancement effects of stimulants: a randomized controlled trial testing methylphenidate, modafinil, and caffeine. *Psychopharmacology*, *238*(2), 441-451. https://doi.org/10.1007/s00213-020-05691-w

Sharif, S., Guirguis, A., Fergus, S., & Schifano, F. (2021). The use and impact of cognitive enhancers among university students: a systematic review. *Brain Sciences*, *11*(3), 355. https://doi.org/10.3390/brainsci11030355

Smith, M. E., & Farah, M. J. (2011). Are prescription stimulants "smart pills"? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals. *Psychological Bulletin, 137*(5), 717–741. https://doi.org/10.1037/a0023825

Studer, P., Wangler, S., Diruf, M. S., Kratz, O., Moll, G. H., & Heinrich, H. (2010). ERP effects of methylphenidate and working memory load in healthy adults during a serial visual working memory task. *Neuroscience letters*, *482*(2), 172-176. https://doi.org/10.1016/j.neulet.2010.07.030

Turner, D. C., Robbins, T. W., Clark, L., Aron, A. R., Dowson, J., & Sahakian, B. J. (2003). Relative lack of cognitive effects of methylphenidate in elderly male volunteers. *Psychopharmacology*, *168*(4), 455-464. https://doi.org/10.1007/s00213-003-1457-3

Van der Schaaf, M. E., Fallon, S. J., Ter Huurne, N., Buitelaar, J., & Cools, R. (2013). Working memory capacity predicts effects of methylphenidate on reversal learning. *Neuropsychopharmacology*, *38*(10), 2011-2018. https://doi.org/10.1038/npp.2013.100