



## **Can Changes in Dopamine Levels in the Brain**

### **Be Used to Influence Concentration? A**

### **Systematic Review**

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## **Abstract**

This systematic review explores the role of dopamine in the prefrontal cortex and its impact on concentration abilities in individuals with attention deficit/hyperactivity disorder (ADHD). It looks at attempts to manipulate dopamine levels through pharmacological interventions and assess their efficacy in enhancing cognitive functions. Only articles on the drug methylphenidate (MPH) were found. Using functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and magnetic resonance spectroscopy (MRS), the review examines the neurobiological basis of pharmacological effects. The findings underscore the critical function of dopamine in regulating attention and other executive functions and reinforce the dopamine deficit hypothesis of ADHD. This research highlights the role of the prefrontal cortex and striatum in the manifestation and treatment of ADHD. The results suggest that future research should focus on personalized medication strategies that employ neuroimaging markers. The results call for a broader application of multimodal therapy, integrating pharmacological treatments with behavioral interventions to manage ADHD symptoms and improve cognitive function.

*Keywords:* dopamine, ADHD, prefrontal cortex, concentration

# Can Changes in Dopamine Levels in the Brain Be Used to Influence Concentration? A Systematic Review

## Introduction

The influence of dopamine levels in the prefrontal cortex (PFC) on attentional processes is a critical area of study, especially in the context of conditions like ADHD, which are characterized by altered dopamine dynamics (Kollins & Adcock, 2014). This thesis systematically reviews how variations in dopamine levels influence concentration and cognitive control by examining human subjects with ADHD along with non-human animal models where dopamine levels can be measured directly. Such research bridges the gap between neurochemical changes and behavioral outcomes. By exploring the neural pathways between the PFC and striatum, this review aims to delineate the role of dopamine in attention regulation with broader neurological implications. The objective is to better inform the development of targeted therapeutic strategies for ADHD and potentially other neuropsychiatric disorders.

## Attention deficit / hyperactivity disorder (ADHD)

The *Diagnostic and statistical manual of mental disorders, fifth edition* (DSM-V-TR; APA, 2022) defines ADHD as a pattern of inattention (difficulty sustaining focus, following through on instructions, and organizing tasks) or hyperactivity/impulsivity. Hyperactivity refers to excessive motor activity when not appropriate or excessive fidgeting (e.g., tapping) or talkativeness. Impulsivity involves hasty actions that occur in the moment without forethought and have high potential for harm to the individual. ADHD interferes with development of socialization: patients may struggle to pay attention during conversations, act impulsively in social settings, or find it hard to wait their turn. These behaviors can lead to misunderstandings,

conflicts, and difficulty forming or maintaining relationships. ADHD is frequently classed as a neurodevelopmental disorder that impacts social and academic/occupational activities. It is categorized into three types by the DSM-V-TR (APA, 2022, p.42): predominantly inattentive, predominantly hyperactive/impulsive, and combined.

### **Dopamine**

Dopamine is a neurotransmitter: a chemical messenger that transmits signals in the brain and other areas of the body. It plays a crucial role in regulating movement, emotion, cognition, motivation, and feelings of pleasure. Dopamine pathways are particularly important in the brain's reward system, influencing how reinforcement, motivation, and substance addiction develop. Its levels are essential for physical and mental health, with altered levels implicated in such neurological and psychiatric disorders as Parkinson's disease, schizophrenia, and depression. The interest here is in connection to ADHD.

### **Prefrontal cortex (PFC)**

The PFC is the forward portions of the frontal lobes. It is involved in such complex behaviors as planning, decision-making, problem-solving, self-control, and social behavior. The PFC integrates information from various brain regions to guide behavior with respect to consequences. It is crucial for attention, working memory, and regulation of emotions and impulses. Dysfunction in the prefrontal cortex has been linked to psychiatric disorders, including ADHD, schizophrenia, and depression.

### **The relationship between ADHD, PFC and dopamine**

Over the years, studies (e.g., Ohno, 2003) have shown that the mesocorticolimbic dopamine system is important in the development of ADHD. (The mesocorticolimbic dopamine system includes the midbrain dopamine centers such as the ventral tegmental area, limbic system including nucleus accumbent, and PFC). Ohno writes (p. 1) that results have been inconsistent and that a wide range of conclusions, some in direct opposition to one another, have been produced on the basis of comparable findings.

It is still not clear whether ADHD is characterized by hypo- or hyperdopaminergic function in the brain. While traditionally dopamine is thought to enhance basal ganglia function, excessive dopaminergic signaling could lead to hypofunctionality of this area (Bullock, 2016). This might be attributed to feedback inhibition or receptor desensitization, where overstimulation by dopamine leads to reduced responsiveness of the basal ganglia (Schöneberg, 2008). Sagyolden et al's (2005) hypodopaminergic theory is supported by experiments conducted with non-human animals deficient in dopamine (see, e.g., Leo et al., 2013).

On the other hand, research conducted with dopamine transporter knockout in mice (Leo et al., 2013) implies that hyperdopaminergic function is the underlying abnormality. The truth is probably somewhere in the middle. In their study, Wu et al. (2012) provide an in-depth look at how dopamine receptors D1–D5 and their dysfunction are implicated in ADHD. Their meta-analysis lends further evidence to the variability in dopamine receptor activity among ADHD patients. These two studies together demonstrate that there are the multiple dopamine levels associated with ADHD, contributing to the complex picture of how dopamine influences attention and concentration in this disorder.

## **Essential role of non-human subjects**

The use of non-human subjects, particularly mice and rats, is indispensable in the study of dopamine pathways due to the inherent challenges associated with directly measuring neurotransmitter levels in human patients. Direct measurement of dopamine levels in humans is not only technically challenging but also limited by ethical considerations, which restrict the use of invasive methods.

Mice are widely used in neuroscience research due to their genetic, biological, and behavior similarities to humans, including brain structure and function. This makes them valuable models for studying neurological diseases, brain development, and neuropharmacology. Their shorter lifespans and rapid reproduction allow for quick and efficient study of genetic and environmental influences on the brain (see., e.g., Justice et al., 2016). Rats are larger, allowing for easier surgeries and the use of electronic implants for complex neuroscience studies. Their size means they can be a better choice for repeated sample collection and imaging (Ellenbroek et al., 2016). Rats have a more social nature compared to mice, which affects housing and experimental dynamics. Their genetic diversity offers a closer representation of human conditions in certain studies (p4). However, rats typically require more space and may be more costly to maintain. Although the systematic review looks only at human patients with ADHD, I will make reference to a number of studies involving rats in this introduction, the better to provide background for the discussion to follow.

## **Atomoxetine**

Atomoxetine, used for ADHD treatment in children, adolescents, and adults, is a selective norepinephrine reuptake inhibitor (SNRI). The PFC has many norepinephrine transporters (NETs) but few dopamine transporters, leading to dopamine uptake by NETs. Atomoxetine's blockade of NETs increases dopamine levels in the PFC and norepinephrine levels in the entire brain (Clemow & Bushe 2015; Vanicek et al. 2014). This selective increase in dopamine levels does not appear to have a general effect on dopamine levels elsewhere in the brain.

Bymaster et al. (2002) show that atomoxetine raises dopamine levels in rats' PFC only. Atomoxetine effects on rats' PFC provides a biological basis for its effectiveness in treating ADHD in humans by managing symptoms related to dopamine dysregulation.

It would be careless not to mention the effects of atomoxetine on neurotransmitters other than dopamine. Atomoxetine does not allow DASB, a serotonin transporter ligand, to bind, suggesting an interaction with serotonin systems. Ding et al. (2014) examined how atomoxetine blocks norepinephrine and serotonin receptors. Their PET data shows that the time under which serotonin and norepinephrine transporters are blocked varies with dosage, with greater impact on norepinephrine transporters. It is not clear if atomoxetine's therapeutic benefits are derived from its effects on norepinephrine alone, or a combination of norepinephrine and serotonin transporters. The bottom line is that atomoxetine may work in more than one way to help ADHD. It could be that higher dopamine availability in itself does not account for increases in attention or concentration.

### **Methylphenidate**

Methylphenidate (MPH) is another medicine that has been extensively explored and, indeed, the only one for which I found relevant studies. It is considered the pharmacological therapy of choice for treatment of ADHD over one's lifetime. MPH blocks absorption of

dopamine and norepinephrine, which results in increased levels of dopamine and norepinephrine in the striatum and PFC (Groom, 2022). Although MPH is known to inhibit the dopamine transporter, which is the primary mechanism responsible for removal of extracellular dopamine, it is not known whether it has a substantial impact on levels of extracellular dopamine at the therapeutic dosages normally administered.

Volkow et al. (2001) investigated the effects of oral MPH on extracellular dopamine in the human brain using PET on 11 healthy individuals. The researchers discovered that oral MPH greatly enhanced levels of extracellular dopamine. This was concluded from a large decrease in availability of D2 receptors in the striatum. In their discussion, Volkow et al. argue that MPH's amplification of weak dopamine signals in patients with ADHD should boost task-specific signaling, thereby enhancing attention and lowering distractibility.

### **Estimating dopamine levels in the brain**

The importance of the dopaminergic pathways to understanding how dopamine operates is key. In their review of non-human animal studies, mostly rats, Liu and Kaeser (2019) explore how axonal processes shape dopamine signaling with spatial and temporal precision. This precision refers to the ability to control the location and timing of dopamine release in the brain accurately. Liu and Kaeser also evaluate recent research on the dopamine secretory apparatus. The current working paradigm has been that dopamine, upon release, diffuses to impact a large number of target cells via widespread receptors. Based on their study, Liu et al. (2019) report that dopamine release is rapid and forms tiny signaling hotspots. Liu and Kaeser (2019) conclude that dopamine is often released in regions of the brain that are highly focused. It's clear from their study as from other studies that dopamine plays a wide range of roles in the brain.

Microdialysis is a technique used to measure concentration in the brain of neurotransmitters such as dopamine (see, e.g., Stangler et al., 2021; Jaquins-Gerstl et al., 2015). A probe perfuses a solution that collects neurotransmitters from the surrounding tissue. Samples are then collected over time and analyzed. This technique offers insights into the timing (temporal resolution) of neurotransmitter release and the specific brain regions involved (spatial resolution), providing a detailed view of chemical signaling in the brain. Bymaster et al. (2002) used microdialysis to measure dopamine levels in various parts of the rat's brain. The results indicate that atomoxetine increases extracellular levels of norepinephrine and dopamine in the rat's prefrontal cortex.

PET scans can be used to measure dopamine levels in both humans and non-human animals. Anderson et al. (2016) used PET scans with  $^{11}\text{C}$  raclopride, which binds to dopamine D2/D3 receptors. By comparing the binding potential of  $^{11}\text{C}$  raclopride across scans, they could infer the release of dopamine with high probability and so estimate dopamine levels.

Using fMRI, Suzuki et al. (2019) examined the ventral medial prefrontal cortex (vmPFC) of healthy human patients during tasks involving reward anticipation and outcome, albeit without directly measuring neurotransmitter levels. Their focus is how administration of atomoxetine affects neural responses to reward processing observed through changes in fMRI signals, as influenced by dopamine among other neurotransmitters.

Magnetic resonance spectroscopy (MRS) and fMRI provide complementary insights into brain function and structure (see, e.g., Birur et al., 2017). MRS is invaluable for non-invasively detecting changes in key metabolites like catecholamines, which are crucial for understanding conditions such as mood disorders (Mehta et al., 2019). While fMRI measures changes in blood flow related to neural activity, highlighting areas active during specific tasks (Ekstrom, 2010),

MRS offers a detailed view of the brain's metabolic processes, including neurotransmitter and metabolite levels (Agarwal & Renshaw, 2012). Their integration allows researchers to correlate cerebral blood flow with biochemical changes, enhancing understanding of the neurobiological basis of cognitive functions and disorders such as ADHD.

### **Dopamine and the brain's reward system**

Dopamine affects the processing of rewards in direct and indirect ways. Anderson et al. (2016) used PET with <sup>11</sup>C raclopride to investigate the contribution of striatal dopamine to value-based orienting of attention in human subjects, on the hypothesis (supported by the results) that <sup>11</sup>C raclopride is useful for predicting how much those stimuli can be used to distract individuals. The researchers found that attentional capture by previously reward-associated but currently irrelevant distractors correlated with dopamine release in the dorsal striatum. This release demonstrates dopamine's significant role in reinforcing behaviors by signaling the occurrence of an unexpected reward. Anderson et al. found that, when a reward is given, sensory impressions become more noticeable when the prize is related to stimuli previously associated with reward. By correlating dopamine release with attentional capture by reward-associated distractors, the study provides empirical evidence that dopamine not only signals rewards but also modulates attention towards cues associated with those rewards and, by extension, sensory information in general.

In a separate study, Anderson (2016) reports that dopamine signaling plays a major role in how value-driven attention can be captured using PET. Different amounts of dopamine released in the striatum in response to distractors accurately predicted for all participants the amount of distraction caused by stimuli previously associated with reward.

Recent studies (Zhang et al., 2016) have shed light on the intricate dynamics of the dopamine reward system managed by the PFC and striatum. These regions, connected via dopaminergic pathways, significantly influence decision-making and behavioral reinforcement.

Zhang et al. (2016) demonstrate how the PFC and striatum coordinate via phase-locking values to process reward predictions in monkeys, revealing differing neural synchronizations in response to reward sizes. The researchers used two Japanese monkeys equipped with microelectrodes surgically implanted in the lateral prefrontal cortex and striatum. The monkeys' neural activity was monitored through single-unit recordings and local field potentials, alongside eye movements and behavioral responses, during a sequential paired-association task with asymmetric reward schedules. These measurements were used to analyze the neural and behavioral correlates of decision-making, focusing on how reward information influences neural connectivity patterns between the prefrontal cortex and striatum. Their synchronization underlies the behavioral responses in tasks involving rewards, suggesting that they could be used to influence ADHD symptoms related to reward sensitivity and attention. Understanding these connections not only clarifies the neurobiological substrates of ADHD but also opens up potential interventions aimed at modulating this crucial dopaminergic system to enhance cognitive and behavioral outcomes for affected individuals.

### **Aims of the present study**

There is a general indication across many studies that elevated levels of dopamine in the prefrontal cortex – along with other areas of the brain implicated in the dopaminergic pathways – significantly influence concentration. The context of ADHD patients was highly useful as they constitute a group whose key symptoms include impaired concentration and attention. There is overwhelming evidence that dopamine levels correlate with the amount of attention these individuals can provide or give. The studies cited above use PET scans and other reliable tests to reach their conclusions. There is, however, honest debate about the role of other neurotransmitters, as many of the medications that increase dopamine in the prefrontal cortex also increase extracellular serotonin and norepinephrine, both of which are also associated with attention and concentration.

Westbrook et al. (2020) conclude that, instead of dopamine having had a direct impact on the concentration or attention of their study's participants, it impacted participants' motivational level, affecting attention by heightening the desire to achieve a reward or otherwise successful outcome. Westbrook et al. call into question the common assumption of a direct impact. Regardless, the literature indicates that elevated dopamine levels in the prefrontal cortex impact levels of concentration, even if the connection is indirect.

The primary goal of this study is to assess the effects of pharmacological interventions that modify dopamine levels in the prefrontal cortex on the concentration abilities of individuals with ADHD. The study aimed to compare the efficacy of various dopaminergic medications on improving concentration and offer a preliminary understanding of how these medications influence concentration in ADHD. Unfortunately, only studies on MPH were found.

## Methods

### Search strategy

This study sought out peer-reviewed empirical studies published in English after the year 2000. The date is based on significant advances in neuroimaging, pharmacology, and neuropsychology that have occurred over the past two decades. The search string was designed to capture a broad spectrum of studies relevant to dopamine's impact on cognitive functions related to the PFC. It was (dopamin\* OR haloperidol OR methylphenidate OR atomoxetine) AND (concentrat\* OR attention OR intelligen\*) AND (PFC OR "prefrontal cortex" OR "executive function").

The databases searched were PubMed, PsycArticles, and Cochrane Library, using English language and publication time filters (articles published after 2000) across all platforms. The search was conducted April 9, 2024. I applied the search filters “clinical trial” and “randomized controlled trial” for PubMed, which yielded 175 results, and “empirical study” and “quantitative study” for PsyArticle, yielding in 29 results. In Cochrane Library, the filter “trials” produced 404 results.

The software Zotera was used to manage and remove duplicates, resulting in 289 unique records for further evaluation. Initial screening was based on titles and abstracts. After this first stage, 102 records were retained. In the 102 records, full texts for three studies could not be retrieved, leaving 99 articles for full-text review. Following this second screening, five studies met all the criteria and were selected for inclusion.

**Inclusion and exclusion criteria**

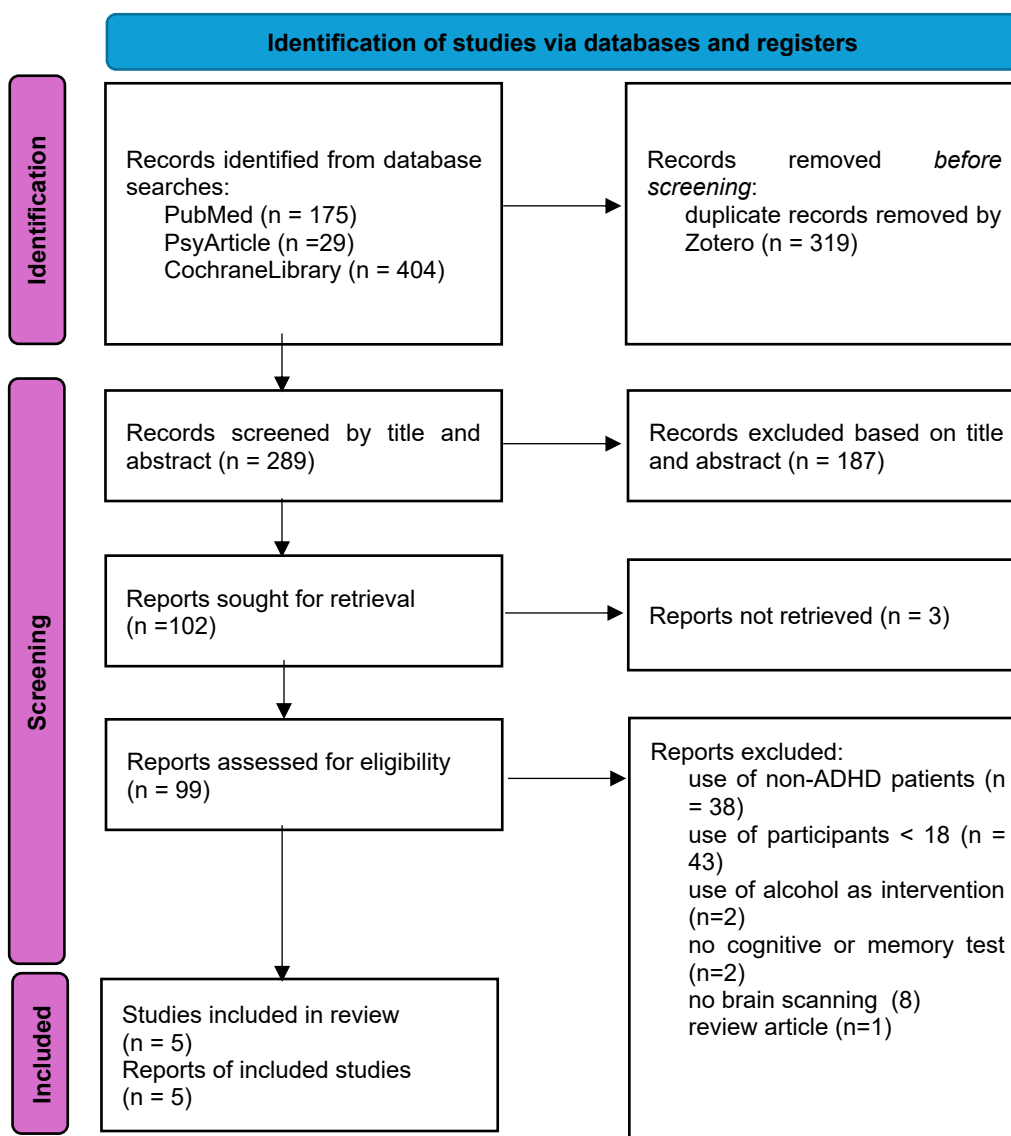
The inclusion criteria were that (1) studies must involve pharmacological interventions known or believed to alter dopamine levels in the PFC; (2) studies must focus on participants diagnosed with ADHD; (3) study participants must be adults 18 years or older; and (4) studies must employ brain scanning.

Studies focusing on non-cognitive abilities as measured by standardized tests like the Conners Adult ADHD Rating Scale were included, but studies including participant groups with potentially confounding behavioral or social factors were excluded, such as criminals. The studies must use medications known to affect the dopamine system in the brain.

**Data extraction**

Data extracted comprised author(s)' names, year of publication, total participants, gender distribution, age range, mean age, concentration ability as evaluated through cognitive tests such as the Conners Adult ADHD Rating Scale and Go/No-Go tasks, clinical assessments and self-reported concentration levels, brain-imaging techniques used and key findings related to the effects of dopamine-altering pharmacological interventions on concentration ability.

**Figure 1**  
*PRISMA Flow Chart of the Selection Process*



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. <https://doi.org/10.1136/bmj.n71>

## Results

The studies unequivocally show that MPH application improves executive function in adults with ADHD. That improvement is linked to increased activity in brain areas implicated in ADHD including the PFC and anterior cingulate cortex; see Table 1.

### **Wiseman et al. (2022)**

Wiseman et al. (2022) evaluated the effect of MPH on neurometabolites and brain activity in adults with ADHD. The focus was on dose-dependent task-related neural activity and glutamate changes following MPH administration. The research design was a double-blind, placebo-controlled, crossover (a research design where participants are subjected to more than one treatment or condition, one after the other) with a single dose of MPH (10 or 15mg) or matching placebo. The study included eight right-handed adults with ADHD (18-36 years) who were not on any stimulant medication and had no other Axis 1 psychiatric disorders. Recruitment was carried out at a university-based adult ADHD clinic and through local ads. Under each condition, participants underwent fMRI scanning in relation to executive function, working memory, and attention. High-field-strength MRS was used to evaluate metabolites, with emphasis on glutamate, across brain regions.

The results indicate that MPH boosted activation in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) during a sustained attention task. Glutamate levels in the ACC correlated positively with frontal and cingulate cortical activity during response inhibition in areas of greatest change following MPH administration compared to placebo. The study identified age-related differences in glutamate levels and processing speed: young people had higher glutamate levels in the DLPFC and performed better on pattern comparison processing speed compared to older people.

**Table 1***Summary of the Main Findings*

Study	Sample size	Imaging method	Mean age	Age range	Gender	Key findings
Wiseman et al. (2022)	8 ADHD adults	fMRI, MRS	27.6	18-36 years	no data	MPH increased DLPFC and ACC activation; ACC glutamate correlated with inhibitory control-related activity
Schweitzer et al. (2004)	10 ADHD adults, 11 healthy controls	PET	ADHD:31.5 control:29.2	no data	all male	MPH improved ADHD symptoms and PASAT performance but did not normalize brain activity; ADHD group showed greater subcortical activation during executive functioning
Fallu et al. (2006)	30 ADHD adults	open-label trial, neuropsychological tests	36.8	19-54 years	17 males 13 females	OROS-MPH improved ADHD symptoms, executive functions, and quality of life; well-tolerated with no serious adverse events
Cherkasova et al. (2014)	15 ADHD adults, 18 healthy controls	PET with [11C] raclopride	ADHD:29.87 control:25.44	18.67-38.52 years	all male	ADHD group exhibited greater striatal dopamine release; dopamine release correlated with ADHD symptoms and response inhibition deficits
Sweitzer et al. (2018)	17 ADHD smokers, 20 non-ADHD smokers	fMRI with Go/No-Go task	ADHD:31.2 control: 29.8	18-55 years	19 females 18 males	smoking abstinence decreased occipital/parietal activation in ADHD smokers; MPH improved inhibitory control and increased fronto-striatal activation

**Schweitzer et al. (2004)**

Schweitzer et al. (2004) examined the neuroanatomical correlates of executive function in adult men with ADHD following treatment with MPH. The study aimed to establish whether MPH normalized activation patterns in ADHD patterns: i.e., made them resemble the activation patterns in healthy individuals.

The participants were ten adult males with ADHD (combined type) and eleven healthy male controls matched by sex, age, and intelligence. ADHD participants were either stimulant-treatment-naïve or had not used stimulant medications for a considerable period before the study. As in the previous study, participants were drawn from a university-affiliated adult ADHD clinic and through local ads.

The study employed PET with [15O] water for measuring changes in regional cerebral blood flow during the Paced Auditory Serial Addition Task (PASAT) vs. a control task. PASAT assesses executive functions such as working memory, attention, response inhibition, and information processing speed. Participants were scanned twice: once between medication and once after being medicated with an optimal dose of MPH for three weeks.

Results show that MPH led to improvement in ADHD symptoms and PASAT performance but did not appear to normalize task-related brain activity. Normalization means achieving a state where the brain activity of ADHD patients during executive tasks closely resembles that seen in people who do not have ADHD, suggesting a correction of the atypical neural activity that is often characteristic of the disorder. MPH decreased cerebral blood flow in the PFC while increasing it in the right thalamus and precentral gyrus. Reduced activation of the PFC can be explained as MPH improving signal-to-noise ratio via reduction of task-irrelevant neural activity. The ADHD group showed reduced cerebral blood flow in the ACC and superior temporal gyrus

in both the open and structured tasks, indicating continued dysfunction despite symptom improvement. Among both medicated and unmedicated ADHD groups, but not the control group, executive function correlated with higher subcortical activation in the basal ganglia and cerebellar vermis. The authors suggest the absence of normalization could be the result of the single dose of MPH and that prolonged treatment might be needed. They also suggest that adults with ADHD use different PFC pathways than the typical ones when executing executive functions.

### **Fallu et al. (2006)**

Fallu et al. (2006) conducted an open-label pilot study assessing the safety, tolerability, and efficacy of OROS-MPH (a sustained release formulation) in adults with ADHD. The study also investigated satisfaction with treatment and treatment impact on quality of life.

The study was performed in uncontrolled and open-label mode with a 38-day treatment duration. Participants were treated with OROS-MPH, with an initial dose of 18mg once a day, incrementally increased to a maximum daily dose of 72mg depending on clinical response and tolerability. The main determinant of efficacy was the difference in the investigator-rated Conners' Adult ADHD Rating Scale (CAARS) total score and subscale scores for inattention and hyperactivity/impulsivity. Secondary outcomes were measured through executive function tests (the Stroop Color-Word Test, WAIS-III Working Memory Index, and Controlled Oral Word Association Test), the Clinical Global Impression Severity (CGI-S) and Improvement (CGI-I) scales, and the Sheehan Disability Scale (SDS) for quality of life.

The trial included 30 adults aged 18-65 diagnosed with ADHD according to DSM-IV-TR criteria. Participants were required to have a baseline CAARS score  $\geq 24$ , a CGI-S score  $\geq 4$  (moderately ill), and a Wender Utah Rating Scale (WURS) score indicative of childhood ADHD.

Comorbidity with psychiatric disorders, substance abuse, and previous non-response to MPH treatment were all exclusion criteria.

Results revealed considerable improvement in ADHD symptoms as confirmed by a decrease in CAARS total score as well as decreased scores for the inattention and hyperactivity/impulsivity sub-scales (Fallu et al., 2006). Significant improvements occurred in executive function, especially in the areas of response inhibition (Stroop Color-Word Test), working memory (WAIS-III Working Memory Index), and verbal fluency (Controlled Oral Word Association Test). Quality of life, as measured by the SDS, showed significant improvement in the areas of work/school, social life, and family life. The CGI-S and CGI-I scales showed that most of the subjects had significant improvement in ADHD severity and overall function. Tolerance of OROS-MPH was quite good; there were no serious adverse effects, although headaches, loss of appetite and insomnia were reported. The authors conclude that OROS-MPH represents a safe and effective treatment for adults with ADHD, addressing core symptoms and executive function deficit. Nevertheless, they note the shortcomings of an open-label, uncontrolled design and emphasize the need for larger, randomized, placebo-controlled trials to confirm these results.

#### **Cherkasova et al. (2014)**

Cherkasova et al. (2014) studied striatal dopaminergic function in drug-naïve adults with ADHD using PET with [<sup>11</sup>C]raclopride. The study investigated the link between striatal dopamine responses, ADHD symptoms and neurocognitive function. The study used a double-blind randomized placebo-controlled design. Participants underwent two PET scans: one after receiving a lactose placebo and the other after receiving d-amphetamine (0.3mg/kg, delivered orally). In a separate drug-free session, neurocognitive tests (the stop-signal paradigm and the

anti-saccade task) were administered. Regions of interest (ROIs) reflecting the functional organization of the striatum – limbic, associative, and sensorimotor subregions – were used in analysis of the PET images. Dopamine release was measured as percentage change in [11C]raclopride binding potential between placebo and d-amphetamine conditions.

The study included 15 treatment-naïve, non-comorbid adult males with ADHD (aged  $29.87 \pm 8.65$  years) and 18 healthy male controls (aged  $25.44 \pm 6.77$  years). ADHD participants met DSM-IV diagnostic criteria, as confirmed by structured clinical interviews. Exclusion criteria were a history of substance dependence, any current Axis I disorders other than ADHD, and use of psychotropic medications.

Compared to the healthy controls, the ADHD group showed higher d-amphetamine-induced decreases in striatal [11C]raclopride binding, particularly within the associative and sensorimotor striatal regions. This indicates increased dopaminergic response in the striatum. In both groups, the magnitude of d-amphetamine-induced change in [11C]raclopride binding potential was positively associated with the symptom severity of ADHD and negatively associated with performance on response inhibition measures. In individuals with ADHD, an increase in dopaminergic response as measured by [11C]raclopride binding potential changes was associated with greater symptom severity and poorer performance on response inhibition tasks. The authors suggest that increased striatal dopamine release in ADHD could be driven by response-inhibition deficits. The observation that increased striatal dopamine release in ADHD, as suggested by changes in [11C]raclopride binding potential, is associated with greater symptom severity and poorer performance on response inhibition tasks can appear contradictory to the "Dopamine Deficiency" hypothesis at first glance. This hypothesis typically posits that ADHD symptoms are primarily due to insufficient dopamine levels within certain brain circuits, particularly those

involving the prefrontal cortex. However, the findings in the study could be seen as consistent with a more nuanced understanding of the dopamine deficiency hypothesis.

The amplified phasic release of dopamine in the striatum, which is indicated by the study, might reflect a compensatory mechanism for underlying tonic dopamine deficiencies in other parts of the brain, such as the prefrontal cortex. Essentially, while overall dopamine production might be lower, response to specific stimuli could trigger exaggerated releases, leading to spikes of high dopamine levels that fail to normalize cognitive and behavioral responses effectively. This phenomenon could explain why increases in dopamine during tasks requiring high levels of inhibition correlate with worse performance—because the dopamine response is improperly regulated and timed, rather than uniformly deficient.

Furthermore, this pattern suggests that ADHD involves complex dysregulations of dopamine transmission, not merely low dopamine levels, underscoring the importance of considering both the regional specificity of dopamine activity and the dynamics of its release in understanding and treating ADHD. They conclude that their results support a model of amplified phasic dopamine release in ADHD : i.e., refers to the increased and rapid release of dopamine in response to stimuli). The authors admit that the small sample size and male-only participants restrict the generalizability of results.

### **Sweitzer et al. (2018)**

Sweitzer et al. (2018) examined changes in inhibitory control-related behavior and brain activity in smokers with and without ADHD during smoking withdrawal. They use voxel-wise analysis was employed to examine fMRI data. This analytical technique involves evaluating each voxel — the smallest distinguishable 3D unit in the brain scan — individually across the whole brain. The purpose of this method is to identify regions where there are statistically significant changes in brain activity that correspond to the different conditions imposed during the study sessions. The study sought to address the part played by catecholamine transmission in these changes by testing the effects of 40mg MPH administration once only.

The study used a double-blind, placebo-controlled, crossover design. Participants completed three fMRI sessions. MPH effects were studied using a within-subject design with three counterbalanced sessions: (1) smoking as usual + placebo, (2) 24h smoking abstinence + placebo, and (3) 24h smoking abstinence + MPH. A modified go/no-go task was used to assess both sustained and transient inhibitory control during each session. The fMRI data were analyzed with whole brain voxel-wise analysis to detect regions with significant group differences refer to the variations observed in fMRI brain activation patterns between the two participant groups and medication effects. By using this method, the study aimed to reveal how MPH influences brain function in the context of smoking abstinence, particularly looking at areas involved in inhibitory control, which may differ between smokers with and without ADHD."

The sample comprised 17 adult daily smokers diagnosed with ADHD and 20 smokers with no history of ADHD. All subjects were healthy right-handed smokers aged 18-55 who smoked at least 10 cigarettes a day. ADHD participants fulfilled DSM-IV diagnostic criteria; controls had

no psychiatric diagnosis. The exclusion criteria were that subjects should not be taking psychoactive drugs; there should be no history of drug abuse or dependence; and the subjects should not have contraindications for MRI scanning or administration of MPH.

Results indicate a significant abstinence effect in the occipital/parietal cortex during sustained inhibition, with more abstinence-induced activation decreases in ADHD smokers relative to non-ADHD smokers. Behavioral performance (the modified go/no-go task during fMRI scanning) was related to activation in the occipital cortex, parietal cortex, and bilateral insula during sustained inhibition in both groups (Sweitzer et al., 2018). Administration of MPH enhanced behavioral performance and increased sustained inhibitory related activation in both groups. With respect to transient inhibition, while MPH did not alter prefrontal or striatal activation in either group it did enhance prefrontal activation in both groups and increased striatal activation in the ADHD group. The authors propose that abstinence-induced alterations in catecholamine transmission in visual-attention regions may be related to inhibitory control deficits, increasing susceptibility to smoking among individuals with ADHD.

## **Discussion**

The goal of this systematic review was to select studies that address the question: can changes in dopamine levels in the PFC be used to influence concentration in ADHD patients? Notably, the majority of studies retrieved predominantly involved the use of MPH, and following the criteria set for this systematic review, all the studies analyzed were centered on MPH. The studies show that MPH administration caused enhanced executive function associated with greater ACC and PFC activation. Those studies used fMRI, PET, and MRS to demonstrate the neurobiological mechanisms of medications in alleviating ADHD symptoms and enhancing cognitive performance.

## **Relationship between study results and ADHD theories**

The systematic review's results align with the dopamine deficit hypothesis of ADHD, which suggests impaired dopaminergic transmission as a principal cause for deficits in executive function (Volkow et al., 2009). Modafinil, another class of stimulants, has been demonstrated to increase levels of dopamine in the prefrontal cortex and striatum of healthy subjects and ADHD patients. This has a positive influence on aspects of cognition including attention, working memory, and response inhibition (Wiseman et al., 2022; Schweitzer et al., 2004; Switzer et al., 2018).

The data are also consistent with the dual-pathway model of ADHD (Sonuga-Barke, 2003), which integrates deficits in executive function and reward processing to account for ADHD. For both of these pathways, dopamine is a key neurotransmitter (Schweitzer et al., 2004; Switzer et al., 2018).

The role of the prefrontal-striatal circuit in both the development of ADHD and its treatment emerges as a crucial element from the review. Zhang et al. (2017) identify the prefrontal-striatal loop as a part of the brain's reward and cognitive control systems, suggesting its dysfunction may underlie the symptomatic manifestations of ADHD. Studies such as those by Schweitzer et al. (2004) and Switzer et al. (2018) highlight how MPH activates this neural circuit enhancing prefrontal and striatal communication. This activation supports the well-established understanding that this circuit is central to managing the cognitive and behavioral symptoms associated with ADHD medication. This circuit represents a potential focal point for pharmacological interventions aimed at treating ADHD, underpinning the development of targeted therapeutic strategies.

### **Comparison and interpretation of study results**

The fMRI studies included in the review, such as those by Schweitzer et al. (2004) and Sweitzer et al. (2018), employ markedly different methodologies, which impacts the comparability of their findings. Schweitzer et al. (2004) utilized a placebo-controlled, single-dose MPH study design, focusing on the immediate effects of the drug in isolation. In contrast, Sweitzer et al. (2018) implemented a complex triple-condition study design that investigated the effects of regular smoking vs. abstinence without MPH administration. The variation in study design is significant because it affects the experimental conditions under which data are collected, influencing the specific aspects of neural and behavioral responses that are measured. The differing designs raise challenges in directly comparing results across studies because each design tests different variables and interactions. For instance, this triple-condition design of Switzer et al. (2018) allows for the examination of how abstinence and MPH interact, which could influence dopamine levels and brain activation patterns differently than the single-dose intervention studied by Schweitzer et al. (2004). This makes it difficult to isolate the effects of MPH from other variables like smoking behavior. Such discrepancies in design can lead to variations in outcomes and must be carefully considered when synthesizing data across studies, especially when attempting to draw broader conclusions about the effects of pharmacological interventions on neural activity in ADHD and related behaviors.

Non-human animal models and human being studies have demonstrated both similarities and significant differences in traits and responses. Variations in dosing, treatment duration, and species differences play significant roles in the pharmacokinetics and drug responses observed in non-human animal studies compared to human studies see, e.g., (Kuvaczinski & Segal, 2002).

Non-human animal studies are vital as they allow researchers to observe how pharmacological interventions cause complex and nuanced changes in neural systems, in way that may not be ethically or practically replicable in human subjects. Furthermore, psychiatric disorders exhibit significant heterogeneity, with different subgroups responding variably to therapeutic drugs (Volkow et al., 2009); non-human animal models are instrumental to dissecting these subgroup responses under controlled experimental conditions. The temporal effects of drugs, including differences in short-term vs. long-term exposure, can be studied first in non-human animals to predict potential neural adaptations in humans (Fusar-Poli et al., 2012). Such research underscores the critical role of non-animal models in developing and refining treatments that are effective and tailored to diverse patient needs.

### **Exploring drug mechanisms**

Research into the mechanisms of action for ADHD medications like MPH reveals that these drugs increase concentrations of neurotransmitters like dopamine and norepinephrine in the prefrontal cortex, which may help in balancing and coordinating neural activity (Berridge et al., 2006). ADHD is associated with neurodevelopmental abnormalities, including reduced cortical thickness and smaller brain volume, which are likely influenced by the pharmacological treatments (Castellanos & Proal, 2012). The enduring effects of these drugs on neurodevelopment and brain structure remain a significant area of inquiry. Integrating neurochemical analyses with neuroimaging research could enhance our understanding of how these substances modify neural circuits and networks. For example, neurochemical studies can detail the molecular actions of the drugs, while neuroimaging can visualize the resultant changes in brain connectivity and function following drug administration (Rubia et al., 2014). To advance understanding of ADHD pharmacotherapy – a complex interplay of neurochemical and structural

changes – future research should synthesize findings across diverse methodologies to build a cohesive knowledge base.

## **Limitations**

Several limitations to the studies in this review should be borne in mind when interpreting the results. One of the most pressing issues when analyzing the efficacy of ADHD therapy is the heterogeneity of patient populations. ADHD is a heterogeneous disorder, with diverse symptoms, distinct subtypes, and other conditions interacting with it (Faraone et al., 2015; Kessler et al., 2006). Such variety clearly influences treatment response and can make it more difficult to compare findings across studies.

While PET and fMRI provide valuable insights into brain function, each has limitations that could impact the interpretation of ADHD studies. PET, though excellent for tracking neurochemical changes, offers relatively limited spatial resolution, which makes it difficult to precisely localize brain activity to specific small regions. On the other hand, fMRI boasts slightly superior temporal resolution, allowing it to capture rapid changes in brain activity. However, fMRI is highly sensitive to motion artifacts; even minor movements by participants can distort the data, leading to potential inaccuracies in interpreting brain function during tasks. These imaging limitations must be carefully managed to ensure accurate assessments of how ADHD treatments affect brain activity (Glover, 2011; Logothetis, 2008).

The study authors applied different drug administration strategies, with differences in dosage and duration of treatment. Researchers should standardize treatment regimens. Future research needs to use larger samples in, well-designed studies thorough clinical characterization of the patients enrolled in the studies.

The limitations of this thesis reflect the inherent complexities of studying neuropsychiatric conditions such as ADHD. First, the studies included in the systematic review may have varied in their methodological rigor, affecting the consistency and generalizability of findings. All of the neuroimaging studies rely on small sample sizes due to the high costs and technical requirements of fMRI and PET. Variation in ADHD symptoms and treatment responses influenced by genetic, environmental, and neurobiological factors adds a layer of complexity. While this thesis attempts to determine the neurobiological underpinnings of ADHD through pharmacological interventions, it focuses on dopamine without detailed exploration of other neurotransmitters like norepinephrine and serotonin, which are also implicated in ADHD. Finally, the use of non-human animal studies to infer human neurobiology, while necessary and informative, always carries the caveat that such findings may not translate to human conditions.

### **Social and ethical aspects**

This review critically appraises the current evidence regarding the impact of pharmacological interventions in terms of cognitive function and brain activity in adults with ADHD. The long-term use of ADHD medications involves complex ethical and neurodevelopmental considerations. Ethically, it's crucial to ensure informed consent and evaluate prescription practices critically to avoid dependency and protect patient autonomy. Neurodevelopmentally, extended use of stimulants may alter brain and behavioral development, potentially impacting emotional regulation and natural coping mechanisms. These concerns underscore the importance of careful therapeutic oversight and highlight the need for further research into long-term effects of ADHD treatments. Psychiatrists and psychologists should find this research integral in formulating personalized treatment plans that consider individual variability in drug responses, which could revolutionize the therapeutic landscape for ADHD by

improving treatment efficacy and reducing side effects. Cognitive neuroscientists may be interested in how the study leverages neuroimaging techniques to elucidate the neurobiological underpinnings of ADHD and the effects of its various treatments, potentially aiding future research into other cognitive disorders. Philosophers and cognitive scientists should engage with the ethical considerations of altering brain chemistry and the broader implications for concepts of normalcy and mental health.

## **Conclusion**

The primary goal of this study was to assess the effects of pharmacological interventions that modify dopamine levels in the prefrontal cortex on the concentration abilities of individuals with ADHD. Additionally, the study aims to compare the efficacy of various dopaminergic medications on improving concentration and offer a comprehensive understanding of how these medications influence concentration in ADHD. I found that MPH, an amphetamine-like medication, has been best for improving cognitive abilities and brain function in adults with ADHD. The results support the dopamine deficit hypothesis and confirm the role of the prefrontal cortex and striatum in manifestation of the disorder and effectiveness of treatment.

Considering the present state of ADHD diagnosis and therapy, the future studies should propose to devise optimized medication approaches that use neuroimaging markers and simultaneously adopt multimodal therapy models to improve patient outcomes (Cortese & Coghill, 2018). Multimodal therapy takes a comprehensive approach that combines treatments to address the disorder's complexities. These include pharmacological options, behavioral therapies, educational interventions, and lifestyle changes. The goal is to tackle ADHD from multiple angles, enhancing the overall effectiveness of treatment by addressing neurobiological, behavioral, and psychoeducational aspects simultaneously. This integrated strategy aims to

improve cognitive functions, manage symptoms more effectively, and support better overall outcomes for individuals with ADHD.

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