Cover Page

Title:

The Neurocognitive Effects of Extended-Release Methylphenidate in Healthy Adults: A Review and Placebo-Controlled Randomized Controlled Trial

NCT Number: Not yet assigned

Date:

28 July 2026

Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects

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A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree of Doctor of Philosophy

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Johannesburg, South Africa, June 2025

This thesis adheres to the **'block' format** as prescribed by the *University of the Witwatersrand Style Guide for Theses and Dissertations*. This structure ensures clarity, logical progression, and alignment with institutional academic standards.

1. CHAPTER 1 INTRODUCTION

1.1. Introduction

1.1.1 Methylphenidate and Attention Deficit Hyperactivity Disorder

Methylphenidate (MPH) is a central nervous system stimulant used in South Africa and other regions, including the United States of America (USA) and the United Kingdom (UK). Its main therapeutic use is for Attention Deficit Hyperactivity Disorder (ADHD) (Challman & Lipsky, 2000).

Attention Deficit Hyperactivity Disorder is a clinically diagnosed medical condition without pathognomonic diagnostic tests. Managing ADHD continues to be challenging due to the lack of specific diagnostic tests or investigations, but supported by widely used scales, symptom scores and checklists. These include self-reporting and observer tools for adults such as the *Adult ADHD Self-Report Scale (ASRS-v1.1, 2005)* (Kessler, 2005) *and* the *Conners' Adult ADHD Rating Scales (CAARS)* (Evans & Preston, 2011)**.** The *Vanderbilt ADHD Diagnostic Rating Scale* (*Vanderbilt ADHD Diagnostic Rating Scale (VADRS) - Psychology Tools*, 2003) is primarily used for children and includes both parent and teacher versions. Other tools for children and adolescents include the *Behavior Rating Inventory of Executive Function (BRIEF)* (Gioia et al., 2015) and the Swanson, Nolan, and Pelham Teacher and Parent Rating Scale (SNSAP-IV) (*ADHD_snap-Iv_26.Pdf*, 2014). The focus of the above assessment tools is on behaviour and aspects of cognitive function, and the tests can be utilised for diagnosis and evaluating treatment effectiveness.

Assessing and managing ADHD often requires a multidisciplinary approach that combines non-pharmacological and pharmacological treatments to alleviate symptoms (Quintero et al., 2022). Among the primary pharmacological options are stimulants such as MPH. Despite extensive research conducted over many years, clear guidelines for treating ADHD have yet to be established, and much remains to be understood (Elsayed et al., 2020).

The Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5) (American Psychiatric Association & American Psychiatric Association, 2013) of the American Psychiatric Association is primarily used for diagnosing ADHD. In South Africa the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) published by the World Health Organization (International Statistical Classification of Diseases and Related Health Problems, 2019) (*ICD-10 Version:2019*, 1992) is used, despite there being an updated version (*ICD-11*, 2022). This medical classification list includes specific pathology codes based on signs, symptoms, diseases, causes of injury and similar descriptors. Healthcare professionals use these codes to classify and then code details of conditions being managed and treated. In many countries, including South Africa, they are used for health insurance claims. These listings also include ADHD as a recognised medical condition.

Attention Deficit Hyperactivity Disorder is a chronic condition usually starting in childhood (before age 12 years) and may persist into adulthood. Although there are no typical or characteristic features to make a definitive diagnosis, a diagnosis is usually made by excluding other conditions, and on being associated with certain symptoms on the above-mentioned rates and scales. A key feature is dysfunction in social and occupational or academic activities (Weis et al., 2019).

The mainstay of treatment is pharmacological, primarily central nervous system stimulants. Methylphenidate is, in South Africa and indeed universally, the drug of choice and is a potent amphetamine-like stimulant drug with similarities to cocaine. The mechanism of action of MPH is however different from that of amphetamine. There are some similar responses observed and others that are not in individuals with and without ADHD. Solanto suggests this is due to stimulants not specifically addressing a unique neurobiological deficit in ADHD, but rather through having compensatory effects (Solanto, 1998). She suggests that it enhances the functioning of both dopaminergic and noradrenergic systems. These compensatory effects involve increasing the activity in dopaminergic and noradrenergic pathways by enhancing the release and inhibiting the reuptake of dopamine (DA) and norepinephrine (noradrenaline). This mechanism assists in improving attention and control over behaviour, thereby compensating for the deficits associated with ADHD.

Others like Volkow and Surman suggest that MPH exerts its therapeutic effects partly by enhancing DA signals (Volkow et al., 2002; Surman et al., 2013). The variability in individual responses is partly due to differences in DA levels, and MPH's effects depend on the context. Given that DA boosts task-specific neuronal signalling and reduces noise, they also propose that MPH-induced increases in DA could enhance attention and reduce distractibility. Furthermore, since DA influences motivation, these increases in DA would make tasks more engaging, thereby improving performance.

Numerous studies have shown the benefit of treatment of ADHD with MPH, with the intent of normalising the underlying central nervous system dysfunction and returning the homeostasis of neurological and social function (Schrantee et al., 2016; Surman et al., 2013).

Several scenarios highlight the importance of MPH use and ADHD treatment in sports. Some athletes have a legitimate need for MPH to function normally and optimally, and they should be allowed to compete without gaining an unfair advantage over their peers. However, there is a possibility that other athletes may use stimulants without an underlying ADHD condition, thus not normalising any underlying neuropathology. In the absence of rigid data showing that MPH enhances performance in athletes without ADHD, such use is based on the belief that a stimulant with amphetamine-like properties will achieve the desired outcome.

1.1.2 Use of Methylphenidate in Individuals Without ADHD

The use of methylphenidate in individuals without ADHD is relevant in two primary contexts. Firstly, athletes may use MPH to enhance performance, which contrasts with individuals with ADHD who experience social and academic dysfunction and respond positively to stimulant treatment that normalises their dysfunction.

1.1.2.1Methylphenidate use in healthy athletes

Healthy athletes may use MPH as a doping agent, aiming to covertly enhance performance while avoiding detection of an adverse analytical result (positive test) or other anti-doping rule violation. Illegally and knowingly using MPH to enhance performance can potentially give these athletes an advantage over others due to the different effects of MPH on individuals without ADHD. Such use violates anti-doping

regulations while raising significant ethical concerns regarding competitive equity and athlete welfare.

Alternatively, they might seek to legitimise its use by applying for a Therapeutic Use Exemption (TUE) (*Therapeutic Use Exemptions (TUEs)*, 2024). A TUE permits athletes to use a medication or method listed on the World Anti-Doping Agency's (WADA) Prohibited List (*The Prohibited List*, 2024) due to a legitimate medical condition. This exemption ensures athletes can receive necessary treatment without gaining an unfair competitive edge. However, there are no data or evidence to support the notion that there is performance enhancement in ADHD athletes on MPH with a TUE. In theory, their use would normalise pathology and neural homeostasis and not enhance performance beyond physiological limits.

To secure a TUE, athletes must apply through their relevant anti-doping organisation (ADO), providing comprehensive medical documentation from their physician. The application is then reviewed by a Therapeutic Use Exemption Committee (TUEC), which determines whether to grant the exemption based on medical necessity and the absence of performance enhancement and no reasonable alternative therapy. If approved, the TUE outlines the dosage, frequency, route of administration, and duration of the treatment. Athletes must comply with these conditions and notify the ADO of any changes. If the TUE is denied, athletes have the right to appeal the decision.

As a stimulant and, therefore, a substance that has the theoretical potential to enhance sporting performance, MPH is a prohibited substance that appears on the prohibited substance list of the World Anti-Doping Agency (*The Prohibited List*, 2024). This prohibits athletes from using MPH in competition unless they have a TUE (*Therapeutic Use Exemptions (TUEs)*, 2024). A TUE is therefore a concession whereby a competitive athlete is allowed to use a prohibited substance, and its issuance is reliant on specific criteria, including that the substance will not unduly enhance performance and is required to return health status to a premorbid state. Despite extensive research on MPH and its psychosocial effects, there is a lack of studies on the physiological parameters and physical effects of this medication, particularly in relation to sport or exercise (Berezanskaya et al., 2022; Garner et al., 2018), perspectives grounded in theoretical concepts (Reardon & Factor, 2016). A study in children indicated that MPH

treatment in those with ADHD may have a negative impact on activities requiring explosive movements and maximal speed (Meckel et al., 2011). In a study by Mahon et al, results showed that MPH increases submaximal heart rate (HR) but does not affect oxygen consumption (VO_2) and work rate or rate of perceived exertion (Mahon et al., 2008). They reported that without medication, the physiological responses during peak exercise are reduced in some, but not all, boys with ADHD. The Borg Rating of Perceived Exertion (RPE) scale, created by Swedish researcher Gunnar Borg (Borg & Dahlström, 1962), is a tool used to assess an individual's perceived effort, exertion, breathlessness, and fatigue during physical activity (Williams, 2017). The scale helps measure how hard a person feels their body is working, based on physical sensations such as an elevated heart rate, faster breathing, increased sweating, and muscle fatigue. The Borg Rating of Perceived Exertion is a commonly used psychophysical tool for evaluating an individual's subjective sense of effort during physical activity (Scherr et al., 2013).

Following the use of MPH for those diagnosed with ADHD, and in accordance with TUE regulations, such athletes should apply for TUEs to use MPH and remain eligible to compete. Given the clinical diagnosis and often challenging verification of ADHD, which relies on subjective information, WADA has established expert group guidelines to assist TUE Committees in managing these applications (WADA, *TUE Physician Guidelines - ADHD*, 2023).

Data from WADA on TUE applications for MPH are not publicly available. There is some information that circumstantially suggests that there are a high number of applications. In 2009, it was reported that there was a substantial increase in TUEs in American baseball, with almost 8% of players using medication for ADHD (Associated Press, 2009). In 2012, 116 Major League Baseball players in the USA had TUEs for ADHD, comprising a substantial 9% of all League players. Australia's anti-doping 2013 annual report lists 202 TUEs approved across 58 sports in 2012, with swimming, cycling, American football and athletics having the most. While it shows some patterns in prescription drug use among athletes, it lacks details on specific drugs like MPH (Partridge, 2013). The authorities refused to disclose the number of TUEs per substance, citing confidentiality concerns. The reported increase in ADHD stimulant prescriptions suggests TUEs for these drugs might increase (Partridge, 2013).

Therapeutic Uses Exemption applications to the ITA (International Testing Agency) in 2024 exceeded 1000, of which approximately 50% were for stimulants (personal communication). Moreover, stimulants accounted for nearly 60% of TUE submissions in Canada and the USA (personal communication). In a review of TUEs at Olympic and Paralympic Games 2016-2022, less than 1% of Olympic athletes and less than 3% of Paralympic athletes had valid TUEs. As expected, there were differences in the substances and methods used for various medical conditions. However, the overall number of TUEs remained low, showing that they are not common in very elite sports (Vernec et al., 2024). Their study aimed to examine the prevalence of TUEs among athletes competing in four Olympic and four Paralympic Games and identify the prohibited substances and methods associated with TUEs. Data from WADA's Anti-Doping Administration and Management System were analysed in a cross-sectional observational study, covering athletes from the Rio 2016, Pyeongchang 2018, Tokyo 2020, and Beijing 2022 Olympic and Paralympic Games. Among 28,583 Olympic athletes, 0.9% had a TUE. Among 9,852 Paralympic athletes, 2.8% had a TUE. At the Summer Olympics, the most common TUE substances were glucocorticoids (0.5% in Rio) and stimulants (0.4% in Tokyo). At the Summer Paralympics, diuretics (0.8% in Rio) and stimulants (0.8% in Tokyo) were most frequently reported. Trends in Winter Games were similar but with lower TUE numbers. The authors concluded that the prevalence of athletes with valid TUEs was low—less than 1% in the Olympics and less than 3% in the Paralympics. While there were variations in prohibited substances and methods used for different medical conditions, the findings suggest that TUEs are not widely utilised in elite sports. The article underscores the need for transparency and careful monitoring to ensure the appropriateness of TUEs for stimulants in elite sports and a better understanding of the effects on performance and other factors, such as health risk.

The WADA 2022 testing report, which are the latest available figures, reported that of 412 Adverse Analytical Findings (AAFs), which are 'positive tests' in athletes without TUE's, 110 were MPH-related (27% of all stimulant positives) (*Anti-Doping Testing Figures Report*, 2022). The next most common was amfetamine (sic) (amphetamine), with 69 AAFs (17%), closely followed by cocaine with 63 (15%). This was followed by Octodrine (1,5-dimethylhexylamine) with 20 AAfs (5% of stimulants).

It is noted that these data are disparate to figures from almost two decades ago (2006) where out of 490 AAFs, 32 (6.5%) were for MPH (World Anti Doping Agency, 2006). Those for MPH were the 4th highest, following amphetamine, cocaine and ephedrine. Around the halfway time period since, in 2015, out of 528 positive stimulant tests, MPH was the most commonly detected substance, accounting for 96 tests (18%), followed by amphetamines with 80 tests (15%) (World Anti-Doping Agency, 2016). This indicates that the abuse, or possibly inadvertent use, of MPH not only remains prevalent among elite athletes, but is increasing.

Should an athlete have an AAF for MPH without a TUE, they will have several options. Firstly they may apply for a retroactive TUE, which is granted under exceptional circumstances (e.g. for emergency treatment, no time to apply before the doping control, or other exceptional circumstances), but the same rules for granting a TUE apply (*"TUE" - Drug Free Sport - Drug Free Sport*, 2024). Thus, this should not be seen as a "way out". Secondly, they may choose to have the B sample tested under their (or appointed nominee's) observation and have a tribunal (hearing), or thirdly, they may accept the outcome and face sanctions.

Methylphenidate is a 'specified substance' on the WADA Prohibited List. It clarifies that "*specified Substances and Methods" identified in Article 4.2.2 should not in any way be considered less important or less dangerous than other doping substances or methods. Rather, they are simply substances and methods which are more likely to have been consumed or used by an Athlete for a purpose other than the enhancement of sport performance*" (*The Prohibited List*, 2024) This may therefore influence sanctions that may be imposed with an AAF, and be relatively lenient.

Article 10.3 of the World Anti-Doping Code (WADC) outlines the sanctions for violations involving specified prohibited substances. For a first violation, the penalty ranges from a minimum reprimand or warning to a maximum of one year of ineligibility from competition and sporting activities. A second violation results in a mandatory two-year period of ineligibility, while a third violation leads to a lifetime ban from sport (*The Prohibited List*, 2024). Since MPH is a specified substance, athletes have the opportunity to argue for a reduced sanction (*The Prohibited List*, 2024).

It is not known whether competitive athletes taking MPH or stimulants do have an advantage and whether their performances are improved whilst taking the medication,

compared to if they were not. In 2016, a Russian-based hacking group called Fancy Bear (also known as Fancy Bears and APT28) gained access to WADA's TUE database. It started publicising information on international athletes worldwide (Fancy Bears, 2016). Their actions in this regard are believed to be retaliatory for the exposure of alleged systematic doping of Russian athletes by the Russian authorities. The intention appears to have been one of exposing doping by athletes whom the TUE process has legitimised. Portions of the exposed information revealed that some athletes in various sports were granted TUE's for stimulants. It is unclear which medical conditions the TUE certificates provide information on, although a few may have mentioned ADHD in the comments section of the certificates. As elite sportsmen and women, the performances of these athletes have been exceptional, and it is impossible to determine what role the stimulants may have had on their performances.

There are a number of scenarios for the importance of MPH use or ADHD treatment in sports. Some athletes have a legitimate need for its use to function 'normally' and optimally and should be allowed to compete but not have an unfair advantage over peers.

There is a possible scenario in which athletes might use stimulants without having an underlying ADHD condition and, therefore, would not 'normalise' the underlying neuropathology. They may apply for a TUE under false pretence, as the diagnosis is not simple, and try to 'legalise' their use. Alternatively, they may use it illegally and knowingly to enhance performance. They potentially will have an effect different to that in those with ADHD and therefore have a possible advantage over other athletes.

A level playing field is essential to strive for and ensure fairness in sport. If an athlete receives a clinical diagnosis of ADHD and is granted a TUE, could that athlete potentially have an unfair advantage in sport?

There is evidence that MPH modulates muscle strength. The study by King et al demonstrates that MPH can affect brain connectivity during muscle-fatiguing exercise. It further supports that the central nervous system regulates motor drive to maintain homeostasis (King et al., 2017).

With respect to endurance activities, Swart et al demonstrated that MPH allowed for longer exercise at higher stress levels, revealing a muscular reserve. This suggests

that endurance performance is not solely limited by muscle fatigue but is also regulated by the central nervous system to maintain whole-body homeostasis and keep an emergency reserve (Swart et al., 2009).

No research was found on the effect of MPH on physiological exercise parameters in healthy adults.

1.1.2.2Methylphenidate use for academic enhancement

There is evidence that in children and adolescents with ADHD the use of neurocognitive stimulants can improve symptoms with some effect on academic performance (Douglas et al., 1986; Kortekaas-Rijlaarsdam et al., 2019). This is more so with acute effects rather than long-term effects (Carlson & Bunner, 1993) and there are also inconclusive outcomes (de Faria et al., 2022).

Other than the scenario of the use of MPH in sports, MPH is used in healthy adults as a neurocognitive enhancer in the academic environment. In the Netflix documentary series "Take Your Pills" (Klayman, 2018), the use of prescription MPH stimulants like Adderall and Ritalin among college students and professionals seeking cognitive enhancement was explored. One key finding highlighted in the film was that while students who used these stimulants believed their performance had improved, objective assessments did not support this perception - suggesting a perceived/placebo-like effect of academic or cognitive enhancement (Klayman, 2018).

Numerous studies have reported on the (mis)use of MPH in university students to enhance academic performance (Barrett et al., 2005; Bogle & Smith, 2009; Teter et al., 2003), including in South Africa (Constantinou & Aguiyi, 2022; Jain et al., 2017; Steyn, 2016). Such use presents potential health risks (Steyn, 2016), and according to a group of Brazilian authors “*should be considered a serious public health problem, especially due to risks of harm and adverse effects associated with its use*.”(Cândido et al., 2019).

1.1.3. Study rationale

This PhD study was envisaged due to its perceived relevance to the physical performance of healthy adults in their daily activities and sports participation and its implications for doping control regulations. It aimed to assess several physiological parameters relevant to sports, including cognitive function, balance, and health risks related to cardiac events such as cardiovascular incidents. The widespread use of MPH among athletes, whether for legitimate medical purposes or as a performance-enhancing substance, has raised concerns. This trend extends beyond sports, with increasing use among healthy adults in academic settings for cognitive enhancement. Additionally, there are growing concerns about the potential risk of sudden cardiac death in athletes using MPH.

Therefore, this study further aimed to provide additional data and information on the potential harmful effects of MPH, particularly on the cardiovascular system.

1.2 STATEMENT OF THE PROBLEM

Despite the widespread use of MPH for managing ADHD in South Africa and elsewhere around the world, there remains a significant gap in understanding its physiological and physical effects. While MPH is effective in normalising central nervous system dysfunction in ADHD patients, its impact on individuals without ADHD, especially in the context of sports and academic performance, is not well-documented. Given that MPH is a WADA-prohibited substance in competitive sports during competition without a TUE and its widespread use among athletes and students, there is an urgent need to investigate its effects on physical performance, physiological parameters, and cardiovascular health risk. The study framework explored the implications of MPH use in healthy adults, focusing on its potential to enhance various performance parameters, side effects and potential cardiovascular risks.

1.3 AIM OF THE STUDY

The primary aims of the study were to determine the effects of MPH in drug-naïve healthy adults on:

a. physiological parameters
b. neurocognitive function
c. balance
d. physical performance (muscle strength)
e. cardiovascular risk and cardiac electrical activity

1.4 OBJECTIVES OF THE STUDY

The objectives of the study were to measure the effects of MPH in healthy adults using:

a. Surveillance of medical history and habitual levels of physical activity using questionnaires
b. Anthropometric measurements, including body height, weight, BMI, waist circumference, hip circumference and waist/hip ratios
c. Muscle strength tests using a handgrip dynamometer
d. Neurocognitive function using computerised software
e. Objective postural balance tests
f. Cardiopulmonary physiological measures, including heart rate, blood pressure, maximum oxygen consumption, oxygen pulse and other variables on a cardiopulmonary exercise test (CPET)
g. Cardiac electrical activity using electrocardiography

1.5 RESEARCH QUESTION

What are the physiological and physical effects of MPH on physical, physiological and cardiac electrical risks in drug-naïve healthy adults?

1.6 HYPOTHESIS

Methylphenidate use in drug-naïve healthy adults has no significant effect on muscle strength and physiological exercise parameters, postural balance, cognitive function and cardiac health parameters.

1.7 NULL HYPOTHESIS (N0)

Methylphenidate use in drug-naïve healthy adults enhances muscle strength, physiological exercise parameters, postural balance, cognitive function and cardiac health parameters.

1.8 ALTERNATIVE HYPOTHESIS

Methylphenidate use in healthy adults significantly enhances muscle strength and physiological exercise parameters, postural balance, and cognitive function and affects cardiac health risk parameters.

This PhD thesis is presented in the traditional monograph format in accordance with the style guidelines provided by the University of Witwatersrand. The monograph structure has been chosen to provide a comprehensive and cohesive exploration of the research topic, allowing for an in-depth presentation of the study's objectives, methodology, findings, and conclusions. This format aligns with the university's requirements and ensures clarity and consistency throughout the document.

2. CHAPTER 2 - LITERATURE REVIEW

Methylphenidate is a central nervous system stimulant that increases dopamine in the brain. It has been used for the treatment of ADHD for decades in both children and adults. It is also prescribed for adult narcolepsy. Athletes with ADHD use MPH for legitimate medical reasons but may also use it for performance enhancement. In addition, healthy adults use MPH for academic or recreational purposes. However, despite extensive research on ADHD, stimulant treatment and MPH, there is little research on the effects in healthy adults. This study was designed to explore its potential impact on physical performance. It also assessed various physiological parameters, including muscle strength, cognitive function, balance, health risks and cardiovascular function in healthy adults. The following literature review aligns with the study's objectives, methodology, and outcome measures, providing essential context for assessing the benefits and risks of this widely used stimulant.

2.1 Health Screening

Participants who signed informed consent were scheduled to undergo a cardiopulmonary exercise test. Before conducting exercise testing, ensuring participant safety is paramount. The American College of Sports Medicine (ACSM), a leading professional organisation with over 45,000 members and certified professionals, is dedicated to advancing scientific research and translating findings into practical applications within exercise science and sports medicine. The ACSM's mission emphasises the promotion of healthier lifestyles through physical activity and exercise (source: https://www.acsm.org/). Additionally, the ACSM provides critical resources, research and advocacy to support the fields of sports medicine and exercise science (source: https://www.acsm.org/certification), making it a reliable source for the following guidelines.

Before performing a maximal exercise test, it is essential to complete a pre-participation health screening and a health history questionnaire (ACSM, 2015). These forms gather comprehensive information about the participant's current and past medical conditions, medications, surgical history, and exercise training background. The Physical Activity Readiness Questionnaire (PAR-Q+) and its electronic

counterpart, ePARmed-X (Addendum A), are utilised to efficiently determine whether medical clearance is required (Miller, 2023).

Methylphenidate use is associated with contraindications outlined by pharmaceutical manufacturers, based on both established and theoretical risks. These contraindications include thyroid disorders and cardiovascular conditions (e.g., hypertension, angina, cardiomyopathies, prolonged QT syndrome), among others (Novartis, 2018). Given these potential risks, this study's comprehensive health screening and cardiovascular risk assessment were critical components.

To evaluate the participant's current activity level, the Physical Activity/Exercise Stages of Change questionnaire was administered (Addendum B). For health risk screening and risk stratification, the ACSM Risk Stratification Screening Questionnaire was employed (Addendum C). The PAR-Q+ was completed during the initial assessment, while all other questionnaires were administered at the initial assessment and repeated at testing points 2 and 3. These tools have been rigorously assessed for reliability, sensitivity, and specificity, demonstrating high validity across all three metrics (Warburton et al., 2011).

2.2 Methylphenidate pharmacokinetics and mechanism of action

Methylphenidate, a CNS stimulant, was first synthesised in 1944 and later marketed by the Ciba-Geigy Pharmaceutical Company under the trade name Ritalin. Initially, during the 1950s, Ritalin was used to treat a variety of conditions, including chronic fatigue, depression, and narcolepsy (Leonard et al., 2004). Over time, its primary therapeutic application shifted to the management of attention deficit disorder (ADD) and ADHD. While ADD may include symptoms of hyperactivity in some cases, it does not universally do so. Research has been conducted in either or both conditions, and specific terminology will be used per the cited publications. In general contexts, ADHD will serve as the default acronym.

Methylphenidate is a piperidine-derived CNS stimulant with a chemical structure containing two chiral centres, resulting in four possible enantiomers. Modern pharmacological formulations utilise a racemic mixture, excluding the four enantiomers, as studies have shown that these enantiomers lack significant CNS

stimulant effects (Challman & Lipsky, 2000). Although MPH shares similarities with amphetamines, its mechanism of action differs. Methylphenidate primarily facilitates the release of stored DA from presynaptic vesicles and inhibits its reuptake into presynaptic nerve terminals. In contrast, amphetamines block DA reuptake and more selectively enhance the release of newly synthesised DA. Both compounds, however, share the primary pharmacologic effect of increasing central DA and norepinephrine (noradrenaline) activity (Faraone, 2018).

Methylphenidate inhibits DA and norepinephrine transporters, has agonist activity at the serotonin type 1A receptor, and redistributes the vesicular monoamine transporter-2 protein. Although both MPH and amphetamines affect the norepinephrine system, research has mainly concentrated on the effects of MPH on the DA system (Scahill et al., 2004). Dopamine and its agonists are crucial in regulating the cardiovascular, renal, hormonal, and central nervous systems by stimulating alpha- and beta-adrenergic receptors and dopaminergic receptors (Horwitz et al., 1962).

The dual mechanism of MPH - promoting DA release and inhibiting its reuptake - results in increased extracellular DA levels, particularly in the basal ganglia and cortex, and to a lesser extent in other brain regions. However, the magnitude of DA elevation varies among individuals (Volkow et al., 2001). When administered orally, MPH is almost completely absorbed and is primarily metabolised into ritalinic acid via de-esterification in the liver (Vedrenne-Gutiérrez et al., 2024). Peak plasma concentrations are achieved within 1 to 3 hours after a standard oral dose, with a plasma half-life of 1.5 to 2.5 hours. Studies involving adults and children taking 20 mg of extended-release MPH have demonstrated rapid absorption, followed by two distinct concentration peaks approximately 4 hours apart (Lyseng-Williamson & Keating, 2002). Food intake enhances absorption, but MPH exhibits low protein binding, possibly contributing to its relatively short half-life (Challman & Lipsky, 2000; Scahill et al., 2004).

Using positron emission tomography (PET) scan data, Volkow et al. (2001) confirmed in a study of healthy adults that one of the therapeutic effects of MPH may stem from its ability to enhance DA signalling in the brain. They also noted that individual variability in response to MPH may be attributed to differences in baseline DA levels, suggesting that individuals with varying DA levels may experience differing effects from the medication. Furthermore, DA enhances task-specific neuronal signalling while reducing background noise, improving attention, and decreasing distractibility. Since DA also modulates motivation, increased DA levels induced by MPH can make tasks more engaging and rewarding, thereby enhancing performance (Volkow et al., 2001).

2.3 Methylphenidate medical indications

Methylphenidate was first approved for the treatment of ADD and ADHD by a health authority in Switzerland in 1954 (Trenque et al., 2014). Since then, it has become the most widely prescribed medication for ADHD worldwide.

The therapeutic effects of MPH are mainly attributed to its capacity to increase the activity of central DA and norepinephrine, which enhances executive and attentional functions (Faraone, 2018). Executive functions are higher-order cognitive processes that enable reasoning, planning, problem-solving, and regulating daily activities. These functions are governed by interconnected neural networks, mainly involving the prefrontal cortex, and are modulated by interactions with other brain regions responsible for cognition, emotion, and behaviour (Blair, 2017). Notably, executive function has also been linked to postural balance and gait (see Section 3.10, Postural Balance).

The concept of attention, as described by James (James, 1890), is often summarised by his statement, “Everyone knows what attention is.” He further elaborated that attention encompasses the “focalization, concentration, and consciousness” of mental processes. Attention can be analysed in greater depth by considering its task-oriented aspects, the ability to sustain focus, and its process-oriented nature (Yantis, 2002).

Methylphenidate is widely used for treating ADHD (Huss et al., 2017) with long-acting formulations considered the most effective (Swanson & Hechtman, 2005; PubChem, 2025). Individual responses to MPH vary significantly, necessitating dose adjustments to achieve optimal clinical outcomes. A review by Huss et al. on dose optimisation for ADHD treatment highlights that long-acting MPH is both effective and well-tolerated, with individualised dosing improving efficacy and safety. Clinical trials suggest an effective non-extended-release dose range of 40–80 mg per day in adults, with titration guided by symptom control and adverse effects (Huss et al., 2017).

Additionally, it is approved for treating narcolepsy in adults (Franceschini et al., 2020; Novartis, 2018; Yoss & Daly, 1959)

Beyond its primary use in treating ADHD, MPH has been studied for other conditions, such as traumatic brain injury, stroke, sarcopenia, and cancer (Challman & Lipsky, 2000). In South Africa, medications are categorised into different schedules under the Medicines and Related Substances Act of 1965 (Act No. 101 of 1965) (Department of Health, 2020). These schedules are determined by the potential risks and benefits associated with the medications.

Schedule 0: Over-the-counter medications with minimal risk, available without a prescription.

Schedule 1: Low-risk medications, available without a prescription but often kept behind the counter.

Schedule 2: Medications requiring pharmacist advice but no prescription.

Schedule 3: Prescription medications requiring authorization from a healthcare professional.

Schedule 4: Prescription medications with a higher risk of side effects or misuse.

Schedule 5: Medications with a higher potential for addiction and stricter control.

Schedule 6: Medications with a high potential for abuse and addiction, requiring strict regulation.

Schedule 7: Controlled substances used for medical purposes under strict conditions.

Schedule 8: Highly controlled substances, often limited to research or very specific medical uses.

The specific rules for selling or supplying Schedule 6 medicines and substances are outlined in Section 22A of the Act, which imposes strict regulations. According to Section 22A(6)(i), these substances cannot be provided through repeat prescriptions, while Section 22A(6)(o) restricts the amount dispensed to no more than a 30-day supply based on the prescribed dosage. Additionally, direct advertising of Schedule 6 substances to the general public is prohibited.

In South Africa, Ritalin® LA 20 mg, a modified-release formulation supplied by Novartis Pharmaceuticals, is classified as a Schedule 6 medication. It is available in dosages of 10 mg, 20 mg, 30 mg, and 40 mg (Novartis, 2018). According to the package insert, MPH is a CNS stimulant with more pronounced effects on mental than motor activities. Its exact mechanism of action in humans is not fully understood, but its stimulant effects are believed to result from inhibiting DA reuptake in the striatum without inducing DA release. The formulation is designed to produce two concentration peaks approximately 4 hours apart, allowing for once-daily dosing. The pharmacokinetic profile of MPH is similar in hyperactive children and healthy adults.

The recommended starting dose for Ritalin LA® is 20 mg, with titration upward in symptomatic individuals as needed (Haertling et al., 2015). While clinical studies have suggested various maximum doses, no specific scientific rationale supports a predetermined upper limit (Ching et al., 2019). Ching et al. (2019) emphasise that MPH titration should be guided by clinical criteria rather than a fixed maximum dose, with positive outcomes observed in practice (Pelham et al., 2001). In this study, the usual starting dose of 20 mg of extended release (long-acting) MPH was used in the healthy adults cohort, and not titrated as no clinical symptoms required monitoring.

2.4 Methylphenidate off-label use

The use of drugs for unapproved use is usually termed “off-label” use (Commissioner, 2019). Up until recent years, averaging within the last decade, MPH-regulated use has been limited to ADHD and narcolepsy in children and adults (Trenque et al., 2014). In recent years it has been used more extensively in adults who have either continued

its use since childhood or were diagnosed as adults with ADD (Castells et al., 2011; Chamakalayil et al., 2021; Faraone, 2018). Other uses are, therefore, off-label. Despite the absence of clinical trials endorsing its use for other conditions, some clinical off-label practices have continued, including for cognitive enhancement in students (Barrett et al., 2005; Outram, 2010), after cerebrovascular accidents (Grade et al., 1998), autism spectrum disorder (Quintana et al., 1995; Sturman et al., 2017), fatigue in oncology and malignant brain glioma's for improved neurobehaviour (Meyers et al., 1998), Alzheimer's disease and even depression in geriatrics (Verghese et al., 2025). In the 1980s MPH was advocated for use in oncology together with narcotics in pain management (*Cancer Treatment Reports*, 1981). In a French pharmacovigilance study of 181 adverse drug events with MPH use, more than 40% were ascribed to off-label use (Trenque et al., 2014). In addition to use for cognitive enhancement, MPH has the potential to be used as a recreational drug (Freese et al., 2012), the population most likely to be the university student body. In our study, over 10% of university students indicated that cognitive- and sports performance-enhancing substances were used for recreational purposes (Constantinou & Aguiyi, 2022).

Across the globe MPH is used for non-medical/cognitive enhancement purposes, even though this practice is affected by social, legal, and ethical factors (Sharif et al., 2021).

2.4.1 Methylphenidate use in athletes

Athletes diagnosed with ADHD should not face unfair discrimination in competition, even though MPH is classified as a prohibited substance in sports. The World Anti-Doping Agency (WADA) lists MPH as prohibited during competition but not out of competition. It is categorised as a specified stimulant under classification S6.B (WADA, Prohibited List, 2024). Specified substances are those more likely to be used unintentionally or for legitimate medical purposes rather than for performance enhancement. This classification does not diminish the substance's potential health risks, but acknowledges the higher likelihood of inadvertent use, such as for the treatment of ADHD. This classification also influences the sanctions imposed for an AAF. Athletes diagnosed with ADHD or narcolepsy who are aware of doping regulations may apply for a TUE, which, if granted, permits the use of MPH without resulting in an AAF (WADA, Therapeutic Use Exemptions, 2024). In cases where an

AAF occurs, a retroactive TUE application can be applied for, and if the criteria are met, the TUE may be granted retroactively. The rationale for this process is to normalise pathology, allowing athletes with a legitimate medical condition to compete in a physiologically normal state.

In 2008, Eichner reported a significant increase in ADHD diagnoses among athletes and a rise in the use of ADHD medications for performance enhancement (Eichner, 2008). Following the ban on amphetamines in Major League Baseball, the Mitchell Report noted a nearly fourfold increase in ADHD drug exemptions, with almost 8% of players diagnosed with ADHD by 2007. Similar trends emerged in U.S. college sports, with a survey of a college ice hockey conference revealing that 52% of players used stimulants, primarily pseudoephedrine (27%), along with ephedra or amphetamines (1%) (Eichner, 2008). Recent data indicate a substantial rise in the use of MPH in sports. WADA's statistics on TUE applications reveal that in 2022 there were over 1,500 TUE applications and approvals, with 70–80% of applications being approved (*Therapeutic Use Exemptions (TUEs)*, 2024). These statistics highlight the transparency and fairness of the TUE process, ensuring athletes receive necessary medical treatment while maintaining the integrity of sports.

In cases where healthy athletes without an ADHD diagnosis seek performance enhancement through artificial means, stimulants may be used. Data from AAFs suggest that some athletes use stimulants to boost performance. The Anti-Doping Administration and Management System, a centralised platform managed by WADA, coordinates anti-doping programmes, testing, and TUE processes. According to 2022 testing figures, stimulants accounted for 15% (412 occurrences) of all AAFs and 0.3% (1 occurrence) of all atypical findings (ATFs), which indicate unusual results requiring further investigation (*Therapeutic Use Exemptions (TUEs)*, 2024). Among all sports, MPH was the most commonly detected stimulant (27%), followed by amphetamines (17%) (*Therapeutic Use Exemptions (TUEs)*, 2024).

A systematic review by Berezanskaya et al. (2022) examined the impact of ADHD medications, including MPH, on athletic performance, including in children with ADHD and healthy athletes and healthy non-athletes, addressing concerns about their potential for abuse. The review analysed nine studies from over 13,000 abstracts and

found that six studies demonstrated significant improvements in athletic performance with stimulant medications ($p < 0.05$), with varying effect sizes. This suggests that stimulant medications may have a more consistent and notable effect on athletic performance in individuals with ADHD compared to those without. However, the chronic use of stimulant medications in the ADHD population might be a contributing factor to these differences. A meta-analysis of two studies within the review yielded conflicting results, highlighting the need for further research.

In a related study, Marques et al. (2021) explored the bidirectional relationship between physical activity (PA) and DA levels in their article, "Bidirectional Association between Physical Activity and Dopamine Across Adulthood—A Systematic Review." They reported that most studies confirm that PA enhances DA availability, positively influencing motivation, mood, and cognitive function. While some evidence suggests that DA regulates exercise motivation, findings remain inconsistent. The authors propose that PA may serve as a non-pharmacological strategy to support mental health and manage neurodegenerative diseases, given dopamine's role in mood regulation. The review underscores the need for further research to elucidate the mechanisms linking DA and PA.

2.4.2 Methylphenidate use by students

Students may use MPH to improve academic performance- (Bogle & Smith, 2009; Steyn, 2016) or as a recreational drug (Arria & Wish, 2006; Babcock & and Byrne, 2000; DuPont et al., 2008). Arria and Wish (2006) suggest an extremely high number of students have used prescription stimulants at least once in their lifetime without a prescription (Arria & Wish, 2006). At a South African university, a study amongst students living in residences revealed MPH is frequently used off-label, misused through prescription diversion, and involved in illicit trade (Zyl et al., 2017). At yet another South African university, the illegal users sourced it predominantly from friends and also by using faked prescriptions, purchasing it without a prescription, or from family (Dreyer et al., 2016). A recent South African study by Louw and Davids (2022) revealed that postgraduate medical students specialising in various fields engaged in MPH self-prescription practices. While some studies suggest that short-term MPH use may enhance academic performance, the evidence remains insufficient

to draw definitive conclusions about its benefits, even for students with ADHD (de Faria et al., 2022b).

The use of MPH to enhance cognitive function has been demonstrated in numerous settings at school, and more so at higher education institutions (Clemow, 2017; Outram, 2010). Monteiro et al (2017) reported in a systematic review that obtaining scientific data on the true motivations for MPH use is challenging due to methodological limitations in studies. Research on cognitive enhancement is limited, but short-term effects like increased alertness and energy have been observed. Combined with easy access to the drug, this has contributed to its growing use among university students (Monteiro et al., 2017).

Methylphenidate significantly enhanced mathematics productivity and accuracy (Kortekaas-Rijlaarsdam et al., 2019). Additionally, it increased reading speed but did not significantly improve reading accuracy (Kortekaas-Rijlaarsdam et al., 2019). Other studies showed increased alertness and wakefulness, without any benefits in learning or memory (Finger et al., 2013). Outram (2010) discusses how MPH is perceived as a cognitive enhancer or “smart drug” due to several factors, including “academic and media speculation”, “association with academic success”, “blurring of treatment and enhancement”, and “sociocultural desire for pharmacological solutions” (Outram, 2010)**.** While the incentive may be to enhance academic success (dos Santos Christo et al., 2023) the benefit in healthy students is unclear (Erasmus & Kotzé, 2020).

Barrett et al (2005) suggested that students who misuse MPH have personality traits that increase their use of other substances compared to peers (Barrett et al., 2005). A Brazilian study among medical students reported widespread non-medical use of MPH and an association between its use and risky alcohol consumption (Silveira et al., 2014). Use of MPH amongst students appears to have been most studied in medical students (Amaral et al., 2022) and is highly prevalent (Abbasi-Ghahramanloo et al., 2018; Silveira et al., 2014). Abbasi-Ghhramanloo’s study found that the prevalence of prescription-type opioid, MPH , and sedative-hypnotics use among students in the past year was 16.1%, 3.3%, and 10.3%, respectively. After controlling for other factors, results suggested that sedative-hypnotic use in the past year (OR = 5.7) and lifetime illicit drug use (OR = 27.6) were linked to MPH use among students.

In their study, Silveira et al reported that 34.2% of participants had used MPH, with 23% using it without medical indication, particularly among 6th-year students compared to 5th-year students (32.9% vs. 13.2%, p = 0.004). Non-medical MPH use was associated with potentially hazardous alcohol use, as 33.3% of non-medical users had an AUDIT score ≥ 8 (p = 0.029), highlighting a significant link between these behaviours. A study at a South African university reported that medical students primarily use MPH for non-medical purposes. However, their overall knowledge of the drug remains limited (Jain et al., 2017), with a similar finding in an Iranian study among medical students (Habibzadeh et al., 2011). Students and young doctors use MPH for either potential academic benefit, or recreational use. Many are otherwise healthy adults, with no firm evidence of benefit or health risk.

Beyer et al (2014) questioned whether MPH provides cognitive benefits for healthy students and doctors and whether these benefits outweigh the risks of its use. They conclude that it is philosophically justifiable if long-term research demonstrates that the risks are minimal and the benefits substantial (Beyer et al., 2014). On the other hand, the side effects have been found to exceed the benefits (Javed et al., 2019). Also, in a recent review, data indicated that non-medical use of MPH offers little cognitive or academic advantage and may lead to academic stagnation and health risks (Wei & Sinnott, 2023).

Numerous researchers have identified the greater potential public health risk (Acosta et al., 2019; Onal et al., 2024; Sharif et al., 2021; Teter et al., 2003) on a broader scale. The medical ethics in dealing with this is a significant challenge (Koren & Korn, 2021).

2.5 Effects on body composition

Anthropometry is defined as the measurement of body size, weight, and proportions. These are measurements used in epidemiological studies and may assess nutritional status, body composition and fat distribution (Willett, 2012).

There is little research on the effect of MPH on anthropometry or body composition in adults compared to children and their growth projections. However, influences of MPH on changes through normal childhood growth trajectories are documented in children and adolescents with ADHD. Methylphenidate may influence resting and postprandial energy expenditure (Lorello et al., 2008).

In a drug/placebo trial involving adults without ADD/ADHD, MPH was shown to affect eating patterns and facilitate weight loss over 60 days (Fatemi, 2018). Goldfield et al found that MPH significantly reduced energy intake, particularly dietary fat consumption in a randomised, double-blind, placebo-controlled crossover trial involving 14 adults over a month. This effect was not mediated by changes in hunger but may have been related to the reduced reinforcing value of food, supporting the DA - related reward deficiency model of obesity (Goldfield et al., 2007).

Studies on weight loss over a very short period, like one or two weeks, are limited and often focus on the potential risks and short-term effects rather than sustainable results. However, some research indicates that short-term interventions (<13 weeks) involving strict dietary changes and increased physical activity can lead to modest weight loss (Rotunda et al., 2024).

Methylphenidate can therefore help reduce weight, appetite, and food intake (Vedrenne-Gutiérrez et al., 2024). Although long-term (1->4 years) weight loss may be expected from taking MPH in children with ADHD (Çevikaslan et al., 2021; Díez-Suárez et al., 2017; Zhang et al., 2010), it may also promote weight loss in those with overweight/obesity (Mellström et al., 2020). This change is associated with early fat loss and slower increase in bone and lean tissue (Poulton et al., 2012).

A study by Davis et al involved two drug-challenge sessions (MPH and placebo) conducted one week apart. Each session lasted two hours and occurred at the same time of day for each participant. It was found that MPH significantly suppressed appetite, cravings, and snack-food consumption compared to placebo (Davis et al., 2012). The short duration of my study over 14 days on active drug may be too short to affect weight or body composition but may have been expected to influence appetite.

2.6 Methylphenidate Impact on Physiological Parameters

The effects of DA on various physiological parameters have been extensively studied. Dopamine receptors are classified into D-1 and D-2 types, each with distinct roles. D-1 receptors enhance hormone release and neurosecretory cell activity, while D-2 receptors inhibit the release of neurotransmitters and hormones. D-1 receptors mediate vascular relaxation in the cardiovascular system, and D-2 receptors inhibit norepinephrine release. Studies suggest that DA receptor classification is consistent

across different physiological systems (Stoof & Kebabian, 1984). Dopamine receptors are widely distributed in the CNS, regulating movement, cognition, emotions, and hormone release. In the peripheral system, these receptors are primarily located in the kidneys, blood vessels, and pituitary gland, influencing sodium balance, vascular tone, and hormone secretion (Missale et al., 1998). Research on DA receptor signal transduction has identified several second messengers, including cAMP, calcium, potassium, and arachidonic acid. These receptors also indirectly modulate other mechanisms, such as Na+/H+ exchangers, Na+-K+-ATPase, and cell growth and differentiation pathways. However, conflicting reports in the literature regarding the modulation of these messengers and mechanisms are likely due to the use of different tissues or cell lines. It is now understood that many components of signal transduction pathways, including receptors, G proteins, and effectors, have multiple isoforms with distinct expression patterns and regulatory properties (Missale et al., 1998).

Dopamine infusions, commonly used in treating heart failure, exert their effects through peripheral receptors, significantly enhancing the cardiac index while causing a notable increase in heart rate (Stoner et al., 1977). Dopamine influences the heart by increasing contractility, elevating heart rate, and constricting coronary arteries (Neumann et al., 2023). Although acute oral administration of MPH increases DA levels primarily in the brain rather than the systemic circulation, it has been shown to elevate heart rate in children and adults. However, this effect was not statistically significant (Schrantee et al., 2016). Schrantee et al concluded that while no systemic vascular effects were observed, it remains challenging to distinguish between the effects of DA neurotransmission and direct DA actions on the microvasculature (Schrantee et al., 2016).

Despite MPH being recognised as a CNS stimulant, warnings persist regarding its cardiovascular effects, including elevated blood pressure and risks of myocardial infarction and cerebrovascular accidents (Entringer, 2025). Increased heart rate is listed as a common side effect (Entringer, 2024). It has been shown that children, adolescents, and adults treated with MPH exhibit significant increases in heart rate and systolic blood pressure compared to baseline, in contrast to placebo groups (Liang et al., 2018). Untreated children with ADHD tend to have higher heart rates and

reduced heart rate variability compared to their peers, but these differences may be mitigated with MPH treatment (Buchhorn et al., 2012). Other studies have demonstrated increased heart rates in children with ADHD treated with MPH, both at rest and during exercise (Ballard et al., 1976; Boileau et al., 1976; Cohen et al., 1971; Wilens et al., 2004).

A randomised, double-blind trial by Urman et al. (1995) examined the cardiovascular effects of MPH in anxious and non-anxious children with ADHD (URMAN et al., 1995). Results indicated dose- and time-dependent increases in heart rate and blood pressure, with anxious children showing significantly higher diastolic blood pressure increases, particularly one-hour post-dose. This suggests that anxiety may influence the cardiovascular response to stimulant medications in children with ADHD.

Increases in blood pressure have been documented in children taking MPH (Wilens et al., 2004), with Hennissen et al. (2017) reporting statistically significant increases in systolic blood pressure. Aman and Werry (1975) also reported that MPH slightly increased heart rate and significantly raised blood pressure. A study by Brown and Sexson (1989) investigated the short-term effects of MPH on 11 male adolescents with ADHD using a double-blind, crossover design. Participants received a placebo and three doses of MPH (0.15, 0.3, and 0.5 mg/kg) for two weeks each. Results showed significant dose-dependent increases in diastolic blood pressure. However, in another study, MPH was associated with slight increases in blood pressure and heart rate (Stiefel & Besag, 2010), although these changes typically remain within normal ranges (Lamberti et al., 2015).

Adults with ADHD are at higher risk for age-related cardiovascular issues and may experience greater sensitivity to stimulant medications than children. A review of 20 clinical trials (10 with sufficient cardiovascular data) found that CNS stimulant treatment for adult ADHD significantly increased resting heart rate and systolic blood pressure compared to placebo. Stimulant use also raised the risk of a resting heart rate >90 bpm (4.2% vs. 1.7%, OR=2.75). Given the association between elevated resting heart rate and cardiovascular morbidity, the need for further research was identified to explore the clinical significance of these findings in adults with ADHD (Mick et al., 2013).

Li et al. (2017) investigated the exposure-response relationships of blood pressure and heart rate changes in healthy adults taking MPH. Data from seven clinical trials and a meta-database of published studies were analysed. Blood pressure and heart rate changes were closely linked to MPH blood levels, with no observed time lag. Immediate-release MPH formulations produced greater peak effects on blood pressure and heart rate than extended-release formulations at equivalent doses. Yet, despite these cardiovascular effects, MPH significantly elevates resting and postprandial energy expenditure without causing marked increases in heart rate or blood pressure (Lorello et al., 2008). A systematic review by Berezanskaya et al. (2022) found that MPH administration increased heart rate, core temperature, hormone levels, and rates of perceived exertion during athletic performance, with effect sizes ranging from small to large.

In a PhD thesis, Van Breda (2018) proposed that the effect of MPH on heart rate is centrally mediated rather than a direct peripheral stimulant effect. Volkow et al. (2003) provided evidence that central dopaminergic effects partially drive MPH-induced blood pressure increases and may involve dopamine-triggered elevations in peripheral adrenaline levels. Methylphenidate's cardiovascular effects on systolic blood pressure and heart rate in healthy male adults closely align with its brain pharmacokinetics. However, individual variability and the involvement of multiple neurotransmitters and adaptive processes suggest that brain binding alone does not fully predict cardiovascular responses (Volkow et al., 1996).

The Central Governor Theory, introduced by Timothy D. Noakes in 1996, posits that the brain regulates physical performance to prevent harm, with fatigue acting as a protective mechanism rather than a purely physiological limit (Noakes, 1998). This theory has influenced the understanding of endurance, pacing, and the mind-body connection in sports (Noakes, 1998; Pompeu, 2022). In line with this theory, Swart et al. (2009) found that healthy elite cyclists taking MPH cycled 32% longer than those on placebo before their power output dropped to 70% of the starting value. When the placebo trial ended, those on MPH had higher power outputs, oxygen consumption, heart rates, ventilatory volumes, and blood lactate levels, indicating that MPH allowed longer exercise at higher stress levels, revealing a muscular reserve. The authors concluded that the CNS regulates endurance performance to maintain whole-body homeostasis and preserve an emergency reserve.

A master's thesis by Chabreck (2015) explored the impact of ADHD medications on exercise performance, focusing on pain perception, blood lactate levels, heart rate, and perceived exertion (Chabreck, 2015). The study found that while heart rate and perceived exertion increased across all groups, ADHD stimulant medication did not significantly alter these measures compared to control groups or non-medicated individuals. The researcher recommended further research on the effects of psychostimulants in healthy individuals to confirm these findings. Further, in my study, in addition to measuring resting heart rate and arterial blood pressure, selected cardiopulmonary exercise test (CPET) variables were recorded (Table 2.1). These included gas exchange measurements, generating the standardised Wasserman 9-panel plot (Wasserman, 2000) using a Wattbike® cycle ergometer (Woodway, Waukesha, Wisconsin, USA). Cardiopulmonary exercise testing objectively assesses exercise capacity, evaluating cardiovascular and respiratory efficiency, musculocellular function, and overall fitness. It helps identify physical capabilities, deficiencies, and areas for improvement in training regimens.

A study by Meckel et al. (2011) explored the effects of MPH on exercise performance in adolescent boys (16–18 years old) with ADHD, focusing on endurance, using a 2000-meter run. No significant differences in endurance were found, leading the authors to hypothesise that MPH-induced tachycardia might negatively affect aerobic performance. Similarly, Mahon et al. (2008) reported that stimulant medication increased heart rate during submaximal exercise but did not alter other cardiorespiratory measurements or perceived exertion. In a study by Boileau et al. (1976), oxygen consumption was measured using indirect calorimetry in 27 hyperactive children during rest, exercise, and recovery phases. Participants underwent two sessions: one after ingesting MPH and another after taking a placebo. While heart rate and blood pressure increased significantly with MPH, oxygen consumption did not show significant changes. Similarly, a dissertation by Joyce Elaine Ballard (1975) examined the effects of MPH on the circulorespiratory responses of hyperactive children during rest, exercise, and recovery. Methylphenidate significantly elevated cardiovascular strain, increasing heart rate and blood pressure, but did not enhance exercise performance or oxygen utilisation, suggesting its primary effects are on the CNS, improving attention and focus rather than physical capabilities.

An extensive literature search revealed no studies on the effects of MPH on CPET measurements in healthy adults.

A study with the stimulant lisdexamfetamine (LDX) assessed cardiopulmonary impact in 15 adults with ADHD. Participants underwent psychiatric evaluation, echocardiography, and exercise testing, with LDX titrated to 70 mg daily over six weeks and follow-ups for six months. No significant changes in cardiac performance or metabolic/ventilatory variables at maximum exertion were observed, although some changes in heart structure and heart rate recovery were noted. The study concluded that LDX did not cause clinically meaningful changes in heart function or exercise capacity (Hammerness et al., 2013).

Numerous studies have investigated using MPH in various medical conditions to enhance exercise capacity or reduce fatigue. A feasibility study on sarcoidosis-associated fatigue found that MPH was well-tolerated and safe. However, no significant difference in fatigue scores was observed between MPH and placebo groups, with both showing improvement from baseline (Atkins, 2018). A review of interventions for posttraumatic fatigue, based on 360 articles published between 2014 and 2016, identified nine studies meeting the inclusion criteria. Pharmacological interventions, particularly dopaminergic agents, yielded mixed results (Shuman-Paretsky et al., 2017).

Table 2.1 Physiological parameters measured during CPET

Measurement	Description
Respiratory Exchange ratio (RER) at maximum test	Describes ratio of CO_2 output to O_2 uptake (V˙CO2/V˙O2) as a function of time and reflects patient effort (RER at least ≥ 1). Depends on rate of lactate increase during progressive exercise.
$V0_{2peak}$ ml/kg/min	Maximum volume of oxygen in millilitres consumed per minute per kilogram of body weight
VT (ml.min^{-1}) Ventilatory Threshold	Point at which VCO_2 deviated from linear relationship with $V0_2$. Indicative that oxygen-dependant energy systems are starting to contribute relatively more to energy production with slight increase in blood lactate levels above resting levels.
VO_2 ml/kg/min at ventilatory threshold	Oxygen volume consumed at VT
VT as % of VO_{2peak} (VO2 at VT / VO_{2peak})	Metric for assessing endurance capacity. Indicates intensity at which one can sustain exercise before experiencing significant increase in breathing rate due to accumulation of metabolic by-products.
VE/$VC0_2$ slope	Volume of CO_2 expelled per litre of air ventilated. Indicates ventilatory efficiency. Increase in slope indicates increased dead space ventilation in lung, pulmonary vascular disease or pulmonary limiting disease.
VO_2/work rate (ml/min/watt)	Measure of efficiency of oxygen uptake relative to work being performed and helps to assess efficiency of cardiovascular and respiratory systems during exercise. The higher the value, the better the efficiency.
Oxygen Uptake Efficiency Slope (OUES)	Parameter to assess efficiency of body's oxygen uptake during exercise. A higher value indicates more efficient oxygen uptake. Can also provide insight at submaximal exercise effort.
VO_2/VE) (ml/min 02)/L/min)	Ratio indicates how much oxygen being consumed by body for each litre of air ventilated and assesses efficiency of respiratory system. A higher VO2/VE ratio suggests efficiently using oxygen taken in indicating good respiratory and cardiovascular function.
Oxygen pulse (ml/beat)	A proxy for stroke volume and predictor for coronary artery disease and all-cause mortality

After: (*Interpreting The Cardiopulmonary Exercise Test*, 2018) (Haley et al., n.d.) (Uchida, 2018) (*Respiratory Formulas, Calculations, and Equations (2025)*, n.d.) (Crisafulli et al., 2007) (Laukkanen JA, Kurl S, Salonen JT, et al, 2006)

2.7 Methylphenidate and Neurocognitive Performance

Neurocognitive function was assessed in this study using the CNS Vital Signs® (CNSVS) software (CNS Vital Signs, North Carolina, USA), a computerised neurocognitive test battery designed for clinical screening. The following neurocognitive domains were evaluated: Attention, Verbal and Visual Memory (to assess short-term and long-term memory), Executive Function (EF) (including the Stroop Test to measure cognitive flexibility, inhibitory control, and problem-solving skills), Processing Speed, and Psychomotor Speed. Executive function is also associated with maintaining postural stability and walking patterns (Blair, 2017).

CNS Vital Signs® is a validated neuropsychological test battery comprising seven tests that assess a range of cognitive functions. A 2014 study by Iverson et al. demonstrated no significant gender differences in these domain scores among adults, supporting its applicability across diverse populations (Iverson et al., 2014).

It is widely used in clinical and research settings for conditions such as concussion, Huntington's disease, ADD, ADHD, traumatic brain injury and other neurological disorders (Brooks et al., 2019; Cook, 2011; Gualtieri et al., 2006; Hume et al., 2017; Iverson et al., 2008; King et al., 2018; Lanting et al., 2012; Stafford, 2024). Key challenges in ADHD, for example, include deficits in executive functions, which CNSVS effectively evaluates (Alotaibi M, 2022).

The assessment, performed via an online webpage, takes approximately 30 minutes to complete. It evaluates cognitive processes through ten standard subtests: Verbal Memory, Visual Memory, Finger Tapping, Symbol Digit Coding, Stroop Test, Shifting Attention Test, and Continuous Performance Test. Three additional optional tests—Perception of Emotions, Non-Verbal Reasoning, and 4-Part Continuous Performance, can also be administered. The test provides composite scores for the five cognitive domains mentioned above and a “Global Neurocognitive Score”, offering a comprehensive evaluation of cognitive function.

CNS Vital Signs® measures both single-test domains (specific cognitive abilities) and multiple-test domains (integrated results from multiple tests), as illustrated in Figure 2.1. Gualtieri and Johnson (2006) provide detailed information on the populations for which the assessment is normed, its reliability and validity, scoring methods, test

procedures, clinical applications, research uses, and interpretation. DesRuisseaux et al. (2025) further support the construct validity of CNSVS executive function tests but suggest that modifications to the current composite scores could enhance the prediction of EF performance.

The normative database for CNSVS was established using data from 1,069 subjects aged 7–90 years (Gualtieri & Johnson, 2006). Test-retest reliability was evaluated in a study of 99 participants over an average interval of 62 days, demonstrating reliability comparable to traditional neuropsychological tests (Gualtieri & Johnson, 2006). Concurrent validity studies involving 180 participants, including healthy individuals and those with neuropsychiatric conditions, confirmed that CNSVS has validity similar to conventional neuropsychological assessments.

CNS Vital Signs Clinical Domain Description

Single Test Domain Multiple Test Domain

Neurocognitive Index (NCI)	Measure: An average score derived from the domain scores or a general assessment of the overall neurocognitive status of the patient. Relevance: Summary views tend to be most informative when evaluating a population, a condition category, and outcomes.
Composite Memory	Measure: How well subject can recognize, remember, and retrieve words and geometric figures. Relevance: Remembering a scheduled test, recalling an appointment, taking medications, and attending class.
Verbal Memory	Measure: How well subject can recognize, remember, and retrieve words. Relevance: Remembering a scheduled test, recalling an appointment, taking medications, and attending class.
Visual Memory	Measure: How well subject can recognize, remember and retrieve geometric figures. Relevance: Remembering graphic instructions, navigating, operating machines, recalling images, and/or remember a calendar of events.
Psychomotor Speed	Measure: How well a subject perceives, attends, responds to visual-perceptual information, and performs motor speed and fine motor coordination. Relevance: Ability preform simple motor skills and dexterity through cognitive functions i.e., use of precision instruments or tools, performing mental and physical coordination i.e., driving a car, playing a musical instrument.
Reaction Time*	Measure: How quickly the subject can react, in milliseconds, to a simple and increasingly complex direction set. Relevance: Driving a car, attending to conversation, tracking and responding to a set of simple instructions, taking longer to decide what response to make.
Complex Attention	Measure: Ability to track and respond to a variety of stimuli over lengthy periods of time and/or perform mental tasks requiring vigilance quickly and accurately. Relevance: Self-regulation and behavioral control.
Cognitive Flexibility	Measure: How well subject is able to adapt to rapidly changing and increasingly complex set of directions and/or to manipulate the information. Relevance: Reasoning, switching tasks, decision-making, impulse control, strategy formation, attending to conversation.
Processing Speed	Measure: How well a subject recognizes and processes information i.e., perceiving, attending/responding to incoming information, motor speed, fine motor coordination, and visual-perceptual ability. Relevance: Ability to recognize and respond/react i.e., fitness-to-drive, occupation issues, possible danger/risk signs or issues with accuracy and detail.
Executive Function	Measure: How well a subject recognizes rules, categories, and manages or navigates rapid decision making. Relevance: Ability to sequence tasks and manage multiple tasks simultaneously as well as tracking and responding to a set of instructions.
Simple Attention	Measure: Ability to track and respond to a single defined stimulus over lengthy periods of time while performing vigilance and response inhibition quickly and accurately. Relevance: Self-regulation and simple attention control.
Motor Speed	Measure: Ability to perform movements to produce and satisfy an intention towards a manual action and goal. Relevance: Preparation and production of simple manual dexterity actions e.g. manipulate and maneuver objects.
Social Acuity	Measure: How well a subject can perceive, process, and respond to emotional cues. Relevance: Spectrum screen, ability to recognize social cues or read facial expressions. Provides insight into inappropriate behavior, decreased inhibition, insensitivity to social standards, and social behavioral regulation.
Reasoning	Measure: How well is subject able to recognize, reason and respond to non-verbal visual-abstract stimuli. Relevance: Problem solving skills, ability to forge insights, discern meaning, and ability to perceive relationships.
Sustained Attention	Measure: How well a subject can direct and focus cognitive activity on specific stimuli. Relevance: How well a subject can focus and complete task or activity, sequence action, and focus during complex thought.
Working Memory	Measure: How well a subject can perceive and attend to symbols using short-term memory processes (4PCPT). Relevance: Ability to carry out short-term memory tasks that support decision making, problem solving, planning, and execution. Enables "right-now" responses.

Figure 2.1 Clinical domain descriptions in the CNSVS (*CNSVS-BriefInterpretationGuide.Pdf*, n.d.)**.**

CNS Vital Signs® also showed discriminant validity in diagnosing mild cognitive impairment, dementia, ADHD, depression, and brain injuries, and can even detect malingering (Gualtieri et al., 2006; Gualtieri & Johnson, 2006). A study involving 40 healthy, active volunteers (16 men, 24 women; average age 21 years) examined the psychometric properties of CNSVS across three sessions, spaced one week apart. Participants showed improvements in six of the nine neurocognitive domains during the second and/or third sessions compared to the first. The results suggest clinicians should utilise reliable change indices to account for practice effects and distinguish meaningful score changes linked to pathology (Littleton et al., 2015). Test-retest reliability has been established elsewhere too (Jones, 2011), with baseline tests required due to practice effects (Ikoma, 2019; van der Linden et al., 2017).

Batistela et al (2016) examined the effects of acute MPH administration on cognitive performance in healthy young adults. Participants received 10 mg, 20 mg, 40 mg, or a placebo and were tested on attention, episodic memory, and working memory. No significant differences in cognitive performance were found across doses (Batistela et al., 2016).

The question “What is the role of dopamine on psychometric tests?” was posed to Microsoft Edge Co-Pilot AI, and the response was:

“*Dopamine plays a significant role in various cognitive and emotional processes, which can influence performance on psychometric tests. Here are some key points about how dopamine affects these tests:*

1. ***Cognitive Functions**: Dopamine is crucial for executive functions such as working memory, attention, and problem-solving. Higher dopamine levels in certain brain regions can enhance these cognitive abilities, potentially leading to better performance on tests measuring these skills.*
2. ***Motivation and Reward**: Dopamine is often referred to as the “reward chemical” because it is involved in the brain’s reward system. It influences motivation and the ability to experience pleasure. This can affect how individuals approach and perform on tasks that are perceived as rewarding or challenging.*

3. ***Emotional Regulation****: Dopamine also plays a role in regulating mood and emotions. Imbalances in dopamine levels can lead to mood disorders such as depression or anxiety, which can negatively impact test performance.*
4. ***Attention and Focus****: Dopamine is essential for maintaining attention and focus. Conditions like ADHD are associated with dopamine dysregulation, which can lead to difficulties in sustaining attention and thus affect performance on related psychometric tests.*
5. ***Learning and Adaptability****: Dopamine is involved in learning processes, particularly in adapting to new information and experiences. It helps reinforce learning by providing a sense of reward when new skills or knowledge are acquired.*

Understanding the role of dopamine can provide insights into individual differences in test performance and help develop strategies to optimise cognitive and emotional functioning."

Sources: "Dopamine and Cognitive Function," National Institute of Mental Health: "The Role of Dopamine in Motivation and Reward," Harvard Medical School: "Dopamine and Emotional Regulation," American Psychological Association: "Attention Deficit Hyperactivity Disorder and Dopamine," Mayo Clinic: "Dopamine and Learning," Journal of Neuroscience.

It states in small print at the end of the response, "AI-generated content may be incorrect". A comprehensive review of the literature validates the AI response.

In reviewing the uses of the CNSVS and potential enhancement effects of MPH on neuroactive substances, the psychometric tests were included in this PhD study.

2.8 Impact of Methylphenidate on Postural Balance

In recent years the Biodex Balance System™ (Biodex Medical Systems, Shirley, New York) has become a tool for researchers to evaluate postural stability (*Balance System™ SD - Balance - Physical Medicine*, 2024). This versatile system offers objective measurements and records an individual's ability to maintain balance at a specific joint when subjected to dynamic stress.

The assessment administers four tests using a Modified Clinical Test of Sensory Interaction on Balance (mCTSIB) (*Balance System™ SD - Balance - Physical Medicine*, 2024). This tests visual, vestibular and somatosensory feedback systems under four sensory conditions. These are:

Eyes Open

Firm Surface Provides a baseline. The information is available from all three sensory inputs: Somatosensory, visual and vestibular.

Eyes Closed

Firm Surface Visual not available: somatosensory and vestibular are available. If the participant performs poorly, the vestibular or somatosensory may be compromised, with an increase in visual dependency.

Eyes Open

Unstable (Foam) Surface: Somatosensory compromised; visual and vestibular are available. If the participant performed poorly, visual or vestibular may be compromised, with an increase in somatosensory dependency.

Eyes Closed

Unstable (Foam) Surface: Visual not available; somatosensory compromised, only vestibular available. As an example, concussed athletes are most likely to present problems in this condition. If performance is reduced beyond normal or baseline readings, the vestibular system may be disrupted.

The effects of psychostimulant medications, such as MPH on postural balance remain a topic of conflicting evidence. In children with ADHD, balance disturbances are commonly observed (Amini et al., 2018). Some studies suggest that MPH improves balance in children with ADHD (Bucci et al., 2016; Jacobi-Polishook et al., 2009; Sarafpour et al., 2018), while others report no significant effects (Alotaibi et al., 2023). Most research in this area lacks robust randomised controlled trials (RCTs), and existing RCTs primarily examine only the immediate effects of MPH in children. The impact of MPH on postural balance in adults with ADHD remains poorly understood (Alotaibi et al., 2023).

Individuals with ADHD are at an increased risk of falls and injuries, which may be linked to balance issues associated with ankle plantarflexor spasticity (Jansen et al, 2019). While stimulant medications have been shown to improve plantarflexor spasticity and postural control in children with ADHD, their effects on adults are less clear. A study investigating the effects of stimulants on static balance and muscle tone in adults with ADHD found that participants exhibited better static balance and motor performance while on medication compared to off medication (Alotaibi M, 2022). Jansen et al. (2019) concluded that the primary postural issue in adults with ADHD is a disruption in stable, long-term sensorimotor behaviour, which aligns closely with the impulsivity and hyperactivity characteristics of ADHD (Jansen et al., 2019).

In geriatric populations without ADHD, studies have demonstrated that MPH can improve gait and executive function in healthy older adults (Shorer et al., 2013; Stapleton, 2018). In Parkinson's disease (PD), which is characterised by motor symptoms such as tremor, bradykinesia, rigidity, and postural instability, as well as non-motor symptoms like depression, cognitive impairment, and fatigue, treatment primarily focuses on restoring DA levels. However, standard treatments do not address the presynaptic DA transporter, a key regulator of DA availability. Methylphenidate, which blocks both presynaptic DA and norepinephrine transporters, has shown potential in treating severe gait disorders and non-motor symptoms in advanced PD (Devos et al., 2013). Conversely, Espay et al. (2011) reported that MPH did not improve gait and, in some cases, worsened motor function, sleepiness, and quality of life in PD patients (Espay et al., 2011).

Research on the effects of MPH on postural balance in healthy younger adults is limited, with most studies focusing on older populations or individuals with specific medical conditions. Further investigation is needed to clarify the impact of MPH on balance in this demographic.

2.9 Muscle Strength Tests (handgrip strength) - Effects of Methylphenidate

The combined findings of a systematic review and meta-analysis indicate that handgrip strength assessment is a reliable and accurate method for evaluating both

healthy individuals and diverse clinical populations (Bobos et al., 2020). It is also a valid prognostic indicator for general health, early mortality (all-cause and cardiovascular) (Soysal et al., 2021). This method is quick, simple to administer, highly reproducible, and yields easily recordable results. Handgrip strength testing is commonly used to establish baseline performance measures and track changes over time (Innes, 1999).

A study by King et al. (2017) investigated the effects of MPH on force output and brain connectivity during a fatiguing handgrip task. Methylphenidate is known to enhance force output, and the study explored the underlying neural mechanisms using functional MRI (King et al, 2017). The results demonstrated that MPH increases grip force and alters brain connectivity, particularly between the insular cortex, hand motor cortex, and orbital frontal cortex. These findings support the hypothesis that the central nervous system regulates motor drive to maintain homeostasis during fatigue (King et al., 2017).

In a separate study, Meckel et al. (2011) examined the impact of MPH on upper body strength in children with ADHD, using the number of completed pull-ups as a measure of strength. The findings revealed that MPH treatment did not significantly improve pull-up performance compared to non-medicated controls, suggesting that MPH may not enhance upper body strength in this population (Meckel et al., 2011).

2.10. Physical Activity Effects of MPH

King and colleagues (2018) further explored how individual characteristics, such as habitual physical activity levels and age, influence the performance-enhancing effects of MPH. Their findings suggest that individuals with lower levels of physical activity and younger age exhibit a more pronounced ergogenic response to MPH, potentially due to differences in dopaminergic function (King et al., 2018).

A systematic review by Hirschbeck et al. (2022) examined the effects of psychiatric medications, including stimulants, on physical performance. The review identified 36 studies analysing various psychotropic drugs, such as antidepressants, antipsychotics, sedatives, and stimulants. Most studies were randomised controlled trials with small sample sizes and single-dose designs. The findings indicate that stimulants, including MPH, can enhance physical performance. However, due to

methodological limitations, drawing definitive conclusions remains challenging (Hirschbeck et al., 2022).

2.11. Cardiac electrical activity

The use of pharmacological treatments for ADHD has risen significantly in recent years (Danielson et al., 2018). While these medications are generally effective, safe, and well-tolerated, concerns remain about rare but serious cardiovascular adverse events, including sudden cardiac death, in children, adolescents, and adults. Martinez-Raga et al. (2013) critically reviewed the evidence on the potential link between ADHD medications and serious cardiovascular risks, such as corrected QT interval (QTc) prolongation and sudden cardiac death. There is some evidence suggesting an increased risk of cardiovascular events associated with the use of stimulant medications. Theoretically, stimulants may elevate cardiovascular risks by increasing blood pressure, heart rate, and inflammation, as well as prolonging the cardiac QT interval (Westover & Halm, 2012). In response to these concerns, pharmaceutical companies and the U.S. Food and Drug Administration (FDA) (2018) have issued warnings about potential cardiovascular risks, leading to the withdrawal of some stimulant medications due to safety concerns (Aggarwal et al, 2015). While the evidence is not definitive, stimulant use in adults may be associated with increased cardiovascular risks. Given the inconsistent findings from population-based safety studies, Zito and Burcu (2017) emphasise the importance of conducting baseline and continuous cardiac monitoring for individuals using stimulants.

Numerous arrhythmias have been reported with non-methylphenidate stimulants such as cocaine, which affect the DA transporter (Dominic et al., 2022). These negative effects may manifest in the short term, and over the long term stimulants like MPH may increase cardiovascular risks as cardiovascular disease prevalence rises with age (Groff et al., 2025). Topriceanu et al. (2022) suggest that MPH is arrhythmogenic due to its direct and indirect sympathomimetic effects, although this remains a theoretical claim without empirical evidence.

A review of MPH cardiovascular risks utilising a comprehensive search of databases (PubMed, EMBASE, PsychINFO) identified relevant studies up to July 2012, including

clinical reports and population-based studies (Martinez-Raga et al., 2013). The review concluded that stimulant medications, including MPH, are generally safe, with minor, transient, and clinically insignificant increases in blood pressure and heart rate across age groups. There is no evidence linking ADHD medications in adults to sudden cardiac death, serious cardiovascular events, or torsades de pointes at therapeutic doses (Fay & Alpert, 2019; Habel et al., 2011; Martinez-Raga et al., 2013; Zhang et al., 2010) nor to QTc prolongation (Rodgers, 2022).

A study by Schelleman et al. (2012) investigated whether MPH use in children and adults for ADHD increases the risk of serious cardiovascular events compared to non-use. Researchers analysed Medicaid and commercial insurance data, comparing new MPH users to matched non-users. While the study found a 1.8-fold increased risk of sudden death or ventricular arrhythmia in MPH users, they noted an inverse relationship between dosage and risk, and the lack of a clear dose-response relationship suggests that this association may not be causal. The risk of stroke and myocardial infarction was not statistically different between the two groups.

In another systematic review, Westover and Halm (2012) found no increased risk of myocardial infarction, stroke, or sudden cardiac death in stimulant users. However, one study reported a higher risk of transient ischaemic attacks in stimulant users, and another noted an increased risk of sudden death or ventricular arrhythmia with MPH use but no elevated risk for stroke or myocardial infarction (Westover & Halm, 2012). In older individuals (>66 years), there is a 40% increased risk of cardiac events (defined as myocardial infarction, stroke, transient ischaemic attack, or ventricular arrhythmia) within 30 days of stimulant initiation, but this attenuates over time (Tadrous et al., 2021).

In an *in vivo* and *in vitro* study using various very high doses, Wakamatsu et al. (2009) suggested that MPH is unlikely to influence ventricular repolarisation at therapeutically recommended doses in individuals with ADHD. Awudu and Besag (2014) reported that while small heart rate and blood pressure increases have been observed with MPH, most studies report no statistically significant findings and face methodological limitations. They concluded that large studies have not shown a clear link between MPH treatment and sudden death in children with ADHD.

Short-term MPH treatment for ADHD in children caused no abnormal blood pressure or QT interval changes based on age, height, and gender. While blood pressure and QTc interval increased, these remained within normal ranges, and no significant changes were found in echocardiographic parameters or QT interval (Omidi et al., 2021). Even an overdose of MPH is unlikely to significantly affect the QRS or QT intervals (Hill et al., 2010).

In a study investigating the acute effects of MPH on ECG parameters in children with ADHD, no significant changes were observed in QTc or T-peak to T-end (TpTe) values after MPH administration. However, a slight increase in the TpTe/QTc ratio was noted. The findings suggest that MPH has minimal impact on ECG parameters, with TpTe/QTc ratios potentially serving as an additional evaluation metric in borderline cases (Lamberti et al., 2015). In a double-blind crossover study of hyperactive children, MPH did not cause any ECG changes (Aman & Werry, 1975).

In an editorial in the British Medical Journal, Jackson (2016) examined the cardiovascular risks associated with MPH, highlighting mixed findings from different studies. The author concluded that while MPH poses a measurable triggering risk for acute cardiovascular events in vulnerable subgroups, its overall safety profile in the general ADHD population appears favourable, provided clinicians adhere to screening and monitoring protocols. A self-controlled case series analysis conducted in South Korea using national health insurance data to investigate the acute cardiovascular risks associated with methylphenidate initiation in children and adolescents with ADHD concluded there was an increased risk of arrhythmias, particularly within the first few days of use and in children with congenital heart disease (Shin et al., 2016). In contrast, U.S.-based cohort studies found no significant difference in cardiovascular event rates between children using MPH and non-users. The variation in results may stem from the studies addressing different aspects, with case-only studies focusing on short-term triggers and cohort studies assessing long-term cumulative risks. The overall risk of severe cardiovascular events is low in both types of studies.

The haemodynamic effects of acute MPH administration were evaluated by Kelly et al. (2005). They emphasised the need, based on clinical acumen, to carefully monitor blood pressure, heart rate, and overall cardiovascular responses, particularly in patients with pre-existing cardiovascular risks.

In a letter to the editor, Aggarwal et al. (2015) state that while stimulant medications for ADHD can cause minor cardiovascular changes, there is no strong evidence linking them to an increased risk of sudden cardiac death. They conclude that routine ECG screening is not recommended, but careful patient evaluation and monitoring are essential to ensure the safe use of these medications (Aggarwal et al., 2015).

In a recent retrospective, population-based cohort analysis (>26 000 patients) by Garcia-Argibay et al. (2024) the potential cardiovascular risks associated with short-term MPH use in individuals aged 12–60 years was evaluated. Using data from a Swedish national registry, they compared rates of ischaemic heart disease, venous thromboembolism, heart failure, or tachyarrhythmias one year before and six months after MPH treatment initiation. The study found a small increased risk of cardiovascular events in individuals taking MPH (1.51 per 10,000 person-weeks) compared to matched controls (0.77 per 10,000 person-weeks). However, the risk was not significantly influenced by preexisting cardiovascular conditions.

The literature underscores MPH as a potent CNS stimulant with well-documented effects on DA and norepinephrine neurotransmission, primarily used for ADHD and narcolepsy (Faraone, 2018; Volkow et al., 2002). However, its off-label use—particularly among healthy adults for cognitive enhancement, athletic performance, or recreational purposes—remains understudied, with conflicting evidence on its physiological and cognitive impacts (Berezanskaya et al., 2022; Monteiro et al., 2017). Critically, gaps persist in understanding MPH's acute and chronic effects on cardiovascular function, neuromuscular performance, and neurocognition in healthy populations, necessitating rigorous investigation.

Key findings from the literature:

1) Cardiovascular Effects:
    a. Methylphenidate is associated with transient increases in heart rate and blood pressure, particularly during initial use (Liang et al., 2018; Mick et al., 2013).
    b. Case-only studies report elevated arrhythmia risk in vulnerable subgroups (e.g., congenital heart disease) (Shin et al., 2016), while cohort studies show no cumulative cardiovascular risk in general populations (Martinez-Raga et al., 2013).

2) Cognitive function:
    a. Methylphenidate enhances executive function (e.g., attention, working memory) in ADHD patients (Blair, 2017), but its efficacy in healthy adults is debated (Batistela et al., 2016). Dopaminergic modulation may improve task-specific focus but not necessarily memory or learning (Kortekaas-Rijlaarsdam et al., 2019).
3) Muscle Strength and Physical Performance:
    a. Methylphenidate may enhance motor drive via CNS-mediated mechanisms (King et al., 2017) but does not uniformly improve strength or endurance (Meckel et al., 2011). Handgrip dynamometry is a robust prognostic marker for overall health and neuromuscular function (Bobos et al., 2020; Soysal et al., 2021).
4) Postural Balance:
    a. Conflicting evidence exists on MPH's impact on balance, with improvements noted in ADHD populations (Bucci et al., 2016) but limited data for healthy adults.
5) Safety and Risk Stratification:
    a. ACSM pre-participation screening (PAR-Q+, risk stratification) mitigates risks for vulnerable participants (Miller, 2023).

In light of prevailing knowledge and opinion, and in keeping with this study's objectives, the study set out to determine the effects of MPH on the topics covered in the literature review. To evaluate the participants' current physical activity level, the Physical Activity/Exercise Stages of Change questionnaire was administered (Addendum B). For health risk screening and risk stratification, the ACSM Risk Stratification Screening Questionnaire was employed (Addendum A). This study integrates multidimensional assessments—cardiovascular (ECG, CPET), neurocognitive (CNSVS), neuromuscular (handgrip, balance), and metabolic (energy expenditure)—to address critical gaps. There is clinical relevance in that despite widespread off-label use, no study has comprehensively evaluated MPH's effects on physical and cognitive performance in healthy adults. Validated tools (e.g., CPET, Biodex) and controlled dosing (20 mg MPH LA) align with translational research standards. Findings will

inform guidelines for MPH use in non-clinical contexts (e.g., sports, academia) and highlight potential risks (e.g., cardiovascular strain).

Various assessment tools were used to measure outcomes and electrocardiography tracings were used to assess cardiac electrical changes. This approach aligns with the ethical principles of research as outlined by the University of the Witwatersrand and the Helsinki Declaration ("World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects.," 2001).

This study's design is grounded in a critical synthesis of existing literature, targeting understudied yet high-impact domains. The measurements chosen are empirically justified, ethically sound, and poised to yield actionable insights into MPH's off-label applications.

3. CHAPTER 3 - METHODS

3.1 RESEARCH DESIGN

This was a prospective, descriptive, interventional, randomised, double-blind cross-over, placebo-controlled study of the effect of Methylphenidate in drug-naïve healthy adults.

Due to the nature of the cross-over design, the participants were their own controls.

3.2 STUDY POPULATION

The study population was comprised of participants based in the greater Johannesburg, Ekurhuleni and Tshwane (Pretoria) metropolitan areas in Gauteng Province, South Africa. The study site was selected to ensure the study was conducted in a controlled lab setting to minimise environmental variability. It also ensured that the laboratory that prepared the standardised capsule formulation was accessible and under adequate quality control. The participants were all consenting healthy adults who were drug-naïve for MPH. The methodologically robust approach utilised a crossover randomised study design, making it highly appropriate for investigating current trends in MPH use among young adults.

In 2004, prescription and dispensed medication records from the suburban Johannesburg area indicated that over 13,000 patients were receiving stimulant medication for ADHD. However, these figures did not confirm ADHD diagnoses, as they were not reliant on ICD-10 coding (Truter, 2009). There are no recent data, but it would be reasonable to expect that the figures have increased over time.

3.2.1 Participant recruitment

Due to the nature of the study, purposive sampling was considered appropriate for selection of individuals. Further, snowball sampling was implemented to reach a larger and more specific population, as current participants can help recruit others who meet the criteria.

Purposive Sampling

Purposive sampling, also known as judgmental or selective sampling, is a non-random method where researchers choose participants based on specific characteristics needed for the study (Wang & Luo, 2015). The types of purposive sampling was initially used were to target individuals with ADHD, and included homogeneous sampling (focusing on this patient group), typical case sampling (targeting typical cases), and critical case sampling (targeting cases crucial for the research question).

Snowball Sampling

Snowball sampling, also known as chain-referral sampling, is useful for studying hard-to-reach or hidden populations (Parker et al., 2019). In this method, current participants recruit future participants from their acquaintances, continuing until the desired sample size is achieved.

In an initial effort to recruit participants, direct approaches were made to 49 psychiatric, paediatric, general practice and psychology practices that treat ADHD. These were identified through personal communications, online searches which included practice websites, the Health Professions Council of South Africa (HPCSA) i-register, hospital websites, and the Attention Deficit Hyperactivity Disorder Support Group of South Africa (ADHASA). The plan was for information brochures (addendum A) and posters (Addendum B) to be emailed (as electronic media) or printed hard copies to be delivered to interested practitioners and/or participants.

Despite an intensive recruitment process over ±11 months, and notwithstanding interest shown by the approached healthcare professionals, following the onset of the COVID-19 pandemic and its restrictive national and international regulations, no participants were actually recruited.

An alternate approach was taken, and potential participants were targeted through social media (Facebook, Instagram), email databases of known healthcare professionals, posters at the University of Witwatersrand (Wits), university newsletters, and emails sent to the Wits student body. The latter followed a detailed process of permission from various offices and registrars, eventuating in a single email release to 40, 093 students**.** This prolonged the recruitment process by 10 months, attracting drug-naïve healthy individuals. The study design was then adjusted to include only this group, without a cohort of ADHD-diagnosed and treated individuals.

The cross-over, double-blind methodology was therefore used in these healthy individuals to address the above aims and objectives of the study.

3.2.2 Sample size

To calculate the sample size for studying the effect of MPH on muscle strength, the parameters of expected effect size, desired power of the study, and significance level (alpha) were considered. For muscle strength studies, a moderate effect size (*d* = 0.5) is often used if no prior data is available. For the probability of detecting an effect if there is one, a power of 0.8 (80%) was used. The significance level (α) to avoid the probability of a Type I error (false positive or rejecting a true null hypothesis.) was set at 0.05.

Beta (β) represents the probability of making a Type II error in hypothesis testing or failing to reject a false null hypothesis. This is the risk of concluding that there is no effect or difference when there is in fact an effect.

Using a sample size formula, for a two-sample t-test (comparing MPH group vs. placebo group), the sample size was calculated using the following formula:

$$n = \left(\frac{(Z_{\alpha/2} + Z_{\beta}) \cdot \sigma}{\Delta} \right)^2$$

Where:

- (Z_{\alpha/2}) is the critical value of the normal distribution at α/2 (e.g., 1.96 for α = 0.05).
- (Z_{\beta}) is the critical value of the normal distribution at β (e.g., 0.84 for β = 0.2).
- (\sigma) is the standard deviation of the outcome measure.
- (\Delta) is the expected difference in means between the two groups.

Using this formula, the calculated sample size was 62.72 (63) participants to detect a moderate effect size with 80% power at a 0.05 significance level. To adjust for

dropouts, using a 10% dropout rate, an increase of sample size of 10% was adjusted to approximately 70.

A similar sample size of 64 was determined using G*Power, an online software programme (Faul et al., 2007). For a cross-over study in which participants act as their own controls, this required sample size would equate to 32-35 participants. However, there is reduced within-subject variation as a result of repeated measures, and therefore a slightly lower sample size can be used.

The final sample size using the cross over study was 30, where saturation of recruitment was achieved. Final complete data sets were available in 28 participants. Other studies assessing strength and exercise performance have used fewer (approximately half) the number of participants (Meckel et al., 2011; Wilkison et al., 1995).

3.2.3 Inclusion and Exclusion Criteria

Healthy adult individuals, using the below criteria:

Inclusion criteria

- Healthy individuals who after being informed of the study were willing to participate
- Ages between 14- 50 years
- Participants willing to accept that both active MPH and placebo/inactive formulation would be administered for 4 weeks
- Participants willing to undergo a series of non-invasive investigations and assessments

Exclusion criteria

- The use of any other medication that could affect physical or cognitive performance, electrocardiogram tracings or balance
- Any physical or other affliction that could affect the successful completion of the physical performance tests

Following the above-mentioned extensive period of purposive and snowballing sampling, saturation was reached when no more participants were recruited for a period of two months.

3.3.3. Study location

The study was carried out at the University of the Witwatersrand Department of Exercise Science and Sports Medicine's Exercise Laboratory, Wits Education Campus, Parktown, Johannesburg

3.3.4 Study Design

This study utilised a randomised, double-blind, placebo-controlled cross-over design. The study involved drug-naïve healthy adults who were randomly assigned to either the Methylphenidate (MPH) group or the placebo group after the baseline tests (Figure 3.1).

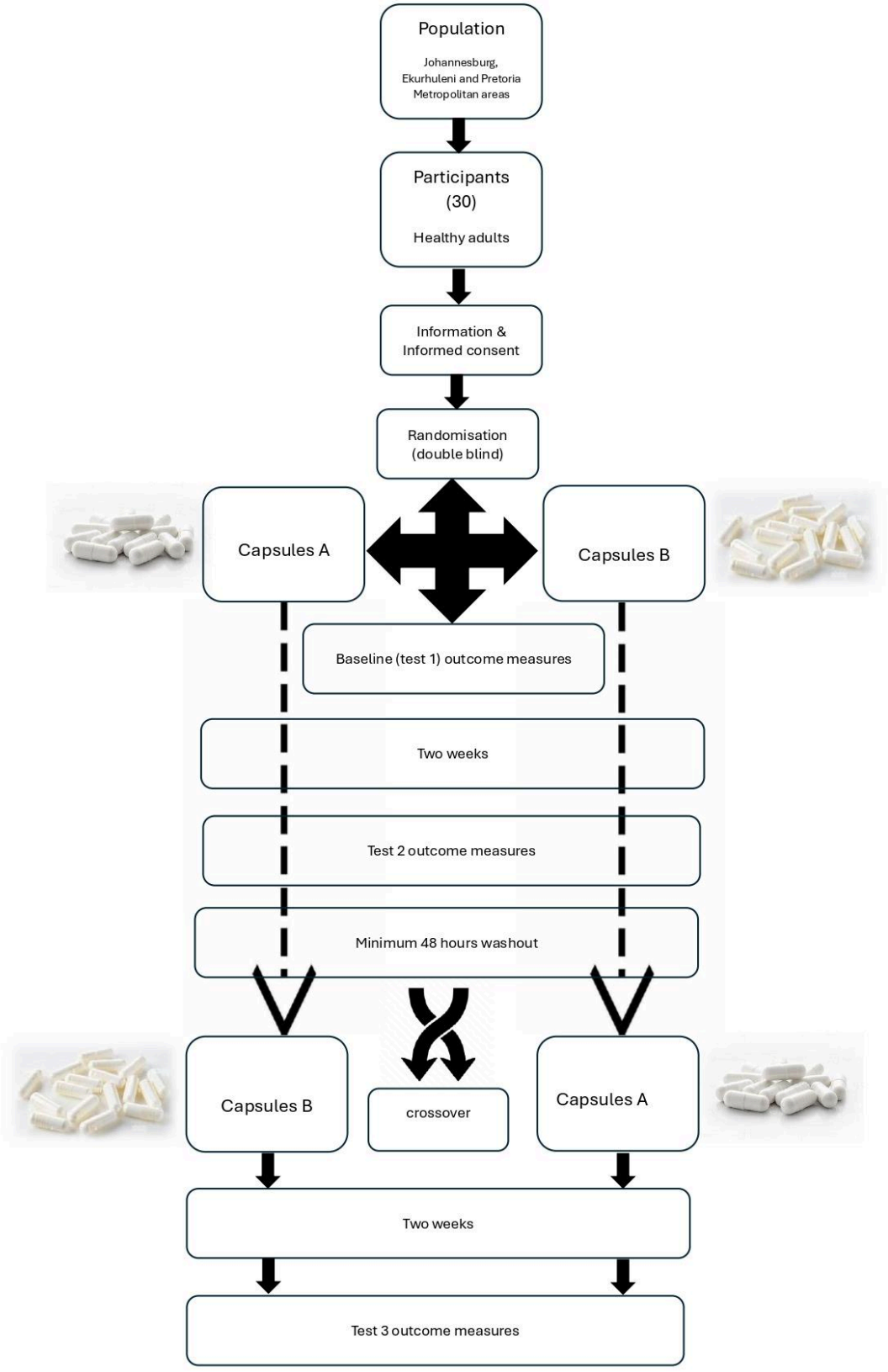


Figure 3.1: Study flow

3.4 Study Registration

The study was registered with the Pan African Clinical Trials Registry (PACTR) (Trial #: PACTR202011697726048) (*Pan African Clinical Trials Registry (PACTR)*, 2022)> The PACTR is a WHO International Clinical Trials Registry Platform primary register, catering for clinical trials conducted in Africa.

3.5 Participation procedure

After the potential participants were provided with information about the study (Addendum C) and had any questions answered, they had the free choice to participate or not. If they agreed to be included, they were required to sign an informed consent document after any queries were answered (Addendum D). Participants were reimbursed for their time and travel for each visit.

They were then allocated a file, on which a 4-numbered random code was written. The first code was randomly generated e.g. 4321 via a computer random number generator, and thereafter numbers were used sequentially e.g. 4322, 4323 as they enrolled in the study.

3.6 Randomisation and substance crossover

After signing informed consent, participants were randomly allocated to one of two groups: either allocated to start with taking capsule A or capsule B. In order to avoid bias, the randomisation process used was a simple random sampling approach with no deciphering possible, and with each participant having an equal chance of being assigned to either group. By combining randomisation, counterbalancing, washout periods, blinding, and statistical controls, sequence effects were minimised, improving the internal validity of the study.

3.7 Randomisation process

3.7.4 Preparation of the letters

Thirty pieces of paper had either A or B written on them and folded into equal sized squares.

3.7.5 Mixing the Numbers

All the labelled slips were placed into a cardboard box container. The box was shaken to ensure the slips of paper were thoroughly mixed.

3.7.6 Random Selection

Each participant inserted their hand into the box, was free to further mix the slips and then select one without looking. The researcher was present when this occurred and, on most occasions, so was a research assistant. Only one piece of paper was selected. The capsule letter (A or B) written on the selected slip was recorded on a separate coded sheet that had been coded with the participant's code. A different coded sheet (kept separately) had the participants code and name for later deciphering. This was kept away from the study file throughout the study and would only be accessed under exceptional circumstances such as severe side effects, or to decode at the conclusion of the study.

Figure 1 has the study design, illustrating flow from recruitment of participants, randomisation, outcome measures at baseline, capsules, outcome measure testing then washout and crossover with final testing.

3.8 Study procedure

After participants had signed informed consent, had files created, they underwent the baseline test battery.

The Department of Pharmacy and Pharmacology assisted in the study by creating similar looking capsules which contained either placebo (sucrose) or active ingredient (Methylphenidate) (Figures 3.2-3.5). The MPH source was Ritalin™ LA 20mg capsules, purchased from a pharmaceutical wholesaler after completing the required forms and providing legal prescription for the schedule medication. These were given to the Department of Pharmacy and Pharmacology which was also provided with empty opaque capsules. The Department provided the placebo sucrose and assisted in decanting the Ritalin and re-encapsulating into unmarked empty capsules. The same procedure was followed with the sucrose, so providing two batches of capsules labelled either A or B. These were dispensed via pharmacy packaging, and marked either as A or B. The Head of Department assigned two highly qualified technicians—

one holding a doctorate degree and the other a doctoral candidate—to process the capsules. To ensure accuracy and reliability, they conducted mutual quality control checks throughout the procedure. The Department was the custodian of the coding, which was only revealed when data analysis was undertaken (Addendum E), thus maintaining the double-blind chain until completion of the data collection.

Figure 3.2: Capsules A provided by Department of Pharmacy and Pharmacology, University of the Witwatersrand

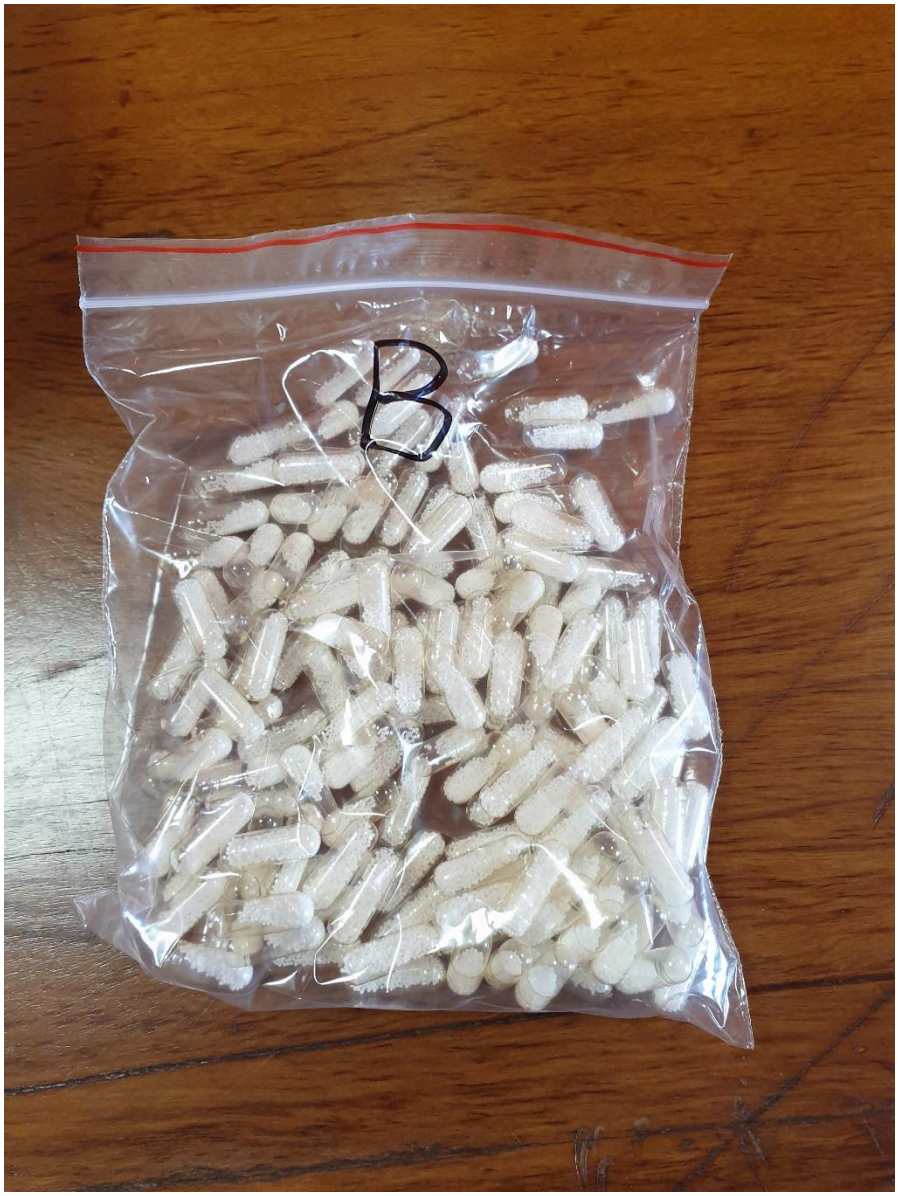


Figure 3.3: Capsules B provided by Department of Pharmacy and Pharmacology, University of the Witwatersrand

Figure 3.4: Mechanism for dispensing

Figure 3.5: Packaging for dispensing of capsules

At the end of the baseline tests, the participants were provided with the capsules they had randomly selected, either A or B. They were instructed to take one capsule daily at a similar time before noon for a period of 14 uninterrupted days. A second visit was scheduled for the second test battery to coincide with the day taking the last of the capsules.

If there were any delays for the second test (or subsequent third), additional capsules of the same ingredient were proved to allow uninterrupted supply before the next test. This occurred with 3 participants with maximum 4 days additional capsules required.

Using pharmacodynamic information, half-life data and clinical trials data, it was deemed that taking the capsules for 2 weeks was adequate for clinical responses.

The start and end dates of the study were different for each individual participant as their entry into the programme varied. However, all followed the duration of 2 weeks taking the first capsule, followed by a washout of 2 days and then taking the alternate capsule for two weeks.

All tests were repeated at a similar time of day to avoid any diurnal physiological variations. The process was sequentially followed, starting with resting heart rate, blood pressure and anthropometry. The computer psychometric test was then done, followed by the balance test. The last test was the cardiopulmonary exercise test with electrocardiography.

During the study period, the participants were advised to continue their usual exercise/ physical activities and dietary habits, with no guidance or interference.

3.9 Outcome Measurements / Measuring Tools

All outcome measures were performed at baseline and repeated following the taking of the respective capsules (test 2 and test 3) except for the Physical Activity Readiness Questionnaire (PAR-Q) and ACSM Risk Stratification Screening Questionnaire which were completed once only at the baseline assessment stage. Data were manually recorded on a data recording sheet and filed in the participant's file. All data were electronically captured by the researcher, with some assistance from a research intern. The latter was quality-checked by the researcher.

3.9.1 Questionnaires

Several questionnaires were completed by the participants to assess habitual physical activity levels and risk with exercise. These included:

3.9.1.1 Physical Activity Readiness Questionnaire (PAR-Q) (Addendum F)(*The New PAR-Q+ and ePARmed-X+*, 2016)

The PAR-Q is considered the international standard for pre-participation exercise screening. In this context it was utilised as a health screen before the maximal

cardiopulmonary exercise testing to ensure its safety. It was completed once at the beginning of the study and before taking active/placebo capsule.

3.9.1.2 Physical Activity/Exercises Stages of Change (PARMed) (Addendum G)(*The Maximal Ramp Test*, 2023)

This questionnaire was used with the new PAR-Q to also assess exercise risk and provide clearance for participation. It also establishes current physical activity levels. For the latter it was used initially and at the two testing points after placebo/ active capsule to determine if there were any changes in the participant's physical activity levels that would potentially confound the test results. It also allowed to inquire and record any reported side or adverse effects.

3.9.1.3 ACSM Risk Stratification Screening Questionnaire (Addendum H)

This was completed initially to delve deeper into any health risks identified, and to stratify them.

3.9.2 Anthropometry

To better characterise participants and enable a more in-depth analysis of results e.g. examining the relationship between BMI and MPH, anthropometric measurements were performed, including stature (body height), weight, body mass index (BMI), waist circumference, hip circumference and waist/hip ratios.

3.9.2.1 Height and Weight

Body weight was measured using a Seca Scale (Seca 787, Seca GmbH & Co. Hamburg, Germany) (Figure 3.6). The scale was checked and calibrated. Participants were asked to remove footwear and wore gym/athletic clothing, avoiding heavy clothing. Participants stood centrally on the scale, ensuring even distribution of weight. The participant's weight in kilograms (kg) was recorded to the nearest decimal place.

Height was measured using a stadiometer (Seca 213, Seca GmbH & Co, Hamburg, Germany) (Figure 3.7). The stadiometer is permanently located on a flat and stable surface. The participants stood with their back against the stadiometer, bare feet flat

with heels together against the built-in vertical surface. The participant's head was held straight in the Frankfort horizontal plane (where a line from the lower border of the eye socket to the upper border of the ear canal should be horizontal). The headpiece was lowered manually until it made firm contact with the crown of the participant's head. Height in centimetres (cm) was recorded to the nearest decimal place.

Body Mass Index (BMI) was calculated using the formula:

$$BMI = \text{weight (kg)} / \text{height(m)}^2$$

3.9.2.2 Waist and Hip ratio

A non-elastic, flexible measuring tape was used to measure the waist and hip circumferences (Figure 3.8). Participants wore minimal clothing around these areas to ensure accurate measurements. They stood upright with their feet together and arms relaxed at their sides. The narrowest part of the torso, located just above the iliac crest and below the rib cage, was identified using anatomical landmarks. The measuring tape was placed around the waist at this point, kept parallel to the floor and held snugly without compressing the skin. After a normal exhalation, measurements were recorded in centimeters (cm) to the nearest decimal.

For measuring hip circumference, the patient stayed in the same standing position. The widest part of the buttocks was identified, and the tape measure was placed around the hips at this point, keeping it parallel to the floor and snug without compressing the skin. The hip circumference was recorded in centimeters (cm) to the nearest decimal. The Waist/Hip ratio was then calculated and documented.

Figure 3.6 Seca® body weight scale

Figure 3.7 Seca® stadiometer

Figure 3.8 Inelastic flexible tape measure

3.10 Physiological parameters

The rationale for inclusion of the outcome measures which, as per the study objectives, included heart rate (HR), blood pressure (BP) and other cardiovascular indices derived from the cardiopulmonary exercise test (CPET) including oxygen uptake kinetics, and ventilatory thresholds, was that these are commonly included in studies examining performance effects and the effects of MTH due to its potential cardiovascular and physiological impacts.

The reasons for incorporating these measures are:

1. Cardiovascular Effects: MPH is a stimulant that increases sympathetic nervous system activity, potentially leading to elevated HR and BP. Monitoring these parameters helps assess acute and chronic cardiovascular risks.
2. Exercise Performance and Safety: CPET evaluates aerobic capacity, oxygen consumption (VO_2max), and ventilatory efficiency. Methylphenidate may influence exercise tolerance, endurance, and metabolic responses. Changes in HR, BP, and CPET parameters help determine whether MPH alters performance metrics, which is essential for understanding its effects on physical activity and athletic performance.

Including these measures ensures a comprehensive evaluation of MPH's impact on both cardiovascular function and exercise performance.

Therefore, the physiological measurements were resting heart rate, arterial blood pressure and selected measurements from the cardiopulmonary exercise test (CPET) battery.

Brachial blood pressure (systolic and diastolic mmHg) was measured on the left arm after 5 minutes rest using a Medinox mx™ electronic measuring cuff (Medinox, Germiston, South Africa), which is SAHPRA (South African Health Products Regulatory Authority) certified (Figure 3.9). Three readings were taken and the average recorded.

Figure 3.9 Medinox mx™ sphygmomanometer

The CPET system (Metalyzer RB-R3), Cortex, Leipzig, Germany) was used to measure gas exchange, generating the standardised Wasserman 9-panel plot. Participants wore a well-fitted facemask which monitored oxygen and carbon dioxide levels as well as gas flow. The exercise used a ramp test on a Wattbike® cycle ergometer (Woodway, Waujesha, Wisconsin, USA) (Figures 3.10-3.12). After inputting age, gender and weight, the Maximum Ramp Test (*The Maximal Ramp Test*, 2023) involved an increase in resistance by a set amount every minute until exhaustion. The incremental amount was determined by the level of fitness/physical activity of the participant, and the same parameters were used for each of the repeat tests.

Participants exercised to the point of volitional exhaustion. Medical monitoring was sustained throughout the test in case of any abnormal features on the

electrocardiogram (ECG) or symptoms that would necessitate termination of the test according to criteria of the American College of Sports Medicine (ACSM) (ACSM, 2023).

Of the measurements measured and/or calculated, Table 3.1 lists the measurements and the descriptors for each.

Table 3.1 Physiological parameters measured during CPET

Measurement	Description
Respiratory Exchange ratio (RER) at maximum test	Describes ratio of CO_2 output to O_2 uptake ($V\dot{}CO2/V\dot{}O2$) as a function of time and reflects patient effort (RER at least ≥ 1). Depends on rate of lactate increase during progressive exercise.
$V0_{2peak}$ ml/kg/min	Maximum volume of oxygen in millilitres consumed per minute per kilogram of body weight
VT ($ml.min^{-1}$) Ventilatory Threshold	Point at which VCO_2 deviated from linear relationship with $V0_2$. Indicative that oxygen-dependant energy systems are starting to contribute relatively more to energy production with slight increase in blood lactate levels above resting levels.
VO_2 ml/kg/min at ventilatory threshold	Oxygen volume consumed at VT
VT as % of VO_{2peak} (VO2 at VT / VO_{2peak})	Metric for assessing endurance capacity. Indicates intensity at which one can sustain exercise before experiencing significant increase in breathing rate due to accumulation of metabolic by-products.
$VE/VC0_2$ slope	Volume of CO_2 expelled per litre of air ventilated. Indicates ventilatory efficiency. Increase in slope indicates increased dead space ventilation in lung, pulmonary vascular disease or pulmonary limiting disease.
VO_2/work rate (ml/min/watt)	Measure of efficiency of oxygen uptake relative to work being performed and helps to assess efficiency of cardiovascular and respiratory systems during exercise. The higher the value, the better the efficiency.
Oxygen Uptake Efficiency Slope (OUES)	Parameter to assess efficiency of body's oxygen uptake during exercise. A higher value indicates more efficient oxygen uptake. Can also provide insight at submaximal exercise effort.
VO_2/VE) (ml/min 02)/L/min)	Ratio indicates how much oxygen being consumed by body for each litre of air ventilated and assesses efficiency of respiratory system. A higher VO2/VE ratio suggests efficiently using oxygen taken in indicating good respiratory and cardiovascular function.
Oxygen pulse (ml/beat)	A proxy for stroke volume and predictor for coronary artery disease and all-cause mortality

After: (*Interpreting The Cardiopulmonary Exercise Test*, 2018) (Haley et al., n.d.) (Uchida, 2018) (*Respiratory Formulas, Calculations, and Equations (2025)*, n.d.) (Crisafulli et al., 2007) (Laukkanen JA, Kurl S, Salonen JT, et al, 2006)

Figure 3.10 WattBike®

Figure 3.11 and Figure 3.12 Participants undergoing CPET on Wattbike® cycle ergometer and connected to CPET Metalyzer system

3.11 Neurocognitive function

Neurocognitive function was assessed using psychometric computer-based software CNS Vital Signs (CNSVS) (CNS Vital Signs, North Carolina, USA) (Figures 3.13 and 3.14).

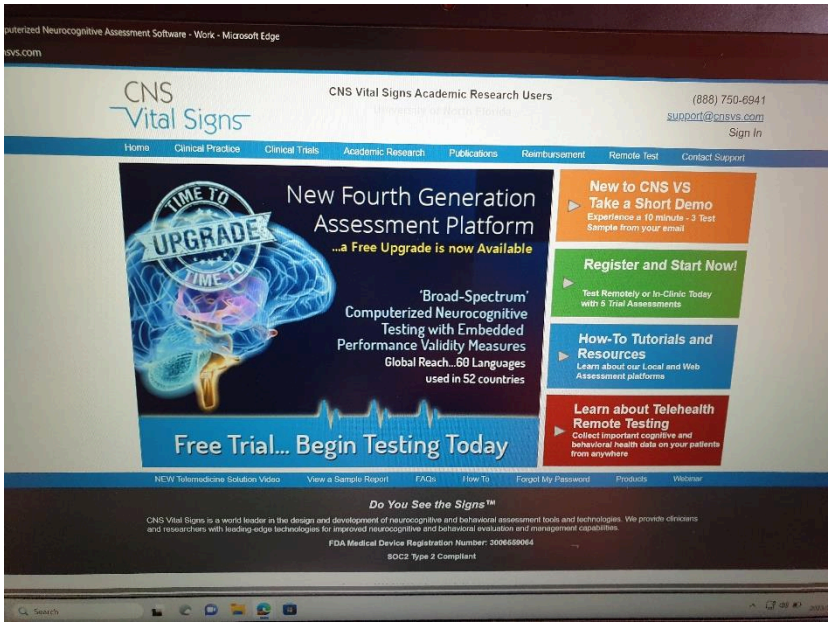


Figure 3.13: Homepage of the CNS Vital Signs website

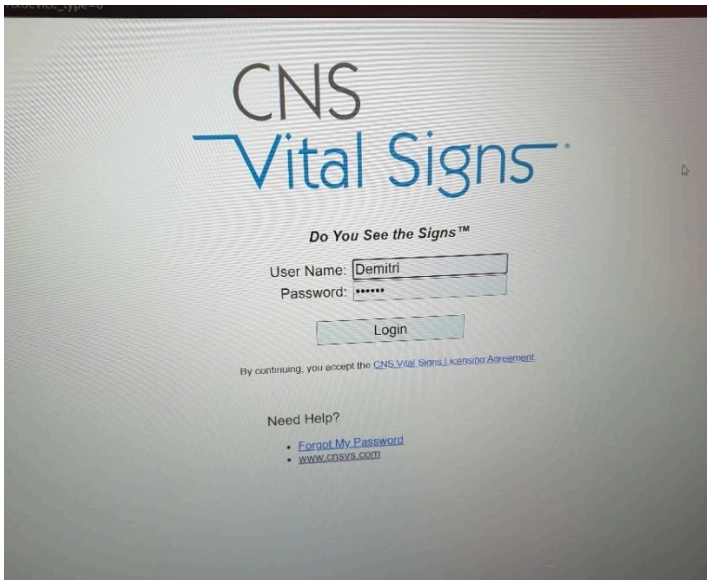


Figure 3.14: Login page for the CNS Vital Signs® test

The CNS Vital Signs ADHD software suite was used. This includes a comprehensive battery of tests completed on a computer, designed to measure various cognitive functions and behavioural symptoms usually associated with ADHD including reaction time, memory, psychomotor speed, complex attention, and processing speed. This suite of tests was included in this study as the mechanism of action of MPH as a central stimulant associated with increased dopamine levels, potentially enhances these functions. A key example of MPH use in healthy populations is university students taking it for cognitive enhancement (Finger et al., 2013). Methylphenidate has indeed been shown to have an effect in some cognitive domains in healthy volunteers (Linssen et al., 2014).

The following neurocognitive tests were assessed(Stafford, 2024) as below. Details of what the test entailed are contained in Addendum I.

- **Attention**: Continuous Performance Test (CPT) to measure sustained and selective attention.
- **Memory**: Verbal and Visual Memory Tests to evaluate short-term and long-term memory.
- **Executive Function**: Tests such as the Stroop Test to assess cognitive flexibility, inhibitory control, and problem-solving skills.
- **Processing Speed**: Symbol Digit Coding Test to measure the speed of information processing.
- **Psychomotor Speed**: Finger Tapping Test to assess motor speed and coordination.

The CNS Vital Signs software was installed and operational on a computer accessible to participants, with password access and used solely for the study. The participants used their randomly allocated code as their ID for the tests. There was input of demographic information and baseline data required for data interpretation which included age, gender and relevant medical history, but excluded specific identifiers. The test was date stamped at each of the three repeat test dates.

The tests were scheduled at optimal times to ensure participants were alert and focused, usually on the same day as the other test batteries. They were conducted

alone in a quiet closed room with no access to other people but with the researcher available in an office close-by for any assistance. Clear instructions on the testing process were provided, and participants verbally confirmed they understood the required tasks. The testing is not limited in time duration and provides examples for the participants before they voluntarily press the space bar to proceed.

Data of the tests were analysed by the CNS Vital Signs software to score the tests and generate comprehensive reports (Addendum J). These scores were used in the study results management. The CNSVS tests have demonstrated strong construct validity, as evidenced by their ability to differentiate between healthy controls and individuals with cognitive impairments (Gualtieri & Johnson, 2006). Test-retest reliability for the CNSVS domains is high, with intraclass correlation coefficients (ICCs) ranging from 0.80 to 0.95. The Standard Error of Measurement (SEM) for the Memory Composite score is X, indicating the range within which an individual's true score is likely to fall. Additionally, the Smallest Worthwhile Change (SWC) for the Processing Speed score was calculated as 0.2 × SD, resulting in a value of Y, which represents the minimal clinically important difference.

3.12 Postural Balance

Methylphenidate has been shown to positively affect postural balance in adults with ADHD (Alotaibi, 2022; Alotaibi et al., 2023) and in healthy elderly adults (Ben-Itzhak et al., 2008; Shorer et al., 2013). No studies have explored similar effects, if any, in healthy (younger) adults.

The Biodex Balance System™ (Biodex Medical Systems, Shirley, New York) (Figures 3.15-3.20) was used to measure balance. The procedure for the test started with participant height, weight and age required for system calibration.
The test was conducted without wearing shoes. A detailed explanation of the procedure was followed by baseline calibration using the coordinates of the feet placements on the standing platform. A trial was performed to familiarise the participant with the test before measurements were recorded.

The test was then sequentially performed as per the testing protocol, measuring sway with open and closed eyes on a firm and foam surface. The system’s display monitored

the participant's balance performance in real-time, which was then recorded and report generated (Figure 3.20).

The assessment administered four tests using a Modified Clinical Test of Sensory Interaction on Balance (mCTSIB). This tests visual, vestibular and somatosensory feedback systems under four sensory conditions. These are:

Eyes Open

Firm Surface Provides a baseline. The information is available from all three sensory inputs: Somatosensory, visual and vestibular

Eyes Closed

Firm Surface Visual not available: somatosensory and vestibular are available. If the participant performs poorly, the vestibular or somatosensory may be compromised, with an increase in visual dependency.

Eyes Open

Unstable (Foam) Surface: Somatosensory compromised; visual and vestibular are available. If the participant performed poorly, visual or vestibular may be compromised, with an increase in somatosensory dependency.

Eyes Closed

Unstable (Foam) Surface: Visual not available; somatosensory compromised, only vestibular available. As an example, concussed athletes are most likely to present problems in this condition. If performance is reduced beyond normal or baseline readings, the vestibular system may be disrupted.

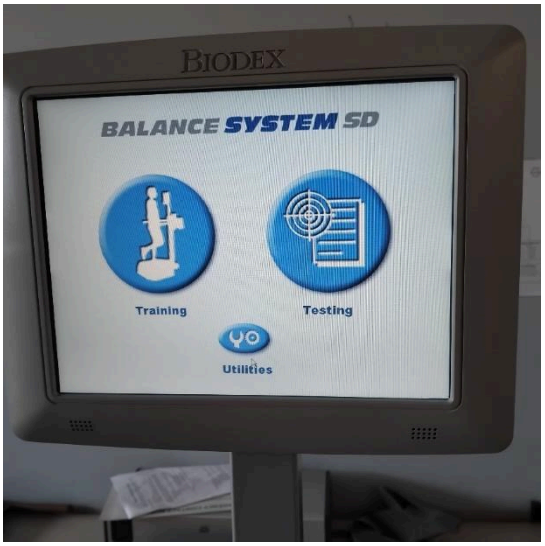


Figure 3.15 Biodex Balance System

Figure 3.16 Participant on Biodex Balance System

Figure 3.17 Biodex Balance home screen

Figure 3.18 Test selection screen

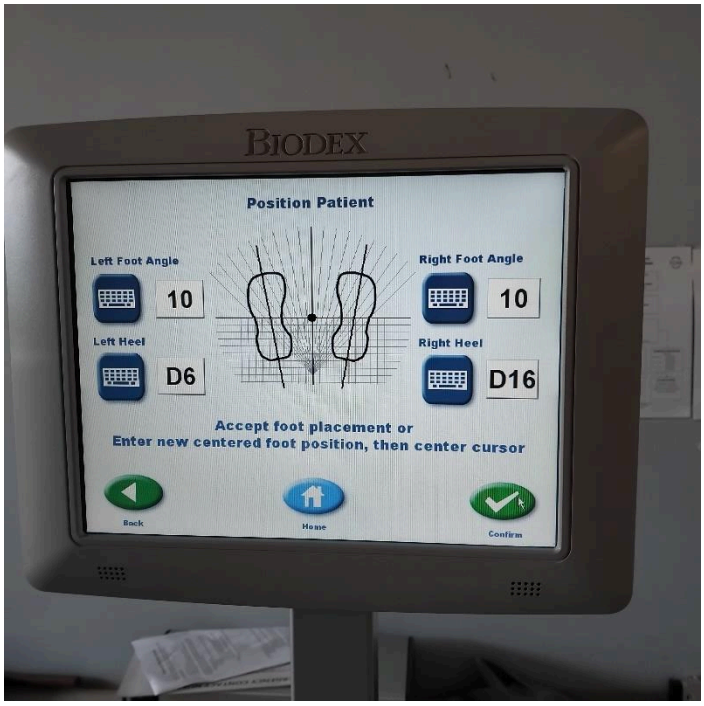


Figure 3.19 Foot position calibration screen

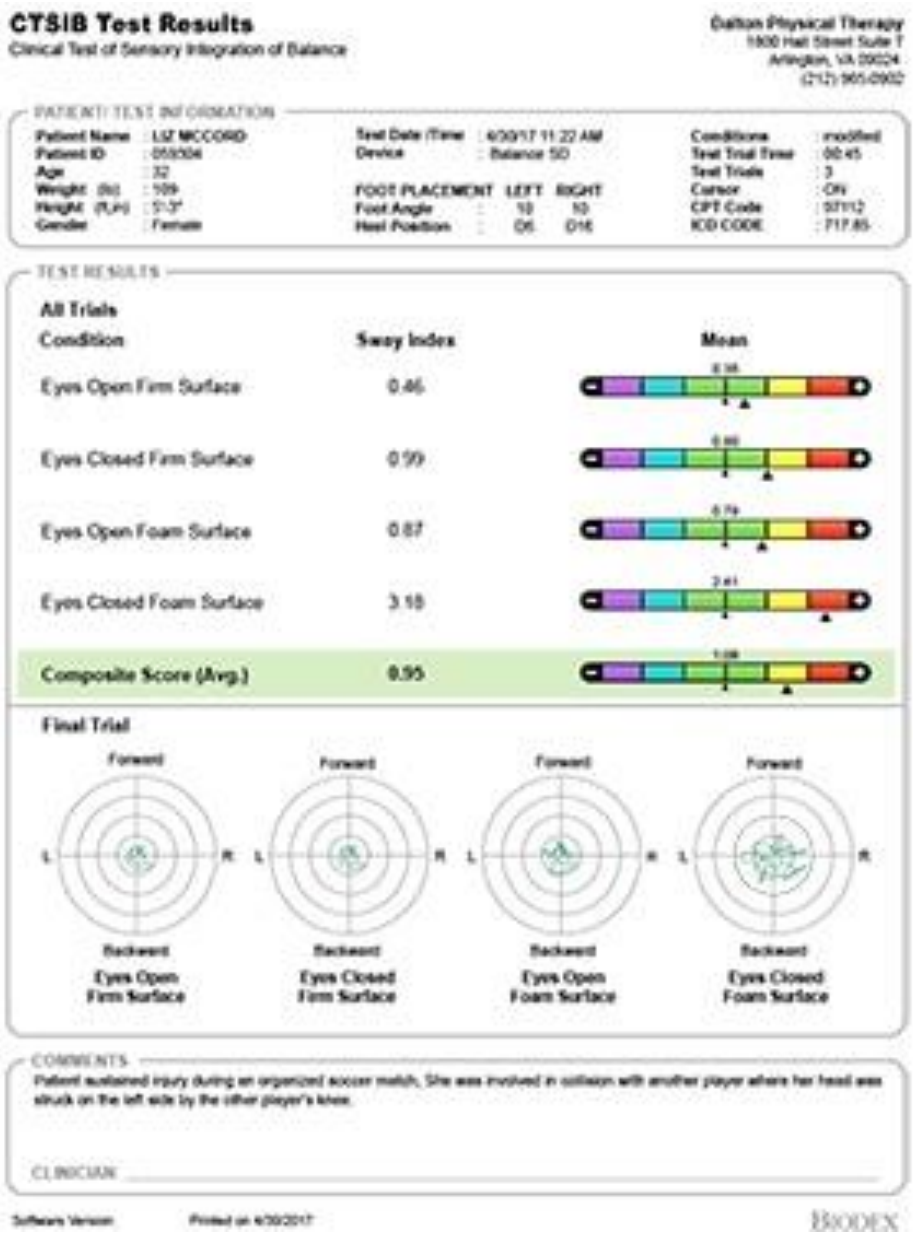


Figure 3.20 Biodex™ Balance report example

3.13 Muscle Strength

Grip strength is a useful indicator of muscular strength and endurance, with a positive correlation between handgrip strength and total muscle strength (Artero et al., 2011). There is a strong link between handgrip strength and both neuromuscular and cardiovascular aspects of physical fitness (Artero et al., 2011). This indicates that

handgrip strength may serve as a highly reliable standalone predictor of overall physical fitness.

There is ongoing debate about whether a consistent difference exists between dominant and non-dominant handgrip strength. The "10% rule" suggests that the dominant hand is about 10% stronger, but findings are inconsistent. While some studies support this rule in right-handed individuals, it does not hold for left-handed individuals, whose grip strength is often similar in both hands. Other studies report smaller or insignificant differences. Variability in study populations and external factors such as work and leisure activities further complicate conclusions. Due to this inconsistency, the 10% rule is not considered a reliable measure for assessing disability (Innes, 1999).

Considering the above, in this study the dominant hand strength was measured. Reliability and validity is ensured when using the same instrument (Innes, 1999).

Muscle strength tests were conducted using a handgrip dynamometer (Grip-D grip strength dynamometer, Takei™ Scientific Instruments Company, Japan) (Figure 3.21). España-Romero et al (2010) examined the impact of elbow position on handgrip strength in adolescents and evaluated the clinimetric properties of various dynamometers, including the Takei™. Testing with the elbow fully extended yielded the highest handgrip strength, particularly with the Takei™ dynamometer, which demonstrated superior criterion-related validity (systematic bias: 0.49 kg, $p < 0.05$) and reliability (systematic bias: 0.02 kg, $p > 0.05$) compared to others. These findings suggest that using the Takei™ dynamometer with the elbow extended is optimal for assessing maximal handgrip strength. As shown by Marion and Niebuhr (1992), activity-specific warm-ups, like submaximal grips, can significantly increase grip strength with gains of about 1 standard deviation. This clinically significant improvement highlights the importance of consistency in testing conditions when tracking progress. Measurements were standardised at each test, without warm-ups, at similar time of day, with participants standing with feet shoulder width apart. The dominant arm holding the dynamometer was held at the side with elbow slightly flexed and not touching the body. The dynamometer handle was held to fit the participant’s hand size, with the second joint of the index finger forming a right angle.

The dynamometer was zeroed before the test. The participant was instructed to exert maximal grip force on the dynamometer for a duration of 3-5 seconds, whilst breathing normally. The test was performed three times with a 30 second rest between each test to mitigate fatigue. All three measurements were recorded in kilograms and the average was calculated and recorded.

Figure 3.21 Takei™ grip-D handgrip dynamometer

3.14 Cardiac electrical activity

An electrocardiogram (ECG) was utilised to assess cardiac risk in the participants as stimulant medications may have cardiovascular effects. Methylphenidate can lead to modest increases in heart rate and blood pressure. While these changes are typically insignificant, certain individuals may have pre-existing cardiac conditions that could be exacerbated by stimulant use. An ECG can help identify underlying heart abnormalities

such as structural cardiac defects or arrhythmias, which may contraindicate stimulant therapy or necessitate closer monitoring.

Additionally, some medications have been associated with QT interval prolongation, a measure of delayed ventricular repolarisation that can increase the risk of a specific type of arrhythmia known as torsades de pointes. Although studies have found that commonly prescribed stimulants like methylphenidate do not significantly prolong the QT interval, assessing the QT interval via ECG remains a precautionary measure, especially in patients with other risk factors for QT prolongation (Zorn, 2015).

Clinical guidelines suggest that obtaining an ECG may be reasonable before initiating stimulant therapy in patients with a history of cardiac disease, significant family history of sudden cardiac death, or when clinical evaluation suggests potential cardiac issues. This approach was adopted in this study to ensure the safe use of a stimulant medication by identifying individuals who may be at increased risk for adverse cardiac events.

A 12-lead ECG Customed Cardio 300 (custo med GmbH (sic), Ottobrunn, Germany) (Figure 3.22) Bluetooth system was integrated with the Metalyzer CPET system (Figure 3.23) and used to monitor and record resting and exercise ECG during the CPET.

Post-test the ECG tracings were scrutinised for rate, rhythm and pattern parameters for normality as per accepted physiological or pathological features.

Figure 3.22 Customed ECG system

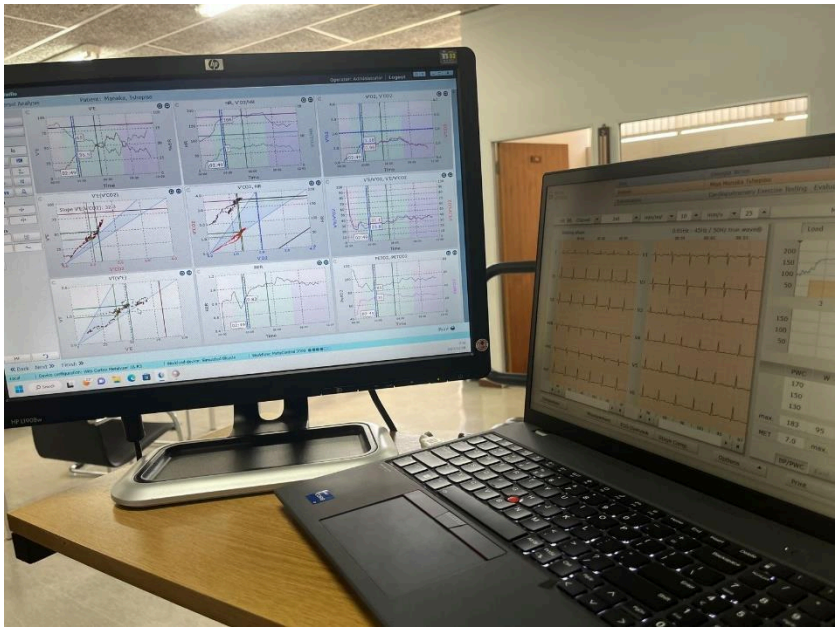


Figure 3.23 Simultaneous CPET and ECG monitoring

The ECG tracings were screened by the researcher, who has competency in reviewing these, and if any showed abnormalities, would have been reviewed by a specialist cardiologist.

4 Data analysis

Data (Appendix J) were captured on a Microsoft Excel® spreadsheet, with coding to prevent identification of individual participants. Data were analysed using the Excel XL Miner Analysis Toolpak (Excel, Microsoft Corporation. (2016) and STATISTICA V13 software package (INC StatSoft - Tulsa, USA, 2001). Statistical significance was set at $P < 0.05$.

Data are presented in the results section as follows:

a) Physiological Parameters:

Descriptive statistics: Mean and standard deviation were used to summarise the physiological data.

Inferential statistics: ANOVA was employed to compare groups. Effect sizes were calculated using Cohen's *d* to quantify the magnitude of differences between groups.

b) Neurocognitive Function:

Descriptive statistics: Measures of central tendency and variability (e.g., mean, median, standard deviation) were reported.

Inferential statistics: Repeated measures ANOVA was used to analyse differences between groups. Effect sizes were reported using Cohen's *d* to indicate the strength of the observed effects.

c) Balance:

Descriptive statistics: Balance data were summarised using means and standard deviations.

Inferential statistics: Paired t-tests and MANOVA were used to assess the effects of interventions on balance. Effect sizes were calculated using Cohen's *d* to evaluate the practical significance of the findings.

d) Physical Performance (Muscle Strength):

Descriptive statistics: Means, standard deviations, and ranges were reported for muscle strength measurements.

Inferential statistics: ANCOVA was used to evaluate the impact of placebo and MPH on muscle strength. Effect sizes were reported using Cohen's *d* to quantify the magnitude of the intervention effects.

Cohen's *d*: Used for t-tests, ANOVA, and pairwise comparisons, with values interpreted as small (0.2), medium (0.5), and large (0.8).

e) Cardiac Electrical Activity:

Descriptive narrative summarises the data in the results

5. Ethical considerations

Ethical clearance for this study was obtained from the HREC (Human Research Ethics Committee-Medical, of the University of Witwatersrand, Johannesburg, South Africa) before the start of the study (clearance number 180611, Addendum K) and further permission to extend recruitment (Addendum L). Each participant was provided with an information document, and any queries addressed before signing informed consent.

The study was conducted following standard ethical guidelines related to confidentiality, privacy and anonymity. Participants were assigned a code, and outcome measures were captured using the code and non-identifiable information. Codes were kept separate in a secure location.

Data will be stored safely in a secure environment by the researcher for a period of five years after which all information will be destroyed.

6. Budget and Funding:

A detailed budget was formulated, encompassing expected expenditures. This was partially funded by a grant from the National Lottery Distribution Trust Fund (Grant number: 19011). The balance of the budget was self-funded.

4. CHAPTER 4 - RESULTS

Data analysis involved consolidating the data into the three test collection periods': baseline, with placebo and with MPH. The results present the findings from the descriptive and inferential analyses of the data. Observations with missing values were excluded from the analysis.

4.1 Demographic characteristics

The participants were mostly female (n=27, male=3). Of the 30 participants, 28 completed all data sets at baseline, after capsules A and after capsules B. Data analysis was performed where there were complete data sets. The mean age of all was 30.2 years (M 40.0 years [27-53], F 29.1 [19-54]). Males tended to be taller (M 168.0±6.0; F 161.8±8.0cm) and weighed more than the females (M 82.0±18; F 68.8±13.0kg) with greater BMI's (Table 1). There were no significant changes in weight/BMI's during the study period (p=0.99).

Data for age and sex were aggregated for analyses.

Table 4.1: BMI data for females (n=25) and males (n=3) Data are presented as means and standard deviation (SD).

	Females (n=25)			**Males (n=3)**		
	Baseline Mean±SD	**Placebo Mean±SD**	**MPH Mean±SD**	**Baseline Mean±SD**	**Placebo Mean±SD**	**MPH Mean±SD**
BMI (kg/m^2)	26.3±5.0	26.2±4.9	26.2±4.8	29.1±4.0	29.0±4.0	29.2±4.0

SD standard deviation. MPH methylphenidate

4.2 Physiological Parameters

4.2.1 Heart Rate

The mean resting heart rate at baseline was 79 ± 12 bpm. The mean ± SD after placebo was 73 ± 14 bpm, and after MPH it was 74 ± 14 bpm. A few baseline resting

HR measures were noted to be higher than those with placebo or MPH, which may have been related to anxiety.

There was a significant difference between baseline and placebo ($t(28)=2.22$, $p=0.034$), with the baseline resting heart rate higher. There was a tendency for the baseline to be higher than that of the MPH group, but not significantly different. ($t(28)=1.57$, $p=0.064$). No significant difference was noted between placebo and MPH readings ($p=0.7$) (Table 4.2).

Table 4.2 Participant Heart Rates (bpm)

Participants Code	Sex	Baseline	Placebo	MPH
8188	F	84	73	81
8191	F	84	85	85
8193	F	78	77	78
8194	F	58	64	90
8198	F	110	110	105
8199	F	77	78	82
8200	M	71	74	63
8201	F	73	76	78
8202	F	65	76	85
8203	F	93	89	100
8205	F	73	84	84
8206	M	81	70	72
8207	F	75	71	70
8208	F	83	80	78
8209	M	65	58	77
8213	F	78	84	86
8214	F	77	83	64
8212a	F	79	84	75
8189	F	84	54	55
8190	F	65	65	65
8192	F	92	89	87
8195	F	66	60	60
8196	F	85	53	54
8197	F	100	48	48
8204	F	94	58.8	60
8210	F	90	48	49
8212b	F	85	71	71
8213b	F	61	69	71
Mean±SD		**79±12**	**73±14**	**74±14**

MPH methylphenidate, M male, F female, SD standard deviation

4.2.2 Blood pressure

There were no significant differences in systolic blood pressure between baseline and placebo ((t(28)=1.41, p=0.17) and MPH groups (t(28)=0.63, p=0.54) respectively and between the groups (p=0.66). (Table 4.3).

There were no significant differences in diastolic blood pressure between baseline and placebo (baseline vs placebo (t(28)=0.7, p=0.49) and MPH groups (t(28)=0.65, p=0.52) respectively and between the groups (p=0.69). (Table 4.3).

Table 4.3 Participant Blood Pressure (mmHg)

Participants Code		Baseline		Placebo		MPH	
	Sex	SBP	DBP	SBP	DBP	SBP	DBP
8188	F	127	79	117	83	118	82
8191	F	115	79	120	86	116.5	75
8193	F	134	94	128	92	130	90
8194	F	140	98	134	99	129	102
8198	F	115	82	116	83	105	75
8199	F	123	72	119	75	119	72
8200	M	131	92	133	96	118	87
8201	F	123	89	110	90	123	95
8202	F	125	86	120	84	118	100
8203	F	120	87	134	90	144	93
8205	F	105	72	105	76	108	71
8206	M	129	83	110	81	130	82
8207	F	114	83	102	80	101	70
8208	F	110	73	108	70	104	72
8209	M	131	91	137	99	147	84
8213	F	116	73	109	77	106	77
8214	F	122	81	109	79	100	77
8212a	F	108	78	125	86	137	88
8189	F	113	80	111	70	118	76
8190	F	118	88	110	77	122	80
8192	F	112	80	121	85	119	85
8195	F	124	82	109	72	124	78
8196	F	115	85	113	78	98	66
8197	F	117	83	120	68	112	80
8204	F	114	81	92	69	108	77
8210	F	113	74	114	76	117	80
8212b	F	113	72	115	74	117	78
8213b	F	113	72	127	71	114	73
Mean±SD		**119±8**	**82±7**	**117±11**	**81±9**	**118±12**	**81±9**

MPH methylphenidate, M male, F female, SBP systolic blood pressure, DBP diastolic blood pressure, SD standard deviation

4.2.3 Cardiopulmonary Exercise Testing (CPET)

As part of the study objectives, cardiovascular responses were assessed using cardiopulmonary exercise testing (CPET). This approach was chosen because such measures are frequently incorporated in research investigating effects on cardiovascular and physiological functions, and, in this study, the effect of methylphenidate (a stimulant) has the potential to influence these parameters. Table 2.1 from the literature review chapter is also shown here for easy reference and outlines the parameters along with their explanations.

Table 2.1 Physiological parameters measured during CPET

Measurement	Description
Respiratory Exchange ratio (RER) at maximum test	Describes ratio of CO_2 output to O_2 uptake ($V\dot{}CO2/V\dot{}O2$) as a function of time and reflects patient effort (RER at least ≥ 1). Depends on rate of lactate increase during progressive exercise.
$V0_{2peak}$ ml/kg/min	Maximum volume of oxygen in millilitres consumed per minute per kilogram of body weight
VT ($ml.min^{-1}$) Ventilatory Threshold	Point at which VCO_2 deviated from linear relationship with $V0_2$. Indicative that oxygen-dependant energy systems are starting to contribute relatively more to energy production with slight increase in blood lactate levels above resting levels.
VO_2 ml/kg/min at ventilatory threshold	Oxygen volume consumed at VT
VT as % of VO_{2peak} (VO2 at VT / VO_{2peak})	Metric for assessing endurance capacity. Indicates intensity at which one can sustain exercise before experiencing significant increase in breathing rate due to accumulation of metabolic by-products.
$VE/VC0_2$ slope	Volume of CO_2 expelled per litre of air ventilated. Indicates ventilatory efficiency. Increase in slope indicates increased dead space ventilation in lung, pulmonary vascular disease or pulmonary limiting disease.
VO_2/work rate (ml/min/watt)	Measure of efficiency of oxygen uptake relative to work being performed and helps to assess efficiency of cardiovascular and respiratory systems during exercise. The higher the value, the better the efficiency.
Oxygen Uptake Efficiency Slope (OUES)	Parameter to assess efficiency of body's oxygen uptake during exercise. A higher value indicates more efficient oxygen uptake. Can also provide insight at submaximal exercise effort.
VO_2/VE) (ml/min 02)/L/min)	Ratio indicates how much oxygen being consumed by body for each litre of air ventilated and assesses efficiency of respiratory system. A higher VO2/VE ratio suggests efficiently using oxygen taken in indicating good respiratory and cardiovascular function.
Oxygen pulse (ml/beat)	A proxy for stroke volume and predictor for coronary artery disease and all-cause mortality

After: (*Interpreting The Cardiopulmonary Exercise Test*, 2018) (Haley et al., n.d.) (Uchida, 2018) (*Respiratory Formulas, Calculations, and Equations (2025)*, n.d.) (Crisafulli et al., 2007) (Laukkanen JA, Kurl S, Salonen JT, et al, 2006)

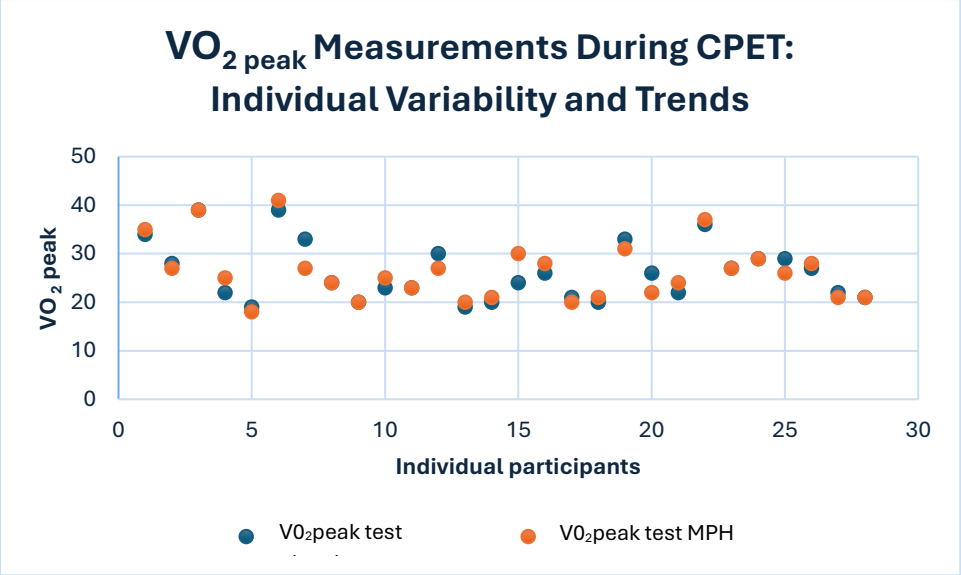
The following data were extracted from the CPET: $VO_{2\ peak}$, First Ventilatory Threshold Deflection Point (VT1), VT1 as % of VO_2 peak, VE/VCO_2 slope, VO_2 Work Rate (ml/min/watt), and Oxygen Uptake Efficiency Slope (OUES) and Oxygen Pulse (ml/beat)

The VO_2 peak (Figure 4.1) and oxygen pulse did not significantly differ between the groups (Table 4.4). The VT1 between groups did not differ significantly (p=0.22) with wide variability (Figure 4.2), although the numbers may suggest a trend towards an MPH effect, with a small effect size of 0.23 (Cohen's *d*). The VO_2 at the first VT deflection point, indicating oxygen consumption at the point where increasing oxygen-dependant energy systems are activated, were similar (Figure 4.3).

Table 4.4 Oxygen-related CPET parameters

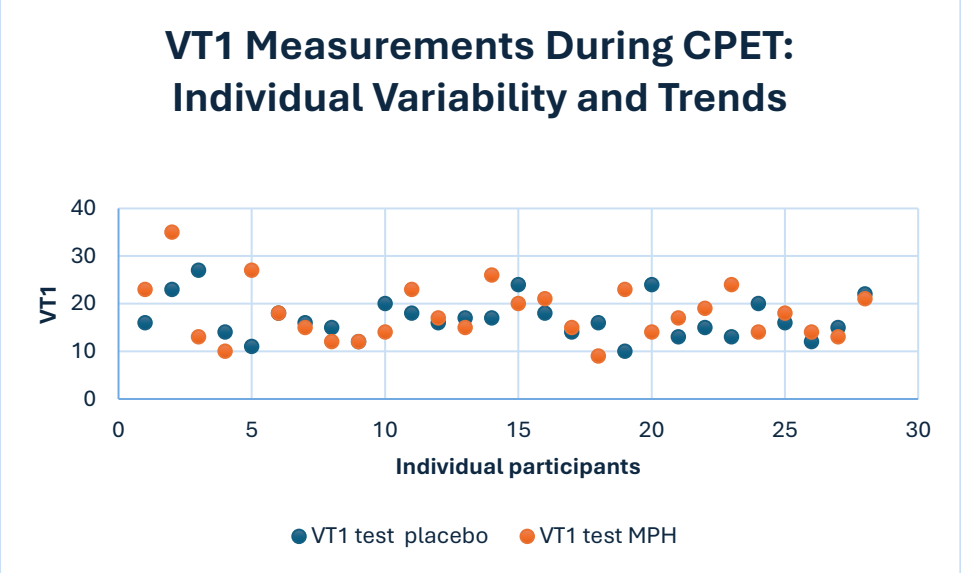
Parameter	Baseline	Placebo	MPH	p
VO_{2peak} (ml/kg/min)	25.9±5.5	26.9±6.1	26.5±6.1	0.82
VT1	16.1±4.6	16.9±4.3	18.2±6.1	0.34
VT1 % VO_{2peak}	62.0±15.8	62.9±16.5	67.1±16.5	0.52
O_2 Pulse (ml/beat)	10.5±2.7	11±3.3	10.5±3.2	0.85

Data are presented as means ± SD. SD standard deviation. MPH methylphenidate



Numbers on X-axis are for numerical convenience and not individual codes

Figure 4.1 VO_{2peak} Individual Variation

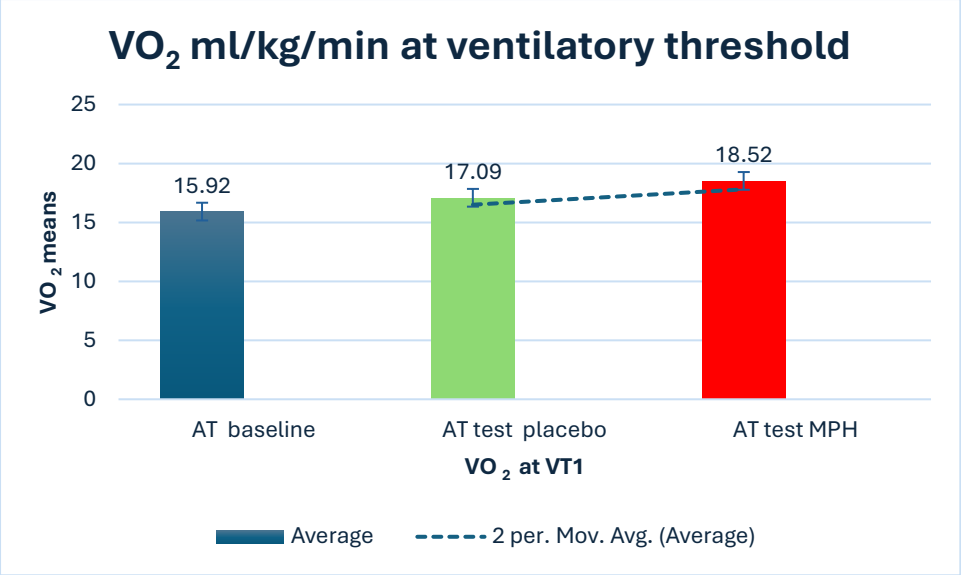


Numbers on X-axis are for numerical convenience and not individual codes

Figure 4.2 First Ventilatory Threshold Deflection Individual Distribution

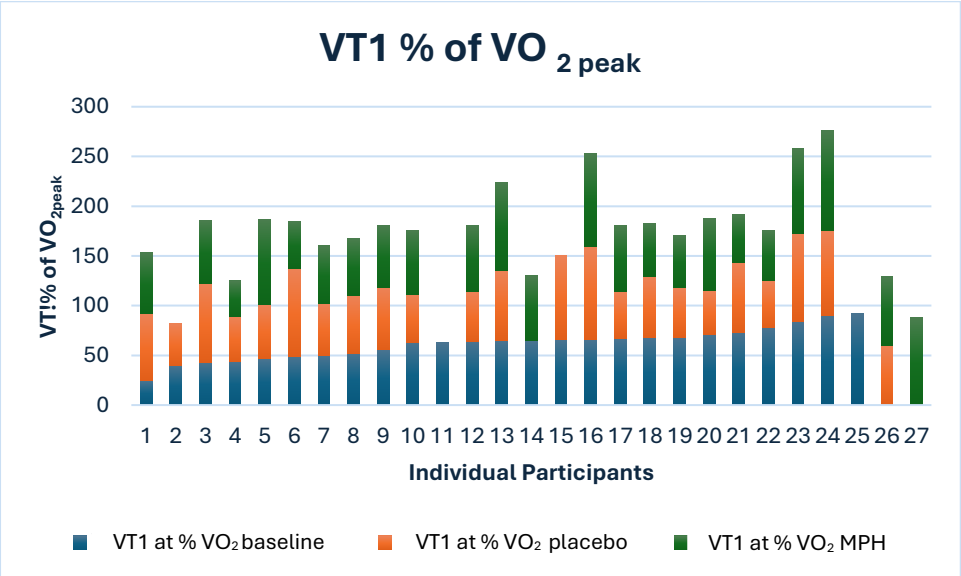
Similarly, VT1 as a percentage of VO_2 peak did not significantly differ between groups (Figure 4.4); however, there were variations in this parameter when differentiated for zones at baseline (i.e. up to 50% of VO_2, 51-75% and >75%) differed for individuals

(data by individual code) with placebo and MPH (Figure 4.4). However, VT1 as a percentage of VO_2 between groups was not significantly different (p=0.52) (Figure 4.4) and Cohen's *d* test indicates a small effect size (0.26). No differences were noted in the slopes (Table 4.5), indicating no differences in ventilatory or respiratory efficiency.



MPH methylphenidate

Figure 4.3 Oxygen Consumption Means at First Ventilatory Threshold Deflection



MPH methylphenidate. Numbers on X-axis are for numerical convenience and not individual codes

Figure 4.4 VT1 Baseline, Placebo and MPH for Individuals

Table 4.5 CPET Slopes

Parameter	Baseline	Placebo	MPH	p
VE/$VC0_2$ slope	43.2±11.5	45.5±13.8	46.2±12.0	0.66
VO_2/work rate slope (ml/min/watt)	11.7±3.8	12.0±3.2	10.8±3.2	0.47
Oxygen uptake efficiency slope (OUES) VO_2/VE) (ml/min 0_2)/L/min)	1.9±0.7	1.9±0.7	1.8±0.7	0.73

Data are presented as means ± SD. SD standard deviation. MPH methylphenidate

4.2.4 Neurocognitive Function

The CNS Vital Signs test is a non-invasive and adaptable computerised neurocognitive assessment tool that objectively measures brain function during cognitive stress with millisecond-level accuracy (*CNSVS-BriefInterpretationGuide.Pdf*, 2024). It evaluates a wide range of cognitive domains quickly and effectively, incorporating over 50 evidence-based rating tools to detect clinical symptoms, behaviours, and coexisting conditions. It enables repeated assessments to track neurocognitive changes over time.

CNS Vital Signs is a computerised cognitive assessment tool that evaluates various brain functions, including memory, attention, processing speed, and executive function. Test results are presented as **raw scores**, **standard scores**, and **percentiles**, which provide insight into cognitive performance compared to normative data. CNS Vital Signs generates raw scores for each cognitive function tested. These raw scores reflect an individual's performance on reaction time, accuracy, and memory recall tasks. However, raw scores alone lack context, so they are converted into standard scores and percentiles for meaningful interpretation.

Standard scores are calculated from raw scores and adjusted to fit a normal distribution with a mean of 100 and a standard deviation of 15. This system allows for easy comparison across different cognitive domains and age groups. Thus, 115 and above (≥1 SD above the mean) indicates superior cognitive performance; 85–115 (within ±1 SD of the mean) falls within the normal range, and 70–84 (1–2 SD below the mean) suggests below-average cognitive performance. Below 70 (≥2 SD below the mean) indicates significantly impaired cognitive function, which may require further assessment.

The **percentiles** provide a ranking system that compares an individual's performance to a normative reference group. The percentile value indicates the percentage of people in the normative group who scored lower than the individual. Thus, the 50th Percentile represents the median, or average, performance; the 75th Percentile Means the individual scored better than 75% of the reference group; and the 25th Percentile Indicates performance higher than only 25% of the reference group. As an example of interpretation, suppose an individual receives the following results for:

Memory:

- Standard Score: 92
- Percentile: 30

What This Means:

- A standard score of 92 falls within the 85–115 range, indicating average cognitive function.
- A percentile rank of 30 suggests the individual performed better than 30% of the reference group, which is still within the normal range.

Considerations and Limitations

- **Normative Comparison**: Results are benchmarked against a reference population, so interpretation depends on the quality and relevance of that data.
- **Context Matters**: Factors like age, education, medical history, and other personal variables should be considered when evaluating results.

The following scores and indices were analysed (Table 4.9) and presented in a report (Figure 6.1).

- neurocognitive index standard score
- neurocognitive index percentile
- composite memory participant index
- composite memory standard score
- composite memory percentile
- verbal memory participant score
- verbal memory standard score
- verbal memory percentile
- visual memory participant score
- visual memory standard score
- visual memory percentile
- psychomotor speed participant score
- psychomotor speed standard score
- psychomotor speed percentile
- reaction time participant score
- reaction time standard score
- reaction time percentile
- complex attention participant score
- complex attention standard score
- complex attention percentile
- cognitive flexibility
- processing speed participant
- processing speed standard
- processing speed percentile
- executive function participant
- executive function standard
- executive function percentile
- simple attention participant
- simple attention standard
- simple attention percentile
- motor speed

Table 4.9: Description of CNS Vital Signs Clinical Domain

CNS Vital Signs Clinical Domain Description

Single Test Domain Multiple Test Domain

Neurocognitive Index (NCI)	Measure: An average score derived from the domain scores or a general assessment of the overall neurocognitive status of the patient. Relevance: Summary views tend to be most informative when evaluating a population, a condition category, and outcomes.
Composite Memory	Measure: How well subject can recognize, remember, and retrieve words and geometric figures. Relevance: Remembering a scheduled test, recalling an appointment, taking medications, and attending class.
Verbal Memory	Measure: How well subject can recognize, remember, and retrieve words. Relevance: Remembering a scheduled test, recalling an appointment, taking medications, and attending class.
Visual Memory	Measure: How well subject can recognize, remember and retrieve geometric figures. Relevance: Remembering graphic instructions, navigating, operating machines, recalling images, and/or remember a calendar of events.
Psychomotor Speed	Measure: How well a subject perceives, attends, responds to visual-perceptual information, and performs motor speed and fine motor coordination. Relevance: Ability preform simple motor skills and dexterity through cognitive functions i.e., use of precision instruments or tools, performing mental and physical coordination i.e., driving a car, playing a musical instrument.
Reaction Time*	Measure: How quickly the subject can react, in milliseconds, to a simple and increasingly complex direction set. Relevance: Driving a car, attending to conversation, tracking and responding to a set of simple instructions, taking longer to decide what response to make.
Complex Attention	Measure: Ability to track and respond to a variety of stimuli over lengthy periods of time and/or perform mental tasks requiring vigilance quickly and accurately. Relevance: Self-regulation and behavioral control.
Cognitive Flexibility	Measure: How well subject is able to adapt to rapidly changing and increasingly complex set of directions and/or to manipulate the information. Relevance: Reasoning, switching tasks, decision-making, impulse control, strategy formation, attending to conversation.

Table 4.9 Cont'd: Description of CNS Vital Signs Clinical Domain

Cognitive Flexibility	Measure: How well subject is able to adapt to rapidly changing and increasingly complex set of directions and/or to manipulate the information. Relevance: Reasoning, switching tasks, decision-making, impulse control, strategy formation, attending to conversation.
Processing Speed	Measure: How well a subject recognizes and processes information i.e., perceiving, attending/responding to incoming information, motor speed, fine motor coordination, and visual-perceptual ability. Relevance: Ability to recognize and respond/react i.e., fitness-to-drive, occupation issues, possible danger/risk signs or issues with accuracy and detail.
Executive Function	Measure: How well a subject recognizes rules, categories, and manages or navigates rapid decision making. Relevance: Ability to sequence tasks and manage multiple tasks simultaneously as well as tracking and responding to a set of instructions.
Simple Attention	Measure: Ability to track and respond to a single defined stimulus over lengthy periods of time while performing vigilance and response inhibition quickly and accurately. Relevance: Self-regulation and simple attention control.
Motor Speed	Measure: Ability to perform movements to produce and satisfy an intention towards a manual action and goal. Relevance: Preparation and production of simple manual dexterity actions e.g. manipulate and maneuver objects.
Social Acuity	Measure: How well a subject can perceive, process, and respond to emotional cues. Relevance: Spectrum screen, ability to recognize social cues or read facial expressions. Provides insight into inappropriate behavior, decreased inhibition, insensitivity to social standards, and social behavioral regulation.
Reasoning	Measure: How well is subject able to recognize, reason and respond to non-verbal visual-abstract stimuli. Relevance: Problem solving skills, ability to forge insights, discern meaning, and ability to perceive relationships.
Sustained Attention	Measure: How well a subject can direct and focus cognitive activity on specific stimuli. Relevance: How well a subject can focus and complete task or activity, sequence action, and focus during complex thought.
Working Memory	Measure: How well a subject can perceive and attend to symbols using short-term memory processes (4PCPT). Relevance: Ability to carry out short-term memory tasks that support decision making, problem solving, planning, and execution. Enables "right-now" responses.

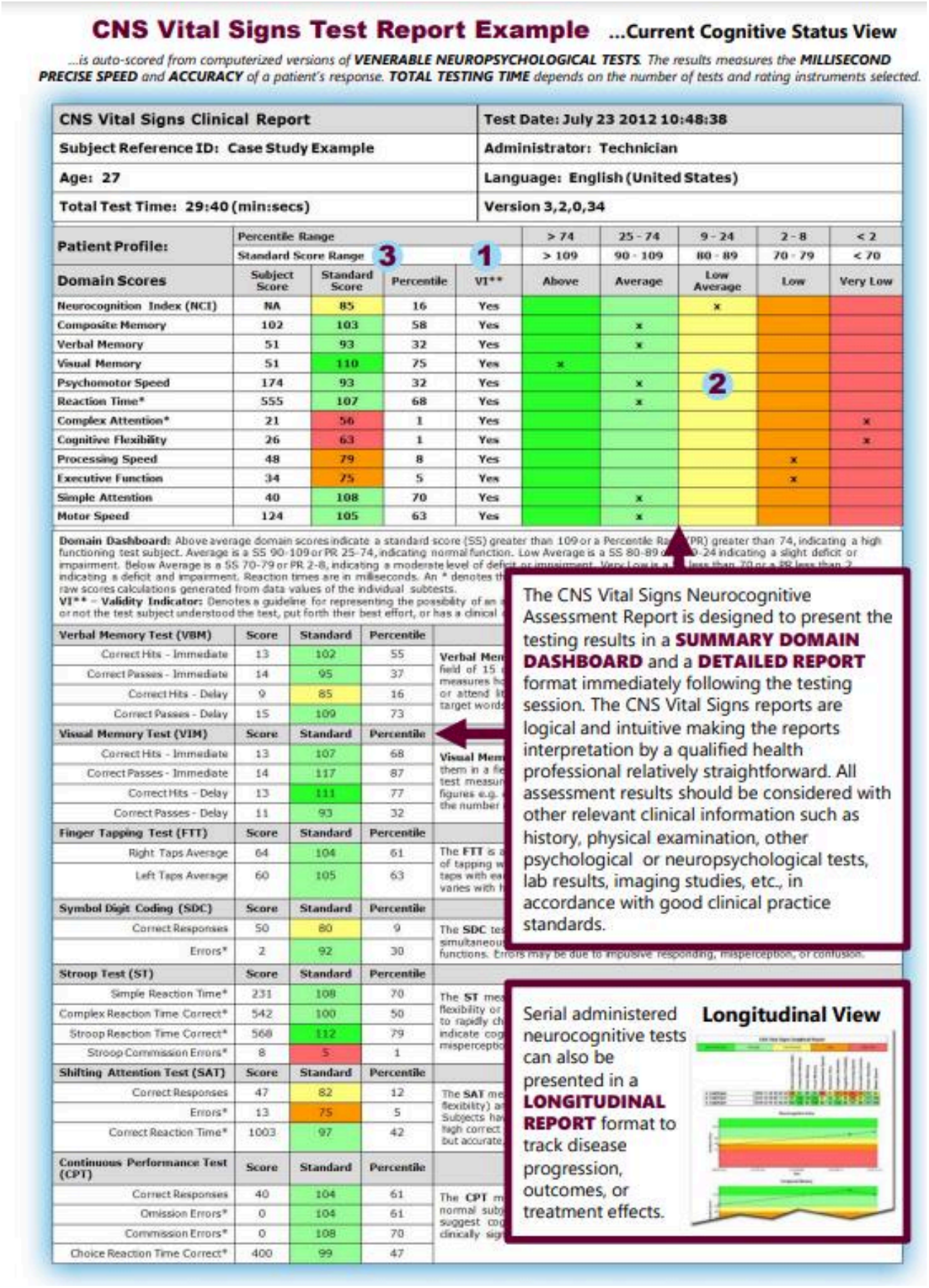


Figure 4.5 CNS Vital Signs Report (*CNSVS-BriefInterpretationGuide.Pdf*, n.d.)

Several statistically significant differences were observed between baseline and placebo, as well as between baseline and MPH at the 0.05 significance level (Table 4.10). The effect sizes for these comparisons were large, with d = -2.13 for Baseline vs. Placebo and d = -1.89 for Baseline vs. MPH. However, no significant difference was found between Placebo and MPH, with a small effect size (d = 0.15).

Moderate effects were observed in:

- Reaction Time (Participant Score): Reduced in MPH group.
- Reaction Time (Standard Score): Higher in placebo and MPH groups.
- Complex Attention (Percentile): Higher in placebo and MPH groups.
- Executive Function (Percentile): Higher in placebo and MPH groups.

Small-to-moderate effects were seen in:

- Processing Speed (Percentile): Higher in placebo, lower in MPH.

No statistically significant differences were found across the majority of conditions for cognitive parameters.

In addition to Table 4.10, results are displayed in histogram figures for ease of visual perception. They provide a clear way to represent data distributions, making it easier to visually see patterns, trends, and outliers (Figures 4.6-4.37). They show means and standard deviation bars to show the precision of the means.

Table 4.10 Neurocognitive Performance Metrics Across Conditions

Parameter	Mean±SD (Baseline Placebo MPH)	p-value (Baseline vs placebo, baseline vs MPH, Placebo vs MPH)	Cohen's *d* (Baseline vs placebo, baseline vs MPH, Placebo vs MPH)	Cohen's ^ (Baseline vs placebo, baseline vs MPH, Placebo vs MPH)	Cohen's *d* (Baseline vs placebo, baseline vs MPH, Placebo vs MPH)	Effect Size Interpretation
Neurocognitive Index (Standard Score)	68.6±29.1 77.4±34.6 73.7±31.5	0.41 0.61 0.74	-0.27	-0.17	0.11	No effect
Neurocognitive Index (Percentile)	17.9±23.1 22.7±27.5 24.1±28.3	0.53 0.44 0.87	-0.19	-0.24	-0.05	No effect
Composite Memory (Participant Index)	93.3±14.1 92.1±16.3 89.7±15.7	0.82 0.46 0.64	0.07	0.24	0.15	No effect
Composite Memory (Standard Score)	73.5±28.1 79.1±32.3 79.2±30.7	0.57 0.55 0.99	-0.19	-0.19	-0.003	No effect
Composite Memory (Percentile)	21.0±28.1 26.0±32.3 21.7±30.7	0.62 0.94 0.68	-0.16	-0.03	0.13	No effect
Verbal Memory (Participant Score)	44.4±8.1 45.9±9.3 44.2±8.7	0.59 0.96 0.57	-0.18	0.02	0.57	No effect
Verbal Memory (Standard Score)	76.8±27.1 77.1±32.3 76.1±30.7	0.97 0.94 0.92	-0.02	-0.06	0.68	No effect
Verbal Memory (Percentile)	20.0±28.1 26.0±32.3 21.7±30.7	0.92 0.74 0.68	-0.03	0.11	0.13	No effect
Visual Memory (Participant Score)	41.8±7.1 43.5±8.3 43.5±7.7	0.49 0.47 1.00	-0.22	-0.23	0.00	No effect
Visual Memory (Standard Score)	89.2±19.1 93.3±22.3 91.6±21.7	0.54 0.71 0.81	-0.20	-0.12	0.08	No effect
Visual Memory (Percentile)	25.0±29.1 35.1±32.3 32.3±30.7	0.31 0.45 0.79	-0.33	-0.24	0.09	No effect
Psychomotor Speed (Participant Score)	140.1±59.1 146.5±54.3 134.9±62.7	0.72 0.78 0.53	-0.11	0.09	0.20	No effect

Parameter	Mean±SD (Baseline Placebo MPH)	p-value (Baseline vs placebo, baseline vs MPH, Placebo vs MPH)	Cohen's *d* (Baseline vs placebo, baseline vs MPH, Placebo vs MPH)	Cohen's ˆ (Baseline vs placebo, baseline vs MPH, Placebo vs MPH)	Cohen's *d* (Baseline vs placebo, baseline vs MPH, Placebo vs MPH)	Effect Size Interpretation
Psychomotor Speed (Standard Score)	65.4±39.1 73.7±34.3 67.6±42.7	0.46 0.86 0.61	-0.23	-0.05	0.16	No effect
Psychomotor Speed (Percentile)	22.7±29.1 28.3±34.3 25.4±30.7	0.57 0.77 0.77	-0.18	-0.09	0.09	No effect
Reaction Time (Participant Score)	750.5±209.0 681.5±174.3 663.3±230.7	0.26 0.21 0.78	0.36	0.40	0.09	No effect
Reaction Time (Standard Score)	62.0±34.1 81.8±29.3 87.5±42.7	**0.05** **0.04** 0.63	- 0.62	- 0.66	-0.16	Baseline vs placebo borderline significant. Baseline vs MPH statistically significant.
Reaction Time (Percentile)	19.0±29.1 24.7±32.3 26.7±30.7	0.56 0.42 0.84	-0.18	-0.26	-0.06	Small effect
Complex Attention (Participant Score)	24.5±32.7 20.5±41.2 27.8±45.7	0.71 0.77 0.54	0.11	-0.08	-0.17	No effect
Complex Attention (Standard Score)	24.9±106.2 43.3±123.5 33.2±129.9	0.58 0.81 0.78	-0.16	-0.07	0.08	No effect
Complex Attention (Percentile)	24.8±27.5 39.6±32.7 35.6±32.5	0.10 0.23 0.66	-0.49	-0.35	0.13	Moderate increase with MPH
Cognitive Flexibility (Standard)	26.0±27.2 86.9±29.5 82.3±31.2	**<0.001** **<0.001** 0.61	-2.1	-1.89	0.15	No effect
Cognitive Flexibility (Percentile)	19.1±26.2 35.7±30.5 26.0±35.2	0.04 0.44 0.30	-0.59	-0.22	0.29	No effect
Processing Speed (Participant Score)	47.1±17.2 53.8±16.5 51.3±16.8	0.15 0.38 0.60	-0.41	-0.25	0.15	No effect
Processing Speed (Standard Score)	83.1±22.3 90.1±20.5 83.9±20.8	0.23 0.90 0.29	-0.34	-0.040	0.30	No effect
Processing Speed (Percentile)	23.8±28.2 34.8±31.5 29.9±32.3	0.19 0.48 0.58	-0.37	-0.20	0.16	No statistically significant differences Small-moderate effect between baseline and placebo, lower effect with MPH

Parameter	Mean±SD (Baseline Placebo MPH)	p-value (Baseline vs placebo, baseline vs MPH, Placebo vs MPH)	Cohen's *d* (Baseline vs placebo, baseline vs MPH, Placebo vs MPH)	Cohen's ˆ (Baseline vs placebo, baseline vs MPH, Placebo vs MPH)	Cohen's *d* (Baseline vs placebo, baseline vs MPH, Placebo vs MPH)	Effect Size Interpretation
Executive Function (Participant Score)	25.1±26.3 39.7±16.5 39.5±20.8	**0.02** **0.04** 0.97	-0.67	-0.59	0.01	Statistically significant differences between baseline and both placebo and MPH, with moderate effect sizes. No differences between placebo and MPH.
Executive Function (Standard Score)	68.1±32.2 89.1±23.5 86.5±26.8	0.01 0.04 0.72	-0.76	-0.61	0.10	No effect
Executive Function (Percentile)	18.7±25.2 35.1±30.5 29.3±35.2	0.04 0.23 0.53	-0.59	-0.34	0.17	Moderate increase with MPH
Simple Attention (Participant Score)	30.9±24.2 25.1±32.5 25.3±35.2	0.51 0.54 0.98	0.20	0.18	-0.01	No effect
Simple Attention (Standard Score)	-0.15±316.2 -50.7±432.5 -50.7±532.5	0.66 0.71 1.00	0.14	0.11	0.00	No effect
Simple Attention (Percentile)	30.4±27.2 36.8±30.5 40.7±32.3	0.45 0.27 0.67	-0.22	-0.34	-0.12	No effect
Motor Speed	77.7±45.2 87.1±37.5 70.5±50.4	042 0.58 0.19	-0.23	0.15	0.36	No effect

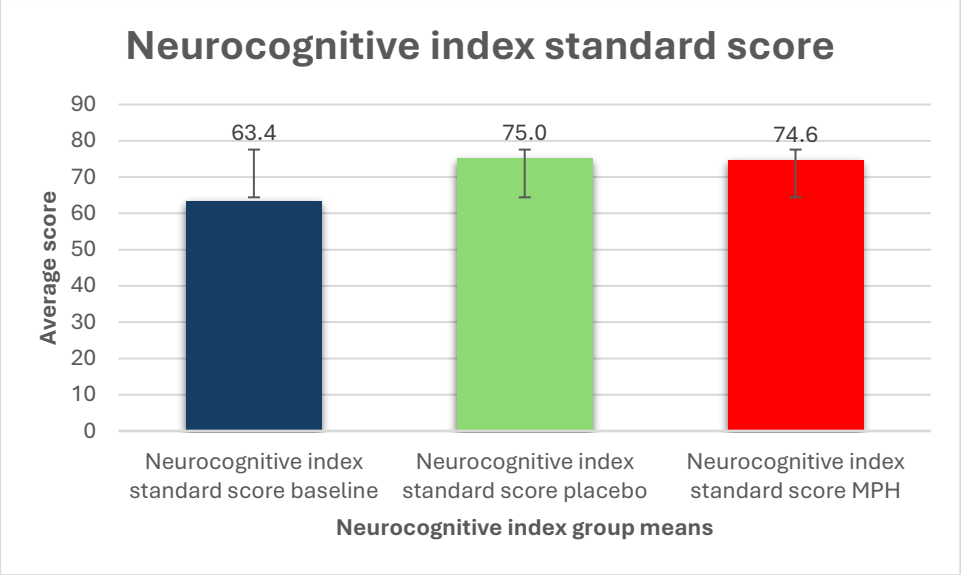


Figure 4.6 Psychometric Neurocognitive Standard Scores

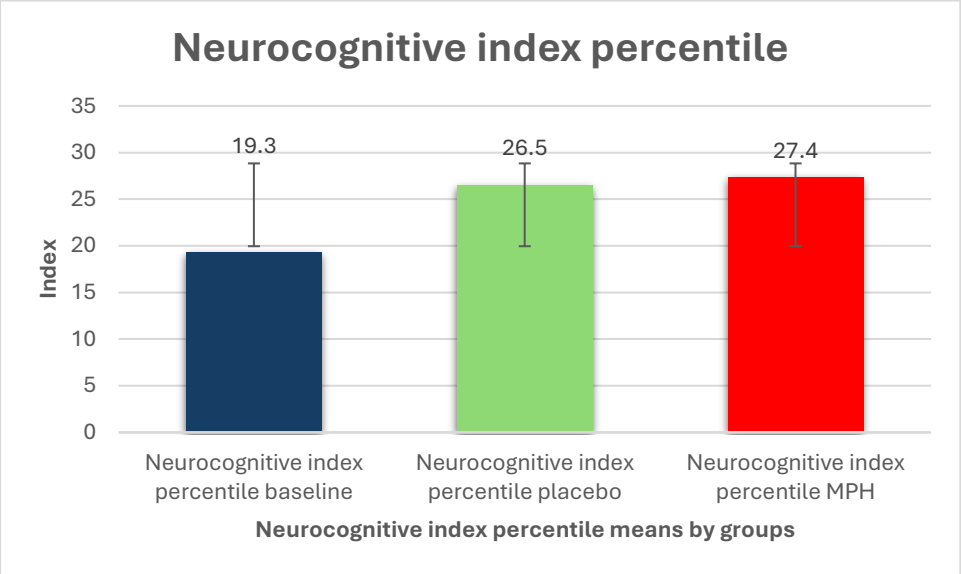


Figure 4.7 Psychometric Neurocognitive Percentile Scores

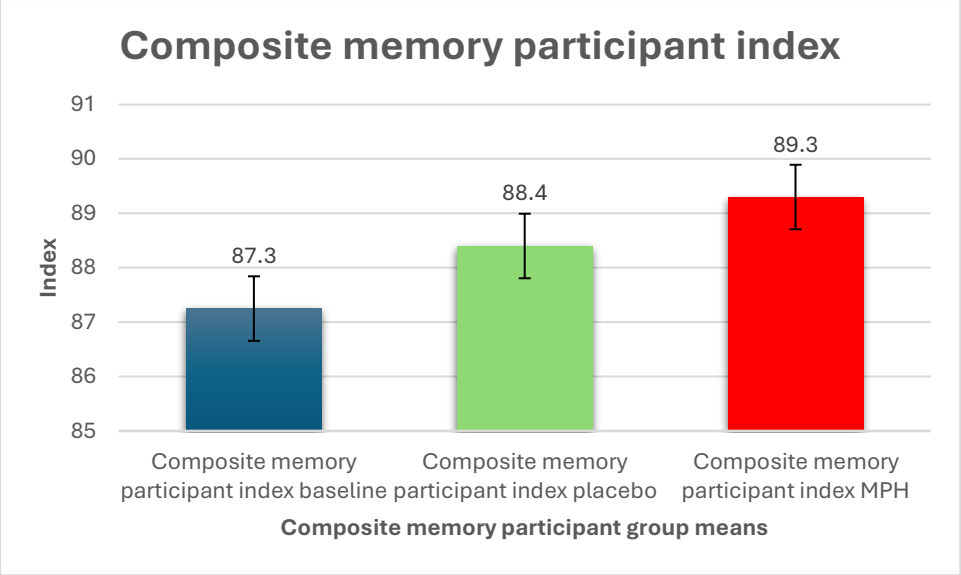


Figure 4.8 Psychometric Composite Memory Participant Index Scores

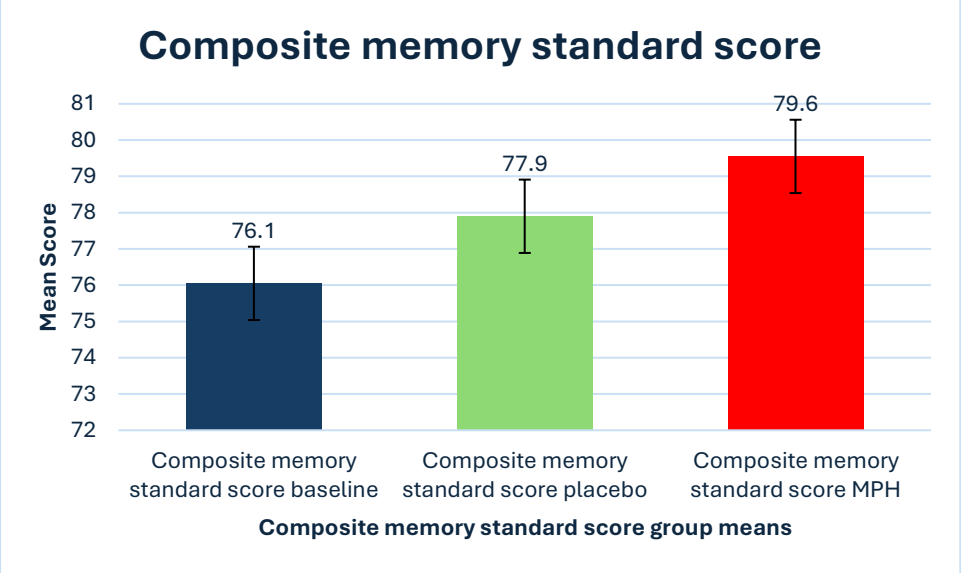


Figure 4.9 Psychometric Composite Memory Standard Scores

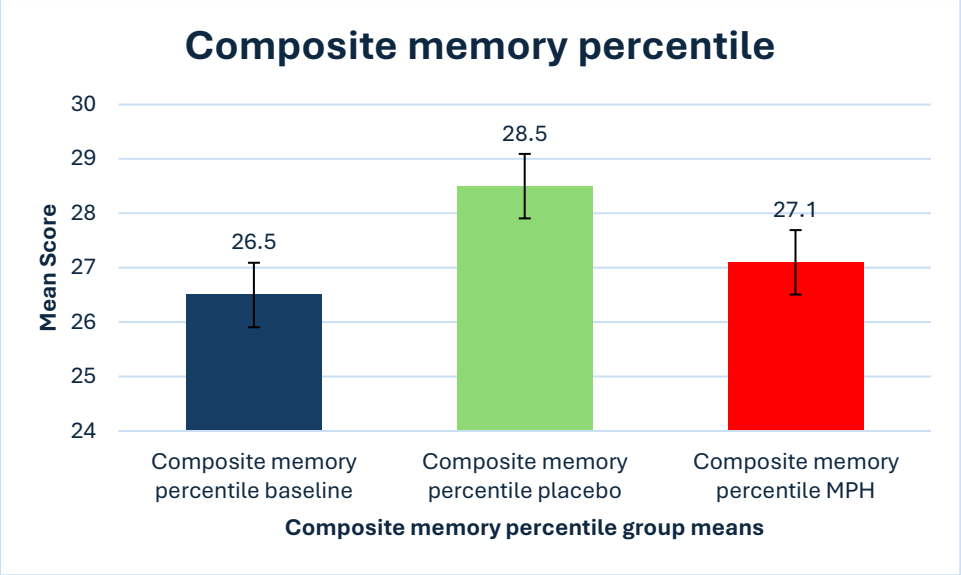


Figure 4.10 Psychometric Composite Memory Percentiles

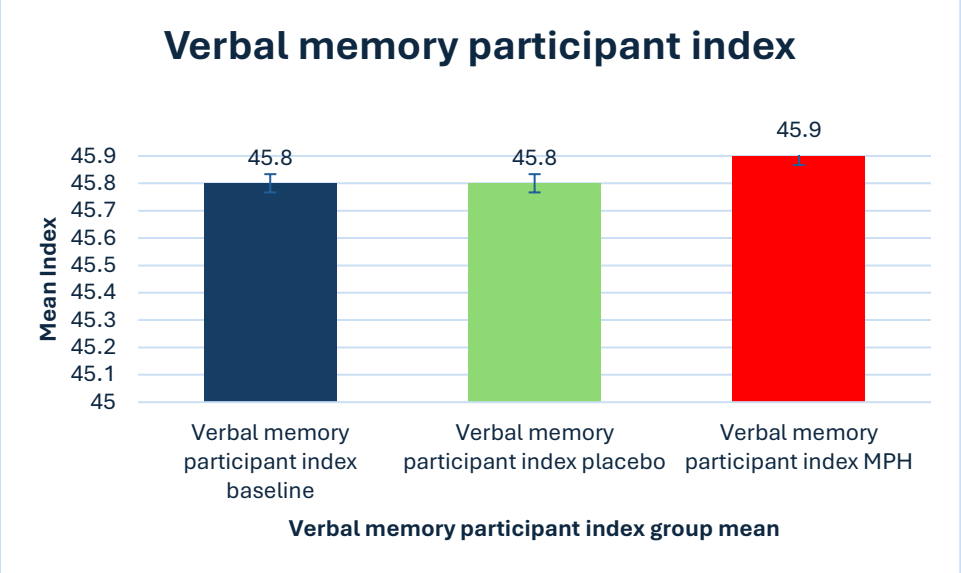


Figure 4.11 Psychometric Verbal Memory Participant Index

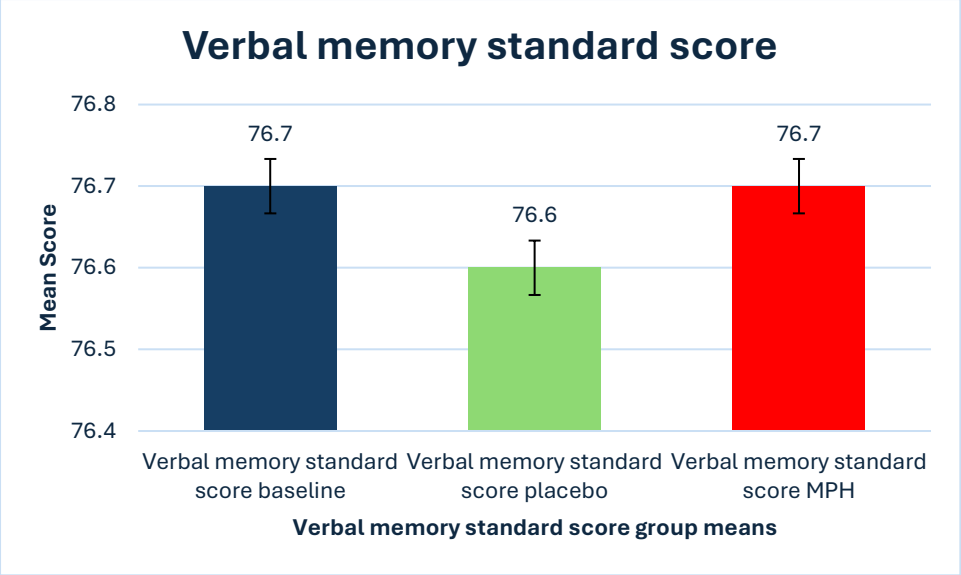


Figure 4.12 Psychometric Verbal Memory Standard Scores

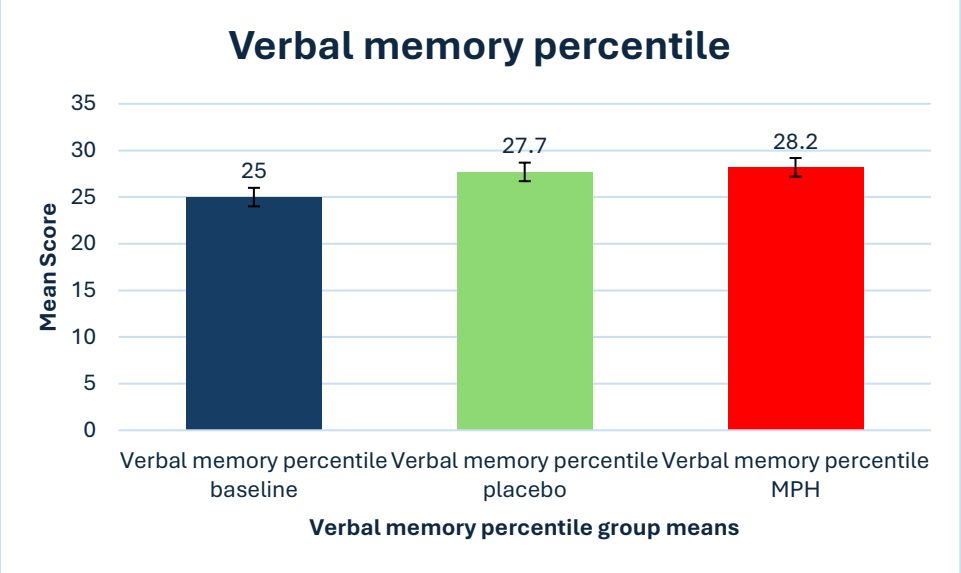


Figure 4.13 Psychometric Verbal Memory Percentile Scores

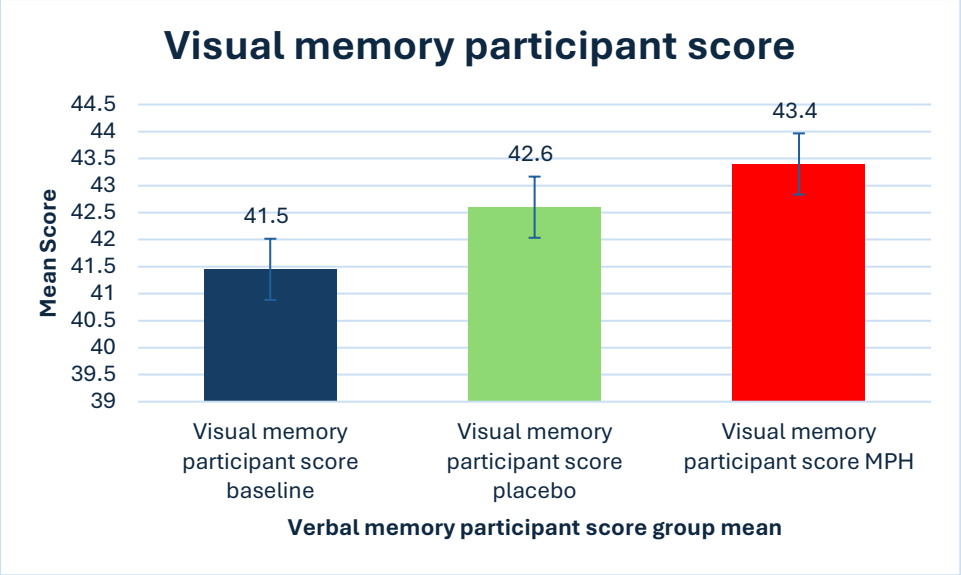


Figure 4.14 Psychometric Verbal Memory Participant Scores

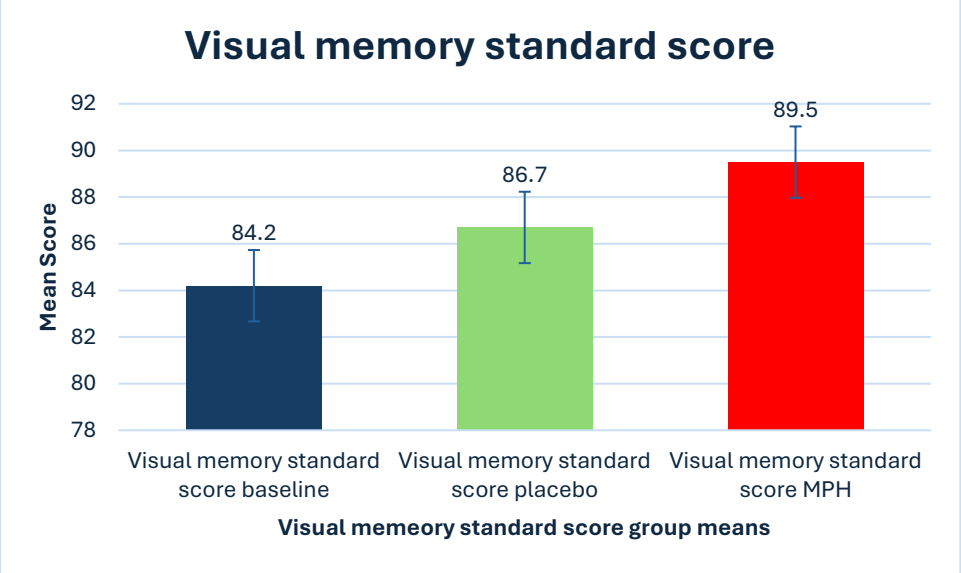


Figure 4.15 Psychometric Visual Memory Standard Scores

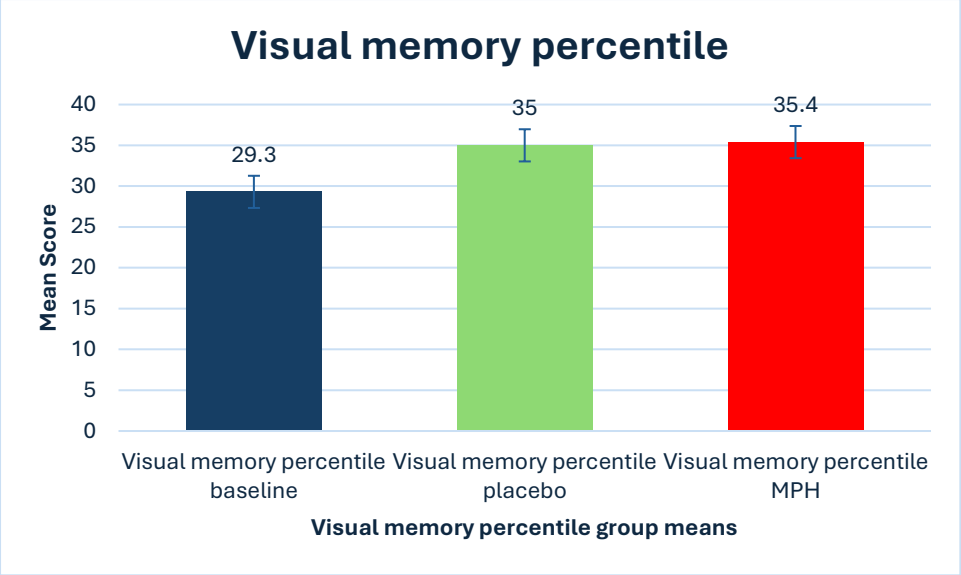


Figure 4.16 Psychometric Memory Percentile Scores

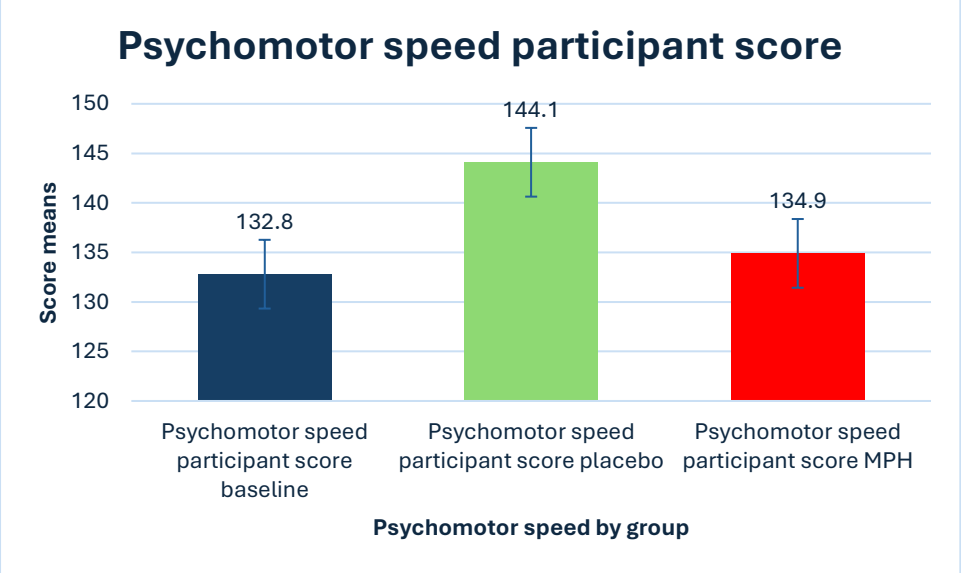


Figure 4.17 Psychometric Speed Participant Scores

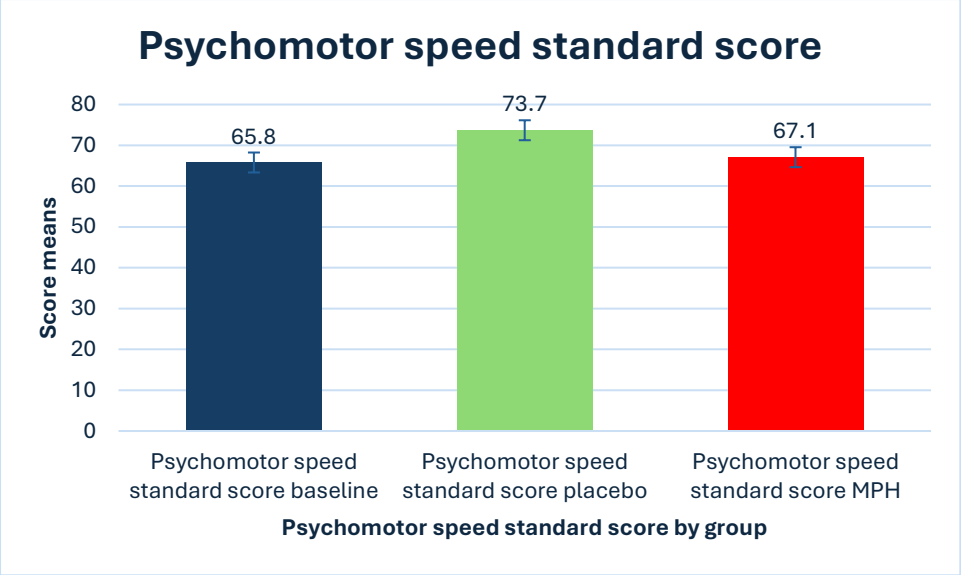


Figure 4.18 Psychometric Speed Standard Scores

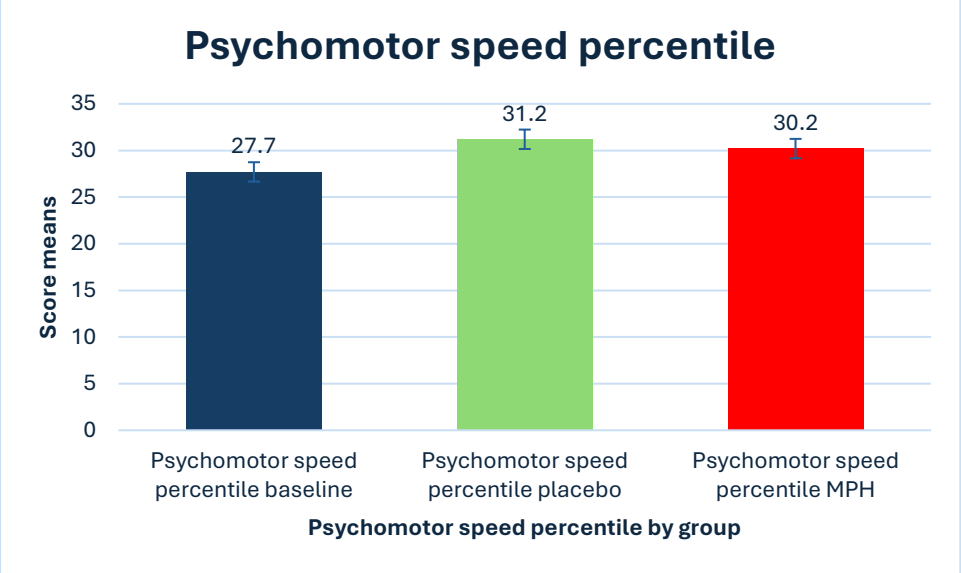


Figure 4.19 Psychometric Speed Percentile Scores

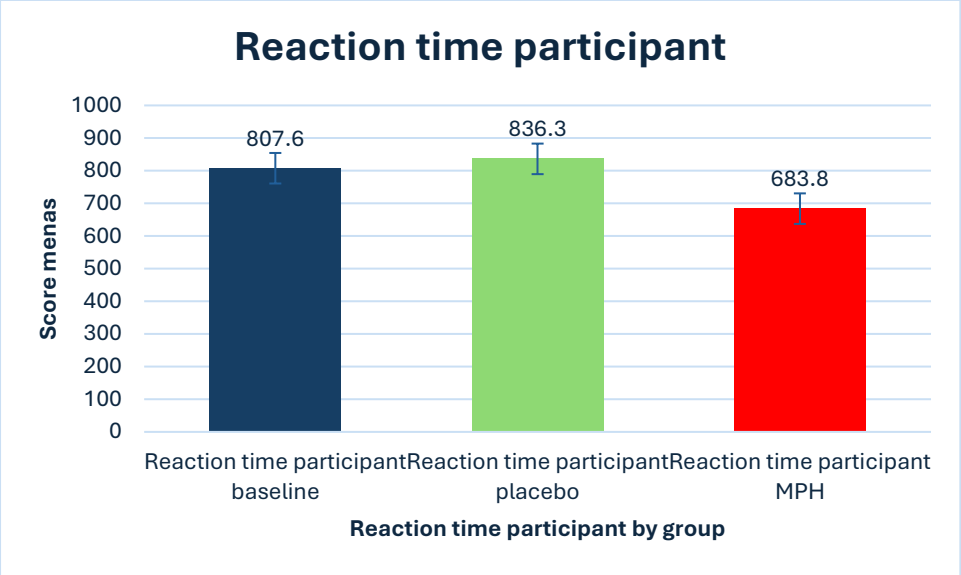


Figure 4.20 Psychometric Participant Reaction Times

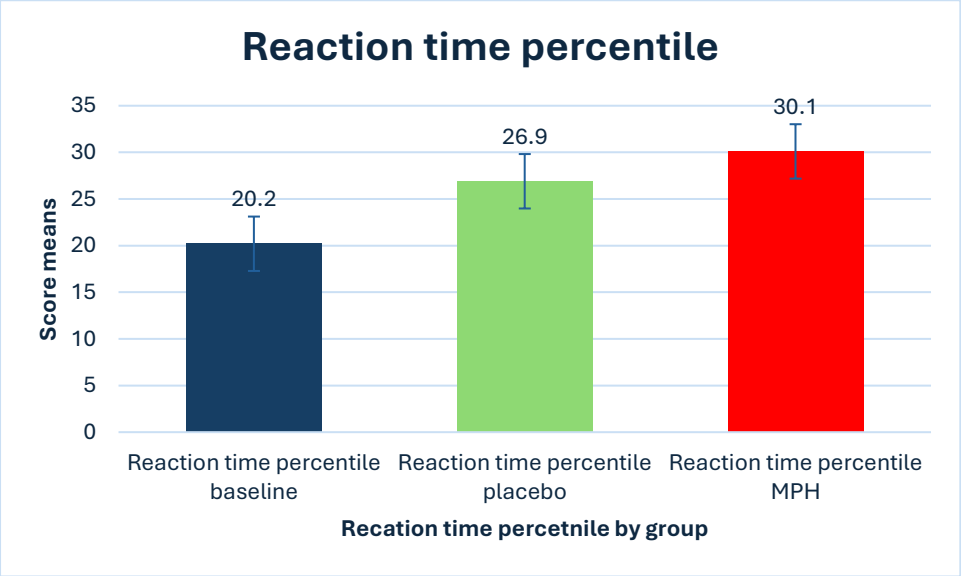


Figure 4.21 Psychometric Reaction Time Percentile

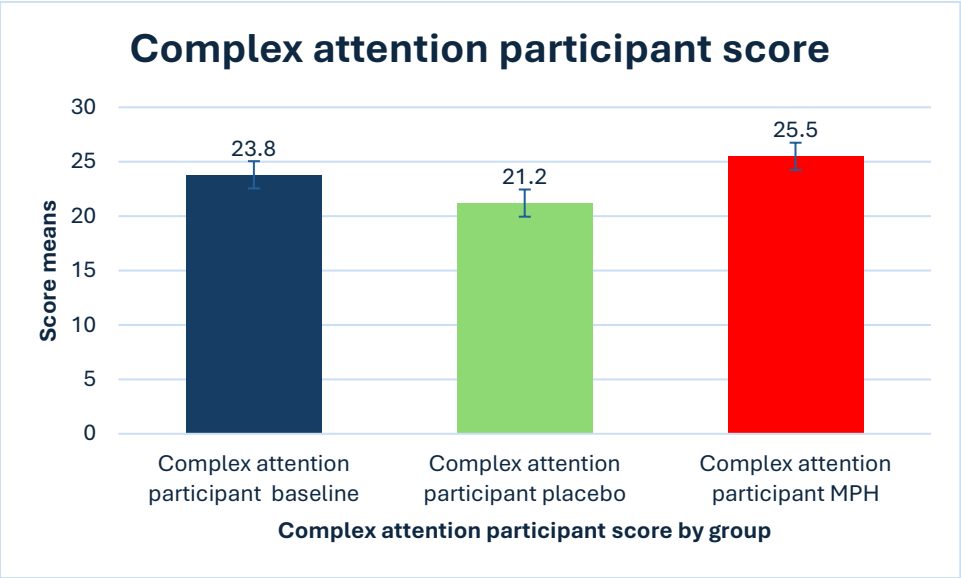


Figure 4.22 Psychometric Complex Attention Participant Scores

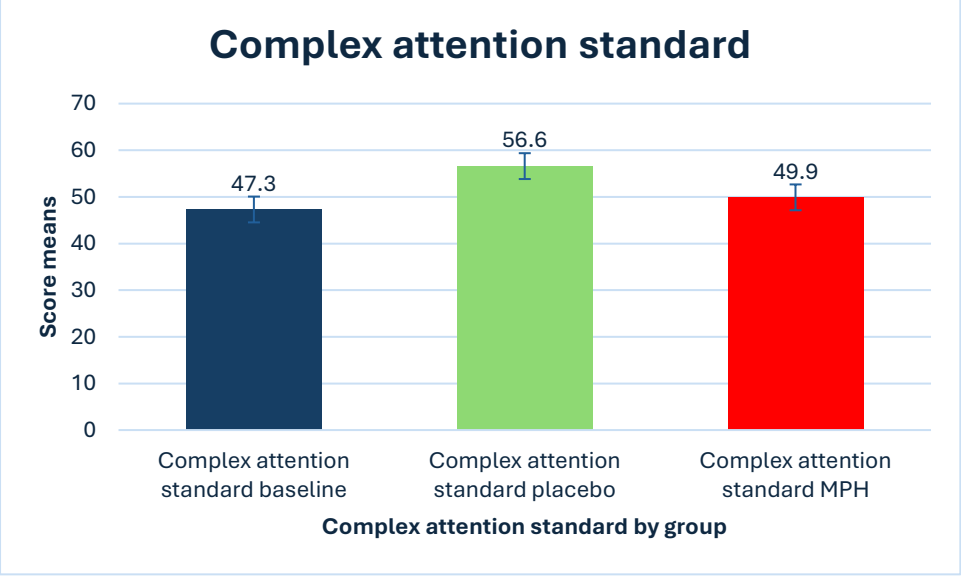


Figure 4.23 Psychometric Complex Attention Standard Scores

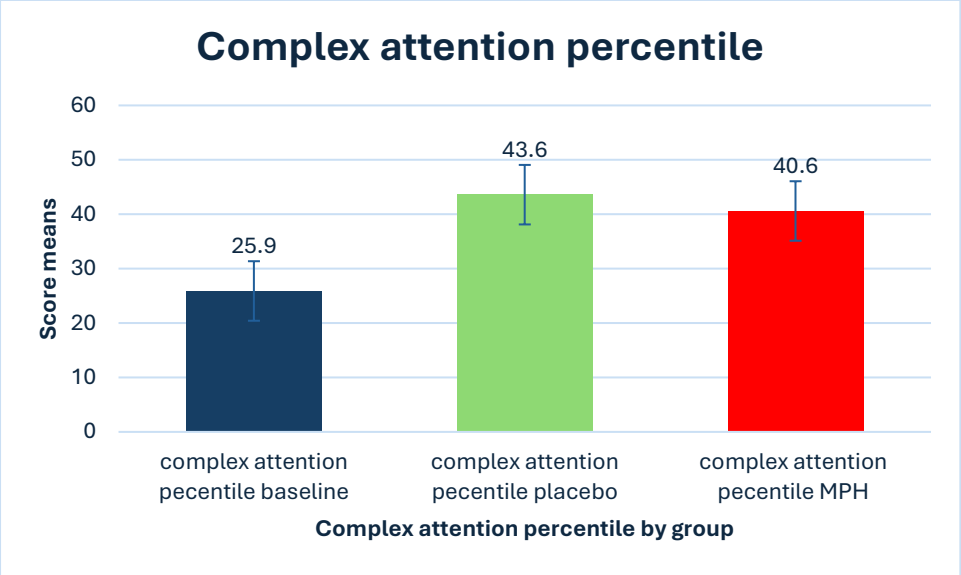


Figure 4.24 Psychometric Complex Attention Percentiles

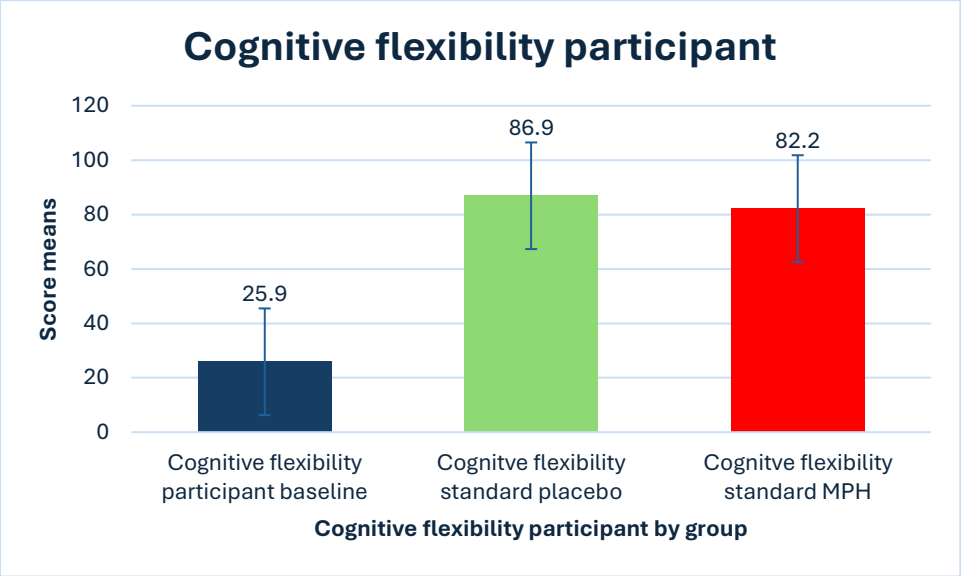


Figure 4.25 Psychometric Cognitive Flexibility Participant Scores

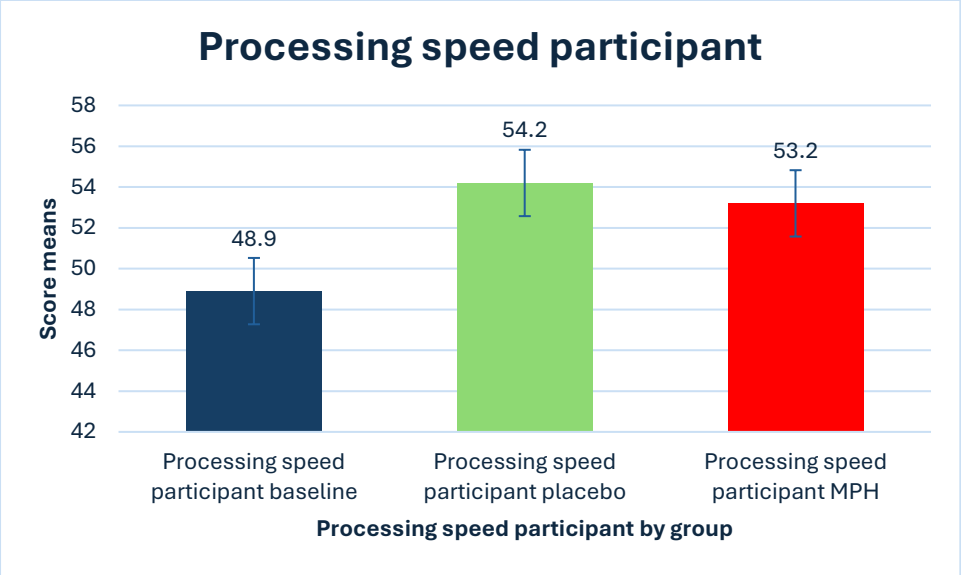


Figure 4.26 Psychometric Processing Speed Participant Scores

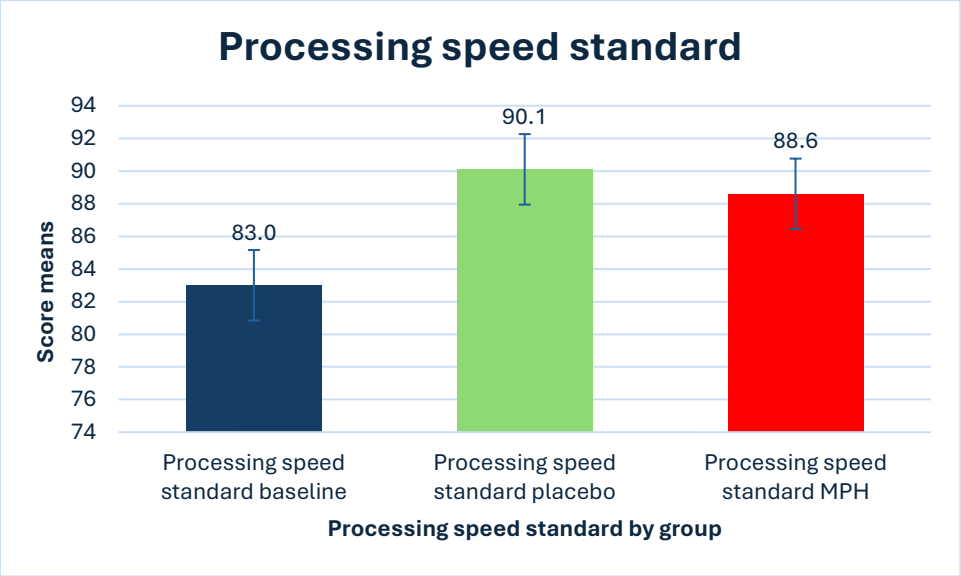


Figure 4.27 Psychometric Processing Speed Standard Scores

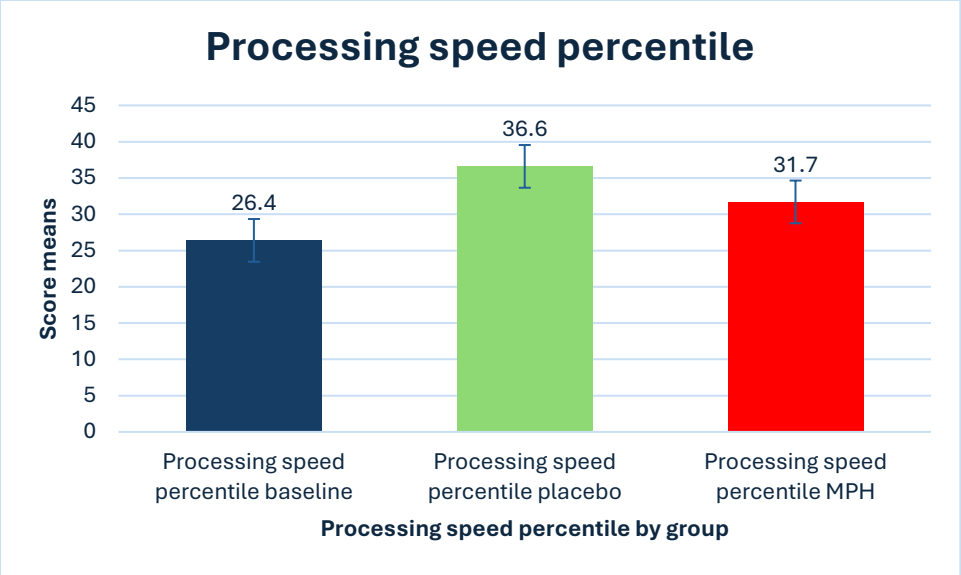


Figure 4.28 Psychometric Processing Speed Percentile Scores

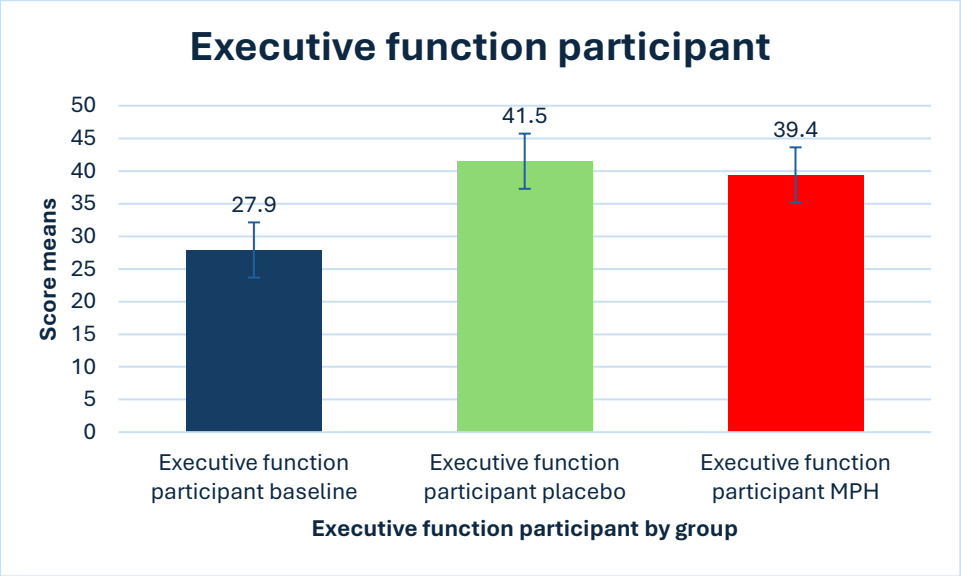


Figure 4.29 Psychometric Executive Function Participant Scores

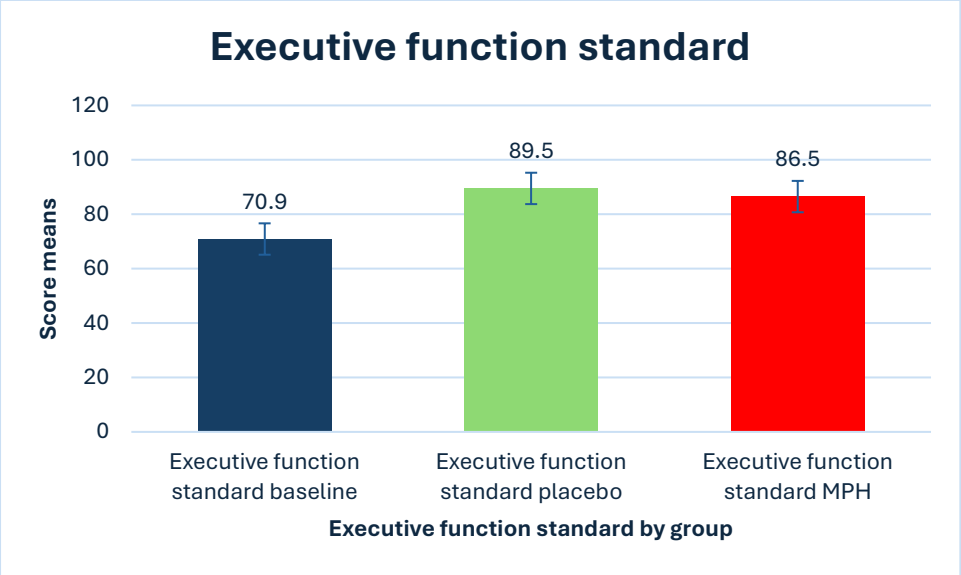


Figure 4.30 Psychometric Executive Function Standard Scores

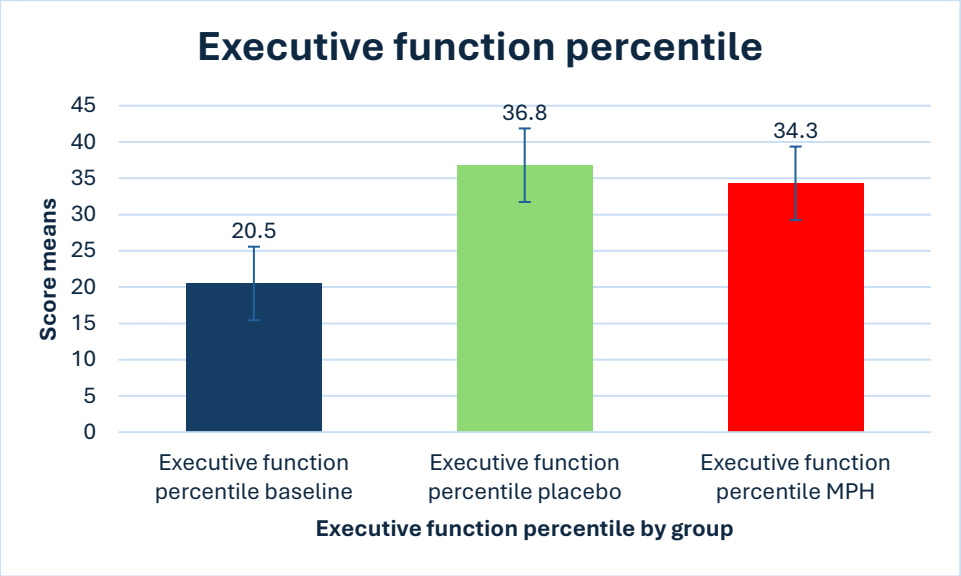


Figure 4.31 Psychometric Executive Function Percentile Scores

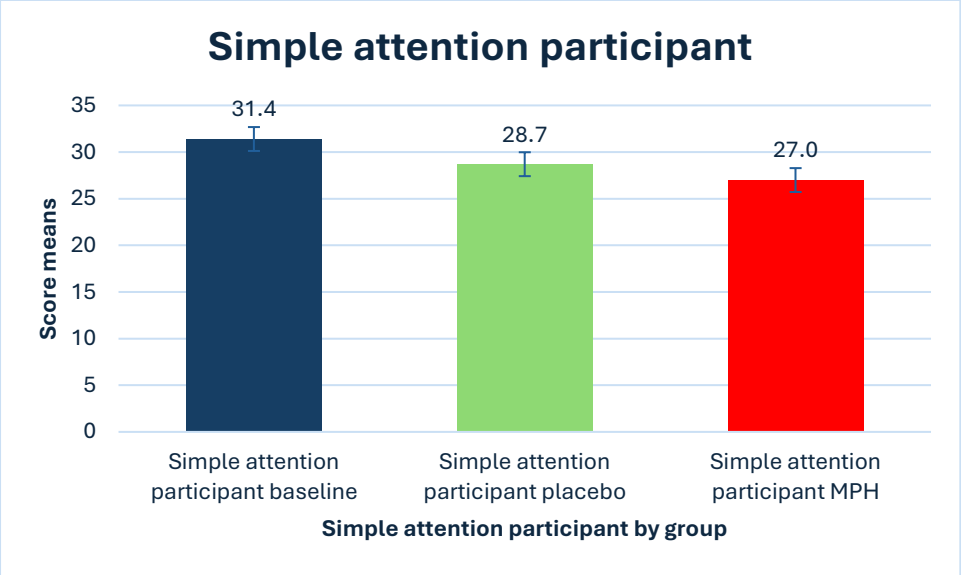


Figure 4.32 Psychometric Simple Attention Participant Scores

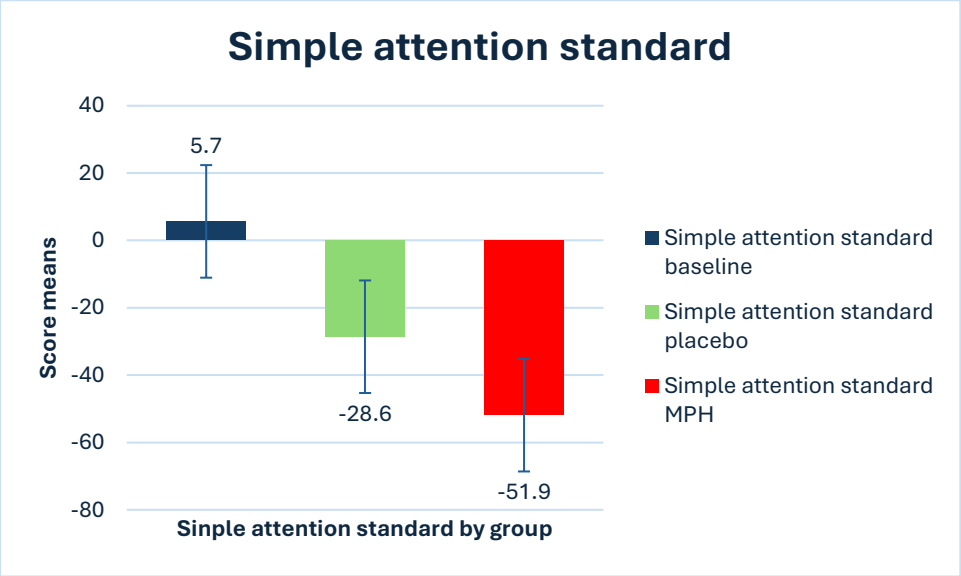


Figure 4.33 Psychometric Simple Attention Standard Scores

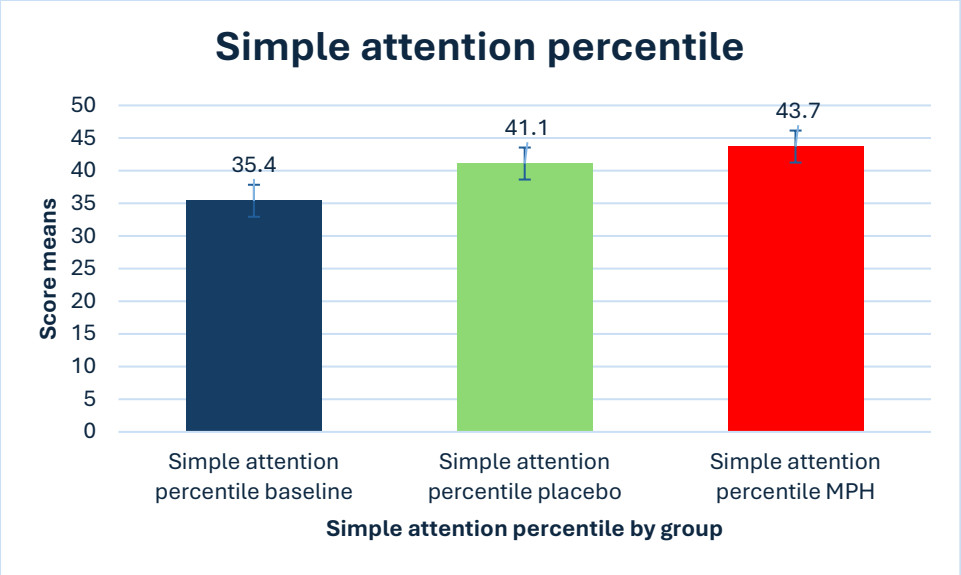


Figure 4.34 Psychometric Simple Attention Percentile Scores

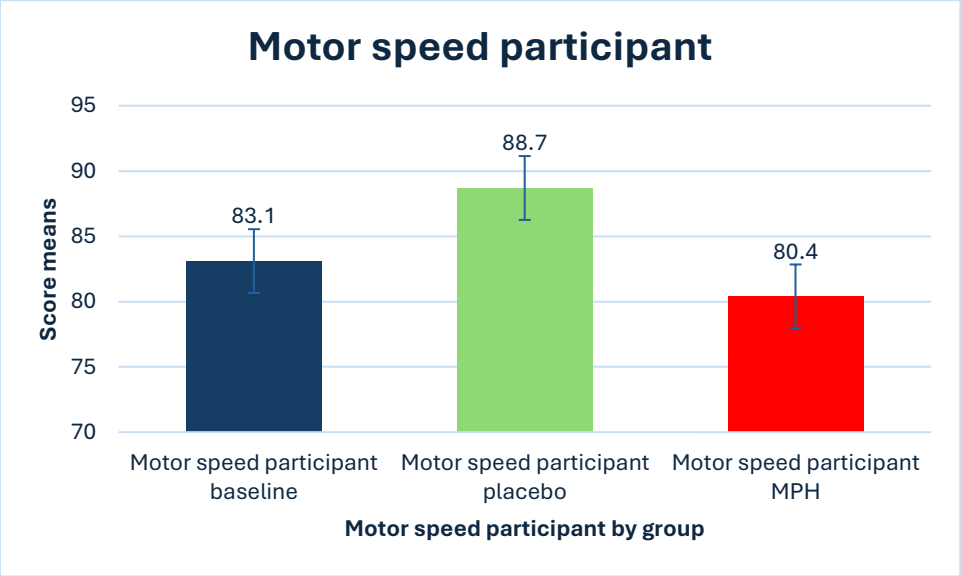


Figure 4.35 Psychometric Motor Speed Participant Scores

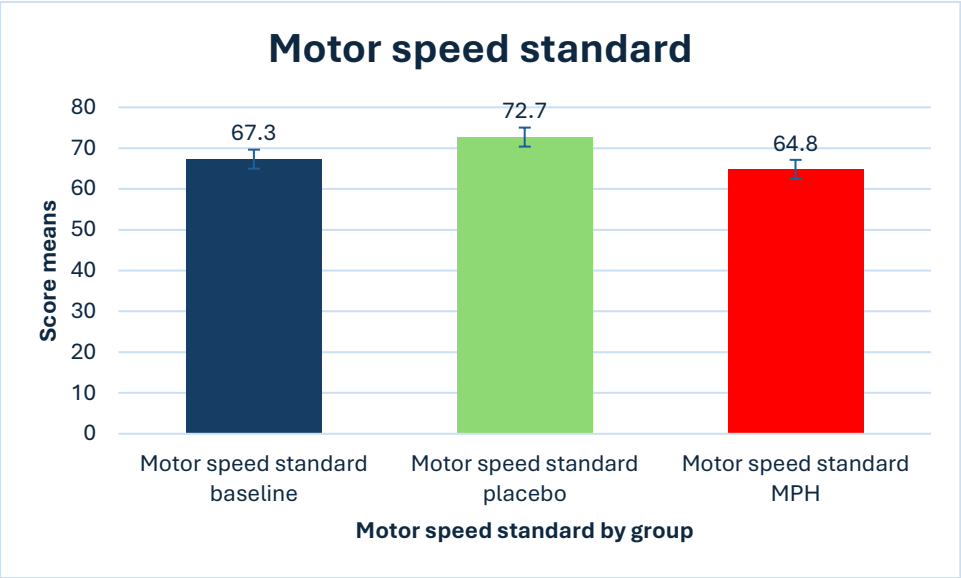


Figure 4.36 Psychometric Motor Speed Standard Scores

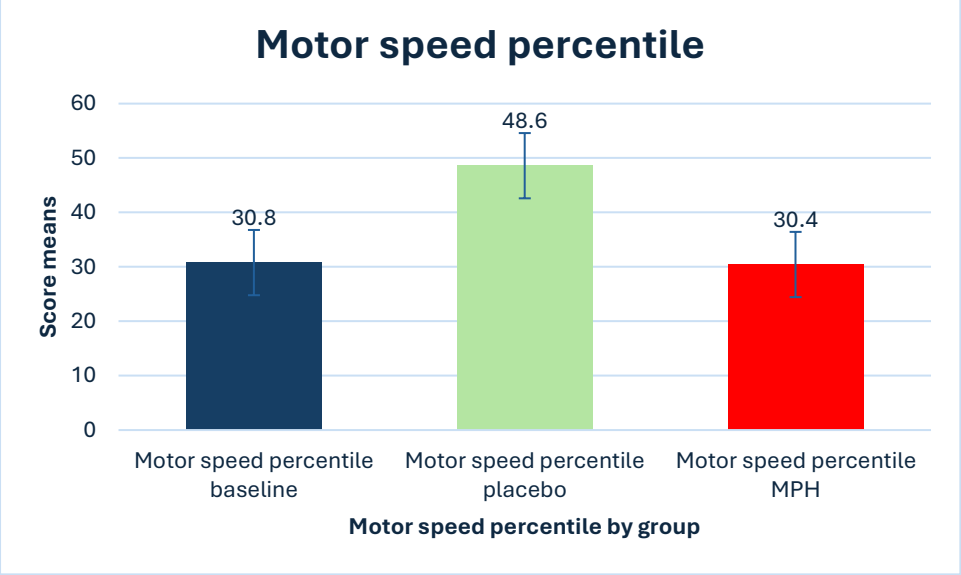


Figure 4.37 Psychometric Motor Speed Percentile Scores

4.2.5 Balance

Methylphenidate has been shown to enhance postural balance in adults with ADHD (Alotaibi et al., 2022; Alotaibi et al., 2023) and in healthy older adults (Ben-Itzhak et al., 2008; Shorer et al., 2013). However, its potential effects on postural balance in healthy younger adults remain unexamined.

The Modified Clinical Test of Sensory Interaction on Balance (mCTSIB) was used to measure postural balance using four scenarios: Eyes open on an (i) unstable (foam) surface and (ii) stable (firm) surface, and with eyes closed on an (iii) unstable (foam) surface and (iv) stable (firm) surface.

There were no significant differences between the groups with eyes open on a firm surface (p=0.74), eyes closed on a firm surface (p=0.98), eyes open foam surface (p=0.78), and eyes closed on foam surface (p=0.55) (Figure 4.38, Figure 4.43).

Individual differences were likewise similar, with no differences on placebo or MPH relative to baseline tests, as depicted in radar graphs (Figures 4.39 - 4.42). One outlier was noted with eyes open on an unstable surface in the MPH group (Figure 4.38 and Table 4.6).

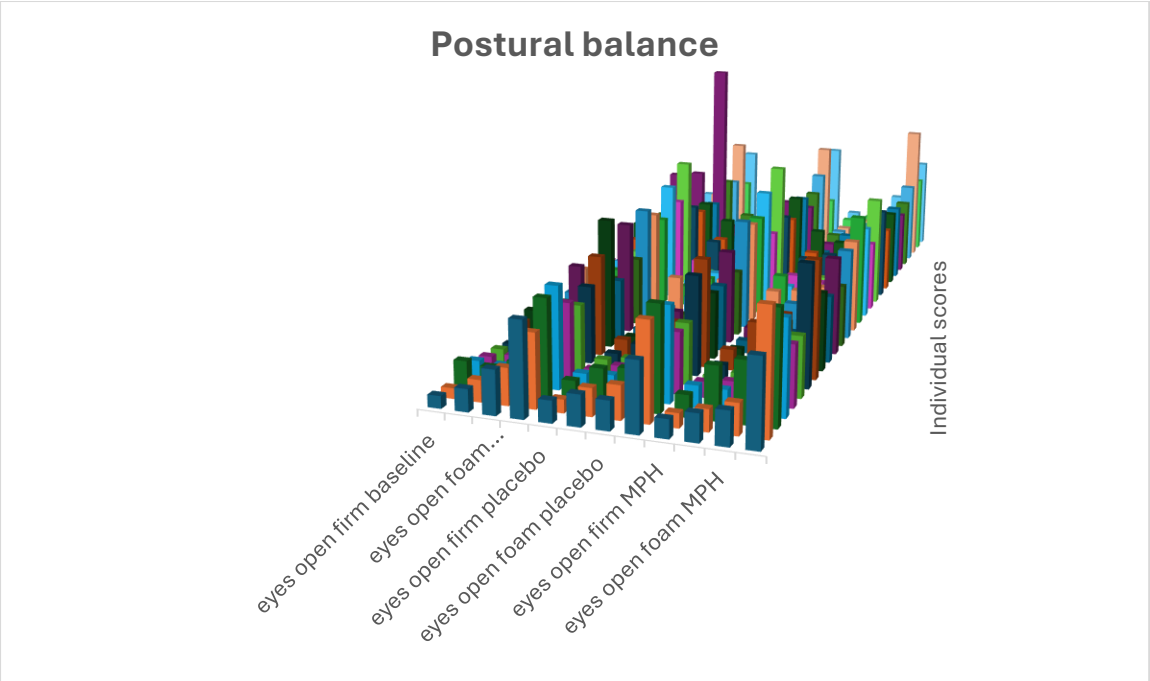
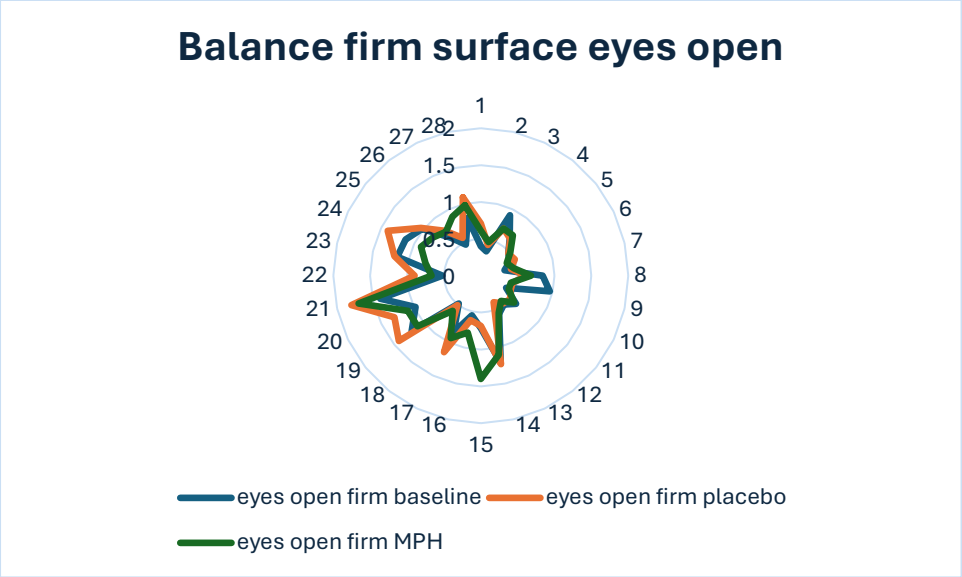
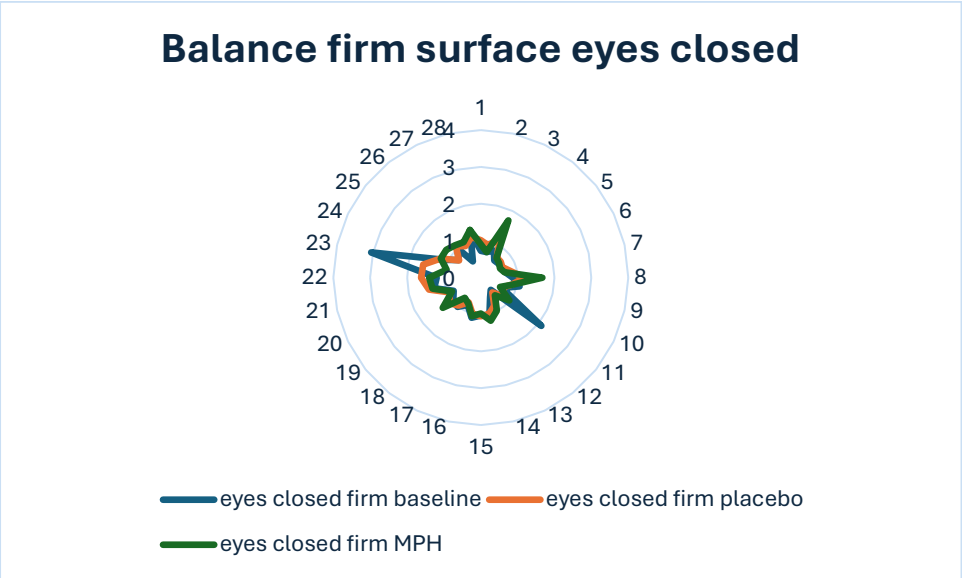


Figure 4.38 Composite Graphic of Postural Balance Tests



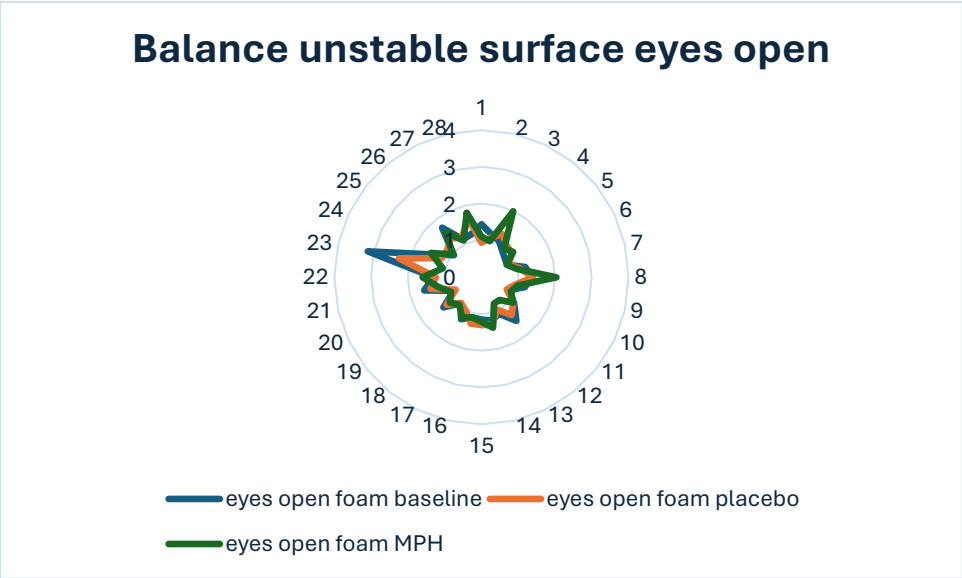
MPH methylphenidate

Figure 4.39 Postural Balance Eyes Open on Firm Surface for Individuals



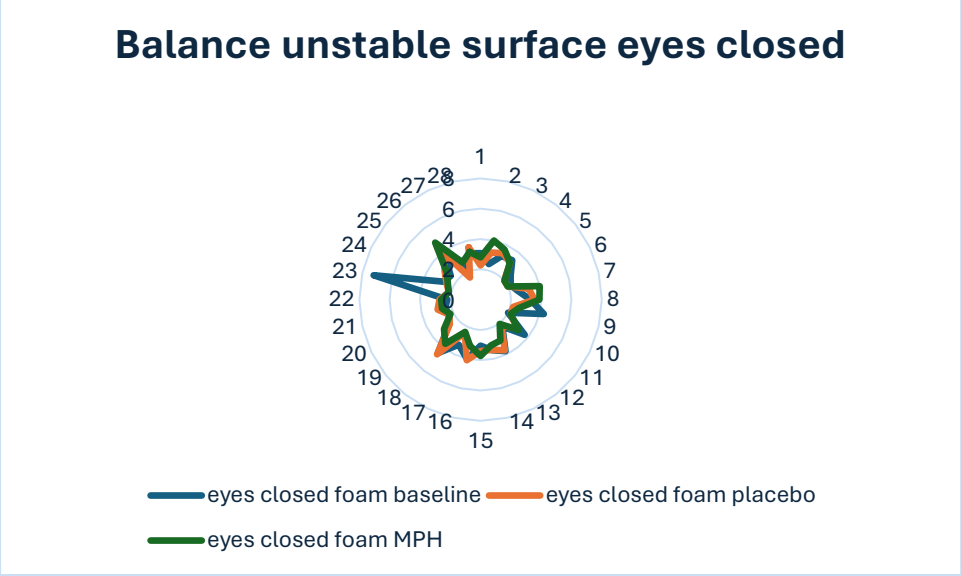
MPH methylphenidate

Figure 4.40 Postural Balance Eyes Closed Firm Surface for Individuals



MPH methylphenidate

Figure 4.41 Postural Balance Eyes Open Unstable (foam) Surface for Individuals



MPH methylphenidate

Figure 4.42 Postural Balance Eyes Closed Unstable (foam) Surface for Individuals

Table 4.6: Postural Balance Scores for Individuals

Participant	Eyes Closed Firm Baseline	Eyes Open Foam Baseline	Eyes Closed Foam Baseline	Eyes Open Firm Placebo	Eyes Closed Firm Placebo	Eyes Open Foam Placebo	Eyes Closed Foam Placebo	Eyes Open Firm MPH	Eyes Closed Firm MPH	Eyes Open Foam MPH	Eyes Closed Foam MPH
1	0.73	1.44	3.06	0.71	1.01	0.94	2.26	0.61	0.90	1.10	2.80
2	0.71	1.20	2.40	0.43	0.90	1.10	3.18	0.47	0.71	1.01	4.00
3	0.82	1.10	3.20	0.71	1.20	1.30	3.40	0.71	1.72	1.99	3.66
4	0.59	0.91	3.33	0.64	0.70	1.10	3.10	0.70	0.68	1.00	3.10
5	0.61	0.82	2.53	0.48	0.69	1.06	1.99	0.51	0.63	1.10	2.01
6	0.63	0.78	2.19	0.51	0.65	0.81	2.00	0.39	0.58	0.77	1.99
7	0.67	1.23	2.54	0.42	0.82	1.07	3.26	0.46	0.66	0.99	4.00
8	0.87	1.38	3.30	0.61	1.18	1.40	3.55	0.68	1.67	2.04	3.88
9	1.08	1.21	4.28	0.44	0.86	0.93	2.20	0.42	0.87	1.01	2.57
10	0.64	0.81	2.01	0.45	0.63	0.77	2.19	0.42	0.58	0.89	2.20
11	2.10	1.14	3.71	0.51	0.87	1.10	3.09	0.58	0.99	1.10	3.21
12	0.43	1.52	2.28	0.48	0.51	1.32	2.18	0.44	0.61	0.79	2.04
13	0.59	1.10	3.78	0.40	0.85	0.98	3.70	0.56	1.00	0.79	3.01
14	1.04	1.21	3.43	1.23	1.01	1.32	3.40	1.10	1.20	1.41	3.10
15	1.03	1.15	3.05	0.68	1.05	1.30	3.40	1.40	0.98	1.21	3.72
16	1.12	1.12	4.03	0.62	1.01	1.30	4.10	0.79	1.07	1.12	3.12
17	0.82	1.27	3.30	1.15	0.75	1.00	2.42	0.94	0.78	1.22	2.36
18	1.01	0.90	4.52	0.51	0.97	0.89	4.61	0.61	0.70	0.96	3.72
19	0.95	1.32	2.68	1.42	1.10	1.21	2.60	1.10	1.32	1.10	3.10
20	0.82	0.84	2.31	1.30	0.92	0.78	2.30	1.10	0.87	0.92	2.20
21	1.30	1.60	2.40	1.80	1.44	1.42	2.90	1.70	1.34	1.20	2.60
22	1.20	1.30	2.20	0.90	1.62	1.24	2.70	0.67	1.40	1.60	2.60
23	3.05	3.17	7.24	1.20	1.60	2.30	2.15	0.77	0.95	1.08	2.15
24	1.11	1.43	2.72	1.40	1.20	1.20	2.50	0.90	1.20	1.52	2.40
25	0.76	0.96	2.51	1.04	0.75	1.19	3.03	0.83	1.20	0.99	2.84
26	1.02	1.72	3.84	0.78	1.08	1.35	3.92	0.76	1.12	1.55	4.81
27	0.49	1.14	2.06	0.57	0.95	1.21	1.62	0.89	1.07	1.11	2.73
28	1.28	1.20	3.14	1.09	1.13	1.65	3.54	0.98	1.32	1.79	3.23
Mean	**0.98**	**1.27**	**3.18**	**0.74**	**0.98**	**1.16**	**2.96**	**0.73**	**1.00**	**1.19**	**3.07**
±SD	**±0.56**	**±0.56**	**±1.14**	**±0.32**	**±0.29**	**±0.23**	**±0.77**	**±0.29**	**±0.35**	**±0.33**	**±0.89**

Table 4.7: Postural Balance Means, Standard Deviations, Effect Sizes, and Confidence Intervals

Condition	Mean±SD (Placebo)	Mean±SD (MPH)	Cohen's *d*	95% CI (Placebo)	95% CI (MPH)
Eyes Open Firm	0.64±0.3	0.64±0.25	0.01	(0.551, 0.719)	(0.554, 0.720)
Eyes Closed Firm	0.89±0.27	0.91±0.29	0.06	(0.796, 0.981)	(0.808, 1.003)
Eyes Open Foam	1.11±0.28	1.11±0.28	0.00	(1.016, 1.205)	(1.018, 1.206)
Eyes Closed Foam	2.99±0.73	3.03±0.72	0.05	(2.746, 3.239)	(2.783, 3.272)

MPH methylphenidate, SD standard deviation, Cohen's *d* effect size, CI confidence intervals

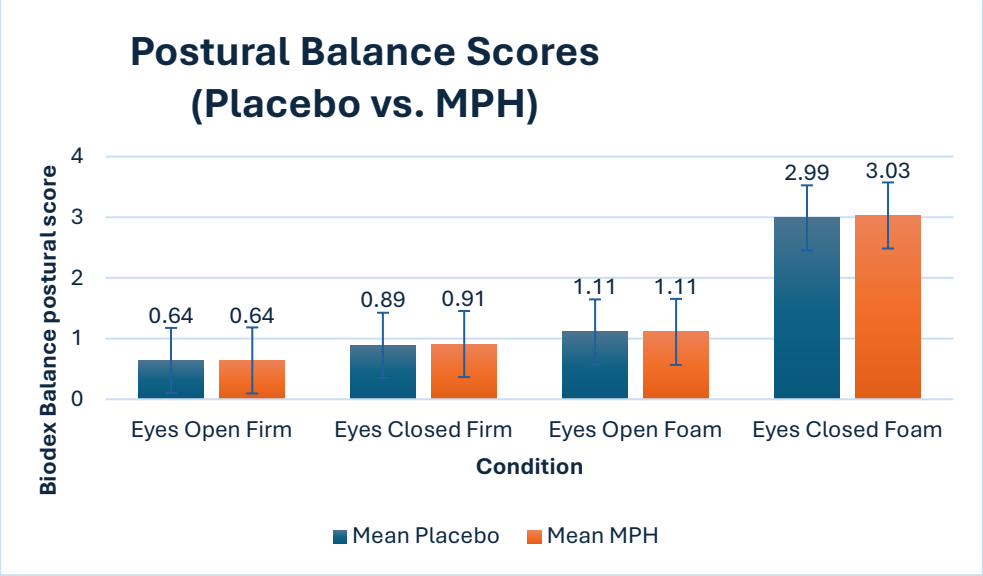


Figure 4.43 Postural Balance Scores

The means for the MPH and placebo groups are very similar across all conditions, suggesting a minimal impact of MPH on postural balance (Table 4.7). Cohen's *d* values are close to zero, indicating a negligible effect size. Confidence intervals overlap significantly, reinforcing that there is no meaningful difference between the two conditions. Although statistical significance was not reached, it is important to consider whether the magnitude of change observed in balance measures could be clinically meaningful. Thus, the effect size measure (Cohen's *d*) was calculated to provide

additional insight into whether any subtle balance improvements with MPH could be relevant in a real-world setting. This is not apparent.

4.2.6 Physical Performance (Muscle strength)

Handgrip strength (kg) measures using a digital hand dynamometer with the dominant hand did not show any significant difference between the groups (p=0.52) (Table 4.8). An analysis of variance (ANOVA) was performed to assess differences in handgrip strength between males and females across three conditions: baseline, placebo, and methylphenidate (MPH). The results revealed no statistically significant differences between groups in any condition:

- **Baseline:** $F(1, 26) = 1.88$, $p = 0.18$
- **Placebo:** $F(1, 26) = 3.02$, $p = 0.09$
- **MPH:** $F(1, 26) = 0.77$, $p = 0.39$

Despite the lack of statistical significance, effect sizes (Cohen's *d*) suggested medium to large effects:

- **Baseline:** $d = 0.93$
- **Placebo:** $d = 1.20$
- **MPH:** $d = 0.58$

These findings, summarised in Table 4.8, indicate that while group differences were not statistically significant, the observed effect sizes were substantial.

Table 4.8. Handgrip Strength (Total and by Gender)

Parameter	Total (Mean ± SD)	Females (n=25) (Mean ± SD)	Males (n=3) (Mean ± SD)	p-value	Cohen's *d*
Baseline	27.1±6.6	26.5 ± 6.6	30.9 ± 6.4	0.18	0.93
Placebo	27.99 ± 7.8	27.5 ± 7.5	33.3 ± 5.7	0.09	1.20
MPH	28.3 ± 7.6	27.54 ± 7.9	30.7 ± 8.7	0.39	0.58

MPH = methylphenidate; data are presented as means ± SD. Cohen's *d* effect size

4.2.7 Cardiac electrical activity

Resting and effort ECG morphological and electrical parameters were reviewed for any abnormalities. These included P Waves, PR interval, QRS complex, ST segments, T Waves, PR interval, QT intervals (and QT corrected (QTc), and RR intervals. The amplitude (height), duration (width), and shapes of the P Waves, T Waves and QRS complexes were reviewed. In addition, the rhythm and axes were analysed.

Clinical assessment of the ECG tracings at baseline and with placebo and MPH at rest, during exercise and in recovery did not reveal any differences (Appendix M). Therefore, none were secondarily reviewed by specialist cardiologists.

5. CHAPTER 5 – DISCUSSION

5.1 Overview of Findings

This study investigated the effects of methylphenidate (MPH) on physiological, neurocognitive, postural balance, and physical performance (muscle strength) parameters in drug-naïve healthy adults using a randomised, double-blind, placebo-controlled crossover design. It further evaluated cardiovascular risk side effects using physiological responses and electrocardiogram changes.

The results revealed several key findings:

5.1.1 Physiological Parameters:

Resting heart rate was significantly higher at baseline compared to placebo, but no significant differences were observed between placebo and MPH. Blood pressure (both systolic and diastolic) remained stable across all conditions.

Cardiopulmonary exercise testing (CPET) showed no significant differences in VO_2 peak, first ventilatory threshold (VT1) inflexion point, or oxygen pulse between baseline, placebo, and MPH conditions. However, small effect sizes suggested a small trend toward improved oxygen utilisation with MPH.

5.1.2 Neurocognitive Function:

Significant improvements were observed in reaction time, complex attention, and executive function when comparing baseline to both placebo and MPH. However, no significant differences were found between placebo and MPH, suggesting that the observed improvements may be due to practice effects or placebo responses rather than MPH itself. Effect sizes for cognitive flexibility were large (Cohen's *d* = -2.13 for baseline vs. placebo and -1.89 for baseline vs. MPH), indicating substantial improvements in cognitive performance from baseline, but between placebo and MPH a very small effect size was noted (Cohen's *d* 0.17).

5.1.3 Balance:

No significant differences were observed in postural balance across the four sensory conditions (eyes open/closed on firm/foam surfaces) between baseline, placebo, and MPH. Effect sizes were negligible, suggesting that MPH has no impact on postural balance in healthy adults.

5.1.4 Physical Performance (Muscle Strength):

Handgrip strength did not differ significantly between placebo and MPH. However, medium to large effect sizes were observed when comparing males and females, with males consistently demonstrating greater strength.

5.1.5 Cardiovascular risk and cardiac electrical activity

No abnormalities were detected in resting or exercise ECG tracings across all conditions and no significant changes in resting heart rate or blood pressure, indicating that MPH did not adversely affect cardiac risk or electrical activity in this healthy cohort.

5.2 Interpretation of Findings

The study involved 28 participants, and there might have been individual variations in response to MPH as illustrated in presented figures.

5.2.1 Physiological Parameters

The lack of significant changes in heart rate and blood pressure aligns with previous studies suggesting that MPH, at therapeutic doses, does not exert substantial cardiovascular effects in healthy individuals (Gualtieri & Johnson, 2006). The small effect sizes observed in CPET parameters (e.g. VT1, oxygen pulse) suggest subtle trends toward improved oxygen utilisation with MPH, although these did not reach statistical significance. However, these findings should be interpreted cautiously, as they did not reach statistical significance and may be influenced by individual variability. While statistically marginal, a 1–3% change in VO_2 kinetics could be physiologically meaningful in elite athletic performance, where marginal gains are often pursued. However, for most healthy adults, such minor improvements likely lack

clinical relevance, reinforcing that MPH's ergogenic potential in this population is limited.

5.2.2 Neurocognitive Function

The observed improvements in reaction time, complex attention, and executive function from baseline to MPH conditions (Cohen's *d* = -1.89) are neurobiologically plausible, given MPH's known action as a DA and norepinephrine reuptake inhibitor in prefrontal-striatal circuits (Arnsten, 2006) and with the known cognitive-enhancing effects of MPH in clinical and healthy populations (Finger et al., 2013). However, the parallel improvements seen with placebo (*d* = -2.13) and the absence of significant MPH-placebo differences (*d* = 0.17) suggest these enhancements suggest that these effects may not be robust enough to be clinically meaningful in healthy adults.

They primarily reflect either:

1. **Practice effects** from test repetition, as the CNS Vital Signs battery shows significant learning effects across administrations, or
2. **Expectation-driven placebo responses** mediated by prefrontal DA release.

While the large effect sizes for cognitive flexibility might suggest MPH's potential to enhance higher-order functions, three critical considerations emerge:

1. **Clinical meaningfulness**: The minimal clinically important difference for cognitive tests typically requires *d* ≥ 0.5 (Borland et al., 2022) making the observed MPH-placebo difference (*d* = 0.17) functionally negligible.
2. **Neurochemical ceilings**: Healthy adults may have limited capacity for further dopaminergic enhancement due to baseline receptor occupancy (Volkow et al., 2002), unlike ADHD populations with pre-existing hypodopaminergia.
3. **Task specificity**: The improvements may have been most pronounced in timed tasks potentially reflecting increased arousal rather than true cognitive enhancement.

5.2.3. Balance

The absence of significant differences in postural balance across all conditions is consistent with the limited literature on MPH's effects on balance in healthy adults. While MPH has been shown to improve balance in individuals with ADHD and older adults (Alotaibi et al., 2022; Ben-Itzhak et al., 2008), these effects do not appear to extend to healthy younger adults. This may be due to ceiling effects, as healthy individuals already exhibit optimal balance performance, leaving little room for improvement. The dissociation between cognitive trends (medium effects) and null findings in balance/physical performance suggests MPH's actions are domain-specific, primarily modulating CNS pathways governing attention rather than peripheral neuromuscular function. This aligns with PET evidence showing MPH's preferential binding to striatal dopamine transporters (Volkow et al., 2001).

5.2.4. Physical Performance (Muscle Strength)

The lack of significant differences in handgrip strength between placebo and MPH conditions suggests that MPH does not enhance muscle strength in healthy adults. However, the medium-to-large effect sizes observed when comparing males and females highlight the importance of considering gender differences in physical performance studies. Males consistently demonstrated greater handgrip strength, which is consistent with established norms (España-Romero et al., 2010).

5.2.5. Cardiac Electrical Activity

The absence of ECG abnormalities across all conditions is reassuring and aligns with previous research indicating that MPH does not significantly alter cardiac electrical activity in healthy individuals (Shorer et al., 2013). This finding supports the safety of MPH use in healthy populations, at least in the short term.

5.3 Integrated Interpretation of Cross-Domain Findings

It was shown in the literature review how variable results have been reported on the effects of MPH in those with ADHD and although the study focused on drug-naïve

healthy adults one should consider how results might differ from those in individuals with ADHD. There were also varying results between the outcome measures.

The dissociation between MPH's effects across physiological, neurocognitive, and physical domains underscores its system-specific mechanisms of action and highlights critical considerations for its off-label use in healthy adults:

- **Central vs. Peripheral Effects: A Neurochemical Dichotomy**
  - **Neurocognitive Enhancement (Central):**
    The observed directional improvements in executive functioning are consistent with MPH's well-characterised pharmacological action of potentiating dopaminergic neurotransmission in cortico-striatal pathways (Arnsten, 2006). The absence of statistically significant differences between MPH and placebo conditions likely reflects neurobiological saturation effects in healthy individuals, where intact dopaminergic tone limits further cognitive optimisation - in contrast to ADHD populations characterised by pre-synaptic dopamine deficiency (Volkow et al., 2002). This neurochemical ceiling effect suggests fundamental differences in MPH's mechanism of action between clinical and non-clinical populations.
  - **Null Effects on Physical Performance (Peripheral):**
    The absence of improvements in handgrip strength or postural balance implies MPH does not augment peripheral neuromuscular or vestibular function. This contrasts with its efficacy in ADHD-related motor control deficits (Bucci et al., 2016), further supporting its CNS-specificity in non-clinical users.

2. Cardiovascular-Physiological Coupling

- **Stable Haemodynamics Despite Cognitive Trends:**
  While MPH increased cognitive arousal (reflected in reaction time), it did not significantly alter heart rate, blood pressure, or ECG parameters. This dissociation suggests that cognitive enhancement in healthy adults may occur independently of cardiovascular strain at therapeutic doses—a critical safety insight for off-label use.
- **CPET Implications:**

The small, non-significant improvements in oxygen utilisation (VT1, O_2 pulse) lacked concordance with cognitive or physical outcomes. This may reflect MPH's limited ergogenic potential in healthy populations, as aerobic capacity is more tightly coupled to peripheral (e.g., muscular, vascular) than central adaptations.

3. **Translational Implications**

- **For Athletic Performance:**

  The lack of meaningful improvements in physical or aerobic metrics challenges the perception of MPH as a "universal enhancer" in sports. Its utility may be restricted to sports requiring sustained attention (e.g., endurance events) rather than strength or power.

- **For Cognitive Enhancement:**

  The modest, placebo-matched cognitive effects question the risk-benefit ratio of off-label MPH use in healthy adults

5.3 Implications of the Study

This study contributes to the growing body of literature on the effects of MPH in healthy adults. The findings suggest that while MPH may enhance certain cognitive functions, these effects are not significantly different from those observed with a placebo. Our findings in healthy adults suggest a ceiling effect, where intact dopaminergic systems limit further enhancement. This dichotomy highlights the importance of diagnosis-specific risk/benefit assessments for MPH use. This has important implications for the use of MPH as a cognitive enhancer in healthy populations, as the benefits may be modest and potentially outweighed by the risks of long-term use.

The study also highlights the importance of considering practice effects and placebo responses in cognitive research. Future studies could incorporate larger sample sizes to better isolate the pharmacological effects of MPH from practice and placebo effects. Due to the possibility of varying outcomes over time, longitudinal research designs

should be emphasised to clarify causal relationships, monitor developmental pathways, and address within-individual variability. These studies would generate strong evidence of long-term effects and ensure the reliability of findings in exploring complex phenomena.

5.4 Limitations

Several limitations should be acknowledged:

1. **Sample Size:** The study included a relatively small sample size (n=28), which may have limited the ability to detect small but meaningful differences between conditions.
2. **Practice Effects:** The crossover design, while methodologically robust, may have introduced practice effects, particularly in the neurocognitive assessments.
3. **Healthy Population:** The findings may not generalise to clinical populations or individuals with pre-existing conditions.
4. **Short-Term Use:** The study assessed the effects of MPH over a short period (14 days), acknowledging the short term effects and half-life of MPH. Longer-term studies are needed to evaluate MPH use's sustained effects and potential risks in healthy adults.
5. **Gender Imbalance:** The female-predominant sample (25F:3M) limits generalisability, given known sex differences in DA receptor and MPH metabolism density (Andersen & Teicher, 2000).
6. **Fixed-Dose Design:** A single 20 mg/day dose may overlook dose-response relationships.
7. **Ecological Validity:** While CNS Vital Signs is validated, its computerised tasks may not capture real-world cognitive demands (e.g., multitasking under stress).
8. **Dietary/Activity Confounders:** Uncontrolled variables (e.g., nutrition, exercise fluctuations) may have introduced noise, particularly given MPH's appetite-suppressant effects (Goldfield et al., 2007).

9. **Drug-Naïve Status:** While focusing on drug-naïve individuals is a strength for understanding baseline effects, it means the results might not directly apply to individuals who have been using MPH chronically.
10. **Measurement Timing:** The timing of the outcome measurements after the 14-day treatment period might have captured steady-state effects but might have missed peak drug effects or any potential acute changes that occurred earlier

5.5 Future Research Directions

Future research should aim to:

1. **Address Individual Variability**: future research could explore factors contributing to this variability.
2. **Increase Sample Size**: Larger studies would provide more statistical power to detect subtle differences between conditions.
3. **Extend Duration:** Longer-term studies are needed to assess the sustained effects of MPH and potential risks associated with prolonged use.
4. **Control for Practice Effects:** Incorporating longer crossover periods or alternative study designs could help mitigate practice effects and better isolate the pharmacological effects of MPH.
5. **Personalised Dosing Trials**: Investigate dose optimisation based on pharmacogenomics and baseline cognition.
6. **Real-World Cognitive Testing:** Use ambulatory assessments (e.g., smartphone-based tasks) to enhance ecological validity.
7. **Longitudinal Safety:** Monitor cardiovascular/metabolic outcomes in chronic users, leveraging wearable technology.

5.6 Conclusion

In conclusion, this study provides evidence that MPH does not significantly enhance cardiovascular physiological, postural balance, or physical performance (muscle

strength) parameters in healthy adults. While improvements in certain cognitive functions were observed, these effects were not significantly different from those seen with placebo, suggesting that the benefits of MPH as a cognitive enhancer in healthy populations may be limited. The study further demonstrated no significant increases in cardiovascular parameters or cardiac electrical activity changes, suggesting an absence of short-term risks associated with the intervention. The findings underscore the importance of considering practice effects and placebo responses in cognitive research and highlight the need for further investigation into the long-term effects of MPH use in both healthy populations.

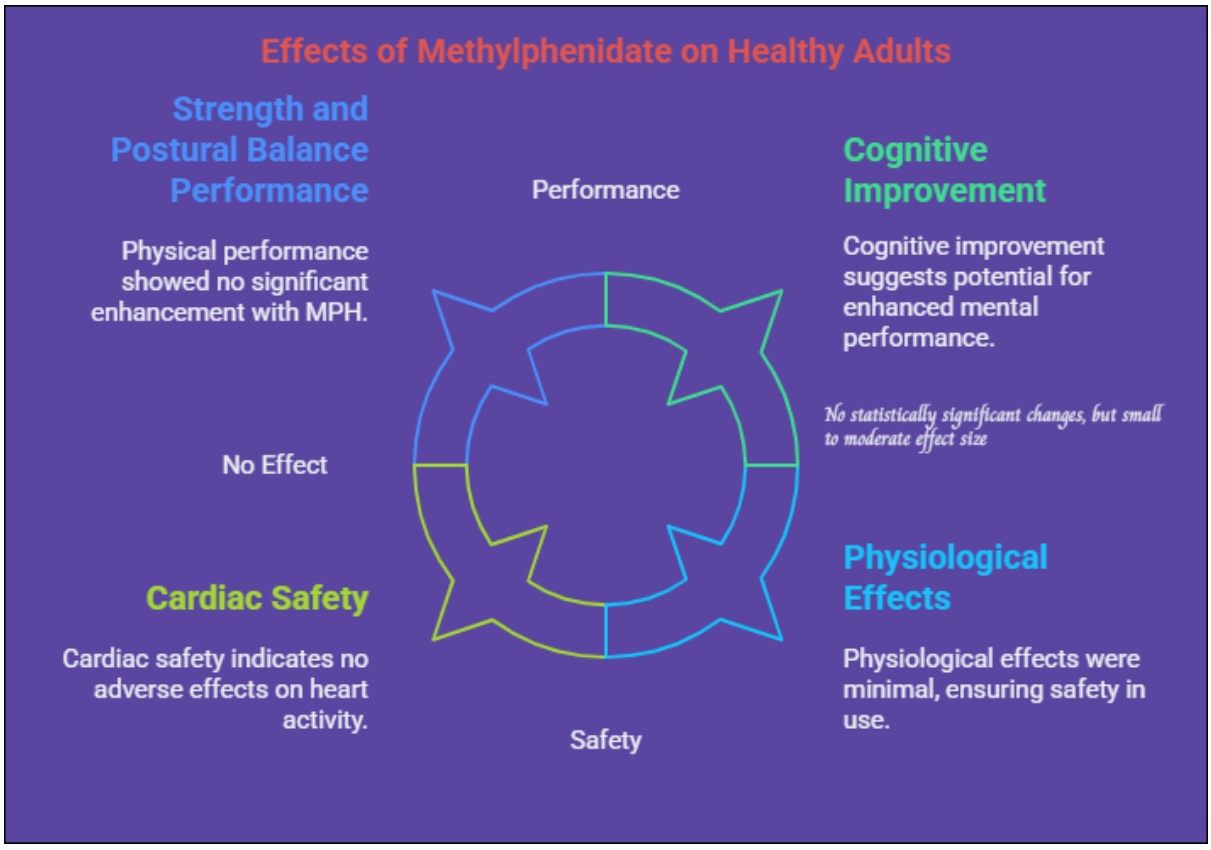


Figure 5.1 Infographic summarising study findings

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275. ADDENDUMS

ADDENDUM A: Physical Activity Readiness Questionnaire (PAR-Q)

PAR Q Participant code:.....

Physical Activity Readiness Questionnaire (PAR-Q)

PATIENT'S NAME: _____ **DOB:** _____

DATE: _____

HEALTHCARE PROVIDER'S NAME: _____

Please read the questions below carefully, and answer each one honestly. Please check YES or NO.

☐ Yes	☐ No	Has your healthcare provider ever said that you have a heart condition and that you should only do physical activity recommended by a healthcare provider?
☐ Yes	☐ No	Do you feel pain in your chest when you do physical activity?
☐ Yes	☐ No	In the past month, have you had chest pain when you were not doing physical activity?
☐ Yes	☐ No	Do you lose your balance because of dizziness or do you ever lose consciousness?
☐ Yes	☐ No	Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?

Excerpted from the Physical Activity Readiness Questionnaire (PAR-Q) © 2002. Used with permission from the Canadian Society for Exercise Physiology.

ADDENDUM B: Physical Activity/Exercise Stages of Change (PARMed)

Participant code.....

Exercise Stages of Change Questionnaire

Goal: To do physical activity or exercise regularly, such as accumulating:

- 150 minutes of moderate physical activity per week, or
- 75 minutes of vigorous physical activity per week, or
- a combination of moderate and vigorous physical activity each week, such as
    - 75 minutes of moderate and 40 minutes of vigorous physical activity, or 90 minutes of moderate and 25 minutes of vigorous physical activity

Examples of Moderate-Intensity Activity

- Brisk walking
- Biking<10 mph (16kph)
- Ballroom dancing
- General gardening, such as weeding
- Golfing (no cart)
- Any other physical activity where the exertion is similar to these

Examples of Vigorous-Intensity Activity

- Jogging, running
- Tennis
- Biking>10 mph (16kph)
- Aerobic dancing
- Heavy gardening, such as digging
- Any other physical activity where the exertion is similar to these

Regular physical activity means meeting or exceeding the physical activity goal described above.

For each statement, please mark yes or no.

1. I am currently physically active (at least 30 minutes per week). ☐ Yes ☐ No
2. I intend to become more physically active in the next 6 months. ☐ Yes ☐ No
3. I currently engage in **regular** physical activity. ☐ Yes ☐ No
4. I have been **regularly** physically active for the past 6 months. ☐ Yes ☐ No

Exercise Stages of Change - Scoring Key

- *No* to 1, 2, 3, and 4 = Pre-contemplation stage
- *No* to 1, 3, and 4, Yes to 2 = Contemplation stage
- *Yes* to 1 and 2, No to 3 and 4 = Preparation stage
- *Yes* to 1 and 3, Yes or No to 2, No to 4 = Action stage
- *Yes* to 1, 3, and 4, Yes or No to 2 = Maintenance stage

ADDENDUM C: ACSM Risk Stratification Screening Questionnaire

ACSM Risk Stratification Screening Questionnaire

Assess your health by marking all true statements.

You have had:

___ a heart attack
___ heart failure
___ cardiac arrhythmia
___ known heart murmur
___ congenital heart disease
___ any heart surgery
___ coronary angioplasty
___ heart palpitations

You have:

___ experienced chest pain with mild exertion
___ experienced dizziness, fainting, or blackouts with mild exertion
___ experienced unusual fatigue or shortness of breath during usual activities
___ been prescribed heart medications (please indicate):

Check all that apply:

___ you are a man older than 45 years
___ you smoke
___ your blood pressure is greater than 140/90
___ you take blood pressure medication
___ you are completely physically inactive
___ you currently have bone/joint problems
___ you have had a recent injury/surgery
___ you are a diabetic or take medicine to control your blood sugar
___ you have been diagnosed with high cholesterol >200 (or HDL is less than 35 mg/dL or LDL is greater than 169 mg/dL)
___ you have a close blood relative who had a heart attack before age 55 (father/brother) or age 65 (mother/sister)

___ Other (specify) _____

Use the following risk stratification scoring table (page) to sum the total number of risk factors present in your patient in determining their current level of cardiovascular disease risk.

Risk Stratification Scoring

Positive Risk Factors	Defining Criteria	Points
Age	Men ≥ 45 years, Women ≥ 55 years	+1
Family History	Myocardial infarction, coronary revascularization, or sudden death before 55 years of age in father of other 1st degree male relative or before 65 years of age in mother or other 1st degree female relative	+1
Cigarette Smoking	Current cigarette smoker or those who quit within the previous six months, or exposure to environmental tobacco smoke (i.e., secondhand smoke)	+1
Sedentary Lifestyle	Not participating in at least 30 minutes of moderate-intensity physical activity on at least three days/week for at least three months	+1
Obesity	Body mass index ≥30 kg/m^2 or waist girth >102 cm (40 inches) for men >88 cm (35 inches) for men	+1
Dyslipidemia	Low-density lipoprotein (LDL) cholesterol ≥ 130mg/dL (3.37 mmol/L) or high-density lipoprotein (HDL) cholesterol <40mg/dL (1.04mmol/L) or currently on lipid-lowering medication; If total serum cholesterol is all that is available, use serum cholesterol >200 mg/dL (5.18mmol/L)	+1
Prediabetes	Fasting plasma glucose ≥100 mg/dL (5.50 mmmol/L) but <126 mg/dL (6.93 mmol/L) or impaired glucoe tolerance (IGT) where a two-hour oral glucose tolerance test (OGTT) value is ≥140 mg/dL (7.70 mmol/L), but <200 mg/dL (11.00mmol/L)	+1
Negative Risk Factors	**Defining Criteria**	**Points**
High HDL Cholesterol	≥60 mg/dL (1.55 mmol/L)	-1

Total CVD Risk Score: _____

* See Appendix E for Risk Categories and related recommendations for Screening, Clinical Testing, and Exercise Recommendations.

ADDENDUM D: Information brochures for participant recruitment

You are invited to participate in a study being undertaken at Wits University to measure the effects of Methylphenidate on physical and cognitive performance (e.g. attention)

Information

- You will be given detailed information
- Research done according to ethical principles and confidentially
- You will need to sign consent, and complete some forms
- Measurements and tests will be done at Wits (Education Campus, Parktown) (with nominal travel reimbursement)

Tests

- Tests include a fitness test and computer task tests
- Duration 1 to 1½hours

Medication

- You will either continue to take Methylphenidate or placebo (inactive capsule)
- Methylphenidate side effects may include eexcitement, dry mouth, insomnia, excessive sweating, loss of appetite
- After 2 weeks, the tests will be repeated
- You will then take the other capsule for 2 weeks and then the tests will be repeat

For more information or to participate please contact:

Prof D Constantinou

011 717 3396 / 011 717 3372 demitri.constantinou@wits.ac.za

ADDENDUM E: Posters for participant recruitment

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Are you taking or been prescribed Methylphenidate?

(Ritalin / Concerta/ Aceria / Medikinet / Contramyl / Mefedinel / Neucon / Radd)

Adults and children from 8 years old are invited to participate in a study being undertaken at Wits University to measure the effects on physical and cognitive performance (e.g. attention)

INFO

- You will be given detailed information
- Research done according to ethical principles and confidentially
- You will need to sign consent, and complete some forms

TESTS

- Measurements and tests will be done at Wits (Education Campus, Parktown) (with nominal travel reimbursement)
- Tests include a fitness test and computer task tests
- Duration 1 to 1½hours

Medication

- You will either continue to take Methylphenidate or placebo (inactive)
- Methylphenidate side effects may include excitement, dry mouth, insomnia, excessive sweating, loss of appetite
- After 2 weeks, the tests will be repeated
- You will then take the other capsule for 2 weeks and then the tests will be repeated

For more information or to participate please contact:

Prof D Constantinou

011 717 3396 / 011 717 3372 demitri.constantinou@wits.ac.za

ADDENDUM F: Information document for participants

Information Document for adult participants

The University of the Witwatersrand Centre for Exercise Science and Sports Medicine
Study title: Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects

Good day. My name is Demitri Constantinou, and this study forms a part of my PhD at the University of the Witwatersrand.

In this study we hope to answer questions about the effects of a drug called Methylphenidate, which is often prescribed by doctors to patients who are diagnosed as having Attention Deficit Hyperactivity Disorder (ADHD), on aspects of human function. These will include the control of the heart, muscle strength and aerobic fitness, balance, and conscious mental processes.

Invitation to participate: We are inviting you to take part in this research study

What is involved in the study

The study will involve several tests to be conducted on you before treatment by the specialist has been started. The adult participants will form one of the two groups in the study (the other contains only children). Your group will be randomly divided and given medication to take for 2 weeks. The medication will either be active Methylphenidate, or a placebo. A placebo is inactive medication. Neither the researcher nor the participant will know which medication will be provided, so that tests are not influenced. Then there will be a 3 day period of no medication and then the medication (either Methylphenidate or the placebo) will be swopped around, so the same people will now take the other treatment for a further 2 weeks. A 2 week period is not a significant time to delay treatment of this chronic condition, but long enough for purposes of the study. The dosage should not be changed during the period of the study. The information derived may have a significant contribution to science. The results will be analysed to measure any changes.

The measurements will be performed at the Centre for Exercise Science and Sports Medicine on the Wits Education Campus in Parktown, Johannesburg during the first quarter of 2019. There is no cost to participants, except for their time and all participants will be compensated with R100 per visit for testing. The procedures will take approximately an hour to complete. You will be one of approximately 70 people from the greater Johannesburg area.

A questionnaire will be completed which includes medical and physical activity details, followed by the tests being performed.

The tests will comprise:

Anthropometric and physiological parameters

1. **Anthropometry**: Height (m) and weight (kg). These will take less than 2 minutes to complete
2. **Physiological parameters** (about 20 minutes) Electrocardiogram (ECG) and heart rate – after 5 minutes rest and taken from the electrocardiogram (ECG). Blood pressure (mmHg)
   The maximum minute power (MMP), maximum heart rate (MHR), power to weight ratio, VO_2max estimate, METs (metabolic equivalents) will be determined using a Wattbike® for adults. These tests start at slow speeds and intensities and are gradually increased
3. **Postural balance** (5 minutes) will be measured using the Biodex Balance system, which involves standing on a platform which measures the balance with eyes open and with eyes closed
4. **Physical parameters** (10 minutes) : Muscle strength will be determined by handgrip strength (kg) on the dominant side using a hand dynamometer which is essentially a squeeze test.. Leg power will be measured using a jumping test .
5. **Psychometric tests** (20 minutes) : ImPACT® or similar programme is a computer-administered test that assesses attention, verbal visual memory and learning, numerical sequencings, process speed and reaction time, therefore analysing six neurocognitive areas.

In this study, the ImPACT® test will be used to measure changes in neurocognitive function that MPH may have. In addition the Stroop test will be used as an online tool using numbers and colours and also used for testing the above (attention, memory, reaction time etc.)

The tests conducted will be performed 4 times – at the start, after having been on the first medication or placebo, before starting on the switched over placebo/medication and at the end of the study period.

Academic and sport performances: In order to assess changes in academic and sporting performance, where relevant to individual participants, records will be kept by the participants and the treating doctors to be completed at start of study, halfway and at the end.

Risks: All the tests are largely non-invasive. There are minimal risks, and no more than would be found in everyday activities. The most bodily stressful activity will be walking and running for a short period of time, or cycling. All precautions will be taken to ensure this is done safely. The researcher who will be conducting the testing is a qualified medical doctor. Should there be any injury, this will be assessed and managed by him. Where a participant's wellbeing is not at risk, the first placebo group would have a delay in their treatment for approximately 4 weeks (maximum), but this is not limb or life threatening and similar studies on many medications have been conducted in this way. In the case of the second placebo group, the delay would come down to about two weeks (maximum).

Benefits: There are no direct benefits being in the study; however there will be information on strength, aerobic fitness, electrocardiogram and health screening that may be provided to the individual. The participant will be given pertinent information on the study while involved in the project and after the results are available.

Participation is voluntary: Refusal to participate will involve no penalty and the subject may discontinue participation at any time without penalty. Normal medical care will not be affected.

Confidentiality: Every effort will be made to keep personal information confidential. Personal information may be disclosed if required by law. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Research Ethics Committee and the South African Health Products Regulatory Authority (SAHPRA) (where appropriate). All of these instances would be very exceptional.

Contact details of researcher/s: (for further information / reporting of study related adverse events) Demitri Constantinou. Tel. No. 011 717 3372, Fax No. 086 63 63173, Email: demitri.constantinou@wits.ac.za

Contact details of supervisors: Professor AD Rothberg at Email: alan.rothberg@wits.ac.za and Professor M Lambert at Email: mike.lambert@uct.ac.za

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Study Information Sheet.

ADDENDUM G: Informed Consent Document

Informed Consent (Adult participants)

The University of the Witwatersrand Centre for Exercise Science and Sports Medicine

Study Title: Methylphenidate: Physiological, neurocognitive, balance, and physical performance

- I hereby confirm that I have been informed by the study primary investigator, Demitri Constantinou, about the nature, conduct, benefits and risks of the clinical study: Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects. I have also received, read and understood the Participant Information Leaflet regarding the study.
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be anonymously processed in a computerised system by the primary researcher Demitri Constantinou • I may, at any stage, without prejudice, withdraw my consent and participation in the study. This will in no way affect the medical care I am receiving for Attention Deficit Hyperactivity Disorder (ADHD) • I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.

PARTICIPANT:

Printed Name:Signature:

Date: _____

PRINCIPAL INVESTIGATOR

I, Demitri Constantinou, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

Signature:

_____

Date:

_____

ADDENDUM H: Pharmacy coding key (for blinding)

Participant code and capsule

	Code	First capsule	Second capsule
1	8207	A	B
2	8209	A	B
3	8212b	B	A
4	8210	B	A
5	8206	A	B
6	8212a	A	B
7	8211	A	B
8	8214	A	B
9	8215	B	A
10	8213	A	B
11	8208	A	B
12	8213b	B	A
13	8190	B	A
14	8202	A	B
15	8200	A	B
16	8192	A	B
17	8188	B	A
18	8201	B	A
19	8205	A	B
20	8204	B	A
21	8203	A	B
22	8189	B	A
23	8195	A	B
24	8198	A	B
25	8199	A	B
26	8197	B	A
27	8194	B	A
28	8193	A	B
29	8196	B	A
30	8191	A	B

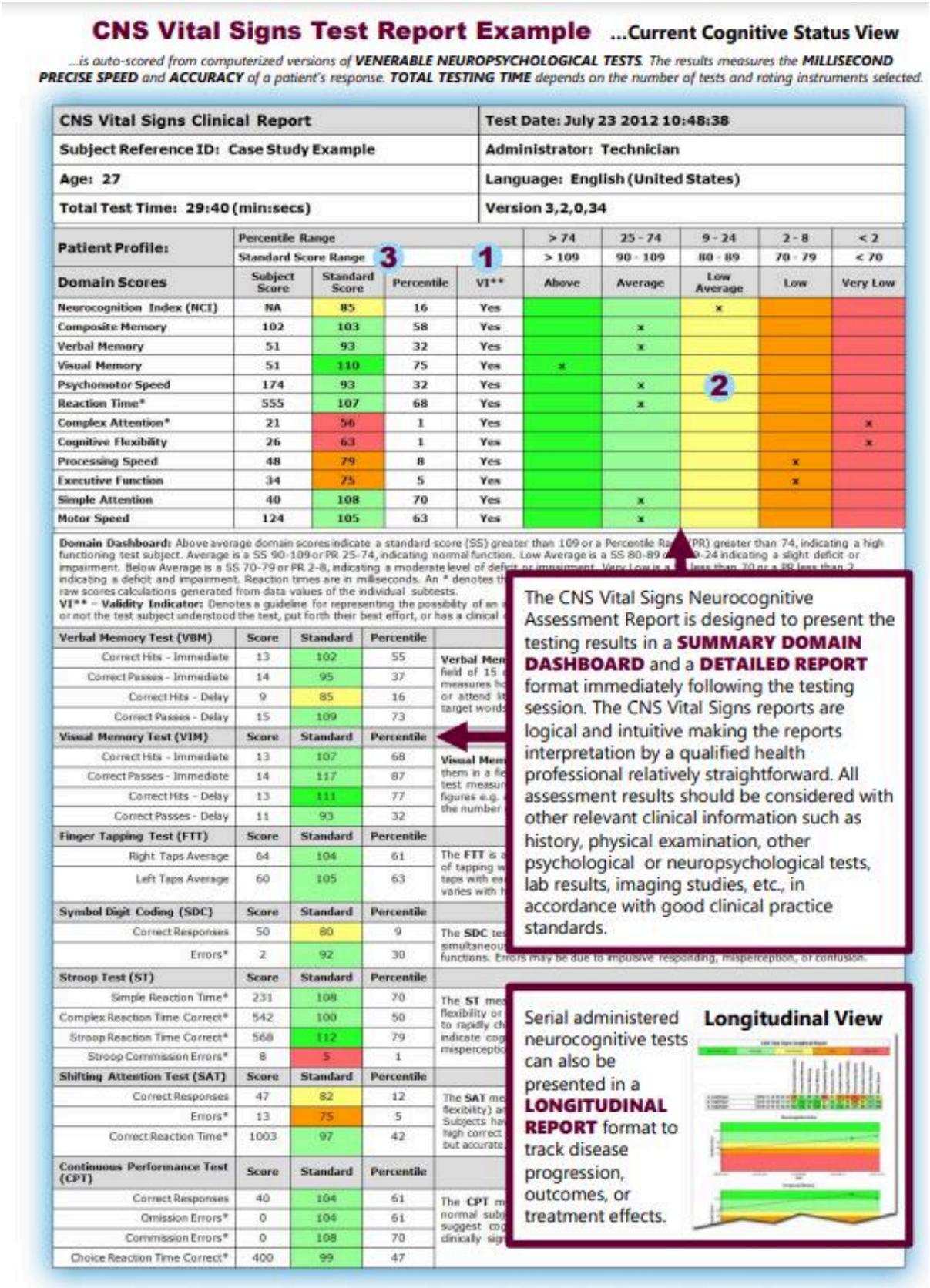
ADDENDUM I: CNS Vital Signs test details

CNS Vital Signs Clinical Domain Description

Single Test Domain Multiple Test Domain

Neurocognitive Index (NCI)	Measure: An average score derived from the domain scores or a general assessment of the overall neurocognitive status of the patient. Relevance: Summary views tend to be most informative when evaluating a population, a condition category, and outcomes.
Composite Memory	Measure: How well subject can recognize, remember, and retrieve words and geometric figures. Relevance: Remembering a scheduled test, recalling an appointment, taking medications, and attending class.
Verbal Memory	Measure: How well subject can recognize, remember, and retrieve words. Relevance: Remembering a scheduled test, recalling an appointment, taking medications, and attending class.
Visual Memory	Measure: How well subject can recognize, remember and retrieve geometric figures. Relevance: Remembering graphic instructions, navigating, operating machines, recalling images, and/or remember a calendar of events.
Psychomotor Speed	Measure: How well a subject perceives, attends, responds to visual-perceptual information, and performs motor speed and fine motor coordination. Relevance: Ability preform simple motor skills and dexterity through cognitive functions i.e., use of precision instruments or tools, performing mental and physical coordination i.e., driving a car, playing a musical instrument.
Reaction Time*	Measure: How quickly the subject can react, in milliseconds, to a simple and increasingly complex direction set. Relevance: Driving a car, attending to conversation, tracking and responding to a set of simple instructions, taking longer to decide what response to make.
Complex Attention	Measure: Ability to track and respond to a variety of stimuli over lengthy periods of time and/or perform mental tasks requiring vigilance quickly and accurately. Relevance: Self-regulation and behavioral control.
Cognitive Flexibility	Measure: How well subject is able to adapt to rapidly changing and increasingly complex set of directions and/or to manipulate the information. Relevance: Reasoning, switching tasks, decision-making, impulse control, strategy formation, attending to conversation.
Processing Speed	Measure: How well a subject recognizes and processes information i.e., perceiving, attending/responding to incoming information, motor speed, fine motor coordination, and visual-perceptual ability. Relevance: Ability to recognize and respond/react i.e., fitness-to-drive, occupation issues, possible danger/risk signs or issues with accuracy and detail.
Executive Function	Measure: How well a subject recognizes rules, categories, and manages or navigates rapid decision making. Relevance: Ability to sequence tasks and manage multiple tasks simultaneously as well as tracking and responding to a set of instructions.
Simple Attention	Measure: Ability to track and respond to a single defined stimulus over lengthy periods of time while performing vigilance and response inhibition quickly and accurately. Relevance: Self-regulation and simple attention control.
Motor Speed	Measure: Ability to perform movements to produce and satisfy an intention towards a manual action and goal. Relevance: Preparation and production of simple manual dexterity actions e.g. manipulate and maneuver objects.
Social Acuity	Measure: How well a subject can perceive, process, and respond to emotional cues. Relevance: Spectrum screen, ability to recognize social cues or read facial expressions. Provides insight into inappropriate behavior, decreased inhibition, insensitivity to social standards, and social behavioral regulation.
Reasoning	Measure: How well is subject able to recognize, reason and respond to non-verbal visual-abstract stimuli. Relevance: Problem solving skills, ability to forge insights, discern meaning, and ability to perceive relationships.
Sustained Attention	Measure: How well a subject can direct and focus cognitive activity on specific stimuli. Relevance: How well a subject can focus and complete task or activity, sequence action, and focus during complex thought.
Working Memory	Measure: How well a subject can perceive and attend to symbols using short-term memory processes (4PCPT). Relevance: Ability to carry out short-term memory tasks that support decision making, problem solving, planning, and execution. Enables "right-now" responses.

ADDENDUM J: CNS Vital Signs report example



CNS Vital Signs Test Report Example ...Current Cognitive Status View

*...is auto-scored from computerized versions of **VENERABLE NEUROPSYCHOLOGICAL TESTS**. The results measures the **MILLISECOND PRECISE SPEED** and **ACCURACY** of a patient's response. **TOTAL TESTING TIME** depends on the number of tests and rating instruments selected.*

CNS Vital Signs Clinical Report	Test Date: July 23 2012 10:48:38
Subject Reference ID: Case Study Example	Administrator: Technician
Age: 27	Language: English (United States)
Total Test Time: 29:40 (min:secs)	Version 3,2,0,34

Patient Profile:	Percentile Range				> 74	25 - 74	9 - 24	2 - 8	< 2
	Standard Score Range				> 109	90 - 109	80 - 89	70 - 79	< 70
Domain Scores	Subject Score	Standard Score	Percentile	VI**	Above	Average	Low Average	Low	Very Low
Neurocognition Index (NCI)	NA	85	16	Yes			x		
Composite Memory	102	103	58	Yes		x			
Verbal Memory	51	93	32	Yes		x			
Visual Memory	51	110	75	Yes	x				
Psychomotor Speed	174	93	32	Yes		x			
Reaction Time*	555	107	68	Yes		x			
Complex Attention*	21	56	1	Yes					x
Cognitive Flexibility	26	63	1	Yes					x
Processing Speed	48	79	8	Yes				x	
Executive Function	34	75	5	Yes				x	
Simple Attention	40	108	70	Yes		x			
Motor Speed	124	105	63	Yes		x			

Domain Dashboard: Above average domain scores indicate a standard score (SS) greater than 109 or a Percentile Ra... (PR) greater than 74, indicating a high functioning test subject. Average is a SS 90-109 or PR 25-74, indicating normal function. Low Average is a SS 80-89 o... 0-24 indicating a slight deficit or impairment. Below Average is a SS 70-79 or PR 2-8, indicating a moderate level of defi... impairment. Very Low is a ... less than 70 or a PR less than 2 indicating a deficit and impairment. Reaction times are in milliseconds. An * denotes th... raw scores calculations generated from data values of the individual subtests.
VI – Validity Indicator:** Denotes a guideline for representing the possibility of an ... or not the test subject understood the test, put forth their best effort, or has a clinical ...

Verbal Memory Test (VBM)	Score	Standard	Percentile
Correct Hits - Immediate	13	102	55
Correct Passes - Immediate	14	95	37
Correct Hits - Delay	9	85	16
Correct Passes - Delay	15	109	73
Visual Memory Test (VIM)	**Score**	**Standard**	**Percentile**
Correct Hits - Immediate	13	107	68
Correct Passes - Immediate	14	117	87
Correct Hits - Delay	13	111	77
Correct Passes - Delay	11	93	32
Finger Tapping Test (FTT)	**Score**	**Standard**	**Percentile**
Right Taps Average	64	104	61
Left Taps Average	60	105	63
Symbol Digit Coding (SDC)	**Score**	**Standard**	**Percentile**
Correct Responses	50	80	9
Errors*	2	92	30
Stroop Test (ST)	**Score**	**Standard**	**Percentile**
Simple Reaction Time*	231	108	70
Complex Reaction Time Correct*	542	100	50
Stroop Reaction Time Correct*	568	112	79
Stroop Commission Errors*	8	5	1
Shifting Attention Test (SAT)	**Score**	**Standard**	**Percentile**
Correct Responses	47	82	12
Errors*	13	75	5
Correct Reaction Time*	1003	97	42
Continuous Performance Test (CPT)	**Score**	**Standard**	**Percentile**
Correct Responses	40	104	61
Omission Errors*	0	104	61
Commission Errors*	0	108	70
Choice Reaction Time Correct*	400	99	47

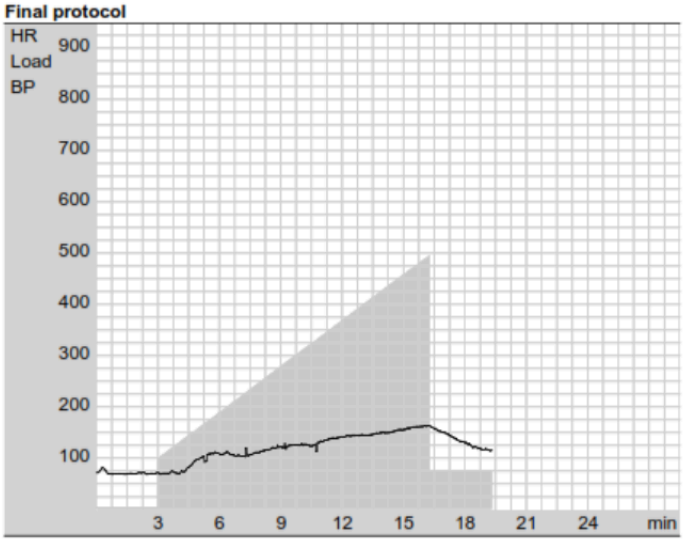
The CNS Vital Signs Neurocognitive Assessment Report is designed to present the testing results in a **SUMMARY DOMAIN DASHBOARD** and a **DETAILED REPORT** format immediately following the testing session. The CNS Vital Signs reports are logical and intuitive making the reports interpretation by a qualified health professional relatively straightforward. All assessment results should be considered with other relevant clinical information such as history, physical examination, other psychological or neuropsychological tests, lab results, imaging studies, etc., in accordance with good clinical practice standards.

Serial administered neurocognitive tests can also be presented in a **LONGITUDINAL REPORT** format to track disease progression, outcomes, or treatment effects.

Longitudinal View

ADDENDUM K: Example of ECG Raw data (anonymised)

Final protocol



Summary

Overall duration	19:20	min
Load duration	13:16	min
Duration recovery	3:04	min
Max. load	496	W
% of target 110 W	450	%
HR peak	163	bpm
BP rest		
BP max.		
HRxBP, max.		
MET, maximum	28.4	

Evaluation data

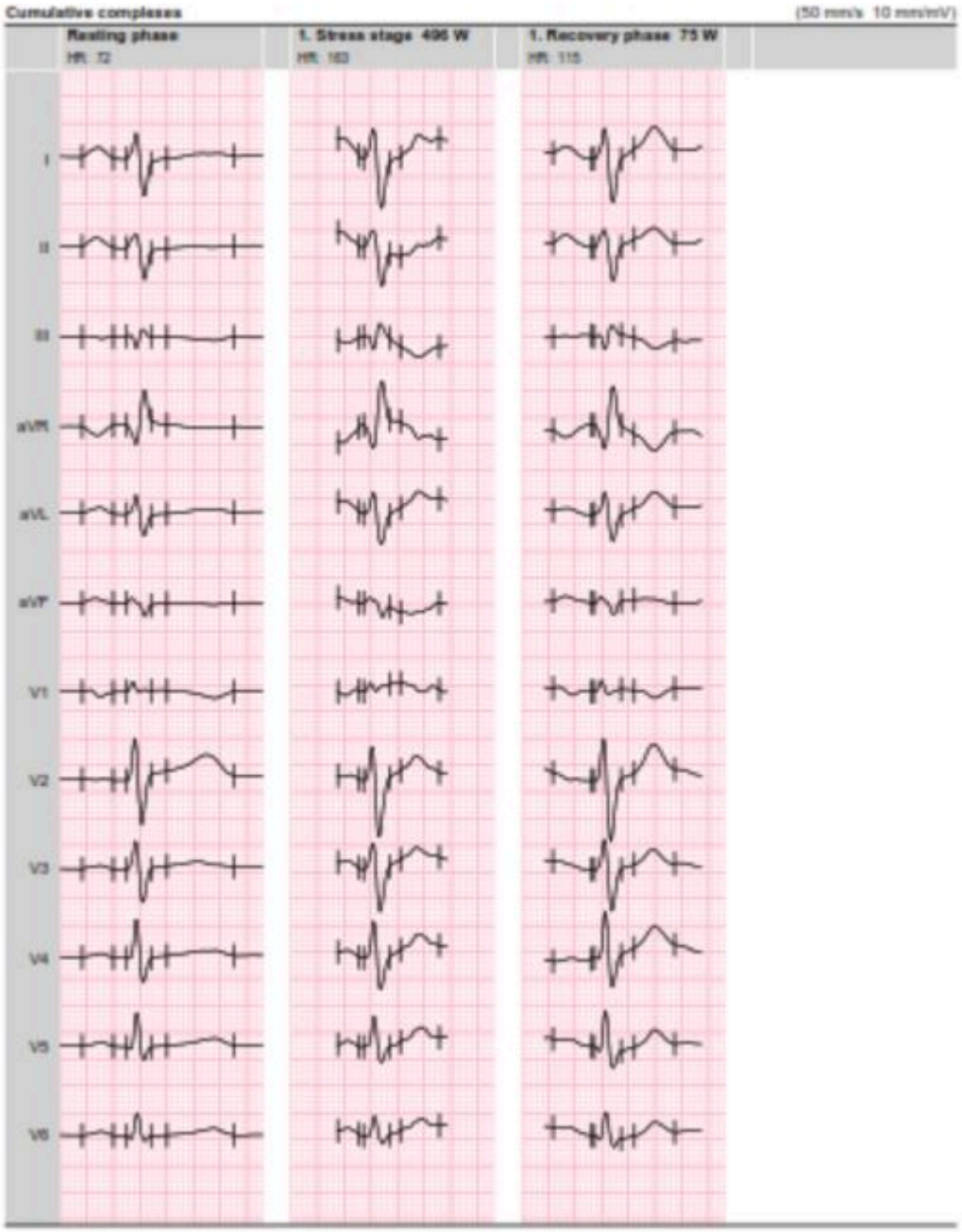
PWC	W	W / kg	Ref. value
170			
150			
130			
max. 163	496	8.0	

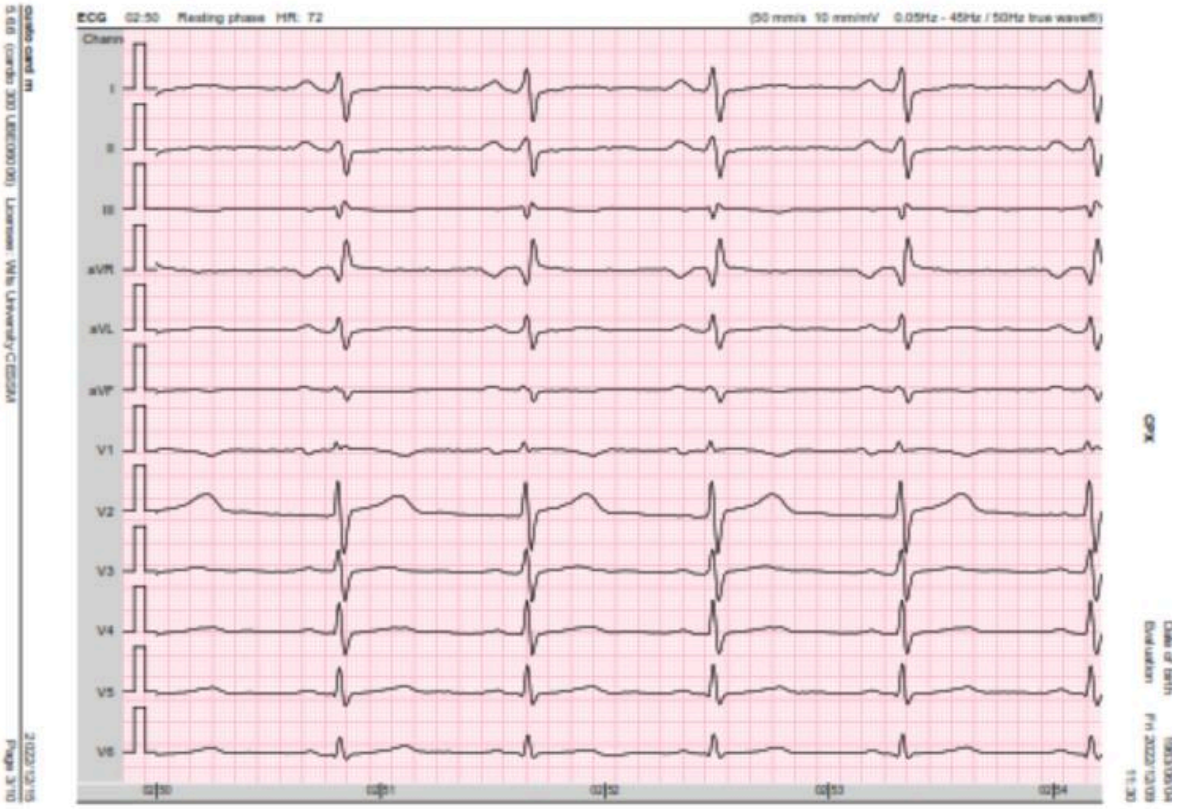
Measured values

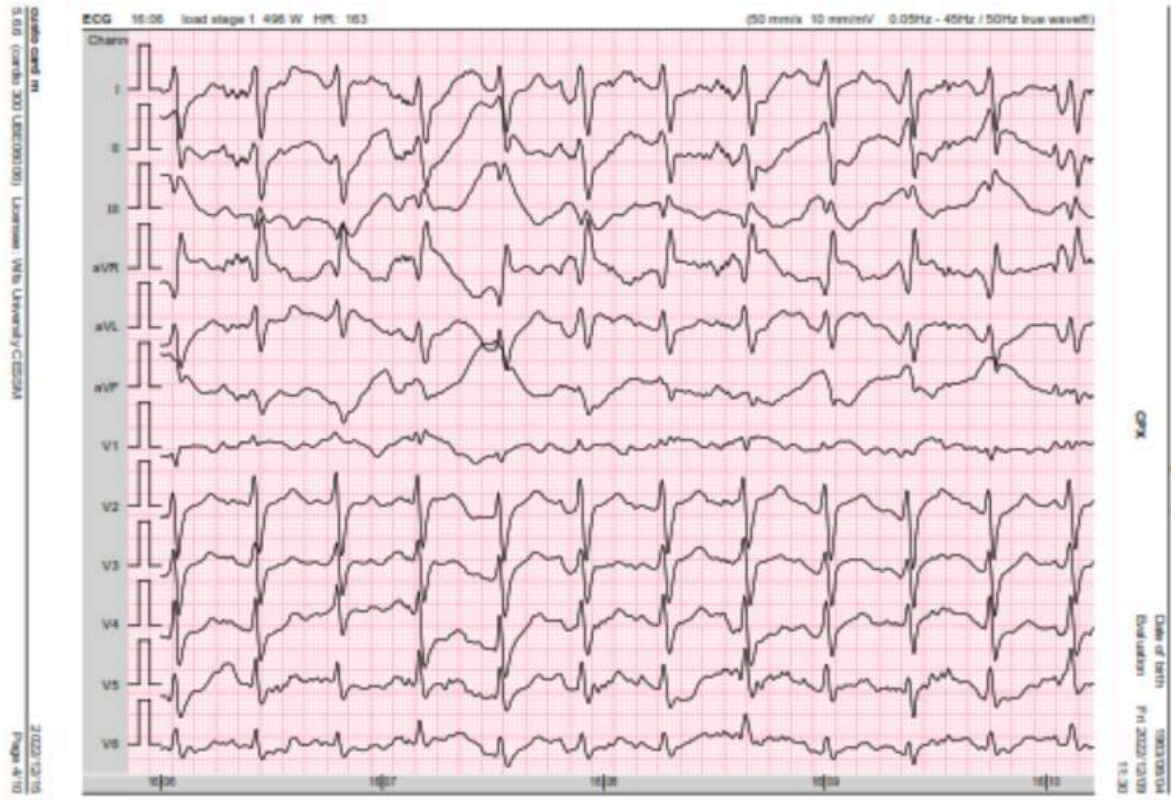
	Duration	Load		HR	MET	BP	ST Measurement (mV)											
		W	W/kg				I	II	III	aVR	aVL	aVF	V1	V2	V3	V4	V5	V6
R	03:00	0	0.00	72	1.0		-0.00	-0.02	-0.02	0.01	0.01	-0.02	0.02	0.18	0.07	0.05	0.03	0.02
1	13:16	496	8.00	163	28.4		0.03	-0.17	-0.20	0.07	0.11	-0.18	0.16	0.19	0.19	0.16	0.10	0.10
Rec	03:04	75	1.21	115	5.1		0.20	0.16	-0.04	-0.18	0.11	0.06	0.02	0.15	0.09	0.19	-0.00	0.00

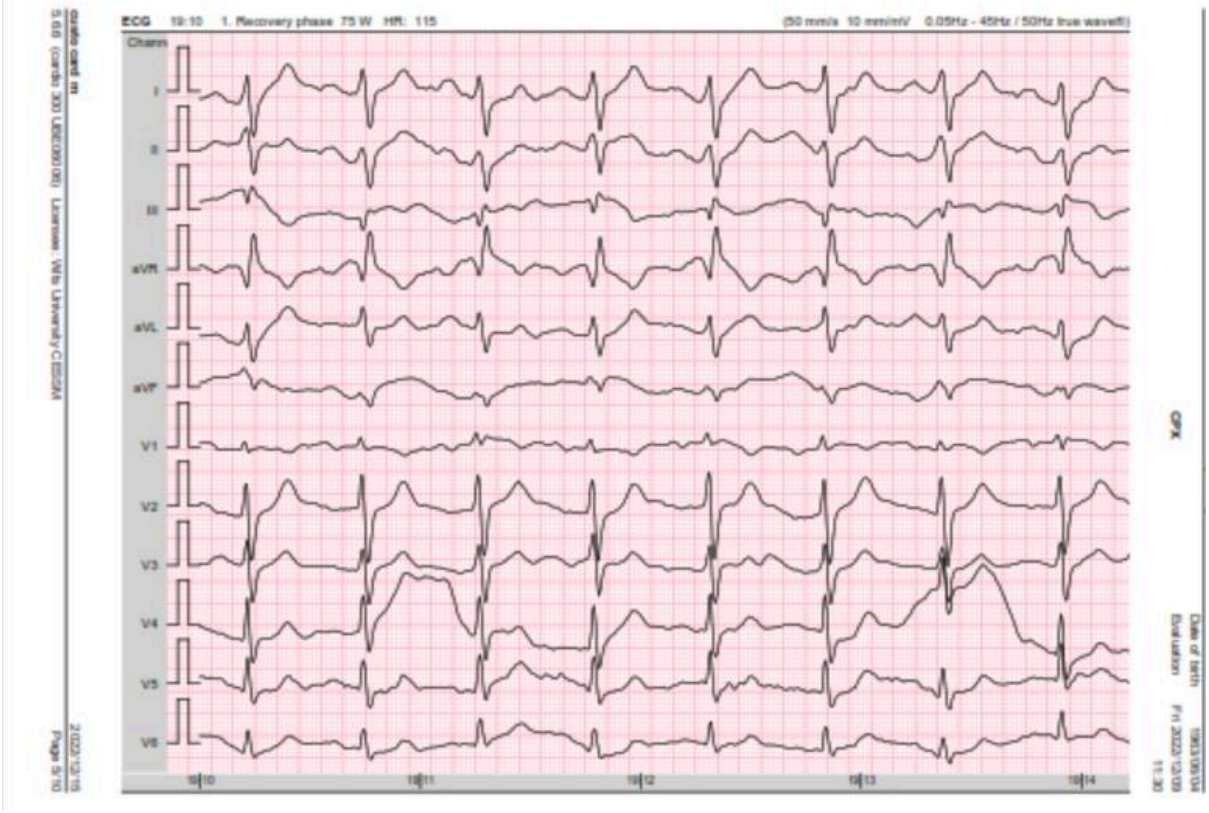
Report/Assessment

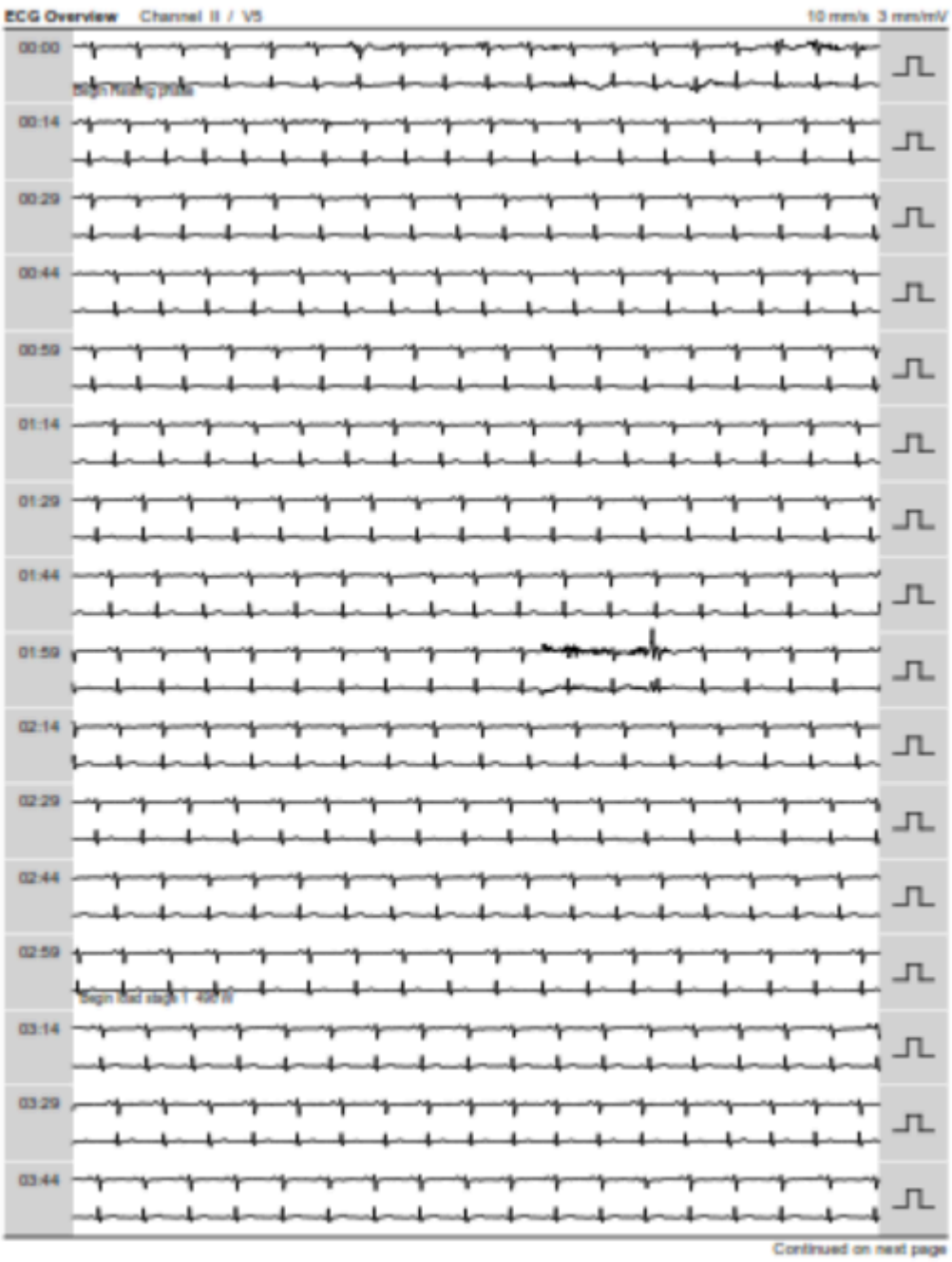
max. load: 496 W in Load stage 1 at 16:06 min, 450% of target 110.0 W, MET: 28.4
Resting HR: 72 /min, Max. HR: 163 /min at Load stage 1 at 16:06 min
max. ST inclination at channel I: 0.20 mV at Recovery phase 1, max.ST Depression at channel III: -0.20 mV at Load stage 1
VPB: 2

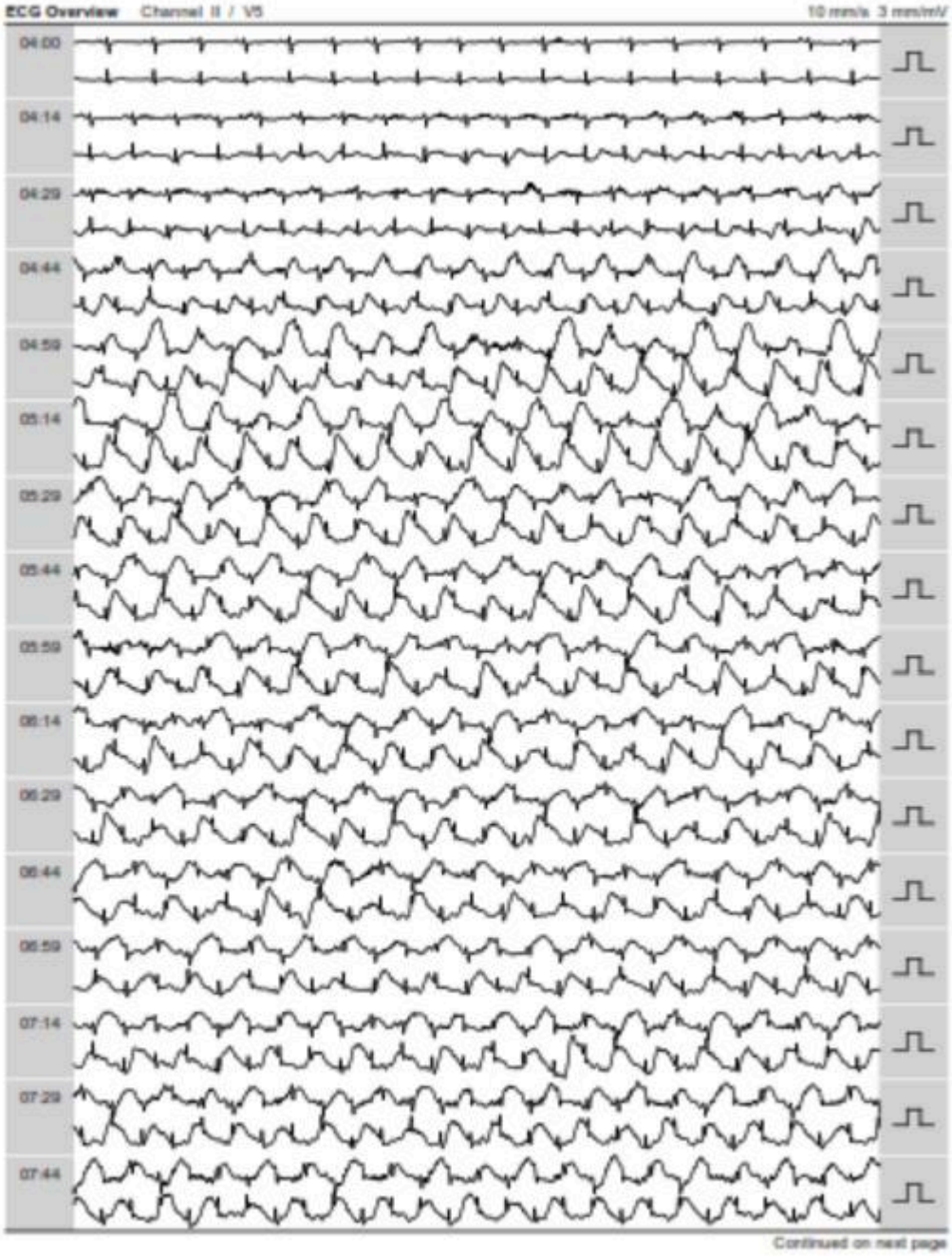

Cumulative complexes
(50 mm/s 10 mm/mV)
Resting phase
HR: 72
1. Stress stage 496 W
HR: 163
1. Recovery phase 75 W
HR: 115
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

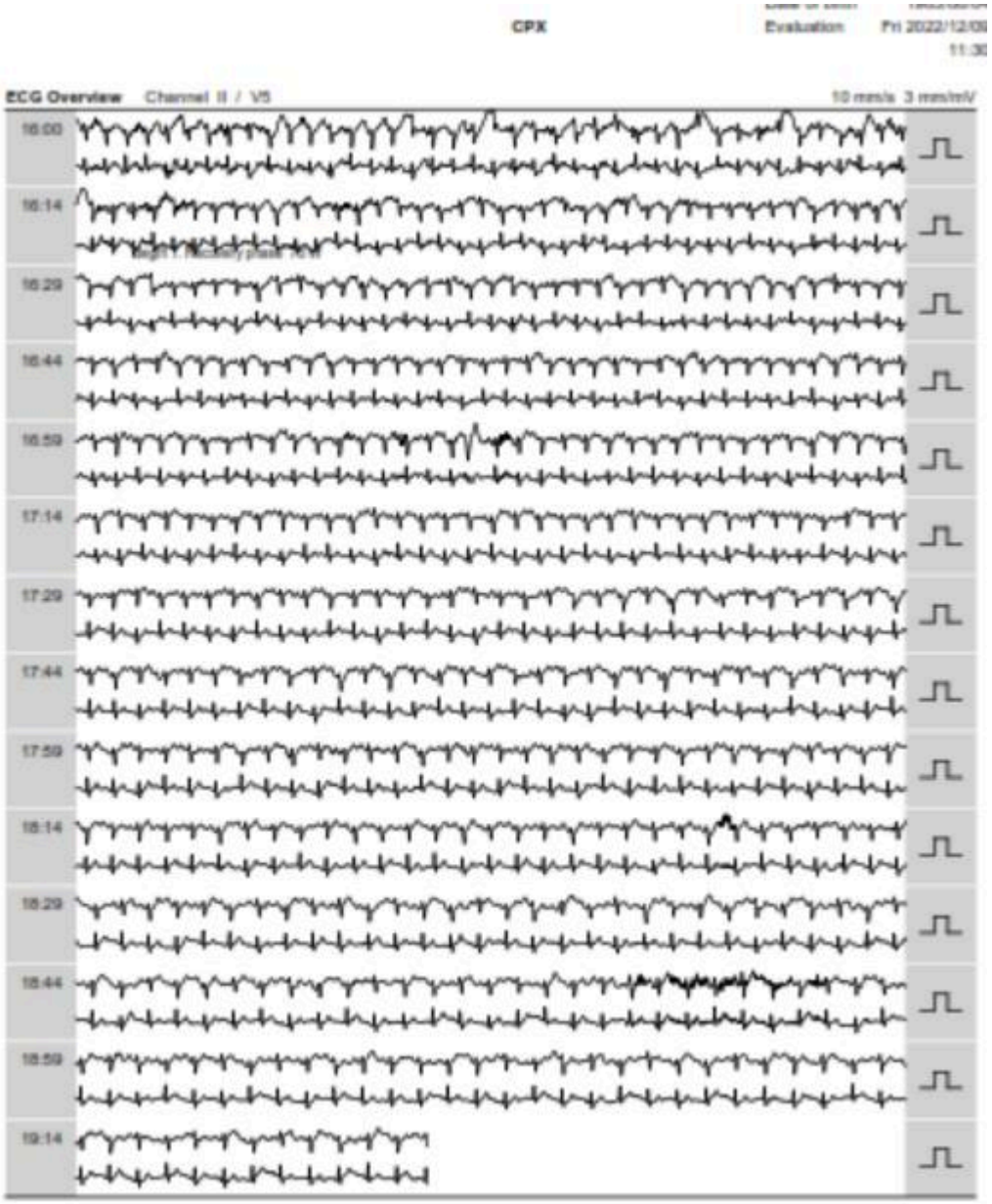

ECG 02:50 Resting phase HR: 72
(50 mm/s 10 mm/mV 0.05Hz - 45Hz / 50Hz true wavelt)
Chann
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
02:50
02:51
02:52
02:53
02:54


ECG 16:06 load stage 1 496 W HR: 163
(50 mm/s 10 mm/mV 0.05Hz - 45Hz / 50Hz true wavelt)
Chann
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
16:06
16:07
16:08
16:09
16:10


ECG 19:10 1. Recovery phase 75 W HR: 115
Channel
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
19:10
19:11
19:12
19:13
19:14


ECG Overview Channel II / V5
10 mm/s 3 mm/mV
00:00
00:14
00:29
00:44
00:59
01:14
01:29
01:44
01:59
02:14
02:29
02:44
02:59
03:14
03:29
03:44
Continued on next page


ECG Overview Channel II / V5
10 mm/s 3 mm/mV
04:00
04:14
04:29
04:44
04:59
05:14
05:29
05:44
05:59
06:14
06:29
06:44
06:59
07:14
07:29
07:44
Continued on next page


CPX
Evaluation
ECG Overview
Channel II / V5
10 mm/s 3 mm/mV
16:00
16:14
16:29
16:44
16:59
17:14
17:29
17:44
17:59
18:14
18:29
18:44
18:59
19:14

ADDENDUM L: HREC Ethical Clearance (Clearance Number 180611)

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Professor D Constantinou
School of Therapeutic Sciences
Centre for Exercise Science and Sports Medicine
Medical School
University

E-mail: Demitri.Constantinou@wits.ac.za

CC: Supervisor: Professor AD Rothberg <Alan.Rothberg@wits.ac.za>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 13/11/2018

REF: *R14/49*

PROTOCOL NO: **M180611** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Methylphenidate: Physiological, neurocognitive, balance and physical performance effects*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000\Iain0007\Clearscan.wps

ADDENDUM M: Permission to extend recruitment

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2023/05/02

Professor D Constantinou
School of Therapeutic Sciences
Centre for Exercise Science and Sports Medicine
Medical School
University

Sent by e-mail to: Demitri.Constantinou@wits.ac.za

Dear Professor Constantinou

Re: **Protocol Ref No:** M180611
Protocol Title: *Methylphenidate: Physiological, neurocognitive, balance and physical performance effects*
Principal Investigators: Professor D Constantinou

Thank you for your e-mail of 2023/03/30.

I can confirm that we have noted and approve of proposal to extend your participant recruitment pool by approaching University staff and students and placing an advert in social media.

Thank you for keeping us informed.

Yours Sincerely

J. Burns

Mr I Burns
For the Human Research Ethics Committee (Medical)