2022

Factors Influencing Balance and Muscle Tone in Adults With Attention-Deficit/Hyperactivity Disorder

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FACTORS INFLUENCING BALANCE AND MUSCLE TONE IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

BIRMINGHAM, ALABAMA

2022

PSYCHOSTIMULANT MEDICATION TO IMPROVE BALANCE AND MUSCLE TONE IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDERS

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REHABILITATION SCIENCE

ABSTRACT

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental condition prevalent in children globally and continues to persist into adulthood. Executive function (EF) impairments are core ADHD deficits, specifically response inhibition, and believed to drive ADHD symptoms. Psychostimulant medications (PS) is the first line treatment to manage ADHD symptoms. Overall, individuals with ADHD are at greater risk of falls and physical injuries compared to healthy individuals. Perhaps adults with ADHD balance impairments are secondary to ankle plantarflexor (PF) spasticity. Using psychostimulant medications (PS) improves PF spasticity and postural control in children with ADHD, but the effects on adults with ADHD are unclear. Furthermore, moderate-to-vigorous physical activity (MVPA) has also been found associated with static balance in healthy adults. We designed a within-subject repeated measure study to assess PS effects on static balance and muscle tone and to identify if MVPA and response inhibition are associated with static balance in adults with ADHD. The findings of this dissertation are intended to guide future research concerning the improvement of balance in adults with ADHD. Study 1 documented that using PS medication was associated with improved static balance and functional motor performance compared to off medication state in adults with ADHD. Study 2 determined that adults with ADHD exhibited a slight increased PF spasticity (measured by the Modified Ashworth Scale). In addition, this study demonstrated that using PS was

associated with reduced the reflex mediated component spasticity (measured by a dynamometer) only among adults with the predominantly Inattentive subtype of ADHD. Study 3 identified significant associations between MVPA and response inhibition with static balance during off medication state only. In summary, this dissertation demonstrates the effects of using PS on static balance and PF spasticity, and associations between MVPA and EF with static balance performance in adults with ADHD during off and on medication status. The findings of this research project may guide clinicians and researchers who work with this population to attend to PS use and develop interventional programs that aim to improve static balance.

Keywords: psychostimulant medication, postural sway, spasticity, stretch reflex, muscle tone, attention-deficit/hyperactivity disorder, balance, motor performance, physical activity, MVPA, executive function, response inhibition.

DEDICATION

I would like to dedicate this dissertation to my parents and people who are special to my heart. In addition, I would like to dedicate this dissertation to my nephews and nieces who were born while I was far away from home completing my doctoral training. I wish I was there to watch them grow. I hope that one day when they grow up and get bored enough to read my dissertation, they will appreciate how much I love them.

ACKNOWLEDGMENT

In the name of Allah, I thank God for providing me with infinite blessings and help to complete my doctoral studies.

I would like to thank the irreplaceable Dr. Donald Lein, who provided me with countless guidance and motivation through this journey. I am grateful for Dr. Lein who helped me mature professionally and taught me much about life and science. I would like also to thank Dr. Robert Motl and Dr. Despina Stavrinos, who devoted a lot of their time to help me refine and improve the quality of this project. Each one of them has sincerely provided me with lots of great discussions and ideas that guided my professional maturation. I also thank Dr. Scott Snyder and Dr. Harshvardhan Singh for their endless assistance and constant support. I am grateful that I was able to work with this great team of scientists that provided me a wide span of expertise.

Secondly, I would like to thank Elisa Lewis, Scarlett Naftel, and Katherine Sims for their help and encouragement. I appreciate the friendships and discussions with the faculty members in the University of Alabama at Birmingham Physical and Occupational Therapy Departments (Drs. David Morris, Gavin Jenkins, William Reed, Christopher Hurt, Matthew Ithurburn, John Lowman, Carmen Capo-Lugo, Patricia Perez, Sheree York). Special thanks to Drs. David Brown and William Thompson for their encouragement and guidance through the program. Moreover, I am thankful for the participants' time in helping me collecting the information needed to complete this project.

Finally, I would like to thank my family, starting with my parents, siblings, and people who are close to me for their patience and support. Without it, I don’t know if I could have got to this moment of writing this section. Thanks to my friends and in this journey who had provided me with many emotional and professional support. I am also grateful for having Lisa Lein, my Alabama mom who provided with unconditional support. I have grown up professionally and emotionally completing this project thanks to everybody around me who knew my potentials and skills and helped me refine them in a good way.

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LIST OF ABBREVIATIONS

ADHD: Attention-Deficit/Hyperactivity Disorder

AMP: Amphetamine

ASRS-5: The World Health Organization Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for DSM-5

COP: Center of Pressure

CWIT: Color-Word Interference Test

DA: Dopamine

D-KEFS: Delis-Kaplan Executive Function System

DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th edition

EF: Executive Function

FAEC: Feet-Apart Eyes Closed

FAEO: Feet-Apart Eyes Open

FDA: Food and Drug Administration

FMPT: Functional Motor Performance Tests

FTEC: Feet-Together Eyes Closed

FTEO: Feet-Together Eyes Open

LSUT: Lateral Step-Up Test

MANOVA: Multivariate Analysis of Variance

MAS: Modified Ashworth Scale

MPH: Methylphenidate

MVPA: Moderate-to-Vigorous Physical Activity

NE: Norepinephrine

OPTIMAL: Optimize Performance Through Intrinsic Motivation and Attention for Learning

PA: Physical Activity

PF: Ankle Plantarflexors

PFRS: Ankle Plantarflexors Resistance to Stretch

PS: Psychostimulant Medications

RI: Response Inhibition

SA: Sway Area

SD: Standard Deviation

sEMG: Surface Electromyography

SLEC: Single Leg on Firm Surface with Eyes Closed

SLEO: Single Leg on Firm Surface with Eyes Open

SOT: Sensory Organization Test

SPSS: Statistical Package for the Social Sciences

SV: Sway Velocity

TBI: Traumatic Brain Injury

TMT: Trial Making Test

TUG: Timed-Up and Go

WHO: World Health Organization

η_p^2: Partial Eta Square

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that is highly prevalent in the US, with an estimated 6.1 million children and adolescents diagnosed with ADHD.[1] ADHD persists into adulthood, with approximately 1.0%[2]-4.4%[3] of US adults aged 18-54 years (female 38.0%) being diagnosed with ADHD.[3] The American Psychiatric Association classifies ADHD into three diagnostic subtypes: predominantly Inattentive, predominantly Hyperactive-Impulsive, or Combined.[4] Individuals with ADHD are at high risk of physical injury across all three ADHD diagnostic subtypes,[5] potentially affected by balance and motor impairments.[6,7]

Pathophysiology and Theories of ADHD

Executive function (EF) is a set of neurocognitive processes that maintain appropriate problem-solving skills to achieve future goals.[8] EF includes several higher-level cognitive functions, including attention, working memory, behavioral inhibition, goal-orientation, planning, and problem-solving.[8] EF systems have widely distributed neural networks, including the prefrontal cortex,[9] basal ganglia,[10] and thalamus.[11] Interconnections between these networks regulate attention, thoughts, emotion, behavior, and actions.[12] It is well-established that ADHD is associated with EF deficits.[13,14] Dr. Russel Barkley's Unifying Theory of ADHD suggests that ADHD core deficit is driven by four main executive domains— behavioral inhibition, working memory, regulation of motivation, and motor control.[15] Further theories have been constructed and validated the

unifying theory of ADHD, including the integrative theory of ADHD[13] and the executive function theory of ADHD.[14] The latter two theories concluded that ADHD symptoms were driven by varying measures of response inhibition, vigilance, and spatial working memory.[13,14]

Evidence suggests that individuals with ADHD have reduced volume or hypofunction of white and gray matter in the brain, leading to impairments in attention, speed of processing responses, and other behavioral issues.[12] However, an imaging study tracked the development of brain areas in ADHD concluded that individuals with ADHD might have a delay in cortical maturation rather than deficits.[16] Moreover, the network activities responsible for EF is maintained by neurotransmitters, mainly Dopamine (DA), and Norepinephrine (NE).[12] DA receptor density in ADHD is lower than normal, reducing the functionality of the dopaminergic system.[17] This hypothesis is in perfect agreement with mechanism of action of psychostimulant medications (PS) used to treat ADHD,[12] since these medications improve DA and NE concentrations in the prefrontal cortex and basal ganglia.[12,18]

Diagnosis of ADHD

Despite efforts to find diagnostic markers for ADHD,[19-21] no marker of ADHD exists due to the complexity of the diagnosis. The *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-V) guides physicians in making an ADHD diagnosis in the US.[4] The DSM-V requires children to meet six (five for adults) of the listed symptoms in the DSM-V for each of the inattention or hyperactivity-impulsivity for at least six months to be diagnosed with ADHD.[4] Additionally, several rating scales exist to identify the DSM-V diagnostic criteria of ADHD, including the Conners' Adult Rating

Scale,[22] Barkley Adult ADHD Rating Scale,[23] and The World Health Organization Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for DSM-5 (ASRS-5).[24]

Neuropsychological assessments are also used for ADHD diagnosis. Adults with ADHD exhibit deficits in several executive domains, such as sustained attention, response inhibition, and working memory.[14] Development in neuroimaging techniques documented structural and functional differences between adults with ADHD and controls.[25] These structural changes include smaller caudate, putamen, and amygdala volumes.[26] Functional network deficits include the frontostriatal and frontoparietal networks (i.e., the executive function network).[27] Deficits in these networks could explain executive function[14] and motor deficits found with adult ADHD.[28]

Treatment Options for Adult ADHD

While treating ADHD approaches are multimodal, the first-line treatment for ADHD is the Food and Drug Administration (FDA) approved psychostimulant (PS) Methylphenidate (MPH) and Amphetamine (AMP), available in immediate- or extended-release forms.[29] Both MPH and AMP types of PS primarily increase DA concentrations in the brain through slightly different mechanisms. Both MPH and AMP inhibit DA and NE reuptake in the presynaptic neuron by blocking monoamine transporters (DA and NE transporters), resulting in increasing these neurotransmitters in the extracellular level.[30] In addition to inhabitation DA and NE reuptake, AMP, compared to MPH, increases the secretion of these neurotransmitters from the presynaptic terminal.[30] While both MPH and AMP showed efficacy in managing ADHD symptoms, AMP have moderately greater effect than MPH.[30] Evidence suggested that PS use was also associated with increased

blood flow in the putamen.[31] The abovementioned mechanisms are believed to alleviate ADHD symptoms and improve different EF domains including response inhibition.[32] Extended-release PS are preferred over immediate-release as suggested by international practice guidelines,[33,34] as they produce less euphoric effects and reduce drug removal difficulties.[35] Other non-stimulant medications are also available and approved by the FDA to treat ADHD, such as Atomoxetine and Guafacine.[36]

Issues with pharmacological treatment include limited efficacy observed over the long-term (≥6 months), mainly due to poor adherence to medication and interference of coexisting psychiatric conditions that require discontinuation of treatment.[37] Additionally, using PS was associated with lower bone mineral density,[38] which may threaten the safety of the long-term use of PS for ADHD. Major non-pharmacological treatments comprise physical activity, cognitive behavioral therapy, neurofeedback, and cognitive training.[39] Multiple factors play a role in non-pharmacological treatments effectiveness, such as modality of physical activity[40] and type of cognitive behavioral therapy.[41] However, these interventions showed superior efficacy when combined with pharmacological treatment.[42,43]

Injuries and Psychostimulants Effect in Individuals with ADHD

Individuals with ADHD sustain more physical injuries than controls across their lifespan, including pedestrian injuries, traffic and driving-related accidents, and skeletal fractures.[44] ADHD medication, particularly PS, showed preventative effects against physical injuries in adults with ADHD.[44] However, those individuals who took PS still had greater number of injuries and falls when compared to individuals without ADHD.[45] While the exact mechanisms that explain the occurrence of these injuries is not fully

understood, ADHD symptoms and deficits in executive functioning are deemed driving factors.[44] Little evidence exists on motor issues with ADHD in relation to physical injuries.[28,46] However, adults with ADHD are more prone to falling,[47] which may be related to balance performance. Since falling is multifactorial and could result in severe detrimental health consequences (e.g., traumatic brain injury [TBI]),[47] it is warranted to identify potential factors that contribute to falls and injuries to inform future interventions that target reducing falls and injuries in this population.

Factors That May relate to Balance/Motor Deficits in Adults with ADHD

Psychostimulants: Motor impairments that exist in adults with ADHD,[28] may be due to dopamine hypofunction.[48] Dopamine hypofunction caused by the decreased number of D2/D3 receptors in the basal ganglia found in adults with ADHD may also affect motorperformance.[48] Proper function of the basal ganglia is important since these nuclei are contribute to regulating including balance.[49] Optimizing balance performance may be critical for maintaining upright posture and motor function.[7] Previous research has shown that PS help improve balance and motor performance in children. (reference) PS primarily increases DA and NE concentrations in the presynaptic neuron of several brain areas, such as the striatum, which is believed to improve balance in children with ADHD.[50] No research studies have been found that looked if PS would improve balance in adults with ADHD.

Increased muscle tone: Studies have found increased muscle tone in children[7] and adults[28] with ADHD. In addition, the same assessment battery used in the previous two studies also found impairments in balance performance. Increased muscle tone is negatively associated with motor function (e.g., walking) in other populations, such as

individuals with Multiple Scelerosis.[51] While the relationship between balance and muscle tone exists in other population (e.g., individual post stroke),[52] the relationship between these outcomes has not been established in adults with ADHD. Furthermore, using PS was associated with improvements and muscle tone in children with ADHD.[7] However, no evidence examined PS effects on balance and muscle tone in adults with ADHD.

Moderate-to-Vigorous Physical Activity; MVPA, in the form of exercise, may be a factor to enhance motor performance and balance in adults with ADHD. A systematic review that investigated the effects of several exercise forms found that aerobic and balance training improved balance performance in older adults.[53] Evidence suggests that different forms of MVPA (e.g., aerobic exercise) yielded positive effects on ADHD symptoms and executive function, mainly through increasing blood flow in the prefrontal cortex and boosting DA concentration in the brain.[40] Identifying associations between MVPA and motor/balance performance in ADHD could inform future interventions aim to improve balance function in this population.

Executive Function: EF function may also be associated with motor performance,[54] and balance in adults with ADHD,[55] possibly through neural networks like the nigrostriatal network.[56,57] Understanding associations between EF and balance performance in individuals with ADHD could inform future interventions (e.g., EF training) for enhancing balance performance.

Specific Aims

The purpose of this dissertation was to examine the relationships between balance, muscle tone, MVPA, and executive function with and without PS use in adults

with ADHD. We recruited adults aged 18 to 55 years with a diagnosis of ADHD by their physician or psychologist.

Specific Aim 1: Examine Effects of Psychostimulant Medication on Balance Performance in Adults with ADHD

Manuscript 1 addresses aim1 and details our study protocol and findings concerning the association of PS on balance performance. Our hypothesis was that using PS will be associated with better balance performance compared to an off-medication state. Forty-five participants completed a within-subject repeated-measure design study to achieve this aim. During one visit, participants underwent a set of objective balance tests on force platform when they were on their PS. During another visit, participants underwent the same tests, but were asked to skip using PS for 24 hours before testing.

Specific Aim 2: Determine Muscle Tone Level and Examine the Effects of Psychostimulant Medication on Muscle Tone in Adults with ADHD

Manuscript 2 describes a study that addresses aim 2. This study determined average muscle tone in ADHD and examined the association of PS on muscle tone. Our first hypothesis was adults with ADHD will exhibit a slight increase in muscle tone. Second, using PS will be associated with lower muscle tone compared to an off-medication status. Thirty-nine participants completed a within-subject repeated-measure design study to accomplish this aim. During one visit, participants underwent ankle plantar flexor muscle tone assessment using the Modified Ashworth Scale (MAS) and device-measured muscle resistance to stretch to identify spasticity levels during on-

medication state. During another visit, participants underwent the same protocol and were asked to skip using PS for 24 hours before testing to determine difference in muscle tone between off and on medication status.

Specific Aim 3: Examine Associations Between MVPA and Response Inhibition with Balance Performance in Adults with ADHD

This aim was described through the findings presented in Manuscript 3. This cross-sectional study used device measured MVPA levels and response inhibition to compare the performance of these two variables with balance performance during off medication and on medication states in adults with ADHD. Our hypothesis was that MVPA and response inhibition will be significantly associated with balance performance, despite medication status. Forty participants wore an accelerometer for seven days scheduled between two assessment sessions (off and on medication) to estimate MVPA levels (minutes/day). During both sessions, participants completed neuropsychological assessment using the Delis-Kaplan Executive Function System (D-KEFS) to measure response inhibition performance.

EFFECT OF PSYCHOSTIMULANT MEDICATIONS ON STATIC BALANCE PERFORMANCE IN ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: WITHIN-SUBJECT REPEATED-MEASURE STUDY DESIGN

by

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Submitted to Gait & Posture

Format adapted for dissertation

ABSTRACT

Objective: This study examined the effect of psychostimulant medication (PS) on balance and functional motor performance in adults with attention-deficit/hyperactivity disorder (ADHD).

Methods: Participants completed two sessions (off-medication and on-medication) in a within-subject repeated-measure study design, and there was a minimum of seven days between the two sessions. During both sessions, participants stood for 30-seconds per condition on a force platform, and the conditions were: feet-apart with 1) eyes-open and 2) eyes-closed; feet-together with 3) eyes-open and 4) eyes-closed. Participants performed three trials of timed up and go (TUG) and lateral step-up test (LSUT) during both sessions. Outcome measures were sway area (SA [cm^2]), average sway velocity (SV [cm/s]), TUG average time (s) and average number of LSUT repetitions. Data were analyzed using multivariate repeated measures analysis of variance and paired t-tests for examining PS effects on balance (SA and SV) and functional motor performance (TUG and LSUT), respectively.

Results: The sample included 45 adults (35 females; mean age=28.4±6.3 years). The repeated-measures MANOVA indicated that that PS was associated with better SA [$F(1,44)=9.6;p=0.003;\eta_p^2=0.18$], but not with SV [$F(1,44)=1.0;p=0.319;\eta_p^2=0.02$]. PS was associated with significantly better SA with decreasing base-of-support [$F(1,44)=9.9;p=0.003;\eta_p^2=0.18$]. Additionally, PS use was associated with better TUG [$t(1,44)=2.65;p=0.014$;Cohen's $d=0.39$], but not LSUT performances [$t(1,44)=-0.68;p=0.499$;Cohen's $d=-0.10$].

Conclusions: PS was associated with better SA and TUG in adults with ADHD. Further studies are needed to investigate the effects of PS on balance performance using rigorous designs in this population.

Impact: Healthcare providers should screen for PS status and balance when treating adults with ADHD to enhance safe motor performance.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that adversely affects motor function.[1] The American Psychiatric Association classifies ADHD into three subtypes: predominately Inattentive, predominately Hyperactive-Impulsive, and Combined.[2] ADHD prevalence is estimated at 6.1 million US children in 2016.[3] Further, ADHD persists into adulthood with approximately 4.4% of US adults aged 18-44 years (females 38%) diagnosed with ADHD.[4] Other estimates suggest that 1.0% of US adults aged 18-54 years were diagnosed with ADHD.[5] Children[6] and adults[7] with ADHD have exhibited greater postural sway area during standing, indicating poor static balance performance. Adults with ADHD displayed decreased dopaminergic activity in the basal nuclei[8] and cerebellum,[7,9] and this may be associated with balance impairments.[7]

Psychostimulant medication (PS), such as Methylphenidate (MPH) and Amphetamine (AMP) derivatives, are commonly prescribed to treat ADHD symptoms,[10] and may improve balance performance in children with ADHD.[11,12] Approximately 1.5% of the overall U.S adults reported current ADHD medication use.[13] AMP has improved different motor outcomes, such as knee muscle strength and acceleration in healthy adult athletes without ADHD.[14] Motor improvements by MPH were associated with increased activations in different areas in the prefrontal cortex, specifically the pre-supplementary motor area,[15] that contributes to motor planning and performance.[16] PS might improve static balance performance in adults with ADHD, but this has not yet been investigated in this population.

To our knowledge, there is also no direct investigations of the effects of PS medication on static balance and functional motor performance tests (FMPT), such as timed up and go (TUG), in adults with ADHD, despite researchers recommending performing FMPT when assessing individuals at risk for balance impairments.[17]

The purpose of this study was to examine the effects of MPH- and AMP-based stimulants on static balance performance in adults with ADHD. The study further determined if PS affected functional motor performance in adults with ADHD. The alternative hypothesis was using PS will be associated with better balance performance (i.e., postural sway area [SA] and sway velocity [SV]) and FMPT (i.e., timed up and go [TUG] and lateral step-up test [LSUT]) when performing these tasks in this population.

METHODS

Participants

Participants met the following criteria: a) aged 20-55 years, b) diagnosed with ADHD confirmed by a physician or psychologist, c) used MPH- or AMP-based stimulants to treat ADHD symptoms for a minimum of three months,[12] d) reported being in good physical health, e) spoke and read English, and f) ambulated freely in the community. Participant's recruitment was by posting fliers around campus, advertising in the University of Alabama at Birmingham (UAB) Reporter (https://www.uab.edu/reporter/) and sending emails to potential participants using the UAB Informatics for Integrating Biology and the Bedside (i2b2) records. Participants enrolled in this study consented to participate in this study. The UAB Institutional Review Board approved this study protocol and study forms (Protocol number: IRB-300006200).

Procedures

This study used a within-subject repeated-measure design. Participants completed testing on two separate sessions held on two different days in the Human Performance Laboratory at UAB. In one session, participants were instructed to forego their PS medication 24 hours before testing (off-medication) to ensure no systematic PS effects on balance performance.[7,18] and other outcome measures (e.g., driving score).[19] In the other session, participants were on their medication (on-medication). Participants were randomized to attend off-medication or on-medication prior to data collection using an online randomization generator (https://www.random.org/), with a minimum of seven days scheduled between the two sessions. PS compliance was measured using a self-reported question. All participants reported being on the assigned medication status for each session. Data collection started in May 2021 and finished in February 2022. During the first session, participants completed in order the following tasks: a) questionnaire [questionnaire included questions concerning demographics, PS-use characteristics, other medication use (Appendix1), ADHD symptoms (Appendix 2), b) body mass and height measurement, c) static balance tasks, and d) FMPT (i.e., TUG and LSUT). During the second session, participants completed ADHD symptoms, static balance tasks, and FMPT tasks. The order of FMPT (i.e., TUG and LSUT performances) and static balance tasks were randomized during both sessions (Figure 1).

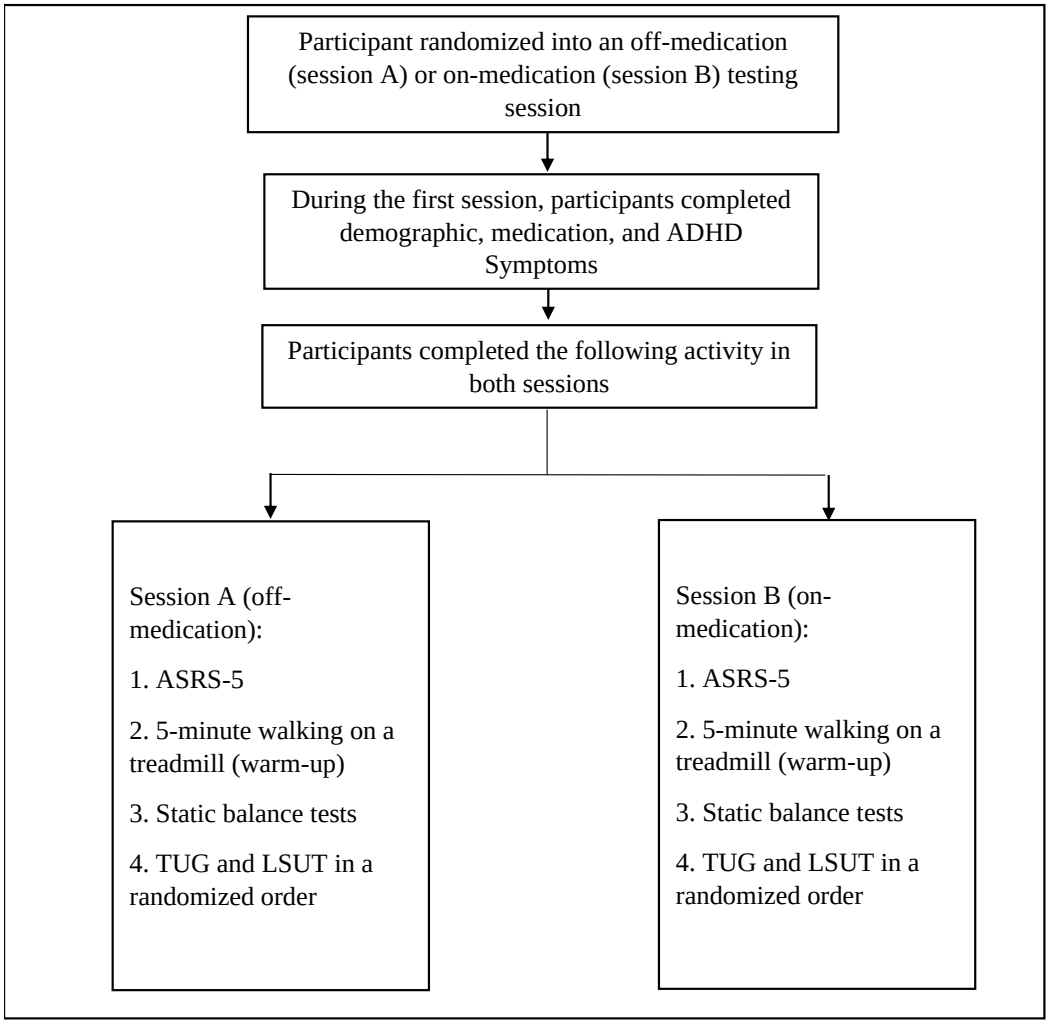


Figure 1. Summarized Study Procedures.

Outcome Measures

Demographic and Anthropometrics

Participants provided demographic information using a self-reported questionnaire containing items concerning age, sex, race, and education level. Additionally, body mass in kg and body height in cm were obtained using a weight scale (Garmin Ltd, Southampton, United Kingdom) and a stadiometer (Charder HM200P

Stadiometer, Taichung City, Taiwan). Body mass index (BMI) was calculated by dividing body mass by square body height (kg/m^2).

ADHD Symptoms

Participants completed the updated version of the World Health Organization (WHO) Adult ADHD Self-Report Screening Scale for DSM-5 (ASRS-5) to assess ADHD symptoms when they were off and on their medication.[20] This questionnaire is a 6-item tool adopted from Composite International Diagnostic Interview for DSM-5 (CIDI-5.0) and designed for adults aged 18 years or older. In addition to measuring ADHD symptomology, this survey determined effects of PS on ADHD symptoms, using the cut-off score per the proprietary scoring rules for the DSM-5 developed by New York University (NYU) and Harvard University (HARVARD). NYU and HARVARD provided permission to use the ASRS-5 proprietary scoring rules in this study. The ASRS-5 has excellent sensitivity (91.4%), specificity (96.0%) and area under the curve (AUC= 0.94) in identifying ADHD symptoms.[20]

Static Balance and Postural Sway Variables

Prior to static balance testing, participants performed a 5-minute walk on a treadmill. The Borg Scale for Perceived Exertion[21] guided participants to ensure a relatively light 5-minutes warm-up. Participants maintained a score between 6 and 11, which corresponds to light exertion.[21] Participants performed static balance tasks on a force platform (1000 Hz, AMTI, Watertown, MA, USA) in stocking feet. Participants performed four different tasks for 30-seconds per task: standing with feet shoulder-width apart with 1) eyes open (FAEO) and 2) eyes closed (FAEC); and standing with feet-

together with 3) eyes open (FTEO) and 4) eyes closed (FTEC). These testing tasks displayed sensitivity to balance impairments in adults with ADHD.[7] These measures are reliable and valid in assessing static balance in healthy adults without ADHD.[22] There were no significant associations between postural SA and SV with anthropometric measures in this study. Therefore, there was no control for anthropometric measures in the analyses. Postural data processing was conducted using a software written in MATLAB (MathWorks Inc., Natick, MA, USA). The analyzed Center of Pressure (COP) trajectory was for 20-seconds, excluding the first and last 5-seconds of each trial for additional accuracy.[23] The calculated postural sway data were SA (cm^2) and average SV (cm/s) for each condition. Postural sway calculations were based on equations from Doyle et al.[24]

Functional Motor Performance Tests

This study included two functional motor performance tests (FMPT): the timed up and go (TUG) and lateral step-up test (LSUT) to assess functional mobility and lower-extremity strength, respectively. Participants performed three trials of each test, with 60-seconds rest intervals between the trials. Participants practiced the tests before collecting the data. For TUG, participants stood up from a 45-cm height armchair, walked at their typical pace around a cone placed three meters from the chair, then walked back to the chair and sat down. Time (s) elapsed to complete the task represented the score of this test, recorded using stopwatches. TUG has excellent test-retest reliability in healthy adults (ICC > .97).[25] TUG is also a valid test for assessing dynamic balance in adults with balance impairments due to vestibular hypofunction.[26] For LSUT, participants stood on a 20-cm height step with their hands on their waists and nondominant foot on the step. The

participants then touched the top of the step with their dominant foot (foot flat) and back down to the floor as many times as possible in 15 seconds.[27] This test examined the non-dominant leg's muscle strength.[27] The counted the number of completed cycles represented the score of this test. The LSUT also has an excellent test-retest reliability (ICC = .94),[27] and this test is valid for assessing lower-extremity muscle strength,[27] which is associated with balance in healthy young adults.[28]

Data Processing and Statistical Analyses

The IBM Statistical Package for the Social Sciences (IBM SPSS, Chicago, IL, USA) v.28 was used to conduct the data analyses. Descriptive statistics characterized participants concerning age, sex, race, body measures, education level, ADHD subtypes, and ADHD medication. Four participants' data were not included in the analyses because they did not complete both testing sessions. Skewness values and box plots determined the univariate normality assumption for each dependent variable. To determine the effects of PS on postural sway (dependent variables were SA and SV), a 2 (medication status: on vs. off medication) × 2 (feet position: feet-apart vs feet-together) × 2 (visual input: eyes open vs eyes closed) repeated-measures multivariate analysis of variance (MANOVA) guided the analyses. Paired *t*-tests displayed the differences between off-medication and on-medication status during FMPT performance (TUG and LSUT). Cohen's (*d*) values of ≤ 0.3 indicate a small effect size, values of 0.5 indicate a medium effect size, and values of ≥ 0.8 indicate a large effect size.[29] Effect sizes for F-statistics were presented as partial eta-squared (η_p^2) and interpreted as small (0.01), medium (0.06), and large (0.14).[29]

While there were no violations to the normality assumption for TUG and LSUT variables, normality assumption violations existed for postural SA and SV. Additionally, Pearson correlation analyses examined the linearity assumption for using MANOVA with postural SA and SV variables (Appendix 3).[30] MANOVA robustness may control the Type I errors due to non-normally distributed data.[31,32] However, some researchers necessitate data transformation (e.g., square root transformations) to minimize the effect of normality violations when performing MANOVA.[33] When calculating the MANOVA on the postural sway data, the investigator analyzed these data with and without square-root transformations. There were no interpretive differences between performing MAVOVA with the original or transformed values. Thus, the MANOVA interpretation on the original values was presented in this study.

RESULTS

Participants Characteristics

A total of 49 adults with ADHD met the inclusion criteria. However, only 45 (91.8%) participants [35 females (77.8%); mean age=28.4 ± 6.3 years] completed both sessions (Figure 2). Most participants were diagnosed with Inattentive subtype (n=15; 33.3%) or Combined subtype (n=14; 31.1%) ADHD (Table 1). A greater number of participants used AMP-based stimulants (n=37; 82.2%) than MPH based stimulants (n=8; 17.8%) (Table 1). Most participants were Caucasian (n=33; 73.3%) were pursuing or received graduate degrees (n= 22; 48.9%) (Table 1). On average, the participants were overweight based on average BMI (mean BMI = 27.9 ± 7.7). ASRS-5 scores were significantly better when on-medication compared to off-medication [$t(1,44)= 7.1$; $p<0.001$; Cohen's $d=1.06$].

Table 1. Demographic and clinical outcomes characteristics of participants.

Characteristic	**All participants (n= 45)**	
	Mean	**SD**
Age (y)	28.4	6.3
Sex n (%)		
Male	10	22.2%
Female	35	77.8%
Race n (%)		
Caucasian	33	73.3%
Black or African American	6	13.3%
Asian	3	6.7%
Mixed of Two Races	3	6.7%
Body Mass (kg)	81.9	23.9
Body Height (cm)	170.5	9.0
Body Mass Index (kg/m^2)	27.9	7.7
Dominant leg n (%)		
Left	6	13.3%
Right	39	86.7%
Education Level n (%)		
Did Some College	8	17.8%
Undergraduate	14	31.1%
Graduate Level	23	51.1%
ADHD Subtype n (%)		
Inattentive	15	33.3%
Hyperactive	2	4.4%
Combined	14	31.1%
Unspecified	1	2.2%
Not Determined	13	28.9%
Psychostimulant Medication n (%)		
MPH based (min-max dose in mg)	8 (10-70.0)	17.8%
AMP based (min-max dose in mg)	37 (5.0-70.0)	82.2%
Adult Self-Report ADHD Scale-5		
Off-medication	18.4	2.4
On-medication	13.5	4.2

Note: FAEO: Feet apart with eyes open; FAEC: Feet apart with eyes closed; FTEO: Feet together with eyes open; FTEC: Feet together with eyes closed.

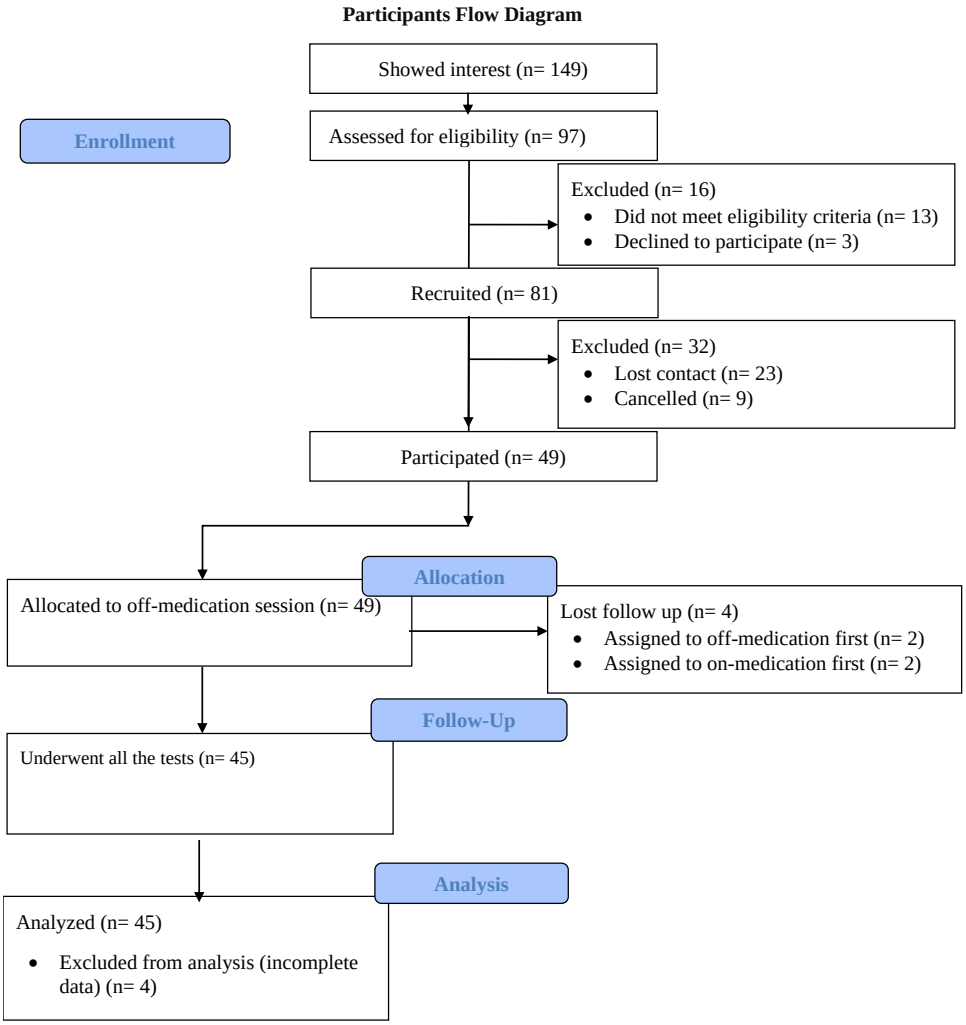


Figure 2. Flow diagram of the recruitment process.

PS Effects on Outcome Measures

The repeated-measure MANOVA identified a main effect of PS on SA [$F(1,44)=9.6;p=0.003;\eta_p^2=0.18$], but not SV [$F(1,44)=1.0;p=0.319;\eta_p^2=0.02$]. When on PS, participants exhibited less SA compared to when they were off their medication. Medication use explained about 18% of the variance in the linear composite of postural SA of the four tasks. Medication type (i.e., MPH- or AMP-bases stimulant) significantly moderated the effects of PS on postural SA [$F(1,43)=4.9;p=0.032;\eta_p^2=0.10$], but not SV

[$F(1,43)=0.7;p=0.799;\eta_p^2<0.01$]. Using MPH-based stimulants was associated with greater reduction in postural sway than using AMP-based stimulants, explaining about 10% of the variance in the linear composite of postural SA of the four tasks (Table 2)

Table 2. Change in outcome measures between off-medication and on-medication status measured by A. MANOVAs and B. paired *t*-tests.

Outcome measure	**Off-medication**		**On-medication**		**F (1,44) or T (1,44)**	**η_p^2 or Cohen's *d***
	Mean	**SD**	**Mean**	**SD**		
A.						
Sway Area (cm^2)						
FAEO	1.5	2.2	1.5	1.5		
FAEC	1.9	2.1	1.4	0.9		
FTEO	6.5	5.5	4.6	2.1		
FTEC	9.2	5.8	7.5	4.7		
Medication					**9.6****	**0.18**
Medication x Foot Position					**9.9***	**0.18**
Medication x Eye Condition					0.9	0.02
Medication x Foot Position × Eye Condition					0.1	0.01
Medication x Medication Type (*F*=1,43)					**4.9***	**0.10**
Sway Velocity (cm/s)						
FAEO	0.9	0.5	0.9	0.4		
FAEC	1.1	0.4	1.1	0.3		
FTEO	1.5	0.4	1.6	1.1		
FTEC	2.4	0.9	2.2	0.8		
Medication					1.1	0.01
Medication x Foot Position					0.4	0.01
Medication x Eye Condition					1.5	0.01
Medication x Foot Position × Eye Condition					2.4	0.01
Medication x Medication Type (*F*=1,43)					0.1	0.01

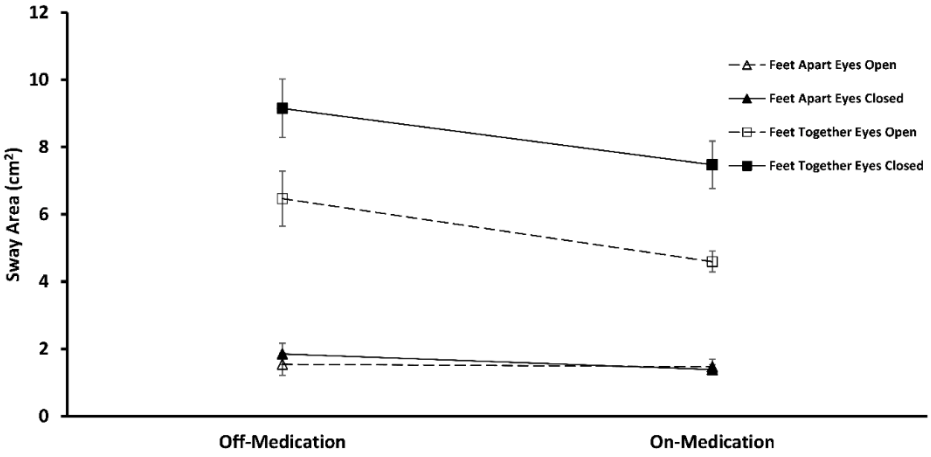
B.

Timed-Up and Go (s)	8.0	1.2	7.7	1.1	**2.7***	**0.39**
Lateral Step-Up (repetitions)	16.3	3.0	16.9	2.9	0.7	0.10

*$p < 0.05$; ** $p < 0.01$

Note: FAEO: Feet apart with eyes open; FAEC: Feet apart with eyes closed; FTEO: Feet together with eyes open; FTEC: Feet together with eyes closed; Medication Type: methylphenidate- vs amphetamine-based stimulants; Foot Position: feet-apart vs. foot-together; Eye Condition: open vs closed.

Additionally, there was a significant medication × feet position (i.e., feet-together or feet-apart) interaction effect [$F(1,44)=9.9;p=0.003;\eta_p^2=0.18$]. Medication and feet position interaction effect showed that using PS was associated with decreased SA during feet-together tasks (Figure 3). Medication status and feet position interaction effect accounted for 18% of the decrease in the linear composite of postural SA of the four tasks (Table 2). However, no statistical differences between off-medication and on-medication status existed when assessing SV (Figure 4).



S

Figure 3**.** Differences between off-medication and on-medication performance in postural sway area (cm^2).

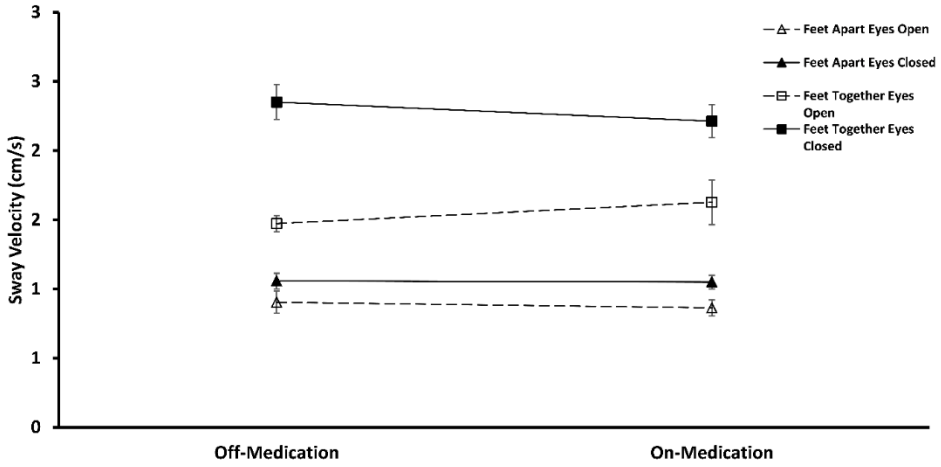


Figure 4. Differences between off-medication and on-medication performance in postural sway velocity (cm/s).

Participants TUG performance was significantly better when on medication versus off medication [$t(1,44)=2.7$;$p=0.014$;Cohen's $d=0.39$], indicating a small-medium effect size. However, there was no significant difference in LSUT performance when comparing medication status [$t(1,44)=-0.7$;$p=0.499$;Cohen's $d=-0.10$].

DISCUSSION

To our knowledge, this is the first investigation of PS effects on balance performance in adults with ADHD. This study indicated that using PS was associated with better SA, but there was no difference in SV, when on-medication compared with off-medication. The results further indicated that some motor performance measures (i.e., TUG performance) were significantly better when on versus off PS.

Children aged 8-12 years with ADHD significantly reduced their postural SA after one month of MPH treatment.[34] Additionally, children aged 10-12 years with ADHD on their medication displayed similar postural SAs of healthy controls in the

sensory organization test (SOT) except for one condition that relies primarily on the vestibular system.[35] Furthermore, the findings of this study revealed significant medication by foot position on postural sway and indicated that improvements by PS are more pronounced with feet-together conditions representing a greater challenge for postural control (i.e., narrow base of support). Other researchers have reported that using PS significantly improved balance when scaling up challenges to the balance task (i.e., dual tasking) in children aged 7-16 years with ADHD.[11] Moreover, the results of this study denoted no significant interaction effects medication by eyes open/closed status by PS. A possible reasons is that using PS improves dopaminergic activity in the frontal lobe, basal ganglia, and cerebellum, but not in the occipital lobe that primarily receives and processes visual signals from the retina.[36]

Postural SV measures the postural oscillation frequency during quiet standing that is regulated by the gamma feedback loop.[37] Postural SV improved after one month of using MPH in children aged 8-12 years.[34] In contrast, using PS was not associated with better postural SV in the current sample of adults with ADHD. In addition, participant' SV scores were similar to normative data for healthy controls during feet-apart tasks (0.9±0.4 vs 0.8±0.4 cm/s for eyes open and 1.1±0.3 vs 1.0±0.3 cm/s for eyes closed).[38] This observation suggests that using PS may not affect SV scores in adults.

Balance improvements might result from the increased dopaminergic activity driven by PS medications.[39] PS increases the level of dopamine in the prefrontal cortex, nigrostriatal region of the basal nuclei, and cerebellum,[36] which are involved in motor regulations and balance.[40] Studies found that PS enhanced brain activity in the right

middle frontal gyrus, superior temporal gyrus, anterior cingulate cortex, and pre-supplementary motor area.[15,41] Some of these areas contribute to motor planning and performance.[16] Additionally, PS improves attention span in the short[42] and long term.[43] These improvements in attention may be associated with motor improvements based on the OPTIMAL theory.[44] Interestingly, this study showed that the association between the use of MPH-based stimulants with postural SA was stronger than the use of AMP-based stimulants with SA. This observation necessitates direct comparison between PS types on postural SA.

Improvements in TUG performance found in this study can reflect improvements of other motor performance constructs, such as muscle strength,[45] which is associated with balance.[28] Additionally, the TUG, simulate activity of daily living (ADL) tasks, such as rising from a chair, turning around, and sitting down on a chair. Improvements in TUG performance might indicate that using PS might improve overall ADL in adults with ADHD. Similarly, a few studies in children aged 7-12 years with ADHD demonstrated that PS improved motor performance, such as the timed 20m agility test,[46] reciprocal coordination and walking tests,[12] and the movement ABC manual dexterity index.[47] To that end, using PS may yield improvements in motor performance in children and adults with ADHD.

LSUT may have a ceiling effect for adults with ADHD. A data split analysis, based on normative values (18.1±2.3 repetitions) for LSUT for healthy adults without ADHD),[48] indicated significant improvements in LSUT among those who performed ≤ 16 repetitions (n= 22) when on-medication compared to off-medication [$t(1,21)$=-

2.2;p=0.037;d=0.48]. Those who performed greater than 16 repetitions (n= 23) had no significant improvements in LSUT between on-off medication status [t(1,22)=1.5;p=0.145;d=0.32]. This analysis suggests that if an adult with ADHD performed greater than 16 repetitions in LSUT, using PS is less likely to change their scores, indicating a ceiling effect. Further research is needed to examine this observation.

All healthcare providers should screen balance performance, motor function, and PS use and compliance when providing healthcare services to adults with ADHD. Since ADHD symptoms improved in this sample, we can assume that attention improved. According to the theory of motor learning,[44] improvements in attention could improve motor performance, such as balance. Thus, healthcare providers should check medication status and if a patient is taking ADHD medication, ensure that PS adequately controls ADHD symptoms when providing healthcare services to this population.

Limitations

This study has few limitations. First, the lack of participant blinding might threaten the internal validity of these findings. Ideally, providing placebo medication allows for controlling any bias, but the cost was beyond the scope of this study. Second, the age range of this sample of adults with ADHD was 20-55 years, which may restrict the generalization of the findings to children, adolescents, and older adults. Third, differences in PS class and dose might account for test performance variability. However, all participants reported considerable control of their symptoms measured by the ASRS-5. Fourth, most of the participants in this study were females (77.8%); thus, these findings may not generalize to male adults with ADHD.

CONCLUSION

Using PS was associated with improvements in static balance and motor performance in adults with ADHD, specifically, when increasing level of challenge. Future studies should examine the effects of PS on balance and motor performance using more rigorous research designs. Finally, future studies should determine if balance and exercise training with and without medication could alter balance and motor performance in this population.

ACKNOWLEDGMENTS AND FUNDING

The authors thank NYU and HARVARD for providing permission to use the proprietary scoring rules for the ASRS-5. The authors also thank the UAB Informatics for Integrating Biology and the Bedside (i2b2) for their help in the recruitment. The authors also thank Dr. Christopher Hurt and Dr. Daniel Kuhman for creating MATLAB software for postural sway calculations. Finally, the authors thank the Saudi Arabian Cultural Mission to the US (SACM) and Northern Border University in the Kingdom of Saudi Arabia for supporting the first author's doctoral studies.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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EFFECT OF PSYCHOSTIMULANT MEDICATIONS ON MUSCLE TONE IN ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: WITHIN-SUBJECT REPEATED-MEASURE STUDY DESIGN

by

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Submitted to Journal of Attention Disorders

Format adapted for dissertation

ABSTRACT

Objective: To determine PF spasticity and the effect of PS on PF spasticity and ankle plantarflexor resistance to stretch (PFRS) in adults with Attention-Deficit/Hyperactivity Disorder (ADHD).

Methods: Participants completed two visits (off-medication and on-medication). During both visits, the Modified Ashworth Scale (MAS) was administered to measure PF spasticity. Two device-measured (isokinetic-dynamometer [Biodex] and surface electromyograph [sEMG]) tests assessed PFRS: reflex mediated, and non-reflex mediated.

Results: Adults with ADHD (n= 39, 31 females; mean age=28.6±6.7 years). Overall, adults with ADHD displayed elevated PF spasticity (average MAS>1). PS use was not associated with changes in PFRS [$F(1,38)=0.001;p=0.972;\eta_p^2=0.01$]. A sub-analysis indicated that PS was associated with reduced PFRS [$F(2,36)=4.449;p=0.019;\eta2=0.20$], specifically with the reflex-mediated component, among the predominantly inattentive ADHD subtype.

Conclusions: Adults with ADHD displayed increased PF spasticity. PS use was associated with reduced reflex mediated PFRS in adults with the predominantly Inattentive subtype of ADHD only.

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder associated with adverse behaviors.[1] Based on the American Psychiatric Association classification, ADHD has three subtypes: predominately Inattentive, predominately Hyperactive-Impulsive, and Combined.[2] ADHD prevalence among US adults aged 18-44 years is approximately 4.4% with a 2:1 male: female ratio.[3] Other researchers estimated approximately 1.0% of US adults aged 18-54 years are diagnosed, with ADHD.[4] Psychostimulant medication (PS), including Methylphenidate (MPH) and Amphetamine (AMP) based stimulant medications, are commonly used to treat ADHD symptoms.[5] We focus on muscle tone in ADHD and the effects of PS in the current study.

Carpenter et al. define muscle tone as "the constant muscular activity that is necessary as a background to actual movement in order to maintain the basic attitude of the body, particularly against the force of gravity."[6] Muscle tone has two major components: the active/contractile and viscoelastic/passive (e.g., tendon, ligaments, and fascial muscle coverings) components.[7] Spasticity is a sensorimotor disorder manifested by intermittent or continuous involuntary muscle activity, that causes increased muscle tone.[7] Spasticity is assessed by passively stretching a muscle, which is composed of the reflex mediated and non-reflex mediated components.[8] The stretch reflex mediates the reflex mediated component of spasticity.[8] Two reliable methods to spasticity include the computerized dynamometry[9] and Modified Ashworth Scale (MAS).[10]

Researchers have reported a slight increase in spasticity level of the ankle plantarflexor (PF) in children[11] and adults[12] with only predominantly inattentive ADHD, leaving uncertainty about PF spasticity existence in other ADHD subtypes. However, two drawbacks potentially exist in these two studies. First, both studies only examined the

predominately inattentive ADHD, which may not be generalizable to other ADHD subtypes. Second, the researchers in both studies used the same PF spasticity subscale from the motor function neurological assessment battery (MFNU). The MFNU has been established as reliable for assessing motor function in individuals with ADHD,[12,13] but the PF spasticity subscale psychometric properties have not been studied and reported in ADHD. Ideally, using a valid and reliable test for PF spasticity would strengthen the confidence in the findings of increased tone in children[11] and adults[12] with ADHD. Increased PF spasticity negatively interferes with motor function, such as walking in adults post stroke.[14] Using PS for ADHD may reduce PF spasticity in children aged 8-12 years with ADHD.[11] Researchers have not yet reported PS effects on PF spasticity in adults with ADHD, which, if increased, may restrict range of motion and limit motor function.

This study investigated PF spasticity level and MPH-/AMP-based PS effects on PF spasticity and plantarflexor resistance to stretch (PFRS) in adults with ADHD. This study also examined if these effects differed by ADHD subtypes. The first hypothesis was that adults with ADHD would exhibit PF spasticity. The second hypothesis was that using PS would be associated with reduced PF spasticity and PFRS compared with an off-medication state in adults with ADHD. Finally, we hypothesized that PS use would be associated with reduced PF spasticity among the predominantly Inattentive subtype of ADHD.

METHODS

Participants

Participants were eligible for inclusion in this study based on the following criteria: a) aged 20-55 years, b) diagnosis of ADHD confirmed by a physician or psychologist, c) current use of MPH- or AMP-based PS for ADHD symptoms for three months or greater, d) self-reported good physical health, e) fluent in English, and f) community ambulators. Several methods were used to recruit participants, including posting flyers around a university campus, advertising in the UAB eReporter (https://www.uab.edu/reporter/) and sending email invites to possible participants using the University of Alabama at Birmingham (UAB) Informatics for Integrating Biology and the Bedside (i2b2) records. Participants who satisfied inclusion criteria and voluntarily provided written consent to participate in this study were enrolled. The UAB Institutional Review Board approved this study protocol and procedure (Protocol number: IRB-300006200).

Procedures

This was a within-subjects repeated-measures design. All data collection was performed in the Human Performance Laboratory at UAB. Participants met with the investigators twice, with a range of seven days to four weeks scheduled between the two visits. Investigators randomized the order of off or on medication visits. For the off medication visit, participants were instructed to skip their PS medication 24 hours before testing to ensure no systematic PS effects on the central nervous system.[15,16] For the on-medication visit, participants took their medication as prescribed by their physician on the day of testing. All participants reported compliance to the assigned medication status

by answering a self-reported question during both visits. Data collection occurred between May 2021 and February 2022.

During the first visit, participants completed the following tasks in the following order: a) questionnaire [demographics, psychostimulant medication-use characteristics, other medication use, and ADHD symptoms], b) body mass and height measurements, c) Modified Ashworth Scale (MAS) assessment of non-dominant plantarflexors, d) non-dominant ankle plantarflexors maximum voluntary isometric contraction (MVIC), e) reflex mediated PFRS assessment of non-dominant plantarflexors, and f) non-reflex mediated PFRS examination of non-dominant plantarflexors. MAS, MVIC, and reflex and non-reflex resistance to torque trials were performed on the non-dominant leg for consistency. The non-dominant leg was determined by asking participants: "what leg do you kick a ball with?" The MVIC, reflex mediated PFRS assessment, and non-reflex mediated PFRS examination were performed on a dynamometer with surface electromyography (sEMG) applied to the non-dominant lower leg to monitor muscle activity during these tests. During the second visit, participants completed the same tests in the same order as the first visit except they completed only the items concerning ADHD symptoms of the initial questionnaire and body anthropometrics were not re-measured. The order of PFRS was not randomized because MVIC test determined the pre-reflexed mediated contraction level and concerns of the damping effect associated with stretch reflex due to repeated stretches to ankle plantarflexors (Figure 5).[17]

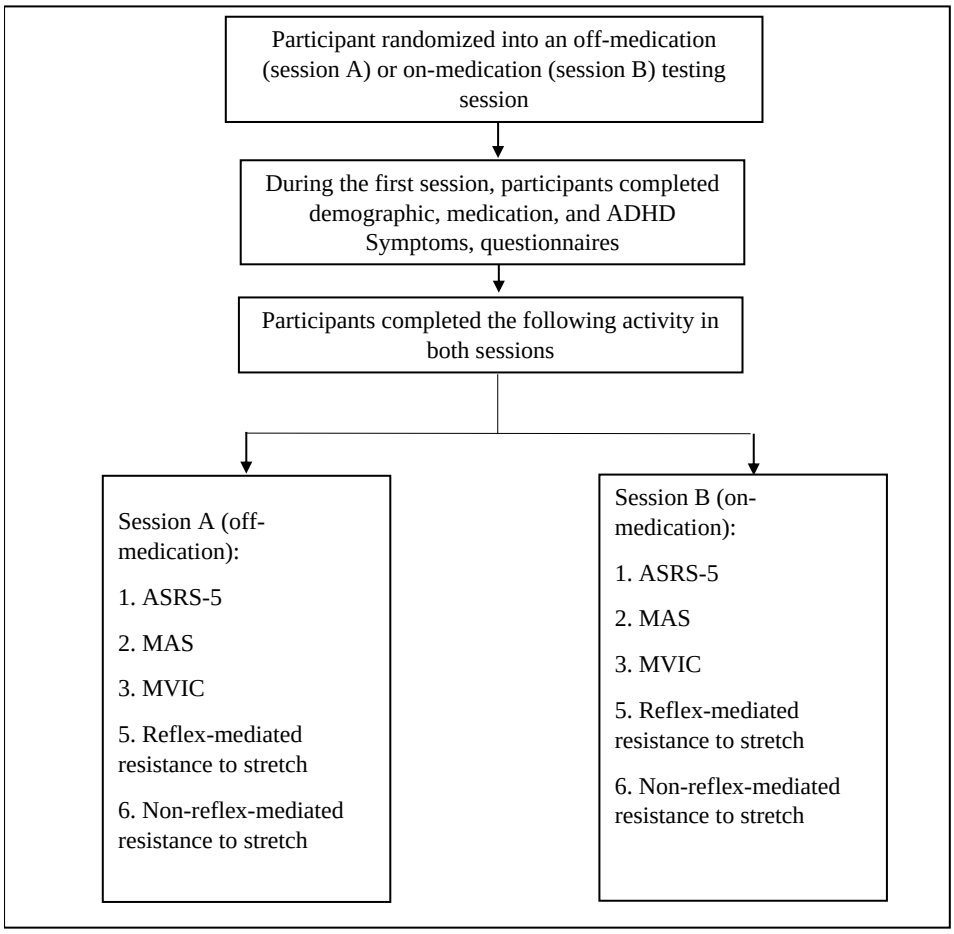


Figure 5. Summarized study procedures.

Outcome Measures

Demographic and Anthropometrics

Participants reported age, sex, race, education level, and ADHD medication use. ADHD subtype was confirmed by participants' treating physician or psychologist via a letter. A scale (Garmin Ltd, Southampton, United Kingdom) and stadiometer (Charder HM200P Stadiometer, Taichung City, Taiwan) were used to measure body mass in kg and body height in cm, respectively. Calculation of BMI was determined by dividing body mass by body height squared (kg/m^2).

ADHD Symptoms

The participants completed the updated version of the World Health Organization (WHO) Adult ADHD Self-Report Screening Scale for DSM-5 (ASRS-5) during both visits.[18] The ASRS-5 is a 6-item questionnaire adopted from Composite International Diagnostic Interview for DSM-5 (CIDI-5.0) and designed for adults aged 18 years or above. The ASRS-5 has excellent sensitivity (91.4%), specificity (96.0%) and area under the curve (AUC= 0.94) in identifying ADHD symptoms.[18] The investigators used the ASRS-5 to measure ADHD symptomology and to determine PS effects on ADHD symptoms. This questionnaire was graded using the cut-off score per the proprietary scoring rules for the DSM-5 version. Investigators received permission to use the ASRS-5, which was created by New York University (NYU) and Harvard University (HARVARD).

Ankle Plantarflexion Maximum Voluntary Isometric Contraction

Participants sat on the isokinetic dynamometer Biodex System 3 (Biodex Medical Systems, Shirley, NY, USA) with ankle joint in neutral position at 0^{o} and knee joint at 60^{o} of flexion. Straps were applied to the ankle (2 straps), thighs, waist, and upper body to minimize contributions of other muscles, such as the quadriceps. Participants performed three MVIC trials for ~ 5 s with 45 seconds rest between trials to minimize fatigue. Participants pushed against a non-yielding foot plate with their non-dominant socked foot. The average of the closest two trials ($\leq$ 10% change) was calculated and used to determine pre-stretch isometric contraction level for reflex mediated PFRS trials.

Reflex and Non-Reflex Mediated Resistance to Stretch

The resistive torque for ankle plantarflexors was assessed during passive ankle dorsiflexion movement at ~ 180^{o} s^{-1} for two separate conditions: a) reflex mediated resistive torque (i.e., isometric plantarflexor contraction at ~ 30% of its MVIC followed by a passive plantarflexor stretch) and b) non-reflex mediated resistive torque of the plantarflexors (i.e., passive ankle dorsiflexion) using the same dynamometer and set-up to measure plantarflexor MVIC.[8] During reflex mediated resistance to stretch condition, participants performed one-second isometric plantarflexor contractions at ~ 30% of an individual's MVIC at 35-degrees of plantarflexion before their plantarflexors being passively stretched into 5-degrees of dorsiflexion. Before testing, participant's ankle sagittal plane passive range of motion was measured for safety (Table 1). Participants received visual input by watching a line that represented 30% of their MVIC on the dynamometer's computer screen.

During the non-reflex mediated resistance to stretch, participants were instructed to relax their ankle plantarflexors as their plantarflexors were passively stretched from 35-degrees of plantarflexion to 5-degrees of dorsiflexion.[8] Pre-stretch isometric contraction torque levels (Biodex), short stretch reflex amplitude (sEMG), and the amplitude of plantarflexor muscle activity during the last 30 ms (sEMG) of muscle activation prior to the stretch, were collected during reflex mediated trials. This information was collected to validate that the stretch reflex occurred during these trials due to the pre-stretch isometric contraction torque level. The Biodex set-ups for these two conditions were the same as the MVIC assessment except for the ankle position. Five trials of both of these tests were performed and the average of the closest three resistive peak torque values (≤ 10% change) was calculated for the reflex mediated and non-reflex

mediated resistive torque, respectively. These values were then normalized to body mass to control for anthropometric effects on torque.

sEMG wireless electrodes (Delsys Inc, Boston, MA, USA) were applied to the following lower leg muscles: 1) soleus, 2) gastrocnemius medial head, 3) tibialis anterior. The electrode placed on the tibialis anterior was to ensure reciprocal inhibition occurred during the stretch reflex of PF. Surface Electromyography for the Non-Invasive Assessment of Muscles (SENIAM) guidelines for sEMG electrode placement were used to guide electrode placement.[19] Before electrode placement, participant's skin was shaved, abraded with sandpaper, and cleaned with alcohol to minimize skin resistance to EMG signal.[20] To reproduce electrode placements between visits, the investigators measured the distance (cm) from bony landmarks to the electrode site during the first visit, and used this information to place the electrodes during the second visit.

The sEMG base station was connected to PowerLab 8/35 system (ADInstruments, Sydney, Australia) and signals were amplified by a factor gain of 909. sEMG signals were rectified and filtered using band-pass digital filters (20 Hz to 1 kHz).[20] sEMG data were collected at a sampling frequency of 2kHz. Three channels were used from Trigno EMG 1-16 Adaptor (ADInstruments, Sydney, Australia) to the PowerLab (one channel per sEMG electrode). Another channel was coming from the isokinetic dynamometer to the PowerLab to synchronize reflex and non-reflex-mediated resistance to muscle stretch torque vales and sEMG values. LabChart software v8 was used to process sEMG data. Stretch reflex onset was visually identified as the first major EMG deflection recorded following the stretch, which was also used to quantify reflex amplitude (i.e., the peak of the EMG deflection).[20] Stretch reflex was present if the reflex amplitude (mV) exceeded

the mean plus the standard deviation of the 30ms average amplitude before the stretch.[20] If a stretch reflex was present, the reflex mediated torque was recorded from the Biodex and used in the data analyses.

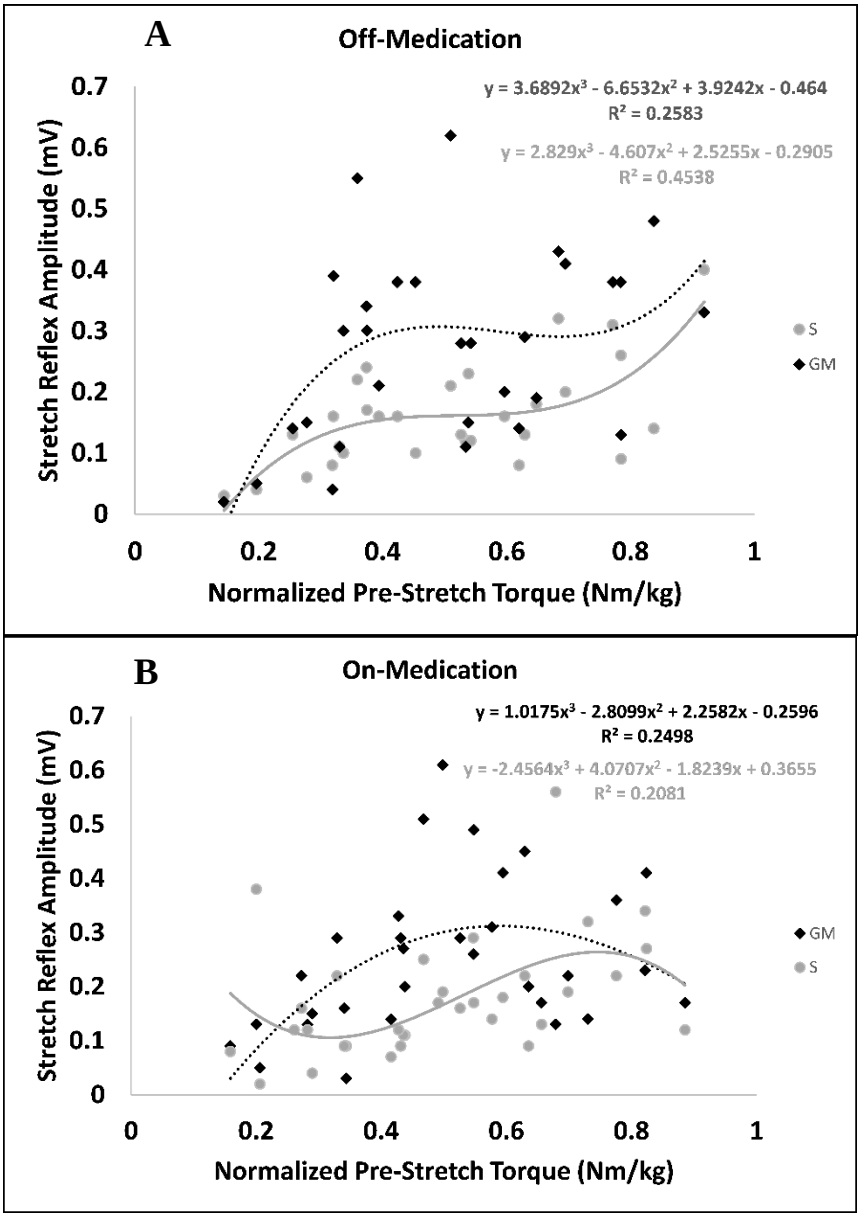
Modified Ashworth Scale

The MAS was used to assess PF spasticity level in the current study. Participants lied supine on a treatment table with head along midline and arms alongside the trunk, with hips and knees in straight position.[21] Participants removed shoes, but wore socks. The rater tested the non-dominant leg. On the non-dominant leg, the rater stabilized the distal leg around the ankle joint with one hand and placed the other hand under the heel. The rater passively and rapidly stretched the participant's ankle from plantarflexion to dorsiflexion within one second.[21] The rater determined MAS score after performing three passive plantarflexor stretches.[21] To decrease the measurement bias, one investigator performed all MAS evaluations. This investigator was blinded to medication status (i.e., off or on medication). The MAS has good intra-rater reliability scores for lower leg (intraclass correlation = 0.644; Cohen's kappa= 0.488).[10]

Data Processing and Statistical Analyses

The Statistical Package for the Social Sciences (SPSS; IBM Corp., Armonk, NY, USA) v.28 was utilized to perform the data analyses. Descriptive and frequency statistics were generated to characterize the age, sex, race, body measures, education level, ADHD subtype, and ADHD medication of the sample. Means and standard deviations were used to describe PF spasticity level per medication status. To validate the reflex mediated trials and ensure consistency of this measure across medication status, the average of three

stretch reflex amplitude was plotted against the average of three pre-stretch isometric contraction torque during reflex mediated trials to ensure that stretch reflex presence occurred due to pre-stretch isometric contraction torque level (Figure 6A-B). Further, the average of three reflex-mediated torque trials was also plotted against the average of three pre-stretch isometric contraction torque levels to determine if pre-stretch isometric contraction torque level mediated average reflex mediated trials torque (Figure 6C-D). Torque values of pre-stretch isometric contraction showed a very good internal consistency when off and on medication using intraclass correlations coefficients (ICC: 0.866, 0.745-0.930).


A
Off-Medication
y = 3.6892x³ - 6.6532x² + 3.9242x - 0.464
R² = 0.2583
y = 2.829x³ - 4.607x² + 2.5255x - 0.2905
R² = 0.4538
S
GM
Stretch Reflex Amplitude (mV)
Normalized Pre-Stretch Torque (Nm/kg)
B
On-Medication
y = 1.0175x³ - 2.8099x² + 2.2582x - 0.2596
R² = 0.2498
y = -2.4564x³ + 4.0707x² - 1.8239x + 0.3655
R² = 0.2081
GM
S
Stretch Reflex Amplitude (mV)
Normalized Pre-Stretch Torque (Nm/kg)

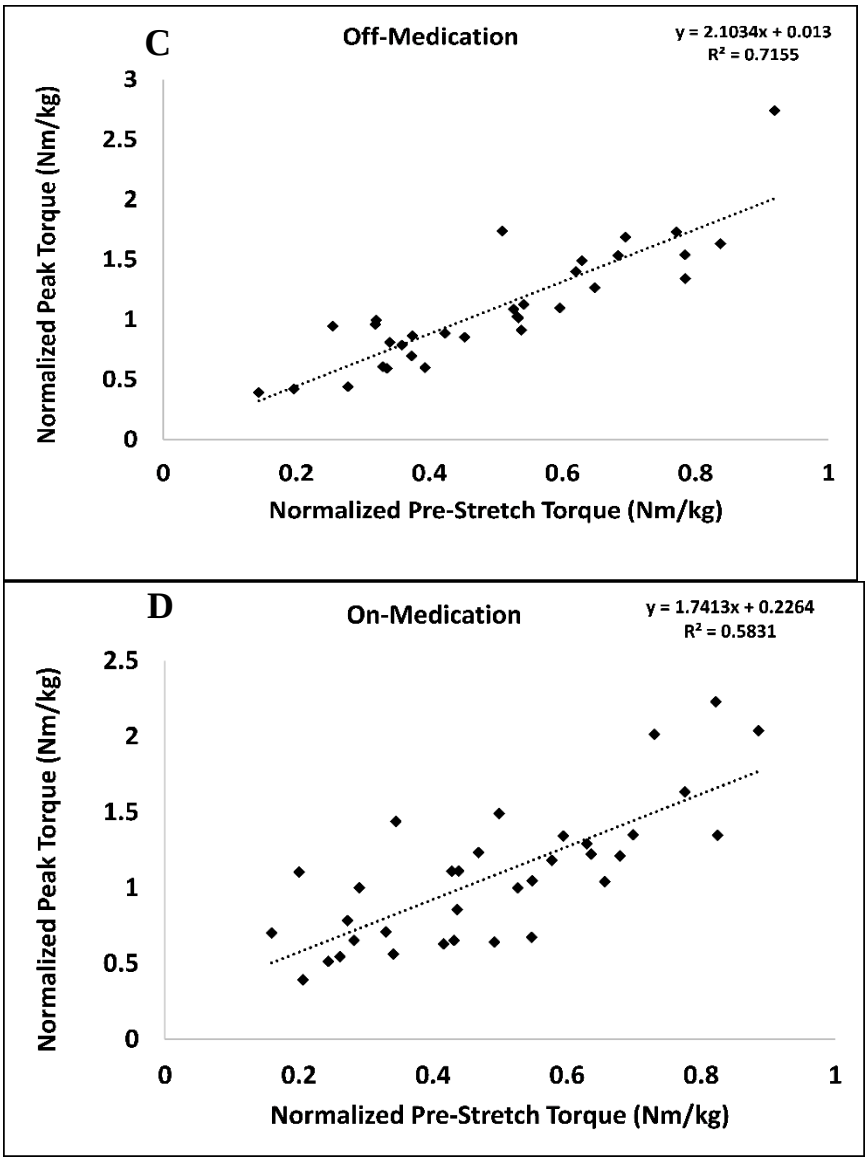


Figure 6**.** Stretch reflex of soleus and gastrocnemius (medial head) are influenced by pre-stretch isometric torque during a) off-medication and b) on-medication. Third-order polynomial line was fitted in the data. Peak resistive torque is a function of background torque during c) off-medication and d) on-medication.

Since the reflex mediated and non-reflex mediated trials were significantly associated with each other during off-medication (r= .50, p=0.001) and on-medication status (r= .48, p=0.002), a 2 (medication status: off vs. on medication) × 2 (PFRS test: reflex mediated vs non-reflex mediated) repeated-measures multivariate analysis of

variance (MANOVA) was conducted to determine the effects of PS on PFRS (reflex- and non-reflex mediated resistance to stretch). This analysis was repeated and included ADHD subtype as a group factor to determine effects of PS on PFRS by ADHD subtypes. Additional three separate MANOVAs were performed for each ADHD subtype to determine which group exhibited a significant difference in PFRS by medication status. Skewness values and box plots determined no significant violations to the univariate normality assumption for each dependent variable. Regarding the MAS, the score was transformed to 0 to 5 (0=0, 1=1, 1+=2, 2=3, 3=4, 4=5) for data processing. Finally, because MAS scores were ordinal, Wilcoxon matched-pair signed-rank was conducted to examine PS effects on MAS. Further, three Wilcoxon matched-pair signed-rank test per ADHD subtype examined effect of PS on MAS by ADHD subtypes.

RESULTS

Participants Characteristics

The sample included 39 adults with ADHD who met the selection criteria and completed both visits [31 females (79.5%); mean age =28.6 ± 6.7 years]. Most participants were diagnosed with Inattentive subtype (n=14; 35.9%) or Combined subtype (n=13; 33.3%) ADHD, used AMP-based stimulants. (n=31; 79.5%), were Caucasian (n=28; 71.8%), enrolled in graduate studies or obtained a graduate degree (n= 20; 51.3%), and were on average overweight (mean BMI = 27.7 ± 7.5) (Table 3).

Table 3**.** Demographic and clinical outcomes of participants.

Characteristic	**Inattentive n=15**		**Combined n=12**		**Unspecified n=12**		**All participants n= 39**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (y)	28.3	7.0	27.17	5.9	30.6	7.0	28.6	6.7
Sex n (%)								
Male	4	26.7	1	8.3	3	25.0	8	20.5
Female	11	73.3	11	91.7	9	75.0	31	79.5
Race n (%)								
Caucasian	11	73.3	8	66.7	9	75.0	28	71.8
Black or African American	2	13.3	2	16.7	2	16.7	6	15.4
Asian	2	13.3	1	8.3	0	0.0	3	7.7
Mixed of Two Races	0	0.0	1	8.3	1	8.3	2	5.1
Body Mass (kg)	79.5	21.4	83.7	26.6	77.8	25.4	80.3	23.8
Body Height (cm)	171.8	8.1	165.5	6.9	171.2	10.5	169.7	8.8
Body Mass Index (kg/m^2)	26.7	5.8	30.4	9.2	26.3	7.5s	27.7	7.5
Dominant leg n (%)								
Left	4	26.7	1	8.3	1	8.3	6	15.4
Right	11	73.3	11	91.7	11	91.7	33	84.6
Education Level n (%)								
Did Some College	3	20.0	2	16.7	3	25.0	8	20.5
Undergraduate	5	33.3	3	25.0	3	25.0	11	28.2
Graduate Level	7	46.7	7	58.3	6	50.0	20	51.3
Psychostimulant Medication n (%)								
MPH based	4	26.7	2	16.7	2	16.7	8	20.5
AMP based	11	73.3	10	83.3	10	83.3	31	79.5

Adult Self-Report ADHD Scale-5								
Off-medication	18.33	2.2	18.6	2.4	18.5	3.1	18.5	2.5
On-medication	13.53	3.5	12.3	4.4	13.3	4.0	13.2	3.9
Ankle Passive Range of Motion								
Off-medication, min-max	10.0, 2-20	5.8	8.8, 2-15	4.2	6.1, 2-12	3.2	8.4, 2-20	4.8
On-medication, min-max	10.0, 2-20	5.9	6.5, 2-18	4.5	6.8, 2-15	4.2	7.8, 2-20	5.1
Maximum Voluntary Isometric Contraction (Nm/kg)	1.6	0.6	1.4	0.6	1.8	0.7	1.6	0.6
Off-medication	1.4	0.6	1.5	0.7	2.0	0.7	1.6	0.7
On-medication								
Modified Ashworth Scale								
Off-medication	1.3	1.2	1.0	1.1	1.0	1.1	1.1	1.1
On-medication	1.3	0.9	1.0	1.0	1.3	1.2	1.2	1.0

Presence of Spasticity and Differences in Spasticity and PFRS by Medication Status

Overall, MAS scores documented increased PF spasticity level (off-medication: mean= 1.1±1.1; on-medication: mean= 1.2±1.0), but there was no difference in MAS scores based on medication status (p>0.05). The average MVIC normalized torque values were 1.6 ± 0.6 during off medication and 1.6 ± 0.7 during on medication, and these values were not different as a function of medication status (p>0.05). Additionally, there was no significant difference in MAS between medication status (p>0.05). Moreover, there was no significant difference in MAS between off-medication and on-medication by ADHD subtype (all p>0.05).

The repeated-measure MANOVA indicated no significant differences in PFRS tests between off- and on-medication for the total sample [$F(1,38)= 0.001$; p=0.972; η_p^2=0.01]. There was no significant medication by PFRS test interaction [$F(1,38)= 0.001$; p=0.971; η_p^2=0.01] (Table 4)

Table 4. Change in outcome measures between off-medication and on-medication status.

Outcome measure	**Off-medication**		**On-medication**		**F (1,38)**	**η_p^2**
	Mean	**SD**	**Mean**	**SD**		
Plantarflexors' Resistance to Stretch (PFRS)						
Reflex-Mediated Torque (Nm/kg)	1.1	0.5	1.1	0.5		
Non-Reflex Mediated Torque (Nm/kg)	0.2	0.1	0.2	0.1		
Medication					0.001	0.01
Medication by PFRS					0.001	0.01
Medication by PFRS by ADHD Subtype F (2,36)					**4.449***	**0.20**

*$p < 0.05$.

Note: Medication: off- vs on-medication; PFRS: reflex- vs non-reflex muscle resistance to stretch; ADHD Subtype: predominantly inattentive, combined, or not determined.

There was a significant three-way medication by PFRS test (i.e., reflex mediated vs non-reflex mediated resistance to stretch) by ADHD subtype interaction on PFRS [$F(2,36)= 4.449$; $p=0.019$; $\eta_p^2=0.20$]. These effects explained about 20% of the variance in the linear composite of reflex and non-reflex mediated trials (Table 4).

The three separate MANOVAs revealed significant medication by PFRS interaction in the inattentive subtype [$F(1,14)= 8.349$; $p=0.012$; $\eta_p^2=0.37$], but not the Combined [$F(1,11)= 1.367$; $p=0.267$;s $\eta_p^2=0.11$] or not determined groups [$F(1,11)= 1.368$; $p=0.267$; $\eta_p^2=0.11$]. PS use was associated with decreased reflex mediated PFRS trials when on medication compared with off medication status in only the predominantly inattentive group, explaining about 33% of the variance in the linear composite of reflex and non-reflex mediated trials (Figure 7).

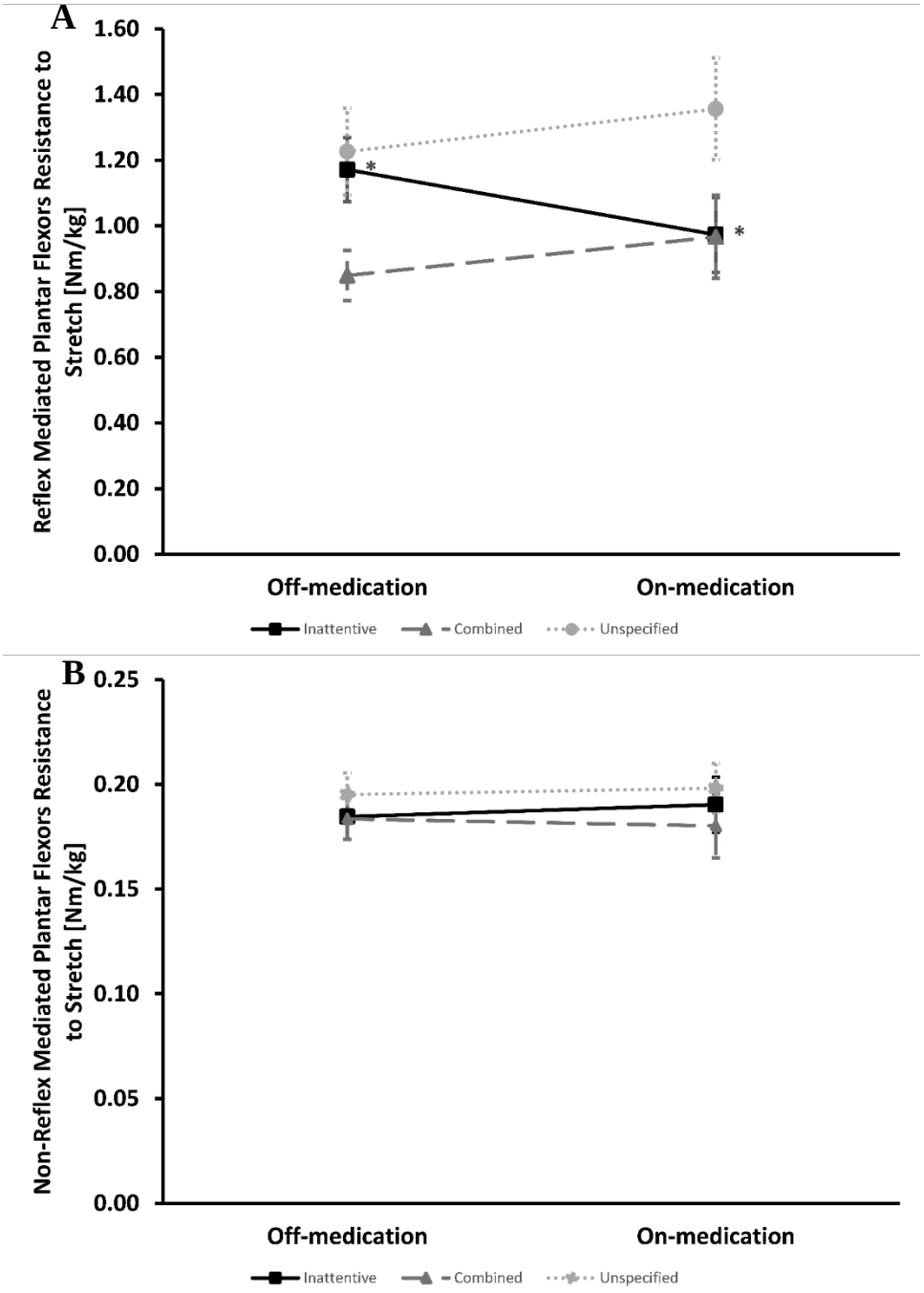


Figure 7**.** Effect of psychostimulant on plantar flexor resistance to stretch during a) reflex mediated trial, and b) non-reflex mediated trials.

DISCUSSION

The current study provided evidence that individuals with ADHD displayed increased PF spasticity level when evaluated with MAS. However, MAS scores did not change significantly when off and on medication. Additionally, this study observed no significant PS effects on PFRS in adults with ADHD as an entire sample, but PS use was associated with decreased PFRS among the adults with the predominantly inattentive subtype of ADHD. This association was significant with the reflex mediated trials of PFRS, but not with the non-reflex mediated PFRS trials. These findings indicate that using PS may help adults with Inattentive ADHD in ameliorating the increased reflex mediated spasticity.

The findings of the current study were consistent with previous research that reported a slight increase in PF spasticity in children[13] and adults[12] with the predominantly inattentive subtype of ADHD. We further found a slight increased PF spasticity in adults with the combined subtype of ADHD. The mechanism behind this heightened PF spasticity is not fully understood. In the current study, PS was associated with decreased PFRS only in adults with predominantly inattentive ADHD. This finding is consistent with a previous study that reported PS reduced heightened PF spasticity in children with predominantly inattentive ADHD.[11] That study assessed PF spasticity at baseline and 90 minutes following PS administration, yet PS effects on increasing dopamine are short-term and may decline several hours after PS consumption.[22] By comparison, participants in our study took PS medication as prescribed by a doctor, and we manipulated the effect of PS by measuring spasticity during off and on medication status. Across both studies, PS was associated with reduced PF spasticity in

predominantly inattentive ADHD. This suggests that dopaminergic upregulation by PS might contribute to reducing spasticity regardless of the PS type and drug administration time in adults with predominantly inattentive ADHD. More studies need to examine why using PS was associated with reduced spasticity only in inattentive ADHD but not the other subtypes.

MAS scores indicated increased PF spasticity in this study. These findings is consistent with other research that reported increased PF spasticity in children[11] and adults with ADHD.[12] However, unlike one of those previous studies,[11] MAS scores in this study did not show a change in PF spasticity when participants took PS medication. Such findings may not be surprising since the test and rater scale definitions of MFNU are comparable with the MAS. Perhaps having fewer categories to select (0= normal tone, 1= moderate problems, and 2= severe problems) when using the MFNU subscale makes the MFNU easier for clinicians to detect changes in PF spasticity. The multiple categories found in the MAS may overlap, causing difficulties for raters to detect small changes in PF spasticity. More studies are needed to determine if PF spasticity subscale of MFNU and MAS tests are sensitive to small changes in PF spasticity.

The study assessed the reflex mediated and non-reflex components of PFRS using a dynamometer coupled with sEMG confirmation. This protocol was guided by a previously used protocol.[8] However, the previously published method could not consistently produce stretch reflexes across all participants even when using Jendrassik maneuver.[8] To overcome this inconsistency of producing a stretch reflex, this study used a ~ 30% of MVIC pre-stretch isometric contraction since a previous study showed that a

pre-stretch isometric contraction of > 25% of MVIC facilitated consistent reflex occurrence.[20] In addition, this level of pre-stretch isometric contraction reduced variability in stretch reflex responses.[23] Like the previous study,[23] this study also found that using a pre-stretch isometric contraction of > 25% yielded consistent stretch reflex responses across all participants.

This study has several clinical implications. First, this study documented that individuals with ADHD had elevated PF spasticity. This result, coupled with previous findings,[12,13] implies that clinicians should be checking all individuals with ADHD for spasticity. This low-level increased spasticity may fully or partially explain the spasticity-related pain and discomfort[12] that an adult with ADHD may be experiencing. Increased tone may be related with difficulties in gait[24] or possibly balance.[25] Previous studies have reported that adults with ADHD have a greater number of falls and injuries,[26] which may be related to the increased spasticity observed in this study and others.[12,13] Thus, healthcare providers should be checking for PS compliance in adults, especially those with predominately inattentive ADHD, since these medications seem to help reduce spasticity and possibly help prevent tone-related pain. Furthermore, incorporating rehabilitation interventions that reduce spasticity, such as dynamic stretching,[27] electrical stimulation coupled with moderate aerobic exercise[28] warrants additional research in this population.

Limitations

This study has several limitations. First, the study design did not allow to examine causal effects of PS on PFRS. More robust study designs, such as randomized controlled

trials (RCTs) may confirm or negate the findings of this study. Second, the age range of this sample of adults with ADHD was 20 to 55 years restricts generalizing these findings to children, adolescents, and older adults. Finally, this study did not examine if increased PF spasticity found in adults with ADHD could significantly interfere with activities of daily living or physical injuries. Further research is needed to examine the relationship between PFRS and the before-mentioned correlates in adults with ADHD.

CONCLUSION

Adults with ADHD were found to have slightly increased levels of PF spasticity upon clinical examination. Furthermore, using PS was associated with decreased PFRS, indicating a decreased spasticity compared to being off-PS, specifically among adults with predominantly inattentive ADHD. These findings suggest that healthcare providers should screen for spasticity, check PS compliance (especially in adults with predominantly inattentive ADHD) and consider spasticity reduction strategies when treating adults with ADHD. Further studies are needed to examine PF spasticity and physical function in this population.

ACKNOWLEDGEMENT

The authors thank NYU and HARVARD for agreeing to use the proprietary scoring rules for the ASRS-5 in this study. The authors also thank the UAB Informatics for Integrating Biology and the Bedside (i2b2) for their assistance in the recruitment. Finally, the authors thank the Saudi Arabian Cultural Mission to the US (SACM) and Northern Border University in the Kingdom of Saudi Arabia for supporting the first author’s doctoral studies.

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MODERATE-TO-VIGOROUS PHYSICAL ACTIVITY AND RESPONSE INHIBITION PREDICT BALANCE IN ADULTS WITH ADHD

by

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Submitted to Medicine & Science in Sports & Exercise

Format adapted for dissertation

ABSTRACT

Purpose: To examine associations between moderate-to-vigorous physical activity (MVPA) and response inhibition (RI) with static balance performance in adults with Attention/Deficit-Hyperactivity Disorder (ADHD) during off and on psychostimulant medication (PS).

Methods: Participants visited the laboratory twice while off and on medication. During both sessions, participants underwent the Delis-Kaplan Executive Function System (D-KEFS) subtests: the Trail Making Test (TMT) and Color-Word Interference Test (CWID) to assess RI. Participants completed posturography assessment on a force platform in four conditions: feet-apart eyes open (FAEO), feet-apart eyes closed (FAEC), feet-together eyes open (FTEO), and feet-together eyes closed (FTEC). Postural sway area (cm^2) was calculated for each condition. Participants completed the single-leg standing test with eyes open (SLEO) and with eyes closed (SLEC). Finally, participants wore an ActiGraph GT9X-link on a belt around the waist to estimate MVPA levels. Data were analyzed using Pearson correlation and linear regressions.

Results: This sample included 40 adults with ADHD (30 females; mean age=29.0±6.3 years). During off-medication, there was a significant association between MVPA and SLEC (r=-0.38;p<0.05). Further, there were significant associations between MVPA level and FTEO (r=-0.37;p<0.05) and between TMT Number-Letter Switching and FTEO (r= -0.35; p< 0.05). MVPA significantly predicted SLEC (β=0.30;p=0.017). MVPA and TMT Number-Letter Switching significantly predicted FTEO (F(1,38)=5.550;adjusted R^2=0.189;p=0.008), explaining ~19% of the variance in FTEO. Both MVPA and TMT Number-Letter Switching were significant predictors (β=-

0.33,p=0.027 and β=-0.31,p=0.039, respectively). During on-medication, there was significant association between TMT Number-Letter Switching and FAEC (r=0.32;p<0.05). TMT Number-Letter Switching score significantly predicted FAEC (β=0.17; p=0.047).

Conclusion: MVPA and RI significantly predicted static balance in adults with ADHD during off-medication, but not during on-medication.

INRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder with three subtypes: predominately Inattentive, predominately Hyperactive-Impulsive, and Combined.[1] Approximately 1.0%[2] to 4.4%[3] of the US adults aged 18-54 years have a diagnosis of ADHD with males diagnosed two times more frequently than females.[3] Adults with ADHD have increased rates of falls and physical injuries across their life-spans,[4] and this may be associated with balance impairments in children[5] and adults[6] with ADHD.

Psychostimulant medication (PS), including Methylphenidate (MPH)- and Amphetamine (AMP)-based stimulant, are commonly used to treat ADHD symptoms.[7] PS improves balance in children[5] and adults (manuscript under review) with ADHD. PS may improve executive function and symptoms by upregulating dopamine concentrations in the prefrontal cortex and basal ganglia[8,9] and thereby improve balance performance. PS may further improve balance by upregulating dopamine concentrations in motor regions of the brain, such as the nigrostriatal pathway, an area involved with motor regulation in the brain.[8] Physicians commonly recommend that adults with ADHD to take medication holidays, specifically during weekends and vacations.[10] In fact, it is common that adults with ADHD ask their physicians for medication holidays.[10] Thus, this population can be at a greater risk of balance-related injuries during these unmedicated periods.[6]

Moderate-to-vigorous physical activity (MVPA) and response inhibition are two other variables that may be associated with improving balance in adults with ADHD. MVPA significantly predicted postural sway performance in young adults without ADHD.[11] Several types of MVPA are used for improving balance and prevent falls in older adults,[12,13] however, the relationship between MVPA and balance in adults with

ADHD is unknown. MVPA-based interventions could be potential candidates for improving balance in adults with ADHD, since MVPA was associated with greater gray matter volume of prefrontal cortex and striatum areas in young adults without ADHD.[14] Determining if MVPA could improve balance, would be beneficial to help decrease balance-related injuries that occur with greater frequency in this population whether off or on medication.

Improved response inhibition may also be important for improving balance. Response inhibition, a part of executive function, is important for ignoring unnecessary sensory input, overcoming primary reflexes, and avoiding distractors.[15] Similar to MVPA, better response inhibition function was associated with gray matter network in the prefrontal cortex in adults without ADHD,[16] and may be associated with balance in healthy adults without ADHD.[17] Adults with ADHD displayed impairments in response inhibition tasks measured by neuropsychological assessments,[18] which may be related to their balance impairments.[6] Therefore, establishing associations between response inhibition and balance could inform future intervention for improving balance in adults with ADHD.

To date, researchers have not examined associations between MVPA levels, response inhibition, and balance performance in adults with ADHD, yet determining those associations could help identify factors to inform interventions for improving balance function in this population. Improving balance in this population may decrease injuries commonly incurred in individuals with ADHD.[4] Therefore, this study investigated if MVPA levels and response inhibition were associated with static balance performance in adults with ADHD when off and on PS. We hypothesized that MVPA

levels and response inhibition performance would significantly predict balance performance in adults with ADHD when off or on PS.

METHODS

Participants

Prior to participating in the study, participants provided written informed consent, approved by the Institutional Review Board (Protocol number: IRB-300006200) at the University of Alabama at Birmingham (UAB). Participants were recruited by posting fliers around a university campus, advertising in the UAB eReporter (https://www.uab.edu/reporter/) and sending email invites to potential participants using the UAB Informatics for Integrating Biology and the Bedside (i2b2) data. To enroll in this study, participants met the following inclusion criteria: a) aged 20-55 years, b) diagnosed with ADHD validated by a physician or psychologist, c) used MPH- or AMP-based PS to control ADHD symptoms for a minimum of three months,[19] d) reported being in good physical health, e) spoke and read English proficiently, and f) ambulated freely in the community.

Procedures

Data collection for this cross-sectional study occurred in the UAB Human Performance Laboratory between May 2021 and February 2022. Participants visited the laboratory twice with a range of seven days to four weeks scheduled between the two sessions. Participants were randomly assigned (https://www.random.org/) to come to the first session off or on PS. For the off medication session, investigators directed the participants to skip PS medication 24 hours before data collection to ensure no systematic

PS effects on the central nervous system.[20,21] Prior to participating on the day assigned to take PS medication, investigators instructed participants to use PS medication as prescribed by a treating physician. All participants reported being on the assigned medication status by answering a self-reported question during both sessions. In both sessions, participants completed: a) questionnaire [demographics, psychostimulant medication-use information, other medication use, and ADHD symptoms, b) two Delis-Kaplan Executive Function System (D-KEFS) subtests (i.e., trail making test [TMT] and color-word interference test [CWIT]), c) weight and height measurements, and d) balance tests. Participants completed these tasks in the order listed in both visits. Slight differences in testing occurred during the second session when compared to the first session. The differences included not answering demographic and medication-related questions as well as not measuring height and weight in the second visit. In addition, participants were given an accelerometer, along with instructions, to measure physical activity for seven days at the completion of the first session to wear between the first and second sessions. The non-dominant leg was used for balance tests and the side to place the accelerometer. The non-dominant leg was decided by asking participants, “Which leg do you kick a ball with?” (Figure 8).

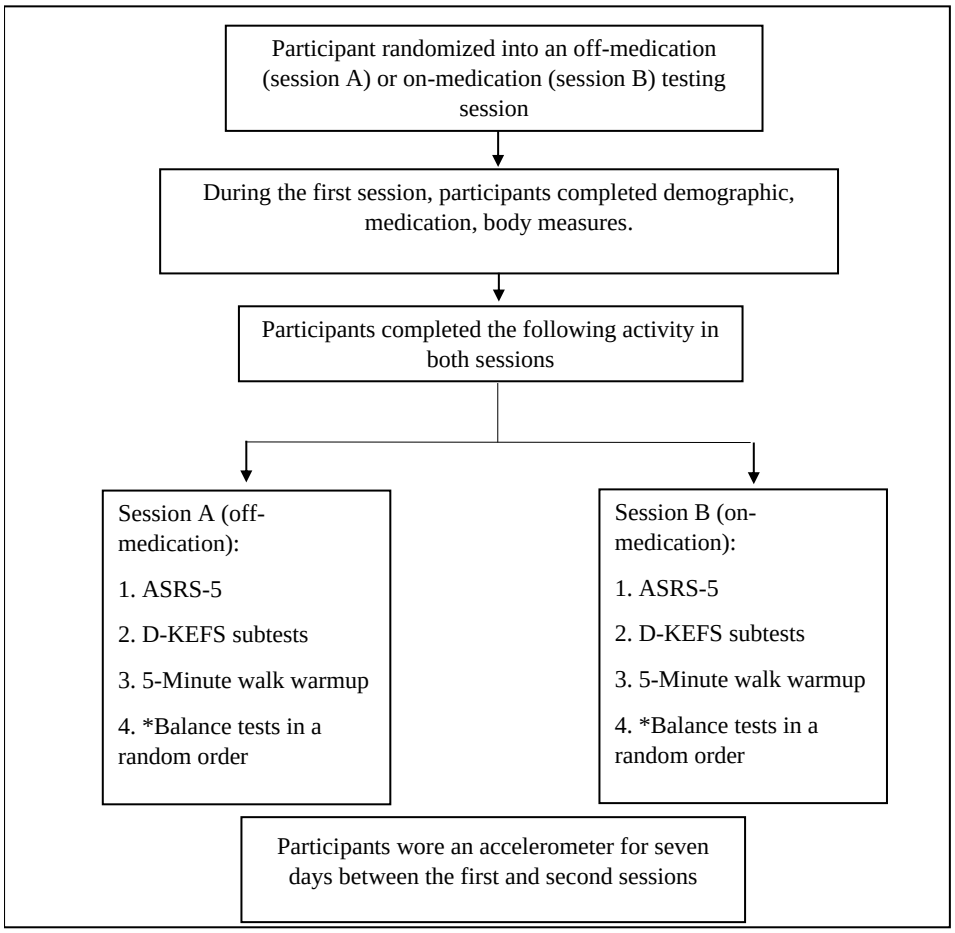

Figure 8. Summarized study procedures.

Outcome Measures

Demographic and Anthropometrics

Age, sex, race, ADHD medication, and educational level were collected via a customized questionnaire. ADHD subtype was confirmed by a physician or psychologist report. Investigators collected weight (kg) and height (cm) by using respectively a scale (Garmin Ltd, Southampton, United Kingdom) and a stadiometer (Charder HM200P Stadiometer, Taichung City, Taiwan). BMI was calculated by dividing weight by body height squared (kg/m^2).

ADHD Symptoms

Investigators used the updated version of the World Health Organization Adult ADHD Self-Report Screening Scale for DSM-5 (ASRS-5) to measure participants' ADHD symptoms and to determine PS effects on ADHD symptoms. The ASRS-5 is a 6-item questionnaire adopted from Composite International Diagnostic Interview for DSM-5 (CIDI-5.0) for adults aged 18 years or older.[22] The ASRS-5 has excellent sensitivity (91.4%), specificity (96.0%) and area under the curve (AUC= 0.94) in detecting ADHD symptoms.[22] Participants completed this questionnaire when off and on their medication. Investigators scored this questionnaire using the proprietary scoring rules for the DSM-5 version with permission from New York University (NYU) and Harvard University (HARVARD).

Delis-Kaplan Executive Function System

The D-KEFS employs nine subtests that comprehensively measure high-level cognitive function and frontal lobe integrity.[23] Two subtests were employed for the purpose of this study to assess response inhibition. To test response inhibition using these two subtests, participants completed a series of preceding tests (e.g., number sequencing, and naming color) to ensure meeting sufficient lower cognitive skill levels. The selected two subtests of the D-KEFS were: 1) *Trail Making Test (TMT)* for testing attention, cognitive flexibility and response inhibition, and 2*) Color-Word Interference Test (CWIT)* for testing response inhibition and cognitive flexibility.

TMT comprises five conditions and is designed to measure temporal sequencing and mental flexibility. Condition 1 (visual scanning) teases out fundamental processes,

such as visual scanning. Conditions 2 (Number Sequencing) and condition 3 (Letter Sequencing) measure number and letter sequencing while ignoring distractive stimuli. Condition 4 (Number-Letter Switching) is a set-shifting task that examines higher-level cognitive skills and requires alternating connecting numbers and letters in sequence. TMT Number-Letter Switching is the variable of interest for balance, and it tests response inhibition and cognitive flexibility. Condition 5 (Motor Speed) tests motor speed where participants draw over a dotted line from a start point to an endpoint as fast as possible.[24] The executive domains assessed in this subtest are cognitive flexibility and response inhibition.

The CWIT is based upon the original Stroop-Color Word Test and consists of four conditions: Conditions 1 (Naming Color) and Condition 2 (Reading color) serve as lower-level screening of color naming and word reading. Condition 3 (Inhibition) creates a further challenge by printing color names with different color ink and requires participants to name the ink color. Condition 4 (Inhibition/Switching) builds upon the previous condition and introduces a switch task, where some of the words are outlined within a box where participants names the ink color but read the word if it is outlined in a box.[24] Additionally, CWIT Inhibition and Inhibition/Switching conditions are theorized to assess sustained attention indirectly.[24] The executive function domains assessed in this subtest are cognitive flexibility and response inhibition. Participants completed these two D-KEFS subtests in both sessions (off- and on-medication) because improvements in executive function delivered by psychostimulant medications may account for improving motor performance.[25,26]

TMT Number-Letter Switching, and CWIT Inhibition, and CWIT Inhibition/Switching were the variables of interest for response inhibition in this study. The D-KEFS scaled scores for each individual subtest were the primary outcomes for all the D-KEFS tasks and determined by following the technical manual guidlines[23] and using PsychCropCenter software 2.0.1 (Harcourt Assessment, Inc, San Antonio, TX, USA). These tests showed good psychometric properties in adults with ADHD.[27] Higher D-KEFS scores represent better response inhibition performance.

Postural Sway Measurements and Single Leg Standing Tests

Participants performed a 5-minute walk on a treadmill before undergoing balance testing. The Borg Scale for Perceived Exertion[28] cued participants to maintain light exertion during their warm-up. Investigators instructed and monitored the participants to keep a score between 6 and 11, which indicates light exertion.[28] Participants performed all static balance tests on a force platform (1000 Hz, AMTI, Watertown, MA, USA). Participants underwent four different tests to measure sway area. Each test lasted 30-seconds and included: standing with feet shoulder-width apart with 1) eyes open (FAEO) and 2) eyes closed (FAEC); and standing with feet-together with 3) eyes open (FTEO) and 4) eyes closed (FTEC). Participants practiced all balance tests prior to data collection. These test conditions significantly discriminated adults with ADHD from a healthy comparison group concerning balance performance.[6] These tests are also reliable and valid in measuring static balance in healthy adults without ADHD.[29] Anthropometric measures were not associated with postural sway area in this study. Therefore, postural sway area scores were not adjusted for these measures. Software written in MATLAB (MathWorks Inc., Natick, MA, USA) was used to process postural sway data. The Center

of Pressure (COP) trajectory was analyzed for 20-seconds, eliminating the first and last 5-seconds of each trial for additional accuracy.[30] A 12Hz low-pass Butterworth (4^{th} order) was applied during data extraction. The calculated variables were sway area (cm^2) for each test condition. Postural sway calculations were performed using postural sway equations provided by Doyle et al.[31]

Participants also completed two other balance tasks: 1) single leg test on a firm surface with eyes open for 30-seconds (SLEO), and 2) single leg test on a firm surface with eyes closed for 30-seconds (SLEC) for 30-seconds (SLFEO). Participants placed their hands on their waists during each test. An experienced physical therapist (DL) provided instructions and guarded participants during the tests. If a participant touched the floor with the non-weightbearing foot, the examiner recorded the time (i.e., touch time [s]) and asked the participant to open their eyes and get back in the position and then close them again. Participants resumed their position and completed the 30-second trial. Participants were familiarized with all balance conditions before data collection. The single leg tests showed an excellent test-retest reliability in healthy adults.[32] Postural sway and balance tests were randomized prior to each session.

Physical Activity-Accelerometry Measure

Between the two testing sessions, participants received instructions and demonstration on how to wear a small (3.5 × 3.5 x 1 cm) and lightweight (14g) accelerometer device (ActiGraph GT9X link, ActiGraph, LLC. Pensacola, FL, USA) secured with a waistband belt clip near the anterior superior iliac spine (ASIS) of the non-dominant side.[33] Participants wore the device for seven days, starting the day after the first testing session, during the waking hours of the day. The GT9X link accelerometer

measures movement by generating an electrical signal proportional to the force acting on it along three orthogonal axes (tri-axial) and provides more accurate estimates of movement if worn near the ASIS.[34] Raw data were post-processed using ActiLife 6 software (ActiLife, ActiGraph, LLC. Pensacola, FL, USA). Data were expressed as counts per epoch (epoch length was 60-seconds, sample frequency was 30Hz) to quantify physical activity data of at least one valid day (i.e., ≥ 10 hours of wear time) for more accurate physical activity estimates.[35,36] The Troiano's cut-off points in counts per minute (CPM) classified physical activity levels as follows: 0-99 CPM range indicates sedentary behavior, 100-2019 CPM range indicates light physical activity (LPA) and ≥ 2020 range indicates MVPA.[36] The derived physical activity outcome was MVPA average minutes/day and average steps/day.[11] MVPA measures showed a very good test-retest reliability (Intraclass correlation; ICC= 0.83) in healthy adults using GT9X device.[37]

Data Processing and Statistical Analyses

The Statistical Package for the Social Sciences software v27.0 (SPSS; IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Means and standard deviation (SD) were used to summarize age, and body measures. Frequencies were used to summarize sex, race, education level, ADHD subtype, and ADHD medication type.

The following variables of interest were chosen for correlation and multiple linear regression statistical analyses: MVPA (minutes/day), TMT (Number-Letter Switching), CWIT (Inhibition, and Inhibition/Switching), postural sway area (FAEO, FAEC, FTEO, and FTEC), and SLEC when off and on medication. The specific D-KEFS scores represent response inhibition function. While all participants successfully completed the targeted response inhibition tests (i.e., TMT Number-Letter Switching, CWIT Inhibition,

and CWIT Inhibition/Switching) and their preceding tasks, we would have excluded a participant's response inhibition score if he/she could not complete the preceding tasks for response inhibition tests (e.g., naming color and letter sequencing). Single leg standing balance scores for SLEO tasks was not challenging for participants and therefore excluded from the analysis. Only four and five participants of the total sample (n=40) could not complete 30-seconds without touching the floor with the other non-weightbearing during off- and on-medication, respectively.

Skewness and box plots statistics showed no violation of the normality assumption of each variable entered in the analyses. Pearson correlations were used to examine the associations between the variables of interest: MVPA, TMT, CWIT, postural sway areas, and SLEC. Correlation coefficients were interpreted as weak correlation (0.1-0.3), moderate correlation (0.3-0.5), and strong correlation (>0.5).[38] Additionally, only those variables with significant correlations in the bivariate analyses were entered into univariate and multivariate linear regression models to identify balance predictors. Significant associations existed between MVPA and SLEC touch time, MVPA and FTEO, and TMT Number-Letter Switching during off-medication (all $p< 0.05$). There was also significant association between TMT Number-Letter Switching and FAEC during on-medication TMT Number-Letter Switching. These associations yielded three regression models: Model 1 (off-medication): predictor was MVPA level, and the dependent variable was SLEC. Model 2 (off-medication): predictors were MVPA level and TMT Number-Letter Switching. The Model 2 dependent variable was postural sway area during FTEO. Model 3 (on-medication): predictor was TMT Number-Letter Switching, and the dependent variable was postural sway area during FAEC. Multi-

collinearity was tested for the multivariate linear regression model using variance inflation factor (VIF) index. Values greater than 5 indicated multi-collinearity.[39] An alpha level of 0.05 was the criterion for statistical significance for all statistical tests and model-building.

RESULTS

Participants Characteristics

A total of 40 adults with ADHD met the inclusion criteria and completed both sessions [30 females (75.0%); mean age =29.0 ± 6.4 years]. Most participants were diagnosed with Inattentive subtype (n=13; 32.5%) or Combined subtype (n=11; 27.5%) ADHD, used AMP-based stimulants (n=35; 87.5%), were Caucasian (n=30; 75.0%), involved in graduate studies or received a graduate degree (n= 22; 55.0%). On average, participants were slightly overweight (mean BMI = 28.0 ± 7.7) (Table 5).

Associations Among the outcomes

Off-medication Status

The correlation analyses identified a significant positive moderate to strong association between MVPA and SLEC (r=0.38; p< 0.05). Engaging in MVPA was associated with a longer time until touching the floor with the non-weightbearing leg, indicating better static balance performance. Furthermore, there was a negative significant moderate-to-strong association between MVPA level and FTEO sway area (r=-0.37; p< 0.05) and between TMT Number-Letter Switching and FTEO (r=-0.35; p< 0.05), indicating that engaging in MVPA and better response inhibition scores were associated with lower sway area (better static balance). There were no significant

associations between the other D-KEFS variables or MVPA with static balance scores (all p >0.05) (Table 6; Figure 9).

Table 5. Demographic and clinical outcomes of participants.

Characteristic	**All participants n= 40**	
	Mean	**SD**
Age (y)	29.0	6.3
Sex n (%)		
Male	10	25.0
Female	30	75.0
Race n (%)		
Caucasian	30	75.0
Black or African American	5	12.5
Asian	2	5.0
Mixed of Two Races	3	7.5
Body Weight (kg)	81.8	22.4
Body Height (cm)	170.5	9.4
Body Mass Index (kg/m^2)	28.0	7.7
Dominant leg n (%)		
Left	5	12.5
Right	35	87.5
Education Level n (%)		
Did Some College	5	12.5
Undergraduate	13	32.5
Graduate Level	22	55.0
Psychostimulant Medication n (%)		
MPH based	5	12.5
AMP based	35	87.5
Adult Self-Report ADHD Scale-5		
Off-medication	18.6	2.4
On-medication	13.6	4.0

MVPA score significantly predicted SLEC (β=0.30; p= 0.017). Further, the multivariate analysis showed that MVPA level and TMT Number-Letter Switching significantly predicted FTEO sway area (F(1,38)= 5.550; adjusted R^2= 0.189; p= 0.008), explaining about 19% of the variance in FTEO sway area. Both MVPA level and TMT Number-Letter Switching were significant predictors (β=-0.33,p=0.027 and β=-0.31,p=0.039, respectively) (Table 7).

Table 6. Pearson Correlation Coefficients Among the Variables of Interest.

Variable	n	M	SD	1	2	3	4	5	6	7	8	9
Off-Medication												
1. SLEC (touch time in seconds)	40	11.3	10.2	—								
2. FAEO (sway area in cm^2)	40	1.5	2.2	-0.18	—							
3. FAEC (sway area in cm^2)	40	1.7	1.7	-0.11	0.16	—						
4. FTEO (sway area in cm^2)	40	6.4	5.5	-0.04	-0.02	**0.40***	—					
5. FTEC (sway area in cm^2)	40	9.2	5.8	-0.21	0.06	**0.46****	**0.52****	—				
6. MVPA (minutes/day)	40	13.2	12.8	**0.38***	0.01	-0.16	**-0.37***	-0.01	—			
7. TMT Number-Letter Switching	40	11.5	1.8	0.01	-0.21	-0.05	**-0.35***	-0.16	0.11	—		
8. CWIT Inhibition	40	11.3	2.7	0.19	-0.15	0.04	-0.28	-0.11	**0.33***	**0.44****	—	
9. CWIT Inhibition/Switching	40	10.5	2.8	0.03	-0.27	0.03	-0.28	-0.04	0.19	**0.34***	**0.72****	—

On-Medication												
1. SLEC (touch time in seconds)	40	13.7	10.8	—								
2. FAEO (sway area in cm^2)	40	1.4	1.4	0.08	—							
3. FAEC (sway area in cm^2)	40	1.3	0.8	**-0.34***	**0.45****	—						
4. FTEO (sway area in cm^2)	40	4.6	2.0	-0.17	**0.38***	**0.45****	—					
5. FTEC (sway area in cm^2)	40	7.6	4.8	**-0.34***	0.22	**0.43****	0.25	—				
6. MVPA (minutes/day)	40	13.2	12.8	0.27	-0.18	-0.22	-0.28	-0.08	—			
7. TMT Number-Letter Switching	40	11.4	1.5	-0.17	-0.11	**0.32***	0.14	0.13	0.04	—		
8. CWIT Inhibition	40	11.6	2.0	-0.07	0.16	0.22	0.12	-0.11	0.04	0.25	—	
9. CWIT Inhibition/Switching	40	10.4	2.7	-0.06	0.13	0.23	0.15	-0.14	0.08	0.19	**0.72****	—

Note: SLEC: single leg on firm surface with eyes closed; FAEO: Feet-apart standing balance test with eyes open; FAEC: Feet-apart standing balance test with eyes closed; FTEO: Feet-together standing balance test with eyes open; FTEC: Feet-together standing balance test with eyes closed; MVPA: moderate-to-vigorous physical activity. TMT: Trial Making Test; CWIT: Color-word interference test.

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

Table 7. Predictors of Balance from Multivariate Linear Regression Analyses during off-medication status.

Effect	Estimate	SE	Standardized Beta	95% CI		*p*
				LL	UL	
A. Outcome SLEC touch time [$F(1,38) = 6.218$, adjusted $R^2 = 0.118$, $p = 0.017$]						
Intercept	7.312	2.191		2.877	11.747	0.002
MVPA	**0.300**	**0.120**	**0.375**	**0.056**	**0.543**	**0.017**
B. Outcome FTEO sway area [$F(1,38) = 5.550$, adjusted $R^2 = 0.189$, $p = 0.008$]						
Intercept	19.005	5.059		8.754	29.255	<0.001
MVPA	**-0.143**	**0.062**	**-0.334**	**-0.269**	**-0.017**	**0.027**
TMT Number-letter Switching	**-0.941**	**0.438**	**-0.311**	**-1.829**	**-0.052**	**0.039**

Note: SLE: Single leg standing balance test with eyes closed; FTEO: Feet-together standing balance test with eyes open: MVPA: Moderate-to-vigorous physical activity; TMT: Trial Making Test

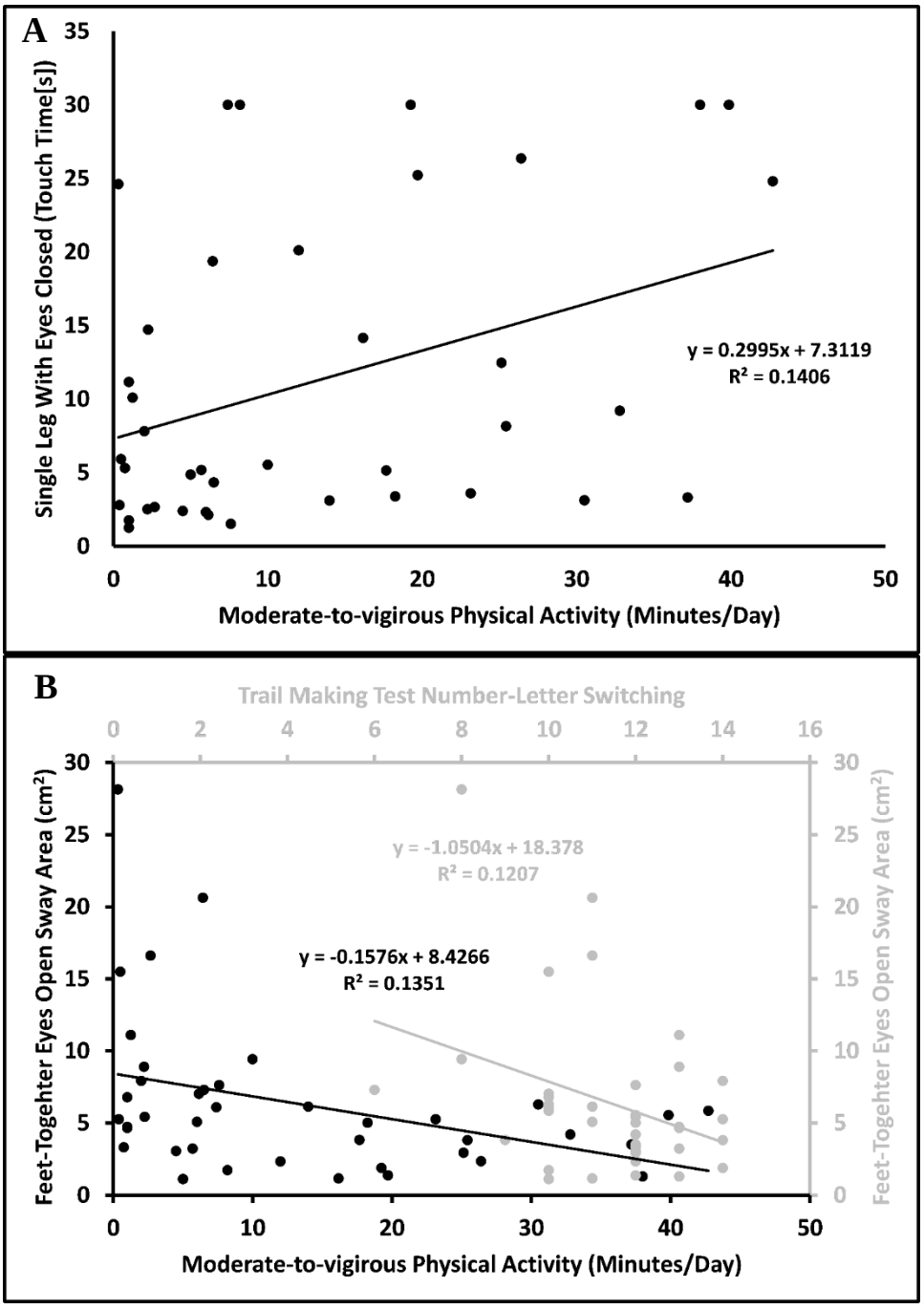

Figure 9. A) Moderate-to-vigorous physical activity plotted against single leg standing balance test on firm surface with eyes closed touch time, and B) Moderate-to-vigorous physical activity and trail making test number-letter switching score plotted against feet-together with eyes open balance test during off-medication status.

On-medication Status

A significant moderate positive association was found between TMT Number-Letter Switching and FAEC sway area (r= 0.32; p< 0.05) (Table 6). No other significant associations existed between MVPA and D-KEFS variables with static balance scores (all p >0.05). TMT Number-Letter Switching significantly predicted FAEC sway area (β=0.17; p= 0.047) (Table 8; Figure 10).

Table 8**.** Predictors of Balance from Univariate Linear Regression Analyses during on-medication status.

Effect	Estimate	SE	Standardized Beta	95% CI		*p*
				LL	UL	
A. Outcome FAEC sway area [$F(1,38) = 4.213$, adjusted $R^2 = 0.076$, $p = 0.047$]						
Intercept	-0.657	0.938		-2.557	1.243	<0.001
TMT Number-letter Switching	**0.168**	**0.082**	**0.316**	**0.002**	**0.333**	**0.047**

Note: FAEC: Feet-apart standing balance test with eyes closed; TMT: Trial Making Test.

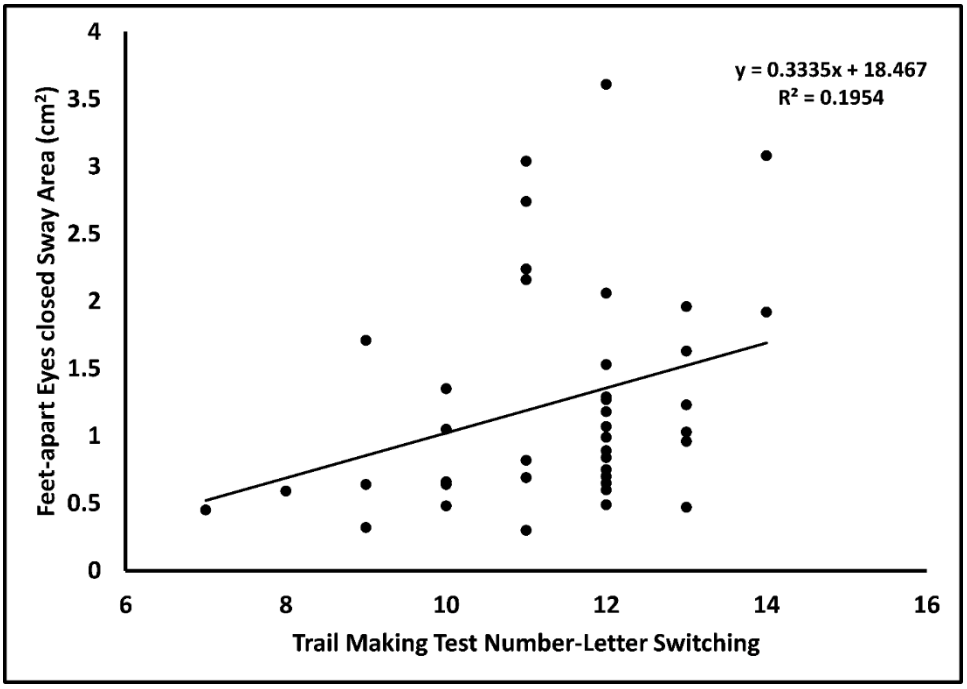

Figure 10**.** Trail Making Test Number-Letter Switching plotted against feet-apart standing balance test with eyes open.

DISCUSSION

We conducted the first study that examined associations between MVPA and response inhibition with static balance, and our findings indicated that engaging in MVPA and better response inhibition scores significantly predicted better static balance performances in individuals with ADHD during the off-medication status. Greater MVPA levels and better response inhibition scores both predicted decreased sway area during FTEO, whereas higher MVPA level was the only predictor of improved SLEC performance when participants were off medication. However, during on-medication status, there were no significant associations between MVPA levels and static balance scores. Surprisingly, during on-medication status, better response inhibition scores weakly but significantly indicated worse static balance performance. Overall, the findings of this study partially supported our hypothesis, which was that MVPA levels and

response inhibition would significantly predict static balance performance during off medication status.

Like healthy young adults,[11] MVPA was associated with better static balance in adults with ADHD in this study. Engaging in MVPA improves activations of the prefrontal cortex and somatosensory cortex,[40] which might improve balance.[41] MVPA might also increase the circulating dopamine concentrations in children with ADHD.[42] Researchers discuss that static balance improvements could be attributed to improving the dopaminergic effect in children with ADHD.[5] Our results suggest that adults with ADHD could benefit from programs that include MVPA in addition to their PS medication to improve their static balance, especially on their medication holidays, since this practice is common among adults with ADHD.[10]

The study's findings demonstrated that increased MVPA levels only predicted participants' static balance performance during off medication, but not when on medication. During on-medication status, the associations between MVPA levels with FTEO and SLEC scores were moderate and were approaching significance [r=-0.3, p=0.090; and r=0.3, p=0.082; respectively]. Significant associations may not have been reached since only seven adults met physical activity levels suggested by the Physical Activity Guidelines for Americans (PAG) in this study (i.e., ≥ 150 minutes/week).[43] Perhaps having fewer adults who engage in MVPA in this sample could have dampened the magnitude of the association between MVPA and static balance performance when they were on their PS. While limited evidence exists, a previous study also showed that adolescents with ADHD and not on PS had low MVPA levels (mean= 4.2 ± 2.3 minutes/day of MVPA), measured by an accelerometer.[44] In this study, we found even

among those who use PS, MVPA level on average is less than PAG guideline for MVPA (mean= 13.2 ± 12.8 minutes/day of MVPA).[43] Therefore, further studies need to examine approaches to motivate individuals with ADHD to engage in greater levels of MVPA, despite their medication status.

Little research exists on the direct relationship between response inhibition and static balance, particularly in this population. Past work has found associations between response inhibition and clinical balance outcomes in people with Parkinson's.[45] The current study also showed that response inhibition predicted static balance in adults with ADHD. Therefore, response inhibition domain of executive function may be important for regulating posture across different populations. Future studies should determine if improving response inhibition could improve balance in different populations at risk of balance impairments (e.g., older adults).

Surprisingly, better response inhibition scores were associated with poorer FAEC scores during on-medication. FAEC condition of postural control test is considered less challenging compared to feet-together conditions and one-leg standing with eyes closed due to decreasing the base of support and having no vision. A previous study in children with ADHD found that even being on PS, children performed significantly better when the balance task became more challenging.[5] Therefore, participants may did not attend to the directions to remain still when performing this task since it lacks challenge. Previous studies had shown that using PS may improve static balance performance in children[5] and adults (manuscript under review) with ADHD, specifically when challenge increased with balance tasks.

Future research should examine whether improving MVPA and response inhibition function could improve balance in adults with ADHD. This study suggests that healthcare providers should assess physical activity levels and response inhibition when providing healthcare services to this population, especially when injuries are being reported by their patients. Implementing strategies to improve MVPA and response inhibition may help with balance impairments in this population, despite the lack of strong evidence. However, implementing these strategies is not harmful, even if incorporating these strategies did not improve balance since increasing MVPA was associated with other beneficial effects, such as reducing the risk of coronary artery disease[46] and weight loss.[47] In this sample, participants displayed an increased BMI corresponding to being overweight.

Limitations

This study has several limitations. First, analyses of this study were cross-sectional, which did allow concluding causal effects of these findings. Second, the age range in this study included only adults, limiting generalizing these findings to children, adolescents, and older adults with ADHD. Third, the findings determined that MVPA combined with PS may improve static balance during a short medication holiday, but longer effects are unknown. Finally, the study design does not allow us to determine if MVPA by itself provides protective effects on balance impairments in adults with ADHD not using PS.

CONCLUSION

MVPA and response inhibition domain of executive function significantly predicted static balance in adults with ADHD. However, these relationships were observed when off-medication status only. We would recommend that regular MVPA be recommended to individuals who take PS for ADHD to help improve static balance during medication holidays. These findings could inform researchers to target physical activity and cognitive behavioral therapy when designing interventions for balance impairments in this population. Finally, the low physical activity levels, compared to the recommended physical activity guidelines (i.e., ≥ 150 min/week),[141] in this population could be a critical issue that requires future research to analyze behavioral drivers of physical activity for increasing physical activity levels among individuals with ADHD.

ACKNOWLEDGEMENT

The authors thank NYU and HARVARD for granting permission to use the proprietary scoring criteria for the ASRS-5. The authors also thank the UAB Informatics for Integrating Biology and the Bedside (i2b2) for assisting in recruitment. Thanks to Dr. Christopher Hurt and Dr. Daniel Kuhman for writing the MATLAB software. Finally, the authors thank the Saudi Arabian Cultural Mission to the US (SACM) and Northern Border University in the Kingdom of Saudi Arabia for supporting the first author's doctoral studies.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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CONCLUSION

In this research project we found that using psychostimulant medications (PS) was associated with improved balance performance in adults with Attention-Deficit/Hyperactivity Disorder (ADHD). We also found that using PS was associated with reduced reflex-mediated portion of ankle plantarflexor resistance to stretch (PFRS), a measure of spasticity, in adults with predominantly Inattentive ADHD. However, using PS did not affect spasticity as measured by the Modified Ashworth Scale (MAS). We also found that when adults with ADHD where off their PS that response inhibition and moderate-to-vigorous physical activity (MVPA) predicted improved center of pressure measures of balance. MVPA also predicted improved balance measured by a clinical test (i.e., single-leg standing test with eyes closed). The findings of the three studies presented in this dissertation may inform future interventions for balance impairments in adults with ADHD. These findings were also consistent with previous research that found a) beneficial effects of PS on balance performance [50]and muscle tone[7] in children with ADHD, and b) relationship between MVPA[58] and response inhibition[59] with motor performance and balance. This chapter summarizes the results of the three studies in this dissertation, discuss clinical applications, and provides future direction for research and practice based on the findings of this research project.

Summary of Aims

The first aim of this dissertation was to examine PS effects on balance performance in adults with ADHD. We hypothesized that using PS would be associated with better balance performance compared to being off PS. While impairments in balance performance exist among adults with ADHD when being off PS,[6] we examined

differences in static balance performance (i.e., postural sway area and sway velocity) when off and on PS to examine this hypothesis. To minimize learning effect, which may yield false-positive findings, we randomized the order of being off vs. on PS for testing sessions 1 or 2. In Manuscript 1, we detailed that our hypothesis was supported and found that use of PS by individuals with ADHD was significantly associated with better balance performance (i.e., reduced sway area). Interestingly, a sub-analysis revealed that using methylphenidate (MPH), compared to amphetamine (AMP), was associated with significantly better improvements in balance performance. Furthermore, in Manuscript 1 we found that using PS was significantly associated with better Timed-Up-Go (TUG: a functional motor performance test) and trending toward significant positive relationship with the Lateral Step-Up Test (LSUT: a lower-extremity strength test) in adults with ADHD.

The second aim of this dissertation was to determine ankle plantarflexor (PF) spasticity levels and examine PS effects on reducing spasticity levels and ankle plantarflexor resistant to stretch (PFRS) in adults with ADHD. Our hypotheses were in line with previously found increased ankle PF spasticity levels in children[7] and adults[28] with ADHD and that using PS would be associated with lower spasticity levels.[7] We also randomized the order of being off or on medication during the first assessment session to minimize the possibility of finding false-positive results. Overall, our hypothesis was partially supported by the findings in Manuscript 2. We found a slight increased spasticity levels in this sample of adults with ADHD measured by the MAS. Further, there was no significant association between using PS and lower spasticity levels across the entire sample compared to being off PS when measured by MAS or a dynamometer.

However, a sub-analysis identified significantly lower ankle PFRS levels, specifically the reflex-mediated portion of PFRS. associated with using PS than off PS status in adults with Inattentive ADHD when measured by a dynamometer. While this is observation is consistent with previous findings in children with ADHD,[7] there a lack of understanding why these effects were only observed in this group of ADHD. Moreover, the findings of this aim suggested that using MAS might be less sensitive to minimal changes in muscle spasticity levels compared to dynamometer torque values.

The third aim of this dissertation was to examine associations between MVPA and response inhibition performance with balance function in adults with ADHD. We hypothesized that higher MVPA levels and better response inhibition performance would be associated with better balance performance during off and on PS in adults with ADHD. We examined this hypothesis using a clinical balance exam and derived center of pressure (COP) balance parameters. Furthermore, we used multivariate linear regression models to examine if MVPA and response inhibition significantly predicted balance performance. The findings of Manuscript 3 partially supported our hypothesis, where MVPA and response inhibition significantly predicted balance performance derived from COP measurement. Further, MVPA significantly predicted balance performance measured by a clinical test (i.e., single-leg standing test with eyes closed). However, these findings were only observed during off PS status, but not when participants used PS on the day of testing. Given these findings we concluded that engaging in MVPA and response inhibition tasks could only predict balance performance when on medication holidays. While medication holidays are common among individuals with ADHD,[60] it is

important to note that being engaged with higher levels of MVPA and EF training may be worth doing to improve balance, especially during PS holidays.

Clinical Implications and Future Directions

The findings of this dissertation provided further insight on PS effects on balance and motor performance in adults with ADHD. The project findings also provided an understanding into associations between MVPA and EF with balance function. Screening for balance, spasticity, and PS use in adults with ADHD would possibly help identify and treat motor/balance performance which in turn may potentially reduce the risk of fall-related injury found in this population.[5] Previous retrospective studies suggested that using PS was associated with lower odds of injury compared to not using PS in children[61] and adults[62] with ADHD. While the findings of the first two aims found factors associated with PS use, more research is required to prospectively determine the causal effects of PS in improving motor performance and balance to reduce the risk of injury. Further research building off our findings could increase better understanding on how to use our findings as targets for intervention to reduce the risk of injury in this population associated with healthcare issues (e.g., TBI).

Future research should focus on examining causal effects of PS on balance performance and risk of injury simultaneously to determine a) effects of PS on balance, and b) association between changes in balance and risk of injury while controlling for ADHD symptoms. Additionally, research could benefit from examining mechanisms of action of the slightly increased spasticity level found in adults with ADHD. While this issue is limitedly investigated and only specifically studied on Inattentive ADHD,[46,63]

further studies are needed to mechanistically identify differences in neural networks responsible for muscle tone regulation (e.g., Putamen) by ADHD diagnostic subtype.

Future studies may also examine different forms of MVPA in relation to balance performance. The findings of this dissertation suggested that MVPA levels could be targeted in rehabilitation programs for balance impairments. Exercise forms of MVPA should not only help with balance performance, but also reducing other common ADHD symptoms.[40]Aerobic exercise is one candidate for improving ADHD symtpoms[40] but no information exist on its benefits on balance in adults with ADHD. However, other exercise forms that cause moderate to various exertion level (e.g., high intensity resistance training) should also be explored for improving balance and ADHD symptoms in this population.

Executive function performance, specifically response inhibition, may also be a potential intervention target for balance impairments. Training EF in children with ADHD, including response inhibition can be attained using exergaming,[64] inhibitory control and working memory training games (e.g., freezing dance and memorizing shopping list),[65] and computer-based EF training.[66] These intervention demonstrated positive effects on ADHD symptoms. Further studies are needed to determine whether training EF with or without physical activity interventions could improve balance performance in adults with ADHD, since evidence showed that physical activity interventions could improve ADHD symptoms through enhancing executive function.[67] Finally, exploring EF training interventions concerning the risk of injury may help future studies that aims to reduce the risk of injury in this population.

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APPENDIX A

IRB APPROVAL

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

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701 20th Street South
Birmingham, AL 35294-0104
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APPROVAL LETTER

TO: Alotaibi, Mansour Mohmmed

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 20-Mar-2021

RE: IRB-300006200
IRB-300006200-005
Psychostimulant Medications Role in Postural Sway and Ankle Spinal Stretch Reflex in Adults with Attention Deficit Hyperactivity Disorder

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The IRB reviewed and approved the Revision/Amendment submitted on 15-Mar-2021 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Expedited
Expedited Categories:	4, 7
Determination:	Approved
Approval Date:	20-Mar-2021
Expiration Date:	19-Mar-2024

Although annual continuing review is not required for this project, the principal investigator is still responsible for (1) obtaining IRB approval for any modifications before implementing those changes except when necessary to eliminate apparent immediate hazards to the subject, and (2) submitting reportable problems to the IRB. Please see the IRB Guidebook for more information on these topics.

Documents Included in Review:

- IRB EPORTFOLIO