

# Attention-deficit/hyperactivity disorder medication does not alter exercise-induced hypoalgesia following an acute bout of dynamic circuit resistance exercise

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**ABSTRACT:** The primary goal of this study was to investigate the effects of attention-deficit/hyperactivity disorder (ADHD) medications on exercise-induced hypoalgesia (EIH), heart rate, and perceived exertion. Thirty college-age students (10 Controls, 10 ADHD diagnosis, and 10 ADHD diagnosis with medications) completed 2 sessions: 1) a maximal testing session and 2) an experimental session consisting of 3 consecutive dynamic resistance exercise circuits comprised of 12 repetitions of 9 exercises at 60% of 1-repetition maximum using a 1:1 work to rest ratio. All participants, regardless of condition (Controls vs. ADHD without medications vs. ADHD with medications), displayed EIH accompanied by an increase in blood lactate, heart rate, and perceived exertion for the duration of the exercise bout. Therefore, the effects of resistance exercise are not altered by ADHD diagnosis or psychostimulant medication use for ADHD. These findings are intriguing given the known ergogenic and hypoalgesic effects of caffeine, a less potent stimulant.

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## INTRODUCTION

Physicians consider stimulant medications the first line of therapy for young adults with attention-deficit/hyperactivity disorder (ADHD) [1, 2], making stimulants the most frequently prescribed medication for these individuals [3]. In healthy adolescents, ADHD medications increased focus, on-task behaviors, and the ability to learn more information in a short amount of time while reducing time to exhaustion and boosting performance [4]. However, there are mixed reviews about prescribed stimulants' effects on healthy individuals' performance during physical activity. It has been suggested that ADHD medications do not boost actual athletic performance, but rather the perception that athletic performance is enhanced [5]. However, other studies have reported enhanced performance by improved attention to the task, increased acceleration, and better balance when discussing the effects of these medications on sports [6]. Despite these findings, research on the effects of prescribed ADHD medications on exercise performance has been limited. Therefore, a better understanding of the interactions of ADHD medication and exercise would help clarify the advantages and disadvantages of ADHD medications on exercise performance in ADHD individuals.

Research also shows that exercise influences pain perception by decreasing pain sensitivity, which is known as exercise-induced hy-

poalgesia (EIH) [7,8]. This decrease in pain sensitivity occurs during and after higher intensities and longer periods of exercise that are typically considered painful [9,10]. This effect of exercise has important implications from a therapeutic standpoint given the abundance of side effects involved with pharmacological interventions for pain. Moreover, understanding effects of different exercise prescriptions on pain in different patient populations and factors that influence EIH is of utmost importance in adherence to exercise program progression. Therefore, research has focused on discovering ways to increase the effect size and duration of EIH. Caffeine, a less potent stimulant than typical ADHD medications, has been shown to attenuate the feeling of pain produced by exercise [11,12], stimulate the CNS by altering motor unit recruitment, and reduce feelings of fatigue through adenosine receptor antagonism [13]. While the effects of caffeine on EIH have been a topic of recent research, the findings have been controversial due to inconsistencies among studies regarding the time of pain measurement. For example, some investigators have reported pain relief during exercise [14,15] and others have found little to no effect on pain perception after exercise [16,17]. Although caffeine has shown little to no effect on EIH following exercise, other stimulants, such as ADHD medication which

is a stronger stimulant than caffeine, are widely overlooked in EIH research.

Additionally, other stimulants such as amphetamines [18,19] and nicotine [20,21] have been shown to reduce pain perception in healthy individuals. However, the effects of these stimulants on pain during or after exercise have not been examined. Although it is known that exercise will induce hypoalgesia, it is unknown whether there is an enhanced or cumulative effect of stimulants and exercise on this pain phenomenon. Recent evidence suggests that methylphenidate, an ADHD medication, reduces the response to cold pain indicative of a hypoalgesic response [22]. To our knowledge, there are no existing studies that have examined whether ADHD medications produce an altered sense of pain during or after performing resistance exercise. Research has focused on the cognitive benefits of ADHD medication, while failing to completely investigate physical outcomes, such as EIH, produced by these ADHD medications. The aim of the current study was to utilize a standard, high volume, dynamic circuit resistance exercise protocol to examine the effect of ADHD and ADHD medications on mechanical nociception (pain tolerance), blood lactate levels, heart rate, and rating of perceived exertion (RPE). It was thought that the documentation of pain tolerance, lactate, autonomic, and fatigue responses would contribute to the understanding of the impact of stimulants on EIH following resistance exercise. We hypothesized that dynamic resistance exercise would produce temporary increases in pain tolerance in conjunction with changes in blood lactate levels, heart rate, and perceived exertion. Also, it was hypothesized that ADHD medications would augment the effect of resistance exercise on pain perception, heart rate, and perceived exertion.

## MATERIALS AND METHODS

### *Participants*

Thirty participants (18 men and 12 women) with a mean age  $\pm$  SD of  $22.8 \pm 0.8$  years volunteered to participate in the study. The mixed sample was chosen due to the prevalence of ADHD in both genders, even though the prevalence rate is higher in men when compared to women. In addition, previous research has not demonstrated a significant difference in EIH across genders [23]. The sample size was determined by an a priori power analysis using G\*power (Version 3.1.9.2) assuming power of  $(1-\beta) = 0.80$  and a medium effect size ( $f^2 = 0.25$ ). It must be noted that there were more male participants than female participants in the current study, but all data were analyzed as a single group and gender comparisons were not conducted. All participants were recreational exercisers with resistance training experience for a minimum of 2 consecutive months at least 3 times a week. A health history questionnaire was administered to rule out (a) participation in competitive bodybuilding or weightlifting for the previous year, (b) current caffeine or nicotine use within 2 hours of the exercise, (c) history of pituitary, renal, hepatic, cardiovascular, or metabolic disease, (d) current chronic pain or pain disorders, and (e) currently taking any medications that can alter pain test results

(e.g. analgesics, oral contraceptives, etc). This study was approved by the Institutional Review Board of Southeastern Louisiana University and all participants were informed of the benefits and risks of the investigation prior to signing an institutionally approved informed consent document. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### *Preliminary Testing*

For preliminary testing, a three-repetition maximum (3-RM) was performed on all added resistance lifts to be utilized in the experimental session. The lifts included leg press, military (shoulder) press, lat pull downs, pec-deck flys, rows, and leg extensions. The protocol for the 3-RM was a modification of the one-repetition maximum (1-RM) protocol by Kraemer et al. [24] and was conducted in our recent publication on EIH [23]. The weight in pounds of the last successful 3-RM lift was recorded for use in experimental testing. Immediately following the 3-RM, all participants completed a training trial for the pain perception measures to avoid any confounding results due to the novelty of the measure.

### *Experimental Testing*

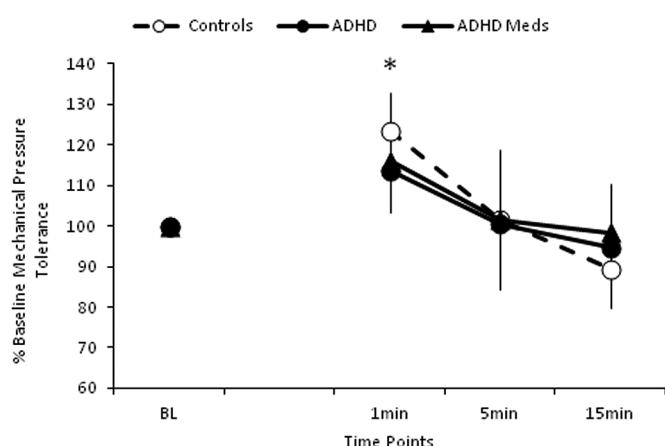
The experimental session was conducted in similar fashion to our previous protocol utilized in other studies [23] and occurred seven days after the preliminary testing day. Prior to exercise, baseline measurements of pain perception, blood lactate concentrations, and heart rate were all assessed. Pain perception was measured with the pressure algometer (Model FDX, Wagner Industries, Riverside, CT, USA) on the dorsal side of the non-dominant hand at the base of the skin web between the thumb and index finger and provided the experimenter with a digital readout of the pressure (N) applied. The location of pain assessment has been previously utilized in other research protocols to evaluate mechanical pain perception before and after exercise [23,25]. Participants were asked to notify the experimenter when “the stimulus becomes intolerable”, which is indicative of pain tolerance. For lactate measurement, capillary blood was collected from a finger prick via an auto-lancet device (Walgreens, Deerfield, IL, USA) and analyzed with a lactate meter (Lactate Plus Meter, NovaBiomedical, Waltham, MA, USA) that provided a digital readout of lactate in mM concentrations. Heart rate was measured using a heart rate monitor (Polar A1 wrist receiver and T31 transmitter, Lake Success, NY)

After baseline measurements were assessed, weight was adjusted to the proper resistance using the Brzycki formula [26] in order to calculate an estimated 1-RM from the participant's 3-RM determined during preliminary testing. As previously utilized by Baiamonte et al. [23], resistance exercise movements were performed at 60% of each participant's 1-RM and the exercise protocol was a circuit training bout of resistance exercise comprised of 3 sets of 12 repetitions with a 1:1 work to rest ratio with 45 s of work and 45 s of rest.

The order of exercises was designed to target the lower body, abdominals, and upper body in sequence and included leg press, planks, military press, lunges, rows, abdominal roll-outs, leg extension, pec-deck flies, and lat pull downs. Across the exercise session, heart rate (HR) and rating of perceived exertion (RPE, 10 pt. Borg scale) were recorded following each set during the 45 s rest period. Cardiovascular responses during the exercise bout were assessed using heart rate, and RPE was measured to determine the degree of heaviness and strain experienced during the bout, which can involve both pain and affective components [27]. Upon completion of the exercise bout, mechanical pain (tolerance) and lactate concentrations, were determined at 1 min, 5 min, and 15 min post-exercise.

*Statistical Analysis*

Statistical analyses of differences in mechanical pain tolerance and lactate levels were determined by separate, Mixed Factorial Analyses of Variance (ANOVA) in which the time points before and after the exercise bout (4 total: 1 pre-exercise and 3 post-exercise) were the within-subjects factors for the two analyses. The between-subjects factor for the two analyses was condition (Controls, ADHD/No Medication, and ADHD/Medication). All data for pain tolerance were normalized to pre-exercise baseline measurements, whereas lactate levels were expressed as mean ± SEM. For HR and RPE, statistical analysis of differences by circuit was determined by separate, Mixed Factorial ANOVAs in which the mean for each round (3 rounds) was the within-subjects factor for both analyses and condition was the between-subjects factor. All data for HR and RPE were displayed as mean ± SEM. Significant main effects were further analyzed using pairwise comparisons and statistical significance was set at  $p < 0.05$ .



**FIG. 1.** ADHD diagnosis and ADHD medications does not increase EIH following resistance exercise. Mean (+/- SEM) baseline mechanical nociception before and after an acute bout of high intensity resistance exercise. Data are presented as percent change from baseline of mechanical pressure tolerated. \* $p < 0.01$  1 minute post-exercise vs. baseline, 5 minutes, and 15 minutes post-exercise time points.

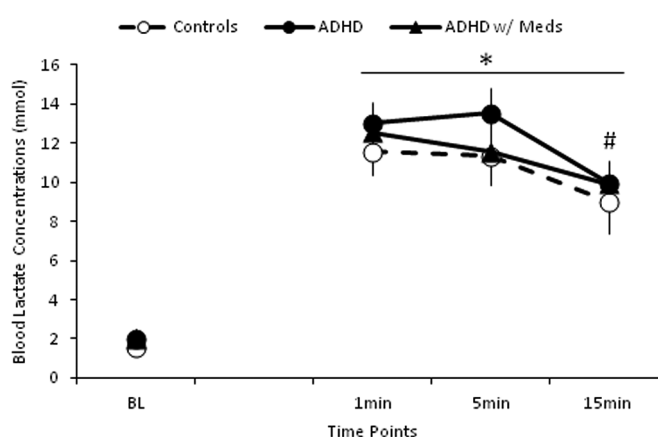
**RESULTS**

*Pain Perception*

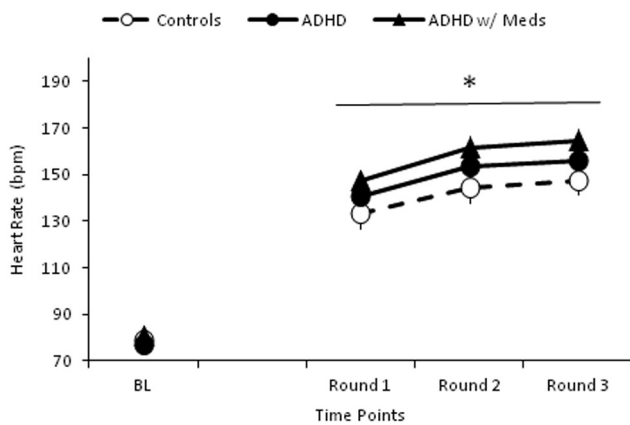
**Pain tolerance.** As shown in Figure 1, results demonstrated statistically significant increases in pain tolerance,  $F(3, 81) = 7.15, p < 0.01$ , following a standard, high volume resistance exercise regimen. Pairwise comparisons indicated significant increases in pain tolerance from baseline measurements to 1-minute ( $p < 0.01$ ) post-workout. Pairwise comparisons also indicated significant decreases in pain tolerance from 1-minute to 5-minutes ( $p < 0.01$ ) and 1-minute to 15-minutes ( $p < 0.01$ ) post-workout. However, there were no significant differences in pain tolerance between the 5-minutes post-workout time point and the 15-minute post-workout time point. In addition, there were no significant interactions or main effect of condition.

*Blood Lactate*

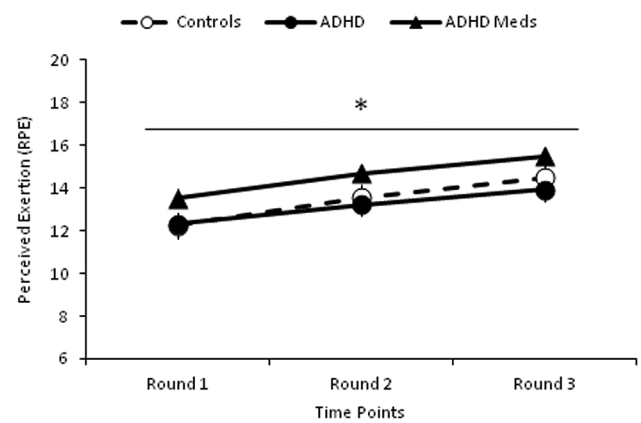
As seen in Figure 2, the results show a significant main effect of Time,  $F(3, 75) = 141.36, p < 0.01$ . Pairwise comparisons indicated that blood lactate levels were significantly higher than pre-workout (baseline) blood lactate levels at 1 minute, 5 minutes, and 15 minutes following the resistance exercise regimen ( $p < 0.01$  for all 3 cases). In addition, there was a statistically significant difference between blood lactate levels at 1-minute post-workout and 15-minutes post-workout ( $p < 0.01$ ) as well as 5-minutes and 15 minutes post-workout ( $p < 0.01$ ). However, there was no significant difference between 1-minute and 5-minute blood lactate levels post-workout. In addition, there was no significant main effect of condition or a significant interaction.



**FIG. 2.** Blood lactate levels increase following resistance exercise in participants without ADHD, with ADHD, with ADHD and medications. Mean (+/- SEM) blood lactate levels before and after participants complete a standard, high volume bout of resistance exercise. \* $p < 0.01$  baseline vs. post-exercise time points; # $p < 0.01$  15 minute time point vs. 1 minute and 5 minute time points.



**FIG. 3.** All participants demonstrate a significant increase in heart rate for each round of exercise. Mean ( $\pm$  SEM) heart rate during each round of the resistance exercise protocol. \* $p < 0.01$  Round 1 vs. Round 2 vs. Round 3.



**FIG. 4.** Resistance exercise protocol produces significant increases in ratings of perceived exertion in all participants. Mean ( $\pm$  SEM) RPE scores for each consecutive round of the exercise bout. \* $p < 0.01$  Round 1 vs. Round 2 vs. Round 3.

### Heart Rate

Data are displayed in Figure 3 and indicate a significant main effect of Time,  $F(2, 54) = 78.52$ ,  $p < 0.01$ , demonstrating that heart rate progressively increased with each consecutive round. Pairwise comparisons showed significant increases from Round 1 to Round 2 to Round 3 ( $p < 0.01$  in all cases). In addition, there was no significant main effect of condition or interaction between the groups.

### Perceived Exertion

Results indicated a significant difference in ratings of perceived exertion across all exercise rounds,  $F(2, 54) = 42.75$ ,  $p < 0.05$ . Pairwise comparisons determined that participants in all groups had increased ratings of perceived exertion from Round 1 to Round 2 to Round 3 ( $p < 0.05$  in all cases). There was no significant main effect of condition or a significant interaction. See Figure 4.

## DISCUSSION

The present study investigated the effects of ADHD and ADHD medication on pain perception, blood lactate levels, heart rate, and perceived exertion following a high intensity resistance exercise workout. It was hypothesized that dynamic resistance exercise would produce temporary increases in pain tolerance in conjunction with changes in blood lactate levels, heart rate, and perceived exertion. In addition, it was hypothesized that ADHD medications would augment the effect of resistance exercise on pain perception, heart rate, and perceived exertion. Significant increases in all dependent variables were seen in each group (Controls, ADHD/No Medication, and ADHD/Medication) when assessing each measure over time. All participants, regardless of group, exhibited a significant increase in pain tolerance measured by the pressure algometer, indicative of EIH [28], and also exhibited robust increases in blood lactate levels, HR, and RPE. It must be noted that the increases in pain tolerance and blood lactate

levels were transient, demonstrating significant increases 1-minute after an acute bout of dynamic resistance exercise and a progression towards baseline levels at the 5-minute and 15-minute post-exercise assessments across all groups. Additionally, heart rate and perceived exertion both increased progressively during the workout with higher scores for each subsequent round across all groups. This supports the hypothesis that a significant increase in pain tolerance would occur following the exercise bout. However, the hypothesis that the medicated group would have significantly higher levels than the non-medicated group was not supported. In summary, these data further demonstrate a concurrent role of physiological (blood lactate levels and heart rate) and psychological processing (RPE) in pain perception following dynamic resistance exercise. These findings suggest that EIH may be mediated by physiological changes during (increased HR) and after an acute bout of exercise (increased blood lactate levels) as well as psychological changes (increased RPE) during the exercise trial. More importantly, these physiological and psychological changes are not altered by the presence of ADHD or ADHD medications.

From a physiological standpoint, most researchers fail to agree on the exact mechanism responsible for pain reduction following bouts of exercise. The most commonly proposed mechanism includes the activation of the endogenous opioid system, in particular the release of beta-endorphins [29]. However, numerous studies have proposed a non-opioid mechanism exhibited by increases in endocannabinoid concentrations, which has been implicated in pain modulation, following exercise [30]. Other hormones such as cortisol, have been related to pain from resistance exercise and have generally demonstrated moderate to high correlations when high intensities and volume of work were performed [31,32]. Another possible mechanism includes physiological links between pain systems and cardiovascular systems, with most experiments focusing on blood

pressure and heart rate [33,34]. Finally, research has demonstrated the importance of exercise-induced metabolites (lactic acid, ATP, bradykinin, potassium, prostaglandin, and cytokines) on pain perception and the sensation of fatigue [35].

It has been suggested that the accumulation of lactic acid is an important modulator of pain and is also described as a physiological marker for metabolic stress [36]. Group III (A-delta) and IV (C) afferents of muscles in contraction have been shown to be stimulated by both mechanical and metabolic stimuli, respectively [37,38]. Previous findings have suggested that lactic acid plays a pivotal role in the stimulation of afferent fibers associated with metabolic stimuli, although it is not the only metabolite involved [39]. Although lactic acid has been linked to metabolic stimuli which are associated with Group IV, evidence suggests lactic acid stimulates both Group III and Group IV following injections of lactic acid at concentrations similar to those produced by muscle contraction [40]. Once in the bloodstream, lactic acid accumulates in the tissue, dissociating a hydrogen ion ( $H^+$ ), resulting in the stimulation of pain receptors via activation of the acid-sensitive ion channel family (ASIC) [41]. Extensive research has shown that all of the ASIC subunits are expressed in sensory neurons involved with nociception, indicating a role for these channels in pain detection [42]. Of the four ASIC subtypes, ASIC3 seems to be the most likely channel responding to muscle contraction. In fact, ASIC3 has been directly linked to the sensation of pain as demonstrated by ASIC3 knockout mice with reduced nociceptive responses to noxious stimuli when compared to wild-type [43]. Therefore, the accumulation of lactic acid stimulates both Group III and Group IV afferents via ASICs, producing a nociceptive response. However, the stimulation of these afferents can activate the endogenous opioid system [44], producing hypoalgesia as demonstrated in the current study. The current study demonstrated significant increases in blood lactate concentrations compared to pre-exercise values in all groups, which is an indicator of changes in lactic acid accumulation and could modulate pain immediately following an acute bout of exercise. More importantly, ADHD and ADHD medications did not alter blood lactate concentrations or hypoalgesia. This indicates that this form of stimulant medication does not alter normal glycolytic responses, nor does it alter other physiological responses that could affect hypoalgesia.

In addition to increases in blood lactate levels due to dynamic resistance exercise, elevations in cardiovascular and ventilatory activity accompany intense dynamic exercise [45]. The exercise pressor reflex, involving stimulation of Group III and IV afferents, is considered the mechanism by which these physiological changes occur and lactic acid accumulation is believed to play a role in this phenomenon [39]. Evidence of cardiovascular alterations is demonstrated in the current study by elevated HR for the duration of the exercise bout in all groups without any significant decline during rest periods. Not only is this a physiological confirmation of effort, consistent HR elevations can be used to indicate important cardiovascular changes during resistance exercise indicative of the exercise pressor reflex.

Therefore, lactic acid accumulation displayed by all participants will stimulate the thin muscle afferents via ASICs producing the exercise pressor reflex of increased cardiovascular activity (HR). As mentioned above, this will activate the endogenous opioid system to produce the hypoalgesia displayed by all groups following the bout of exercise. Not only will lactic acid accumulation result in the recruitment of endorphins from the endogenous opioid system, but will also increase cardiovascular activity which has also been linked to the release of beta-endorphin [46] which has been implicated in the phenomenon of EIH.

There were a few limitations in this study that could be addressed to improve future replication. For the recruitment portion, participant inclusion and exclusion was based on self-report of previous exercise habits as well as previous diagnosis of ADHD. There were no objective measures of ADHD by a clinical psychologist to indicate whether the person was correctly diagnosed with ADHD. In addition, participants taking ADHD medications consisted of prescriptions of various ADHD medications. For example, participants had listed Adderall, Concerta, and Vyvanse as the medications they were currently taking. While these drugs are all stimulants, they have different mechanisms of action and require different time frames for ingestion. In addition, these participants had different doses of the drugs, which was dependent on their diagnoses and severity of the disorder. Future studies should focus on whether EIH is influenced differently from each drug.

## CONCLUSIONS

These results demonstrated that individuals, during and after dynamic resistance exercise, experience physiological (increased blood lactate levels and HR) and psychological (increased RPE) changes. These changes are not altered by the presence of an ADHD diagnosis or the consumption of psychostimulants prescribed for an ADHD diagnosis. Exercise-induced hypoalgesia was present in all participants, but it is a temporary change that does not persist beyond the 1-minute post-workout measurement, in which measurements at 5-minutes and 15-minutes move closer to baseline as the body returns to homeostasis. When examining the ADHD participants taking psychostimulants, there were no significant differences in pain perception or blood lactate levels post exercise when compared to normal, healthy participants. These findings suggest that ADHD medications do not alter normal physiological responses to circuit resistance exercise and are safe for use during circuit training in this patient population.

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## Conflicts of Interest

The authors have no conflicts of interests in relation to the work described in this manuscript.

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