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Effects of Physical Characteristics of Placebos on Exercise Performance

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EFFECTS OF PHYSICAL CHARACTERISTICS OF PLACEBOS ON EXERCISE PERFORMANCE

by

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ABSTRACT

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Previous research has shown that placebos can impact medical conditions such as irritable bowel syndrome and depression as well as elicit analgesic effects and improvements in certain exercise performances. These placebo responses occur from a variety of alterations to the placebo itself or through verbal suggestion of how helpful the placebo will be. This study aimed to observe whether changing the color and quantity of capsules can induce improvements in both vertical jump and hand grip strength. This deceptive, parallel study consisted of 28 participants, with a mean age of 24.9 ($\pm$4.3) years old, that were randomly assigned to receive either two bright red and yellow capsules or a single white capsule, which all contained rice flour powder. Participants were informed that there was a 50% chance of receiving an herbal-amino acid blend or a placebo and were asked to perform two assessments of strength and neuromuscular performance. Both groups attended one session, that started with obtaining informed consent, completing a background questionnaire, performing a body composition test in the BodPod, a 5-minute seated rest with resting heart rate measured, the completion of visual analogue scales of fatigue (VAS-F) and energy (VAS-E), and a warm-up on a Monarch cycle ergometer. Participants then completed familiarization trials for both vertical jump and hand grip dynamometry using the Lode contact mat and Jamar hand dynamometer, respectively, followed by a baseline assessment for both the vertical jump and single hand grip dynamometer consisting

of three attempts with 30-60 seconds of rest between attempts. Subsequently, participants received their randomized treatment along with a standardized script, which was followed by a 15-minute incubation period before repeating the VAS-F, VAS-E, and vertical jump and maximal strength tests. Before debriefing, participants were shown four images and asked to rate the perceived stimulatory properties of each on a 100-mm VAS (VAS-S); the first image was a single white capsule, the second was two red/yellow capsules, the third was two white capsules, and the fourth was a single red/yellow capsule. The primary outcome variables were assessed via mixed analysis of variance (group x time). Results suggested no significant differences between groups for any of the primary outcome variables: vertical jump, grip strength, VAS-F, VAS-E, and change of heart rate over time. However, participants perceived two red/yellow capsules (61.4 ± 4.6) to have a greater stimulatory effect than a single white capsule (26.6 ± 4.1) via the VAS-S ($p < 0.05$). The results agree with previous research that individuals associate higher pill quantity and red-yellow as having stimulatory effects. That said, no effects on physical performance or perceived fatigue or energy were detected. Future research should consider using a combination of aerobic and anaerobic exercise.

TABLE OF CONTENTS

LIST OF TABLES

Table Page

LIST OF FIGURES

Figures Page

CHAPTER 1

INTRODUCTION

Background

The term placebo has been used in a pharmacological context since the 18th century, with its definition dating back to a mistranslated phrase from a Latin psalm meaning "to please" (Jacobs, 2000; Jütte, 2013). Placebo effects and responses function through various psychophysiological pathways in the body and rely heavily on the expectation of how the treatment will impact the person (Linde et al., 2007). If the expectation is for a positive outcome and yields a positive outcome, it is the placebo effect; however, if there is a negative outcome expectancy and it results in a negative outcome, it is considered a nocebo effect (Colloca et al., 2011). These expectations can be altered through verbal suggestion, therapeutic experiences, or interpersonal connections (Colloca, 2018).

The expectancy of an orally administered treatment can also be impacted by various physical characteristics such as capsule size, color, and quantity. Certain colors such as bright red, orange, and yellow are more associated with stimulants, while blue and dark red are associated with depressants (Jacobs et al., 1979). On average, people also have a higher level of expectancy with a greater quantity of capsules (Rickels et al., 1969). In terms of capsule size, one study reported that larger capsules were rated as having stronger effects in a white population (Buckalew & Coffield, 1982a) while the strength of smaller capsules was rated higher in a black population (Buckalew & Coffield, 1982b).

Researchers have attempted to determine what outcomes placebos can impact, and in the literature it is evident that placebos can have analgesic effects (Browne et al., 2004), reduce the

severity of symptoms in patients with irritable bowel syndrome (Kaptchuck et al., 2008), and decrease symptoms of mild anxiety and depression (Rief et al., 2009). Recently, there has been more research into placebos and their responses in regard to exercise performances, primarily aerobically and to a lesser extent anaerobically. Most of the research regarding the placebo effect and aerobic performance shows benefits similar to the drug or treatment the participants are informed to have received, with higher treatment expectancies resulting in greater outcomes (Beedie et al., 2006; Clark et al., 2000; Ross et al., 2015). The research using placebos and anaerobic performances suggests that maximal strength and power output can be increased when a positive expectation is created for the participant (Kalasountas et al., 2007; McClung et al., 2007).

Although there is evidence that placebos can impact physical exercise performance, several gaps in the current literature exist. It is important to note that most of these placebo and exercise performance studies attempted to induce either the placebo response or nocebo response through verbal suggestion and not directly through altering physical characteristics of the treatment such as altering the color or quantity of the treatment (Beedie et al., 2006; Ross et al., 2015). For example, some studies have used verbal descriptions and information to lead some participants to believe that they are receiving an erythropoietin-type drug (Ross et al., 2015), caffeine (Beedie et al., 2006), or carbohydrate (Clark et al., 2000; Hulston & Jeukendrop, 2009) when they are actually receiving a placebo. Thus, the current body of literature has yet to truly delve into the synergistic effects of altering multiple physical characteristics of an orally administered treatment on exercise performance. The current body of literature also does not discuss how the placebo effect can impact explosive power and isometric strength.

Problem

There is a gap in the literature on how altering multiple physical characteristics of an orally administered placebo, while controlling for verbal suggestion, may impact exercise performance. More specifically, outcomes such as vertical jump and isometric hand grip strength have been scarcely studied. The literature currently suggests that using a red, orange, or yellow capsule, and increasing the quantity of capsules, should increase the participant's level of expectancy (Beedie et al., 2012; Craen et al., 1996; Jacobs et al., 1979). The aim of this study was to determine if there were any improvements in vertical jump and single-hand grip strength from a placebo that should generate a high level of expectancy, due to altered physical characteristics. In order to directly study the impact of capsule physical appearance, verbal suggestions of benefit was standardized between treatments.

Hypothesis

Among recreationally active men and women, receiving two red-yellow capsules (size 0), along with a verbal suggestion that they are a beneficial treatment, will result in greater increases in vertical jump and single-hand isometric grip strength when compared to the same verbal suggestion given along with a single white capsule (size 0).

Purpose

This study aimed to investigate how a placebo with multiple alterations to its physical characteristics, while standardizing verbal suggestion, can impact common measurements of relative strength and relative power output.

Delimitations

This study consisted of 28 healthy adults who were recreationally active. All participants were capable of performing a maximal vertical jump and maximal hand grip strength test free of pain. The participants did not have any current lower or upper extremity injuries that could have impacted their performance, have any issues swallowing pills, or aversions or allergies to the capsule ingredients (gelatin and rice flour powder).

Limitations

Each participant had different preconceived thoughts due to different events in their life. We did not be try to induce any placebo responses through the classical conditioning mechanism. The outcomes that were measured, while commonly used in sport settings, did not allow for the examination of biological mechanisms. Although altering capsule sizes has been seen to impact perceived potency/strength, the literature suggests that there is a racial/ethncity effect; therefore, we used an intermediate-sized capsule size of 0.

Operational Definitions

1. Absolute isometric hand grip strength: Maximal hand grip test using a hand grip dynamometer assessing maximal force produced in kilograms (kg).
2. Absolute power: Total amount of power produced from a countermovement vertical jump and will be recorded in Watts (W). Using the Sayers equation to convert centimeter jump height to Watts (Sayers et al., 1999). The Sayers equation will be used because it has been seen to compute more accurate peak power outputs when compared to the Lewis equation (Musa & Toriola, 2006).

3. Capsule size 0: Medium capsule size of 21.3 mm in length and holds a volume of 0.68 ml.
4. Placebo: Physiologically inert substance given to the participant. In this study it will be a gelatin capsule filled with rice flour powder.
5. Placebo response: The change in outcome due to the placebo.
6. Recreationally active: Participates in moderate exercise for a minimum of 3 times a week for 30 minutes at a time.
7. Relative isometric hand grip strength: Maximal hand grip force produced divided by lean mass in kg.
8. Relative power: Absolute power from a countermovement vertical jump in W divided by lean mass in kg.
9. Vertical jump: A maximal counter movement jump from stand still.

Significance

The significance of this study was to observe how altering multiple physical characteristics of a capsule placebo can impact maximal power output of the lower extremities and maximal isometric hand grip strength. If there was an observed response to capsule color and number, then this might be reproduced into another study as an open-label placebo study on exercise performance. The study would need to be replicated using an open-label placebo before on-field applications could be realized, due to the ethical implications with deceiving athletes.

CHAPTER 2

LITERATURE REVIEW

History and Definitions of Placebos

The term placebo was originally used from the Latin psalm "placebo domino in regione vivorum; I will please the Lord in the land of the living" (Jacobs, 2000). The idea of using something to please a patient through psychotherapeutic or psychosomatic means has been around since the time of Socrates (Walach, 2011). It wasn't until the late 18th century that the term placebo transitioned from religious to pharmacological context because of Alexander Sutherland, an English physician (Jütte, 2013). Most credit is associated with another physician, William Cullen, who began his practice after Sutherland (Kerr et al., 2008; Walach, 2011). Cullen prescribed low-dose drugs to treat different illnesses and ailments, not to cure them but to please the patient (Jütte, 2014; Kerr et al., 2008). This laid the framework for what would be later known as an active placebo and for more sophisticated research on placebos (Finniss, 2018; Jütte, 2013, 2014; Kerr et al., 2008). Discussions around the definition of placebo became prevalent in the mid-1900s, with Beecher, an anesthesiologist and researcher, explaining that, although a placebo might physiologically be inert, its effect is not (Macedo et al., 2003). Beecher was also attributed with recognizing how important double-blind placebo-balanced clinical trials are (Smith, 2022).

Unfortunately, there has yet to be a consensus on what operationally defines a placebo (Macedo et al., 2003). Standard definitions of placebos tend to be refined versions of the definition proposed by Arthur K. Shapiro (1964): "A placebo is defined as any therapeutic procedure (or that component of any therapeutic procedure) (1) which is given deliberately to

have an effect, or (2) which unknowingly has an effect, on a patient, symptom, disease, or syndrome, but which is objective without specific activity for the condition being treated. The placebo is also used to describe an adequate control in experimental studies." Therefore, the term placebo has evolved to include not only physiologically inert substances but also any physiologically inert treatments such as sham surgeries and sham acupuncture (Gu et al., 2017; Moffet, 2009). While placebos are believed to please or quell a patient, there are also nocebos, defined as physiologically inert interventions but that the patient believes will have negative effects (Colloca et al., 2011). While there is no consensus in the literature, some researchers believe that there is also a difference between the nocebo effect and the nocebo response; with the nocebo effect relating to the psychosocial interaction between the practitioner and patient with a negative outcome, while the nocebo response is the expectancy of a negative outcome or negative side effects with an inert intervention (Colloca & Miller, 2011).

Placebo Effects in Medical Research

With placebos becoming more popular in medical research, more studies have been conducted attempting to determine what physiological and/or health effects can be altered from placebos (Finnis, 2018). In general, placebo effects appear to be more prominent when used for conditions like irritable bowel syndrome, pain, and depression that involve subjective or pyschosomatic-type outcomes (Kirsch, 2013). A study by Kaptchuck et al. (2008), for example, assessed the effect of sham acupuncture on irritable bowel syndrome. The researchers saw a significant decrease in irritable bowel syndrome severity at a percentage comparable to the drugs which are currently used to treat irritable bowel syndrome. Likewise, Vase et al. (2005) conducted a study concerning pain management of irritable bowel syndrome but used a topical

agent on the inside of the rectum; their study concluded that the placebo resulted in similar analgesic and expected outcomes to that of the lidocaine group.

Placebos have been shown in several instances to be similarly as effective as analgesic medications for relieving pain associated with surgery. Browne et al. (2004) assessed the analgesic effects of placebos compared to bupivacaine bolus injection in the knee after total knee arthroplasty. Although there was no statistically significant difference between the two treatments after 24 hours, there was a greater rating of pain relief with placebo than bupivacaine immediately after the postanesthesia care unit. It is possible this may have been a chance finding (the p-value was 0.05 and pain relief was not different between treatments at other timepoints), but nonetheless, placebo was similarly efficacious as bupivacaine. A study by Levine et al. (1981) compared different dosages of morphine versus placebo after oral surgery and found that the placebo treatment had similar analgesic effects to that of 4 mg or 6 mg of morphine while 8 mg and 12 mg still resulted in greater analgesic effects. A study by Hashish et al. (1988) assessed multiple treatments of ultrasound and self-massaging recovery modalities in dental post-operative patients; their results indicated that sham/placebo ultrasound was effective in reducing pain, swelling, and c-reactive protein relative to no therapy, which the authors suggested could possibly mediated through endogenous opioids.

Research has shown that 30-40% of moderate-to-severely-depressed patients improve from placebo treatments with minimal to no nocebo effects recorded (Brown et al., 1992; Kirsch, 2019; Stark & Hardison, 1985). A meta-analysis of the placebo response in comparison to anti-depressants found that there was a publication year effect, with the effect sizes almost doubling from 1985 to 2005 (Rief et al., 2009). The same meta-analysis also reported that the placebo response was larger in patients with major depression compared to dysthymia, which they

inferred might be related to the cyclical/habitual nature of major depression rather than the chronic effect of dysthymia (Rief et al., 2009).

As highlighted in the research above, the magnitude of a placebo effect will vary because there are multiple moderating factors, especially the condition being treated (Kirsch, 2013). Expectations of the treatment appear to impact the magnitude of the effect, with individuals that hold the expectation of treatment benefit experiencing greater improvements. For example, in a meta-analysis of acupuncture trials, patients who had higher treatment expectations experienced more pain relief than those who had low expectations (Linde et al., 2007).

Other potential moderating variables of the placebo response, however, are often inconsistent between populations and areas of research but may include illness factors (e.g., disease severity), patient/participant characteristics (e.g., biological sex, genes), cultural factors, and trial characteristics (e.g., ratio of participants allocated to real and placebo treatments) (Sonawalia & Rosenbaum, 2022). One review of psychiatry trials found that participants with low baseline symptom severity levels for schizophrenia, depression, and binge eating disorder resulted in greater placebo responses (Weimer et al., 2015). Similarly, a 2015 analysis of systematic reviews and meta-analyses that looked at predictors of placebo response across the medical literature found that age and gender do not play a crucial role in placebo responses, but a decreased level of symptom severity at baseline does appear to impact the placebo response (Weimer et al., 2014). In terms of personality traits, the literature suggests that optimism is associated with more placebo responses, while pessimism, fear, and anxiety are more closely associated with increased rates of nocebo responses (Kern et al., 2018).

Placebo Mechanisms

As previously mentioned, having a pre-conceived expectation of the treatment may, under certain conditions, produce outcomes of larger magnitudes (Linde et al., 2007). The psychophysiological mechanisms by which placebos can create expectancies can be broken down into multiple categories: verbal suggestion, therapeutic experiences, and interpersonal connections (Colloca, 2018). The physiological pathways by which these placebo-expectancy effects work may include endogenous opioid, endocannabinoid, oxytocin, vasopressin, and dopamine systems, depending on the condition (Colloca, 2018).

Placebos with the intent of analgesic effects have been measured under a functional magnetic resonance imaging system to determine if brain activity is altered. The researchers found that when a patient is expecting a treatment to reduce either thermal or electrical pain, there is a reduction in brain activity associated with pain-sensitive regions of the brain (Wager et al., 2012). At least some of the pain relief that patients receive after a placebo is believed to come from the expectation induced by the practitioner's verbal statements, which in turn allows the patient to recall previous periods of time with pain relief, leading to the current belief that placebos operate at the psychoneurobiological level primarily affecting the central nervous system (Colloca et al., 2013).

Beyond expectancy, another pathway by which placebos can operate is through conditioning. Recent research has revealed that classical conditioning may also act as a placebo pathway which can be learned consciously and/or unconsciously (Bąbel, 2019). An experiment by Bąbel et al. (2017) carried out conditioning tests that involved showing different colored lights to participants, followed by administering nonpainful or highly painful stimuli. During subsequent testing, participants experienced placebo and nocebo responses associated with the

different colored lights when a control (moderately painful) stimuli was applied. Importantly, participants were not told about the meaning of the colored lights during the experiment. These results suggest that classical conditioning might act as a pathway without the assistance of expectancy for analgesic effects.

Placebo Variables and Their Respective Effects

With the efficacy of placebos depending on the pre-conceived expectation of the treatment, there are multiple variables that have been altered to impact the expectation of an oral placebo (Jacobs et al., 1979). Common variables of oral placebos that are altered to impact the outcome are color, preparation form, size, and quantity (Blackwell et al., 1972; Jacobs & Nordan, 1979).

Both yellow and bright red-colored capsules have been associated with stimulant effects while blue-colored capsules and dark red capsules have been associated with depressant effects (Buckalew & Coffield, 1982a; Jacobs & Nordan, 1979; Meissner & Linde, 2018). Another study conducted by Buckalew and Coffield (1982b) assessed racial differences and found that the black sample also associated the color orange with stimulatory properties. There have also been studies determining a relation between capsule color and potency of the pill, with red and black ranking the highest for believed strength while white and blue were presumed to have to weakest effect (Sailis & Buckalew, 1984). A systematic review by Craen et al. (1996) concurred with Jacobs and Nordan (1979) that red and yellow capsules acted as stimulants and blue acted as a depressant; however, the analysis also discussed the possibility of preparation form as having an impact, mainly on the difference between tablet and capsule. Some researchers believe that a capsule placebo is “stronger” than a tablet placebo due to the advertisement of capsules having

quicker time-release (Buckalew & Coffield, 1982a). A more recent study by Khan et al. (2010) had results suggesting that, in comparison to tablets, people more often associate capsules with stimulatory effects. Unfortunately, there is minimal research discussing the differences between tablet and capsule placebos (Meissner & Linde, 2018).

Considering the placebo response relies, at least to some extent, on preconceived beliefs of how well a treatment will work, another physical characteristic that can be altered to impact those beliefs is capsule size. A study conducted by Buckalew et al. (1982a) had white participants rank six capsules of varying sizes by their perceived strength of the pill; their findings revealed that with their specific ranking system, 56% and 59% of men and women, respectively, report a positive linear relationship between capsule size and perceived strength. Another study also conducted by Buckalew and Coffield (1982b) assessed capsule size and perceived strength among black participants and showed that there was an inverse relationship between size and strength.

The quantity of capsules is another physical characteristic that can impact a participant's expectancy of the treatment. Blackwell et al. (1972) compared the effects of one or two blue or pink capsules on self-reported psychological measurements. The results suggested that the groups receiving two pills had greater effect sizes but did not have a higher frequency of placebo responses than that of the single-pill groups. Rickels et al. (1969) conducted a study consisting of neurotic anxious participants, who received either 5 or 8 capsules per day of either a placebo or drug. The group that received 8 placebos in one day experienced greater improvements on a Global Improvement Questionnaire filled out by both the clinician and patient.

There is no consensus within the literature as to whether there is a sex effect on placebo responders. However, a 2019 systematic review compared sex differences from experimental

data and clinical randomized control trials (Enck & Klosterhalfen, 2019), with the authors finding that female participants appear to respond to placebos as a result of classical conditioning while male participants appear to respond more from verbal suggestion. In comparison, a 2017 systematic review from Vambheim and Flaten (2017) that assessed the sex differences between placebo and nocebo responses suggested that males respond at higher rates to placebos and lower rates of nocebos when compared to their female counterparts. While the literature suggests that sex and race play a role in placebo responses, there is not enough evidence-based literature to develop a clear conclusion on how these characteristics truly impact the placebo response.

Placebo Effects in Exercise and Sports Research

As the current body of literature has demonstrated, placebos are capable of eliciting varying degrees of psychophysical responses (Browne et al., 2004; Kirsch, 2013; Rief et al., 2009). Researchers have also attempted to induce these psychophysical responses from placebos to elicit greater exercise performances (Hurst et al., 2019). In a recent systematic review, an analysis of 32 studies that used either a nutritional or mechanical placebo found moderate effect sizes across all studies; the largest effect sizes came from the studies where researchers deceived the participants into believing they were receiving illegal substances such as anabolic steroids or erythropoietin supplements (Hurst et al., 2019).

The literature for placebos and exercise performance suggests that when the participants are able to identify correctly whether they are receiving the active treatment or the inert treatment, they will either improve or impair their performance, respectively (Saito et al., 2020). This has been discussed within the literature in regards to open-label placebos, when the participant is told that they are consuming or receiving a physiologically inert treatment. For

example, highly trained female cyclists were able to improve their 1-km time trial by 0.7% when administered an open placebo, which could be enough to make the difference of medaling within their niche population (Saunders et al., 2019). A similar study conducted by Swafford et al. (2019) found that placebos (either traditional or an open-label placebo) had no effect on strength, voluntary contraction, or muscle fatigue; for the open-label placebo, the researchers explicitly informed the participants that they wouldn't experience any effects, although they also told them that open-label placebos have been shown to improve function within clinical trials. A study by Bottoms et al. (2013) agreed with the outcomes of Saunders et al. (2019) where they had participants drink the same solution 30 minutes prior to a raise, activate, mobilize, and potentiate/performance protocol on an arm crank ergometer. The participants were either informed that the solution would be beneficial or impair their performance, which resulted in the positive information group outperforming the other group. This reiterates the importance of expectation to induce greater effects, although most research in the current body of literature comes in the form of single-blind studies and not open-label placebo studies.

Some studies that assess how placebo impacts exercise performance have divided their participants into four groups or conditions: received drug/informed drug, received placebo/informed drug, received drug/informed placebo, and received placebo/informed drug. This type of design, referred to as the fully balanced placebo design, is used to assess the drug response, placebo response, and the combination of both (Hurst et al., 2020; McClung & Collins, 2007). In a study assessing the impact of a placebo or caffeine on 1000-meter running time trials among competitive male runners, there were no statistically significant improvements in any of the experimental trials for the full 1000-meter performance; although, there were statistically significant improved split times for the 200-meter and 400-meter points in the received

caffeine/informed caffeine trial and the received placebo/informed caffeine trial as compared to the other two experimental trials and baseline (Hurst et al., 2020).

A study conducted by McClung and Collins (2007) assessed the impact of placebo versus sodium bicarbonate on 1000-meter running time trial with the same four experimental designs implemented; this resulted in the received sodium bicarbonate/informed sodium bicarbonate group performing the best, with the received placebo/informed sodium bicarbonate performing slightly below but still outperforming the received sodium bicarbonate/informed placebo group. It important to note that the two groups who received sodium bicarbonate had lower levels of blood lactate before the trial when compared to the two groups who received the placebo, suggesting that the placebo had more of a psychophysiological effect than a standard physiological (i.e., blood-buffering) one (McClung & Collins 2007).

In another study assessing placebo effects on maximal strength in untrained individuals, the researchers found improvements in strength measurements for bench press and leg press (Kalasountas et al., 2007). This study did not use a fully balanced design; in trial one, both the groups received two milk-sugar tablets prior to testing along with positive suggestion of how this drug can improve performance. However, during trial two, one group still received the milk-tablets with a positive suggestion and the other group did not receive the milk-tablets but were informed that another coach that previously tested the drug was dissatisfied with the results. The group that received the milk-sugar tablets on the second visit continued to improve their performance on both leg press and bench press. While the group that was informed with the negative suggestion and didn't receive the tablets for the second trial had a reduction in performance for both bench press and leg press. In total, the current body of literature suggests that placebos given with positive information or with the expectation of a drug can improve

anaerobic measurements, including maximal strength, comparable to that of what would be expected from an actual drug or supplement.

Studies have attempted to assess how placebos can impact aerobic performances through proposing the placebo as a carbohydrate (Clark et al., 2000; Hulston & Jeukendrup, 2009), caffeine (Beedie et al., 2006), or, in one case, an erythropoietin-type drug (Ross et al., 2015). In a study by Hulston et al. (2009), the researchers assessed how a placebo would compare to a carbohydrate and electrolyte solution for 60-minute cycling time trial performance; their results suggest a statistically significant difference in power output between the two experimental conditions, with the carbohydrate and electrolyte solution outperforming the placebo. It is important to note that the participants had to complete 120 minutes of submaximal cycling prior to the 60-minute time trial, suggesting that placebos might not be able to create much of a benefit during prolonged exercise when glycogen depletion has occurred. Another study assessed placebo versus a carbohydrate solution for a 40-km cycling time trial, where participants were either given a carbohydrate solution or water and were told they received either the carbohydrate solution or the placebo; their results showed a 4% increase in average power output in the group that received the placebo but were told they received the carbohydrate, suggesting that sub elite level cyclists may benefit from the expectancy of the treatment (Clark et al., 2000).

Studies have also attempted to determine if the placebo effect can mimic the effects of caffeine for aerobic exercise, specifically 10-km time trials. Beedie et al. (2006) told cyclists they would receive a placebo, 4.5 mg/kg, or 9 mg/kg of body mass of caffeine under three separate trials; however, they only received placebos each time. After each trial, participants were asked to guess which condition they thought they received. Their results showed an increase in mean power output from baseline for all experimental conditions. Further, as

compared to baseline trials, power outputs were -1.4%, 1.3% and 3.1% higher for the trials in which participants guessed they received placebo, 4.5 mg/kg and 9 mg/kg of caffeine, respectively. These results suggest that participants associated their improved performance with the higher dosage of caffeine.

Researchers have also attempted to increase the level of expectancy through deceiving participants into believing they are receiving a much stronger substance, like anabolic steroids. In one study, participants were administered subcutaneous saline injections for 7 days but were told it was a fictitious steroid called OxyRBX (Ross et al., 2015). The researchers assessed how it affected the participants in a competition-like 3-km run; the fictious steroid resulted in an improvement of performance by an average of 10 seconds from baseline (Ross et al., 2015).

Gaps/Weaknesses in the Research on Placebos and Exercise Performance

How to induce the placebo response phenomenon and specifically what it can affect is still being researched, particularly in the realm of exercise science. The current literature implies the placebo response is dependent on preconceived beliefs and classical conditioning (Meissner & Linde, 2018). The literature also suggests that preconceived beliefs of pills can be altered from the pill's appearance (Buckalew & Coffield, 1982a; Meissner & Linde, 2018). However, to the knowledge of the author, there haven't been many (if any) studies assessing how specifically altering multiple physical characteristics of a placebo will impact exercise performance. In theory, prescribing participants multiple bright red, orange, or yellow capsules with standardized verbal information should induce an improvement in exercise performance. Through standardizing the verbal cue, a future study would be able to assess how altering the physical characteristics of the capsule alone can impact exercise performance.

A few other weaknesses in the current literature are worth mentioning. The studies that have attempted to assess how placebos impact exercise performance have mostly used aerobic exercise outcomes. In contrast, absolute and relative peak power output or isometric strength changes from a placebo remained understudied. With most exercise performance-related studies, the sample sizes tend to be small, and this remains true among placebo and exercise performance studies. Although some previously mentioned studies have attempted to discover a sex, race, and age effect on expectation and placebo responses, there haven't been enough recent studies to create a definitive conclusion on how these variables impact the placebo response.

Summary

The placebo effect can be closely associated with an expectation response, with a greater expectation resulting in a greater benefit from a treatment. Placebos have been utilized in clinical settings as a way to decrease the symptoms of irritable bowel syndrome, elicit analgesic effects, and improve mild anxiety and depression. Placebos are believed to work through various psychophysiological mechanisms that depend on the expected result of the administered treatment and conditioning. The expectation of an orally administered treatment can be altered through various physical characteristics such as capsule color, size, and quantity. Bright red, yellow, and orange capsules have been associated with stimulants. Greater quantities of capsules have been associated with greater perceived strength. The impact of capsule size is still unclear with white populations perceiving larger capsules to be stronger and black populations perceiving smaller capsules as stronger.

Recently, researchers have begun testing the placebo effect and various modes of exercise, with the literature suggesting that placebos can elicit performance improvements.

Unfortunately, the sport research has not attempted to identify the synergistic effects of manipulating capsule color and quantity while informing the participants that they will be receiving a strong drug/supplement associated with the desired performance improvement. Refer to Table 1 for representation of the proposed effects from the physical characteristics.

Table 1. Placebo characteristics and respective effects

Variable	**Proposed Effect**
Bright red, yellow, or orange	Stimulant
Dark red or blue	Depressant
Large capsule (000)	Greater perceived strength (in white populations)
Average capsule (0)	Neutral effect between populations
Small capsule (4)	Greater perceived strength (in black populations)
Multiple capsules (2+)	Increase in desired outcome effect

000 = Largest capsule size (26.1mm), 4 = Smallest capsules size (14mm).

CHAPTER 3

METHODOLOGY

General Design

This study used a randomized parallel-group study design. Participants were randomly assigned to receive two red-yellow capsules (size 0) or one white capsule (size 0) between repeated physical performance tests. Verbal information about the treatments was standardized between the two treatments.

Deception was used to study the effects of capsule color and number on vertical jump and maximal isometric handgrip strength. According to the American Psychological Association, deceptive studies are allowed if the deception will not cause any foreseeable physical pain or extreme mental distress, if nondeceptive techniques aren't viable for the prospective research, and if the researchers disclose to the participants that deception was used at the earliest time after their participation (American Psychological Association, 2017). This study met all of these criteria.

Participants

This study consisted of 28 participants who were recreationally active individuals between the ages of 18 and 40. Recruitment for this study occurred through posting flyers in different locations at Old Dominion University such as the Student Recreation Center and Webb Center as well as at various community establishments, in the Hampton Roads region of Virginia. Posts on the social media pages of the investigators were also made, and individuals who contacted the Human Performance Laboratory about fitness and body composition testing

were also told about the study. Recruitment communications were conducted via email or in person.

Participants were required to be recreationally active, which was defined as participating in exercise at least three times per week, for at least 30 minutes at a time. The participants had no history of major cardiovascular or metabolic diseases, swallowing issues, or allergies or aversions to the ingredients that were used in the capsules (gelatin and rice flour powder). Of note, participants were screened for allergies or aversions to the following ingredients: guarana, green tea, ginseng, and ginkgo biloba. These ingredients were not actually included in the capsules that participants were given, but they are listed as exclusionary criteria as part of the study deception procedures. In addition, participants didn't have any injuries that could have interfered with maximal upper or lower body exercise. These parameters were set to protect participants who might have had an issue with swallowing the capsule or be at a higher risk of injury from performing the vertical jumps or maximal isometric strength tests.

All participants were required to go through an informed consent process that had been approved by the Old Dominion University Institutional Review Board. When obtaining informed consent, the participant was told that the purpose of the study was to assess how a new supplement impacts vertical jump performance and maximal single-hand isometric strength performance, and that they would receive either a placebo or the new supplement. All participants were deceived about the nature of the study to prevent the study from being an open-label design. This deception was necessary given the study's purpose of understanding how physical characteristics of a placebo impact performance. Telling the participants that the goal was to study capsule color and number would have been likely to induce an effect itself.

Immediately after their data was been collected, each participant was debriefed with the true purpose of the study, and they were given the option to not have their data be used. The

debriefing was meant to ensure that the participants understood why the deception was necessary and that they were not distressed by the experiment.

Procedures

The study consisted of one visit to the Human Performance Laboratory at Old Dominion University. Prior to arriving the participants were informed of the following pre-testing instructions: arrive in or bring athletic wear, be in a fasted state for at least 4 hours, avoid vigorous exercise for at least 24 hours before testing, and avoid caffeine intake for at least 6 hours prior to the testing. The visit began with obtaining informed consent, background/demographic information via a questionnaire, height from a stadiometer (Sena, Hamburg, Deutschland), body composition and weight from the BodPod (COSMED USA, Concord CA, USA). Following the body composition testing, participants put on a polar H-10 heart rate monitor (Polar, Kempele, Finland). Next, they were be asked to complete a visual analogue scale to evaluate fatigue severity (VAS-F), which contained 18 items, and has been proven to be a valid and reliable test for assessing a person's level of fatigue (Lee et al., 1991). Afterwards, participants rested quietly for 5 minutes in a chair. During this rest, their heart rate was recorded during the last minute at 30-second intervals.

Participants then performed a 3-minute cycling warm-up on the Monark 828E (Monark Exercise AB, Sweden) at an intensity of 12 on the Borg scale of 6-20 (Borg, 1982). Participants then became acquainted with performing a countermovement vertical jump measured by the Lode ProJump mat (Lode, Queensland, Australia) and single hand isometric grip strength measured by an m3-200 Jamar dynamometer (Sammons Preston, Warrenville, Illinois, USA).

Participants then performed 3 more maximal countermovement jumps, with hands on hips throughout the jump, using the Lode ProJump mat with 30-60 seconds of rest between bouts. The investigator informed the participant to complete the maximal jump to the best of their ability. Therefore, the researcher did not constrain how deep the participant squatted prior to the jump. The average of the three recorded jumps were recorded as their baseline. Following a 3-minute rest, participants performed a baseline trial of 3 maximal hand grip strength attempts on a digital Jamar hand grip dynamometer using their dominant hand with 30-60 seconds of rest between attempts. The average of the three attempts were recorded as their baseline.

Participants then received their randomized treatment of either the white XPRS Nutra size 0 gelatin capsule (XPRS Nutra, South Jordan, Utah) or the two red-yellow XPRS Nutra size 0 gelatin capsules (XPRS Nutra, South Jordan, Utah). Sex-specific randomization lists were generated using https://www.sealedenvelope.com. Block sizes of two and four were used to ensure that relatively equal numbers of participants received each treatment. Participants in both groups were told the following:

> "Now it's time to administer the study treatment. As we talked about during the consent, you have a 50-50 chance of getting the placebo or the amino acid herbal blend supplement, which has been seen to improve high-intensity aerobic exercise in some past research. The real supplement is thought to take about 15 minutes to kick in, so we will have you rest quietly for those 15 minutes after you ingest your capsules. During this time, please refrain from using your phone or doing any other activities. We will also refrain from conversation since the supplement is thought to impact mood and we want to control for any extraneous factors."

Participants were seated and refrained from distractions such as conversation or using their phones. Heart rate was recorded at 1-minute intervals. After the incubation period, participants filled out the VAS-F questionnaire again. Participants were then asked to complete another 3-minute cycling bout at the same intensity as earlier in the session. This was followed by three more maximal jumps with 30-60 seconds of rest between bouts, with the average of the jumps recorded as their result. Afterwards, they completed three more maximal hand grip strength attempts using their dominant hand with 30-60 seconds of rest between attempts with the average of attempts recorded.

After their second set of performance tests, participants were asked to complete a visual analogue scale questionnaire for stimulatory (VAS-S) effects with four different images; see Appendix A for full questionnaire. The first image was of a single white capsule, the second image was of two red/yellow capsules, the third image was of two white capsules, and the fourth image was of a single red/yellow capsule. Afterwards, the participants were debriefed about the true nature of the study and informed how they were deceived (see Appendix B). At that point in time, they could request to have their results not included in the study's results. Regardless of what their decision was, they were asked to keep the nature of the experiment confidential and not tell others about the true purpose of the study, until completion of the study.

Outcome Variables

Vertical jump using a contact mat, such as the Lode ProJump mat, has been proven to be both a valid and reliable instrument for measuring lower extremity power (Nuzzo et al., 2011). Although they found three-dimensional motion capture to be the gold standard, the contact mat had greater reliability than that of a Vertec, a commonly used device in field settings. Vertical

jump was assessed in this study because it is a common test used by strength and conditioning professionals to objectively measure explosive power output of the lower extremities (Harman et al., 1991). Vertical jump was recorded in centimeters but also converted to Watts using the Sayers equation and expressed in terms of absolute and relative power (Sayers et al., 1999).

Single-hand isometric grip strength was assessed with the m3-200 Jamar dynamometer because it is a reliable and valid for measuring isometric grip strength (Allen & Barnett, 2010). Hand grip strength was assessed in this study because there is a lack of research on how placebos can affect hand grip strength. Although, there have been chronic nutritional studies assessing how nutritional status correlates to contraction strength, leading to the rationale that a placebo may impact single hand isometric strength (Norman et al., 2011).

Statistical Analysis

All statistical analyses were conducted using SPSS software (version 28, Armonk, NY, USA). For outcome variables, vertical jump data and handgrip strength were normally distributed based on the evaluation of histograms and Q-Q plots. VAS-E, VAS-F, and heart rate were right-skewed and therefore transformed using the natural log function, which removed the skew. A mixed repeated measures analysis (group x time) was conducted to test for differences from pre- to post- and between groups for VAS-F, VAS-E, vertical jump performance, and hand grip strength. The same approach (except with four time points instead of two) was used for heart rate to assess changes from baseline across the three time points. The analysis of the VAS-S results used a repeated measures ANOVA to detect differences between image ratings, with Bonferroni adjustments used for any pairwise post-hoc testing. All descriptive statistics are

reported as mean ± standard deviation (SD). A two-sided alpha level of <0.05 was used as the threshold for statistical significance.

CHAPTER 4

RESULTS

Descriptive Statistics

There was a total of 28 participants comprised of 14 males and 14 females. The average age of the participants was 24.9 ± 4.3 years, exercise per week was 421 ± 301 minutes/week, height was 170 ± 7 centimeters, body mass was 76.8 ± 11.9 kilograms, and body fat percentage was 27.6 ± 7.9 %.

Outcome Variables

The following variables were measured pre- and post-intervention: VAS-F, VAS-E, vertical jump, peak power output, relative power output, lean mass relative power output, and hand grip strength. Other outcome variables were baseline heart rate compared to the three 5-minute intervals post-intervention and a VAS-S for perceived capsule stimulatory strength.

Figure 1 depicts that there was a decrease over time for vertical jump height for both conditions ($p < 0.001$). However, no statistically significant between-group effect ($p = 0.325$) or time x group interaction ($p = 0.203$) was found. The same type of significant time effect ($p < 0.001$) but lack of significant between-group and time x group effects were found with peak power output, relative power output, and lean mass power output (data not shown).

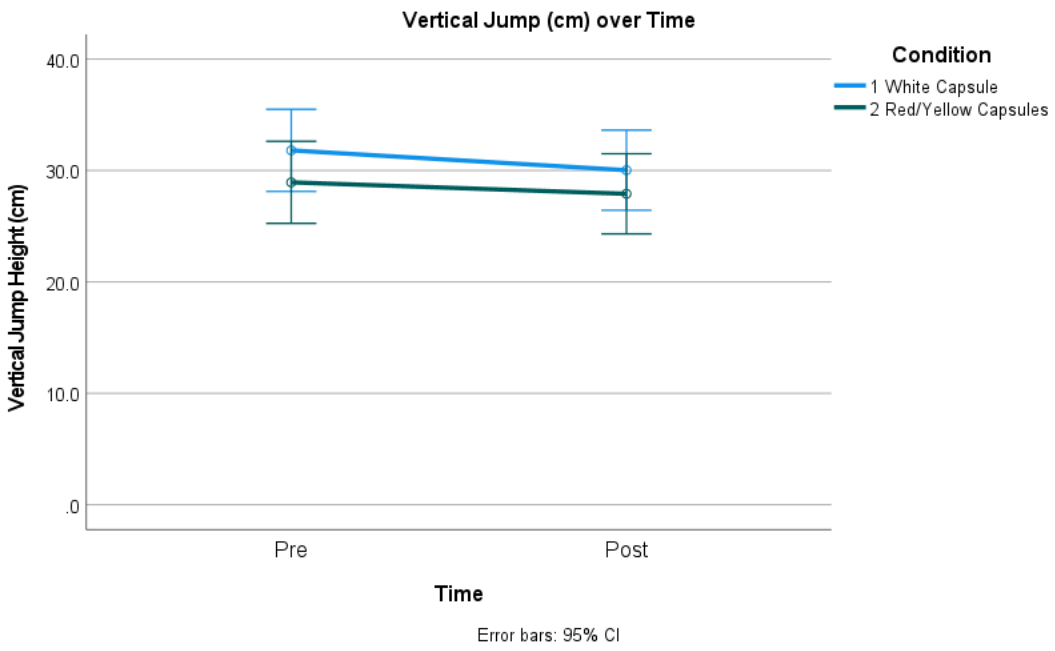

Figure 1. Graph of vertical jump in centimeters from pre to post between conditions.

Log-transformed HR data are shown in Figure 2. There was no statistically significant difference between groups ($p = .578$), nor was there a time x group effect ($p = .560$) based on a Greenhouse-Geisser correction. However, there was an overall time effect ($p < .001$) based on a Greenhouse-Geisser correction. Using pairwise comparisons (least significant difference method), it was seen that there was a statistically significant difference from baseline to every other time point with p-values <.002.

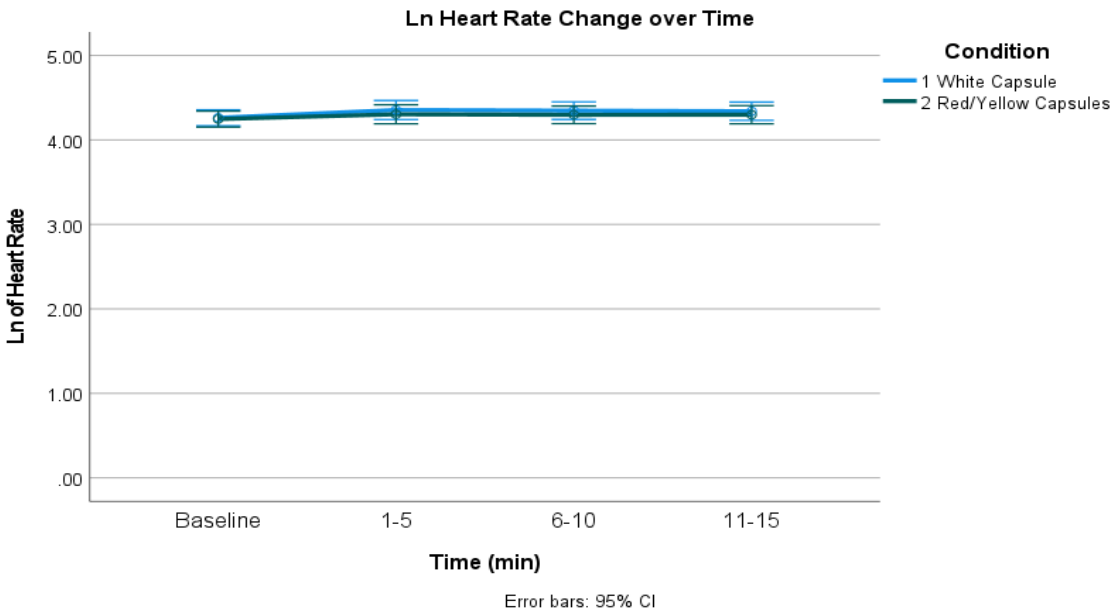

Figure 2. Log-transformed heart rate data over time.

Figure 3 depicts hand grip strength data from pre to post. There was no statistically significant difference over time or time x groups with p-values of .439 and .189, respectively. There was also no between-group difference (p = .530).

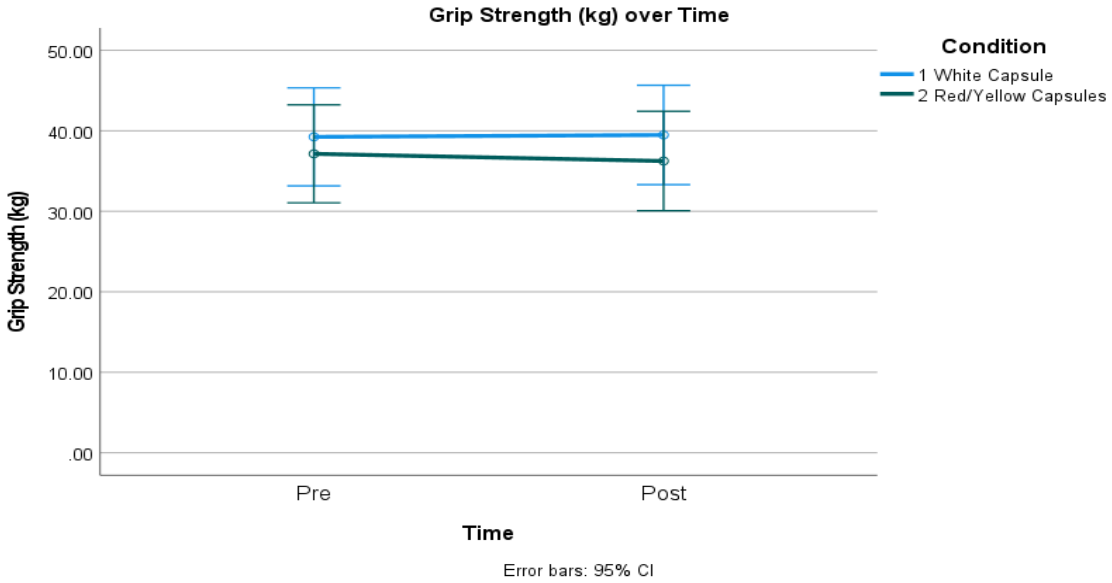

Figure 3. Grip strength differences between conditions and over time.

Figure 4a depicts the log-transformed data for the VAS-F. VAS-F had no difference over time or time x group effect with p-values of .308 and .175, respectively. Also, there was no difference between groups (p = .855). Figure 5b depicts the log-transformed data for VAS-E. There was no difference for the VAS-E over time or time x group effect with p-values of .078 and .482, respectively. There were no significant differences between groups (p = .574).

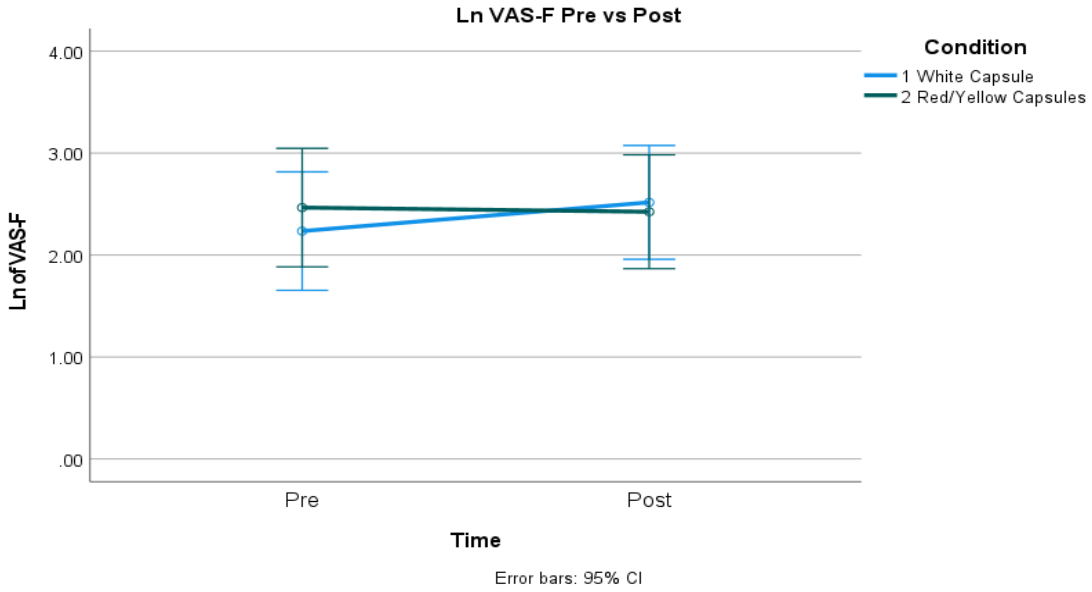

Figure 4a. Depicts the changes over time for the VAS-F between conditions.

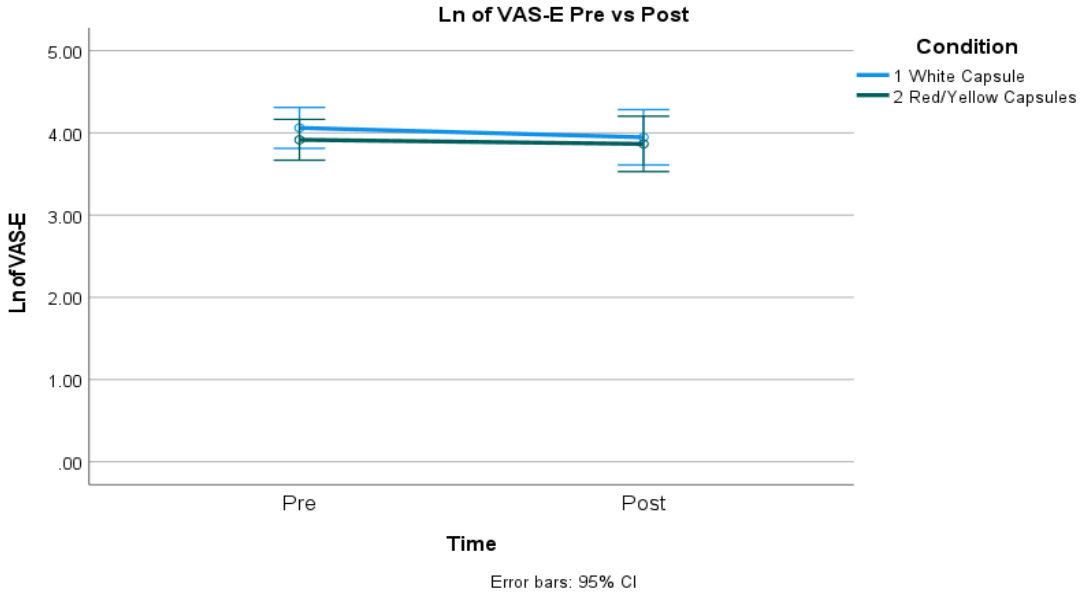

Figure 4b. Depicts the changes in VAS-E over time between conditions.

Table 2 represents the data from the VAS-S. Using a Greenhouse-Geisser correction, there was a statistically significant difference in how participants rated capsule perceived stimulatory strength through different images ($p < .001$). Based on Bonferroni-adjusted pairwise comparisons, participants found two red/yellow capsules to be more stimulatory than a single white capsule ($p < .001$), two white capsules to be more stimulatory than one white capsule ($p = .006$), two red/yellow capsules to be more stimulatory than two white capsules ($p = .007$), and one red/yellow capsule to be more stimulatory than one white capsule ($p = .026$). The difference between two white capsules and one red/yellow capsule was not significant ($p = .574$).

Table 2. Means and standard deviations of VAS-S test.

	Mean	Std. Deviation
1 White Capsule	26.6[a]	4.1
2 Red/Yellow Capsules	61.4[b]	4.6
2 White Capsules	38.3[c]	4.0
1 Red/Yellow Capsule	50.6[c]	5.0

Non-shared superscript letters indicate statistically significant differences with p-value < .05.

CHAPTER 5

DISCUSSION

The primary objective of the present study was to assess how altering physical characteristics of capsules such as color and quantity could impact maximal isometric strength and/or explosive lower extremity exercises. Secondary objectives of this study were to determine if altering the same capsule physical traits could impact either fatigue or energy levels as well as if different capsule characteristics impacted how participants perceived their stimulatory properties. The results from this study suggest that there was no impact on maximal exercise performance. However, the results do suggest that participants perceived red/yellow capsules to be more stimulatory than white capsules. In addition, two capsules were rated as more stimulatory than one capsule, regardless of color. These results further support current literature that color and quantity can both impact an individual's perception of stimulatory effects based on physical characteristics (Jacobs et al., 1979; Meissner & Linde, 2018; Rickels et al., 1969).

While there is some current literature on how placebos can impact physical performance, most of these studies used aerobic exercise along with suggestion (Beedie et al., 2006; Clark et al., 2000; Hulston & Jeukendrup, 2009). This study is unique because it relied solely on the physical characteristics of the capsules to attempt to induce a performance benefit for maximal exercise; the lack of literature solely focusing on the physical traits of capsules/pills/tablets and their effects on exercise make it difficult to compare the present results to other exercise-placebo studies.

While the results suggest that individuals perceived stimulatory differences between quantity and color of capsules, the greatest difference was between multiple red/yellow capsules

and a single white capsule. Therefore, this study suggests that while an individual's perception of stimulatory effects can be altered through the quantity and color of capsules, these changes could be due to preconceived notions about stimulatory effects and color because, as previously discussed, an individual's preconceived notion also plays a role in perception (Meissner & Linde, 2018). However, the lack of improvement in exercise performance could be due to the nature of the exercises being single maximal exercise and not a repeated anaerobic test such as exercise until failure. In general, effect sizes for time or reps until exhaustion tend to be larger than for 1-repeition maximum or single-bout maximal efforts (Astorino et al., 2007).

Other possibilities for the lack of improvements in the primary outcome variables could be due to the standardized verbal suggestion not being convincing/suggestive enough for the participants. Suggesting to participants that the supplement they could receive is a more potent supplement than an herbal blend might yield greater beliefs that the supplement could produce an ergogenic effect like the OxyRBX in an aforementioned study (Ross et al., 2015). However, this might be more difficult to have passed through the IRB if participants are informed they are receiving a more experimental and higher risk supplement as well as possibly being more difficult to reasonably convince the participants of the deception.

Limitations and Weaknesses

This study aimed for 40 participants to in order detect changes in performance, but only 28 individuals completed this study. While changes were found in the VAS-S, there were no significant differences in performances possibly due to a small sample size. This study also used exercises that could be quickly and easily retested but may have limited applicability to athletic performance in the real world. While vertical jump is commonly used on the field to assess

exercise performance, individuals are typically allowed to perform a counter movement without restraining their arms to being planted on the hips. The use of different physical performance tests could have allowed for a greater impact for external validity. This study could have been improved if the sample size was increased and if instead of two groups there were four groups (single white, two white, single red/yellow, and two red/yellow).

Conclusions

This study yielded no significant between-group or group x time effects for the following variables: VAS-F, VAS-E, vertical jump, hand grip strength, or heart rate. The study did find that individuals perceived the largest stimulatory difference to be between two red/yellow capsules and a single white capsule; therefore, the results suggest the perception of stimulatory effects can be impacted via altering the physical characteristics of the capsules. Future directions could increase groups and sample size or alter tested exercises. By including more than two groups, it would allow for a greater possibility of detecting differences between color, quantity, and the between-factor interaction. Future studies should use a combination of anaerobic and aerobic exercises across multiple sessions to allow for full recovery between exercise bouts and allow for the results to be applicable to more exercise performance variables.

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Appendices

Appendix A: Visual Analogue Scale for Stimulatory Effects (VAS-S)

Based on appearance alone, place a mark on each line to rate how stimulatory you feel each of the following treatments would be.

No stimulatory effect

Extremely stimulatory effect

No stimulatory effect

Extremely stimulatory effect

No stimulatory effect

Extremely stimulatory effect

No stimulatory effect

Extremely stimulatory effect

Appendix B: Debriefing Script

"Thanks again for participating in our study. Now that you have finished participating, I'd like to spend a few minutes talking about the study's goal and purpose. During the consent, you were told that the purpose of the study was to evaluate the effectiveness of an amino acid and herbal blend supplement on physical performance. However, the study had a slightly different goal from what you were told. This study was actually conducted to see how different physical characteristics of placebos, like pill color and number, can impact exercise performance. Although you were told that you had a 50-50 chance of receiving the placebo or real supplement, all participants actually received a placebo with nothing more than rice flour powder in it. In other words, there is no chance that you actually received any herbal ingredients or supplemental amino acids. We did this because we are attempting to determine if the color and number of capsules can induce an improvement in vertical jump and single-hand grip strength. Previous research has shown that certain colors are perceived as more stimulatory than others. In addition, some studies have found that people perceive taking multiple pills as being more effective than a single pill. However, little is known how pill color and number impact exercise performance specifically.

In order to best achieve our study's objectives, using a bit of deception was our best option. If we had told you that our goal was to study the effects of pill color and number, your conscious awareness of that could have affected your behavior or responses. We are wanting to understand whether pill color and number operate on a sub-conscious level.

After hearing all of this, do you understand why deception was used for this study? Do you have any questions about why we did this?”

VITA

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Master of Science, Exercise Science — Projected Graduation: August 2023
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CPR and AED certification**.** American Red Cross. October 2021