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ORIGINAL ARTICLE

No acute effects of placebo or open-label placebo treatments on strength, voluntary activation, and neuromuscular fatigue

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Abstract

Purpose Recent evidence suggests that deception may not be necessary for placebos to improve clinical outcomes. We tested the hypothesis that placebo and open-label placebo (OLP) treatments would acutely improve strength and voluntary activation, as well as minimize neuromuscular fatigue, in untrained participants.

Methods Twenty-one males ($n = 11$) and females ($n = 10$) visited the laboratory on three occasions (placebo, OLP, control) to receive each treatment in a randomized, counter-balanced manner. Trials involved a pretest, a 15-min intervention, and posttests. For the placebo trial, participants were informed that they would be ingesting a capsule that would improve their performance and make them feel more energetic. For the OLP intervention, participants were told that the capsules would have no effects. In "Experiment #1", knee extensor maximal voluntary contraction (MVC) peak torque and percent voluntary activation were evaluated. In "Experiment #2", participants performed 20 consecutive MVCs while surface electromyographic signals were detected from the vastus lateralis. Subjective assessments of energy and perceived exertion were examined.

Results The interventions had no effect on strength or voluntary activation, but energy levels increased following treatments ($p = 0.016$, $\eta^2 = 0.257$). Neither treatment influenced neuromuscular fatigue. Though some variables showed moderate-to-large effect sizes, these results were consistent for individuals with lower voluntary activation.

Conclusion Placebo and OLP treatments had minimal influence on strength, voluntary activation, and fatigue resistance. As these findings differ from recent reports, we speculate that placebos and OLPs are more likely to enhance muscle function in patient populations seeking medical care.

Keywords Open-label placebo · Placebo · EMG · Muscle activation

Abbreviations

ANOVA	Analysis of variance
OLP	Open-label placebo
MVC	Maximal voluntary isometric contraction
RMS	Root-mean-squared
ITT	Interpolated twitch technique
EET	Electrically evoked torque
EMG	Electromyographic

Introduction

Placebo effects have been defined as "…the response to a diverse set of environmental and psychological factors surrounding the administration of an active or inactive treatment" (Burke et al. 2018). In addition to consumption of an inert substance, placebo effects can be attributed to aspects of an entire therapeutic encounter, including environmental cues and interactions with medical professionals or scientists (Kaptchuk and Miller 2015). Placebos have a long history in clinical medicine (Jutte 2013), and some medical professionals have admitted to prescribing them to treat patients with debilitating chronic conditions (Fassler et al. 2010; Tilburt et al. 2008; Howick et al. 2013). While the mechanistic contributors to the placebo effect are multifaceted, neurotransmitter release in response to learning phenomena, such as expectancy and conditioning, likely play an important role (Finniss et al. 2010). Furthermore, as placebos are unlikely to cure disease, their utility may be in helping patients

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manage a variety of subjective symptoms (e.g., pain, fatigue, GI distress, etc.). This discrepancy lends itself to a variety of fascinating questions about disease and pain pathophysiology, as well as the patient experience.

Placebos have also been used to study the interaction between expectancy and physical performance in athletic settings. The initial two studies to examine the effects of perceived anabolic steroid use in strength athletes were particularly fascinating. In the early 1970s, Ariel and Saville (1972) examined the placebo effect in well-trained men by informing those that responded well to a pre-intervention training period that they had received anabolic steroids (Dianabol) during the subsequent phase of the study. For the six participants who believed they were using steroids, statistically significant increases in maximal strength for the bench press (9.6%), standing military press (8.5%), and squat (13.8%) exercises were reported, with a smaller effect for the seated press exercise (6.2%). These significant improvements were impressive given the study's small sample size and the advanced training level of the participants. Nearly 3 decades later, Maganaris et al. (2000) performed a similar study, but in addition to analyzing improvements in performance with perceived steroid use, the authors examined the potential decline in the participants' performance after learning that they were actually using a placebo. When the participants were told that they were receiving anabolic steroids, significant improvements in bench press, squat, and deadlift strength were found. However, when a group of participants were correctly informed that they were deceived, their performance returned to baseline. Improvements in performance have also been reported in studies that have examined the effects of placebo treatments during endurance events (Beedie and Foad 2009), with investigations reporting enhanced running time (McClung and Collins 2007) and cycling performance (Beedie et al. 2006). Collectively, while the magnitude of change has varied across studies, there is evidence to suggest that placebo effects are prominent in both strength-power and endurance athletes (Beedie and Foad 2009).

Surprisingly, there is evidence to suggest that deception may not be necessary for placebos to improve patient outcomes. Open-label placebos (OLP) are non-deceptive treatments where participants are informed that they are receiving an inactive substance. The use of OLP treatments have been studied in patients with cancer-related fatigue (Hoenemeyer et al. 2018), chronic lower back pain (Carvalho et al. 2016), irritable bowel syndrome (Kaptchuk et al. 2010), attention-deficit hyperactivity disorder (Sandler and Bodfish 2008), episodic acute migraine attacks (Kam-Hansen et al. 2014), allergic rhinitis (Schaefer et al. 2018), and major depressive disorder (Kelley et al. 2012). Although limitations to OLP study designs have been pointed out (Mestre and Ferreira 2017), patients in these trials have reported reduced pain (Kam-Hansen et al. 2014; Carvalho et al. 2016), disability (Carvalho et al. 2016), and symptom severity (Sandler and Bodfish 2008; Kaptchuk et al. 2010; Hoenemeyer et al. 2018) despite the knowledge that the intervention was inert. It should be noted that traditional placebo treatments may be considered an unethical practice due to the violation of a participant's autonomy and informed consent (Tilburt et al. 2008). A potential advantage of OLP treatments is that they minimize ethical concerns that may arise from deceiving participants and patients.

While the effects of placebo and OLP treatments have been studied for a variety of illnesses, diseases, and exercise-related outcomes, little data exist concerning their ability to influence physical performance measures. We are aware of no previous studies that have compared the effects of placebo and OLP on maximal strength, fatigue, and neuromuscular function. Therefore, the purpose of this study was to compare the effects of placebo versus OLP treatment on knee extensor muscle strength, voluntary activation, and fatigability. We hypothesized that both placebo and OLP treatments would result in enhanced muscle strength and voluntary activation, as well as a reduction in fatigue during isometric testing. Given the relationship between muscle strength and voluntary activation (Clark et al. 2014, 2015; Clark and Taylor 2011), as well as the fact that some individuals demonstrate high levels of voluntary activation (i.e., 100%) (Herda et al. 2011; Oki et al. 2017), we were particularly interested in determining if placebo and OLP treatments could be used to enhance performance in untrained participants that consistently lacked the ability to voluntarily activate their musculature despite maximal effort.

Methods

Study design

This study utilized a repeated measures design to compare placebo treatment, OLP treatment, and a control condition on muscle strength and fatigue resistance in young adults. For ease of comprehension, muscle strength and fatigue resistance analyses have been described as Experiments #1 and #2, respectively. The participants visited the laboratory on four separate occasions, with the first serving as a familiarization session. All visits were at the same time of day (± 1 h). The time between trial days was ≥ 48 h but < 1 week. Conditions in the laboratory were kept constant, including the personnel involved in data collection and analysis. The participants were asked to keep their physical activity levels, sleep, dietary habits, and caffeine consumption consistent throughout the study. Except for the intervention (placebo, OLP, and control) provided during the three trials, all aspects of data collection were identical. All testing involved

maximal voluntary and involuntary unilateral contractions of the knee extensors.

Participants

Twenty-one untrained participants (11 males: mean ± SD age = 23 ± 3 years, mass = 72.0 ± 13.1 kg, height = 1.73 ± 0.06 m; 10 females: age = 22 ± 3 years, mass = 62.2 ± 12.3 kg, height = 1.65 ± 0.07 m) participated in this study. Individuals were recruited via flyers posted throughout the university campus, social media advertisements, word-of-mouth, and announcements made in university classes. During the recruitment process, potential participants were told that the purpose of the study was to compare the effects of an OLP treatment to a well-researched, multi-ingredient dietary supplement known to acutely increase muscle strength and energy levels. Thus, participants were deceived about the placebo, but not the OLP treatment. Participants were informed that they would be compensated $50 for completing the study. For inclusion criteria, healthy males and females had to be between 18 and 35 years of age. Participants had a body mass index ≤ 30 kg/m^2, refrained from moderate-intensity lower-body exercise (average ≤ three times per month) within the previous 6 months, and refrained from dietary supplement consumption within the past year. Exclusion criteria included a history of myocardial infarction, metabolic or neuromuscular disease, hip or knee joint surgery, osteoarthritis of the knee or hip, musculoskeletal pain, or allergies to rubbing alcohol. In addition, individuals with flour, gluten, or wheat allergies were excluded, as were those that were unable to swallow pills. Prior to enrollment, potential participants completed pre-testing health questionnaire and Physical Activity Readiness Questionnaire forms. All participants were made aware of the study procedures prior to enrollment and signed informed consent documents. The University of Central Florida's Institutional Review Board approved of this study (ID # SBE-17-13539). The participants were informed that they were deceived about the placebo treatment at the conclusion of the study's data collection.

Assessment of isometric torque

Isometric torque testing of the dominant knee extensors (based on kicking preference) was performed with a Biodex System 4 isokinetic dynamometer (Biodex Medical Systems, Shirley, NY, USA). The chair was adjusted such that the participant's axis around the knee was aligned with the axis of rotation of the dynamometer. The participants were seated upright with both hip and knee angles set at 110°. Restraining straps were tightly fastened around the participant's hips, waist, chest, and non-dominant leg to limit extraneous movement of the limbs and torso. The tibia of the dominant leg was securely strapped to an Anti-Shear attachment (Biodex Medical Systems, Shirley, NY, USA), which was positioned over the tibialis anterior muscle just superior to the malleoli. Each participant's dynamometer settings were recorded during the familiarization visit to ensure consistency from trial-to-trial. The participants grasped the stabilization handles throughout testing. All testing was preceded by a submaximal warm-up which consisted of three, 10 s isometric contractions at 50% of the participant's perceived maximum torque level followed by 10 s of rest (i.e., 10 s "on," 10 s "off").

Interpolated twitch technique

Electrical stimulation of the quadriceps femoris muscles was used to quantify percent voluntary activation. The methodology used in the present study was similar to that described by Park et al. (2008). Two 7.5 cm × 10 cm PALS Neurostimulation adhesive surface electrodes (Axelgaard Manufacturing Co., LTD, Fallbrook, CA, USA) were placed on the quadriceps muscles, with one over the vastus medialis and one over the vastus lateralis. Specifically, the electrode locations were approximately one-third and two-thirds the distance from the greater trochanter to the base of the patella (Park et al. 2008; Pietrosimone et al. 2011). Permanent marker was used to outline the electrodes to guarantee consistent placement on following testing days. Once the electrode locations were determined, these areas were shaved with a disposable razor. Oil, debris, and dead skin cells were removed with hypo-allergenic tape and cleansed with rubbing alcohol. The electrodes were then placed on the skin and connected to an electrical impedance meter (D175 Electrode Impedance Meter, Digitimer Limited, Hertfordshire, UK) to ensure that impedance was ≤ 7 kΩ (Park et al. 2008). When impedance was > 7 kΩ, the electrodes were removed and further skin preparation was performed. The electrodes were then connected to a constant-current stimulator (DS7AH, Digitimer Limited, Hertfordshire, UK). Prior to voluntary contractions, a series of electrically stimulated isometric contractions of the knee extensors was used to determine the appropriate amount of electrical stimulation required to maximally activate the quadriceps muscles. Participants were asked to stay as relaxed as possible during this part of testing. Each stimulation consisted of a paired pulse stimulation, with two 200-μs pulses separated by 10 ms and began at a current of 160 mA. Successive stimulation intensities were progressively increased by 20 mA and delivered every 20 s. Peak stimulation intensity was determined when peak torque produced via electrical stimulation reached a plateau or displayed two consecutive decreases. The highest evoked electrical stimulation value at the beginning of the plateau or before the decline was used for testing. Electrical

stimulation intensity was determined prior to every testing session.

For contractions involving the interpolated twitch technique (ITT), the participants performed a 5-s isometric maximal voluntary contraction (MVC) of the knee extensors. The participants were provided visual feedback of their torque on a computer monitor, and strong verbal encouragement was provided. The participants were specifically instructed to "push hard and fast". During all contractions, an investigator carefully observed the torque–time curve. When the investigator noticed a clear plateau in torque, the quadriceps femoris muscles were stimulated with a paired pulse stimulation, and the increase in torque over the voluntary level was measured. The participants were instructed to relax upon feeling the stimulation during the MVC. At ~2 s and ~4 s following the MVC, the paired pulse stimulation was again delivered to the relaxed muscles to determine peak electrically evoked torque (EET), with the mean of the two values used during subsequent analyses. Percent voluntary activation was calculated as: $100\% \times [1 - (\text{ITT}/\text{EET})]$. To avoid submaximal effort caused by anticipation of electrical stimulation (Button and Behm 2008), during the pretest of Experiment #1, the participants performed five MVCs separated by 2 min of rest, but were told they may or may not receive stimulation. The ITT was implemented for three of the five MVCs, and the mean values were used for statistical analyses. The two MVCs without the ITT were discarded. Following the pretest of Experiment #1, all testing involved an MVC with ITT, and participants were told that electrical stimulation would be administered.

Muscle fatigue test

Upon the completion of the post-intervention muscle strength test, the muscle fatigue test of Experiment #2 began. This test required the participants to perform 20, 6 s MVCs. Three seconds of rest separated each MVC (i.e., 6 s "on," 3 s "off"). The participants were provided visual feedback of their performance on a computer monitor that was placed 1.5 m in front of them. Strong verbal encouragement was provided throughout the testing. At the conclusion of the muscle fatigue test, the participants performed a final MVC with a doublet pulse administered as described previously to examine the decline in voluntary and involuntary strength. Involuntary strength, which was also quantified as the mean from the three MVCs, was examined as a control variable for Experiments #1 and #2.

Surface EMG signal recording

Bipolar surface electromyography (EMG) signals were recorded from the vastus lateralis during the fatigue protocol of Experiment #2 with a Bagnoli 16-channel Desktop system (Delsys, Inc., Natick, MA, USA). Two sensors were placed over the muscle in close proximity to each other (one proximal, one distal) to minimize variability (Balshaw et al. 2017). For each dependent variable, the mean value from the two signals has been reported. The signals were detected with single differential Bagnoli™ Surface EMG Sensors (Delsys, Inc., Natick, MA, USA). For each sensor, pairwise subtraction of the two electrodes (interelectrode distance = 10 mm) was used to derive a single differential EMG channel. The signals were differentially amplified, filtered with a bandwidth of 20–450 Hz, and sampled at 2000 Hz. Prior to detecting EMG signals, the skin over the vastus lateralis and patella was shaved and cleansed with rubbing alcohol. Oil, debris, and dead skin cells were removed by repeated application and removal of hypo-allergenic tape. The sensors were secured to the vastus lateralis with tape. A reference electrode was placed over the patella. The EMG sensors were placed over the belly of the vastus lateralis at 2/3 the distance from the anterior superior iliac spine to the superior border of the patella, as recommended by the surface electromyography for non-invasive muscle project (Hermens et al. 2000). Surface EMG signal quality was assessed during the submaximal warm-up period to ensure low baseline noise and a signal-to-noise ratio ≥ 5.0.

Torque and EMG signal processing

The analog signal from the Biodex System 4 isokinetic dynamometer and the surface EMG signals were acquired with a Shielded Rack-Mount BNC Connector Block (BNC-2090A, National Instruments, Austin, TX, USA). BNC cables were then used to collect the raw torque and EMG signals with the Bagnoli 16-channel Desktop system (Delsys, Inc., Natick, MA, USA). The torque signal was sampled at 2000 Hz and processed off-line using custom LabVIEW software (version 8.5, National Instruments, Austin, TX, USA). The raw torque signals were scaled to units (Nm) and filtered using a zero-phase shift, second-order Butterworth filter with a 50 Hz low-pass cutoff frequency. To analyze peak torque during each MVC, the highest single data point was utilized. During each of the 20 MVCs during Experiment #2, vastus lateralis EMG amplitude was quantified as the root-mean-squared (RMS) value (Basmajian and De Luca 1985) for a 2-s interval that encompassed the peak torque value. For the mean frequency analyses, each selected signal was processed with a Hamming window and the Discrete Fourier Transform was used to generate the power spectrum. The highest peak torque, EMG amplitude, and EMG mean frequency values from the 20 MVCs were used to normalize all fatigue data such that all variables have been expressed as a percentage. In addition, neuromuscular efficiency was calculated by dividing the normalized peak torque generated by the knee extensors during the MVC

by the normalized vastus lateralis EMG amplitude value (Deschenes et al. 2009).

Participant assessment scales

Two scales were used to determine a participant's subjective energy level and perceived exertion at various points during the study. First, the participants were asked to rate their subjective level of energy with a scale ranging between 0 and 10, with 0 being equivalent to no energy and 10 equivalent to a maximal amount of energy. To determine a subject's perceived exertion, a category-ratio scale of 0–10 was implemented (Borg 1998), with 0 representing "nothing at all" and 10 representing "absolute maximum". The Subjective Assessment of Energy Scale was shown to the subjects before and 15 min after the administration of an intervention, and both scales were shown after the muscle fatigue test. Each participant was thoroughly familiarized with these scales during the initial visit to the laboratory.

Administration of intervention

On three separate days, participants consumed a placebo, an OLP, or engaged in a control condition. Both treatments contained flour, with the placebo and OLP capsules being red and blue, respectively. These colors were selected because red capsules have been associated with stimulant-like effects, whereas blue is related to a calming effect (de Craen et al. 1996). Both days required the participants to consume two capsules, and they were provided 591 ml of bottled water that they could consume ad libitum.

After completing the percent voluntary activation testing of Experiment #1, an immediate 15-min rest period began. At the beginning of the rest period, an oral script was delivered depending on the intervention of that day. For the control trial, participants were told there would be no administration of an intervention and to sit quietly for the duration of the 15 min. For the OLP trial, participants were told that they would be consuming capsules that had no active ingredients and should not feel any effects. They were told, however, that … "clinical studies have shown that OLP treatments enhance function and minimize pain". For the placebo trial, participants were told they were consuming a multi-ingredient dietary supplement that research had shown to effectively improve muscle strength and delay fatigue. Specifically, an investigator stated that "…9 out of 10 published studies within the last 10 years have conclusively proven that the ingredients in this capsule have enhanced muscle strength and/or delayed muscle fatigue. These ingredients act by inhibiting the reuptake of serotonin, norepinephrine, and dopamine. This results in heightened endorphin release and greater concentrations of neurotransmitters in the brain. Previous testing has shown that within 10–15 min people have felt more energetic and active. You should be able to feel similar physiological responses around this time". After the administration of an intervention, the participants remained seated on the dynamometer until the conclusion of the 15-min rest period. The laboratory remained quiet during the rest period. The primary investigator involved in data collection and analysis (A.P.S.) remained blinded to the intervention each participant received, and left the laboratory for this portion of testing. The same investigator provided the treatments and read the scripts to all participants (D.P.K). These two individuals did not discuss the order of treatments and statistical analyses were performed with the investigators blinded to trials and interventions.

Test–retest reliability

To determine test–retest reliability statistics for MVC peak torque, percent voluntary activation, and involuntary strength, we collected additional data on 17 untrained participants. Testing was performed on 2 days separated by 48 h at the same time of day (± 1 h). All variables were based on the mean value for three assessments. Analyses of interest were based on the recommendations of Weir (2005), and included the intraclass correlation coefficient (model 3.1 [ICC]), standard error of measurement (expressed as a percentage of the grand mean [SEM]), and the minimal difference needed to be considered real (MD). For peak torque, the results were as follows: ICC = 0.820; SEM = 6.1%; MD = 29.9 Nm. For voluntary activation, these results were: ICC = 0.741; SEM = 3.77%; MD = 9.94%. For involuntary strength, the results were: ICC = 0.926; SEM = 8.9%; MD = 9.7 Nm.

Statistical analyses

Mean differences in MVC peak torque, percent voluntary activation, involuntary strength, and subjective energy levels were evaluated with two-way (intervention [placebo, OLP, control] × time [pre-intervention, post-intervention]) repeated measures analyses of variance (ANOVAs). For the fatigue data, changes in each of the dependent variables across the MVCs were evaluated with two-way (intervention [placebo, OLP, control] × MVC # [#1, #2, #3, #4, #5, etc.]) repeated measures ANOVAs. When appropriate, follow-up procedures included repeated measures ANOVAs, paired samples *t* tests, and Bonferroni post hoc comparisons. The partial eta squared (η^2) statistic, which typifies the amount of variation attributable to a given factor when partialing out other factors from total nonerror variation, was used to evaluate the effect size for each ANOVA. Stevens (2007) characterized $\eta^2 = 0.01$ as corresponding to a small effect size, $\eta^2 = 0.06$ to a medium effect size, and $\eta^2 = 0.14$ to a large effect size. An alpha level of 0.05 was used to determine statistical significance for all procedures. SPSS software

(version 23.0, IBM Corporation, Armonk, NY, USA) was used for all statistical analyses. We created univariate scatterplots to display individual participant responses for MVC peak torque and % voluntary activation of Experiment #1 and the decline in peak torque of Experiment #2 (Weissgerber et al. 2015).

Results

Experiment #1

Peak torque

Figure 1 shows individual participant peak torque data. The results from the two-way repeated measures ANOVA indicated that there was no time × intervention interaction ($p = 0.566$, $\eta^2 = 0.027$) and no main effects for time ($p = 0.084$, $\eta^2 = 0.141$) or intervention ($p = 0.242$, $\eta^2 = 0.069$). As part of a secondary aim, an analysis of participants that consistently demonstrated voluntary activation less than 100% was performed ($n = 7$). For these participants, the mean ± SD peak torque values for the pretest and posttest, respectively, were as follows: (1) placebo = 166.8 ± 38.2 and 170.8 ± 35.4 Nm, (2) OLP = 169.8 ± 40.5 and 165.0 ± 47.7 Nm, (3) control = 157.5 ± 42.9 and 162.5 ± 42.5 Nm. There was no time × intervention interaction ($p = 0.264$, $\eta^2 = 0.201$) and no main effects for time ($p = 0.557$, $\eta^2 = 0.060$) or intervention ($p = 0.513$, $\eta^2 = 0.105$).

Percent voluntary activation

Figure 2 shows individual participant percent voluntary activation data. Many of the participants demonstrated 100% voluntary activation. The results from the two-way repeated measures ANOVA indicated that there was no time × intervention interaction ($p = 0.567$, $\eta^2 = 0.027$) and no main effects for time ($p = 0.095$, $\eta^2 = 0.133$) or intervention ($p = 0.351$, $\eta^2 = 0.050$). For the participants that demonstrated percent voluntary activation less than 100%, the mean ± SD percent voluntary activation values for the pretest and posttest, respectively, were as follows: (1) placebo = 87.9 ± 11.0 and 91.6 ± 8.7%, (2) OLP = 89.2 ± 5.6 and 86.9 ± 8.9%, (3) control = 83.7 ± 5.2 and 87.2 ± 9.6%. There was no time × intervention interaction ($p = 0.525$, $\eta^2 = 0.093$) and no main effects for time ($p = 0.379$, $\eta^2 = 0.144$) or intervention ($p = 0.063$, $\eta^2 = 0.463$).

Involuntary strength

The mean ± SD involuntary strength values for the pretest and posttest, respectively, were as follows: (1) placebo = 39.6 ± 13.5 and 34.5 ± 11.7 Nm, (2) OLP = 40.3 ± 13.5 and 35.8 ± 12.1 Nm, (3) control = 40.0 ± 13.8 and 35.0 ± 13.5 Nm. The results from the two-way repeated measures ANOVA indicated that there was no time × intervention interaction ($p = 0.717$, $\eta^2 = 0.017$) and no main effect for intervention ($p = 0.601$, $\eta^2 = 0.023$). There was, however, a main effect for time ($p < 0.001$, $\eta^2 = 0.721$), and the Bonferroni pairwise comparison indicated that the values at the posttest were significantly less

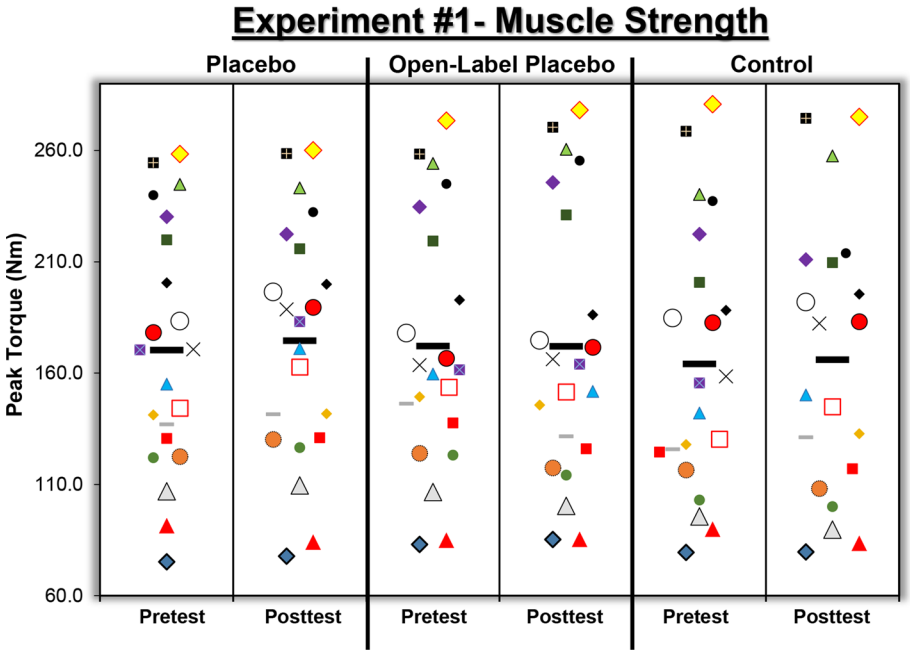

Fig. 1 Individual participant knee extensor maximal voluntary contraction peak torque data for the pretest and posttest for each of the three interventions. Each participant's symbol is displayed consistently across time points and interventions. The black bar corresponds to the mean value

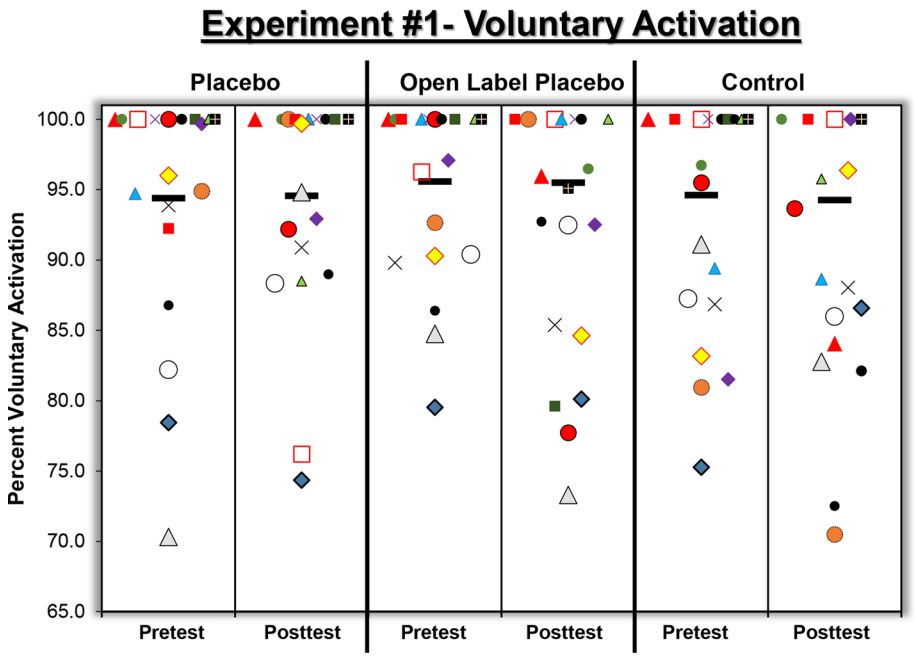

Fig. 2 Individual participant knee extensor percent voluntary activation data for the pretest and posttest for each of the three interventions. Each participant's symbol is displayed consistently across time points and interventions. The black bar corresponds to the mean value

than those during the pretest (marginal means = 40.0 and 35.1 Nm, respectively).

Subjective assessment of energy

The mean ± SD reported level of energy for the pretest and posttest, respectively, were as follows: (1) placebo = 5.5 ± 2.0 and 6.1 ± 2.1, (2) OLP = 5.6 ± 2.3 and 5.8 ± 2.3, and (3) control = 5.2 ± 2.0 and 5.5 ± 2.0. The results from the two-way repeated measures ANOVA indicated that there was no time × intervention interaction ($p = 0.234$, $\eta^2 = 0.070$) and no main effect for intervention ($p = 0.529$, $\eta^2 = 0.031$). There was, however, a main effect for time ($p = 0.016$, $\eta^2 = 0.257$), and the Bonferroni pairwise comparison indicated that the reported level of energy at the posttest was significantly greater than that during the pretest. As part of a secondary aim, an analysis of participants that consistently demonstrated voluntary activation less than 100% was performed ($n = 7$). For these participants, the mean ± SD values for the pretest and posttest, respectively, were as follows: (1) placebo = 4.9 ± 2.1 and 5.4 ± 2.1%, (2) OLP = 4.9 ± 2.1 and 5.1 ± 2.1, (3) control = 4.1 ± 2.0 and 4.5 ± 1.4. There was no time × intervention interaction ($p = 0.776$, $\eta^2 = 0.036$) and no main effects for time ($p = 0.235$, $\eta^2 = 0.225$) or intervention ($p = 0.471$, $\eta^2 = 0.109$).

Experiment #2

Peak torque following fatigue

The mean ± SD reported peak torque values following the fatiguing protocol for the pretest and posttest, respectively, were as follows: (1) placebo = 174.6 ± 54.0 and 135.7 ± 39.0, (2) OLP = 172.1 ± 61.9 and 137.7 ± 41.4, (3) control = 166.1 ± 60.7 and 130.5 ± 37.7. The results from the two-way repeated measures ANOVA indicated that there was no time × intervention interaction ($p = 0.643$, $\eta^2 = 0.019$) and no main effect for intervention ($p = 0.153$, $\eta^2 = 0.091$). There was, however, a main effect for time ($p = 0.001$, $\eta^2 = 0.687$), and the Bonferroni pairwise comparison indicated that peak torque at the posttest was significantly less than that during the pretest (marginal means = 170.9 and 134.7, respectively).

Percent voluntary activation following fatigue

The mean ± SD percent voluntary activation values following the fatiguing protocol for the pretest and posttest, respectively, were as follows: (1) placebo = 94.6 ± 7.8 and 88.1 ± 17.7%, (2) OLP = 92.7 ± 8.8 and 87.7 ± 13.7%, (3) control = 91.6 ± 9.3 and 87.3 ± 16.6%. The results from the two-way repeated measures ANOVA indicated that there was no time × intervention interaction ($p = 0.784$, $\eta^2 = 0.009$) and no main effects for time ($p = 0.199$, $\eta^2 = 0.117$) or intervention ($p = 0.749$, $\eta^2 = 0.014$).

Involuntary strength

The mean ± SD involuntary strength values following the fatiguing protocol for the pretest and posttest, respectively, were as follows: (1) placebo = 35.8 ± 12.1 and 23.4 ± 10.0 Nm, (2) OLP = 35.0 ± 13.5 and 24.1 ± 9.0 Nm, and (3) control = 34.5 ± 11.8 and 23.9 ± 9.4 Nm. The results from the two-way repeated measures ANOVA indicated that there was no time × intervention interaction ($p = 0.344$,

$\eta^2 = 0.051$) and no main effect for intervention ($p = 0.809$, $\eta^2 = 0.007$). There was, however, a main effect for time ($p = 0.001$, $\eta^2 = 0.432$), and the Bonferroni pairwise comparison indicated that the values at the posttest was significantly less than those during the pretest (marginal means = 35.1 and 23.8 Nm, respectively).

Decline in normalized peak torque

The results from the two-way repeated measures ANOVA indicated that there was no MVC # × intervention interaction ($p = 0.480$, $\eta^2 = 0.045$) and no main effect for intervention ($p = 0.206$, $\eta^2 = 0.076$). There was, however, a main effect for MVC # ($p = 0.001$, $\eta^2 = 0.765$), and the Bonferroni pairwise comparisons indicated that the decline in peak torque from MVC #1 became statistically significant at MVC #7. From MVC #1 to MVC #20, the mean percent decline in peak torque was 30.9% (Fig. 3).

Decline in normalized EMG mean frequency

The results from the two-way repeated measures ANOVA indicated that there was no MVC # × intervention interaction ($p = 0.548$, $\eta^2 = 0.045$) and no main effect for intervention ($p = 0.051$, $\eta^2 = 0.147$). There was, however, a main effect for MVC # ($p = 0.001$, $\eta^2 = 0.565$), and the Bonferroni pairwise comparisons indicated that the decline in EMG mean frequency from MVC #1 became statistically significant at MVC #6. From MVC #1 to MVC #20, the mean percent decline in EMG mean frequency was 21.1% (Fig. 4).

Decline in neuromuscular efficiency

The results from the two-way repeated measures ANOVA indicated that there was no MVC # × intervention interaction ($p = 0.272$, $\eta^2 = 0.064$) and no main effect for intervention ($p = 0.099$, $\eta^2 = 0.123$). There was, however, a main effect for MVC # ($p = 0.001$, $\eta^2 = 0.585$), and the Bonferroni pairwise comparisons indicated that the decline in neuromuscular efficiency from MVC #1 became statistically significant at MVC #5. From MVC #1 to MVC #20, the mean percent decline in neuromuscular efficiency was 38.4%.

Subjective assessment of energy

The mean ± SD reported level of energy for the pretest and posttest, respectively, were as follows: (1) placebo = 6.1 ± 2.1 and 4.5 ± 2.3, (2) OLP = 5.8 ± 2.3 and 3.8 ± 2.2, and (3) control = 5.5 ± 2.0 and 3.7 ± 2.2. The results from the two-way repeated measures ANOVA indicated that there was no time × intervention interaction ($p = 0.615$, $\eta^2 = 0.022$) and no main effect for intervention ($p = 0.090$, $\eta^2 = 0.144$). There was, however, a main effect for time ($p = 0.006$, $\eta^2 = 0.317$), and the Bonferroni pairwise comparison indicated that the reported level of energy at the pretest was significantly greater than that during the posttest.

Rating of perceived exertion

The mean ± SD rating of perceived exertion values after the fatiguing protocol were as follows: (1) placebo = 6.3 ± 2.2, (2) OLP = 6.5 ± 2.3, and (3) control = 6.5 ± 2.0. The repeated measures ANOVA was not statistically significant ($p = 0.788$, $\eta^2 = 0.010$).

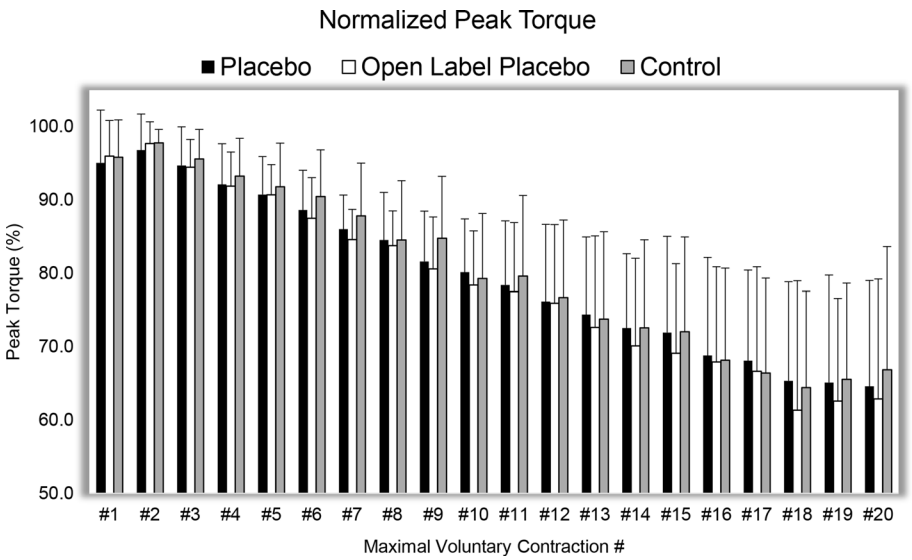

Fig. 3 Mean ± SD normalized peak torque values throughout the fatiguing protocol of Experiment #2. Statistical analyses revealed no differences among the interventions, but the decrease in normalized peak torque became statistically significant at maximal voluntary contraction #7

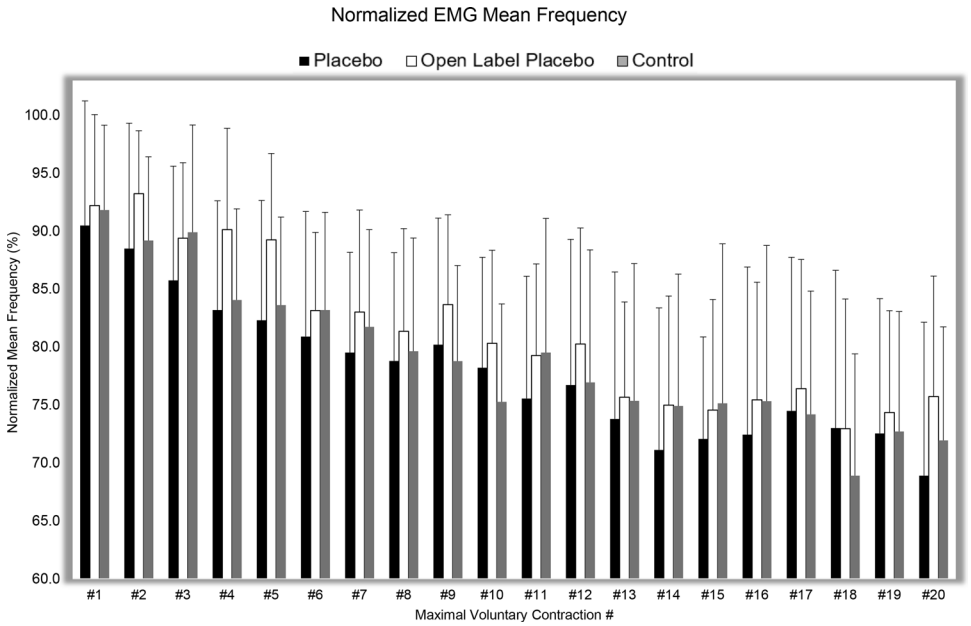

Fig. 4 Mean ± SD normalized electromyographic mean frequency for the vastus lateralis throughout the fatiguing protocol of Experiment #2. Statistical analyses revealed no differences among the interventions, but the decrease became statistically significant at maximal voluntary contraction #6

Discussion

Placebo and OLP treatments have shown promise in enhancing muscular performance in athletes (Ariel and Saville 1972; Maganaris et al. 2000; McClung and Collins 2007; Beedie and Foad 2009) and improving patient outcomes in clinical settings (Sandler and Bodfish 2008; Kaptchuk et al. 2010; Kelley et al. 2012; Carvalho et al. 2016; Hoenemeyer et al. 2018), respectively. We tested the hypothesis that, in untrained adults, placebo and OLP treatments would enhance muscle strength and minimize neuromuscular fatigue. Although a few of the observed effect sizes were moderate or large, the results of the present study largely indicated that these treatments had minimal influence on knee extensor peak torque and voluntary activation, as well as neuromuscular fatigue. While a larger sample size or a different participant population may have yielded significant effects, our findings were consistent in a subset of participants that consistently demonstrated the inability to voluntarily produce their knee extensor musculature's maximal torque-generating capacity. The high baseline knee extensor voluntary activation observed for Experiment #1 was unexpected and likely resulted in a ceiling effect.

In contrast to many previous studies that have examined OLPs (Sandler and Bodfish 2008; Kaptchuk et al. 2010; Carvalho et al. 2016; Schaefer et al. 2018; Hoenemeyer et al. 2018), the results of the present investigation do not support the notion that deception is not an essential component of placebo effects. It is important to reiterate that all these studies have been performed in patient populations, whereas the present study was carried out in healthy adults. The obvious difference between these types of studies is that patient populations with chronic conditions likely enter into a study hopeful that a given intervention will be helpful in relieving specific symptoms, whereas our participants were college-aged and unaccustomed to rigorous exercise but healthy, nonetheless. In addition to patients, our study's participant population differed from many other placebo interventions that have studied athletes (Maganaris et al. 2000; McClung and Collins 2007; Beedie and Foad 2009). It is not inconceivable to suspect that personality characteristics and motivation levels differ among well-trained athletes and the participants in the present study. It is important to reiterate that untrained participants were sought out in the present study because we suspected that those with the inability to voluntarily activate all of their motor units might particularly benefit from placebo and OLP treatments aimed at acutely augmenting strength and neuromuscular plasticity. Our findings revealed, however, that despite the participants' training status, percent voluntary activation was quite high, with only seven individuals showing incomplete activation. As our findings were consistent when considering all of the 21 participants and only those with incomplete voluntary activation, it is clear that placebo and OLP treatments had similar effects regardless of the participant's neuromuscular capacity to generate muscular torque.

Although we observed no time × intervention interactions, it is interesting to note that a main effect for time was observed for our subjective feeling of energy scale during Experiment #1. While intriguing, further analyses revealed that participants noted feeling slightly more energetic following both treatment interventions and the control period. In designing the study, we speculated that improved feelings of vigor would result in lower perceived exertion and

improved physical performance, which would have been supported by other studies (Pageaux and Lepers 2016). This was not the case, however, as we observed no significant increase in MVC peak torque or percent voluntary activation despite improved feelings of energy.

As has been recently noted (Kaptchuk and Miller 2015), the ability for placebos to exert an effect on a given outcome depend on an individual's perception to not just the substance, but the entire therapeutic encounter. To this end, there are a few factors that must be considered when evaluating the results of this study. First, rather than trying to deceive participants by informing them that a specific drug was being administered for the placebo trial (e.g., caffeine), we elected to tell them that they had been consuming a multi-ingredient supplement that previous research had deemed effective. Whereas the advantage of this approach was that it eliminated any biases that the participants may have had about a specific drug or substance, a disadvantage is that they may have found the lack of clarity about what was in the capsule to be ambiguous and even unmotivating. However, attempting to deceive the participants by telling them that the goal of the study was to investigate the effects of a specific substance or drug may have brought about other unintended consequences with respect to enrollment and perceptions about the study. Thus, when dealing with deception trials, investigators may need to carefully consider what participants are informed with respect to the ingredients in a capsule. Second, we suspect that not only were the words read by the investigator important, but so too was the style of delivery. To control for this, the investigator delivered the information about the treatments with a similar demeanor for all participants. It remains to be determined if stronger suggestive statements (e.g., "These capsules will make you feel incredible…") or if altering the level of enthusiasm would positively affect participants' perceptions about a placebo. Finally, we should contrast the advantages and disadvantages of our experimental approach. A repeated measures design offers several advantages, such as allowing each participant to serve as their own control and improved statistical power via reduced error variance. In contrast, when compared to randomized controlled trials, it does pose unique challenges for studies involving deception. In the present investigation, following the first trial, participants knew they had an equal chance or receiving the other two treatments. For the final trial, participants knew what treatment they had been receiving prior to data collection. Though our analyses demonstrated no trend with respect to improved or decreased physical performance over time, it is possible that a repeated measures approach may have influenced the participants' perception about the study treatments. An alternative approach may have been to use a between-participant design with a much greater sample size, but covary for the pretest data to account for differences among treatment groups at baseline. Placebo trials present investigators with a variety of unique challenges, and the results of this study are likely specific to an acute, repeated measures design.

Several methodological considerations and limitations are worthy of consideration. First, it should be noted that the results of this study are specific to isometric testing of the dominant knee extensors. In contrast, placebo studies in athletic populations tend to utilize whole-body assessments, such as cycling (Beedie et al. 2006) and resistance training exercises (Ariel and Saville 1972; Maganaris et al. 2000). It is unclear if other assessments, or single-joint testing of another muscle group (e.g., elbow flexors), would have brought about different results. Second, other than asking participants to keep their diets consistent throughout the study, we did not gather food diaries or carefully controlled for nutritional intake. Though we suspect that this limitation had a minimal influence on study outcomes, this cannot be stated with absolute certainty. Furthermore, though we studied both sexes and observed no noteworthy differences in responsiveness to the interventions between males and females, additional studies with larger samples are needed to fully determine if disparities exist between the sexes. As a final note, it is important to acknowledge that our test–retest reliability analysis showed only moderate consistency for percent voluntary activation. This is timely, as a recent review by Nuzzo et al. (2019) noted that while this variable often shows good reliability, varying results have been reported in the literature, with consistency differing among muscle groups and methodological approaches to quantifying involuntary strength. The combination of the relatively high MD value (9.94%) and the high voluntary activation at baseline (~ 94.0%) suggests that for many participants, the ability for placebo or OLP to exert a large effect on voluntary strength may have been unrealistic. Nonetheless, it is important to keep in mind that voluntary activation was quite variable even in those with lower voluntary activation at baseline. Consistent with the recommendations put forth by Nuzzo et al. (2019), we believe that methodological factors that have the potential to influence the interpretation of voluntary activation data (e.g., varying muscle groups, mode of stimulation, stimulation of nerve versus muscle, etc.) are worthy of further study.

In summary, the results of this study indicated that both placebo and OLP treatments generally had minimal acute effects on muscle strength, voluntary activation, and neuromuscular fatigue. Given the unique experimental design challenges that placebo and OLP trials present, we suspect that our findings may be context specific, and similar investigations performed in motivated, highly trained participants with a between-subjects design might yield different conclusions. Despite our results, we feel that both placebo and OLP treatments are worthy of additional scientific inquiry in other

populations, particularly given the intriguing findings that previous OLP investigations have reported in patient populations (Sandler and Bodfish 2008; Kaptchuk et al. 2010; Carvalho et al. 2016; Hoenemeyer et al. 2018). As the present study was the first to test these hypotheses, additional replication studies are needed to confirm these findings.

Author contributions AS, DF, JS, and MS conceived and designed the research. AS, RM, DK, and MS conducted the laboratory experiments. AS, RM, DK, and MS analyzed the data. AS and MS wrote the manuscript. All the authors read and approved of the final manuscript.

Compliance with ethical standards

Conflict of interest All investigators declared no conflicts of interest in the reporting of this research.

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