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Neural Activation in Blood-Flow-Restricted Versus Non-Blood-Flow-Restricted Exercise: An fMRI Study

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ABSTRACT

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Functional magnetic resonance imaging (fMRI) can be used to track neural activation in the brain during functional activities [1]. The purpose of this study was to investigate brain neural responses to blood flow restricted (BFR) versus control handgrip exercise. Using a randomized crossover design, 25 subjects (12 males, 13 females) completed handgrip exercises during two conditions: BFR vs. control. To familiarize participants with the exercise conditions, one week prior to MRI scanning participants completed each exercise condition once on separate days, with 72 hours between days. The following week fMRI scans were performed at the same time of day, separated by 72 hours. The exercise protocol consisted of five 30-second sets of squeezing a nonmetallic handgrip exerciser (a reported 13.6 kg resistance), doing as many repetitions as possible, with 20-second rest intervals between sets. We saw a significant main effect of exercise condition (BFR versus control) between premotor dorsal (PMd)($F = 5.71$, $p = 0.022$), premotor ventral (PMv)($F = 8.21$, $p = 0.007$), and right ventral striatum (VS_R)($F = 7.36$, $p = 0.01$). When considering anatomical regions of interest, we did not find significant differences between exercise conditions in bilateral S1 ($p > 0.82$), primary motor cortex (M1)($p > 0.33$), supplementary motor area (SMA)($p > 0.66$), cerebellum (CB)($p > 0.70$), insular cortex (INS)($p > 0.45$), anterior cingulate cortex (ACC)($p > 0.24$), or thalamus (TH)($p > 0.66$). Bilateral ACC (ACC_B), right middle frontal gyrus (MFG_R), and the right primary sensory cortex (S1_R) showed significant linear trends ($p = 0.001$) over the five exercise sets. Finally, the S1_R, left primary sensory cortex (S1_L), and the right anterior cingulate cortex (ACC_R) showed a main effect of set ($p < 0.02$). These data demonstrate that acute training with BFR during handgrip exercise results in different neural activation patterns in select areas of the brain, compared to a control. These results show that while completing less work with BFR exercise, subjects can achieve a similar amount of brain neural activation as with a higher-volume exercise. Brain neural activation is important to overall patient health and these findings may be important for prescribing training with BFR in clinical and applied research settings.

Keywords: fMRI, central nervous system, blood flow restriction, handgrip exercise, central fatigue

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Introduction

Developing and maintaining muscle mass is vital as muscle is the only tissue in the human body that produces force. Muscle tissue is subject to atrophy under sedentary or disuse conditions and to hypertrophy under specific training or increased activity conditions. There are few training practices that load a muscle minimally and still achieve hypertrophy. Generally, in order to cause hypertrophy, training practices require a high number of repetitions, which can be time consuming, monotonous, and mentally taxing. Blood flow restriction (BFR), in combination with exercise, is a training practice that requires a lower number of repetitions, with lower resistive loads, yet achieves greater hypertrophy than similar exercise without BFR [2, 3]. BFR exercise techniques limit arterial in-flow, and intermittently hinder venous out-flow from areas of the body [4], which causes a cascade of events that are not clearly understood [5]. Current research on BFR aims at understanding and quantifying its capacity to cause hypertrophy [6-11] or attenuate atrophy [12].

The brain is the command center of the body, and the central nervous system (CNS) affects responses in the periphery [13]. The brain adapts to demands placed on the body that are specific to activities being performed [14]. The integration of peripheral information and the brain's interpretation and acute adaptation to this information are important to understanding the benefits or potential risks associated with different training practices. The study of exercise techniques has primarily focused on peripheral adaptations to the modality, but, just as training builds muscle, the affect it has on the brain is also important.

Researchers have described areas of the brain important in central command [15] and central fatigue [16] separately, but not in combination with dynamic fatiguing contractions and BFR exercise. Central command is a term used to describe signals arising from the CNS that

activate the autonomic nervous system and skeletal muscle contraction simultaneously during exercise [15]. The CNS integrates information from peripheral sources related to exercise and limits the intensity and duration muscle recruitment to prevent damage to the tissue [17]. While fatigue is recognized in the exercising muscle with impaired contraction, the brain makes the decision to stop exercise [16]. When muscles can mechanically contract but are centrally inhibited, that is described as central fatigue [16]. Central fatigue has been implicated in BFR exercise [18]. Although researchers have been studying how the CNS regulates fatiguing muscles and how the fatiguing information affects the CNS activities [19], it is not known exactly how the two interact to modify exercise. As muscles fatigue, they lose the ability to produce force and require a stronger drive from the CNS [20]. With increased fatigue, an increased motor drive is needed to recruit more motor units if the motor output is to be maintained [20]. During fatiguing contractions motor performance is impaired, and such impairment is usually associated with increased perceived effort, as well as failure to produce the necessary force [21]. Inhibitory information from the fatigue-induced pain in muscles can suppress sensorimotor activity and lead to central fatigue [19]. Brain neural activation associated with BFR exercise has not been previously described.

Functional magnetic resonance imaging (fMRI) is an imaging technique used to visualize neuronal structures related to function with spatial and temporal sensitivity better than positron emission tomography [22, 23]. Blood-oxygenation-level-dependent (BOLD) contrast [24] in fMRI is a tool used to define activity in the brain based on hemoglobin oxygenation and deoxygenation characteristics [23, 24]. The brain is highly dynamic and responds to environmental inputs and activities [25]. Because of the nature of the exercise stimulus, we hypothesized that analyzing fMRI images during different exercise conditions would show

distinct neuronal activations. The purpose of this study was to use fMRI BOLD signal differences to compare BFR and control fatiguing handgrip exercise. We were interested in researching the neuronal activation of specific areas of the brain to help determine if using BFR alters activation.

We hypothesized that we would see increased activation in the primary sensory (S1), primary motor (M1), supplementary motor area (SMA), cerebellum (CB), insular cortex (INS), anterior cingulate cortex (ACC), and the thalamus (TH) under the BFR condition relative to the control exercise condition. We hypothesized that different patterns of oxygen consumption would give us a better understanding of how the brain responds to BFR exercise. Improved understanding would help us comprehend the utility of BFR exercise in rehabilitation and training. Achieving equivalent or additional brain neural activation with BFR exercise when patients cannot complete normal exercise may help improve patient quality of life. We acquired fMRI data during both exercise conditions: without BFR and with BFR. Our primary dependent variable was the BOLD signal (using fMRI), and our secondary dependent variables were exercising heart rate, between-set resting heart rate, peripheral oxygenation levels, and number of repetitions completed.

Materials and Methods

Participants

Twenty-five healthy subjects participated in the study (12 males, 13 females, age = 24 ± 4 years, weight = 70.8 ± 11.9 kg, height =1.7 ± 0.1 m, 24 right-handed, 1 left-handed)(Table 1). The fMRI data from four subjects were not included in the fMRI analysis, two due to neurological findings and two due to excessive head motion during data acquisition. Subjects had not been participating in resistance exercise of any kind during the two months prior to

recruitment. All participants were MRI compatible (i.e., no ferrous implants, pacemakers, etc.), did not have permanent upper retainers, and gave written informed consent prior to their participation. The Institutional Review Board of Brigham Young University approved this study.

Grip Strength Testing

Subjects had their dominant-hand grip strength tested using a Jamar (Jackson, MI, USA) hand dynamometer at the second handle position [26]. While standing erect with shoulders adducted and elbows extended, subjects squeezed the device for three seconds at maximal force [26]. Two attempts were made, and the greater of the two values was recorded. Handgrip strength measurements of the dominant hand were collected in order to quantify the percentage of their 1-repetition maximum that each participant was exerting with the 13.6 kg resistance force rings (Hand Grip Strengthener, Iron Crush, Brooklyn, NY, USA) utilized for exercising during the experiment.

Familiarization Week

Subjects were randomly assigned exercise condition order—conditions were arm bands inflated to the optimal individualized pressure (BFR) or no pressure (control). The exercise condition order applied to both the familiarization sessions and the fMRI scans. Upon arrival to the first appointment, all subjects had their resting supine blood pressure taken (Omron Healthcare, Inc., IL, USA). Subjects did their first exercise condition, and then returned to the lab 72 hours later to complete another familiarization exercise session with the exercise condition not yet completed. During both familiarization days, the session began with blood flow measurements to quantify occlusion pressures (Pulse Wave Doppler Ultrasound, GE Logiq P6, GE Healthcare, USA). If the exercise condition was control, the bands were promptly removed after the measurement was taken. During both familiarization exercise periods, researchers collected heart rate via an electrocardiogram (ECG, GE Logiq P6, GE Healthcare, USA) and

peripheral oxygenation via a pulse oximeter (Acc U Rate CMS 500D, USA). Peripheral oxygenation measurements were taken during the 20-second rest periods between exercise sets.

Occlusion Pressure

The magnitude of BFR was measured using ultrasound vascular imaging and integrated ECG. Subjects came into the lab and rested supine on the exam table for 10 minutes prior to data collection. The ultrasound probe (6-15 MHz multilinear probe) was placed on the skin, over the brachial artery. After finding a clear image of the brachial artery, we aligned the probe and placed the sample volume in the middle of the vessel. We then corrected the steer angle to be parallel with the flow and captured a cine clip with a single-gate pulsed Doppler waveform while simultaneously recording the 2D image. Blood velocities were averaged over five waveforms. We then reviewed the cine clip, which was synced with the ECG, and scrolled through to the same point on the QRS complex. From that 2D image frame, we measured the diameter of the vessel and implemented the automated calculation of blood volume flow (mL/min). We recorded the baseline measurement of blood volume, after which we placed BFR arm bands on the participant. According to previous research, we attached the 30 mm KAATSU arm bands (Sato Sports Plaza Ltd., Tokyo, Japan) with a fitting pressure of 25 mmHg [2]. We applied a baseline pressure of 120 mmHg and allowed it to stabilize for 1 minute, before taking another blood flow measurement using the ultrasound (according to the same protocol described previously). We used the blood volume from pre- and during-BFR to find the percentage of occlusion. If the occlusion pressure was not adequate, we applied additional pressure, allowed stabilization, and took another measurement. We occluded the artery between 60 and 80% to ensure that we had the proper pressure necessary to achieve BFR effects [27].

Exercise Protocol

The exercise protocol consisted of five 30-second sets of squeezing a 13.6 kg resistance ring, with 20-second rest intervals between sets. The BFR condition was performed with arm bands placed bilaterally on the upper arm approximately at the location of the deltoid insertion. These bands were attached to a KAATSU nano device (Sato Sports Plaza Ltd., Tokyo, Japan) that controlled cuff pressure. The correct occlusion pressure was applied and maintained (as found via ultrasound blood flow measurements during the familiarization week) during the BFR exercise condition day. During the familiarization week, exercise repetitions completed by the subject under each exercise condition were counted. Only full and complete contractions were considered in the repetition count. If complete contractions could not be achieved, subjects were instructed to continue to try and contract, contracting at the maximal force they could produce, and then relaxing and attempting the contraction again. We assumed that the number of completed contractions during the familiarization week were similar to those completed the week the MRI data were acquired.

Our experiment utilized a block design under two conditions. If BFR was the subject's exercise condition for their MRI day, the optimal pressure found during the familiarization week was applied to the arm bands before the subject entered the MRI scanner—if the subject was under the control exercise condition, they entered the magnet with arm bands applied loosely so that the researcher could easily place two fingers under the bands. Once inside the magnet, subjects viewed a monitor at their head through a mirror attached to the head coil. The monitor displayed instructions to the participant during the data collection period. When first placed in the magnet, the screen displayed instructions to remain as still as possible and to follow the instructions that would appear on the screen once the scan began. As the scan began, the text "Ready" was shown 5 seconds before the word "Squeeze" was displayed for 30 seconds. After

30 seconds of exercise, the text read "Rest" for 15 seconds before "Ready" appeared again on the screen for 5 seconds. The "Ready," "Squeeze," and "Rest" prompts were continued throughout the exercise scan period. On the second day of fMRI data collection the same procedures were followed with the other exercise condition. The fMRI data collection occurred on two separate days with 72 hours between sessions. The order of exercise conditions, BFR or control, was the same order as the familiarization week.

fMRI Data Acquisition

MRI data were collected at the MRI Research Facility at Brigham Young University, using a Siemens TIM-Trio 3.0T MRI scanner (Siemens, Erlangen, Germany). The subject was positioned supine head first in the magnet. The subject's head was placed within a standard 12-channel receive-only head coil. To minimize as much motion as possible, foam pieces were placed on both sides of the head. Subjects wore headphones to minimize noise during fMRI data acquisition and to communicate with researchers outside the magnet, if needed. Functional MRI data were acquired following a localizer scan. The functional scan acquired 39 slices in the transverse plane using gradient-echo, echo-planar T2*-weighted pulse sequences with the following parameters: TE = 28ms; TR = 2500ms for 116 repetitions; slice thickness = 3mm, 0mm gap; field of view = 19.2 × 19.2cm; matrix = 64 × 64; flip angle 90°; voxel size = 3 × 3 × 3mm. Slices were obtained using an ascending interleaved acquisition approach, oriented with the genu and splenium of the corpus callosum. After completion of the functional scan, subjects were partially removed from the MRI scanner and the BFR bands were removed. Subjects were then repositioned and another localizer scan was obtained. Lastly, we acquired a T1-weighted magnetization-prepared rapid acquisition with gradient echo (MP-RAGE) structural scan (TE = 2.26ms, TR = 1900ms, 256 × 215 matrix, field of view = 25 × 21cm, slice thickness 1mm, 0mm gap, 176 slices, 1 average).

Data Analysis

Functional MRI data were processed and analyzed using the Analysis of Functional NeuroImages (AFNI) suite of software [28]. The first five repetition times (TRs) collected during the functional runs were discarded to allow for the magnetic resonance signal to reach steady state. Functional data were co-registered with structural data, underwent slice time correction and were corrected for motion both within- and across-runs. TRs with large motion events, described as > 0.3° of rotation or 0.6 mm of translation in any direction, were excluded from the regression analysis [29]. The TRs immediately before and after the motion event were also omitted from the analysis. Single subject regression results were spatially filtered using a 5mm Gaussian kernel. All structural and functional scans were then aligned to a custom template in Talairach space [30] using Advanced Normalization Tools software (ANTs; Version 1.9; http://sourceforge.net/projects/advants/)[31].

Using AFNI 3dDeconvolve, a regression analysis was completed on the functional data sets. Conditions of no interest included regressors coding for motion. Five additional regressors coding for exercise sets 1-5 were included in the model. Blocks were modeled by convolving the standard hemodynamic response function with a 30-second boxcar function. We defined baseline as the average of all the rest periods between exercise sets. The conditions of interest were: BFR sets 1-5 and control sets 1-5.

We first performed a group-level voxel-wise analysis. Functional data were analyzed using an ANOVA with participants as the random measure and trial type (BFR or control) and sets (1-5) as the within-subject measure. To correct for multiple comparisons, the results of the main effect of exercise condition and the test for linear trends were thresholded with a voxel-wise p-value of $p < 0.02$ and a spatial extent threshold of 40 contiguous voxels. These parameters were determined by conducting a Monte Carlo simulation to produce an overall p-value of $p <$

0.05. For our test of the main effect of set, we used a more stringent p-value of $p < 0.001$ with a spatial extent threshold of 40 contiguous voxels in order to separate active areas. Average beta coefficients were obtained from within the areas of activation and a multivariate modeling approach [32] was taken using SPSS (IBM Corp. IBM SPSS Statistics for Windows, version 23.0. Armonk, NY: IBM Corp).

For analysis of all secondary dependent variables, we used SAS statistical software (version 9.4, SAS Institute, Inc., Cary, NC). A mixed model analysis of variance was used to test for similarity between subjects in weight, sex, repetitions per set, total volume of repetitions, peripheral oxygenation, between-set resting heart rate and exercise heart rate. A stepwise comparison was then conducted to determine if any interactions existed. After the stepwise analysis, the variables indicated as significant to the statistical model were sex, condition, repetitions per set, sex*repetition interaction, and sex*weight interaction and were used as covariates. The dependent variable in the analyses was the total volume of repetitions; we used the Tukey-Kramer adjustment for multiple comparisons.

Results

fMRI

From the group analysis, we found significantly activated clusters in the brain that demonstrated main effects of exercise condition, linear trends, and main effects of set. The regions of interest (ROI) for significant areas of activation with their associated contrast, cluster volume (expressed in μL), peak RAI coordinates, and F-statistics are presented in Table 2.

Main Effect of Exercise Condition

In an anatomical ROI analysis, we did not find significant differences between conditions in bilateral primary sensory cortex (S1)($p > 0.82$), primary motor cortex (M1)($p > 0.33$),

supplementary motor area (SMA)($p > 0.66$), cerebellum (CB)($p > 0.70$), insular cortex (INS)($p > 0.45$), anterior cingulate cortex (ACC)($p > 0.24$), or thalamus (TH)($p > 0.66$). However, we saw significant differences between BFR and control in the premotor dorsal (PMd)($F_{(4,37)} = 5.71$, $p = 0.022$), premotor ventral (PMv)($F_{(4,37)} = 8.21$, $p = 0.007$), and right ventral striatum (VS_R)($F_{(4,37)} = 7.36$, $p = 0.01$)—all demonstrating a decreased activation under the BFR condition (Figure 1).

Linear Trends

Bilateral ACC (ACC_B), right middle frontal gyrus (MFG_R), and the right primary sensory cortex (S1_R) showed significant linear trends (Figure 2). ACC_B exhibited a negative linear trend ($F_{(4,37)} = 12.50$, $p < 0.001$). The linear trend of the MFG_R ($F_{(4,37)} = 13.58$, $p < 0.001$) was also negative. The S1_R had a positive linear trend ($F_{(4,37)} = 12.18$, $p < 0.001$). Both the S1_R and ACC_B appeared to overlap with the activation pattern from the main effect of set. There were no regions with a significant linear interaction between set and exercise condition.

Main Effect of Set

For our main effect of set, we saw significantly different activation patterns in the S1_R ($F_{(4,37)} = 4.00$, $p < 0.001$), left primary sensory cortex (S1_L)($F_{(4,37)} = 3.94$, $p < 0.001$), and right anterior cingulate (ACC_R)($F_{(4,37)} = 3.60$, $p < 0.001$) between the first and last sets. In a pairwise comparison between sets, we found significant differences in the S1_R between sets 3 and 5 ($p = 0.002$), as well as 4 and 5 ($p = 0.02$) (Figure 3). The S1_L also showed differences between sets 3 and 5 ($p = 0.004$) and 4 and 5 ($p = 0.016$) (Figure 4), and the ACC_R showed differences between 1 and 5 ($p = 0.017$) and 2 and 5 ($p = 0.007$) (Figure 5).

Secondary Dependent Variables

Peripheral oxygenation percentage, exercising heart rate, between-set resting heart rate, and numbers of repetitions completed in each set are recorded and organized in Table 3. There was a significantly greater total volume of repetitions completed in the control compared to BFR (146 and 134, respectively) ($p < 0.0001$). There were significant decreases in the number of repetitions completed in sets 1-3 and between sets 3 and 5 as subjects began to fatigue ($p < 0.0001$), as shown in Figure 6. Males had a higher grip strength ($p < 0.0001$). When comparing relative volume of work between males and females, the mean volumes were not different ($p = 0.786$). Heart rate measurements and peripheral oxygenation values were compared between BFR and control. There were not significant differences in exercising heart rate ($p = 0.4084$), between-set resting heart rate ($p = 0.1453$), or peripheral oxygenation ($p = 0.2769$) between exercise conditions.

Discussion

fMRI

We saw the same amount of primary motor cortex (M1) activity during the BFR exercise condition, as compared to the control, even though a lower total volume of repetitions was completed. There is a supposition that BFR exercise "tricks the brain" [33]. While that might not be true for all areas of the brain, we saw that significantly less work during BFR exercise resulted in similar activation patterns in the M1 as in the control condition. During handgrip exercise under BFR, a greater number of fast twitch muscle fibers are recruited [11]. Fast twitch muscle fibers are associated with a high threshold of activation [34]. The similar activation patterns in the M1 might be explained by an increased activation of fast twitch muscle fibers as slow twitch fibers fatigue more quickly during ischemic exercise [11].

Some researchers hypothesized that in sustained and intermittent handgrip exercise an early increase in the sensorimotor cortex followed by a decrease at later stages of the contraction were due to the inhibitory influence of group III/IV afferents [35]. Muscle power output is connected to afferent feedback from exercising muscles [13]. Group III/IV neurons facilitate central fatigue by utilizing inhibitory influences on central motor drive during exercise [36]. Hilty et al. hypothesized that the termination of exercise during fatigue might not be mechanical failure in the muscle, but rather a biological decision to protect the body [37]. Our hypothesis was that we would see increases in the M1, S1, SMA, CB, INS, and TH during the BFR condition because BFR can cause muscle growth under such low loads of exercise. We did not consider the role of central fatigue and how manipulating blood flow could interact with that. Under normal conditions, when the body is in an increased fatigued state, it should go into protection mode [38], but we did not see this protection response by the CNS during the BFR exercise.

During fatiguing contractions, group III/IV afferents send signals to the brain about their local environment, and the central motor drive from the brain adjusts accordingly [36]. By maintaining the central projection of group III/IV afferents through post-exercise ischemia, Gandevia et al. found that the central motor drive and voluntary muscle activation was low and did not recover until circulation was restored [39]. The fatigue associated with BFR should in theory cause greater sensory feedback that inhibits motor drive and levels of muscle activity [40]. However, our results do not show greater sensory feedback or inhibited motor drive. Fatigue in a muscle can be driven peripherally or centrally, and both work in an integrated fashion to produce movements and contractions [41]. BFR has been associated with a decreased ability to centrally activate muscles following exercise, represented as a decreased percentage of

voluntary activation [18]. Significant decreases in percentage of voluntary activation might indicate an inhibition of central drive in the force generation capacity post-exercise with BFR [18]. However, our study measured changes during exercise. We noted the central motor drive was similar in both conditions, although peripherally the muscles exhibited decreased power output during BFR exercise. When blood flow is restricted to an area, the muscle remains fatigued [39]. It appears the brain did not perceive that there was increased peripheral fatigue during BFR exercise, as shown in the maintained output of the motor cortex despite a decreased volume of muscle contractions in later exercise sets. The results, demonstrating no differences in the M1, S1, SMA, CB, INS, and TH between exercise conditions, could support the idea that during BFR exercise, increased central fatigue might not be causing the cessation of muscle contractions. While we did not see differences in many areas of the brain between exercise conditions, we did see differences in the ventral striatum (VS), premotor ventral (PMv) and premotor dorsal (PMd) areas.

Lutz et al. looked at fMRI brain activations during a handgrip task and found that activations in the VS were greater following good versus bad handgrip performances [42]. They proposed that striatal activity reflected the inherently rewarding effects of performing well [42]. Aron et al. also showed that cognitive feedback could lead to similar activation as extrinsic reward stimuli in the VS [43]. Our results showing that VS activation was higher under the control condition may be due to the fact that subjects cognitively perceived their exercise performance being better, as compared to the BFR condition where subjects had a harder time completing repetitions.

Both the PMv and PMd regions are anterior to the motor cortex regions that are activated by both BFR and control conditions. The PMv area is important during precision grasping,

requiring appropriate intrinsic hand muscle activation, and for hand position during motion [44]. PMv inactivation has been shown to modify agonist-antagonist muscle recruitment in forearm movements [45]. Associated with the actions of the PMv, a lesion to the PMd region results in less synchronized grasping and less coordinated proximal muscle recruitment [44]. Our handgrip exercise required the activation of both intrinsic hand muscles and forearm muscles. We saw decreased activation in PMv and PMd areas during BFR. The BFR condition was more difficult and fatiguing, as subjectively observed and reported by participants and shown in the decreased amount of total repetitions completed. As fatigue ensued and pain progressed during BFR, subjects increasingly struggled to complete the handgrip exercise. That lack of precision and muscle activation in the hands and forearms in later BFR exercise sets could explain why we see decreased activation in the PMv and PMd regions.

We saw linear trends in the S1_R, ACC_R and MFG_R. A study by Liu et al. also showed a positive linear increase in the S1 throughout a dynamic handgrip exercise [19]. Although increased ACC activity has been found to be associated with pain processing and increased perceived exertion [46, 15], a study by Sander et al. tracked linear treads of the ACC with handgrip exercises and post-exercise ischemia, and found a decreased linear trend [47], as seen also in our study. Previous research has indicated that decreased activity in the ACC is associated with negative affect both in muscle pain and emotions [47]. The MFG_R, which is part of the prefrontal cortex, is modulated by the ACC and is thought to be directly related to ACC activity [48].

We also found significant linear and main effect of set trends near the occipital lobe. We hypothesize that the difference in occipital lobe activation is due to artifacts from draining dural sinuses. The peak of activation was located between cerebral hemispheres, which does not

contain oxygen-consuming tissue. Because we are changing blood flow during exercise, there could be changes in hemoglobin characteristics. Hyperemia in the brain occurs as a result of neurotransmitter action. As large areas of nervous tissue become active during exercise, it could result in more oxyhemoglobin in the venous system and thus a larger BOLD signal as sets of exercise progress. Another possible explanation proposed by Benwell et al. is that subjects give more attention to visual cues to begin and end exercise as fatigue develops and the task becomes more demanding [49]. While our exercises were fatiguing and we utilized visual cues to prompt tasks during the fMRI, we are not confident in the attention-based explanation for occipital lobe activation considering the peak BOLD signal primarily appears between cerebral hemispheres.

Secondary Dependent Variables

Fatigue is the acute diminishing of performance that includes both an increased perceived effort to produce a desired force, and the eventual inability to produce that force and power output [21]. The first signs that fatigue is forthcoming is an increased perception of exertion at the same exact workload [21]. We used a protocol that would give each participant an allotted amount of time to complete as many repetitions as possible in order to track fatigue progression in each condition. Previous studies showed that BFR conditions elicited fatigue more quickly [50, 3]. Because we used both males and females in the study, we decided that having each participant complete as many repetitions as possible would elicit fatigue in everyone. We assumed all subjects would fatigue to the same degree because their power outputs would change as the sets progressed. We saw the effects of fatigue in the total volume of repetitions subjects were able to complete in each exercise condition—BFR resulting in a lower total volume.

The heart rate measurements under BFR and control conditions were not statistically different, nor were peripheral oxygenation values. Previous studies have shown that reducing

blood flow to working muscles during exercise causes the accumulation of metabolites and an increase in sympathetic nerve activity resulting in an increased heart rate [51, 52]. We did not see those changes. This may be due to the small muscle group utilized (the finger flexors). With a muscle group that requires a larger metabolic demand, BFR may have had a larger sympathetic effect. Further studies should be undertaken using different exercise protocols and larger muscle groups that are reflective of a more complete upper extremity exercise with BFR. One of the reasons that we did not use a larger muscle group exercise was that during pilot work using modified biceps-curls, subjects exhibited too much head motion in the MRI scanner. Although minor motion can be filtered out, large motion events during the fMRI data acquisition give inaccurate results [1].

Limitations

We did not count repetitions during fMRI data acquisition because of restrictions with the scanner environment and noise, it was not possible to have subjects count and report their repetitions in each set during fMRI data acquisition. Subjects also could not perceive accurately if they were fully contracting during the later stages of fatigue, so we could not rely on their self-reporting of repetitions. This is likely not a problem because there were seven days between the familiarization week and fMRI data acquisition, which is not sufficient time to see muscle adaptations [53].

A characteristic of the research design is that we had to use a blocked design in the analysis of our fMRI data. This design requires a baseline throughout the exercise protocol. Exercise is progressive, so there is no real baseline for the entire protocol aside from the initial rest period just prior to the commencement of exercise. Previous studies involving fatiguing handgrip exercise have utilized entire blocks of data as one and did not account for possible

scanner drift [47, 49, 54]. We did not think this was wise considering we likely could have changes in signal that were not due to the actual changes in hemodynamics. During pilot analysis of the rest periods in our fMRI data, we noted that the signal changes had no clear pattern and were fairly random, so we collapsed the rest period data over all the rest sets and called the average signal over the rest periods the baseline for our analysis model.

Conclusion

This study sheds light on how BFR exercise affects the brain. We investigated brain neural activity during two exercise conditions. Acute handgrip exercise with BFR resulted in decreased neural activation patterns in the VS, PMd, and PMv areas, compared to control exercise (Figure 1). These areas are involved in performance reward and coordination and activation of hand and forearm muscles. We found that there were no significant differences in the M1, S1, SMA, CB, INS, ACC, and TH activations between the exercise conditions, suggesting that while doing less work, BFR exercise is able to produce similar activation patterns in those areas. We saw linear trends in the S1_R, MFG_R, and ACC_B, which were consistent with previous research [19, 47, 48]. We also found significant main effects of set in the S1_R, S1_L, and ACC_R. Our results indicate that BFR exercise can illicit similar patterns of brain activation with a lower volume of exercise than normal exercise can at a higher volume, which may improve overall patient health and be important for prescribing training with BFR in clinical and applied research settings. Exercising with BFR may delay the normal response of central fatigue. We saw similar brain neural activation patterns in specific areas of the brain in both exercise conditions, although BFR exercise brought about more peripheral fatigue.

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Table 1. Participant descriptive variables

	Males n = 13	**Females n = 12**
Age (years)	25.2 (1.7)	22.8 (1.4)*
Height (m)	1.8 (0.1)	1.7 (0.1)*
Body mass (kg)	79.3 (8.1)	61.5 (7.7)*
SBP	127.3 (9.8)	105.8 (7.4)*
DBP	75.4 (10.5)	71.4 (4.9)
Max grip strength (kg)	46.6 (18.8)	26.7 (10.0)*
Relative volume of exercise†	52.8 (13.3)	53.8 (12.1)
Occlusive pressure	190.8 (39.4)	175.8 (40.1)
% Occlusion	74.2 (5.1)	75.6 (3.7)

Data presented as mean (SD).
SBP, systolic blood pressure; DBP, diastolic blood pressure.
*$p < 0.05$ from mean of males
†Relative volume of exercise was calculated by dividing ring resistance by the 1-repetition max value, and multiplying that number by the number of repetitions completed

Table 2. The regions of interest (ROI) for significant areas of activation in peak RAI coordinates, F-statistics, associated contrasts, and volume of each cluster identified at the group level.

Contrast	Region	Cluster volume (μL)	X	Y	Z	F
Main effect of exercise condition	PMd	102	-43.5	+1.5	+38.5	5.71*
	VS_R	83	-13.4	-13.5	-9.5	7.36*
	PMv	50	-43.5	-1.5	+26.5	8.21*
Linear trend	ACC_B	254	-1.5	-28.5	+5.5	12.50**
	MFG_R	141	-37.5	-49.5	-3.5	13.58**
	S1_R	44	-34.5	+37.5	+56.4	12.18**
Main effect of set	S1_R	301	-37.5	+22.5	+44.5	4.00**
	S1_L	167	+37.5	+25.5	+47.5	3.94**
	ACC_R	56	-1.5	-28.5	+8.5	3.60**

(*$p < 0.02$; **$p < 0.001$) Main effect of exercise condition showed increased activation in the premotor dorsal (PMd), the right ventral striatum (VS_R), and the premotor ventral (PMv) areas for the control exercise condition. Linear trends showed an increase in right primary sensory cortex (S1_R), but a decrease in bilateral anterior cingulate cortex (ACC_B), and right middle frontal gyrus (MFG_R). Main effect of set showed increased S1, and decreased right anterior cingulate cortex (ACC_R), when comparing set one to set five.

Table 3. Secondary dependent variables

	Set	Males		Females	
		Control	BFR	Control	BFR
Peripheral oxygenation (%)	1	96.9 (2.3)	97.0 (1.4)	97.7 (1.2)	97.2 (2.3)
	2	96.2 (3.5)	97.5 (1.5)	97.9 (2.0)	96.5 (3.8)
	3	96.6 (1.9)	97.0 (1.4)	98.3 (0.7)	97.0 (2.4)
	4	97.9 (1.0)	96.5 (2.8)	98.3 (0.9)	97.2 (2.4)
	5	97.2 (1.8)	97.1 (1.1)	97.8 (0.9)	96.9 (2.4)
Exercising HR (bpm)	1	99.3 (10.1)	101.1 (12.1)	94.9 (13.2)	98.8 (11.3)
	2	96.2 (11.5)	96.5 (15.6)	96.5 (7.6)	94.4 (10.2)
	3	101.2 (15.8)	94.6 (12.3)	93.6 (13.2)	95.2 (11.2)
	4	103.9 (24.7)	100.2 (13.8)	95.9 (14.5)	93.5 (9.2)
	5	107.6 (23.2)	99.5 (15.6)	94.6 (14.5)	94.5 (12.8)
Between set resting HR (bpm)	1	74.7 (7.9)	74.9 (10.0)	68.3 (7.5)	73.9 (8.8)
	2	71.3 (7.4)	71.1 (11.8)	67.0 (7.2)	72.6 (7.3)
	3	72.1 (7.7)	71.9 (11.3)	67.9 (6.0)	73.4 (13.0)
	4	73.0 (8.4)	72.3 (11.8)	67.8 (9.3)	71.5 (8.6)
	5	73.5 (13.2)	70.9 (13.6)	66.4 (8.5)	68.6 (8.1)
Repetitions	1	60.5 (7.2)	57.1 (14.5)	35.9 (9.0)*	36.5 (8.9)*
	2	43.2 (8.4)	39.9 (9.6)	25.3 (7.2)*	23.0 (7.0)*
	3	29.3 (5.6)	27.8 (3.7)	18.4 (5.3)*	14.0 (5.1)*
	4	24.1 (5.2)	21.5 (5.3)	15.3 (6.0)	12.9 (7.1)
	5	23.8 (6.2)	20.0 (5.2)	13.3 (4.7)	12.3 (7.2)

Data presented as mean (SD); bpm, beats per minute; HR, heart rate; *$p < 0.05$ from mean of males within the same set.

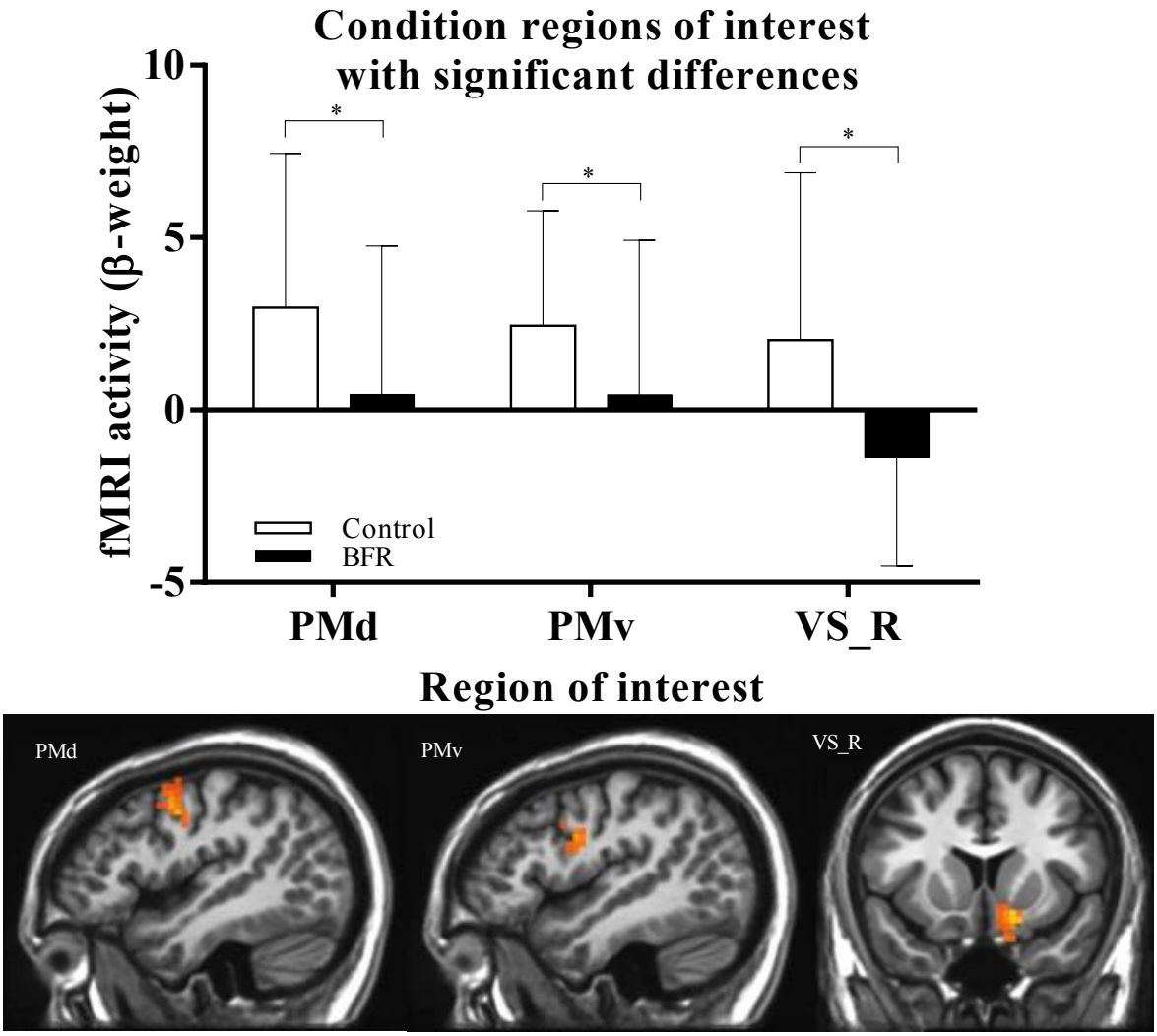

Figure 1. Region of interest (ROI) average beta coefficients and standard deviations for both control and BFR conditions. When comparing the exercse conditions there was a significant difference between control and BFR in the premotor dorsal (PMd) area, the premotor ventral (PMv) area, and the right ventral striatum (VS_R).Asterisks indiate a significant ($p < 0.02$) difference between conditions.

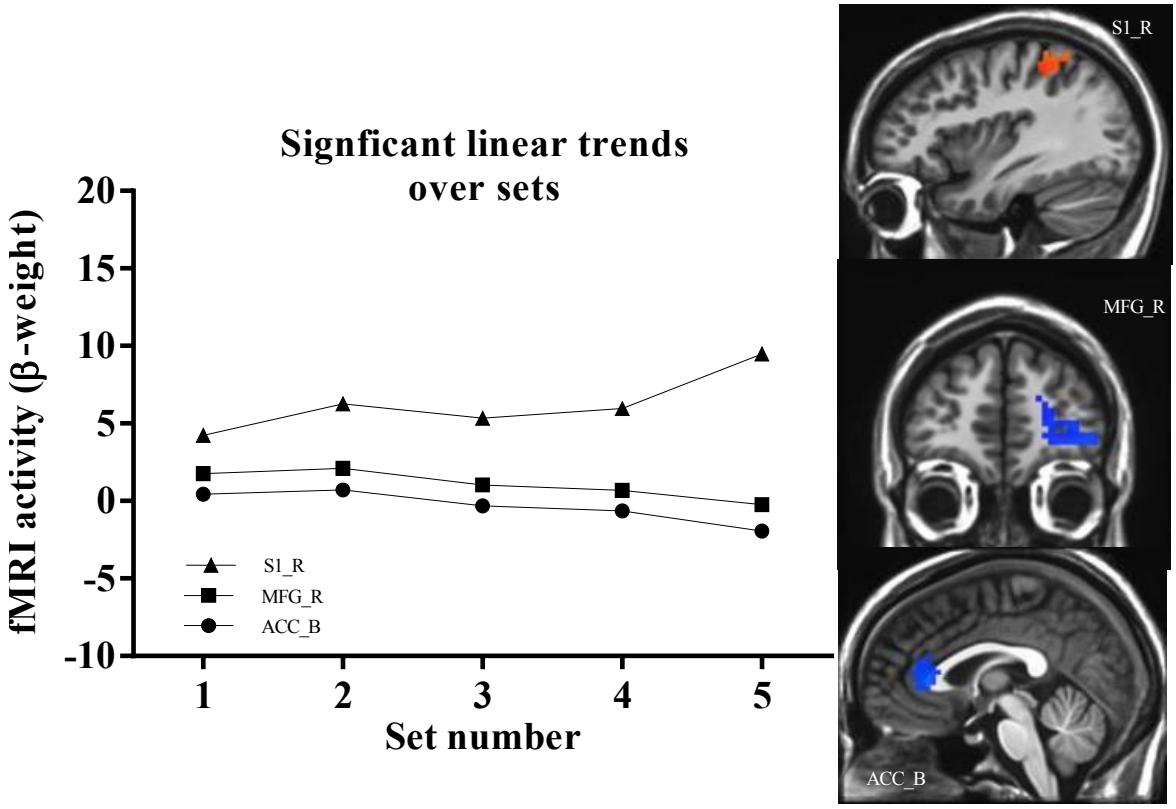

Figure 2. p = 0.001 significance for all areas represented on graph.

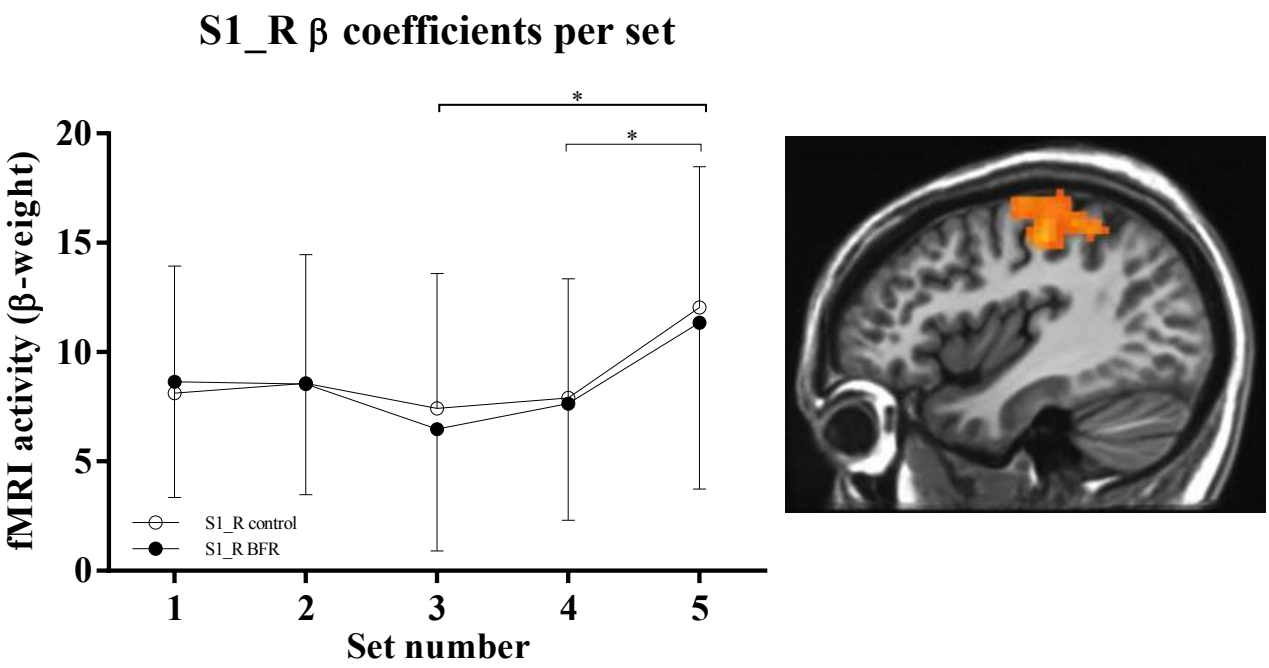

Figure 3. *p < 0.02 significance between set numbers. Error bars representing standard deviations.

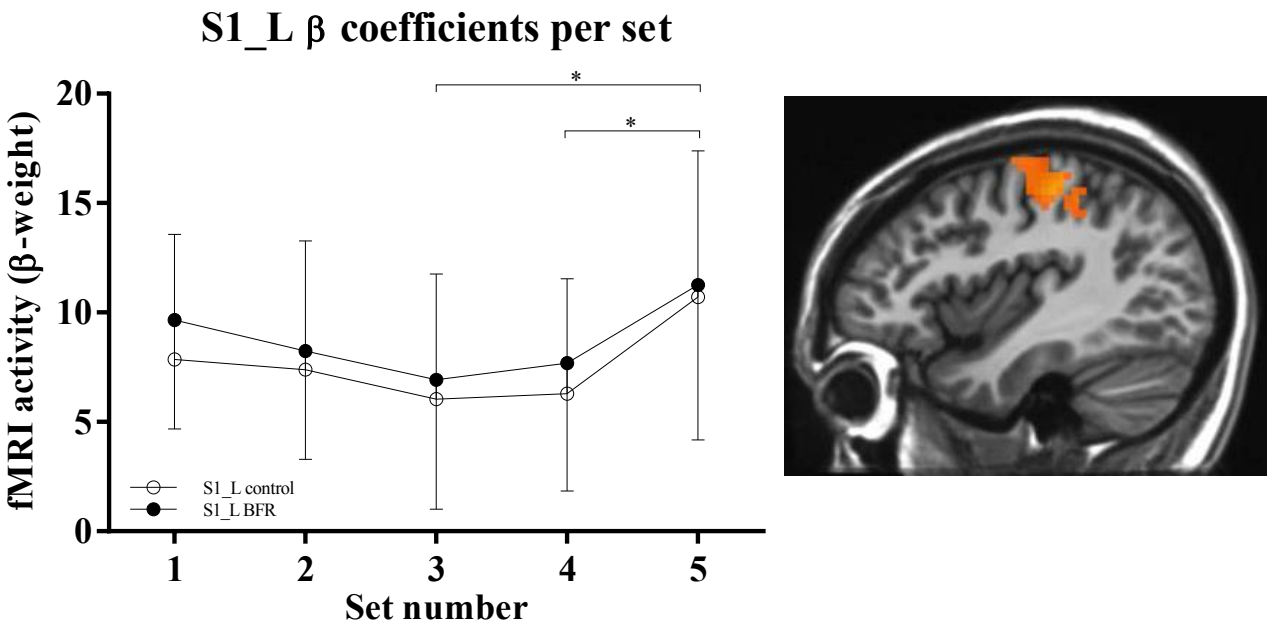

Figure 4. *p < 0.02 significance between set numbers. Error bars representing standard deviations.

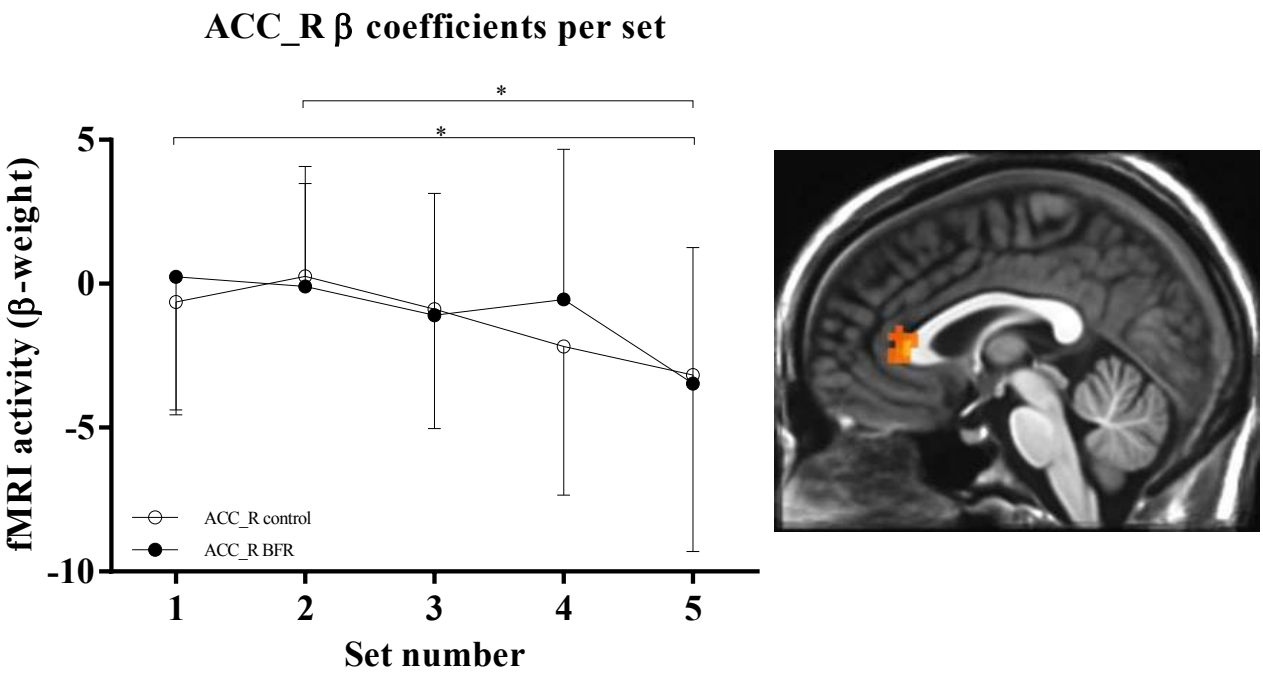

Figure 5. *p < 0.02 significance between set numbers. Error bars representing standard deviations.

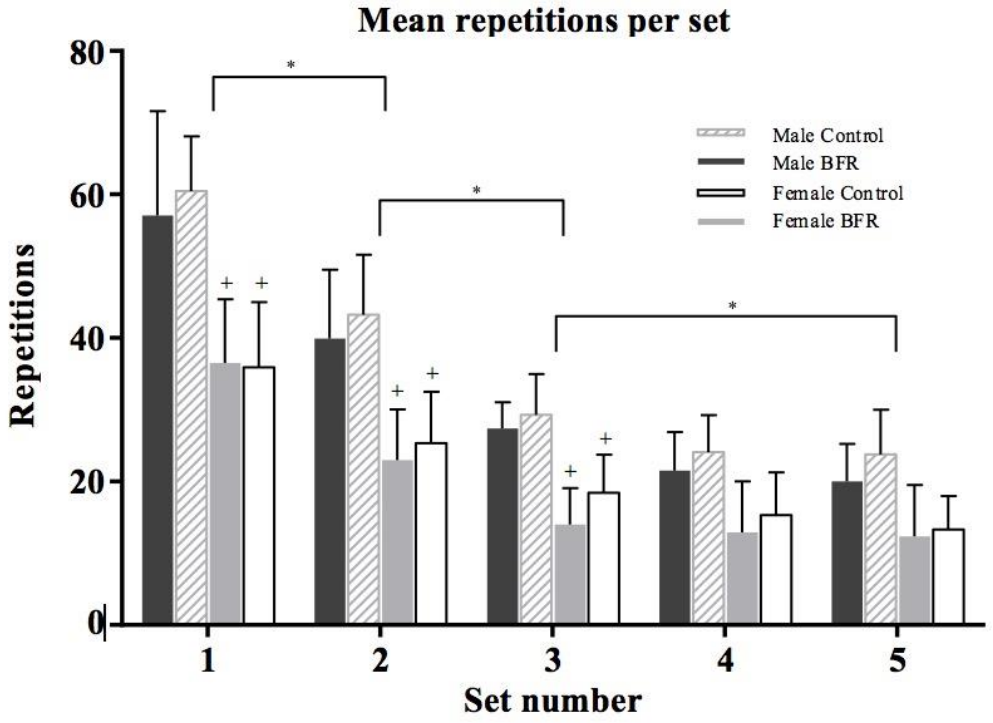

Figure 6. +p < 0.0001 from Males within the same set; *p < 0.0001 decrease in repetitions, controlling for sex. Error bars representing standard deviations.