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ORIGINAL ARTICLE

The corticomuscular response to experimental pain via blood flow occlusion when applied to the ipsilateral and contralateral leg during an isometric force task

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Abstract

Blood flow occlusion (BFO) has been previously used to investigate physiological responses to muscle ischemia, showing increased perceptual effort (RPE) and pain along with impaired neuromuscular performance. However, at present, it is unclear how BFO alters corticomuscular activities when either applied to the exercising or nonexercising musculature. The present study therefore set out to assess the corticomuscular response to these distinct BFO paradigms during an isometric contraction precision task. In a repeated measures design, fifteen participants (age = 27.00 ± 5.77) completed 15 isometric contractions across three experimental conditions; no occlusion (CNTRL), occlusion of the contralateral (i.e., nonexercising) limb (CON-OCC), and occlusion of the ipsilateral (i.e., exercising) limb (IPS-OCC). Measures of force, electroencephalographic (EEG), and electromyographic (EMG) were recorded during contractions. We observed that IPS-OCC broadly impaired force steadiness, elevated EMG of the vastus lateralis, and heightened RPE and pain. IPSI-OCC also significantly decreased corticomuscular coherence during the early phase of contraction and decreased EEG alpha activity across the sensorimotor and temporoparietal regions during the middle and late phases of contraction compared with CNTRL. By contrast, CON-OCC increased perceived levels of pain (but not RPE) and decreased EEG alpha activity across the prefrontal cortex during the middle and late phases of contraction, with no changes observed for EMG and force steadiness. Together, these findings highlight distinctive psychophysiological responses to experimental pain via BFO showing altered cortical activities (CON-OCC) and altered cortical, corticomuscular, and neuromuscular activities (IPS-OCC) when applied to the lower limbs during an isometric force precision task.

KEYWORDS

blood flow restriction exercise, corticomuscular coherence, EEG, EMG, fatigue, perceived exertion

1 | INTRODUCTION

Induced ischemia via blood flow occlusion (BFO) is a common experimental procedure to investigate neuromuscular response within the exercise pressor reflex (Fisher et al., 2015) and to isolate the metaboreflex from central command. During muscle ischemia there is decreased oxygen supply to the muscles with a concomitant increase in metabolite accumulation (H^+, inorganic phosphate [Pi], and adenosine diphosphate [ADP]), triggering group III-IV muscle nerve afferents (Kaufman et al., 1983; Mense & Meyer, 1985; Pollak et al., 2014). Activation of these muscle nerve afferents drives an increased perception of effort and pain during exercise (Gandevia, 2001; Gandevia et al., 1996; Kennedy et al., 2015), facilitating the onset of central fatigue (failure of the central nervous system to "drive" motoneurons) by inhibiting motor output from the motor cortex during exercise (Amann et al., 2015; Taylor et al., 2016). Consequently, both motor unit recruitment and the ability to generate and control force output become disrupted (Amann et al., 2022; Enoka & Farina, 2021; Farina et al., 2012).

While BFO paradigms are typically implemented by occluding the exercising musculature (i.e., ipsilateral), there is growing interest in exploring the perceptual and neuromuscular responses to BFO of nonexercising (typically contralateral) musculature during exercise (Finn et al., 2020). This is useful because this approach can stimulate group III–IV muscle afferents without altering the exercising muscle's metabolic status. Therefore, alterations to neuromuscular control can be better attributed to central modulatory factors rather than impairments to excitation–contraction coupling (Hill et al., 2022). Indeed, researchers have reported elevated perceived pain and fatigue, along with expedited time-to-task failure and impaired contractile function in the exercising leg when occlusion is applied to the contralateral, non-exercising leg (Aboodarda et al., 2020; Azevedo et al., 2022). Recent evidence has also shown that BFO applied following task failure to the nonexercising leg, can prolong the "silent period" of electromyographic (EMG) following motor-evoked potential (MEP) triggered by single-pulse transcranial magnetic stimulation (TMS circuitries; Azevedo et al., 2022). These findings, therefore, suggest a crossover effect, whereby group III–IV afferents can exert inhibitory influences across the central nervous system when activated in nonexercising musculature via occlusion, and thus influence perceptual and central modulatory factors during contraction of the contralateral exercising limb (Aboodarda et al., 2020).

Despite the utility of BFO as an experimental model to investigate physiological responses to muscle fatigue and pain (Mauger, 2013; Tanaka & Watanabe, 2012), an understanding of how this procedure alters the activity of the cerebral cortex remains lacking. However, alternative models of simulated muscle pain (e.g., saline and nerve growth factor injections, and the application of capsaicin and cold pressors to the skin) have been shown to evoke distinct alterations to cortical activity in healthy adults, including decreased electroencephalographic (EEG) alpha activity (~8–12 Hz) across central and posterior regions of the scalp, along with elevated beta activity (~15–30 Hz) across broad regions of the scalp including the frontal and temporal regions (Chang et al., 2001, 2003; Chen & Rappelsberger, 1994). Recent evidence has also shown that hypertonic-induced muscle pain decreases the ratio between alpha and beta activity (i.e., alpha/beta ratio) over the prefrontal cortex while resting, and over both the prefrontal and parietal cortices during exhaustive exercise in healthy males (Canestri et al., 2021). This general shift from slower (i.e., greater alpha activity) to faster (i.e., greater beta activity) cortical oscillations is proposed to reflect increased cellular excitability in the thalamo-cortical system triggered by peripheral nociceptive inputs (Ferracuti et al., 1994) and thus a hyperaroused central nervous system in response to pain (Perlis et al., 2001).

While the cortex-specific response to BFO remains underexplored, there is evidence that it can disrupt the functional synchronization between the cortex and muscles, as expressed by corticomuscular coherence (CMC)—a measure evaluating the frequency-wise similarity between signals recorded from the brain (via EEG or magnetoencephalography; MEG) and contracting muscle (via electromyography; EMG). Typically, CMC reaches its peak (and becomes "significant") across the beta frequency range (~15–30 Hz) for channels spanning the sensorimotor cortex during sustained isometric contractions (Mima & Hallett, 1999). Beta CMC is larger when isometric contractions are steadier and more precise (Kristeva et al., 2007; Witte et al., 2007) and has been proposed to reflect the effective cortical control of motor unit firing via the direct corticospinal pathway (Mima & Hallett, 1999), supporting the upregulation of efferent and afferent signals to promote a stable motor output (Baker, 2007). Indeed, Pohja and Salenius (2003) observed reduced CMC between the first dorsal interosseus and MEG signals following occlusion of the upper arm during a hand contraction task, highlighting how disrupting the sensory feedback loop via deafferentation may impair the rhythmic cortical drive on the spinal motoneuron pool. There is also evidence that CMC can become disrupted by increasing fatigue and pain sensation during muscle contraction (Poortvliet et al., 2019; Ushiyama et al., 2011), and when exposing individuals

to mechanically induced muscle tremors during concomitant muscle contractions (Budini et al., 2014). Therefore, it is possible that the mechano- and metabo-sensitive III-IV afferents induced by BFO may be responsible for the changes in CMC, affecting the efficiency of cortical control and ongoing muscular activity. However, at present, it is unclear how BFO and associated perceptual responses in passive, nonexercising, musculature can alter central modulatory factors and thus cortical and corticomuscular activities that are responsible for innervating the exercising limb.

The aim of the present study is to provide a comprehensive description of the corticomuscular response to BFO during an isometric contraction precision task when applied to the ipsilateral (i.e., exercising) and contralateral (i.e., nonexercising) leg musculature. Building upon evidence from alternative models of pain and fatigue, we expect to determine whether muscle BFO has a direct effect on contractile force control, cortical activity, and CMC. We hypothesized that BFO of both the ipsilateral and contralateral leg would result in poorer force steadiness, increased EMG activity, and decreased CMC compared to a control condition without occlusion. The findings provide novel insights into the neurophysiological mechanisms that underpin the role of different originating sites of BFO on corticomuscular function that may be applicable to populations affected by ischemic pain.

2 | METHOD

2.1 | Participants

Fifteen participants were recruited from the staff and student population of Manchester Metropolitan University (12 males, 3 females, mean age = 27.00 ± 5.77). An a priori sample size calculation was performed based on the large ($d = 2.18$) effects of BFO upon CMC reported by Pohja and Salenius (2003). Consequently, a sample size of at least 12 was required if assuming a large effect size ($\eta_p^2 = .14$) with 80% power and an alpha level of $p = .05$ in a repeated measures design with three levels. An additional two participants were recruited to account for potential data loss often associated with EEG data collection. All participants were free from any known neurological/musculoskeletal disorders or acute/chronic pain/fatigue conditions and were instructed to avoid stimulants (caffeine, alcohol, energy drink, etc.) and intense exercise 48 h prior to testing. Ethical approval was granted by Manchester Metropolitan University's ethics committee (protocol number 34966) and written informed consent was obtained from all participants.

2.2 | Protocol

2.2.1 | Preparation

All participants attended the laboratory once for approximately 2 hr. Upon arrival, participants were debriefed about the study protocol before being sat upon the Amsterdam Dynamometer Chair for the initial maximal arterial occlusion pressure (AOP) assessment representing the amount of pressure required to cease blood flow to a limb (Patterson et al., 2019). Specifically, an 18 cm wide inflatable cuff (CC17 Hokanson Inc, Bellevue, WA 98005, USA) was wrapped upon the upper portion of the right leg (just below the inguinal crease) and gradually inflated by 10 mm/hg every second via an automated rapid inflatable system (Hokanson Inc, Bellevue, WA 98005, USA) until the posterior tibial artery pulse was no longer present. The maximal AOP reached during this procedure was then recorded and applied during the subsequent BFO exercise protocols (mean AOP = 171.79 ± 11.79) (Patterson et al., 2019). These procedures were adopted to reduce high pressures and gradients and avoid limb paraesthesia and loss of limb sensitivity during the BFO protocol (Masri et al., 2020). Following the AOP assessment, participants were prepared for EEG and EMG data collection. The EEG signals were recorded with a conventional gel-based cap (eego sports, Ant Neuro, Hengelo, Netherlands) with 64 AgCl electrodes in a layout based on the extended 10–20 international system (Jurcak et al., 2007). Electrodes CPz and AFz were used as reference and ground, respectively. Naison, Inion, and preauricular points were used as anatomical landmarks to position the EEG cap. Conductive gel for electrophysiological measurements was used (Signa gel, Parker), and impendence was kept below 10 kΩ. The EEG cap was connected to an EEG mobile amplifier (eego sports, ANT Neuro, Hengelo, Netherlands) with additional auxiliary channels to allow for synchronous recording of bipolar surface EMG. Following suitable skin preparation, a pair of bipolar EMG electrodes were placed on the surface of vastus lateralis (VL) of the right leg according to the guidelines set out by SENIAM (Hermens et al., 2000). The participant's right ankle was then securely attached to the chair dynamometer with a 90-degree knee angle, connected to a PowerLab 4/25T (AD Instruments, Bella Vista, Australia) to record knee extension force (in kilograms) via Labchart 8 software (ADinstruments). The force, EEG, and EMG signals were recorded at a sample rate of 1000 Hz and were synchronized using a LabJack U3 device (LabJack Corporation, Lakewood, United States) that was controlled by our custom Psychopy experiment. As such, each contraction "onset" auditory

stimulus produced a square wave trigger timestamp that would be treated as timepoint zero in subsequent analyses. Participants then performed two maximal voluntary contractions (MVC's) separated by 1 min of rest. The max force value achieved across these two attempts was used to personalize the goal force output in the subsequent experimental task.

2.2.2 | Experimental task

The experimental task required participants to complete isometric right knee extensions for 20 s at 15 ± 5% of their MVC, with both the force produced and goal error boundary (i.e., ±5%) visually presented on a monitor using Labchart 8.0 software (see Figure 1). Participants were aware their goal was to maintain their force within the green error boundary for the entirety of each contraction. Each 20-s contraction was followed by 8 s of rest, and each block of five contractions was separated by 2.5 min of rest. The onset and offset of each 20-s contraction were indicated via auditory beeps (10 ms duration) that were controlled by Psychopy. Following an initial familiarization block, participants then completed three experimental blocks (total of 15 contractions) across three conditions; no occlusion (CNTRL), occlusion of the contralateral (i.e., nonexercising) limb (CON-OCC), and occlusion of the ipsilateral (i.e., exercising) limb (IPS-OCC). For the two occlusion conditions, the cuff was inflated at AOP around either the dominant limb thigh for 30 s prior to the first contraction and remained inflated for the entirety of each block (approximately 3 min inflated). The cuff was not worn during the control condition. Each condition was separated by 10 min, during which participants

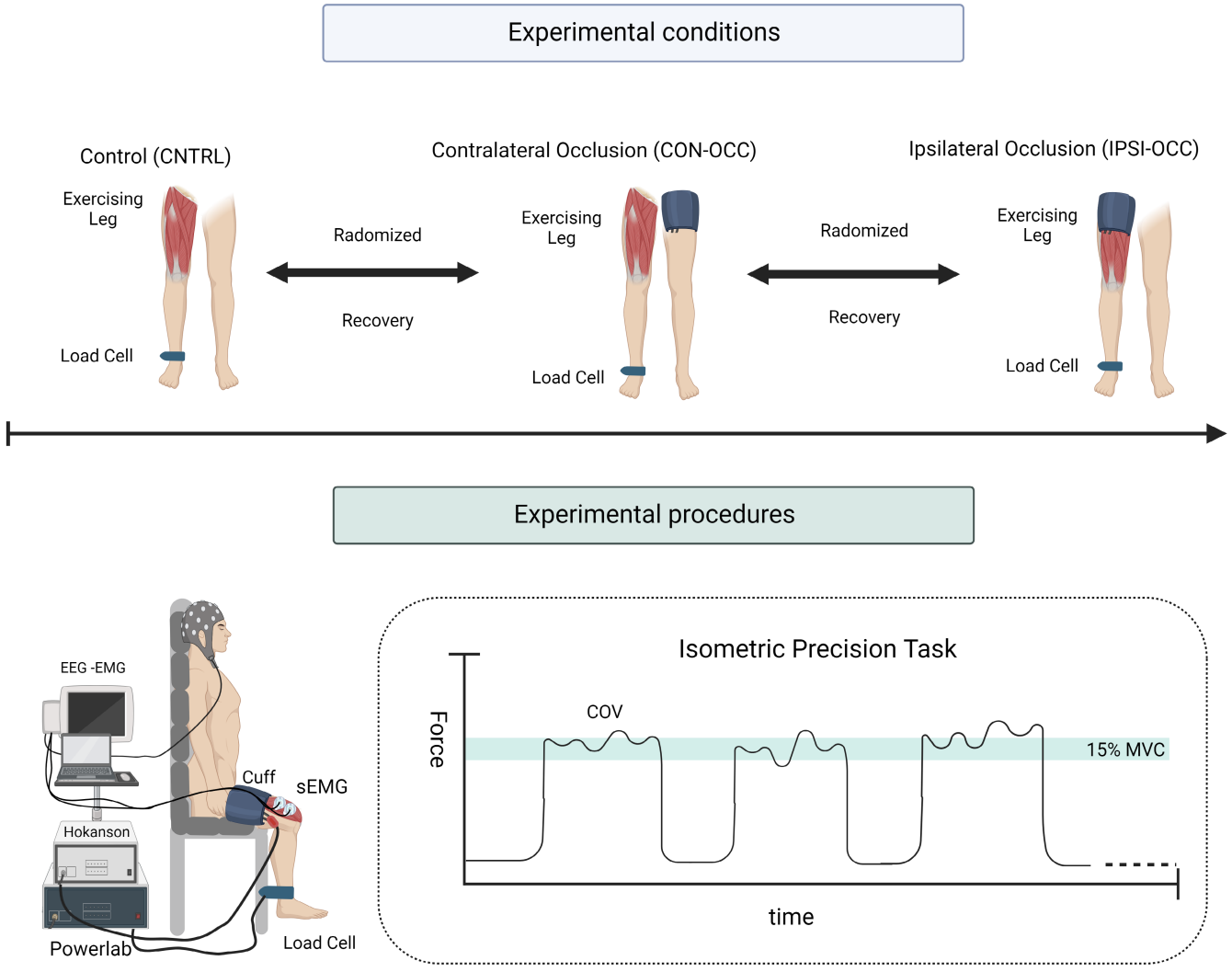

FIGURE 1 Experimental conditions and exercising tasks. Participants perform an isometric precision task wearing an electroencephalographic cap and surface electromyographic electrodes on the vastus lateralis of the exercising leg. The conditions consisted of a control (CNTRL) condition with no occlusion applied, occlusion of the contralateral nonexercising limb (CON-OCC), and occlusion of the ipsilateral exercising limb (IPS-OCC).

completed two MVC's at 2.5 and 5 min postcondition to assess fatigue. The order of conditions was automatically randomized for each participant via the Psychopy stimulation presentation software.

2.3 | Data analysis

For EMG-specific analyses, signals were band-pass filtered using the EEGLAB "basic FIR filter (new)" (10–450 Hz, default filter order, −6 dB cutoff frequency, 2.5 Hz transition bandwidth), and notch filtered (48–52 Hz, default filter order, −6 dB cutoff frequency, 2 Hz transition bandwidth) prior to being cut into epochs ranging from −2 to +22 s relative to the onset auditory stimulus. For EEG and EEG–EMG analyses, signals were band-pass filtered using the EEGLAB "basic FIR filter (new)" (1–45 Hz; default filter order, −6 dB cutoff frequency, 1 Hz transition bandwidth) and downsampled (250 Hz) prior to being cut into epochs ranging from −2 to +22 s relative to the onset auditory stimulus. These epochs were visually inspected, and those showing large EEG contamination from muscular artifacts were discarded (from both EEG and EMG analyses). No bad EEG channels were identified. Independent component analysis (ICA) weights were obtained through the RunICA infomax algorithm (Jung et al., 1998) running on EEG signals. ICA weights that presented obvious nonneural activity (e.g., eyeblinks/movements, line noise, muscular artifact) upon visual inspection were manually rejected. These processing steps were performed using EEGLAB functions (Delorme & Makeig, 2004) for MATLAB. We focused our analysis of force, EEG, and EMG data across three phases of contraction post auditory go stimulus: early (1–7 s), middle (7–13 s), and late (13–19 s). The first second was not considered to allow participants to ramp up their force output to the goal boundary, and the final second was not considered to avoid data containing any anticipatory relaxations. We chose to segment our contraction in this manner to allow us to understand how corticomuscular responses to blood flow restriction progress across the duration of a sustained contraction.

2.4 | Measures

2.4.1 | Pain and perceived exertion

Following the final contraction of each experimental condition, participants were asked to subjectively provide their rating of perceived exertion (RPE) using a Borg scale from 6 to 20 (Borg, 1970), and their general (whole body) perception of pain using a 10-point numeric scale where 0 = "no pain at all" and 10 = "pain as bad as it can be" (Karcioglu et al., 2018). The mean values of RPE and pain were determined for each condition. Rating scales were explained during the familiarization protocol and participant were oriented to their use before starting the trial.

2.4.2 | Force steadiness (CoV)

The force exerted by each participant was analyzed to determine the steadiness of contraction and the degree to which participants successfully maintained their force trace within their goal error boundary. Steadiness was defined as the coefficient of variance (CoV), calculated as the ratio between force standard deviation and the mean force value during each of the task phases (Enoka & Farina, 2021).

2.4.3 | EMG activity

Muscular activity was calculated as the root mean square (RMS) of the EMG signal occurring across each task phase for each trial. Data were normalized across participants by dividing trial-level RMS by the highest RMS value achieved by each participant across all phases and 45 experimental trials (i.e., $\%\ Peak_{task}$). This approach allows relative comparisons across conditions and time windows while being less influenced by interindividual differences in overall muscle strength (Burden, 2010).

2.4.4 | EEG activity and CMC

Time–frequency decomposition was performed through short-time Fast Fourier Transform (FFT) conducted on 209 overlapping windows, each of 1 s length, with central points ranging from −1.5 to 23.5 s relative to the onset of the auditory go stimulus. Prior to FFT, data points in each window were Hanning tapered and zero padded to reach 2 s. This generated complex-valued coefficients in the time–frequency plane with a precision of 120 ms and 0.5 Hz. EEG power (μV2) was calculated for the alpha (8–12 Hz) and beta (15–30 Hz) frequency bands as the squared amplitude of each signal, which was then averaged for the 50 overlapping segments across the early, middle, and late phases. As occlusion was employed throughout an experimental block, no neutral premovement baseline was established. Instead, skewness and interindividual differences in power density distributions were dealt with by employing a median-scaled transformation (Gallicchio et al., 2016; Parr et al., 2019), whereby each participant's values were scaled by their median and then log-transformed (10 × log10). The correlations

between the EEG and EMG (VL) signals were calculated by magnitude-squared coherence. For multiple corrections, we applied a Bonferroni correction defining the significance level of coherence (SL; Rosenberg et al., 1989), determined to be 0.111 in the present study. We measured the individual area under the coherence curve and above the significance level in the beta frequency range (beta Coharea) during the three task phases of the contraction (Chakarov et al., 2009; Mendez-Balbuena et al., 2012; Parr et al., 2022).

2.5 | Statistical analysis

The Gaussian distribution of data was checked via Shapiro–Wilk. Consequently, analyses for Pain and RPE were initially conducted using a non-parametric Friedman's analysis of variance (ANOVA) to assess the main effects of Condition (CNTRL, CON-OCC, IPS-OCC), with post-hoc tests subsequently performed using Wilcoxon-signed rank tests with Bonferroni corrections. Descriptive data for nonparametric variables are presented by the median and interquartile range (iqr). To assess the percentage change in MVC's across experimental blocks (% Δ MVC), a 2 × 3 repeated measures ANOVA was performed to probe the effects of Attempt (2.5 min post, 5 min post) and Block (first, second, third). For force steadiness (CoV) and EMG activity of the VL % ($Peak_{task}$), a 3 × 3 repeated measure ANOVA was performed to probe the effects of condition (CNTRL, CON-OCC, IPS-OCC) and phase (early, middle, late). Descriptive data for parametric variables are presented as the mean and standard deviation (M ± *SD*). Regional effects of alpha power, beta power, and CMC were analyzed through nonparametric permutation testing. The multiple comparison problem (i.e., one test for each comparison) was solved through the "maximum statistic" method (Cohen, 2014). Namely, we compared the *t*-values from paired samples *t*-tests obtained when comparing channel-wise data between conditions and task phases with an empirical distribution of *t*-values constructed in the following way. First, we permuted the data by randomly swapping the condition (CNTRL, CON-OCC, IPS-OCC) and phase (early, middle, late) labels within each participant before running a paired samples *t*-test separately for each channel. We then pooled the *t*-values across channels and stored the two most extreme values (i.e., minimum and maximum). We then repeated this procedure 2000 times to create a distribution of 4000 minimum and maximum *t*-values. Finally, we compared the observed (i.e., nonpermuted) *t*-values of each channel-wise comparison with the empirical distribution of *t*-values described above, and computed *p* values as the proportion of the permutation *t*-values that were more extreme that the *t*-values for each channel. For alpha and beta power, all 63 channels were included to investigate broad regional effects. For CMC, we included the 14 channels spanning the sensorimotor cortex. Effect sizes for Wilcoxon-signed rank tests were reported as *r*, with values of .1, .3, and .5 reflecting small, medium, and large effects, respectively (Cohen, 1992). ANOVA effect sizes were reported using partial eta squared (η_p^2), common indicative thresholds for which are small (0.01), medium (0.06), and large (0.14; Field, 2013). All statistical analyses were performed using IBM SPSS statistics (version 26) with an alpha level of ≤.05.

3 | RESULTS

3.1 | % Δ MVC's across experimental blocks

A significant main effect of Attempt indicated that MVC's were significantly greater 5-min postexercise compared to 2.5-min postexercise ($F(1, 14) = 4.932$, $p = .043$). The main effect of Block ($F(2, 28) = 2.030$, $p = .150$, $\eta_p^2 = .127$) and the Block × Attempt interaction were nonsignificant ($F(2, 28) = 2.183$, $p = .131$, $\eta_p^2 = .135$; Table 1).

3.2 | Pain and RPE

A significant main effect of condition was observed for perceived pain ($X(2) = 17.472$, $p < .001$). Pain was significantly higher during IPS-OCC (median = 4.50, iqr = 2.85) compared with the CNTRL (median = 0.70, iqr = 2.33, $p = .003$) and CON-OCC conditions (median = 3.70, iqr = 2.57, $p = .015$). Subjective pain was also significantly higher during CON-OCC compared to the CNTRL condition ($p = .009$). A significant main effect of condition was also observed for RPE ($X(2) = 17.245$, $p < .001$). RPE was significantly higher during IPS-OCC (median = 15.30, iqr = 3.55) compared to the CNTRL (median = 9.30, iqr = 3.55, $p = .003$) and CON-OCC conditions (median = 11.15, iqr = 2.15, $p = .003$; Table 2).

TABLE 1 Mean (±*SD*) maximal voluntary contraction (MVC) force output as a percentage change relative to the baseline recording (i.e., % Δ MVC), across the three sequential experimental blocks (irrespective of experimental condition) for the attempts occurring at 2.5- and 5-min postexercise.

	First block	Second block	Third block
2.5-min post (% Δ MVC)	0.20 ± 7.53	2.27 ± 9.13	5.33 ± 9.53
5-min post (% Δ MVC)	3.40 ± 9.02	5.13 ± 8.26	5.07 ± 8.23

Note: Positive values indicate elevated MVC force values relative to baseline.

TABLE 2 Median (interquartile range) of the rate of perceived exertion (RPE) and self-report levels of pain on a scale of 0 = "no pain at all" and 10 = "pain as bad as it can be."

	CNTRL	CON-OCC	IPS-OCC
Pain (0_{min}–10_{max})	0.70 (2.33)	3.70 (2.57)	4.50 (2.85)
RPE (6_{min}–20_{max})	9.30 (3.55)	11.15 (2.15)	15.30 (3.55)

3.3 | Force steadiness (CoV)

A significant main effect of Condition was observed ($F(2, 28) = 9.083$, $p < .001$, $\eta_p^2 = .393$), with greater CoV observed during IPS-OCC (3.805 ± 0.332%) compared with the CNTRL (3.059 ± 0.234%, $p = .001$) and CON-OCC conditions (3.148 ± 0.221%, $p = .012$). No difference was observed between the CNTRL and CON-OCC conditions ($p = .969$). A significant main effect of Phase ($F(1.006, 14.089) = 38.492$, $p < .001$, $\eta_p^2 = .733$) revealed greater CoV during the early phase (5.462 ± 0.549%) compared with the middle (2.313 ± 0.160%, $p < .001$) and late 7(2.238 ± 0.161%, $p < .001$) phases. No difference was observed between the middle and late phases ($p = .115$; Figure 3a). The Condition × Phase interaction was not significant ($F(2.011, 28.149) = 2.727$, $p = .082$, $\eta_p^2 = .163$).

3.4 | Vastus lateralis EMG activity

A significant main effect of Condition was observed ($F(2, 28) = 5.338$, $p = .011$, $\eta_p^2 = .276$) with significantly greater EMG activity observed during the IPS-OCC (74.02 ± 4.11% $Peak_{trial}$) compared with the CNTRL (59.59 ± 3.19% $Peak_{trial}$, $p = .015$) and CON-OCC conditions (58.98 ± 2.96% $Peak_{trial}$, $p = .003$). There was no difference between the CNTRL and CON-OCC conditions ($p = .934$). A significant main effect of Phase ($F(1.22, 17.05) = 72.792$, $p < .001$, $\eta_p^2 = .839$) showed greater EMG activity in the late phase (67.37 ± 9.24% $Peak_{trial}$) compared with the early (60.59 ± 8.00% $Peak_{trial}$, $p < .001$) and middle (64.63 ± 8.30% $Peak_{trial}$) phases. EMG activity also significantly increased from the early to middle phases ($p < .001$; Figure 3b). The Condition × Phase interaction was not significant ($F(2.271, 31.788) = 1.761$, $p = .150$, $\eta_p^2 = .112$; Table 3).

3.5 | Alpha power

Permutation testing to control for the multiple comparisons problem in the channel × condition × phase dimensions identified observed *t*-values to surpass the critical threshold if they fell below −3.28 or above 3.31. Results indicated that alpha power was significantly lower during CON-OCC compared with the CNTRL condition across channels F1 ($t = -3.63$, $p = .021$) and F5, ($t = -3.44$, $p = .031$) during the middle phase and across channel AF7 ($t = -3.35$, $p = .039$) during the late phase. Results also indicated that alpha power was significantly lower during IPS-OCC compared with the CNTRL condition across channels CP3 ($t = -3.56$ $p = .025$) and CP5 ($t = -3.88$, $p = .012$) during the middle phase and across channels Cz ($t = -3.42$, $p = .033$), CP3 ($t = -3.70$, $p = .015$), P3 ($t = -3.99$, $p = .009$), CP6 ($t = -3.59$, $p = .023$), and T8 ($t = -3.58$, $p = .024$) during the late phase (Figure 2). Finally, results indicated that for the CON-OCC condition, alpha power significantly decreased from the early stage to the middle stage across channel FT7 ($t = -3.39$, $p = .044$; Topoplots available in Supplementary file 1).

3.6 | Beta power

Permutation testing to control for the multiple comparisons problem in the channel × condition × phase dimensions identified observed *t*-values to surpass the critical threshold if they fell below −3.27 or above 3.31. No differences were observed between conditions at any of the task phases or between any of the task phases for any of the conditions (Topoplots available in Supplementary file 1).

3.7 | CMC

Permutation testing to control for the multiple comparisons problem in the channel × condition × phase dimensions identified observed *t*-values to surpass the critical threshold if they fell below −2.73 or above 2.68. Consequently, results indicated that beta CMC was significantly lower across channels C3 ($t = -3.11$, $p = .008$) and C1 ($t = -3.07$, $p = .024$) during IPS-OCC compared to the CNTRL condition during the early phase of contraction. Beta CMC was also significantly lower during the IPS-OCC compared with the CON-OCC condition across channel CP1 ($t = -3.90$, $p = .002$). For the IPS-OCC condition, beta CMC significantly increased from the early to middle stages across channels CP1 ($t = 2.91$, $p = .035$) and C1 ($t = 3.49$, $p = .010$), from the early to late stages across channels Cz ($t = 2.77$, $p = .047$) and C1 ($t = 3.17$, $p = .021$; Figure 3).

4 | DISCUSSION

The aim of this study was to explore the corticomuscular response to BFO exercise when applied to either the ipsilateral (i.e., exercising leg; IPS-OCC) or the contralateral

		Control	Nonexercising	Exercising
CoV (%)	Early	4.83 ± 1.77	5.24 ± 2.26	6.31 ± 2.96
	Middle	2.24 ± 0.69	2.17 ± 0.54	2.54 ± 0.74
	Late	2.10 ± 0.67	2.04 ± 0.44	2.57 ± 0.90
VL activity (% $Peak_{trial}$)	Early	56.13 ± 18.50	55.80 ± 22.00	69.80 ± 11.45
	Middle	60.07 ± 20.67	59.60 ± 23.59	74.20 ± 10.57
	Late	62.40 ± 21.43	61.67 ± 24.00	78.00 ± 9.22

TABLE 3 Mean (±*SD*) force steadiness, expressed as the coefficient of variance (CoV %), and electromyographic activity of the vastus lateralis for each experimental condition across the early, middle, and late phases of the force contraction (% $Peak_{trial}$).

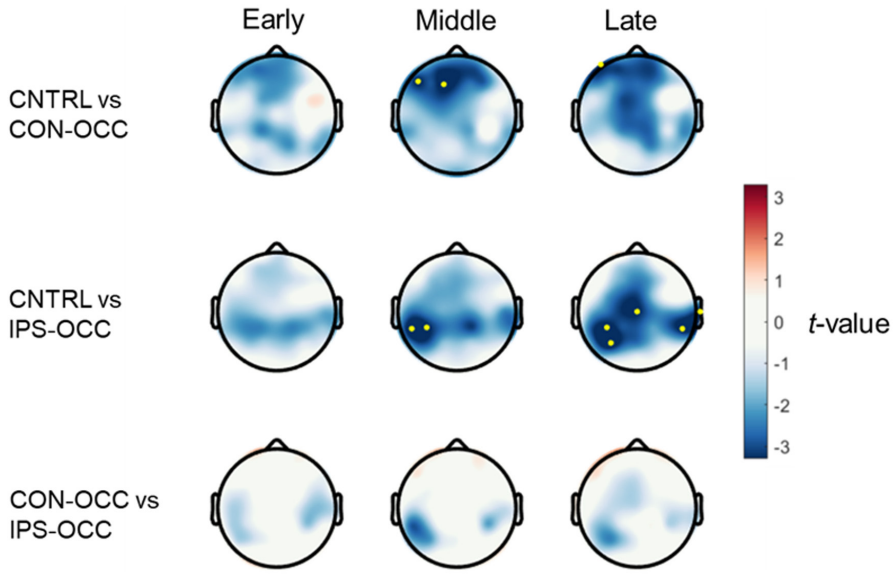

FIGURE 2 Topoplots displaying the paired sample *t*-values comparing regional electroencephalographic alpha activity between conditions at each of the three-time windows. For the top two rows (CNTRL vs CON-OCC; CNTRL vs IPS-OCC) scalp regions that are blue indicate lower alpha activity relative to the CNTRL condition, whereas red regions indicate higher alpha activity relative to the CNTRL condition. For the bottom row, blue regions indicate lower alpha activity in the IPS-OCC condition, whereas red regions indicate lower alpha activity in the CON-OCC condition. Channels highlighted yellow indicate a statistically significant difference.

(i.e., nonexercising; CON-OCC)leg. We observed that IPS-OCC broadly impaired isometric force steadiness, elevated EMG activity of the vastus lateralis, and increased RPE and levels of perceived pain. IPS-OCC also significantly decreased CMC during the early phase of contraction. Compared with the CNTRL condition, IPS-OCC decreased EEG alpha activity across the sensorimotor and temporoparietal regions during the middle and late phases of contraction along with concomitant increases in EMG activity. By contrast, CON-OCC increased perceived levels of pain (but not RPE) and decreased EEG alpha activity across the prefrontal cortex during the middle and late phases of contraction, with no changes in EMG activity compared to the CNTRL condition. Together, these findings highlight distinctive psychophysiological responses to experimental pain via BFO when applied to the ipsilateral (i.e., exercising) and contralateral (i.e., nonexercising) musculature of the lower limbs in the context of isometric force control.

4.1 | Occlusion of the exercising leg (IPS-OCC)

As hypothesized, IPS-OCC elevated perceptual sensations of pain and RPE resulting in altered motor command, characterized by impaired isometric force control, and increased surface EMG activity. As we observed no change in MVC's following the completion of each experimental block, we can ascribe these neuromuscular changes to the effects of occlusion during the exercise task. A common mechanism proposed to explain this modulation of voluntary motor output following occlusion is the accumulation of muscle metabolites that stimulate group III-IV muscle nerve afferents. These afferents direct neural feedback to the sensory areas of the brain and contribute to the sensations of pain and RPE and the modulation of motoneuron output by eliciting inhibitory feedback to the corticomotor circuitries (Amann et al., 2020). Indeed, previous research has established that both increased force variability and

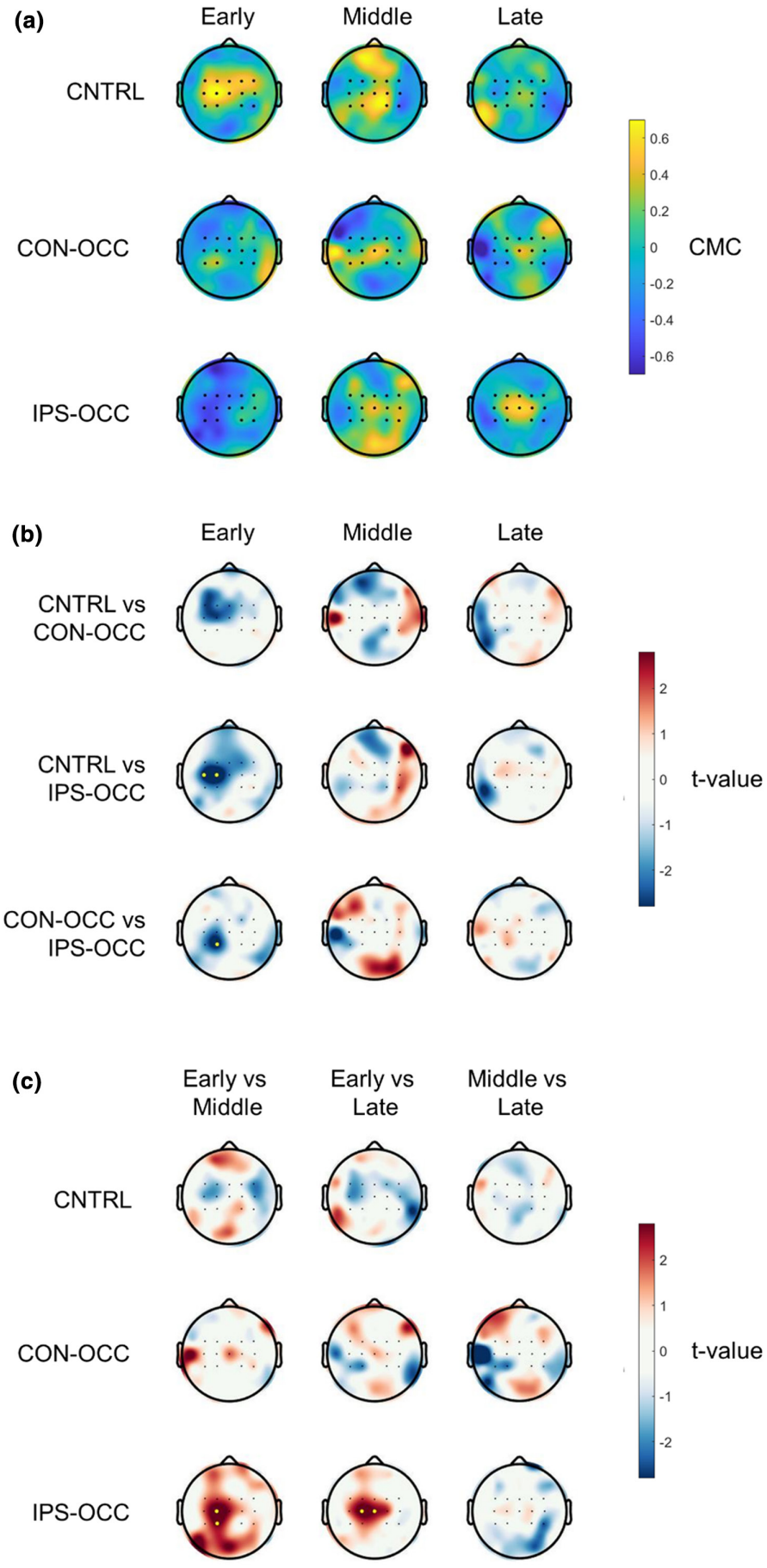

FIGURE 3 (a) Topoplots displaying beta corticomuscular coherence (CMC) between electroencephalographic channels and electromyographic activity of the vastus lateralis. Black points indicate the channels spanning the sensorimotor cortex that were included in statistical analyses. (b) Topoplots displaying paired sample *t*-values comparing beta CMC between conditions at each of the three-time windows. For the top two rows (CNTRL vs CON-OCC; CNTRL vs IPS-OCC) scalp regions that are blue indicate lower CMC relative to the CNTRL condition whereas red regions indicate higher CMC relative to the CNTRL condition. For the bottom row, blue regions indicate lower CMC in the IPS-OCC condition, whereas red regions indicate lower CMC in the CON-OCC condition. (c) Topoplots displaying paired sample *t*-values comparing beta CMC between the three-time windows for each of the three conditions. For the first two columns (early vs middle; early vs late) blue scalp regions indicate lower CMC relative to the early phase, whereas red scalp regions indicate higher CMC relative to the early phase. For the third column (middle vs late), blue scalp regions indicate lower CMC relative to the middle phase, whereas red scalp regions indicate higher CMC relative to the middle phase. Channels highlighted yellow indicate a statistically significant difference.

EMG activity occur under fatiguing conditions during submaximal isometric contractions (Johnson et al., 2004; Missenard et al., 2008). While debated, this phenomenon is thought to be a consequence of additional motor units being recruited to combat peripheral fatigue and ensure the required external force is maintained. As new motor units are recruited, their firing rates can become slower and more rhythmic, resulting in both a greater summation of EMG activity and greater variability in the individual force twitches (Contessa et al., 2009). Such an explanation for our findings seems reasonable, given previous evidence that the reduced oxygen availability during ischemia stimulates the increased activation of motor units comprised of muscle type II fibers during exercise (Miller et al., 1987).

At the cortex, IPS-OCC significantly reduced EEG alpha activity across channels spanning the sensorimotor and temporoparietal regions during the middle and late phases compared with the CNTRL condition. The functional role of alpha activity is to exert inhibitory control of the cortex, whereby higher alpha indicates stronger neuronal inhibition (less activation) and less alpha indicates a greater release from inhibition (more activation) (Garcia-Larrea et al., 2019; Klimesch, 2012; Klimesch et al., 2007). Based on this evidence, our findings indicate that IPS-OCC elevated the cortical activity across sensorimotor and temporoparietal regions of the cortex. Indeed, a reduction of alpha activity across central, posterior, and temporal regions has been observed previously in alternative models of experimental pain (Canestri et al., 2021; Chien et al., 2014) and may reflect a variety of processes involved in the experience of elevated pain and fatigue, including elevated sensory and emotional processing, along with elevated attentional and cognitive demands (Garcia-Larrea et al., 2019). Importantly, IPS-OCC also altered the central motor command by increasing surface EMG activity and reducing force steadiness. The broad reduction in alpha activity across sensorimotor and parietal regions could further imply a compensatory increase in corticomotor excitability to overcome the development of neuromuscular fatigue and maintain the required task force (Goodall et al., 2018; Sidhu et al., 2017, 2018).

Interestingly, IPS-OCC significantly reduced CMC compared with the CON-OCC and CNTRL conditions during the early phase of isometric contraction. This initial disruption of CMC reinforces evidence that interfering with the sensory feedback loop via occlusion may impair the rhythmic interaction between the cortical drive and spinal motoneuron pool (Pohja & Salenius, 2003), resulting in poorer neuromuscular control. Previous work has shown CMC to be modulated under conditions of experimental pain during muscle contraction (Poortvliet et al., 2019; Ushiyama et al., 2011) and when exposing individuals to mechanically induced muscle tremors during concomitant muscle contractions (Budini et al., 2014). Therefore, our findings suggest that the mechano- and metabo-sensitive III-IV afferents induced by BFO are likely to be responsible for the changes in CMC, affecting the efficiency of cortical control and ongoing muscular activity. That said, we also found CMC to subsequently increase across the middle and late phases to become comparable to the CON-OCC and CNTRL conditions. Given that the sensations of pain and fatigue induced by ischemia typically increase the longer a contraction is held (Aboodarda et al., 2020; Jones et al., 2017), it is surprising that the disruption to CMC was not maintained across the length of the isometric contraction. As such, the reduction of CMC during the initial phase of contraction is unlikely to be explained solely by the presence of elevated experimental pain. It is therefore possible that CMC was primarily modulated by altered activation (via cuff compression) and sensitivity (via metabolite accumulation) of mechanoreceptors (Zambolin et al., 2022, 2023) which would have impaired the feedback/feed-forward mechanism required to finely regulate muscle tension and motor unit recruitment in a manner that supports isometric force precision during the early phase of contraction. Additionally, Ushiyama et al. (2011) found that CMC was actually enhanced during isometric contractions of the tibialis anterior when preceded by a fatiguing task, despite increased EMG activity, increased RPE, and poorer force steadiness. The authors suggest that once the development of muscle fatigue limits the ability to maximally activate motor units, the descending sensorimotor drive becomes *more* rhythmic, leading to the enhancement of oscillatory synchronization of motor unit activities. This mechanism could explain the enhancement of CMC across the middle and late phases of contraction observed during occlusion of the exercising leg, though it should be acknowledged that we did not assess myoelectric fatigue in this manner.

It has also been argued that the presence of these afferents impairs CMC by elevating cognitive load and creating a competition between cognitive resources to process perceptions of the pain and to attend to movement control processes, resulting in poorer motor control and poorer force steadiness (Poortvielt et al., 2019). In support of this, recent evidence has also shown that CMC and force steadiness are impaired during isometric contractions when individuals are encouraged to focus internally on the sensation of muscular contraction, rather than solely focusing externally on the visual feedback of the force output (Parr et al., 2023). As such, the presence of experimental pain may impair CMC by functionally decoupling attention away from the motor task.

However, as EEG beta activity was not altered during the IPS-OCC condition, it could be argued that the impairments to CMC might have been primarily driven by changes to peripheral (i.e., EMG), rather than central (i.e., EEG), components of activity. Indeed, previous work has shown reductions in beta CMC, despite increases in both EEG and EMG beta activity, under fatiguing conditions (Yang et al., 2009, 2010). It is argued that such an observation could indicate an impairment to the neuromuscular junction, which in turn would impair the efficient transmission of descending motor command to the periphery, and thus the coupling between cortical and muscular signals (Yang et al., 2009, 2010). That said, beta CMC and cortical beta activity have often been shown to follow different trajectories (see Bourguignon et al., 2019) which suggests that only a subset of cortical beta components underpin CMC (Kilavik et al., 2013). As such, the absence of changes in EEG beta activity during IPS-OCC might not indicate that impaired CMC were driven solely by changes to peripheral activity.

4.2 | Occlusion of the nonexercising leg (CON-OCC)

Contrary to our hypotheses, CON-OCC elevated perceived pain (relative to the control condition) but did not elevate RPE and had no effect on CMC, EMG activity or isometric force control in the ipsilateral-exercising leg. As per previous work, we had expected to observe a crossover effect whereby the activation of nonexercising musculature group III-IV afferents (via occlusion) would have elicited inhibitory feedback to the corticomotor circuitries and thus curtail the central motor output in the exercising limb musculature (Azevedo et al., 2022; Norbury et al., 2022). However, the evidence supporting these crossover effects remains mixed, with several studies showing concurrent rising pain in the contralateral limb, in the absence of perceptual exertion, does not affect muscle activity, voluntary drive, and thus motor unit recruitment (Aboodarda et al., 2020; Kennedy et al., 2015). The magnitude of metabolite accumulation, along with the intensity and duration of the exercise task, is therefore likely to play an important role in determining any crossover effects from occlusion of nonexercising, passive musculature. Indeed, both pain and RPE were significantly higher during IPS-OCC versus CON-OCC, suggesting a greater summation of afferent feedback, and thus metabolite accumulation, between experimental conditions. While CON-OCC elevated pain, the absence of elevated RPE and/or alterations to CMC, neuromuscular activation, and control, imply that this paradigm may have failed to induce a sufficient degree of afferent stimulation (i.e., it was not intense or long enough) to promote any crossover effects. This is supported by the relatively low levels of pain observed during this task (3.46/10), which might not have been significant enough to influence neuromuscular control.

However, CON-OCC significantly decreased alpha activity across channels spanning the prefrontal cortex during the middle and late phases compared with the CNTRL condition. Given that participants also reported heightened pain during this condition, our findings indicate that perceived pain originating from nonexercising (i.e., remote) musculature might be indexed by heightened activation of the prefrontal cortex. While the prefrontal cortex has been strongly implicated in the processing of pain (Ong et al., 2019), it has often been coupled with heightened activation across central and posterior brain regions as observed during IPS-OCC (e.g., Canestri et al., 2021; Chang et al., 2003). One explanation for this localized prefrontal activation is that CON-OCC did not alter central motor command (i.e., EMG activity and force control were not altered) or elevate RPE and therefore did not necessitate a compensatory increase in corticomotor excitability that might have been expressed across the sensorimotor regions. Indeed, there is evidence that when individuals can sense a locus of control over induced experimental pain (i.e., it can be managed), elevated activation of the prefrontal cortex occurs with a concomitant reduction of activity across broader regions of pain processing areas (Bräscher et al., 2016; Ong et al., 2019). As such, activation of the prefrontal cortex during painful stimuli is thought to play a role in top-down cognitive control over pain and the ability to cope with associated nociceptive inputs (Raij et al., 2009). We could, therefore, speculate that this observed pattern of alpha reflects awareness and attention towards the presence of controllable pain (i.e., prefrontal activation) and the ability to downregulate or inhibit the extent to which it subsequently interfered with central motor command processes (i.e., absence of change across central and posterior regions).

5 | STUDY LIMITATIONS

The following limitations should be acknowledged in the interpretation of our findings. For example, while BFO exercise has been extensively used in the literature to induce muscle ischemia and muscle afferent activation, this model of experimental pain cannot isolate the effects of mechano- or metaboreceptor activation and thus reflects a combination of the two. Indeed, cuff compression could have activated mechanoreceptors (Ge & Khalsa, 2003) while progressive muscle ischemia could have led to a progressive increase in metabolite concentration and metaboreceptor activation (Kaufman & Hayes, 2002). Consequently, it is difficult to discern

which had a greater influence on the observed changes in CMC, EEG alpha activity, and central motor command. We also did not measure metabolite concentration during BFO conditions (that would require more invasive and advanced techniques such as NMR spectroscopy or muscle biopsies) and therefore, we cannot determine whether our findings are driven by fundamental differences in metabolite accumulation. We also did not measure exhaustive exercise or implement neuromuscular assessments to discern between central and/or peripheral fatigue (Gandevia, 2001). Implementing measures for detecting changes in motor unit recruitment and firing rate (i.e., via intramuscular or high-density EMG) could be useful strategies to address this short-coming and overcome the limitations of bipolar surface EMG (Esen et al., 2022; Vieira & Botter, 2021). It should also be highlighted that we observed no significant changes in cortical beta activity between our experimental conditions. Previous research has shown that experimental pain can elicit a shift from slower to faster cortical oscillations that can collectively be expressed as a reduction of alpha, an increase in beta, or a reduction in the alpha/beta ratio (Canestri et al., 2021). However, attempts to uncover the cortical dynamics underpinning experimental pain experienced *during* exercise (or motor control) remain lacking. Given the active role cortical beta oscillations are proposed to play in the maintenance of isometric contractions (Engel & Fries, 2010) we could speculate that the absence of any changes in beta activity between conditions might reflect a task-specific dependency on beta activity that remained somewhat consistent between conditions. Our analyses of EEG activity were also limited to investigating periodic oscillatory activity across well-known canonical frequency bands (i.e., alpha [8–12 Hz] and beta [15–30 Hz]), and thus overlooks the possibility that nonoscillatory aperiodic activity (i.e., exponent and offset) contributed to our observed changes in EEG and CMC measures. Emerging evidence demonstrates that aperiodic activity holds putative physiological interpretations and should therefore be considered in future work (Donoghue et al., 2020; Pani et al., 2022), recording EMG signals during MVC contractions for normalization purposes might have allowed more nuanced comparisons to be considered; however, as the pattern of activation was a primary outcome for CMC, this type of normalization is considered appropriate (Besomi et al., 2020).

6 | CONCLUSION

The findings of the present study reveal distinct alterations to corticomuscular function when BFO is applied to the ipsilateral (exercising) and contralateral (nonexercising) leg. At the corticomuscular level, we found IPS-OCC to elicit higher activation of broad central and posterior brain regions and an initial disruption to CMC during the early phase of contraction possibly reflecting an alteration in central motor drive with greater interference on motor unit recruitment and motor control, resulting in poorer force steadiness. By contrast, CON-OCC appeared to only evoke a controllable increase in perceived pain that was expressed as heightened activation of the prefrontal cortex. Together, our findings provide a novel overview of how BFO, as a model of experimental pain, is expressed at the corticomuscular level.

AUTHOR CONTRIBUTIONS

F. Zambolin: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; validation; visualization; writing – original draft; writing – review and editing. **P. Duro Ocana:** Conceptualization; investigation; methodology; project administration; writing – review and editing. **R. Goulding:** Supervision; validation; writing – review and editing. **A. Sanderson:** Supervision; validation; writing – review and editing. **M. Venturelli:** Writing – review and editing. **G. Wood:** Conceptualization; project administration; supervision; writing – review and editing. **J. McPhee:** Supervision; writing – review and editing. **J. V. V. Parr:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; validation; visualization; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or nonfinancial interests to declare.

DATA AVAILABILITY STATEMENT

Supporting data and code are freely available from DOI 10.17605/OSF.IO/QJVU9.

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REFERENCES

Aboodarda, S. J., Iannetta, D., Emami, N., Varesco, G., Murias, J. M., & Millet, G. Y. (2020). Effects of pre-induced fatigue vs. concurrent pain on exercise tolerance, neuromuscular performance and corticospinal responses of locomotor muscles. *The*

Journal of Physiology, *598*(2), 285–302. https://doi.org/10.1113/JP278943

Amann, M., Sidhu, S. K., McNeil, C. J., & Gandevia, S. C. (2022). Critical considerations of the contribution of the corticomotoneuronal pathway to central fatigue. *The Journal of Physiology*, *600*(24), 5203–5214. https://doi.org/10.1113/JP282564

Amann, M., Sidhu, S. K., Weavil, J. C., Mangum, T. S., & Venturelli, M. (2015). Autonomic responses to exercise: Group III/IV muscle afferents and fatigue. *Autonomic Neuroscience*, *188*, 19–23. https://doi.org/10.1016/j.autneu.2014.10.018

Amann, M., Wan, H.-Y., Thurston, T. S., Georgescu, V. P., & Weavil, J. C. (2020). On the influence of group III/IV muscle afferent feedback on endurance exercise performance. *Exercise and Sport Sciences Reviews*, *48*(4), 209–216. https://doi.org/10.1249/JES.0000000000000233

Azevedo, R. A., Jazayeri, D., Yeung, S. T., Khoshreza, R., Millet, G. Y., Murias, J. M., & Aboodarda, S. J. (2022). The effects of pain induced by blood flow occlusion in one leg on exercise tolerance and corticospinal excitability and inhibition of the contralateral leg in males. *Applied Physiology, Nutrition, and Metabolism*, *47*(6), 632–648. https://doi.org/10.1139/apnm-2021-0597

Baker, S. N. (2007). Oscillatory interactions between sensorimotor cortex and the periphery. *Current Opinion in Neurobiology*, *17*(6), 649–655. https://doi.org/10.1016/j.conb.2008.01.007

Besomi, M., Hodges, P. W., Clancy, E. A., van Dieën, J., Hug, F., Lowery, M., Merletti, R., Søgaard, K., Wrigley, T., Besier, T., Carson, R. G., Disselhorst-Klug, C., Enoka, R. M., Falla, D., Farina, D., Gandevia, S., Holobar, A., Kiernan, M. C., McGill, K., … Tucker, K. (2020). Consensus for experimental design in electromyography (CEDE) project: Amplitude normalization matrix. *Journal of Electromyography and Kinesiology*, *53*, 102438. https://doi.org/10.1016/j.jelekin.2020.102438

Borg, G. (1970). Perceived exertion as an indicator of somatic stress. *Scandinavian Journal of Rehabilitation Medicine*, *2*(2), 92–98.

Bourguignon, M., Jousmäki, V., Dalal, S. S., Jerbi, K., & De Tiège, X. (2019). Coupling between human brain activity and body movements: Insights from non-invasive electromagnetic recordings. *NeuroImage*, *203*, 116177. https://doi.org/10.1016/j.neuroimage.2019.116177

Bräscher, A.-K., Becker, S., Hoeppli, M.-E., & Schweinhardt, P. (2016). Different brain circuitries mediating controllable and uncontrollable pain. *Journal of Neuroscience*, *36*(18), 5013–5025. https://doi.org/10.1523/JNEUROSCI.1954-15.2016

Budini, F., McManus, L. M., Berchicci, M., Menotti, F., Macaluso, A., Russo, F. D., Lowery, M. M., & Vito, G. D. (2014). Alpha band cortico-muscular coherence occurs in healthy individuals during mechanically-induced tremor. *PLoS One*, *9*(12), e115012. https://doi.org/10.1371/journal.pone.0115012

Burden, A. (2010). How should we normalize electromyograms obtained from healthy participants? What we have learned from over 25years of research. *Journal of Electromyography and Kinesiology*, *20*(6), 1023–1035. https://doi.org/10.1016/j.jelekin.2010.07.004

Canestri, R., Franco-Alvarenga, P. E., Brietzke, C., Vinícius, Í., Smith, S. A., Mauger, A. R., Goethel, M. F., & Pires, F. O. (2021). Effects of experimentally induced muscle pain on endurance performance: A proof-of-concept study assessing neurophysiological and perceptual responses. *Psychophysiology*, *58*(6), e13810. https://doi.org/10.1111/psyp.13810

Chakarov, V., Naranjo, J. R., Schulte-Mönting, J., Omlor, W., Huethe, F., & Kristeva, R. (2009). Beta-range EEG-EMG coherence with isometric compensation for increasing modulated low-level forces. *Journal of Neurophysiology*, *102*(2), 1115–1120. https://doi.org/10.1152/jn.91095.2008

Chang, P., Arendt-Nielsen, L., Graven-Nielsen, T., Svensson, P., & Chen, A. C. (2001). Different EEG topographic effects of painful and non-painful intramuscular stimulation in man. *Experimental Brain Research*, *141*(2), 195–203. https://doi.org/10.1007/s002210100864

Chang, P.-F., Arendt-Nielsen, L., Graven-Nielsen, T., & Chen, A. C. N. (2003). Psychophysical and EEG responses to repeated experimental muscle pain in humans: Pain intensity encodes EEG activity. *Brain Research Bulletin*, *59*(6), 533–543. https://doi.org/10.1016/S0361-9230(02)00950-4

Chen, A. C. N., & Rappelsberger, P. (1994). Brain and human pain: Topographic EEG amplitude and coherence mapping. *Brain Topography*, *7*(2), 129–140. https://doi.org/10.1007/BF01186771

Chien, J. H., Liu, C. C., Kim, J. H., Markman, T. M., & Lenz, F. A. (2014). Painful cutaneous laser stimuli induce event-related oscillatory EEG activities that are different from those induced by nonpainful electrical stimuli. *Journal of Neurophysiology*, *112*(4), 824–833. https://doi.org/10.1152/jn.00209.2014

Cohen, J. (1992). Statistical power analysis. *Current Directions in Psychological Science*, *1*(3), 98–101. https://doi.org/10.1111/1467-8721.ep10768783

Cohen, M. X. (2014). *Analyzing neural time series data: Theory and practice*. MIT Press.

Contessa, P., Adam, A., & De Luca, C. J. (2009). Motor unit control and force fluctuation during fatigue. *Journal of Applied Physiology*, *107*(1), 235–243. https://doi.org/10.1152/japplphysiol.00035.2009

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

Donoghue, T., Haller, M., Peterson, E. J., Varma, P., Sebastian, P., Gao, R., Noto, T., Lara, A. H., Wallis, J. D., Knight, R. T., Shestyuk, A., & Voytek, B. (2020). Parameterizing neural power spectra into periodic and aperiodic components. *Nature Neuroscience*, *23*(12), Article 12. https://doi.org/10.1038/s41593-020-00744-x

Engel, A. K., & Fries, P. (2010). Beta-band oscillations—Signalling the status quo? *Current Opinion in Neurobiology*, *20*(2), 156–165. https://doi.org/10.1016/j.conb.2010.02.015

Enoka, R. M., & Farina, D. (2021). Force steadiness: From motor units to voluntary actions. *Physiology*, *36*(2), 114–130. https://doi.org/10.1152/physiol.00027.2020

Esen, O., Faisal, A., Zambolin, F., Bailey, S. J., & Callaghan, M. J. (2022). Effect of nitrate supplementation on skeletal muscle motor unit activity during isometric blood flow restriction exercise. *European Journal of Applied Physiology*, *122*(7), 1683–1693. https://doi.org/10.1007/s00421-022-04946-y

Farina, D., Negro, F., Gizzi, L., & Falla, D. (2012). Low-frequency oscillations of the neural drive to the muscle are increased with experimental muscle pain. *Journal of Neurophysiology*, *107*(3), 958–965. https://doi.org/10.1152/jn.00304.2011

Ferracuti, S., Seri, S., Mattia, D., & Cruccu, G. (1994). Quantitative EEG modifications during the cold water pressor test: Hemispheric and hand differences. *International Journal of*

Psychophysiology, *17*(3), 261–268. https://doi.org/10.1016/0167-8760(94)90068-X

Field, A. (2013). *Discovering statistics using IBM SPSS statistics*. SAGE.

Finn, H. T., Kennedy, D. S., Green, S., & Taylor, J. L. (2020). Fatigue-related feedback from calf muscles impairs knee extensor voluntary activation. *Medicine and Science in Sports and Exercise*, *52*(10), 2136–2144. https://doi.org/10.1249/MSS.0000000000002362

Fisher, J. P., Young, C. N., & Fadel, P. J. (2015). Autonomic adjustments to exercise in humans. In *Comprehensive physiology* (pp. 475–512). John Wiley & Sons, Ltd. https://doi.org/10.1002/cphy.c140022

Gallicchio, G., Cooke, A., & Ring, C. (2016). Lower left temporal-frontal connectivity characterizes expert and accurate performance: High-alpha T7-Fz connectivity as a marker of conscious processing during movement. *Sport, Exercise, and Performance Psychology*, *5*(1), 14–24. https://doi.org/10.1037/spy0000055

Gandevia, S. C. (2001). Spinal and Supraspinal factors in human muscle fatigue. *Physiological Reviews*, *81*(4), 1725–1789. https://doi.org/10.1152/physrev.2001.81.4.1725

Gandevia, S. C., Allen, G. M., Butler, J. E., & Taylor, J. L. (1996). Supraspinal factors in human muscle fatigue: Evidence for suboptimal output from the motor cortex. *The Journal of Physiology*, *490*(2), 529–536. https://doi.org/10.1113/jphysiol.1996.sp021164

Garcia-Larrea, L., Perchet, C., Hagiwara, K., & André-Obadia, N. (2019). At-home cortical stimulation for neuropathic pain: A feasibility study with initial clinical results. *Neurotherapeutics*, *16*(4), 1198–1209. https://doi.org/10.1007/s13311-019-00734-3

Ge, W., & Khalsa, P. S. (2003). Encoding of compressive stress during indentation by group III and IV muscle Mechano-nociceptors in rat Gracilis muscle. *Journal of Neurophysiology*, *89*(2), 785–792. https://doi.org/10.1152/jn.00624.2002

Goodall, S., Howatson, G., & Thomas, K. (2018). Modulation of specific inhibitory networks in fatigued locomotor muscles of healthy males. *Experimental Brain Research*, *236*(2), 463–473. https://doi.org/10.1007/s00221-017-5142-x

Hermens, H. J., Freriks, B., Disselhorst-Klug, C., & Rau, G. (2000). Development of recommendations for SEMG sensors and sensor placement procedures. *Journal of Electromyography and Kinesiology*, *10*(5), 361–374. https://doi.org/10.1016/S1050-6411(00)00027-4

Hill, E. C., Rivera, P. M., Proppe, C. E., Gonzalez Rojas, D. H., Wizenberg, A. M., & Keller, J. L. (2022). Greater neuromuscular fatigue following low-load blood flow restriction than non-blood flow restriction resistance exercise among recreationally active men. *Journal of Neurophysiology*, *128*(1), 73–85. https://doi.org/10.1152/jn.00028.2022

Johnson, K. V. B., Edwards, S. C., Van Tongeren, C., & Bawa, P. (2004). Properties of human motor units after prolonged activity at a constant firing rate. *Experimental Brain Research*, *154*(4), 479–487. https://doi.org/10.1007/s00221-003-1678-z

Jones, M. D., Taylor, J. L., & Barry, B. K. (2017). Occlusion of blood flow attenuates exercise-induced hypoalgesia in the occluded limb of healthy adults. *Journal of Applied Physiology*, *122*(5), 1284–1291. https://doi.org/10.1152/japplphysiol.01004.2016

Jung, T.-P., Makeig, S., Bell, A. J., & Sejnowski, T. J. (1998). Independent component analysis of electroencephalographic and event-related potential data. In P. W. F. Poon & J. F. Brugge (Eds.), *Central auditory processing and neural modeling* (pp. 189–197). Springer US. https://doi.org/10.1007/978-1-4615-5351-9_17

Jurcak, V., Tsuzuki, D., & Dan, I. (2007). 10/20, 10/10, and 10/5 systems revisited: Their validity as relative head-surface-based positioning systems. *NeuroImage*, *34*(4), 1600–1611. https://doi.org/10.1016/j.neuroimage.2006.09.024

Karcioglu, O., Topacoglu, H., Dikme, O., & Dikme, O. (2018). A systematic review of the pain scales in adults: Which to use? *The American Journal of Emergency Medicine*, *36*(4), 707–714. https://doi.org/10.1016/j.ajem.2018.01.008

Kaufman, M. P., & Hayes, S. G. (2002). The exercise pressor reflex. *Clinical Autonomic Research*, *12*(6), 429–439. https://doi.org/10.1007/s10286-002-0059-1

Kaufman, M. P., Longhurst, J. C., Rybicki, K. J., Wallach, J. H., & Mitchell, J. H. (1983). Effects of static muscular contraction on impulse activity of groups III and IV afferents in cats. *Journal of Applied Physiology*, *55*(1), 105–112. https://doi.org/10.1152/jappl.1983.55.1.105

Kennedy, D. S., Fitzpatrick, S. C., Gandevia, S. C., & Taylor, J. L. (2015). Fatigue-related firing of muscle nociceptors reduces voluntary activation of ipsilateral but not contralateral lower limb muscles. *Journal of Applied Physiology*, *118*(4), 408–418. https://doi.org/10.1152/japplphysiol.00375.2014

Kilavik, B. E., Zaepffel, M., Brovelli, A., MacKay, W. A., & Riehle, A. (2013). The ups and downs of beta oscillations in sensorimotor cortex. *Experimental Neurology*, *245*, 15–26. https://doi.org/10.1016/j.expneurol.2012.09.014

Klimesch, W. (2012). Alpha-band oscillations, attention, and controlled access to stored information. *Trends in Cognitive Sciences*, *16*(12), 606–617. https://doi.org/10.1016/j.tics.2012.10.007

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: The inhibition–timing hypothesis. *Brain Research Reviews*, *53*(1), 63–88. https://doi.org/10.1016/j.brainresrev.2006.06.003

Kristeva, R., Patino, L., & Omlor, W. (2007). Beta-range cortical motor spectral power and corticomuscular coherence as a mechanism for effective corticospinal interaction during steady-state motor output. *NeuroImage*, *36*(3), 785–792. https://doi.org/10.1016/j.neuroimage.2007.03.025

Masri, B. A., Eisen, A., Duncan, C. P., & McEwen, J. A. (2020). Tourniquet-induced nerve compression injuries are caused by high pressure levels and gradients—A review of the evidence to guide safe surgical, pre-hospital and blood flow restriction usage. *BMC Biomedical Engineering*, *2*(1), 7. https://doi.org/10.1186/s42490-020-00041-5

Mauger, A. (2013). Fatigue is a pain—The use of novel neurophysiological techniques to understand the fatigue-pain relationship. *Frontiers in Physiology*, *4*, 104. https://doi.org/10.3389/fphys.2013.00104

Mendez-Balbuena, I., Huethe, F., Schulte-Mönting, J., Leonhart, R., Manjarrez, E., & Kristeva, R. (2012). Corticomuscular coherence reflects interindividual differences in the state of the Corticomuscular network during low-level static and dynamic forces. *Cerebral Cortex*, *22*(3), 628–638. https://doi.org/10.1093/cercor/bhr147

Mense, S., & Meyer, H. (1985). Different types of slowly conducting afferent units in cat skeletal muscle and tendon. *The Journal of Physiology*, *363*(1), 403–417. https://doi.org/10.1113/jphysiol.1985.sp015718

Miller, R. G., Giannini, D., Milner-Brown, H. S., Layzer, R. B., Koretsky, A. P., Hooper, D., & Weiner, M. W. (1987). Effects of fatiguing exercise on high-energy phosphates, force, and EMG: Evidence for three phases of recovery. *Muscle & Nerve*, *10*(9), 810–821. https://doi.org/10.1002/mus.880100906

Mima, T., & Hallett, M. (1999). Corticomuscular coherence: A review. *Journal of Clinical Neurophysiology*, *16*(6), 501.

Missenard, O., Mottet, D., & Perrey, S. (2008). The role of cocontraction in the impairment of movement accuracy with fatigue. *Experimental Brain Research*, *185*(1), 151–156. https://doi.org/10.1007/s00221-007-1264-x

Norbury, R., Smith, S. A., Burnley, M., Judge, M., & Mauger, A. R. (2022). The effect of hypertonic saline evoked muscle pain on neurophysiological changes and exercise performance in the contralateral limb. *Experimental Brain Research*, *240*(5), 1423–1434. https://doi.org/10.1007/s00221-022-06342-6

Ong, W.-Y., Stohler, C. S., & Herr, D. R. (2019). Role of the prefrontal cortex in pain processing. *Molecular Neurobiology*, *56*(2), 1137–1166. https://doi.org/10.1007/s12035-018-1130-9

Pani, S. M., Saba, L., & Fraschini, M. (2022). Clinical applications of EEG power spectra aperiodic component analysis: A mini-review. *Clinical Neurophysiology*, *143*, 1–13. https://doi.org/10.1016/j.clinph.2022.08.010

Parr, J. V. V., Gallicchio, G., Canales-Johnson, A., Uiga, L., & Wood, G. (2023). Cortical, muscular, and kinetic activity underpinning attentional focus strategies during visuomotor control. *Psychophysiology*, *60*(6), e14249. https://doi.org/10.1111/psyp.14249

Parr, J. V. V., Hodson-Tole, E., & Wood, G. (2022). Short report presenting preliminary evidence of impaired corticomuscular coherence in an individual with developmental coordination disorder. *Research in Developmental Disabilities*, *131*, 104355. https://doi.org/10.1016/j.ridd.2022.104355

Parr, J. V. V., Vine, S. J., Wilson, M. R., Harrison, N. R., & Wood, G. (2019). Visual attention, EEG alpha power and T7-Fz connectivity are implicated in prosthetic hand control and can be optimized through gaze training. *Journal of Neuroengineering and Rehabilitation*, *16*(1), 52. https://doi.org/10.1186/s12984-019-0524-x

Patterson, S. D., Hughes, L., Warmington, S., Burr, J., Scott, B. R., Owens, J., Abe, T., Nielsen, J. L., Libardi, C. A., Laurentino, G., Neto, G. R., Brandner, C., Martin-Hernandez, J., & Loenneke, J. (2019). Blood flow restriction exercise: Considerations of methodology, application, and safety. *Frontiers in Physiology*, *10*, 533. https://doi.org/10.3389/fphys.2019.00533

Perlis, M. L., Kehr, E. L., Smith, M. T., Andrews, P. J., Orff, H., & Giles, D. E. (2001). Temporal and stagewise distribution of high frequency EEG activity in patients with primary and secondary insomnia and in good sleeper controls. *Journal of Sleep Research*, *10*(2), 93–104. https://doi.org/10.1046/j.1365-2869.2001.00247.x

Pohja, M., & Salenius, S. (2003). Modulation of cortex-muscle oscillatory interaction by ischaemia-induced deafferentation. *Neuroreport*, *14*(3), 321–324.

Pollak, K. A., Swenson, J. D., Vanhaitsma, T. A., Hughen, R. W., Jo, D., Light, K. C., Schweinhardt, P., Amann, M., & Light, A. R. (2014). Exogenously applied muscle metabolites synergistically evoke sensations of muscle fatigue and pain in human subjects. *Experimental Physiology*, *99*(2), 368–380. https://doi.org/10.1113/expphysiol.2013.075812

Poortvliet, P. C., Tucker, K. J., Finnigan, S., Scott, D., & Hodges, P. W. (2019). Experimental pain decreases corticomuscular coherence in a force- but not a position-control task. *The Journal of Pain*, *20*(2), 192–200. https://doi.org/10.1016/j.jpain.2018.08.012

Raij, T. T., Numminen, J., Närvänen, S., Hiltunen, J., & Hari, R. (2009). Strength of prefrontal activation predicts intensity of suggestion-induced pain. *Human Brain Mapping*, *30*(9), 2890–2897. https://doi.org/10.1002/hbm.20716

Rosenberg, J. R., Amjad, A. M., Breeze, P., Brillinger, D. R., & Halliday, D. M. (1989). The Fourier approach to the identification of functional coupling between neuronal spike trains. *Progress in Biophysics and Molecular Biology*, *53*(1), 1–31. https://doi.org/10.1016/0079-6107(89)90004-7

Sidhu, S. K., Weavil, J. C., Mangum, T. S., Jessop, J. E., Richardson, R. S., Morgan, D. E., & Amann, M. (2017). Group III/IV locomotor muscle afferents alter motor cortical and corticospinal excitability and promote central fatigue during cycling exercise. *Clinical Neurophysiology*, *128*(1), 44–55. https://doi.org/10.1016/j.clinph.2016.10.008

Sidhu, S. K., Weavil, J. C., Thurston, T. S., Rosenberger, D., Jessop, J. E., Wang, E., Richardson, R. S., McNeil, C. J., & Amann, M. (2018). Fatigue-related group III/IV muscle afferent feedback facilitates intracortical inhibition during locomotor exercise. *The Journal of Physiology*, *596*(19), 4789–4801. https://doi.org/10.1113/JP276460

Tanaka, M., & Watanabe, Y. (2012). Supraspinal regulation of physical fatigue. *Neuroscience & Biobehavioral Reviews*, *36*(1), 727–734. https://doi.org/10.1016/j.neubiorev.2011.10.004

Taylor, J. L., Amann, M., Duchateau, J., Meeusen, R., & Rice, C. L. (2016). Neural contributions to muscle fatigue: From the brain to the muscle and back again. *Medicine and Science in Sports and Exercise*, *48*(11), 2294–2306. https://doi.org/10.1249/MSS.0000000000000923

Ushiyama, J., Katsu, M., Masakado, Y., Kimura, A., Liu, M., & Ushiba, J. (2011). Muscle fatigue-induced enhancement of corticomuscular coherence following sustained submaximal isometric contraction of the tibialis anterior muscle. *Journal of Applied Physiology*, *110*(5), 1233–1240. https://doi.org/10.1152/japplphysiol.01194.2010

Vieira, T. M., & Botter, A. (2021). The accurate assessment of muscle excitation requires the detection of multiple surface electromyograms. *Exercise and Sport Sciences Reviews*, *49*(1), 23–34. https://doi.org/10.1249/JES.0000000000000240

Witte, M., Patino, L., Andrykiewicz, A., Hepp-Reymond, M.-C., & Kristeva, R. (2007). Modulation of human corticomuscular beta-range coherence with low-level static forces. *European Journal of Neuroscience*, *26*(12), 3564–3570. https://doi.org/10.1111/j.1460-9568.2007.05942.x

Yang, Q., Fang, Y., Sun, C.-K., Siemionow, V., Ranganathan, V. K., Khoshknabi, D., Davis, M. P., Walsh, D., Sahgal, V., & Yue, G. H. (2009). Weakening of functional corticomuscular coupling during muscle fatigue. *Brain Research*, *1250*, 101–112. https://doi.org/10.1016/j.brainres.2008.10.074

Yang, Q., Siemionow, V., Yao, W., Sahgal, V., & Yue, G. H. (2010). Single-trial EEG-EMG coherence analysis reveals muscle fatigue-related progressive alterations in Corticomuscular coupling. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *18*(2), 97–106. https://doi.org/10.1109/TNSRE.2010.2047173

Zambolin, F., Giuriato, G., Laginestra, F. G., Ottaviani, M. M., Favaretto, T., Calabria, E., Duro-Ocana, P., Bagley, L., Faisal, A., Peçanha, T., McPhee, J. S., & Venturelli, M. (2022). Effects of nociceptive and mechanosensitive afferents sensitization on central and peripheral hemodynamics following exercise-induced muscle damage. *Journal of Applied Physiology*, *133*(4), 945–958. https://doi.org/10.1152/japplphysiol.00302.2022

Zambolin, F., Peçanha, T., Pinner, S., Venturelli, M., & McPhee, J. S. (2023). Effects of exercise induced muscle damage on cardiovascular responses to isometric muscle contractions and post-exercise circulatory occlusion. *European Journal of Applied Physiology*, 1–8. https://doi.org/10.1007/s00421-023-05255-8

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Figure 1. Topoplots displaying the paired sample *t*-values comparing regional EEG alpha activity between the three-time windows for each experimental condition. For the first two columns (early vs middle; early vs late) scalp regions that are blue indicate lower alpha activity relative to the early phase, whereas red regions indicate higher alpha activity relative to the early phase. For the third column, blue regions indicate lower alpha activity in the late phase, whereas red regions indicate higher alpha activity in the late phase. Channels highlighted yellow indicate a statistically significant difference.

Beta power. No differences were observed between any task phases for any experimental condition.

Figure 2. Topoplots displaying the paired sample *t*-values comparing regional EEG beta activity between the three-time windows for each experimental condition. For the first two columns (early vs middle; early vs late) scalp regions that are blue indicate lower beta activity relative to the early phase, whereas red regions indicate higher beta activity relative to the early phase. For the third column, blue regions indicate lower beta activity in the late phase, whereas red regions indicate higher beta activity in the late phase. Channels highlighted yellow indicate a statistically significant difference.

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