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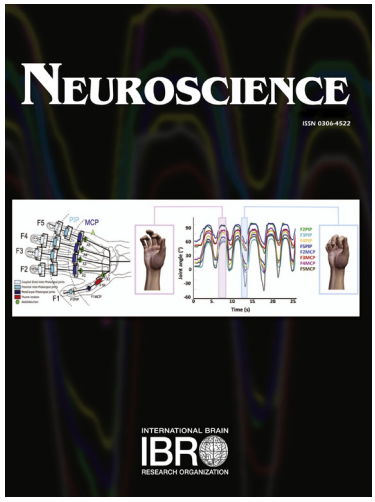

Research Article

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Research report

Acute exercise modulates pain-induced response on sensorimotor cortex ~20 Hz oscillation

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ABSTRACT

Exercise affects positively on self-reported pain in musculoskeletal pain conditions possibly via top-down pain inhibitory networks. However, the role of cortical activity in these networks is unclear. The aim of the current exploratory study was to investigate the effects of acute exercise on cortical nociceptive processing and specifically the excitability in the human sensorimotor cortex. Five healthy adults (mean age 32.8 years) were recorded with a whole-head 306-channel magnetoencephalography (MEG, Elekta Neuromag® Triux™). Participant's right hand third fingertip was stimulated electrically with an intracutaneous non-magnetic copper tip electrode before and immediately after an exercise task. Stimulus intensity was set individually so that the stimulation was subjectively rated as moderately painful, 6-7 on a visual analog scale. The acute exercise task was an isometric three-minute fatiguing left hand contraction with force-level at 30% of maximum voluntary contraction. Data analysis was conducted as event-related evoked field and frequency analysis. Early cortical activations after stimulation were localized in the primary and secondary somatosensory cortices. The main result demonstrated modulation of cortical nociceptive processing in the sensorimotor cortex ~20 Hz rhythm immediately after the acute exercise. In conclusion, acute exercise may have an effect on nociceptive processing in the sensorimotor cortex on oscillatory level. Research on cortical oscillations analyzing interaction between nociception and exercise is limited. This study presents results indicating brain oscillatory activity as a feasible research target for examining mechanisms interacting between exercise and cortical nociceptive processing.

Keywords: magnetoencephalography; exercise; sensorimotor cortex; brain oscillations; electrical stimulation

INTRODUCTION

Pain is an important factor affecting quality of life in various musculoskeletal pain conditions. However, intriguingly exercise therapy has shown positive changes on self-reported pain (van Middelkoop et al., 2010; Pedersen and Saltin, 2015) suggesting an important role for exercise in pain management interventions. Hypoalgesic effect, a reduction of the perception of experimentally induced pain, has been shown to occur after different types of exercise, including aerobic and isometric or dynamic resistance exercise (Naugle et al., 2012; Rice et al., 2019). While long-term physical activity can reduce pain perception, as elegantly demonstrated in athletes by Tesarz et al. (2013), also short bouts of voluntary exercise may induce hypoalgesic effects (Koltyn et al., 2014) suggesting measurable modulation in the processing of nociceptive stimuli and resulting pain perception.

Pain experience is altered by the modulation of ascending and descending nociceptive pathways in a network of primary afferents and specific brain areas involved in pain perception (Apkarian et al., 2005). Brain imaging studies in humans have identified brain areas involved in this network including sensorimotor, limbic and associative brain areas (Duerden and Albanese, 2013). With modern electrophysiological brain imaging methods (e.g. magnetoencephalography, MEG and electroencephalography, EEG) cortical nociceptive processing can be investigated (e.g. event-related cortical activation or spontaneous brain oscillations) with high temporal resolution close to the stimulus onset. Spontaneous brain oscillations at frequencies around 10 Hz (alpha) and 20 Hz (beta) can be observed in MEG recordings in the sensorimotor cortex (Hari and Salmelin, 1997). The brain oscillatory activity is associated with cortical excitability (Ploner et al., 2006a) where event-related suppression or desynchronization of the oscillation amplitude reflects increased cortical excitability and following rebound or synchronization reflects cortical inhibition (Pfurtscheller and Lopes da Silva, 1999). Previous research has shown that alpha band activity in the somatosensory cortex (Ploner et al., 2006b) and beta band activity in the motor cortex (Raij et al., 2004) are modulated by nociceptive stimulation.

Event-related evoked potentials in EEG and corresponding magnetic fields in MEG can be considered as a series of post-synaptic pyramidal neuron responses triggered by a delivered stimulation (Pfurtscheller and Lopes da Silva, 1999), for example, after painful electrical stimulation (Kitamura et al., 1995). Only few studies have concentrated on modulation of

nociceptive cortical processing after any type of exercise using electrophysiological measurements with evoked potential analysis (Friedman et al., 1993; Jones et al., 2016) and measuring cortical activation immediately after stimulus. Presently we are not aware of any studies focusing on sensorimotor brain oscillations as an outcome when investigating interaction between cortical nociceptive processing and exercise.

Exercise has shown hypoalgesic effects and the underlying mechanisms are suggested to involve endogenous opioid system (Koltyn et al., 2014; Naugle et al., 2012; Rice et al., 2019). However, cortical involvement in exercise-induced consequences to nociceptive processing is still unclear. Thus, we asked the wide-ranging question how acute painful stimulus is processed in the brain and whether acute exercise affects this processing.

Here we designed a noninvasive study to explore the effects of acute exercise on cortical nociceptive processing and excitability in the human sensorimotor cortex. We chose an isometric fatiguing contraction of the left hand and utilized an intracutaneous electrical stimulation technique we reported recently (Hautasaari et al., 2018). We used this stimulation technique and a time-locked evoked field and frequency analysis of a whole-head MEG data to assess cortical nociceptive response after exercise.

EXPERIMENTAL PROCEDURES

Participants

Five healthy adult volunteers (mean age: 32.8 ± 7.0 years, 5 females, mean body mass index: 21.8 ± 0.7) were recruited into the study. All participants were right-handed and did not have history of neurological or psychiatric diseases. RBDI mood questionnaire (Raitasalo, 2007), a short version of the Beck Depression Inventory (Beck et al., 1961) modified to Finnish language, was used to verify the absence of depressive and anxiety symptoms among the participants. Prior to magnetoencephalographic (MEG) data collection, the task and the type of stimuli were explained to each participant and a short recording was conducted to ensure that no magnetic objects were present in their head or upper body which could create artefacts in the MEG recording. The study was approved by the Ethics Committee of the University of Jyväskylä and conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent prior to participation.

Stimulation procedures

We used an intracutaneous electrical method for nociceptive stimulation (DeMeTec SCG30, DeMeTec GmbH, Langgöns, Germany) adapted from Kochs et al. (1996). The stimulation was delivered to the participant's third fingertip. The superficial layers of the glabrous skin were lightly drilled with a small stainless steel drill (diameter of 1.5 mm). A non-magnetic copper tip electrode (diameter 1 mm, height 2 mm) was attached into the small skin hole with adhesive tape. A flexible non-magnetic metal ring return electrode (Technomed Europe Ltd., Maastricht, the Netherlands) was tightened in the metacarpophalangeal joint of the third finger. The delivered square-wave current pulse of 0.2 ms duration activated palmar digital branch of the median nerve and likely activated superficial nociceptive nerve terminals. Stimulation intensity (mean 4.0 ± 1.8 mA) was set individually to each participant so that the stimulation was rated as moderately painful, 6-7 on a visual analog scale (VAS 0–10). Participants were asked to describe their perception of the stimulation and they expressed it as a stinging pain. The interstimulus interval during recording was random within the range of 5.5 – 7.5 seconds and 30 repetitions were recorded. Participants were instructed not to move and to focus their gaze on a marker approximately 1.5 meters in front of them during the stimulations. The difference between the evoked fields elicited by the present intracutaneous nociceptive third finger stimulation and the innocuous cutaneous stimulation of the second finger can be evaluated in Fig. 1. The waveform component at 22 ms (intracutaneous stimulation) and at 23 ms (cutaneous stimulation) after stimulation is observable, albeit small. With similar stimulation intensities (intracutaneous mean 4.6 ± 2.2 mA and cutaneous 4.9 ± 1.0 mA), the amplitudes of the 50 ms and the 100 ms components are markedly stronger after nociceptive intracutaneous stimulation (previously collected data from Hautasaari et al. (2018; 2019)).

Exercise task

The acute exercise task was a left hand three-minute isometric grip contraction using a hand dynamometer (Saehan SH5001, Saehan Inc., Korea). The force level was set at 30 percent of maximum voluntary contraction (MVC). MVC force was measured (mean 262.8 ± 44.1 N) at the beginning of the measurement session, at least 30 minutes before the MEG recording to ensure that any mild hypoalgesic effects from the MVC contraction would have subsided (Naugle et al., 2012). The exercise task was strenuous and fatiguing and the rating of perceived exertion (RPE) resulted in a mean of 17.3 ± 1.5 on Borg's RPE scale (6–20) (Borg, 1970).

Experimental procedures

The brain activity recording was conducted twice, before and immediately after the exercise task. Between the two MEG recordings with nociceptive stimulations to the right hand third fingertip, there was 10 minutes of rest to ensure the recovery of the primary afferent responsiveness and to prevent adaptation to the stimulation within session (LaMotte and Campbell, 1978). The exercise task with the left hand was timed to the last three minutes of the 10 min rest period and the second MEG recording was performed immediately after the exercise task. The same individually adjusted stimulation intensity was used in both MEG recordings and the VAS scores were collected after each recording (mean before: 6.0 ± 0.5 and after: 6.6 ± 0.7).

MEG recording

MEG signals were recorded with a whole-scalp 306-channel device (Elekta Neuromag®, Triux©, Stockholm, Sweden) using a bandpass filter of 0.1–330 Hz and digitized at 1000 Hz. The participant's head position in relation to the MEG sensors were determined with five head position indicators (HPI), placed on the participant's scalp and forehead. Prior to the MEG recording, the HPI coil positions were registered with a 3D digitizer (Fastrak®, Polhemus, Colchester, VT, USA) in relation to the participant's three anatomical landmarks (nasion and bilateral preauricular points). Additional points were registered from the scalp surface, nose crest and the forehead for accurate representation of the participant's head shape. The participants were comfortably seated in the MEG device, installed inside a magnetically shielded room (Vacuumschmelze GmbH, Hanau, Germany), for data recording. The participants were instructed to keep their eyes open and to avoid blinking, eye movements and other voluntary movements during the recording while their eye movements and blinks were continuously monitored with electro-oculogram (EOG). The MEG and EOG signals were stored for offline processing and analysis.

Data analysis

The MEG recordings were first preprocessed and then two analysis pathways were adopted, namely event-related field analysis and oscillatory analysis based on spectral contents of the signals. The raw MEG data was first processed with the signal-space separation method (SSS) (Taulu et al., 2004) implemented in MaxFilter software (version 2.2; Elekta Oy, Helsinki, Finland) to suppress environmental electromagnetic interference. The data was preprocessed and analyzed with Brainstorm software (version released 24th Feb 2019) (Tadel et al., 2011).

All data were visually inspected for environmental and physiological artifacts. Artifacts from blinks were identified and corrected with signal-space projectors (Uusitalo and Ilmoniemi, 1997). The data was segmented to epochs surrounding each stimulus onset from -1500 ms to 2500 ms including 500 ms buffers to avoid signal distortions caused by subsequent filtering. A stimulation delay of 3 ms, identified from stimulation artefact, was corrected. The stimulation artifact was removed surrounding the stimulus onset (-4 to 8 ms) by replacing the values in this short time period with linear interpolation.

Evoked field analysis and source estimation

For the evoked field analysis, a 50 Hz notch filter was applied to remove the power line noise and then the data was filtered with a 70 Hz low-pass filter using a linear finite impulse response filter with stopband attenuation at 60 dB. The epochs were segmented for 700 ms time windows (-200, 500 ms) and baseline corrected (-200, -5 ms) before averaging. For source estimation, a forward model was computed using the overlapping spheres method (Huang et al., 1999). Magnetic resonance image (MRI) anatomy template (ICBM152) was aligned and scaled for each participant using their individual digitized head shape. For each participant and for both conditions, source maps were produced from trial averages and derived from the minimum-norm estimate using default parameters. Noise covariance statistics were derived from the empty room recordings collected before each measurement session. Source dipole orientations were constrained to the cortical surface and all MEG channels were included. The current density source maps were normalized with Z-transformation with respect to the baseline (-200, -5 ms). Finally, the source maps were smoothed spatially. Regions of interest (ROI) analysis were explored with Brainstorm's scout function. Scouts were set to cover 20 vertices, corresponding to approximately 4 cm^2 on the cortical surface. Scout locations were determined in source maps as the maximum source amplitudes using the evoked field waveform components after stimulation onset as temporal cues.

Temporal spectral evolution analysis

Temporal spectral evolution analysis (TSE) (Salmelin and Hari, 1994) was adopted to quantify the modulation of rhythmic activity in the ~20 Hz and ~10 Hz sensorimotor cortex rhythms. MEG signals were separately filtered through 15-25 Hz and 8-12 Hz frequency ranges and then rectified. Before averaging each participant's data, the signals were smoothed with 15 Hz low-pass filter and finally segmented to time window of interest (-500, 2000 ms). The stimulus-related changes in both rhythms were quantified from one planar gradiometer channel in each

hemisphere over sensorimotor regions. The gradiometer channels were selected based on their strongest reactivity, i.e. the largest change in amplitude from suppression to rebound. The suppression and rebound amplitudes were converted to relative values by calculating the percentage of the rhythms amplitude decrease and increase in relation to the reference baseline. Suppression and rebound strengths were determined as the mean amplitude ± 5 ms around the maximum value and latencies as the time points at maximum value of the suppression and rebound.

Statistical analysis

The measured electrophysiological parameters: peak latencies and amplitudes of the brain source activations, and oscillation reactivity were compared between conditions within participant. Variables were tested with the Shapiro-Wilk -test for normal distribution. When variables were normally distributed paired samples t-test was utilized and when they were not normally distributed the Wilcoxon signed rank -test was utilized (IBM SPSS 24, IBM, Armonk, NY, USA). Means and medians will be reported for parametrically and non-parametrically tested variables, respectively.

RESULTS

Evoked field and source analysis

Fig. 2 shows the source activations elicited by the nociceptive electrical stimulation before and after exercise. Strongest source activation in the contralateral primary somatosensory cortex (SI) after nociceptive stimuli peaked at corresponding mean time points (before: 45 ± 10.5 ms and after: 48 ± 7.7 ms, $t(4) = -0.995$, $p = 0.376$). Following the aforementioned SI source activity the next source activation was detected in the secondary somatosensory cortex (SII) and peaked in the contralateral (before: 101 ± 17.2 ms and after: 103 ± 16.9 ms, $t(4) = -0.816$, $p = 0.461$) and in the ipsilateral (before: 103 ± 15.7 ms and after: 106 ± 17.8 ms, $t(4) = -1.75$, $p = 0.154$) hemispheres, again showing corresponding latencies before and after exercise. Source mean amplitudes corresponded between conditions in the SI cortex (before: 11.5 ± 7.5 Z-score and after: 9.3 ± 4.0 Z-score, $t(4) = 1.09$, $p = 0.337$) and in the SII cortices, in the contralateral (before: 11.1 ± 5.1 Z-score and after: 11.5 ± 4.6 Z-score, $t(4) = -0.596$, $p = 0.584$) and in the ipsilateral (before: 8.3 ± 1.4 Z-score and after: 8.0 ± 3.4 Z-score, $t(4) = 0.185$, $p = 0.862$) hemispheres. Evoked field analysis did not detect significant differences between conditions in source latencies or amplitudes.

Modulation of sensorimotor ~20 Hz and ~10 Hz rhythms

Fig. 3 illustrates results of the five participants' ~20 Hz rhythm TSE analysis in the grand average waveforms before and after exercise. The strength of the stimulation-elicited suppression increased after the exercise task in the contralateral hemisphere (suppression before: 33.2 ± 7.7% and after: 41.8 ± 11.3%, $t(4) = 2.807$, $p = 0.048$), but the observed modulation at the same time did not reach statistical significance in the ipsilateral hemisphere (suppression before: 33.7 ± 9.6% and after: 38.3 ± 7.8%, $t(4) = 2.577$, $p = 0.062$). The strength of the stimulation-elicited rebound showed a tendency towards decreased amplitude after the exercise, however, this difference did not reach statistical significance in the contralateral (rebound before: 90.6 ± 34.0% and after: 60.5 ± 30.9%, $t(4) = 2.289$, $p = 0.084$) or in the ipsilateral hemispheres (rebound before: 62.2 ± 34.8% and after: 39.5 ± 11.8%, $t(4) = 1.619$, $p = 0.181$). Fig. 4 illustrates the amplitude behavior of the ~20 Hz rhythm in group-level. Furthermore, the modulation of the ~20 Hz rhythm suppression amplitude in contralateral hemisphere occurred to the same direction in each participant (Fig. 5).

The results of the five participants' ~10 Hz rhythm TSE analysis as the grand average is illustrated in Fig. 6. This frequency band did not show differences in the suppression strength (suppression before: 23.7 ± 5.5% and after: 27.2 ± 6.9%, $t(4) = 0.952$, $p = 0.395$) or in the rebound strength (rebound before: 38.5 ± 12.0% and after: 25.5 ± 18.8%, $t(4) = 1.817$, $p = 0.143$) in the hemisphere contralateral to stimulation. Two variables, suppression and rebound strength ipsilateral to stimulation before exercise, were not normally distributed and thus were tested with non-parametric test against corresponding variables after exercise. The suppression strength (suppression before: 27.8% and after 25.7%, $Z = -0.94$, $p = 0.345$) or the rebound strength (rebound before: 16.0% and after: 21.2%, $Z = -0.674$, $p = 0.50$) did not differ in the hemisphere ipsilateral to stimulation before and after exercise.

The mean latencies of the ~20 Hz rhythm (Fig. 3) maximum suppression in the hemisphere contralateral (before: 277 ± 42 ms and after: 287 ± 84, $t(4) = -0.365$, $p = 0.734$) or ipsilateral (before: 260 ± 22 ms and after: 351 ± 83, $t(4) = -2.361$, $p = 0.078$) to the stimulation did not differ between conditions. Neither did the latencies of the maximum rebound in the hemisphere contralateral (before: 822 ± 118 ms and after: 823 ± 253, $t(4) = -0.011$, $p = 0.992$) or ipsilateral (before: 982 ± 279 ms and after: 798 ± 202, $t(4) = 1.622$, $p = 0.180$) to the stimulation. Corresponding non-significant finding for the maximum suppression latency was observed in

the ~10 Hz rhythm (Fig. 6) in the hemisphere contralateral (before: 446 ± 216 ms and after: 468 ± 115 ms, t(4) = -0.331, p = 0.758) and ipsilateral (before: 491 ± 110 ms and after: 457 ± 100 ms, t(4) = 0.580, p = 0.593) to the stimulation. Furthermore, the maximum rebound latencies in the ~10 Hz rhythm did not differ in the hemisphere contralateral (before: 1342 ± 433 ms and after: 941 ± 207 ms, t(4) = 1.581, p = 0.189) or ipsilateral (before: 1150 ± 352 ms and after: 1323 ± 349 ms, t(4) = -1.268, p = 0.274) to the stimulation.

DISCUSSION

The present study reveals modulation in the oscillatory nociceptive processing over sensorimotor cortex after acute exercise in healthy humans. This modulation is observable in the ~20 Hz motor cortex rhythm in our MEG recordings. Fig. 4 illustrates the amplitude behavior of the ~20 Hz rhythm in group-level and Fig. 5 shows the ~20 Hz rhythm suppression amplitude change in contralateral hemisphere of each participant's individual data. Furthermore, our present results support previous findings (Raij et al., 2004) showing that nociceptive stimulation is a powerful modulator of both ~20 Hz and ~10 Hz sensorimotor rhythms. The isometric 3-minute handgrip contraction was performed with the left hand and the nociceptive intracutaneous electrical stimuli were delivered to the right hand. This way we were able to immediately apply the stimulation and register the cortical processes directly after exercise.

In order to assess acute nociceptive processing in the cerebral cortex, we modified the electrical stimulation procedure earlier reported by Kochs et al. (1996). Short electrical pulses directed by 1 mm diameter pin to the fingertip produced a stinging pain -like sensation. Stronger amplitudes of the 50 ms and 100 ms nociceptive evoked fields waveform components compared to innocuous somatosensory evoked fields after finger stimulations can be observed in Fig.1. Previously, Kitamura et al. (1995) have shown similarly that electrical stimulation on fingers with painful intensity increases amplitudes of the evoked fields. The nociceptive stimulation-evoked fields with the strongest amplitude at about 50 ms were generated primarily in contralateral SI area and the sources of the clear deflection at about 100 ms were found in contra- and ipsilateral SII areas (Fig. 2). These cortical sources correspond with previous research, as the contralateral SI cortex activation after peripheral stimulation is robustly reported phenomenon (Kakigi et al., 2000). The current data did not reveal activation in the ipsilateral SI cortex as it has been far more elusive to record possibly due to stimulation type

and intensity, variability among participants or alternatively, weaker response from ipsilateral SI could be masked by stronger ipsilateral SII activation (Allison et al., 1989; Korvenoja et al., 1995; Hautasaari et al., 2019). The bilateral activation in SII cortices is more frequently reported phenomenon and the current finding corresponds with previous research indicating callosal transmission between hemispheres (Frot and Mauguière, 1999; Khoshnejad et al., 2014; Hautasaari et al., 2018).

With the current limited number of subjects, we did not observe amplitude or latency modulation in the observed sources after exercise. Related finding is that Jones et al. (2016) did not find consistent exercise-induced modulation in their somatosensory evoked potentials (SEP) measured with EEG. They speculated that the reason for the lack of clear modulation to the evoked potentials could be the contribution of non-nociceptive pathways to their SEP (Jones et al., 2016). The processing of acute pain involves a network of ascending and descending nociceptive pathways and specific brain areas, including SI, SII, insular, anterior cingulate and prefrontal cortices and thalamus (Apkarian et al., 2005; Duerden and Albanese, 2013). The present data did not reveal consistent activation e.g. in the anterior cingulate cortex (ACC). ACC is likely involved in the conscious and affective processing of pain (Apkarian et al., 2005) and it may be that the ACC is activated at later phase of stimulation processing. Another factor for not detecting consistent ACC activation may be that MEG is predisposed towards sources closer to the sensors. In the present study, we focused on the early automatic processing of the nociceptive stimulation and were able to localize activations to the SI and SII cortices. SI and SII areas are involved in the processing of sensory features of pain (Apkarian et al., 2005). The current data did not reveal modulation in the nociceptive stimulation-induced SI and SII activations after exercise. However, it may be that the present early evoked magnetic fields peaking before 200 ms and corresponding brain activations in the SI and SII cortices may be sensitive to stimulation intensity but not yet involved in integration of nociceptive information towards coherent pain perception.

The present MEG recorded brain oscillations at ~20 Hz (Fig. 3) and ~10 Hz (Fig. 6) rhythms revealed suppression and rebound after nociceptive stimulation in accordance with previous research (Raij et al., 2004), however, only ~20 Hz rhythm was significantly modulated after acute exercise. After acute exercise, the stimulation-induced ~20 Hz rhythm suppression was stronger and it was followed by a tendency towards weaker rebound, in other words, cortical excitability increased and following inhibition decreased (Fig. 4). In previous studies, the ~20

Hz rhythm after somatosensory stimulation has been located to the primary motor cortex (MI) bilaterally (Hari et al., 1997; Salenius et al., 1997; Cheyne et al., 2003; Gaetz and Cheyne, 2006). Furthermore, MI activation has been confirmed after nociceptive stimulation (Raij et al., 2004; Duerden and Albanese, 2013; Melzack and Wall, 1965) implicating probable activation of sensory and motor systems in preparation to react to relevant adverse stimuli (Ploner et al., 2006b; Gaetz and Cheyne, 2006).

In order to understand the possible functional significance of the increased suppression of the ~20 Hz rhythm after acute exercise we believe that transcranial magnetic stimulation (TMS) studies can shed light to this. High-frequency repetitive TMS (rTMS) to MI cortex has been reported to have an analgesic effect (Leo and Latif, 2007). High-frequency rTMS modulates neuronal activity by inducing increased excitability in the stimulated brain area (Pascual-Leone et al., 1998) and may instigate subsequent diminished intracortical inhibition (Kozyrev et al., 2014). While the exact mechanisms for rTMS induced analgesia are not yet clear it is suggested that activity modulation after rTMS spreads from local cortical site (e.g. MI) down to thalamic nuclei and ascending nociceptive information may thus be suppressed in part in the spinothalamic tract (Leo and Latif, 2007).

Similarly to these high-frequency rTMS effects, exercise may have common mechanisms as single pulse TMS studies have shown that fatiguing exercise modulates cortical activity by increasing MI excitability and decreasing intracortical inhibition (Otieno et al., 2019). Furthermore, in addition to simple fatiguing exercise task, previous studies have shown that aerobic exercise (Opie and Semmler, 2019) or strength training (Kidgell et al., 2017) induce modulation in cortical excitability and inhibitory function. Opie and Semmler (2019) suggest that exercise intensity affects the motor cortical response to exercise and increased corticospinal excitability and decreased intracortical inhibition may require relatively high intensity exercise. In study with six subjects, Rio et al. (2015) found that isometric contractions reduced tendon pain in patellar tendinopathy and this reduction was paralleled with reduction in cortical inhibition. These exercise-induced modulatory effects on the MI cortex have been suggested to be driven by a decrease in GABAergic intracortical inhibition following exercise (Otieno et al., 2019; Kidgell et al., 2017). Importantly, changes in cortical excitability may imply neuroplastic effects mediated by long-term potentiation and depression of synaptic activity (Sanes and Donoghue, 2000) and even only an acute bout of exercise may enhance MI neuroplasticity (Singh et al., 2014). Additionally, previous research has suggested that

unilateral exercise task may result in bilateral increases in corticospinal excitability (Carroll et al., 2008; Goodwill et al., 2012). The present data corresponds with these previous studies showing modulation of the sensorimotor cortex oscillatory activity, namely the increase in excitability in the MI cortex (i.e., increased ~20 Hz rhythm suppression) and the trend towards decrease in inhibition in the MI cortex (i.e., decreased ~20 Hz rhythm rebound). Interestingly, Granovsky et al. (2019) reported that increased motor cortex corticospinal excitability is associated with more efficient inhibitory pain modulation, demonstrated with conditioned pain modulation (CPM). However, because of limited research currently available, a comparison between MEG and TMS parameters assessing cortical excitability and inhibition should be interpreted with caution (Mäkelä et al., 2015).

As the present results demonstrate modulation in the cortical level, we can speculate, based on our data and previous findings, that changes in cortical oscillatory activity may be a part of the exercise-induced modulation of nociceptive processing via top-down pathways. Top-down pain modulation has been suggested to exist in the form of a descending pain modulatory circuit with input from multiple cortical brain areas feeding to midbrain and further to the medulla (Ossipov et al., 2010; De Felice and Ossipov, 2016) and furthermore, MI is indicated to be part of this network. Previous research has suggested that beta band oscillatory activity could have a role in neural communication between cortical and subcortical networks (Cheyne, 2013; Hari et al., 1997). In addition, intracranial motor cortex stimulation has been reported to relieve neuropathic pain, possibly via endogenous opioid secretion, especially from periaqueductal gray and anterior and middle cingulate cortices, which receive projections from MI (Maarrawi et al., 2007; Peyron et al., 2007) and are reported to have high density of opioid receptors (Jones, et al., 1991). Comparable effect has been also reported in trained athletes after aerobic exercise, indicating that endurance exercise may mediate antinociceptive mechanism possibly due to an elevated opioidergic tone in the brain resulting from long-term exercise (Scheef et al., 2012). Even though there is evidence that exercise enhances endogenous opioid function in parts of pain network, i.e. in prefrontal, cingulate and insula cortices (Boecker et al., 2008), which may have an important role in pain resilience, there is currently poor understanding of the endogenous opioid system in the brain. Clearly, there is individual variability in endogenous opioid system, however, it appears susceptible to environmental challenges, including exercise (Boecker et al., 2008). Isometric exercise has been shown to induce exercise-induced hypoalgesia with resistance loads in a range of 10%-30% from MVC and with sufficient contraction duration held until exhaustion or for up to five minutes (Rice et al.,

2019). Endogenous opioid system has received most attention in research on exercise-induced hypoalgesia, however, the mechanisms underlying hypoalgesia are not clear and may involve endocannabinoid system, interactions between serotonergic and opioid system and potentially immune system and autonomic nervous system (Rice et al., 2019). Specifically after isometric exercise, the effect may involve multiple systems (Koltyn et al., 2014; Naugle et al., 2012). Interestingly, Crombie et al. (2018) demonstrated, using an isometric exercise task, that opioid system may not be the primary system involved in exercise-induced hypoalgesia but may interact with endocannabinoid system. Of course, with MEG we cannot study directly the role of opioid system in relation to cortical activity. In relevance to the present results, studies on exercise-induced hypoalgesia have shown reduction in pain thresholds irrespective of the side of the exercised limb (e.g. nociceptive stimuli on the right hand and exercise performed with the left hand) (Paris et al., 2013; Koltyn and Umeda, 2007). On the whole, the discussion above supports the idea of centralized pain inhibitory response, in which the increased motor system activity has a role via exercise (Paris et al., 2013; Koltyn and Umeda, 2007; Scheef et al., 2012) or via cortical stimulation (Granovsky et al., 2019; Leo and Latif, 2007).

The current study has several limitations. We did not observe modulation in individual pain experience measured in VAS-scores. The individual stimulation intensity was kept the same in both recordings for each participant and the participants' reported VAS-scores were unchanged after exercise. We did not record separate pain threshold ratings before and after exercise. With our small sample size, these results should be considered exploratory and caution must be applied, as these findings may not be generalizable to a larger population. Inclusion of a non-exercise control group would have provided more robust quantification of the observed changes. Pain processing is reported to include complex network of brain areas. We regarded the whole brain in the source analysis during the analyzed time window. However, in addition to SI and SII cortices, we were not able to confidently identify activation in other brain regions associated with pain processing. This may be due to methodological limitations as MEG is predisposed towards sources closer to cortical surface. Additionally, the current stimulation method is not explicitly nociceptive, although the stimulation produced painful sensation in all participants.

In conclusion, the aim of the current study was to investigate the effects of acute exercise on cortical nociceptive processing. We demonstrated modulation of cortical nociceptive processing in ~20 Hz rhythm immediately after acute exercise. To the best of our knowledge,

research on cortical oscillations considering interaction between nociception and exercise is very limited. The present results indicate brain oscillatory activity as a feasible research target for studies examining mechanisms interacting between exercise and nociceptive processing.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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FIGURE LEGENDS

Figure 1. Grand average gradiometer waveforms of electrical nociceptive intracutaneous stimulation (A) and innocuous stimulation (B) with similar stimulation intensities. Note, stronger amplitudes in 50 ms and 100 ms waveform components after intracutaneous stimulation.

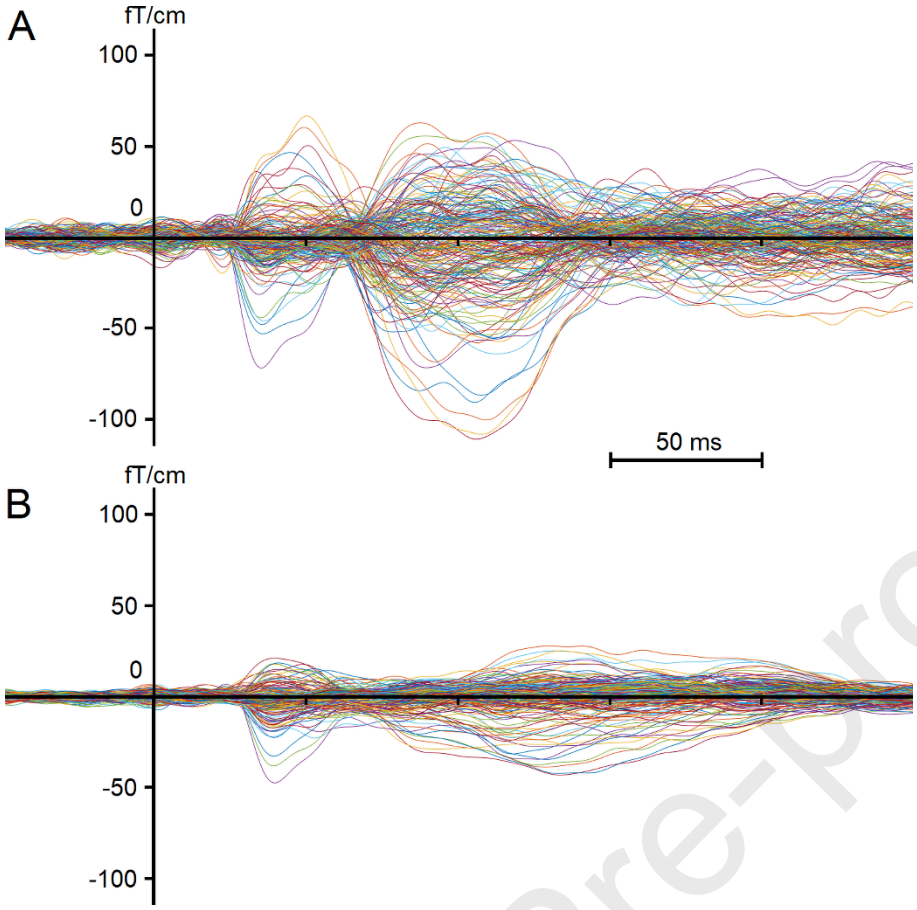
Figure 2. Grand average sources (indicated by blue and red circles) and their activation time courses after intracutaneous stimulation. Early activation localized in contralateral SI cortex (A) with strongest amplitude at 45 ms before exercise and at 48 ms after exercise. Following source activations localized in contralateral (B) and ipsilateral (C) SII cortices with strongest amplitudes approximately at 100 ms.

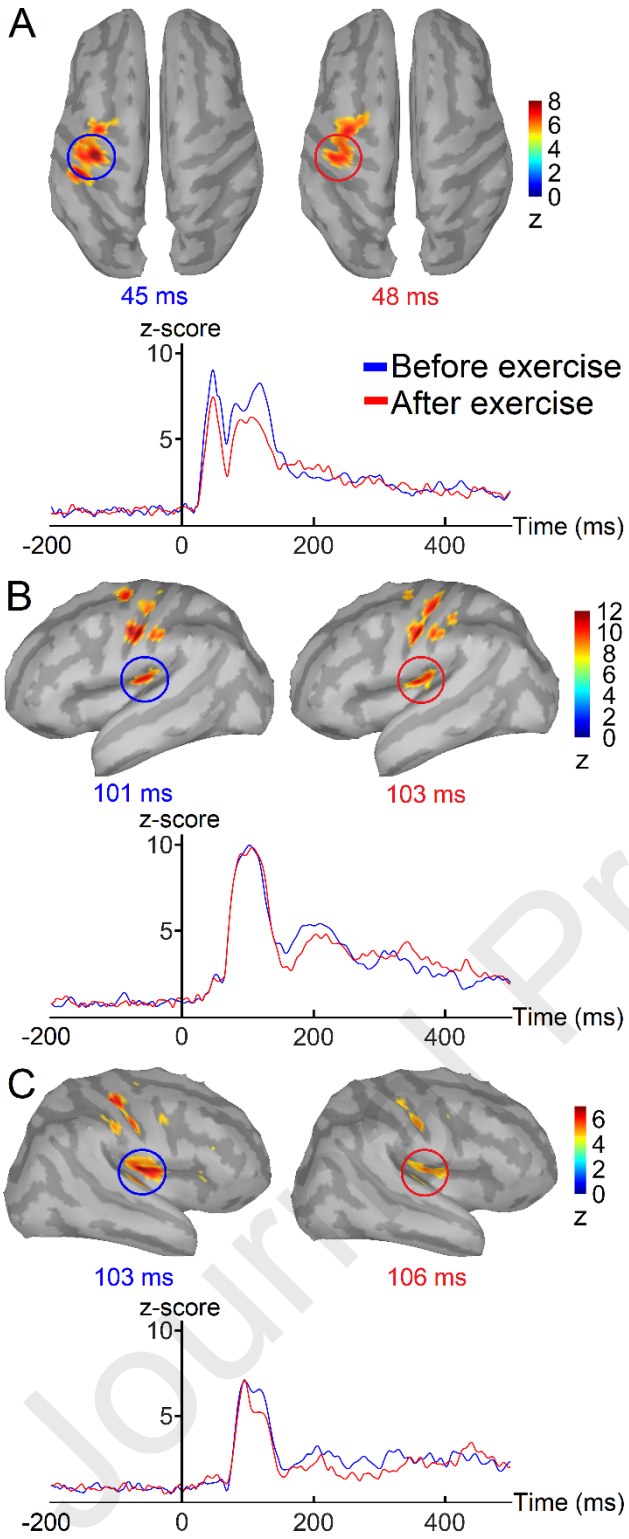
Figure 3. Effect of intracutaneous stimulation on the level of the ~20 Hz rhythm in the contralateral (A) and ipsilateral (B) hemispheres (mean ± SD over 5 participants). Figures on top (A1 and B1) show effects before exercise and figures below (A2 and B2) show effects after exercise. Zero denotes the stimulation onset. Y-axis depicts arbitrary scales for both conditions. Filled squares in the sensor map (middle) show sensor locations among which the most reactive sensor was analyzed for each participant.

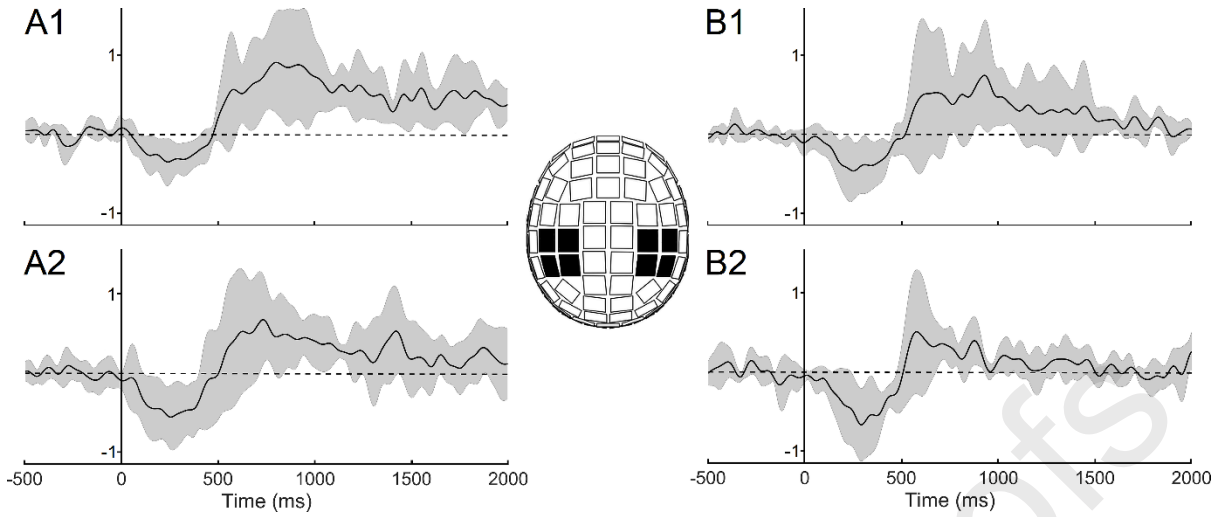
Figure 4. Mean (± SD) amplitudes of the ~20 Hz rhythm suppression (left) and rebound (right). Contralateral and ipsilateral hemispheres depicted separately and comparison between before and after exercise. (*$p \leq 0.05$).

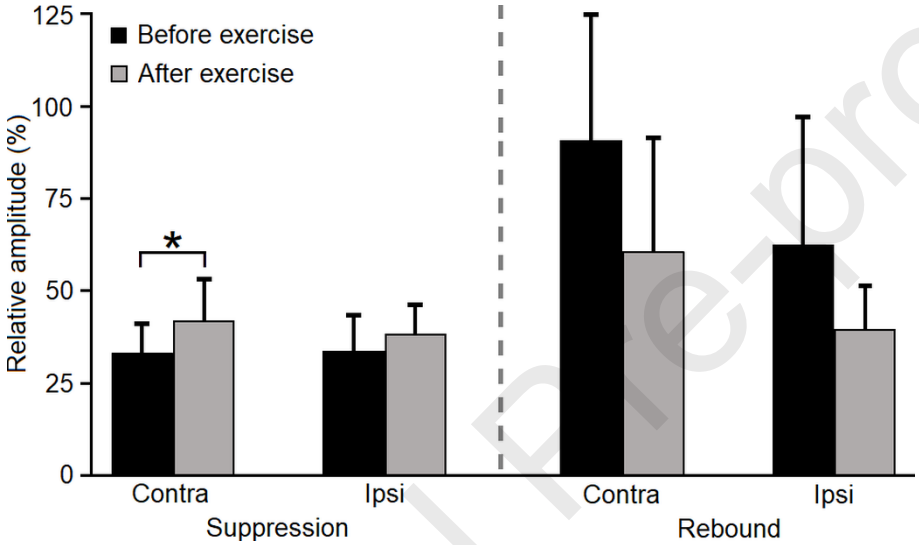
Figure 5. Amplitude change between conditions in the ~20 Hz rhythm suppression in the contralateral hemisphere. Each solid line represents one participant and dashed line depicts the mean of five participants.

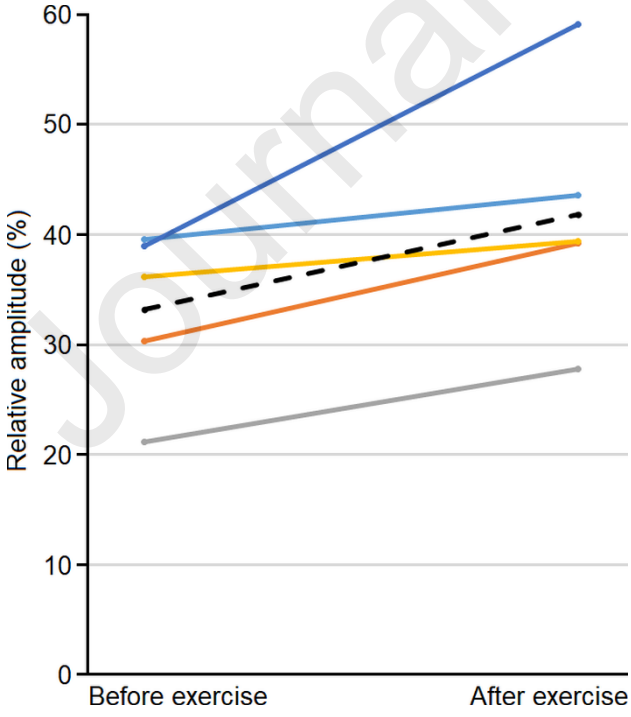
Figure 6. Effect of intracutaneous stimulation on the level of the ~10 Hz rhythm in the contralateral (A) and ipsilateral (B) hemispheres (mean ± SD over 5 participants). Figures on top (A1 and B1) show effects before exercise and figures below (A2 and B2) show effects after exercise. Zero denotes the stimulation onset. Y-axis depicts arbitrary scales for both conditions. Filled squares in the sensor map (middle) show sensor locations among which the most reactive sensor was analyzed for each participant.

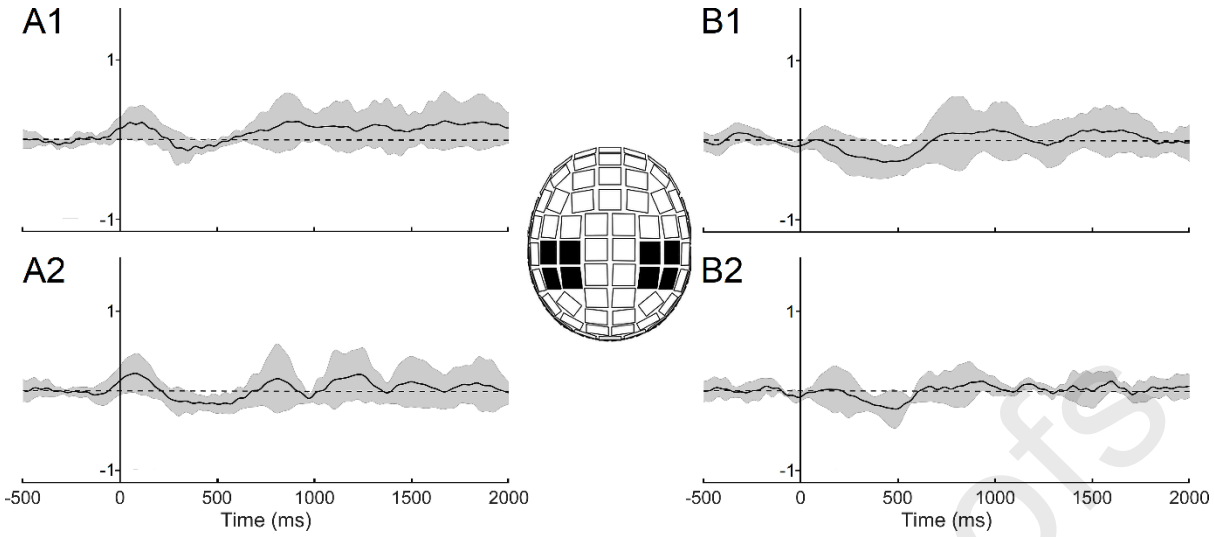












Highlights

- Nociceptive stimulation is a powerful modulator of the ~20 Hz and ~10 Hz sensorimotor rhythm.
- Acute exercise modulates nociceptive stimulation-induced response on ~20 Hz sensorimotor cortex rhythm.
- Brain oscillatory activity may be part of the mechanisms interacting between exercise and cortical nociceptive processing.