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The influence of pain on motor preparation in the human brain

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Pain and motor preparation

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ABSTRACT

The protective function of pain depends on appropriate motor responses to avoid injury and promote recovery. The preparation and execution of motor responses is, thus, an essential part of pain. However, it is not yet fully understood how pain and motor processes interact in the brain. We here used electroencephalography to investigate the effects of pain on motor preparation in the human brain. 20 healthy human participants performed a motor task in which they performed button presses to stop increasingly painful thermal stimuli when they became intolerable. In another condition, participants performed button presses without concurrent stimulation. The results show that the amplitudes of preparatory event-related desynchronizations at alpha and beta frequencies did not differ between conditions. In contrast, the amplitude of the preparatory readiness potential was reduced when a button press was performed to stop a painful stimulus as compared to a button press without concomitant pain. A control experiment with non-painful thermal stimuli showed a similar reduction of the readiness potential when a button press was performed to stop a non-painful thermal stimulus. Together, these findings indicate that painful and non-painful thermal stimuli can similarly influence motor preparation in the human brain. Pain-specific effects on motor preparation in the human brain remain to be demonstrated.

KEYWORDS

Pain; motor preparation; electroencephalography, readiness potential; event-related desynchronization

NEW & NOTEWORTHY

Pain is inherently linked to motor processes but interactions between pain and motor processes in the human brain are not yet fully understood. Using electroencephalography, we show that pain reduces movement preparatory brain activity. Further results indicate that this effect is not pain-specific but independent of the modality of stimulation.

INTRODUCTION

Pain is inherently linked to motor processes. The preparation and execution of motor responses are essential for the protective function of pain (Melzack and Casey 1968). Moreover, physical exercise (Naugle et al. 2012) and the stimulation of motor areas in the brain (Mylius et al. 2012; Nguyen et al. 2011) can alleviate pain. Vice versa, pain critically influences motor behavior (Bank et al. 2013; Hodges and Tucker 2011), which likely contributes to the pathology of chronic pain (Hodges and Smeets 2015). Consequently, the relationship between pain and motor processes increasingly attracts attention (Morrison et al. 2013; Piedimonte et al., 2017; Sullivan 2008; Tabor et al. 2017; Vogt and Sikes 2009; Wiech and Tracey 2013).

The mechanisms underlying interactions between pain and motor processes in the brain are not yet fully understood. Anatomical studies have shown direct nociceptive projections to cingulate motor areas (Dum et al. 2009). Moreover, pain (Apkarian et al. 2005) and movement preparation and execution (Geyer et al. 2012) activate extended networks of brain areas which overlap and interact in cingulate and frontal premotor areas (Misra and Coombes 2015; Perini et al. 2013). Interactions between pain and motor processes can be further disentangled by using electroencephalography (EEG) which records a typical sequence of movement-related responses. During movement preparation, a slow negative wave termed the readiness potential is observed (Brunia et al. 2012; Colebatch 2007; Shibasaki and Hallett 2006). It starts as early as 2000 ms before movement onset and is most consistently observed during the last 500 ms over contralateral sensorimotor areas (Brunia et al. 2012; Colebatch 2007; Shibasaki and Hallett 2006). In addition, movement preparation is associated with decreases of neuronal oscillations at alpha (8-13 Hz) and beta (14-30 Hz) frequencies termed event-related desynchronization (Cheyne 2013; Pfurtscheller and Lopes da Silva 1999; van Wijk et al. 2012). These decreases also begin about 2000 ms before movement onset and are strongest during the last 500 ms over contralateral sensorimotor regions (Cheyne 2013; Pfurtscheller and Lopes da Silva 1999; van Wijk et al.

84 2012). However, whether and how pain influences these movement preparatory phenomena
85 has remained largely unknown yet.
86 In the present study, we used EEG to investigate one specific aspect of the two-way
87 interaction between pain and motor processes, i.e. whether and how pain affects motor
88 preparation in the human brain. Specifically, we hypothesized that pain is inherently linked to
89 motor preparation in the human brain which might manifest as a pain-induced change of the
90 preparatory readiness potential and/or preparatory event-related desynchronization. The
91 results of an ecologically valid motor task in which movements stopped painful stimuli reveal
92 that the amplitude of the preparatory readiness potential was reduced as compared to a
93 motor task without concomitant pain. However, comparable results were found when
94 movements ended non-painful stimuli suggesting a modality-unspecific effect of pain on
95 motor preparation in the human brain.
96

MATERIALS AND METHODS

Participants

21 healthy human participants (9 male; age 27 ± 6 ys, mean ± SD) participated in the main experiment and 24 participants (9 male; age 26 ± 4 ys) took part in a control experiment. Data from one participant and four participants of the main and control experiment, respectively, were excluded due to technical problems during recording and/or poor data quality. Thus, the final analysis included 20 participants (9 male; age 27.3 ± 6.3 ys) for the main experiment and 20 participants (8 male; age 25.8 ± 4.7 ys) for the control experiment. All participants were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). All participants gave written informed consent before participation. The study was approved by the local ethics committee and conducted in conformity with the Declaration of Helsinki.

Paradigm

The study included a main and a control experiment (Fig. 1). During both experiments, participants sat comfortably in a dimly lit room. An infrared thermometer was used to ensure that the skin temperature at the beginning of the experiment (main experiment: 31 ± 2.2 °C; control experiment: 32 ± 1.8 °C) was in the suggested range for thermal sensory testing (Hagander et al. 2000). During the recording, participants were exposed to white noise through headphones to cancel out ambient noise.

Main experiment

The main experiment (Fig. 1A) comprised three conditions: the *pain & buttonpress* condition, the *buttonpress* condition and the *pain* condition. In the *pain & buttonpress* condition, painful heat stimuli were applied with increasing intensity and participants were asked to stop the stimulation by pressing a button when it became intolerable. In the *buttonpress* condition, participants performed button presses without concomitant painful stimulation. In the *pain* condition, painful heat stimuli identical to the *pain & buttonpress* condition were applied but

125 only passively perceived, i.e. participants did not perform button presses to stop the
126 stimulation. The *pain* condition was not further analyzed here as it does not add to the central
127 question of the present study, i.e. the influence of pain on motor preparation. As the
128 durations of the stimuli in the *pain* condition were taken from the *pain & buttonpress*
129 condition, the latter condition was always performed first, followed by the *buttonpress* and
130 *pain* conditions. Painful heat stimuli were applied to the dorsum of the left hand using a
131 thermode (TSA-II, Medoc, Israel) and button presses were performed with the index finger of
132 the right hand. After the *pain & buttonpress* condition, the thermode was slightly displaced in
133 lateral-medial direction to avoid skin damage. Each condition included 60 trials. Stimulation
134 was controlled using MATLAB (Mathworks, Natick, MA, USA) and the Psychophysics
135 Toolbox (http://psychtoolbox.org/).

136 In the *pain & buttonpress* condition (Fig. 1a, top), a heat stimulus with increasing
137 intensity was applied and participants were instructed to stop the stimulation at the maximum
138 pain intensity they were willing to tolerate by pressing the button. Thus, by definition, the
139 participants stopped the stimulation at pain tolerance level assuring that they experienced
140 pain before the button press. A black fixation cross was displayed at the center of a computer
141 monitor. Each trial started when the black fixation cross turned green for 1 s. After a
142 randomly varied interval between 1.5 and 3.5 s, the stimulation temperature increased from a
143 baseline of 40 °C with a changing rate of 0.8 °C/s until the participants stopped the stimulus
144 increase by pressing the button. Participants on average stopped the stimulation at a mean
145 maximum temperature of 47.1 ± 0.9 °C and 10.0 ± 1.2 s after the start of the temperature
146 increase. After the button press, the temperature decreased back to the baseline with a
147 cooling rate of 8 °C/s. The next trial started 4 s after the button press. The mean latency
148 between button presses, i.e. the mean trial duration, was 17.4 ± 1.6 s. A comparison of the
149 peak temperatures of the first and second halves of the condition did not indicate habituation
150 or sensitization effects (47.1 °C for both halves, $p = 0.8$, paired t-test).

151 In the *buttonpress* condition (Fig. 1A, bottom), participants were instructed to press
152 the button at an interval resembling the interval between two button presses in the *pain &*

153 *buttonpress* condition. Again, each trial started when the black fixation cross turned green for
154 1 s and ended 4 s after the button press. Pilot experiments indicated that participants tended
155 to decrease the interval between button presses over the course of the experiment.
156 Therefore, when the interval between button presses was shorter than 7 s for more than two
157 consecutive trials, a red cross was presented for 1 s after the button press to instruct the
158 participants to increase the interval between button presses. Moreover, in these cases, up to
159 15 additional trials were performed aiming at a total number of 60 trials with a duration
160 greater than 7 s for each participant. The mean latency between button presses for this
161 condition was 19.0 ± 10.2 s.

162 As in the *pain & buttonpress* and the *buttonpress* condition no speeded responses to
163 sensory stimuli were performed, reaction times were not assessed. Moreover, in the *pain &*
164 *buttonpress* condition, no single trial pain ratings were obtained so that the relationship
165 between pain intensity and motor preparatory brain activity was not quantitatively assessed.
166

167 *Control experiment*

168 To test for the pain-specificity of the results, a control experiment with a non-painful warmth
169 stimulus was performed (Fig. 1B). Apart from the non-painful warmth stimulus, the control
170 experiment was identical to the main experiment. The control experiment, thus, included a
171 *warmth & buttonpress* condition, a *buttonpress* condition and a *warmth* condition. The
172 *warmth* condition was not further analyzed as it does not add to the central question of the
173 present study, i.e. the influence of pain/warmth on motor preparation.

174 In the *warmth & buttonpress* condition (Fig. 1B, top), participants were instructed to
175 stop a thermal stimulus with increasing intensity by pressing the button as soon as it was
176 perceived as clearly warm. The temperature increased from a baseline of 32 °C. The
177 changing rate was adjusted for each participant during a preliminary training session in order
178 to assure a trial duration comparable to the main experiment, i.e. longer than 7 s (changing
179 rate 0.4 ± 0.1°C/s). If trial durations were shorter than 7 s, additional trials were again
180 presented to obtain at least 60 trials for each participant with a duration comparable to the

main experiment. Cooling rate was 8 °C/s. During this condition, mean maximum temperature was 37.2 ± 2.7 °C/s, mean duration of temperature increase was 15.1 ± 5.9 s and the mean latency between button presses was 22.4 ± 7.5 s. The *buttonpress* condition (Fig. 1B, bottom) exactly matched the *buttonpress* condition of the main experiment. The mean latency between button presses in the *buttonpress* condition was 22.9 ± 11.8 s. A comparison of the peak temperatures of the first and second halves of the condition did not indicate habituation or sensitization effects (37.6 °C vs. 37.5 °C, p = 0.11, paired t-test).

As in the *warmth & buttonpress* and the *buttonpress* condition no speeded responses to sensory stimuli were performed, reaction times were not assessed.

Electroencephalography

Recordings and preprocessing

During both experiments, EEG data were recorded using an electrode cap (Easycap, Herrsching, Germany), BrainAmp MR plus amplifiers (Brain Products, Munich, Germany) and the BrainVision Recorder software (Brain Products, Munich, Germany). The electrode montage included 64 electrodes consisting of all 10-20 system electrodes and the additional electrodes Fpz, FCz, CPz, POz, Oz, Iz, AF3/4, F5/6, FC1/2/3/4/5/6, FT7/8/9/10, C1/2/5/6, CP1/2/3/4/5/6, TP7/8/9/10, P5/6, PO1/2/9/10. Two additional electrodes were placed below the outer canthus of each eye. The EEG was referenced to the FCz electrode, grounded at AFz, sampled at 1000 Hz, and high-pass filtered at 0.015 Hz. The impedance was kept below 20 kΩ. The raw EEG data were preprocessed using the BrainVision Analyzer software (Brain Products, Munich, Germany). Offline analysis included downsampling to 512 Hz, digital highpass filtering at 0.5 Hz, correction for eye movements and muscle artifacts using independent component analysis (Jung et al. 2000) and re-referencing to the average reference. Data from all conditions were segmented into trials of -7 to 5 s with respect to the button press. Trials with artifacts exceeding ±100 µV in any channel were automatically rejected, and an additional visual rejection was performed to exclude remaining artifact-contaminated trials. In the main experiment, the average number of remaining trials was 51 ±

9 for the *pain & buttonpress* and 54 ± 3 for the *buttonpress* condition. In the control experiment, the average number of remaining trials was 51 ± 6 for the *warmth & buttonpress* and 53 ± 5 for the *buttonpress* condition.

Analysis

EEG data were analyzed using FieldTrip, an open-source toolbox for Matlab (Oostenveld et al. 2011). Data were analyzed in the time and time-frequency domain. Analyses were focused on the movement preparation period before the button presses. Neural activity after the button presses was not analyzed since button presses coincided with the termination of the painful stimuli in the *pain & buttonpresses* condition, which prevents an unequivocal interpretation of post-button press activity.

All statistical analyses were performed using nonparametric cluster-based permutation tests comparing the *pain/warmth & buttonpress* and *buttonpress* conditions (Maris and Oostenveld 2007). First, point-by-point t-tests were calculated comparing signal amplitudes between conditions at each electrode and/or time point (see below for more details). Second, clusters of neighboring electrodes and/or time points, whose t-statistic exceeded a critical threshold ($p = 0.05$), were selected and t-values within each cluster were summed up, resulting in cluster-level test statistics. To evaluate statistical significance, the maximum cluster-level test statistic was then compared to a reference distribution of maximum cluster t-value sums obtained by randomly interchanging data across the two conditions and recalculating the cluster-level test statistic 1000 times. This cluster-based procedure deals with the multiple comparison problem, takes physiological plausibility into account and is not affected by partial dependence in the data (Maris and Oostenveld 2007; van Ede and Maris, 2016).

Time domain analysis

A low-pass filter of 30 Hz was applied to the segmented data. For each condition, trials were averaged time-locked to the button press. The statistical analysis was focused on a 2 s-time

window preceding the button press as this period has been shown to include most movement preparatory activity in previous time domain analyses (Brunia et al. 2012; Colebatch 2007; Shibasaki and Hallett 2006). Using the statistical approach outlined above, we tested the effect of pain on movement preparatory brain activity by comparing the amplitude of the potentials between the *pain & buttonpress* and *buttonpress* conditions. In a first step, we performed multi-electrode analysis by clustering across time and electrodes. Subsequently, we restricted the statistical analysis to the electrode Cz, which has been shown to most strongly reflect the readiness potential (Brunia et al. 2012; Colebatch 2007; Shibasaki and Hallett 2006). Here, clustering was performed across time only.

Corresponding analyses were performed for the control experiment, comparing the *warmth & buttonpress* with the *buttonpress* condition. Additionally, we assessed whether the effect of pain on motor preparation significantly differed from the effect of warmth. We computed the difference of the readiness potential between the *pain & buttonpress* and the *buttonpress* conditions and contrasted it against the difference between the *warmth & buttonpress* and the *buttonpress* conditions, both for all electrodes and at electrode Cz only.

Time-frequency domain analysis

We performed time-frequency analysis on the segmented single trials by using a Hanning-tapered sliding window Fast Fourier Transform for frequencies from 1 to 100 Hz. Window length was 0.25 s and step size was 30 ms. To obtain frequency band-specific time courses of EEG signals, we averaged power across theta (4-7 Hz), alpha (8-13 Hz), beta (14-30 Hz) and gamma (40-100 Hz) frequencies. We compared the power time courses of each frequency band in the *pain & buttonpress* and *buttonpress* conditions in a 2 s-time window (Cheyne 2013; Pfurtscheller and Lopes da Silva 1999; van Wijk et al. 2012) before the button press, again using the same statistical approach described above. As a first step, we implemented a multi-electrode analysis testing for differences between the two conditions while clustering across time and electrodes. As previous studied showed that movement-related power changes are most prominent over the sensorimotor area contralateral to the

movement (Cheyne 2013; Pfurtscheller and Lopes da Silva 1999; van Wijk et al. 2012), we restricted our analysis to an average across central electrodes contralateral to the hand performing the movement in a second step (i.e. Cz, CPz, C1, C3, CP1, CP3).

RESULTS

Time domain results

Figure 2 shows movement-related potentials for the two experimental conditions averaged across participants. The left panel shows the typical sequence of movement-related potentials at electrode Cz, where such potentials are strongest (Brunia et al. 2012; Colebatch 2007; Shibasaki and Hallett 2006). During the last 500 ms before the button press, the *readiness potential* was observed as an increasing negativity related to movement preparation. This was followed by the motor potential and the post-movement potential (Colebatch 2007) which were not analyzed here. The comparison of the readiness potential across conditions revealed that its amplitude was lower in the *pain & buttonpress* condition than in the *buttonpress* condition. Cluster-based permutation statistics confirmed a significant difference ($p < 0.025$) between -0.35 s and -0.26 s before the button press (Fig. 2, left, see gray shading). The topography on the right shows the location of the electrode shown on the left (red dot) and the location of electrodes where significant differences between *pain & buttonpress* and *buttonpress* conditions were observed (bold black dots, $p < 0.025$) when clustering was performed across both electrodes and time. The cluster mainly covered central and frontal electrodes and was slightly lateralized to the left hemisphere, i.e. contralateral to the button press. Thus, less brain activity related to motor preparation was recorded when the button press was performed during painful stimulation than when it was performed without concurrent pain.

Time-frequency domain results

Figure 3 displays movement-related activity for the two conditions at theta (4-7 Hz), alpha (8-13 Hz), beta (14-30 Hz) and gamma (40-100 Hz) frequencies averaged across participants. The left panel shows the time courses of frequency-specific brain activity at a selection of electrodes where strongest movement preparatory activity is observed (Cheyne 2013; Pfurtscheller and Lopes da Silva 1999; van Wijk et al. 2012), i.e electrodes covering the sensorimotor area contralateral to the movement (Cz, CPz, C1, C3, CP1, CP3). The figure

shows a decrease of power during the last 2 s before the button press, which was particularly pronounced at alpha and beta frequencies. Additional changes of neural activity were observed during and after the button press but were not further analyzed here. The topography on the bottom shows the location of the electrodes (red dots) shown in the upper two rows. Statistical comparisons performed in the last 2 s of motor preparation did not show significant differences of movement preparatory activity between conditions in any frequency band, neither when using the contralateral electrode selection (left panel) and clustering across time nor when clustering across both time and electrodes ($p > 0.025$).

Control experiment

To test for the specificity of the observed difference of the readiness potential between the *pain & buttonpress* and the *buttonpress* conditions, we performed the same analyses for the control experiment in which non-painful warmth stimuli were applied. Comparable to the main experiment, the amplitude of the readiness potential in the *warmth & buttonpress* condition was lower than in the *buttonpress* condition at electrode Cz (Fig. 4A, left, see gray shading; significant cluster from -0.26 s to -0.19, $p < 0.025$). The right panel shows that this difference was mainly spread over central and posterior electrodes (Fig. 4A, right; $p < 0.025$).

We finally directly compared the difference of the readiness potential between the *pain & buttonpress* and *buttonpress* conditions in the main experiment with the difference of the readiness potential between the *warmth & buttonpress* and *buttonpress* conditions in the control experiment. The left panel of figure 4B shows the grand averages of the difference waves at electrode Cz, the right panel shows the topography of the comparison. No significant differences were observed, i.e. the amplitudes of the potentials differed in a similar way from the *buttonpress* condition both when a painful and a warmth stimulation was applied. Thus, movement preparatory brain activity was reduced when a button press was performed during painful as well as during non-painful thermal stimulation indicating a non-pain-specific effect.

DISCUSSION

In the present study, we investigated whether and how pain influences motor preparation in the human brain. The results show that a movement, which stops an increasingly painful thermal stimulus, is associated with a smaller readiness potential than a similar movement without a concomitant painful stimulus. However, a control experiment indicates that a similar reduction of the readiness potentials occurs when the movement stops an ongoing non-painful thermal stimulus. The pain-associated reduction of the readiness potential is, thus, not pain-specific but likely represents a modality-spanning effect.

Pain and motor processes in the human brain

Despite the crucial relevance of motor responses for the protective function of pain, interactions between pain and motor processes in the brain have rarely been investigated. Anatomical studies revealed that nociceptive pathways project directly and substantially to cortical motor areas (Dum et al. 2009). Functional imaging studies showed overlaps and interactions between pain-related and motor-related activations (Misra and Coombes 2015; Perini et al. 2013). However, due to the limited temporal resolution of functional magnetic resonance imaging, these studies could not analyze processes related to the preparation, execution and aftereffects of movements separately. Neurophysiological recordings using EEG, MEG or intracranial recordings can disentangle these processes by showing their temporal sequence. A few EEG studies addressed interactions between pain and motor processes so far. Some studies investigated the neural correlates of the anticipation of a painful stimulus which serves as a go-cue for a motor response (Babiloni et al. 2006; Babiloni et al. 2008; Babiloni et al. 2010). The results showed that the anticipation of pain yielded an increase of movement-preparatory alpha desynchronization. However, in these studies the painful stimulus served as the go-cue for the movement, so that it was not possible to unequivocally disentangle pain anticipation and movement preparation. Moreover, in these studies the motor response did not have an effect on the pain stimulus and thus no biological function. In contrast, in the present study, we did not simply investigate pain anticipation and

352 motor preparation but the effects of pain on the preparation of a biologically meaningful
353 motor response. Another study investigated EEG activity during the anticipation of painful
354 stimuli which could be stopped by a motor response (Piedimonte et al., 2017). The results
355 showed that EEG responses related to movement preparation did not consistently differ
356 between different expectations of pain. However, this study assessed the influence of
357 different expectations of pain on motor preparatory brain activity whereas the present study
358 assessed the influence of pain on motor preparation. Hence, a direct comparison of both
359 studies appears not appropriate. Another recent EEG study compared arm movements
360 during ongoing pain, ongoing warm stimulation or without concurrent stimuli (Misra et al.
361 2017). Concomitant pain led to increases of movement-preparatory beta desynchronizations
362 and a shortening of reaction times compared to warm stimulation or no stimulation,
363 suggesting a facilitating effect of pain on the motor system. In contrast, the present study
364 does not show an effect of pain on movement-preparatory desynchronizations at beta
365 frequencies. However, the previous study used an externally cued paradigm in which the
366 movement was always performed 2500 ms after onset of the painful stimulus whereas, in the
367 present study, participants were free to press the button at any time. Moreover, in the
368 previous study, the painful stimulus had no functional relationship to the movement whereas
369 participants performed biologically relevant movements which stopped the painful stimuli in
370 the present study. These differences between paradigms could explain the lack of effects on
371 event-related desynchronizations in the current study as compared to previous studies.
372
373 **Externally-paced vs. self-paced movements**
374 We observed a significant decrease in the amplitude of the preparatory readiness potential
375 when movements were performed to stop a painful or non-painful thermal stimulus as
376 compared to movements without these stimuli. In principle, this finding can be explained by
377 three different factors. First, the simple presence of a thermal stimulus or any sensory
378 stimulus might attenuate the readiness potential by directing attention from movement
379 preparation towards the sensory stimulus which is known to influence the readiness potential

(Birbaumer et al. 1990). Second, not the simple presence of the stimulus but the pacing of the movement by the stimulus might yield the decrease of the readiness potential. Based on previous findings, this factor could well explain the present observations. Although each individual could freely determine when to stop the stimulation, the *pain & button press* and *warmth & button press* conditions included responding to an external stimulus whereas movements in the *button press* condition were performed at an internally paced rate. A few studies investigating the difference in preparatory activity between internally generated and externally driven movements indeed reported that the amplitude of the readiness potential was significantly smaller for externally paced than for self-paced movements (Jahanshahi et al. 1995; Jankelowitz and Colebatch 2002) which would be well compatible with the present findings. Third, neither the simple presence of the stimulus nor responding to the stimulus but rather the option to stop the stimulus, i.e. the sense of agency, might cause the decrease of the readiness potential. However, the influence of the sense of agency on the readiness potential has not yet been investigated and its contribution to the present findings therefore remains unknown. Further studies might investigate which of the three factors or which combination of factors explains the effect observed here. In particular, studies comparing the effects of pain with the effects of other sensory modalities might help to more precisely interpret the observed effects.

Limitations

Several limitations apply to the present study. First, we performed the different conditions in a fixed order. This was done to adjust the timing of the stimulations and movements of the *pain* and *buttonpress* conditions to that of the *pain & buttonpress* condition. However, the fixed order implies the risk of an order effect. However, in line with repetition effects in sensory (Grill-Spector et al. 2006) and motor (Hamilton and Grafton 2009) systems repeated finger movements would be expected to be associated with a decrease of related brain activity. In contrast, the present findings could only be explained by an increase of movement preparatory over time with repeated performance. Second, we did not directly assess muscle

activity and/or movement kinematics. Thus, we cannot determine whether the observed difference between movement preparatory brain activity with and without concomitant stimulation is associated with a difference in preparatory muscle activity and/or a difference in movement characteristics. Third, the lack of a pain-specific effect of pain on motor preparation in our study does not rule out the existence of such effects. They may manifest in other EEG features such as connectivity and/or at other locations such as subcortical regions which are not well captured by EEG.

Conclusions

The present study shows that pain reduces movement preparatory activity in the brain in a paradigm with a high ecological validity. This effect is, however, not pain-specific but seems to represent a modality-spanning phenomenon which might reflect the basic difference between stimulus-related and self-paced movements. Pain-specific interactions between pain and motor preparation thus remain to be demonstrated. A better understanding of these interactions promises novel insights into how the protective function of pain is implemented in the brain and how these processes might deviate in chronic pain.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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536 **FIGURE LEGENDS**

537 **Figure 1**. *Paradigm*. *A:* Main experiment. In the *pain & buttonpress* condition, 60 heat stimuli
538 of increasing intensity were applied to the dorsum of the left hand. Participants were
539 instructed to press a button with the right index finger to stop the stimulation at the maximum
540 pain intensity they were willing to tolerate. In the *buttonpress* condition, participants were
541 instructed to perform button presses at about the same interval as in the *pain & buttonpress*
542 condition but without concurrent painful stimulation. *B:* Control experiment. In the *warmth &*
543 *buttonpress* condition, participants were instructed to interrupt the increasing thermal
544 stimulation when it was perceived as clearly warm. The *buttonpress* condition matched that
545 of the main experiment.

546

547 **Figure 2**. *Time domain results of the main experiment*. The left panel shows grand averages
548 of movement-related potentials at electrode Cz. Statistical comparison between *pain &*
549 *buttonpress* and *buttonpress* conditions were performed during the last 2 s of motor
550 preparation, and the grey shaded time window highlights significantly different time periods.
551 In the right panel, electrodes where significant differences were observed are marked by bold
552 black dots. Statistical analyses were performed using cluster-based permutation statistics.

553

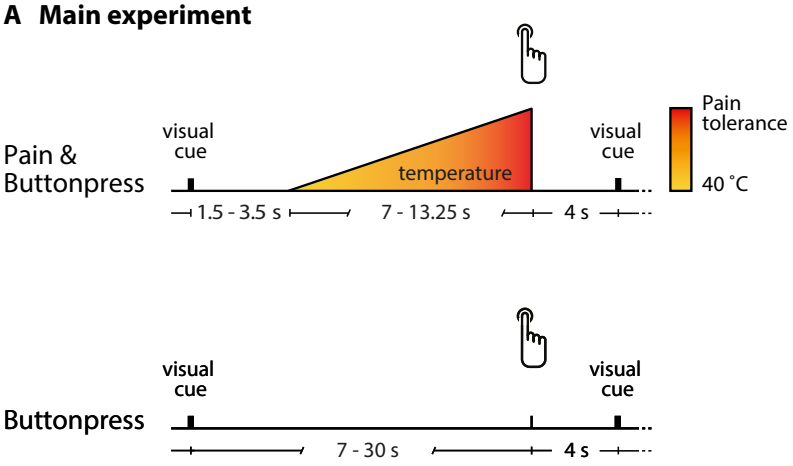
554 **Figure 3**. *Time-frequency domain results of the main experiment.* Upper rows, grand
555 average time courses of frequency band specific brain activity for selected electrodes
556 covering the sensorimotor areas contralateral to movement preparation. Using cluster-based
557 permutation statistics in a time window covering the last 2 s of motor preparation, no
558 significant difference in movement preparatory brain activity was observed between
559 conditions at any frequency band. The topography on the bottom shows the location of
560 electrodes selected for analysis.

561

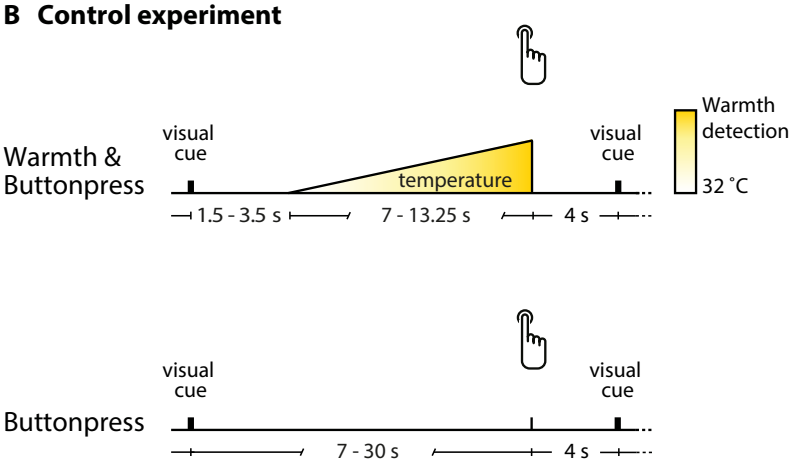
562 **Figure 4.** *Time domain results of the control and the main experiment. A:* The left panel
563 displays grand average movement-related potentials at electrode Cz. The gray shaded time

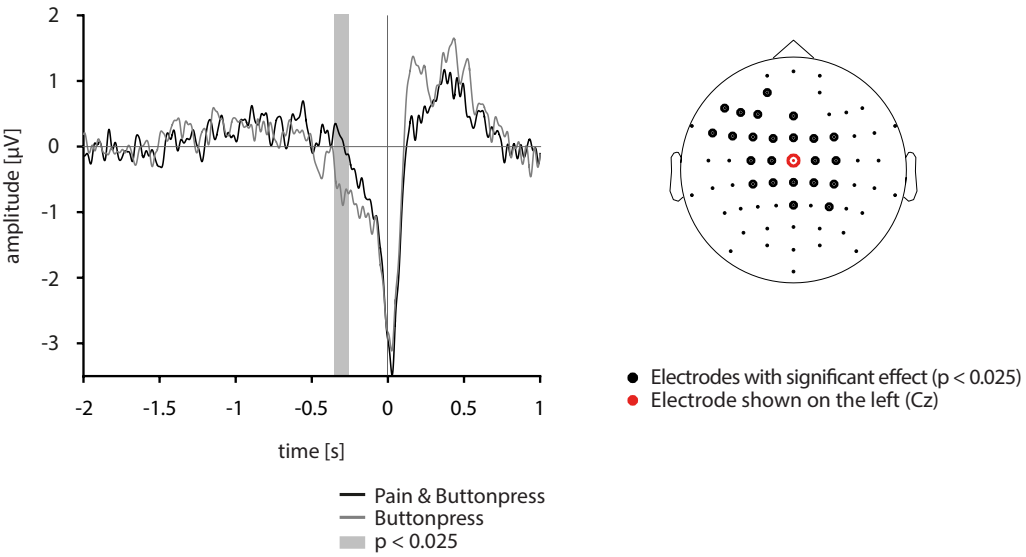
564 window indicates a significant difference between the experimental conditions of the control
565 experiment in the last 2 s before the onset of the movement. The topography on the right
566 shows electrodes where significant differences between the *warmth & buttonpress* and
567 *buttonpress* conditions were observed. *B*: The difference of the readiness potentials between
568 the experimental conditions was calculated for the main and the control experiment and
569 contrasted against each other at Cz only (left) and across all electrodes (right). No significant
570 differences were detected, indicating that pain and warmth affect motor preparation in a
571 comparable way. All statistical analyses were performed using cluster-based permutation
572 statistics during the last 2 s of motor preparation.
573

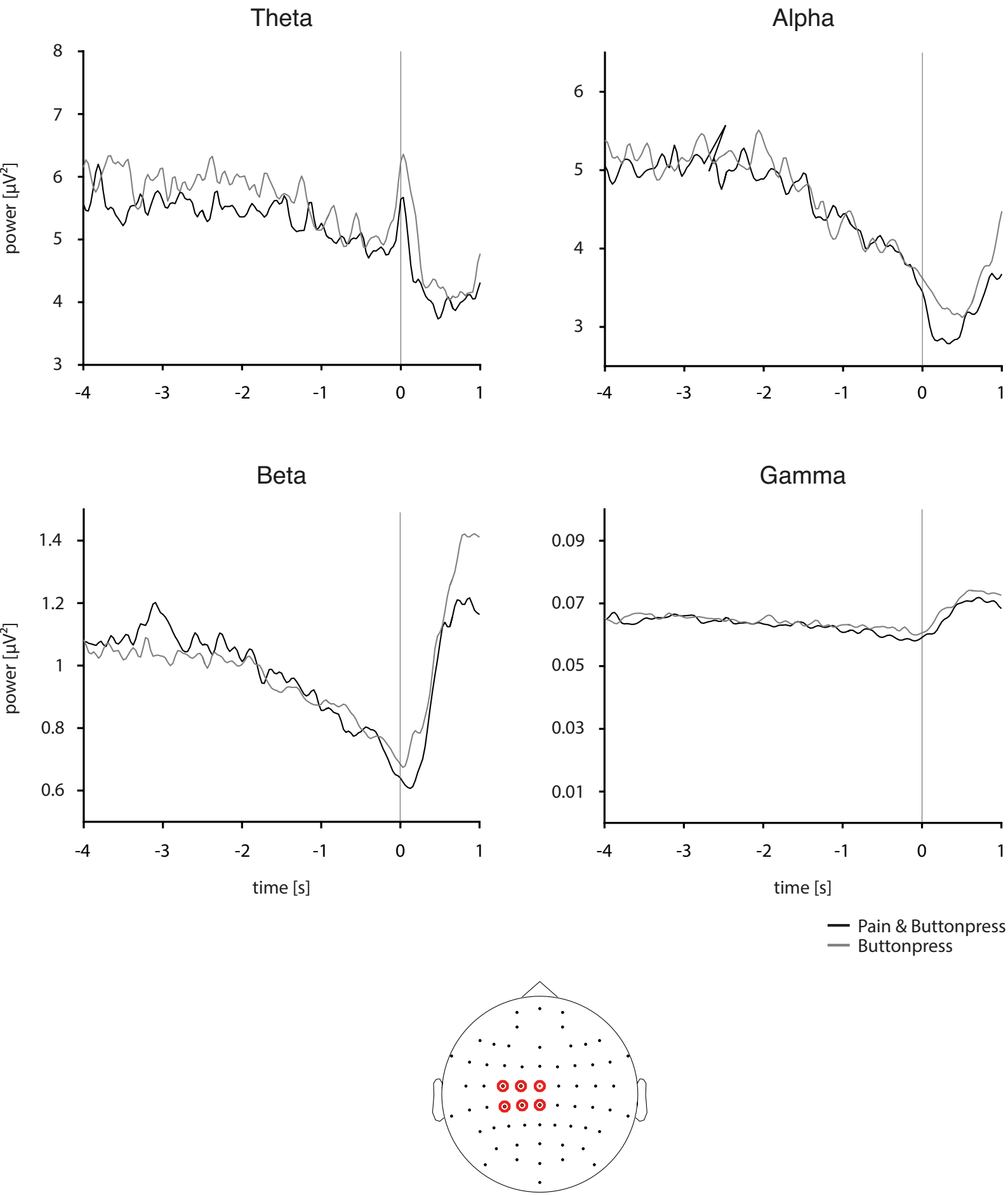
A Main experiment



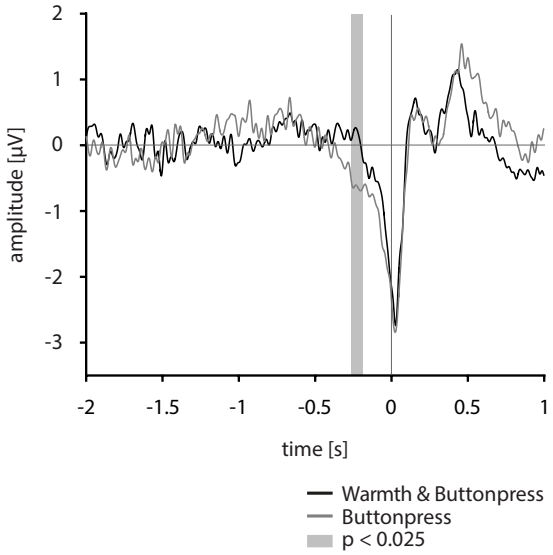
B Control experiment

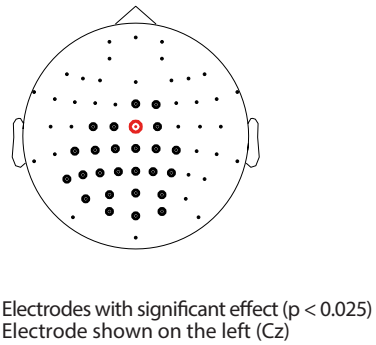



2
1
0
-1
-2
-3
amplitude [µV]
-2
-1.5
-1
-0.5
0
0.5
1
time [s]
Pain & Buttonpress
Buttonpress
p < 0.025
Electrodes with significant effect (p < 0.025)
Electrode shown on the left (Cz)


Theta
Alpha
Beta
Gamma
power [μV²]
power [μV²]
time [s]
time [s]
Pain & Buttonpress
Buttonpress
Electrodes selected for plotting:
mean (Cz,CPz,C1,C3,CP1,CP3)

A Control experiment





B Main experiment vs. control experiment