Conditioned Pain Modulation Analgesia Reduces Beta Oscillations in the Sensorimotor Cortex

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June 2021

A thesis submitted to McGill University in partial
fulfillment of the requirements of the degree of
Master of Science

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Abstract/Résumé

Background: Conditioned pain modulation (CPM) is a "pain inhibits pain" phenomenon whereby a noxious stimulus attenuates the perceived pain of another noxious stimulus in a spatially distant region of the body. A noxious stimulus induces changes in neural oscillatory signals, for which functional roles have been proposed - e.g., beta-synchronization reflecting top-down modulation of painful stimuli - but remains to be established. Examining how CPM affects pain-induced brain signals is intended to clarify the cortical signals and processes involved in the modulation of pain.

Objective: Our primary aim was to characterize the effects of CPM on neural oscillatory signals of pain. Our secondary aim was to interrogate whether patients with chronic pain express less pain inhibition upon CPM than healthy control subjects as measured with subjective reports and the neural correlates from the first aim.

Methods: In this magnetoencephalography (MEG) study, we examined neural responses to electrical pain on the right ankle before, during, and after CPM analgesia induced by an ice pack placed on the left arm. Seventeen patients with chronic pain in their lower body (e.g., lower back, legs, or feet) and seventeen healthy control participants reported pain ratings of the electrical pain after each condition. The patient group was heterogeneous, with 15 patients presenting failed back surgery syndrome, three patients with diabetic neuropathy and one patient with neuropathic pain. Using MEG source imaging and time-frequency decompositions, we examined CPM effects on the spectrum of brain signals induced by the electrical pain (i.e., alpha desynchronization, beta desynchronization, and beta synchronization).

Results: Subjective pain ratings and pain-induced beta synchronization in the sensorimotor cortex were both reduced during CPM. Although the respective effects in the two experimental groups did not differ significantly, *post-hoc* analyses suggested that beta synchronization was reduced in healthy controls but not significantly so in patients with chronic pain.

Discussion: Reduced beta synchronization of the sensorimotor cortex during CPM may be associated with the alteration of top-down modulations of the pain sensation via e.g., attentional processes. The less substantial changes observed in patients with chronic pain may

reflect that they are in a state of “constant CPM” induced by ongoing pain sensations; therefore the experimental conditioning stimulus (ice pack) did not induce further CPM.

Contexte : La modulation conditionnée de la douleur (MCP) est un phénomène de "douleur contre douleur" par lequel un stimulus nocif atténue la douleur perçue causée par un autre stimulus nocif sur une autre partie du corps. Un stimulus nocif induit des signaux oscillatoires neuronaux dont les rôles fonctionnels restent à déterminer. Par exemple, la synchronisation des rythmes bêta a été proposée pour refléter la modulation descendante de stimuli douloureux. Par conséquent, l'examen de la façon dont la MCP affecte les signaux cérébraux induits par la douleur pourrait permettre de mieux comprendre les processus corticaux impliqués dans la MCP et la modulation de la sensation de douleur en général.

Objectif : Notre objectif principal était de caractériser les effets de la MCP sur les signaux neuronaux de la douleur. Notre objectif secondaire était d'explorer si les patients souffrant de douleurs chroniques expriment moins d'inhibition de la douleur lors de la MCP que les sujets sains; ces aspects étant mesurés via des rapports subjectifs et les corrélats neuraux issus de notre premier objectif.

Méthodes : Dans cette étude par magnétoencéphalographie (MEG), nous avons examiné les réponses neurales à une stimulation électrique douloureuse appliquée sur la cheville droite avant, pendant et après l'analgésie par MCP induite par un sac de glace placé sur le bras gauche. Dix-sept patients souffrant de douleurs chroniques dans le bas du corps (par exemple, le bas du dos, les jambes et les pieds) et dix-sept participants sains ont rapporté leurs évaluations de la douleur électrique après chaque essai. Notre groupe de patients était hétérogène : 15 patients souffraient du syndrome d'échec de la chirurgie du dos, trois patients de neuropathie diabétique et un patient de douleurs neuropathiques. En utilisant des techniques d’imagerie de sources MEG et de décomposition temps-fréquence, nous avons examiné les effets de la MCP sur les signaux spectraux induits par la douleur électrique (c'est-à-dire la désynchronisation alpha, la désynchronisation bêta et la synchronisation bêta).

Résultats : L'évaluation subjective de la douleur et le taux de synchronisation bêta induite par la douleur dans le cortex sensorimoteur ont diminué pendant la MCP chez les participants sains. Bien que les effets observés dans les deux groupes expérimentaux ne différaient pas de manière significative, des analyses post-hoc suggèrent que la synchronisation bêta dans le cortex

sensorimoteur était réduite chez les participants contrôles, mais pas de manière significative chez les patients souffrant de douleurs chroniques.

Discussion : La réduction de la synchronisation bêta pendant la MCP pourrait être associée à l'altération des signaux de modulation descendante de la sensation de douleur via, par exemple, des processus attentionnels. Les changements moins importants chez les patients souffrant de douleur chronique pourraient refléter le fait que ces derniers se trouvent dans un état de “MCP constante” en raison de leur douleur continue ; par conséquent, un stimulus de conditionnement expérimental (via comme ici, un sac de glace) n'induit pas de MCP supplémentaire.

Preface and acknowledgements

The study protocol was designed by and the data were collected by Dr. Cecile de Vos and Bart Witjes. The review of literature in chapter 1, data processing, analysis, and a part of data collection in chapters 2 and 3, the interpretation of results in chapter 4, and the concluding analysis in chapter 5 are my contributions. This thesis is original and unpublished.

I would like to thank my supervisors Dr. Cecile de Vos and Dr. Sylvain Baillet for their guidance at every stage of my master's research project. In preparation of the current thesis, I also received invaluable advice on data interpretation from Dr. Mathieu Roy. I would also like to thank the members of the Baillet lab for their suggestions and feedback on the project, especially Jason da Silva Castanheira for his generous help with statistical methods and Marc Lalancette for kindly providing support on MEG data processing. I also appreciate my family and friends for their encouragement and support throughout my studies. Lastly, I would like to thank the Natural Sciences and Engineering Research Council of Canada and Fonds de la recherche en santé du Québec for the studentships.

Hyerang Jin

Chapter 1: Background and rationale

1.1. Endogenous pain modulation

Pain is modulated by endogenous inhibitory and facilitatory mechanisms[1]. Pain perception is variable across individuals and contexts, and early evidence of endogenous pain modulation came from the observation that the majority of injured but alert soldiers in combat situations reported a significant level of stress-induced analgesia[2]. Pain modulation is believed to be mediated by descending pain modulatory pathways from the brain to the dorsal horns of the spinal cord in part via the brainstem to inhibit or enhance the nociceptive inputs[1]. Pain perception can be modulated by both bottom-up (stimulus-driven) factors such as stimulus intensity and top-down (person-driven) factors such as attention and expectations. Various forms of top-down modulation of pain have been reported. Brain-imaging[3] and drug[4] studies have suggested that the placebo response to painful stimuli originates from cortical and subcortical regions (e.g., the anterior cingulate cortex (ACC) and the amygdala) and activates the descending endogenous inhibitory pathways of pain. Another example of top-down modulation of pain is attention. Directing attention to a painful stimulus increases its perceived intensity, while distraction reduces the intensity[5]. Furthermore, brain imaging studies have led to the idea of a "pain matrix", which consists of cortical and subcortical areas (including ACC, the primary and secondary somatosensory cortex (S1 and S2), the insula, amygdala, thalamus, and the periaqueductal grey (PAG)) that consistently activate upon painful stimuli[6]. These areas are not uniquely responsive to pain but are thought to be involved in different brain functions of pain processing and regulation related to cognition, emotion, and sensation[7].

1.2. Conditioned pain modulation

Conditioned pain modulation (CPM) is a pain modulation mechanism by which "pain inhibits pain". In CPM, the perception of a noxious test stimulus (TS) is inhibited in the presence of another noxious conditioning stimulus (CS) applied to a heterosegmental site (i.e., a region of the body related to a different segment of the spinal cord)[8]. The mechanism hypothesized to underlie CPM is called the diffuse noxious inhibitory controls (DNIC)[9,10]. The concept of DNIC

was first developed based on recordings of spinal dorsal horn units in rats. It was revealed that noxious heat attenuated responses in the dorsal horn to noxious electrical stimulations applied to another body part. Animal studies have revealed that DNIC modulate spinal nociceptive processing with descending influences from areas in the midbrain and brainstem (e.g., dorsal reticular nucleus (DRt) and rostral ventromedial medulla (RVM))[11,12]. Therefore, in DNIC, the CS produces ascending nociceptive signals that project to the brainstem, which in turn triggers descending inhibition in the spinal cord to attenuate pain processing of the TS. This descending pain modulatory pathway is thus described as a spino-bulbo-spinal loop and is activated by bottom-up signals (i.e., the CS). In humans, CPM appears to involve both the spino-bulbo-spinal loop and top-down modulation from higher centers of the brain[13–17]. Namely, when subjective pain ratings of the TS decrease in the presence of the CS, the CPM effect may result from a combination of several mechanisms such as the DNIC (spino-bulbo-spinal loop) and top-down processing (e.g., expectation[15] and attention[16]). It remains unclear which supraspinal influences affect the CPM effect and to what extent. Thus, examining the cortical responses during CPM could help us better characterize the cortical processes involved in CPM.

CPM can be used to assess our body's ability to inhibit pain[8–10], with a growing body of research showing its clinical relevance[18]. The CPM effect is generally observed in healthy participants[19,20], and may be present but decreased in populations with chronic pain (e.g., fibromyalgia and irritable bowel syndrome), suggesting a disturbance in the pain inhibitory pathways in these groups[18,21–23]. However, in other populations with chronic pain such as chronic low back pain, the correlation between CPM and clinical pain remains unclear[24]. Furthermore, there is a growing interest in using the CPM effect in clinical practice, such as assessing the predictive value of preoperative CPM on the likelihood of developing postoperative chronic pain[25–27] or assessing the efficacy of pharmacological and therapeutic interventions of chronic pain[28–31]. Therefore, understanding the physiological mechanism of CPM may improve our understanding of the pathophysiology of clinical pain and its management.

1.3. Pain induced neural oscillations

Brain-imaging studies have revealed that CPM is associated with reduced activity in cortical areas such as S1, S2, the ACC, insula, and amygdala[19,20]. In addition, electrophysiological studies have demonstrated that evoked potentials (EPs) in response to painful stimuli measured at the central electrode (Cz) were reduced during CPM[17,32–34]. Alongside the EPs which primarily reflect slow changes in event-related neural responses, painful stimuli also induce event-related spectral perturbations (ERSPs) which are changes in ongoing brain oscillations. ERSPs are expressed as either transient increases (event-related synchronization, ERS) or decreases (event-related desynchronization, ERD) of the oscillation power in a specific frequency band[35]. In particular, previous studies have found that painful stimuli induced 1) a transient suppression of alpha (8-13 Hz) frequency activity (alpha-ERD) across central and posterior brain regions (e.g., somatosensory, motor and visual areas)[35–37], 2) a transient suppression in beta (15-30 Hz) frequencies (beta-ERD) over the sensorimotor cortex[38,39], followed by 3) a transient enhancement in beta frequencies (beta-ERS) in the sensorimotor cortex[40–42]. The respective functional relevance of pain-induced ERSPs remains largely unknown: alpha-ERD and beta-ERD have been suggested to reflect a widespread change of cortical excitability and to be involved in the alerting function of pain[37,39] while beta-ERS has been proposed to reflect top-down modulation of painful stimuli[41].

1.4. Study objectives

The primary aim of the present study was to examine the spatiotemporal characteristics of pain-induced ERSPs (e.g., alpha-ERD, beta-ERD, and beta-ERS) and their changes in response to CPM. We used magnetoencephalography (MEG) source imaging which has a high temporal and spatial resolution (i.e., milliseconds and 2-3 mm)[43]. Our secondary aim was to explore whether patients with chronic pain in their lower body express a reduced CPM effect as measured with subjective reports and ERSP neural correlates.

Chapter 2: Methods

2.1. Participants

Experimental data were collected at two different MEG units; at the Montreal Neurological Institute, Canada (MNI) and at the Donders Institute for Brain, Cognition and Behavior, the Netherlands (Donders).

Seventeen patients with chronic pain (CPs) (50 ± 8 years, 9 men) with pain in their lower body (e.g., lower back, legs, and feet) and seventeen healthy control subjects (HCs) (51 ± 10 years, 10 men) were recruited. 11 subjects from each experimental group were recruited at the MNI, and 6 subjects from each group were recruited at the Donders. We preferentially recruited patients with chronic pain from waiting lists for a spinal cord stimulator implant. Healthy control subjects had no previous history or current experience of chronic pain. The participants had no previous or current experience of other neurological diseases, but moderate, non-painful medical conditions were not an exclusion criterion.

Before the experiment, all participants completed questionnaires related to pain evaluation (the Brief Pain Inventory, BPI)[44], anxiety and depression (the Hospital Anxiety and Depression Scale, HADS)[45], and maladaptive response to pain (the Pain Catastrophizing Scale, PCS)[46]. Ethics approval was obtained from the Institutional Review Board of the Montreal Neurological Institute and the CMO region Arnhem-Nijmegen, and all participants provided informed written consent.

2.2. Stimuli

Brief transcutaneous electrical stimulations were applied at the right ankle to deliver test pain. The participant's skin was first prepared by abrading with skin prep gel then wiping any excess gel with alcohol swabs to create low contact source impedance at the site of electrode application. At both research sites (MNI and Donders), the stimuli were generated with a constant current stimulator (DS7A, Digitimer Ltd) and delivered with silver/silver chloride

electrodes placed 2.5 cm apart on the skin using a conductive paste. One test pain stimulation (TS) was 21 ms in duration and consisted of five 1-ms electrical pulses with 4 ms between two consecutive pulses. The stimuli were delivered at randomized inter-stimulus intervals of 6-10 s to minimize stimulus predictability and adaptation. We adjusted the intensity of the electrical stimulus for each participant prior to the experiment. A short series of ascending and descending test pain stimuli were presented in order to identify the stimulus intensity which induced a reported pain intensity score of 5 on a 0 to 10 numerical scale (0 = no pain, 10 = worst imaginable pain). We delivered the conditioning stimulus (CS) with a commercial ice pack placed on the left forearm. Although a cold water bath is a more standard form of CS, we could not place a water bath on the MEG chair and ice packs have been used as a CS in previous studies[16,47]. We prepared an ice pack (9.5 x 28 cm) containing 500 mL of gel and stored it at -18 °C until approximately five minutes before the application. We wrapped the ice pack in thin fabric to prevent skin damage, with the temperature of the prepared ice pack being approximately -10 °C, and the subjects reported moderate pain. The method of preparation and application of the CS was consistent for all participants at both sites.

2.3. Study protocol

The participants underwent one experimental session comprising three consecutive blocks (Figure 1). The *Before CPM* block consisted of the test pain only (22 electrical stimulations), the *During CPM* block consisted of concurrent test pain and conditioning pain (ice pack), then the *After CPM* block consisted of the test pain only, with the conditioning pain removed. Each block lasted approximately three minutes with a break of approximately two minutes in between blocks. After each block, the participants reported subjective ratings of the mean test pain intensity on a 0 to 10 scale, with 0 representing no pain and 10 representing the worst imaginable pain. Additionally, the subjects reported subjective ratings of the conditioning pain intensity on the same scale after the *During CPM* block.

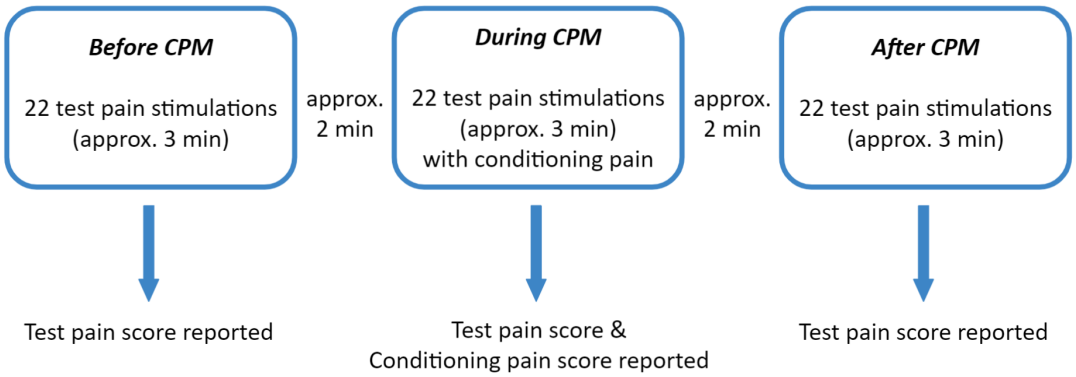

Figure 1. Experimental procedure of the study.

2.4. Regions of Interest

The brain regions hypothesized to present altered oscillations during CPM were defined for each ERSP (Figure 2). Alpha suppression (alpha-ERD) was expected to occur across the whole brain and more prominently in central and posterior regions (i.e., somatosensory, motor, and visual areas)[39]. Thus, we defined the region of interest (ROI) for alpha-ERD to include central and posterior MEG sensors (i.e., central, parietal, and occipital sensors) (Figure 2A). Beta suppression and rebound (beta-ERD and beta-ERS) were expected to occur around sensorimotor areas[39,41], we therefore defined the sensorimotor cortex as the ROI for beta activity in this study (Figure 2B).

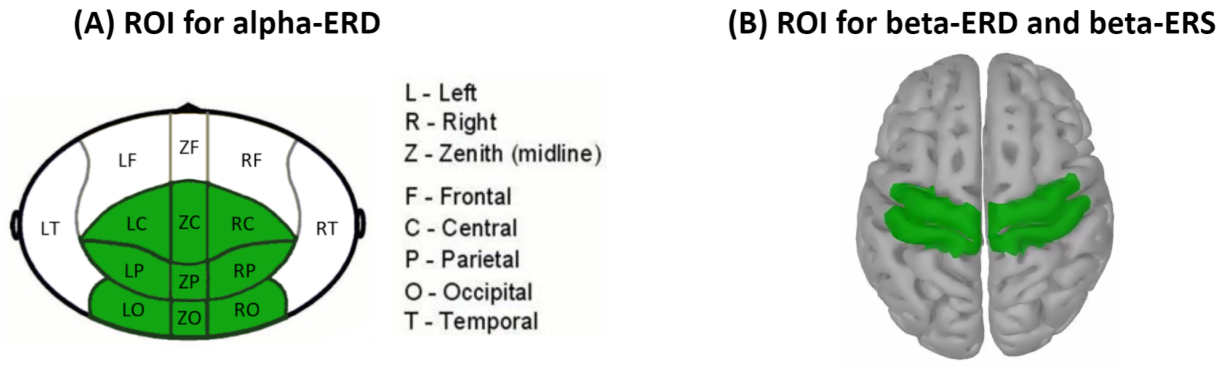

Figure 2. Regions of interest (ROIs). (A) The ROI for alpha-ERD is shown in green: all of the central, parietal, and occipital MEG sensors were included. Image modified from *Brainstorm*

tutorial[48]. (B) The ROI for beta-ERD and beta-ERS is shown in green: medial and superior lateral sensorimotor cortex.

2.5. Data acquisition

At both research sites, the neural signals were recorded with a 275-channel whole-head CTF MEG system with a sampling rate of 2400 Hz in a magnetically shielded room (MSR). The 3rd order gradient compensation was applied for noise reduction. Before the experiment, a two-minute recording of the MSR with no participant was collected to capture noise in the empty room. In each participant, head points were digitized to represent the individual head shape, and fiducial reference points were taken at nasion, left and right pre-auricular points for registration. Participants were free of removable metallic objects, and eye blinks and cardiac activity were recorded simultaneously with dedicated electrodes during the entire acquisition time: two electrodes placed below and above the left eye (vertical electrooculogram) and two electrodes placed on the temples (horizontal electrooculogram) were used to detect eye movements, and two electrodes placed across the chest (one below the right clavicle and one below the left ribs) were used to detect cardiac activity.

2.6. Data pre-processing

The acquired MEG data were pre-processed and analyzed using *Brainstorm*[49]. We first individually selected the stimulus artifact of the test pain visible on MEG sensors (maximum duration 70 ms after stimulus onset) and removed that signal portion with linear interpolation. In each subject, MEG sensors with poor signal quality were removed from the analysis. The maximum number of sensors removed for an individual subject was 14 out of 275 MEG sensors. Then, the data were bandpass-filtered betwee100n 1 and 200 Hz, and a notch filter was applied to remove contamination from power line (i.e., 50Hz, 100Hz, 150Hz, and 200Hz for recordings collected at the Donders, and 60Hz, 120Hz, and 180Hz for recordings collected at the MNI). Signal-space projections based on the spatial distribution of selected artifact events were used to remove artifacts from eye blinks, cardiac activity, movement (1-7 Hz), and muscle activities (40-240 Hz) separately.

Anatomical T1-weighted MRI volumes were used to co-register MEG data to individual anatomy when available (in 7 out of 34 participants). Otherwise, an individual anatomy template was derived from individual's head points and affine transformation of the ICBM152 template anatomy. The overlapping spheres model was used as a forward model, and the MEG time series were reconstructed at each vertex using an unconstrained minimum-norm estimation[50].

2.7. Time-frequency decompositions

To characterize the ERSPs induced by the test pain, we derived time-frequency representations (TFRs) of the signals extracted from the two ROIs (i.e., *central and posterior MEG sensors* and *the sensorimotor cortex*) in every subject. The TFRs in the time range of [-2, 6] s (0 s defined as the test pain stimulation application) and the frequency range of [1, 60] Hz were computed with Morlet wavelets (central frequency 1 Hz, time resolution 3 s). TFRs were then z-scored with respect to pre-stimulus baseline [-1.5, -0.5] s and averaged across all trials, conditions, and subjects in each ROI to obtain the *ROI average TFR*.

ERSP magnitudes in this study are expressed as an increase or decrease in oscillatory power relative to the pre-stimulus baseline (in z-score). In this regard, we defined the time and frequency ranges of each ERSP and used the fixed ranges for all subsequent analyses. The frequency range of interest of each ERSP was pre-defined as [8, 13] Hz for the alpha band and [15, 30] Hz for the beta band. We defined the time range of each ERSP by applying a threshold of ≥ 0.5 z-score to the respective *ROI average TFR* (either *central and posterior MEG sensor average TFR* or *sensorimotor cortex average TFR*).

After computing the TFRs and defining the time ranges of ERSPs, we compared the magnitude and duration of the ERSPs across subjects and groups. The magnitude of an ERSP in an individual's TFR was computed by averaging the signal magnitude in its defined frequency and time ranges. To compute the duration of an ERSP in an individual's TFR, we first averaged the MEG signal magnitude in the predefined frequency range, then smoothed the data across time

using a moving average (*movmean()* function[51] in Matlab) with a window length of 500 ms. We then defined the total duration of the ERSP in each individual with a threshold of ≥ 2 z-score applied to the smoothed data.

The spatial pattern of each ERSP was identified by computing its magnitude at every vertex in the defined time and frequency ranges.

2.8. Power spectral density analysis

After comparing the ERSP magnitudes across groups and conditions, we studied whether the observed differences in ERSPs were due to differences in the ongoing oscillatory power in the absence of the painful stimuli (TS). To this end, we computed the power spectral density (PSD) of data time series over the pre-stimulus baseline of [-2, 0] s using Welch's method, with a 1-second window and 50 % overlap. The PSD was computed for each subject in the sensorimotor cortex ROI in the frequency range of [1, 60] Hz. We then normalized the computed PSD to the individual's total power across the whole frequency range in order to obtain a relative PSD measure which indicates the relative (%) power in each frequency band, with respect to the total signal power.

2.9. Statistical analyses

Statistical analyses were performed in R language and environment[52] and *Brainstorm*[49] with a significance threshold of $p \leq 0.05$. Several analyses involved data with non-normal distributions, thus we used non-parametric tests. The characteristics between the two experimental groups (HC and CP) were compared with Wilcoxon rank-sum tests. To compare the subjective ratings of the test pain as well as ERSPs across experimental groups (between-subject factor) and conditions (within-subject factor), 2 x 3 non-parametric ANOVA-type statistics (ATS) were performed using the "nparLD" package[53]. The significance level was adjusted for multiple comparisons in terms of ROIs and for *post-hoc* pairwise comparisons with the false discovery rate (FDR) adjustment. The associations between neural (e.g., ERSP) and behavioral (e.g., subjective ratings of the test pain) measures were analyzed with Spearman's rho correlation

coefficients. To compare the TFRs of the ERSPs across experimental groups and conditions, we used cluster-based permutation tests in *Brainstorm* with a cluster threshold of 0.05 and 1000 permutations. Although vertex-based correction for multiple comparisons is more conservative compared to cluster-based correction, it enables better spatial precision[54]. Therefore, to contrast the spatial patterns of the ERSP changes induced by CPM and chronic pain, we performed permutation Student's *t*-tests (alpha = 0.05, 1000 permutations) and corrected for multiple comparisons across 15002 vertices on the cortical surface. Lastly, we used paired permutation Student's *t*-tests (alpha = 0.05, 1000 permutations) to compare the pre-stimulus baseline PSD across the three experimental conditions.

Chapter 3: Results

3.1. Clinical data

Participant demographics and characteristics are summarized in Table 1. The CP and HC groups did not differ in age (p = .972). However, the CP group featured significantly higher scores in anxiety (p < .0001, effect size r = 0.71), depression (p < .0001, effect size r = 0.76), and pain catastrophizing score (p < .0001, effect size r = 0.75). All patients with chronic pain had pain in their lower body, with 13 out of 17 patients experiencing chronic low back pain. More specifically, 12 patients had pain in the lower back and additional areas (e.g., legs, feet, higher back), one patient had lower back pain only, and four patients had pain in legs and/or feet.

	Patients with chronic pain n = 17	Healthy control subjects n = 17
Age (year)	50 ± 8	51 ± 10
Sex (male/female)	9/8	10/7
Average Pain severity (BPI) (/10)	5.6 ± 2.1*	0 ± 0
Current Pain severity (BPI) (/10)	4.8 ± 2.2*	0 ± 0
Chronic pain duration (years)	9.9 ± 9.4*	N/A
Pain locations (subjects)	low back (13) right/left leg (6/12) right/left foot (6/8) elsewhere (e.g., hands, shoulder, high back) (6)	N/A
Pain classification	Failed back surgery syndrome (15) Diabetic neuropathy (3) Neuropathic pain (1)	N/A
HADS anxiety	8.5 ± 4.3*	1.9 ± 1.2
HADS depression	8.1 ± 3.7*	1.4 ± 2.4
Pain catastrophizing score	23.0 ± 10.3*	4.2 ± 4.8
Pain medicine† (taker/nontaker)	11/6	3/14
Non-pain medicine (taker/nontaker)	12/5	5/12

Table 1. Subject characteristics (mean ± standard deviation)

*p<0.0001

†opioid, antidepressants, anticonvulsants and NSAIDs

3.2. Behavioral results

Pain stimulus intensity and subjective pain ratings in the two experimental groups are summarized in Table 2. The CP and HC groups did not differ in mean TS intensity (p = .986). Also, the two experimental groups did not differ in subjective pain ratings to TS in any condition (*Before CPM*: p = .821; *During CPM*: p = .739; *After CPM*: p = .876) or CS (p = .446).

	Patients with chronic pain n = 17	Healthy control subjects n = 17
Test pain stimulus intensity (mA, all conditions)	22.1 ± 14.5	20.0 ± 9.2
Test pain rating: *Before CPM* (/10)	3.7 ± 1.3	3.9 ± 1.2
Test pain rating: *During CPM* (/10)	3.5 ± 1.6	3.4 ± 1.4
Test pain rating: *After CPM* (/10)	3.4 ± 1.5	3.2 ± 1.5
Conditioning pain rating (/10)	3.9 ± 2.2	3.3 ± 2.5

Table 2. Pain intensity and subjective pain ratings (mean ± standard deviation)

The pain ratings to TS decreased during CPM in 10 out of 17 participants in the HC group and 7 out of 17 participants in the CP group. Subjective ratings to test pain stimulation were compared across groups and conditions, and a main effect of condition was found (*ATS* (1.95) = 4.76, p = .009) (Figure 3). We did not find a main effect of group (*ATS* (1.00) = 0.01, p = .918) or interaction effect (*ATS* (1.95) = 0.70, p = .491). *Post-hoc* analysis with paired *t*-tests revealed that the subjective ratings reduced significantly in the HC group in the *During CPM* (p adjusted = .034) and *After CPM* (p adjusted = .034) conditions compared to the *Before CPM* condition. We did not find pain rating differences across conditions in the CP group.

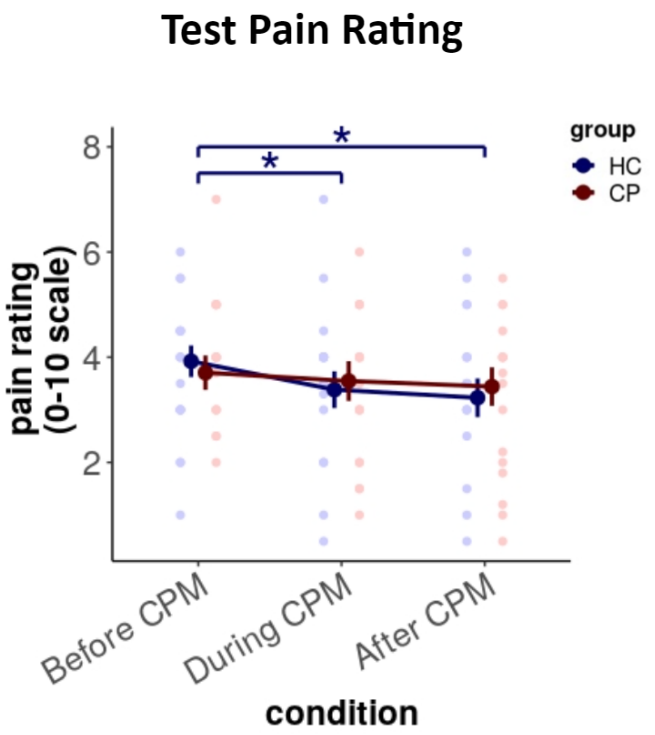

Figure 3. Subjective rating of test pain stimulation (mean ± standard error). A rank-based ANOVA-type test revealed a main condition effect. Subjective ratings were reduced in the HC group only in the *During CPM* and *After CPM* conditions compared to the *Before CPM* condition. *p<0.05

3.3. Characterization of ERSPs induced by painful stimuli

The three hypothesized pain-induced ERSPs (i.e., alpha-ERD, beta-ERD, and beta-ERS) manifested in the current study. Figure 4 presents the average TFRs from the two ROIs: (A) the ROI for alpha-ERD (i.e., central, parietal, and occipital MEG sensors combined), and (B) the ROI for beta-ERD and beta-ERS (i.e., sensorimotor cortex). The stimulus artifact was reduced but was not completely removed, as shown with a significant increase in magnitude around 0 s. Time-frequency decomposition using Morlet wavelets has high frequency resolution but low temporal resolution in the low-frequency region, which explains the spread of the stimulus artifact across time samples in lower frequencies. As expected, Figure 4A and Figure 4B prominently express pain-induced changes in the alpha band (alpha-ERD) and beta band (beta-ERD and beta-ERS), respectively.

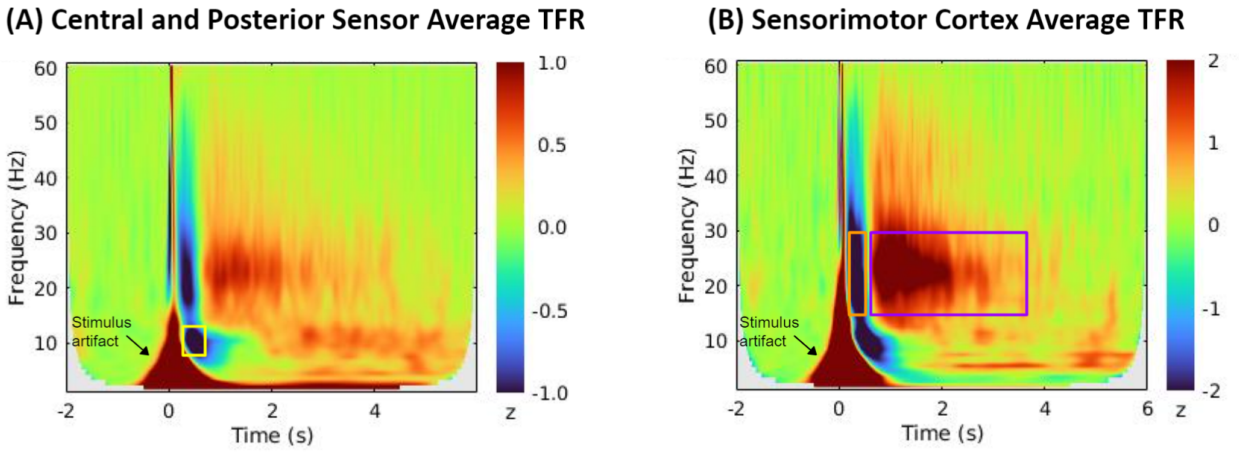

Figure 4. ROI average time-frequency representations (TFRs). TFRs were averaged across all experimental trials, groups, conditions, and subjects in each ROI. A) *Central and posterior MEG sensor Average TFR.* ROI: central, parietal and occipital MEG sensors. Alpha-ERD is prominent in this figure (yellow box). B) *Sensorimotor Cortex Average TFR.* ROI: sensorimotor cortex. Beta-ERD (orange box) and beta-ERS (purple box) are prominent in this figure. The large power increase around 0 s reflects the remaining stimulus artifact.

The time ranges of the ERSPs were defined with a threshold of 0.5 z-score applied to the respective *ROI average TFR* and are shown in Figure 4: alpha-ERD (yellow box: [0.32, 0.76] s), beta-ERD (orange box: [0.16, 0.55] s) and beta-ERS (purple box: [0.61, 3.68] s). The brain maps corresponding to the ERSPs were computed across the entire cortical surface within the defined time and frequency ranges. They included the hypothesized brain regions: alpha-ERD was expressed in central and posterior regions of the brain; beta-ERD was spread around the sensorimotor cortex; beta-ERS was localized to the sensorimotor cortex (Figure 5). Our data therefore confirmed that the three predicted ERSPs induced by painful stimuli were all expressed in the current study in the expected brain regions.

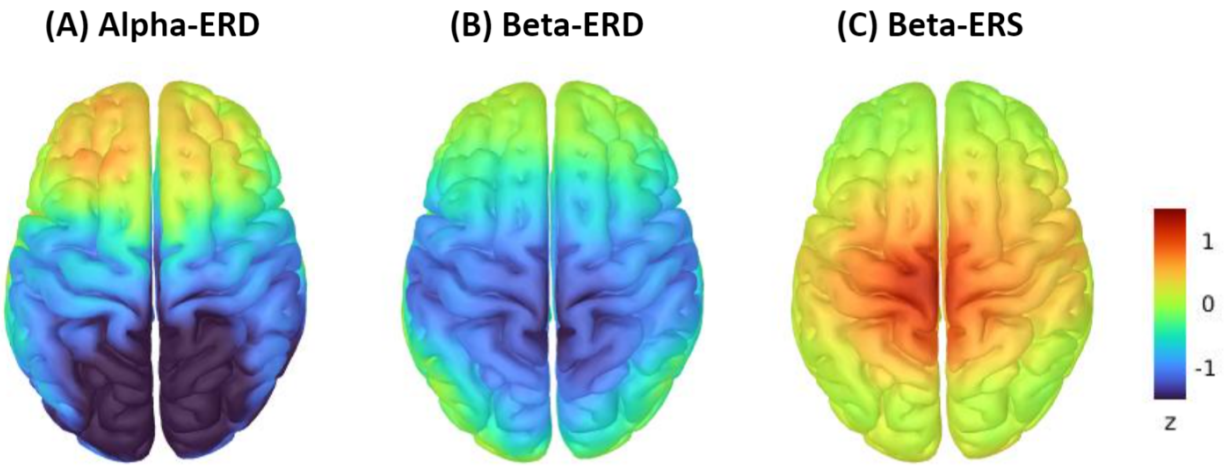

Figure 5. Whole-brain maps corresponding to the respective time occurrences and frequency bands of pain-induced ERSP averaged across all experimental trials, groups, conditions and subjects: alpha-ERD ([0.32, 0.76] s), beta-ERD ([0.16, 0.55] s) and beta-ERS ([0.61, 3.68] s). The frequency range was set to [8, 13] Hz for the alpha band and [15, 30] Hz for the beta band. Our data showed pain-induced ERSPs in the hypothesized brain regions: (A) Alpha-ERD was expressed in central and posterior brain regions, (B) beta-ERD was expressed in sensorimotor cortices, and(C) beta-ERS was localized to sensorimotor cortices.

3.4 The effect of CPM and chronic pain on the ERSPs

We assessed the effect of CPM and chronic pain on the characterized ERSPs with three different approaches; an exploratory analysis, ranked-based ANOVA-type tests, and cluster-based permutation *t*-tests.

We observed a notable difference between ERSPs across the three experimental conditions that manifested as a reduction in magnitude and duration of beta-ERS during CPM (Figure 6). Sensorimotor beta-ERS was indeed reduced during CPM in both groups, and that reduction was followed by a partial recovery in the *After CPM* condition in the HC group. In addition, in all three experimental conditions, the CP group expressed beta-ERS of lower magnitude compared to the HC group.

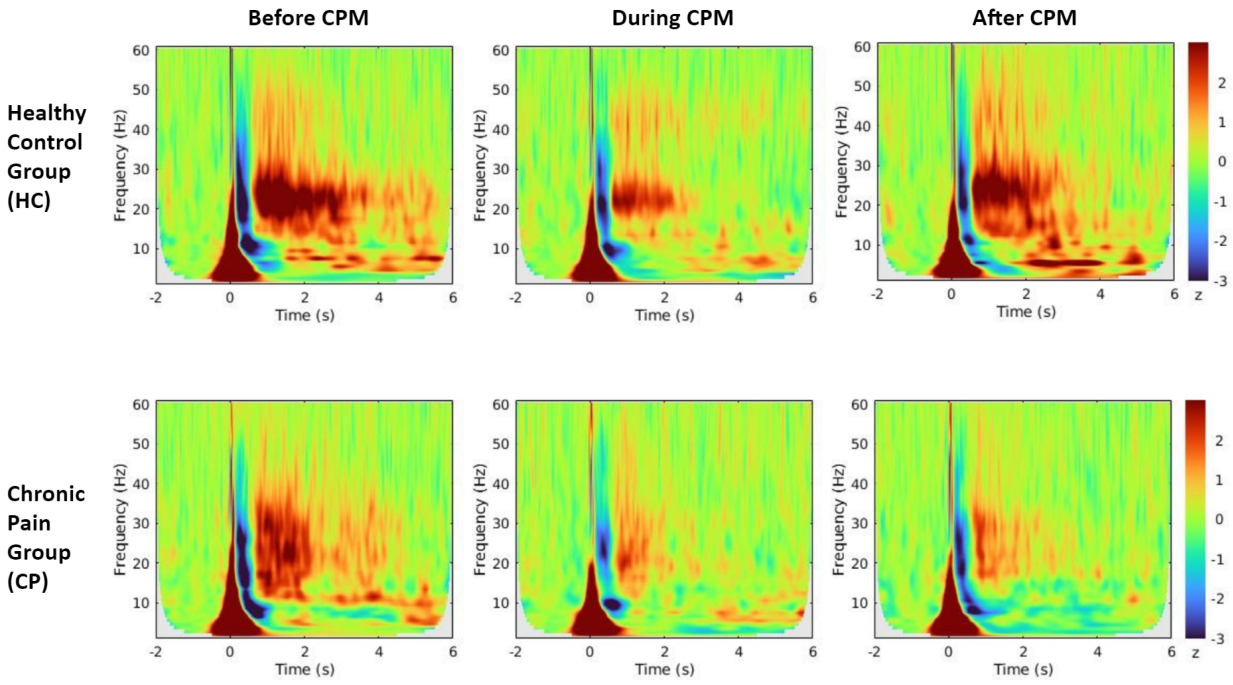

Figure 6. Time-frequency representations before, during, and after CPM averaged in each study group (patients with chronic pain and healthy control subjects) in the bilateral sensorimotor cortex. The magnitude and duration of beta-ERS appeared to be reduced during CPM in both groups.

The results from rank-based ANOVA-type tests confirmed these observations (Figure 7). Among the three ERSPs that we investigated, only beta-ERS was affected by the CPM manipulation. We found a main effect of condition in beta-ERS magnitude (*ATS*(1.98) = 9.06, *p* = .0001). We did not find a main effect of group (*ATS*(1.00) = 2.75, *p* = .097) or interaction effect (*ATS*(1.98) = 0.96, *p* = .381). Pairwise comparisons showed that beta-ERS magnitude was reduced in the HC group during CPM (*p* adjusted = .038). Similarly, when the duration of beta-ERS was compared across groups and conditions, the rank-based ANOVA-type test revealed a main condition effect (*ATS*(1.99) = 8.46, *p* = .0002). There was no main effect of group (*ATS*(1.00) = 1.32, *p* = .251) or interaction effect (*ATS*(1.99) = 1.35, *p* = .258). *Post-hoc* pairwise comparisons revealed that beta-ERS duration in the HC group was significantly shortened during CPM (*p* adjusted = .007). Therefore, both measures of beta-ERS (i.e., magnitude and duration) indicated that they were reduced in the HC group upon CPM.

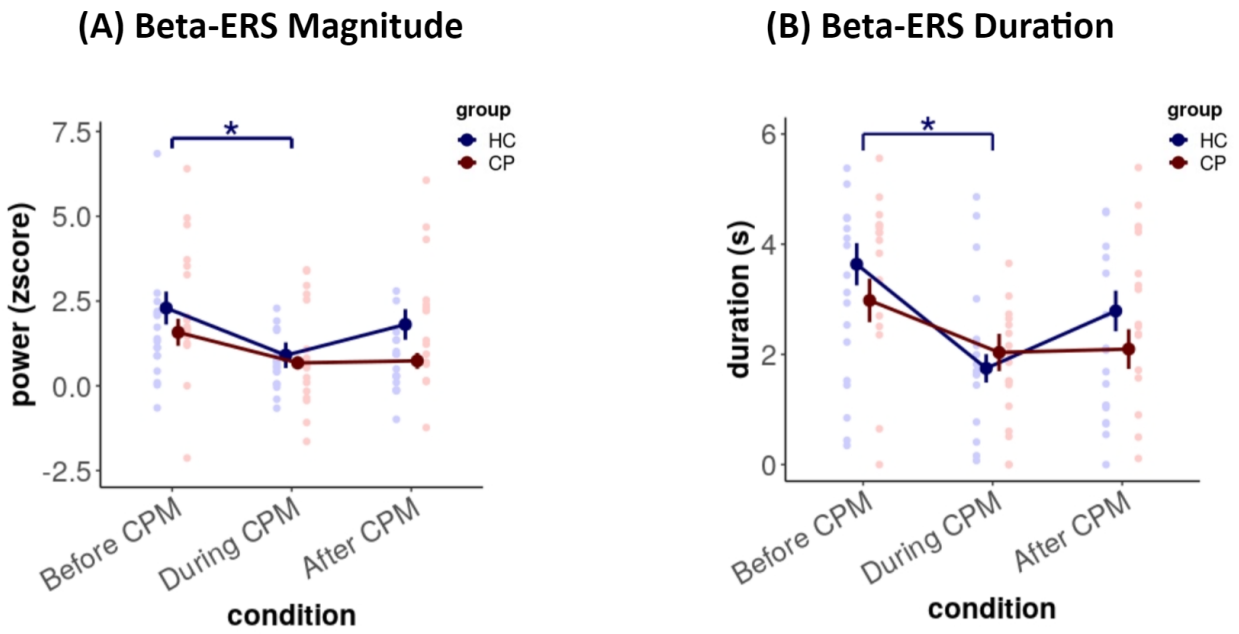

Figure 7. Sensorimotor beta-ERS compared across experimental groups and conditions (mean ± standard error) (A) Beta-ERS magnitude comparison. (B) Beta-ERS duration comparison. Rank-based ANOVA-type tests revealed main effects of condition in both magnitude and duration of beta-ERS, separately. *Post-hoc* analyses showed that beta-ERS magnitude and duration were both reduced significantly during CPM in the healthy control group.
*p<0.05

Lastly, we employed cluster-based permutation statistics to examine the presence of significant cluster effects in TFRs between groups and conditions. In line with the results from the rank-based ANOVA-type tests, the permutation tests revealed a significant cluster in the beta band (around 1-3 s) between the *Before CPM* and *During CPM* conditions (p adjusted =0.006) as depicted in Figure 8A. Comparing the two experimental groups, we found a cluster in the beta band (around 2-3 s), although it was not statistically significant (p = 0.086) (Figure 8B).

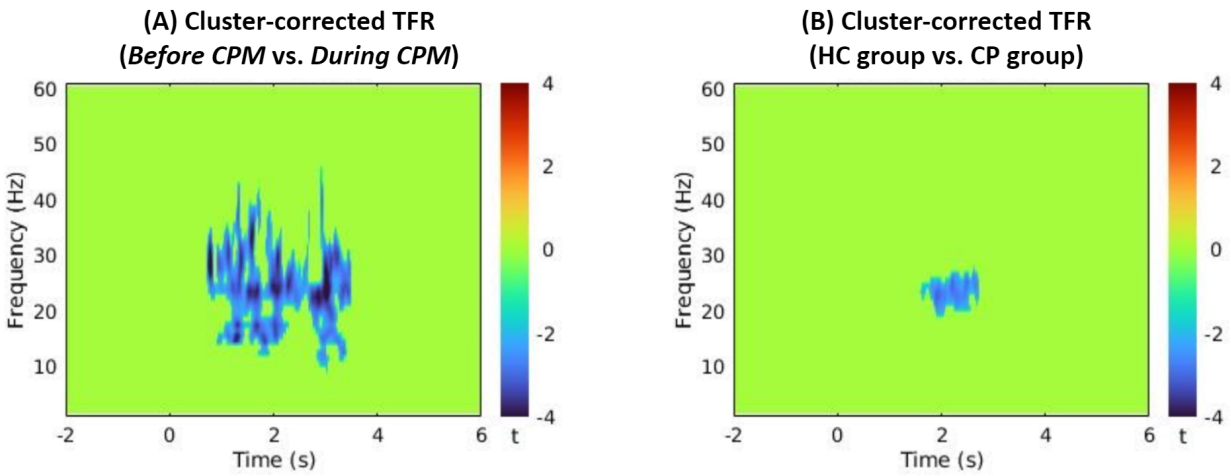

Figure 8. Cluster-corrected time-frequency representation (TFR) of MEG signal magnitude differences in the sensorimotor cortex. The colormap shows the t-values of the cluster-based permutation t-test. (A) Cluster-corrected TFR comparing the *Before CPM* and *During CPM* conditions (*During CPM - Before CPM*). Beta-ERS magnitude decreased during CPM (p adjusted = 0.006). (B) Cluster-corrected TFR comparing the HC and CP groups (*CP - HC*). Beta-ERS magnitude was lower in patients with chronic pain compared to healthy control subjects, although the difference was not significant (p = 0.086).

Taken together, the three approaches used in the current study (i.e., exploratory analysis, ANOVA-type tests, and cluster-based permutation tests) pointed towards the same conclusion that beta-ERS is reduced during CPM in the sensorimotor cortex. *Post-hoc* analyses suggested that the observed reductions in beta-ERS magnitude and duration occurred in the HC group but not significantly so in the CP group. However, we emphasize there was no main group effect or interaction effect from the ANOVA-type tests and cluster-based permutation tests. Therefore, although the attenuation of beta-ERS was more substantial in the HC group, the two experimental groups did not differ significantly.

3.5 Pre-stimulus baseline analysis

We then studied whether the observed changes in beta synchronization were due to changes of ongoing levels of beta-band activity during the application of CPM. We therefore measured

ongoing beta-band signal power over the pre-stimulus baseline ([-2, 0] s) prior to each TS stimulus delivery, as a proxy of ongoing beta activity over the entire condition blocks. The rationale for this approach was that the observed attenuation of beta-ERS upon CPM could be due to increased ongoing oscillatory activity in the beta band as a consequence of CS. These changes are observable at the baseline level before the delivery of the TS. Paired permutation Student's t-tests did not reveal significant differences between the baseline PSDs of the three conditions (Figure 9). Therefore, the differences in beta-ERS we observed previously in the *Before CPM* and *During CPM* conditions were not due to differences in the baseline levels of beta-band brain activity, but instead, were induced by differential beta-band in response to TS.

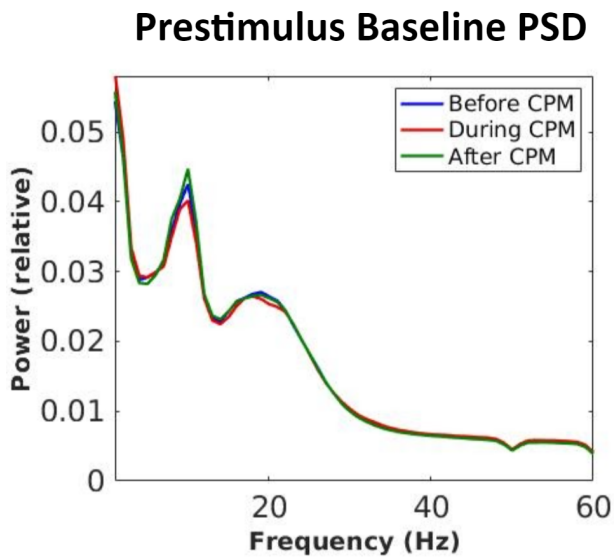

Figure 9. Power Spectral Density (PSD) in each condition during pre-stimulus baseline [-2,0] s in the sensorimotor cortex ROI. The three experimental conditions are indicated with different colors (blue: *Before CPM*, red: *During CPM*, green: *After CPM*). The average PSDs of the three conditions are overlapping, and there was no significant difference between conditions.

3.6 Topography of beta-ERS

We mapped the beta-ERS differences across groups and conditions onto the brain surface. Qualitatively, beta-ERS was reduced during CPM in and around the sensorimotor cortex in both experimental groups (Figure 10). The HC group expressed greater sensorimotor beta-ERS

magnitude compared to the CP group regardless of the condition. Additionally, in contrast to the CP group, the HC group expressed beta-ERS bilaterally over the most inferior and lateral aspects of the sensorimotor cortex.

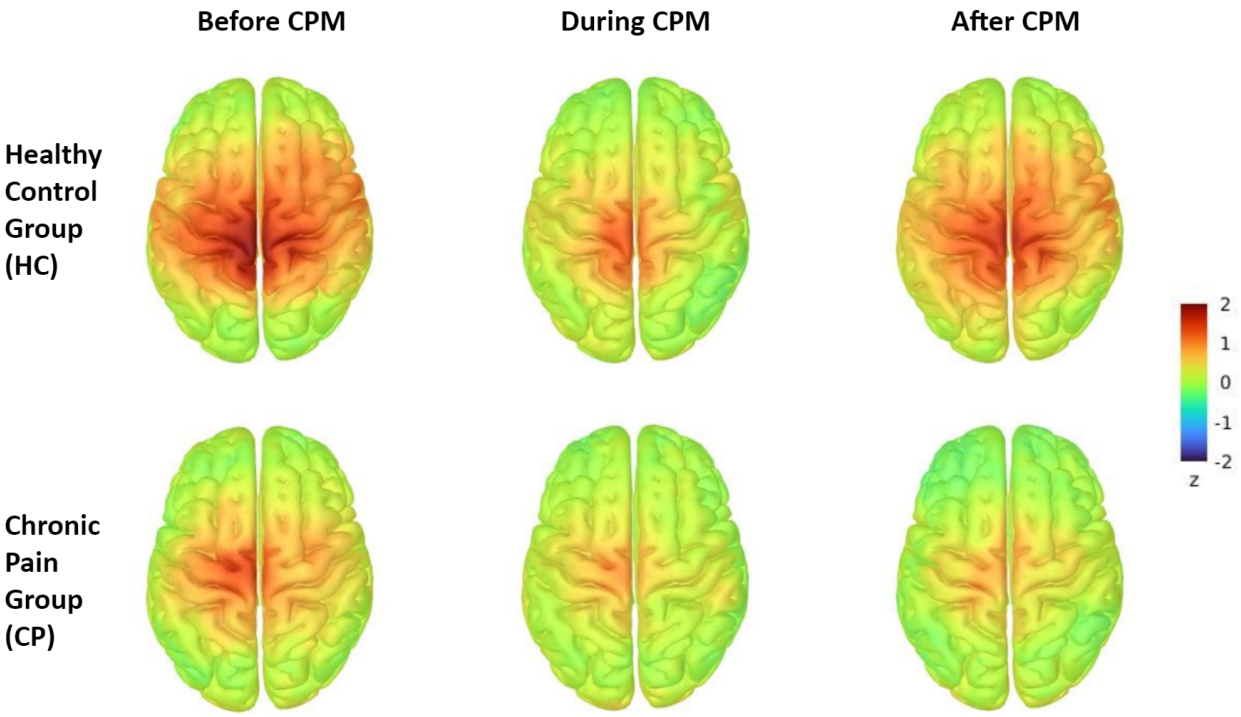

Figure 10. Beta-ERS (time range: [0.61, 3.68] s, frequency range: [15, 30] Hz) cortical topography in each group and condition; z-scores compared to pre-stimulus baseline. In both groups, beta-ERS was attenuated during CPM in and around the sensorimotor cortex. Overall, the chronic pain patient group (bottom row) expressed lower sensorimotor beta-ERS magnitude than the healthy control group (top row).

Permutation Student's *t*-tests (alpha = 0.05, FDR-corrected for multiple comparisons across 15002 vertices) provided further insights into the brain regions in which the beta-ERS differences occurred. Figure 11 illustrates that beta-ERS was attenuated during CPM in the sensorimotor cortex (medial and superior lateral areas) and the supplementary motor area (SMA).

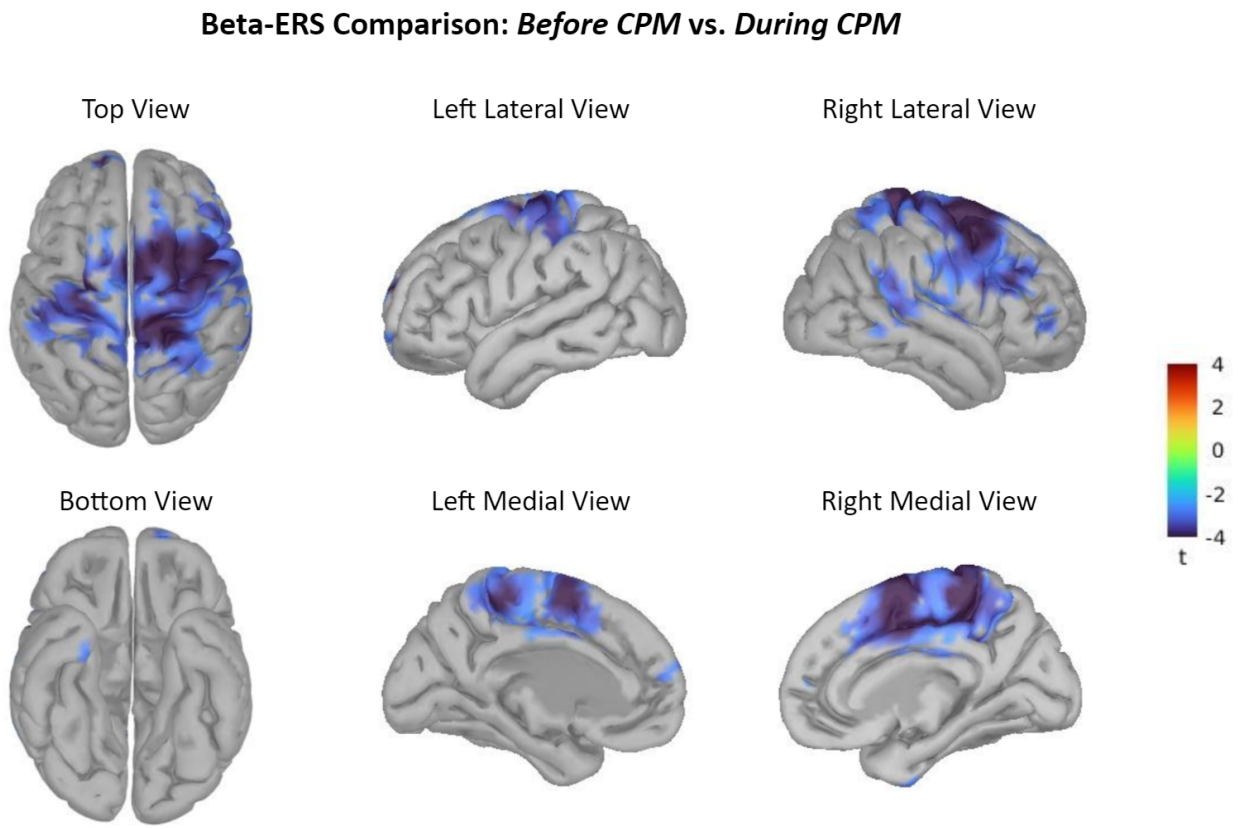

Figure 11. Brain topographies comparing beta-ERS magnitude in the *Before CPM* and *During CPM* conditions regardless of the experimental groups. The brain maps depict the t-values obtained by paired permutation Student's t-tests (alpha = 0.05, 1000 permutations). Cortical regions highlighted in blue represent vertices whose beta-ERS magnitude was lower during CPM.

We did not find differences in beta-ERS magnitude between the two experimental groups. A more lenient alpha value of 0.1 (FDR-corrected for multiple comparisons across 15002 vertices) revealed a potential group difference in beta-ERS magnitude: healthy control subjects expressed greater beta-ERS than patients with chronic pain in medial and inferior lateral aspects of the sensorimotor cortex (Figure 12). This group difference must be regarded as exploratory and remains to be tested in a future study with a greater sample size.

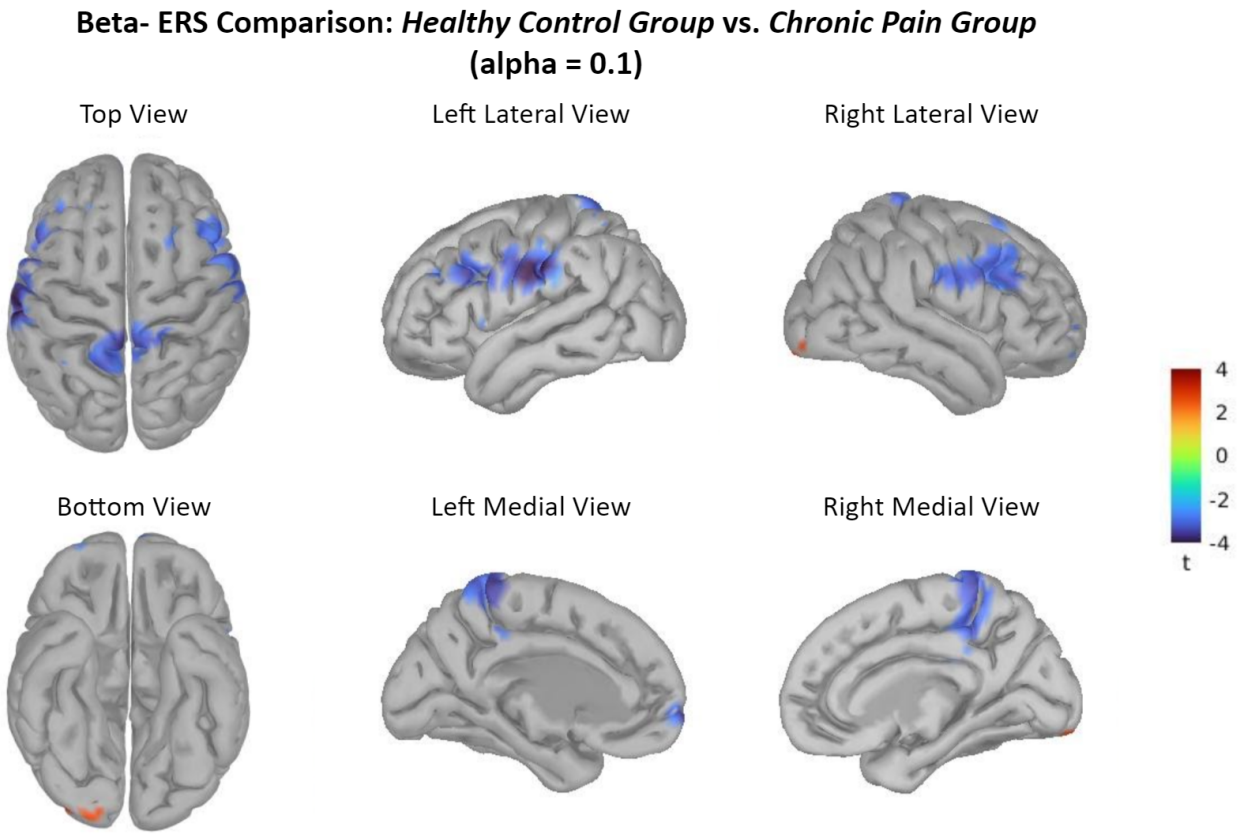

Figure 12. Brain topographies comparing beta-ERS magnitude in the *Healthy Control Group* and *Chronic Pain Group* regardless of the experimental conditions. The brain maps depict the t-values obtained by independent permutation Student's t-tests (alpha = 0.1, 1000 permutations). Cortical regions highlighted in blue represent vertices whose beta-ERS magnitude was lower in the chronic pain group than in the healthy control group.

Taken together, CPM induced a beta-ERS reduction in the hypothesized areas of beta-ERS expression (i.e., sensorimotor cortex). The data also point at group differences in beta-ERS between patients with chronic pain (with pain in their lower body) and healthy control subjects in the bilateral medial and inferior lateral sensorimotor cortices, although these differences remain to be tested.

3.7 Comparison of neural and behavioral effects

The previous analyses demonstrate that CPM induces attenuations in both behavioral (i.e., subjective pain ratings) and neural (i.e., beta-ERS) measures caused by the TS. However, based on Spearman's rho, there was no significant correlation between behavioral and neural measures in response to CPM (r_s = .10, p = .559, N = 34) (Figure 13).

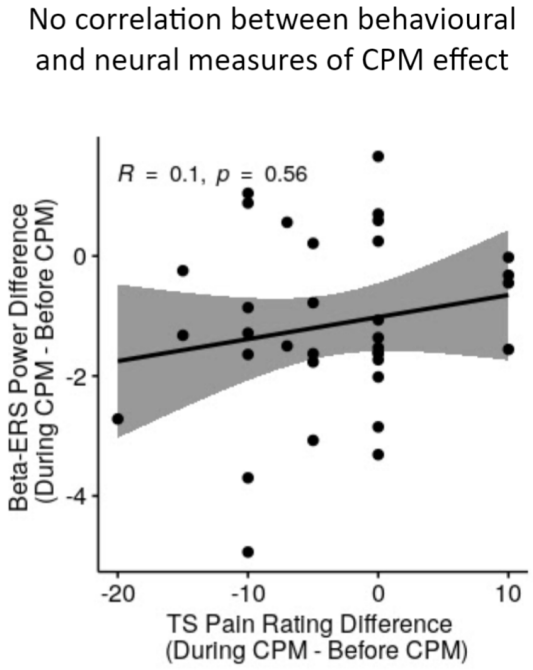

Figure 13. No correlation was found between behavioral (i.e., pain ratings to TS) and neural (i.e., beta-ERS) measures of CPM effect. The regression line is represented in black, and the 95 % confidence interval is shown in grey.

Chapter 4: Discussion

4.1. Main findings

The primary objective of this study was to examine how neurophysiological markers of pain induction (ERSPs) were altered in response to CPM. The secondary objective was to explore whether patients with chronic pain, particularly those with pain in their lower body, expressed such changes differentially with respect to healthy controls. Behaviorally, we found that subjective pain ratings to the pain-inducing test electrical stimulation (TS) were reduced during CPM in healthy control subjects, and that this effect persisted after the conditioning stimulus (ice pack) was removed.

Brain signal analysis demonstrated that event-related synchronization in beta frequencies (beta-ERS) occurred in all three experimental conditions (before, during, and after CPM) over extended portions of the bilateral sensorimotor cortex. Beta-ERS decreased in magnitude and duration under CPM in healthy control subjects. Although we found that CPM induced decreases in both behavioral (subjective pain rating) and neural (beta-ERS) measures of test pain, we did not find a correlation between them. Exploratory analysis with permutation Student's t-tests revealed the spatial patterns of beta-ERS differences. Firstly, beta-ERS was reduced during CPM in the sensorimotor cortex as well as the SMA. Secondly, beta-ERS was weaker in patients with chronic pain compared to healthy controls in bilateral medial and inferior lateral sensorimotor regions.

4.2. Functional roles of beta synchronization

Traditionally, beta band activity has been linked to cortical inhibition[35,40]. For example, beta oscillatory power in the sensorimotor cortex decreases (desynchronization) during voluntary movement execution and increases (synchronization) after movements cease[55]. Similar effects have been reported in sensory responses to peripheral stimulation. Beta desynchronization in the sensorimotor cortex is observed upon stimulus onset and synchronization is observed upon stimulus offset[56,57]. The inhibitory role of beta synchronization is in line with the observation

that it reflects cortical inhibition[40,58]: it is linked to the levels of inhibitory neurotransmitter GABA[59,60], and it is also intimately related to decreases of regional cerebral blood flow[61].

Event-related beta synchronization has also been reported in tasks other than sensorimotor. Beta band oscillations have been proposed to mediate top-down modulation[62] in various tasks (e.g., visual[63], auditory[64], working memory[65], and decision making[66]). Therefore, the pain-induced beta-ERS found in the current study may represent top-down cortical modulation involved in pain processing. Indeed, previously pain studies reported that bottom-up modulations affect almost all examined components of pain-induced brain signals, whereas top-down modulations selectively affect specific components: one study found that bottom-up modulation of pain by varying stimulus intensity induced changes in all frequency bands that were examined (delta, alpha, beta, and gamma) and top-down modulation by selected attention mainly changed alpha suppression[67]; another study found that changing pain stimulus intensity altered all pain-induced responses observed (in the theta, alpha, and gamma bands), while placebo analgesia altered the theta response only[68]; yet another study found that changing stimulus intensity altered the laser-evoked potentials P2, N2, and P400 while selective attention altered the N2 and P400 components only[69]. Therefore, as only beta-ERS out of the three examined ERSPs was altered during CPM in the current study, beta-ERS is more likely to reflect top-down modulation of pain than bottom-up modulation.

In line with the idea that beta-ERS reflects top-down modulation of pain, a study reported that pain-induced beta-ERS in contralateral S1 was increased when the subjects paid attention to the presented pain (vs. the presented visual stimuli)[41]. Attentional influences have been shown to change perceived pain intensity: attending to a painful stimulus resulted in increased pain perception[5], and directing attention towards another task or object reduced pain[70]. Currently, there is mixed evidence of the contribution of attention to the CPM effect. Some studies reported minimal effects of attention[71,72] while others reported that instructing participants to focus their attention on the CS (vs. the TS) induced a stronger CPM effect[16,73]. Therefore, one possible interpretation is that beta-ERS represents an attentional influence on pain processing,

and the reduced beta-ERS reflects reduced attention given to the TS during CPM. A subject might express high beta-ERS in the *Before CPM* condition because they attended to the presented stimulus. The subjects in this study were not instructed to pay attention to the stimulus, but painful stimuli tend to grab attention involuntarily[74]. In the *During CPM* condition, the noxious CS might also involuntarily take some level of attention. If there is a maximum possible physiological capacity in terms of beta-ERS signaling, the presented TS would induce a lower level of beta-ERS in the presence of a concurrent CS as some of the attentional resources would be allocated to the CS. Taken together, reduced beta-ERS during CPM likely indicates a change in the cortical modulation during CPM, and one possible interpretation is that it reflects attentional influences on pain processing.

4.3. CPM and chronic pain

Our data showed a trend towards lower beta-ERS in patients with chronic pain than healthy control subjects. Cluster-based comparison of the sensorimotor cortex TFRs and the exploratory analysis across the whole brain revealed that the CP group produced lower levels of beta-ERS than the HC group in the medial and inferior lateral sensorimotor cortex. Lower beta-ERS in patients with chronic pain is compatible with a possible chronic CPM state due to them experiencing ongoing chronic pain. If this is the case, patients with chronic pain may experience a flooring effect on CPM where experimental CPM (induced by the CS) cannot further reduce TS pain rating or pain-induced beta-ERS. In fact, our *post-hoc* analysis results are in line with this interpretation: CPM induced attenuation in both pain ratings and beta-ERS in the HC group only. However, with the current data, we cannot conclude how patients with chronic pain differed from healthy control subjects in their response to CPM. Indeed the 2x3 ANOVA-type tests did not show any interaction between experimental group and condition. If the flooring effect of CPM is actual in patients with chronic pain, a bigger sample size would be required to reveal group differences with sufficient power.

Additionally, the ROI for beta-ERS defined in the current study included a broader region of the medial and superior lateral sensorimotor cortex. Hence, the lack of group differences in

beta-ERS in the ANOVA-type analysis could also be explained by the broad area of the ROI. Possibly, beta-ERS group differences are more distinct in a specific frequency range within the beta range (15-30 Hz) and more localized areas of the brain.

4.4. Alpha and beta desynchronization

In addition to beta-ERS, we observed strong desynchronization in alpha and beta frequencies (alpha-ERD and beta-ERD) upon delivering the test pain stimulus. Alpha-ERD was expressed globally in the central and posterior part of the brain, and beta-ERD was present broadly around the sensorimotor cortex, consistent with previous studies. We did not find significant differences between experimental groups or conditions in terms of alpha-ERD or beta-ERD. Considering that attenuation in alpha and beta oscillations is related to higher excitability of a system[75], Ploner et al.[39] proposed that the pain-induced suppression in these frequencies across broad regions may be involved in the alerting function of pain to disrupt ongoing behavior. Relating to the possible interpretation that beta-ERS reflects attentional influences on pain processing, alpha-ERD and beta-ERD may initially alert the subject when the TS is presented, then beta-ERS may redirect attentional resources to the presented stimulus. This interpretation is analogous to the dual pathway theory of fear by LeDoux[76], whereby the amygdala's fear response can be triggered via two pathways. The first is the "low road" which directly connects the thalamus to the amygdala to allow for fast behavioral reaction (e.g., increased heart rate and muscle contraction). The second is the "high road" which goes from the thalamus to the cortex then to the amygdala to allow more in-depth evaluation of the given information. Similarly, the pain-induced ERD and ERS found in this study might represent fast and slow responses related to attention in response to pain.

4.5. Limitations

There are several limitations with the present data and analyses. Several patients with chronic pain were on medications to alleviate pain. For example, 7 subjects used opioids and 5 subjects used nonsteroidal anti-inflammatory drugs (NSAIDs) which may have affected their endogenous pain inhibitory system[77]. However, there was no group difference found in behavioral/neural

indicators of CPM between individuals who were using medications and those who were not. In addition, the substantial comorbidities of chronic pain and mental health disorders[78] might bias the comparison analysis. Another limitation to consider is that habituation might play a role in the current study design with three consecutive experimental blocks where the test stimulus was repeatedly given. Whether the reduction in pain ratings and beta-ERS in the *During CPM* block could be an effect of CPM analgesia and/or habituation is unclear. However, one important consideration is the partial recovery of beta-ERS in the *After CPM* condition in the healthy control group, where the experienced CPM effect was substantial. Therefore, the reduction in the magnitude and duration of beta-ERS in the *During CPM* condition cannot be explained by habituation alone.

Chapter 5: Conclusion

The present study aimed to characterize the pain-induced neurophysiological ERSPs in response to CPM. Amongst the three ERSPs that we investigated, only beta-ERS was reduced during CPM. Based on previous findings on the involvement of beta synchronization in top-down modulation, we discuss the finding of reduced beta-ERS as a manifestation of altered top-down modulation of pain during CPM. Furthermore, the effect of CPM on subjective pain ratings and beta-ERS was significant only in healthy control subjects. This may reflect that patients with chronic pain are in a chronic CPM state due to their ongoing pain sensation. In order to identify if and how beta-ERS relates to top-down influences in pain processing, a future study would need to manipulate different top-down factors (e.g., selective attention or placebo hypoalgesia) to observe which factor(s) affect the expression of beta-ERS.

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