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Focal changes in alpha oscillations during short-term memorization of pain:

a high-density electroencephalogram study with source localization.

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Short Title: Alpha power in short-term pain memorization

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ABSTRACT

Memories of painful events constitute the basis for assessing patients' pain. This study explores the brain oscillatory activity during short-term memorization of a nociceptive stimulus. High-density EEG activity (128-electrodes) was recorded in 13 healthy subjects during a match-to-sample sensory discrimination task, whereby participants compared the intensity of a thumb-located electric shock (S2) with a prior-stimulus to the same location (S1) delivered 8-10sec earlier. Stimuli were above or below the individual nociceptive-threshold. EEG activity with intracortical-source-localization via LORETA source reconstruction was analyzed during the inter-stimuli period, and contrasted with a non-memory-related control task.

The inter-stimulus memorization phase was characterized by a focal alpha-activity enhancement, significant during the nociceptive condition only, which progressed from bilateral occipital regions (cuneus and mid-occipital gyri) during the first encoding - memorization phase toward the right-superior and right mid-temporal gyri during the 2-4 sec immediately preceding S2. Initial alpha enhancement in occipital areas/cuneus is consistent with rapid non-specific inhibition of task-irrelevant visual processing during initial stimulus encoding. Its transfer to the right-temporal regions was concomitant to the temporary upholding of the stimulus perceptual representation, previous to receiving S2, and suggests an active and local blockade of external interferences while these regions actively maintain internal information. These results add to a growing field indicating that alpha oscillations, while indicating local inhibitory processes, can also indirectly reveal active stimulus-handling, including maintenance in short-term memory buffers, by objectivizing the filtering out of irrelevant and potentially disrupting inputs in brain regions engaged in internally-driven operations.

Key words: Short-term pain memorization; memory performance; alpha power; EEG; source localization

List of abbreviations

| | |
|-----------|----------------------------------------------|
| EEG : | Electroencephalography |
| LTM : | Long-term Memory |
| STM : | Short-term Memory |
| WM : | Working Memory |
| SP : | Somatosensory Painful |
| SNP : | Somatosensory Non-Painful |
| ISI : | Inter-Stimuli Interval |
| VAS : | Visual Analog Scale |
| ICA : | Independent Component Analysis |
| MEM : | Memorization phase |
| CONT : | Control phase |
| BL: | Baseline |
| ROI : | Region of Interest |
| ANOVA : | Analysis Of Variance |
| SD : | Standard Deviation |
| CNRS : | Centre National de la Recherche Scientifique |
| WMS-III : | Wechsler Memory Scale, Third Edition |
| CPP : | Comité de Protection des Personnes |

Introduction

The recollection of previously endured painful events constitutes the basis for assessing pain in patients, and the way a specific pain is memorized can influence the perception of future pain events (Apkarian et al. 2009). Memory-related mechanisms of synaptic plasticity, such as long-term potentiation and central sensitization, can support the long-lasting imprint of acute pain in the central nervous system and contribute to the transition of acute pain to chronicity (Kissin et al. 2006, Apkarian et al. 2009, Kissiwaa and Bagley 2018, Mazza et al. 2018). Since every painful experience is built both from the perceived sensation and the comparison made with previously undergone pain, the subjective assessment of pain often appeals to long-term memory (LTM) of painful events. However, investigation of the encoding, storing and recalling mechanisms of noxious stimulation is hampered by the impossibility of re-enacting, voluntarily or experimentally, a full painful sensation, except in very exceptional cases (e.g. Lenz et al. 1995).

Nonetheless, certain specific aspects relative to the experience of pain, such as its intensity or duration, can be experimentally assessed via short-term memory (STM) experiments. The mechanisms underlying STM, including working memory (WM), are thought to be highly relevant for understanding the LTM of pain: the quality of early WM processes may condition the establishment of LTM (Bergmann et al. 2013), and memory impairments in clinical pain patients have been shown to be reflected in WM for sensory stimuli (Oosterman et al. 2011; Munoz and Esteve 2005). Clinical studies have demonstrated STM deficits in diseases implying chronic pain symptoms (Moriarty et al. 2011), and a significant decline in performance during WM tasks has been repeatedly found both in patients suffering from chronic pain (Berryman et al. 2013) and in animal models of neuropathic pain (Cardoso-Cruz et al 2018). Therefore, investigating the process of short-term memorization of nociceptive stimuli can give us access to better understanding how maladaptive mnemonic processes of pain retention influence centralized chronic pain induction.

Few previous studies have gathered data on STM for pain. The temporal capacity of short-term memorization of pain stimuli in a sensory discriminatory task was found to have a very rapid decay, between 4 and 14 seconds after stimulus presentation (Rainville et al. 2005). fMRI studies have suggested that regions implicated in the initial integration of a nociceptive signal, such as the somatosensory and posterior parietal cortices and the anterior insula, are reactivated during the memorization phase of the intensity of a painful

stimulus (Albanese et al. 2007, Khoshnejad et al. 2017), while memorization of the stimulus duration also activated the inferior frontal gyrus, striatum and middle temporal gyri (Khoshnejad et al. 2017). Electrophysiological studies in humans have shown a power increase in the alpha frequency band over the parietal scalp during a WM task (Wang et al. 2016), and both alpha and beta oscillations appeared to correlate with WM capacity for phasic nociceptive stimuli (Valentini et al. 2017). However, although electrophysiological approaches provided unique temporal resolution inaccessible to functional imaging, previous EEG data were based on scalp distribution from relatively limited electrode density (25-60 electrodes), did not provide localization of the recorded activity in terms of brain generators, and did not consider possible carry-over effects between each memorization block (Rainville et al. 2005, Wang et al. 2016, Khoshnejad et al. 2017). Carry over effects have been shown to interfere with pre-acquired input in short-term memory task, both with verbal stimuli (Jonides and Nee 2006, D'Esposito et al. 1999) and auditory (Ruusuvirta et al. 2006, Visscher et al. 2009), which results in disruption of task performance.

In this study we aimed to tackle both the temporal and spatial aspects of brain activity during the short-term memorization of a nociceptive stimulus using high-density scalp electroencephalographic recordings (128-channel EEG) together with source reconstruction of brain generators in healthy subjects, and controlling possible memory residual effects by introducing a non-memory sensory task between each pain discrimination block.

Methods

Participants

This study was approved by the Regional Ethics Committee (Comité de Protection de Personnes CPP Sud-Est III, n°2014-A01280-47) and sponsored by the French National Scientific Research Council (CNRS). Participants were recruited through university announcements, and were remunerated for their participation. Inclusion criteria required healthy subjects aged 18 – 50 years, affiliated to a social security regimen, and having given their written consent. Were excluded subjects suffering from neurological disorders, chronic pain, under drug treatment with analgesics or drugs that can alter memory performances; and subjects with abnormal short-term mnemonic capacities (tested at the beginning of the experience with the Wechsler Memory Scale, Third Edition (WMS-III: Wechsler, 1997), with an admission score between 7 to 13 points on the numerical test). Of 15 initial participants 2 were discarded due to insufficient WM scores to ensure a good performance during the full test; hence, 13 healthy volunteers participated to the final recordings (21.7 ± 2.2 y.o; 7 women). Based on previous reports under similar WM versus control condition and reporting an effect size of 0.73 (Wang et al. 2016), we estimated that a sample size $n=13$ subjects allows to disclose a difference in power spectral analysis between the memory and the control condition with a power of 79.8% and error $\alpha=0.05$ (Gpower 3.1.9.2).

Stimulations

Two types of electrical somatosensory stimuli delivered to the hand, nociceptive and non-nociceptive, were used for the experiment.

Somatosensory electrical stimuli were delivered on the right thumb of each subject through a Micromed (ENERGY ©) stimulator. Nociceptive and non-nociceptive stimuli were delivered in different sessions, respectively through a concentric planar electrode (Walter Graphtek GmbH, Lübeck, Germany) and through ring electrodes. As the concentric planar electrode does not enable to deliver non-painful stimuli above perception threshold, ring electrodes had to be used for the non-nociceptive stimulations. The two types of stimuli consisted of monophasic constant current pulses of 100 μ s duration delivered at sub-nociceptive or supra-nociceptive intensities.

For each type of stimulus, two different intensities were used, labeled ‘low’ and ‘high’. Both levels of stimulation were tailored for each subject to ensure that they were identified without errors. For non-nociceptive electrical stimuli, the ‘low’ intensity corresponded to the lowest intensity for which the subject could feel 3 out of 3 consecutive stimuli. For nociceptive stimuli, the ‘low’ intensity corresponded to the lowest intensity for which one given subject evaluated the sensation as ‘painful but tolerable’ in 3 out of 3 stimuli, using the method of limits. Then, ‘high intensity’ stimuli were determined for each subject in the two modalities, at 1.5 times the threshold intensities. If such intensity was not enough to allow distinguishing the two stimulus levels, the ‘high intensity’ stimuli was progressively increased until it allowed 100% discrimination. It was ensured previous to the main experiment that the two intensities were such that (a) each participant could distinguish easily between them, and (b) they were rated clearly as painful for the nociceptive modality and clearly as non-painful for the non-nociceptive one. Once determined in a given subject, the two intensities in each modality were kept stable during the whole experiment.

Experimental procedure

Participants were comfortably seated in front of a computer screen. The main experiment consisted in a match-to-sample memory task in two conditions presented in random order: (i) somatosensory painful (SP); (ii) somatosensory non-painful (SNP). Each of the two memory tasks was contrasted with a corresponding control task of same modality, devoid of memory effort (Figure 1). Overall, the experimental phase lasted around 40 minutes.

Memory Task:

The memory session was composed of 32 trials, each formed of two sensory stimuli to be compared (S1 and S2) separated by an inter-stimulus interval (ISI) of 8-10 sec (mean: 9.0 ± 0.6 sec) and followed by a response period. The two stimulations (S1-S2) were always of the same modality (i.e. two nociceptive, or two non-nociceptive). Subjects were asked to indicate if the second stimulus was of higher, equal, or lower intensity than the first one by pointing on the computer screen. Further, they also indicated the subjective certainty of their response by clicking on a VAS, ranging from “not sure” to “completely sure”. To avoid possible residual memory traces between blocks, a visual task was introduced between each block whereby the subject had to detect

modifications of a visual stimulus (a square, a circle...) presented on a screen for 2 sec followed by a response time where subjects indicated whether the shape had changed color, form, both or none (Figure 1.A).

Control Task:

Control sessions consisted of 20 consecutive stimuli of same modality (10 'high' and, 10 'low' intensity as described above) presented randomly with an ISI of 8-10 sec (mean: 9.0 ± 0.6 sec). For the nociceptive modality, the subjects had to rate the intensity of each stimulus on a VAS ranging from 0 (no pain) to 100 (maximal pain). For the non-nociceptive modality, the subjects had to rate the intensity of each stimulus on a VAS ranging from 0 (no sensation) to 100 (strong but non-painful sensation). Each modality had its own VAS scale to prevent subjects from rating too closely the 'high' and 'low' intensities of the non-nociceptive stimulus. To prevent any tendency to memorize the stimuli received, the same visual task as described above was introduced in between each stimulus. This procedure prevented any effort to memorize the somatic stimulus and allowed comparing the brain activity during the interval between two consecutive stimuli with or without a memory encoding task (Figure 1.B).

Behavioral data

For each subject and type of stimulation, 'high' versus 'low' intensity ratings were compared using Student's T-test to ensure that the two intensity levels were correctly distinguished. A Student T-test was also used to compare certainty rates between each condition (SP, SNP).

Subjects' performances on the visual and memory tasks were assessed as the *proportion of correct answers* for each condition (SP, SNP) specifically for the memory task to ensure that performance was different of chance rate of 33% (3 possible answers: *higher, lower and identical*). A Student T-test was used to compare performances across conditions.

Cochran Q test was used to assess possible changes of performance with time. This binary test identifies correct answers as 1 and incorrect answers as 0, hence enabling to assess the difficulty of each question according to the number of 1 and 0 associated. The test was used to ensure that each trial was evaluated equally and that performance did not decline throughout the session.

EEG recordings and analyses

EEG was continuously recorded during all experimental sessions (control and memory). The recordings were obtained using an electrode cap (Waveguard Cap, ANT) and the Advanced Source Analysis system (ASA™-ANT Software, Netherlands), with 128 electrodes referenced to the nose. Ground was placed on the mid-forehead. An electro-conducting gel was inserted in each electrode to decrease the skin impedance below 5k Ω . Blinks and saccades were recorded on Fp1/Fp2 and F7/F8 electrodes. The EEG signal was continuously sampled at 512Hz.

EEG pre-processing, spectral and scalp topographical analyses were performed on BrainVision Analyzer 2.1© (BrainProducts GmbH, Germany). ICA ocular correction was done to clean the raw EEG data. A band-pass filter was applied to the raw EEG between 1 and 100Hz (-3 dB; slope 48 dB/oct and 12 dB/oct respectively) plus a Notch filter at 50 Hz. The signal was segmented into time windows of 2750 ms duration each. In the memory task, three consecutive time-windows of equivalent duration formed one block: (i) a pre-stimulus baseline from -3000 ms to -250 ms before S1 (BL_{MEM}) (ii) an early memorization period (MEM1) ranging from 1000 ms to 3750 ms after S1 thus excluding the event-related potential triggered by the stimulus, and (iii) a late memorization period (MEM2) from 3750 ms to 6500 ms after S1, thus excluding the anticipation activity occurring in the 1500ms before S2 (Figure 2.A). Defining an early and a late stage allowed us to assess the dynamics of the memorization phase. In the control task, only two EEG segments of same duration (2750ms) were used: (i) a pre-stimulus baseline ranging from -3000 ms to -250 ms before S1 (BL_{CONT}) and (ii) one post-stimulus during the control task (CONT) from 3000 ms to 5750 ms after S1 (Figure 2.B) which avoids both the motor response to the post-stimulus VAS (3000ms after S1) and the motor response to the visual task (2750 ms before S2). Segments containing artefacts (blinks, eye movements, muscle artefacts, electrode artefacts) were excluded from the analysis.

A Fast Fourier Transform (FFT) was applied to every segment, dividing their spectral composition into 5 frequency bands: delta [1.0- 4.0 Hz], theta [4.5 -7.5Hz], alpha [8.0-13 Hz], beta [13.5–30 Hz], and gamma [30–45 Hz]. The spectral power of the different segments described above was then averaged according to their position, across all trials, so as to obtain 5 averaged segments per subject, one for each condition: BL_{MEM} , MEM1, MEM2, and BL_{CONT} , CONT. To eliminate non-specific effects, each baseline was subtracted to the corresponding condition: MEM1- BL_{MEM} ; MEM2- BL_{MEM} ; CONT- BL_{CONT} . To alleviate writing, these subtractions will be referred as MEM1, MEM2 and CONT from here on. The same procedure was done by selecting only correct answer-segments to the memorization task (TRUE) on one hand and incorrect answer-segments (FALSE) on the other: MEM1_{TRUE}, MEM2_{TRUE}, MEM1_{FALSE}, MEM2_{FALSE}, CONT.

For both modalities (non-nociceptive-SNP and nociceptive-SP) and each frequency band, we calculated the standard deviation of the control condition's spectral power for each electrode: SD_{CONT} . This enabled to perform an observational analysis per electrode by comparing averages and selecting electrode clusters where the spectral power during the memory conditions (MEM1, MEM2) either exceeded the control condition power by at least 1 standard deviation or inversely, was below the control condition data minus 1 standard deviation. These clusters were then defined as regions of interest (ROI), where statistical assessment was applied. For both conditions (SP, SNP,) and for every frequency band (delta, theta, alpha, beta, gamma), repeated measures ANOVA were performed on the defined ROI with periods (MEM1 vs. MEM2 vs. CONT) as a within subject factor.

Brain source reconstruction

Brain source reconstruction was performed using Low Resolution Brain Electromagnetic Tomography Analysis (sLORETA-Version 20081104). Source localization of spectral differences was performed by applying sLORETA analysis to each 2750ms-EEG segment (Pascual-Marqui 2008). sLORETA estimates the standard current density in 6239 voxels of 5mm^3 , for each frequency band. These voxels cover the cortical grey matter and the hippocampus, but exclude the thalamus, basal ganglia and brainstem. For the brain model and electrodes

positions, sLORETA uses the Montreal Neurological Institute average MRI brain map (MNI-152), corrected in Talairach coordinates, allowing to link brain regions to Brodmann areas.

As the software is unable to import signals in spectral form, the Fast Fourier Transformation was replicated on each EEG taking account of the 8 pre-defined bands of sLORETA, the alpha and beta bands being divided in two and three sub-bands respectively (alpha 1, alpha 2 and beta1, beta2, beta3). The sLORETA was performed in the frequency domain to localize neural oscillators on the average referenced EEG.

Voxel-by-voxel paired post-hoc t-tests on log-transformed sLORETA data were performed to compare CONT and MEM periods. A non-parametric randomized correction (5000 permutations) was applied to limit type I errors (Pascual-Marqui, 2002). This correction procedure is based on a permutation test. Permutation tests, analog to a type of resampling, serve to quantify p-values of a statistical test by analyzing effects under different rearrangements of data points. In other words, as the null hypothesis is based on arbitrary labelling of observations, statistical significance of an experiment can be leveled by comparing distribution of values obtained when labels are permuted (see Nichols T.E and Holmes AP, 2002 for more details).

Signal to noise ratio was bettered by subtracting the baseline to each corresponding condition. The significance threshold was fixed at $p < 0.05$ after correction for multiple comparisons. Only regions for which at least 7 contiguous voxels appeared to have a significant effect were considered as results. Color-coded statistical results were projected onto 3D MRI images (MNI) using sLORETA.

All statistical analyses except sLORETA were performed with JASP® software with significance level set at $p < 0.05$, and Greenhouse-Geisser correction applied to repeated-measures ANOVA. Bonferroni post-hoc corrections were used when necessary. In all the figures, data are presented as mean \pm SEM.

Results

Behavior

Intensity perception

For all types of stimuli, the differences between high and low stimulus intensities were correctly discriminated during the control task by every subject before initiating the memory task. Ratings for ‘low’ and ‘high’ painful pulses were respectively 44.5 ± 11.3 and 64.7 ± 13.4 ($t(12) = 5.82$, $p = 8.3 \cdot 10^{-6}$) on a 0-100 scale where 0 was defined as non-painful and 100 as maximal pain. Ratings for ‘low’ and ‘high’ non-painful stimuli were respectively 27.9 ± 10.9 and 68.9 ± 12.2 ($t(12) = 7.46$, $p = 7.7 \cdot 10^{-6}$) on a 0-100 scale where 0 was defined as non-felt and 100 as non-painful but perfectly felt (Figure 3A).

Performances on the visual task

The visual task was introduced between memory blocks to erase possible residual memory traces between blocks in the memory condition, and to prevent unwanted recollections in the control task (see methods). For every type of stimulation and for both conditions (control and memory), a high score of correct answers was obtained in the visual discrimination task (>97% correct responses in each condition), with no significant difference between conditions and sessions.

Results of the Cochran Q test showed no significant difference in the distribution of correct and incorrect responses to the memorization task throughout the stimulations for every condition ($Q(45) = 25.6$, $p = 0.79$; $Q(45) = 26.6$, $p = 0.78$ for SP and SNP conditions respectively), indicating that there were no significant changes in performance over time.

Performances on the Memory Task

Overall, the rate of correct answers was well above the chance rate of 33% for both SP and SNP conditions ($48.01 \pm 9.31\%$, $58.24 \pm 14.7\%$, respectively) with 11 out of 13 subjects being above 40% rate of correct answers for the SP condition and 10 out of 13 above 50% for the SNP condition (Figures 3B and 3C). The number of correct answers was higher when subjects compared non-painful relative to painful stimuli, but the difference was barely significant ($t(12) = 2.12$, $p = 0.045$) (Figure 3C).

The certainty rate (estimating the confidence subjects had in their responses accuracy) was also high for all conditions (SP, SNP) ($74.13 \pm 12.31\%$, $69.99 \pm 11.96\%$ respectively). No significant differences in certainty rates were revealed neither between conditions (SP, SNP) nor between correct and incorrect answers within a type of stimulation. No correlation was found between certainty rate and number of correct responses.

EEG Recordings

SP and SNP conditions compared to the control period.

Visual analysis indicated a prominent effect in the alpha band in both the SP and the SNP condition, with a power increase during the memorization period (MEM1, MEM2) relative to the control period (CONT) (Figure 4,5A). The alpha power appeared to progressively intensify from period CONT to MEM 1 to MEM2, and also from condition SNP to SP (Figure 4). Single electrode analysis in each frequency band confirmed that the spectral power in the alpha band was the only EEG band that exceeded $1 * SD$ of the control period in both conditions (SP and SNP), and this during both the MEM1 and MEM2 periods (Figure 5B). No electrodes had a spectral power below the control period minus $1 * SD$. No other effect was apparent in the other frequency bands.

For the pain (SP) condition, memorizing a nociceptive stimulus came with an alpha increase in bilateral parieto-occipital regions during the first memory period MEM1, which then expanded to centro-parietal and right parieto-temporal regions during the late period MEM2 (Figure 5B), thus defining four ROIs detailed in table 1. Results of the repeated-measures ANOVA on these ROIs showed a significant effect of analysis window (MEM1 vs. MEM2 vs. CONT) with a significant increase in the left parieto-occipital region (ROI 3: $F(3,12) = 9.718$; $p = 0.009$) during MEM1 compared to CONT ($t(12) = -3.029$; $p = 0.034$) and even more so during MEM2 compared to CONT ($t(12) = -3.252$; $p = 0.023$) which also appears in the right parieto-temporal and occipital region (ROI 4: $F(3,12) = 8.094$; $p = 0.015$) specifically during MEM2 ($t(12) = -2.931$; $p = 0.041$).

For the non-painful (SNP) condition, MEM1 alpha power also exceeded $1SD$ of CONT alpha power in the right parieto-occipital region, which slightly expanded to centro-parietal and left parietal regions in MEM2 (Figure 5B) thus defining two ROIs detailed in table 1. However, repeated-measures -ANOVA on these ROIs revealed no significant effect of the period. Although spectral changes during the memory tasks were significant

in the pain (SP) condition but not in the SNP, direct spectral composition comparison between the two conditions showed no significant differences in any frequency band.

Brain source reconstruction

A significant current density increase was observed in the low alpha frequency band during memorization of the nociceptive stimulus intensity only, and this during the two memorization periods (MEM1 and MEM2) (Figure 6). During MEM1, this effect was significant in both occipital lobes (cuneus and middle occipital gyri) and the right temporal lobe - middle and superior temporal gyri - ($t(12) = 5.714$; $p < 0.05$). During MEM2, the current density increase was significant in the right temporal lobe - middle temporal gyri and supramarginal gyri - ($t(12) = 5.813$ $p < 0.05$), and even more so in the right superior temporal gyri ($t(12) = 7.232$; $p < 0.01$). Coordinates of the most significant voxels are shown in table 2.

No significant effects were observed during the SNP condition.

Discussion

The goal of this study was to analyze, in healthy subjects, the brain oscillatory activity during the short-term memorization of the intensity of a somatic stimulus, nociceptive or non-nociceptive, both delivered to the same distal body region. Focal activity in the alpha band was enhanced during both memorization conditions relative to the control task, but such effect was statistically significant exclusively during the nociceptive condition. Spectral differences between the memory and the control conditions were localized by source analysis in parieto-occipital and temporal brain regions, with a right-hemisphere predominance.

Parieto-occipital oscillatory activity in the alpha band during short-term memorization is commonly interpreted as reflecting the inhibition of brain areas irrelevant to the memorization task at hand (e.g. Klimesch et al. 2006, Dipoppa et al. 2016, Lozano-Soldevilla 2018). However, a number of studies have challenged the all-inhibitory role of alpha, and suggested a direct implication of the processes underlying alpha oscillations in selective attention and the maintenance of relevant information in memory stores (Piantoni et al. 2017; Schroeder et al. 2018; Palva et al. 2007). Here we posit that the two views are complementary rather than contradictory: while alpha activity may indeed reflect inhibition of external input, it does not reveal a non-specific ‘idle state’ of the cortex, nor it merely represents the inhibition of task-irrelevant regions, “thus routing information to task-relevant regions” (Jensen and Masaheri 2010). While such re-routing may be true in some cases (see below), alpha enhancement can also be essential to the performance of *task-relevant* regions as well, especially when the task involves internally-generated information, as is the case during the maintenance of perceptual representations. By allowing networks to work without perturbation, the blockade of external inputs to an active brain region may be essential to the stabilization of percepts. This is consistent with our present results, and also with recent reports of visual alpha enhancement associated with stable perceptual representations during the alternate experiences of a bi-stable Necker cube (Piantoni et al. 2017).

Short-term memorization of a sensory stimulus needs to activate systems that both ensure stabilization of the information to be retained, and suppression of alternative unrelated activity. It has been posited that working memory (WM) is made of non-discrete phases characterized by two main neural processes: an ‘early’ stage

establishing an internal perceptual image of the stimulus and a ‘late’ stage that maintains the mental image in memory (Bergmann et al. 2013, 2015). In the same vein, Khoshnejad et al. (2013) described the process of pain memorization as consisting firstly in transforming the nociceptive signal into a mental representation of pain, and then storing the latter as an implicit memory. In both of these models, the initial WM phase requires active processes for (i) establishing an internal perceptual model and (ii) suppress the handling of non-relevant concomitant sensory input. Alpha enhancement during this early phase was localized in visual regions, and may correspond to a non-specific inhibition of visual input during the formation of an internal representation of the nociceptive stimulus. Indeed, this early phase is particularly vulnerable to incoming task-unrelated material and competing perceptions (Bergmann et al. 2013; Piantoni et al. 2017), and the alpha enhancement observed in occipital visual areas has been suggested to reflect such inhibition of distracting input (ElShafei et al 2018, Sghirripa et al 2021). In parallel, the concomitant oscillatory enhancement that we observed in the cuneus, known to play a crucial role in the conscious perception of one’s own body (e.g. Whitlock, 2017), might echo its contribution in the development of a perceptual image of pain.

In addition to the early alpha enhancement in occipital areas and cuneus, a significant later increase in alpha current density occurred in the right temporal gyri, which started in MEM1, but greatly strengthened during MEM2, just before the presentation of the second stimulus. In the framework of the two-stage models of WM, this late phase should involve processes contributing to the maintenance of the ‘mental image’ of the first stimulus in memory previous to establishing a comparison with the second stimulus of the pair (Bergmann et al. 2013, 2015; Khoshnejad et al. 2013). Although the right superior temporal gyrus is commonly associated to visuo-spatial processing (Karnath et al. 2001, Shah-Basak et al 2018) it is also thought to play a role in multimodal alertness (Thiel and Fink 2007), and more recently in the memory maintenance of both auditory (Fritz et al 2016) and pain stimuli (Houdé et al 2020). It is therefore tempting to consider that the enhanced right temporal alpha current density was associated with some processes involved in the maintenance of the neural configuration corresponding to the perceptual representation. These processes may have initiated at the earlier phase MEM1 and fully settled during MEM2, explaining the lack of strict difference between these time-windows). As stated above, such an interpretation of alpha activity is not necessarily contradictory with its inhibitory role, since

blocking external inputs may be essential to safeguard the processing of internal (vs. external) information in active brain regions. We can speculate that the inhibitory role of alpha oscillations may be ‘heterotopic’ and non-specific when it occurs in regions *different* from those receiving and processing external stimuli, or on the contrary ‘homotopic’ and specific when it arises in regions directly involved in the processing of internal information.

Behavioral analysis showed a decay in performances when it came to memorize nociceptive stimulations compared to non-nociceptive input. A possible explanation may be that the intensity of the second nociceptive stimulus is poorly evaluated due to pain anticipation, thus biasing its comparison to the first one. Pain anticipation may lead to a ‘nocebo’ effect creating an expected hyperalgesia, as is suggested by the pre-activation of pain- and emotion-related areas, when subjects expect the arrival of a nociceptive stimulus (review in Palermo et al. 2015). One could also consider that the encoding of the first stimulation was erroneous; however, during the non-memorization control task, subjects correctly evaluated and discriminated the different intensities of the stimulation, suggesting that the first stimulation was probably well encoded.

Limitations of the study

The most important limitation of this study is the relatively small subjects’ sample that could be investigated. Two of the initial subjects had to be discarded because of insufficient performances in memory tasks, and changes in the lab’s technical settings precluded adding more participants to the sample. The behavioral and electrophysiological results were however reliable and in general highly significant, and our settings allowed for a power of ~ 0.8 with the number of subjects analyzed; we therefore stand by our results, which should be seen as exploratory. Lack of analysis of possible changes in the gamma band can also be considered as a limitation, since gamma activity has been considered as a direct reflect of both external and internal local information processing (Strube et al. 2021, Yang et al. 2020, Balconi et al 2008, Kaiser and Lutzenberger 2005). The gamma oscillatory activity is however highly sensitive to contamination from high-frequency artifacts, mostly muscle activity whose spectral content largely overlaps with it (Nunez and Srinivasan 2010) and was shown to preclude gamma analysis during pain experiments (Chouchou et al 2021). Intracranial EEG recordings in patients

implanted with intracerebral electrodes might be in the future the best option to explore alpha-gamma coupled activity in pain memorizing experiments.

Although previous data have revealed a collateral effect of posterior alpha enhancement on a somatosensory attentional task performance (Haegens et al. 2012), the behavioral consequence of alpha increase has scarcely been described, and our results remain too faint to conclude any direct causality.

Conclusion

Overall, this study suggests that part of the operations underlying short-term memorization of pain intensity are reflected by activity increase in the alpha band. The initial phase of encoding (MEM1) was associated with by a bilateral parieto-occipital alpha current density increase interpreted as a non-specific-gating and suppression of potentially disrupting input processing. This was followed by a right temporal enhancement of alpha current density which increased and stabilized during the late memorization phase, and could play a role in blocking external input to regions actively maintaining internally generated representations. Such differences between ‘heterotopic’ and ‘homotopic’ changes in alpha activity deserve further investigation, probably using intracerebral recordings to allow precise localization and comparison with changes in higher (gamma) EEG spectral changes.

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Authors' Contribution:

The authors confirm contribution to the paper as follows: study conception and design: Frot M., Garcia-Larrea L.; data collection: Frot M.; analysis and interpretation of results: Caldichoury A.; draft manuscript preparation: Caldichoury A., Frot M., Garcia-Larrea L.; All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors declare no competing interests.

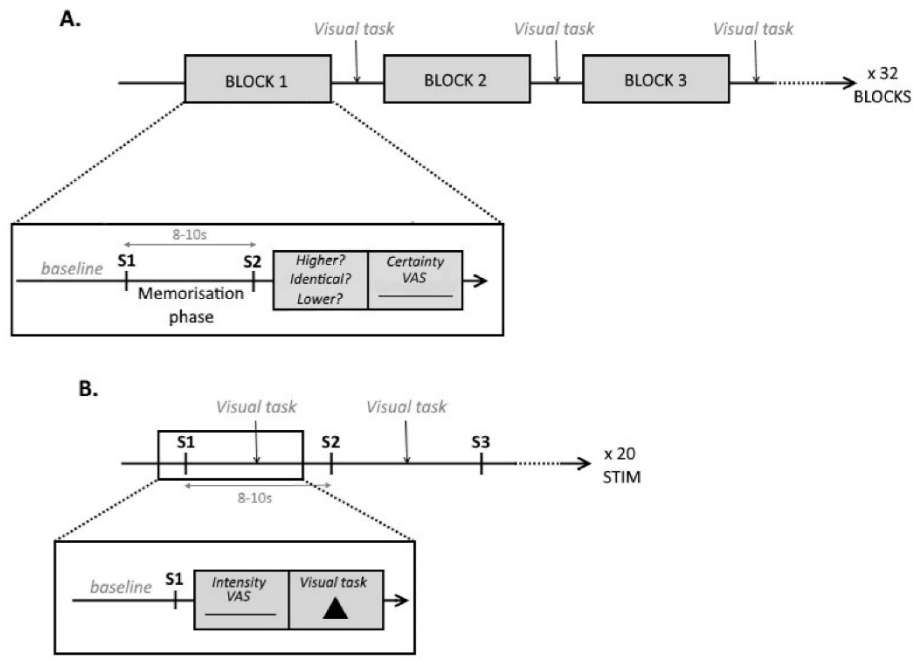


Figure 1 Experimental protocol: A. Memory Task. Thirty-two blocks separated each by a visual task. Each block contains: a baseline period (3s); two painful or non-painful stimulations (S1, S2) with an ISI of 8 to 10s corresponding to the memorization phase; a response period composed of an S1-S2 comparison and a certainty scale (VAS). **B. Control task.** Twenty blocks of 8 to 10s containing each: a baseline period (3s); a painful or non-painful stimulation (S); a response period during which the intensity of the stimulation (S) was to be rated on a VAS; a visual task (4s).

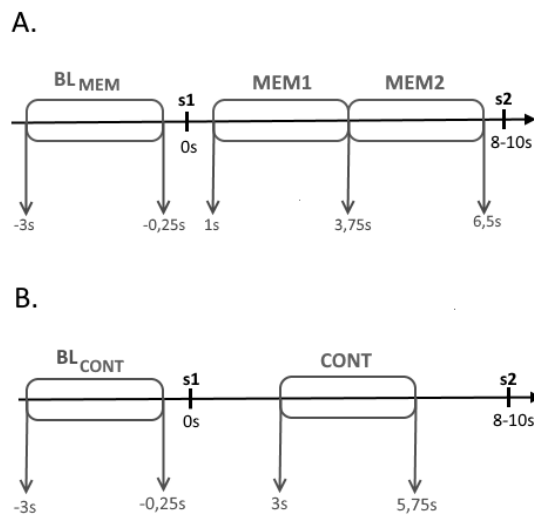


Figure 2 Temporal segments analysis for: A. the memory task (MEM): a baseline (BL_{MEM}) and two periods during memorization of the stimulation intensity (MEM1 and MEM2) and **B.** the control task (CONT): a baseline (BL_{CONT}) and a period during the visual task during which the subject does not memorize (CONT)

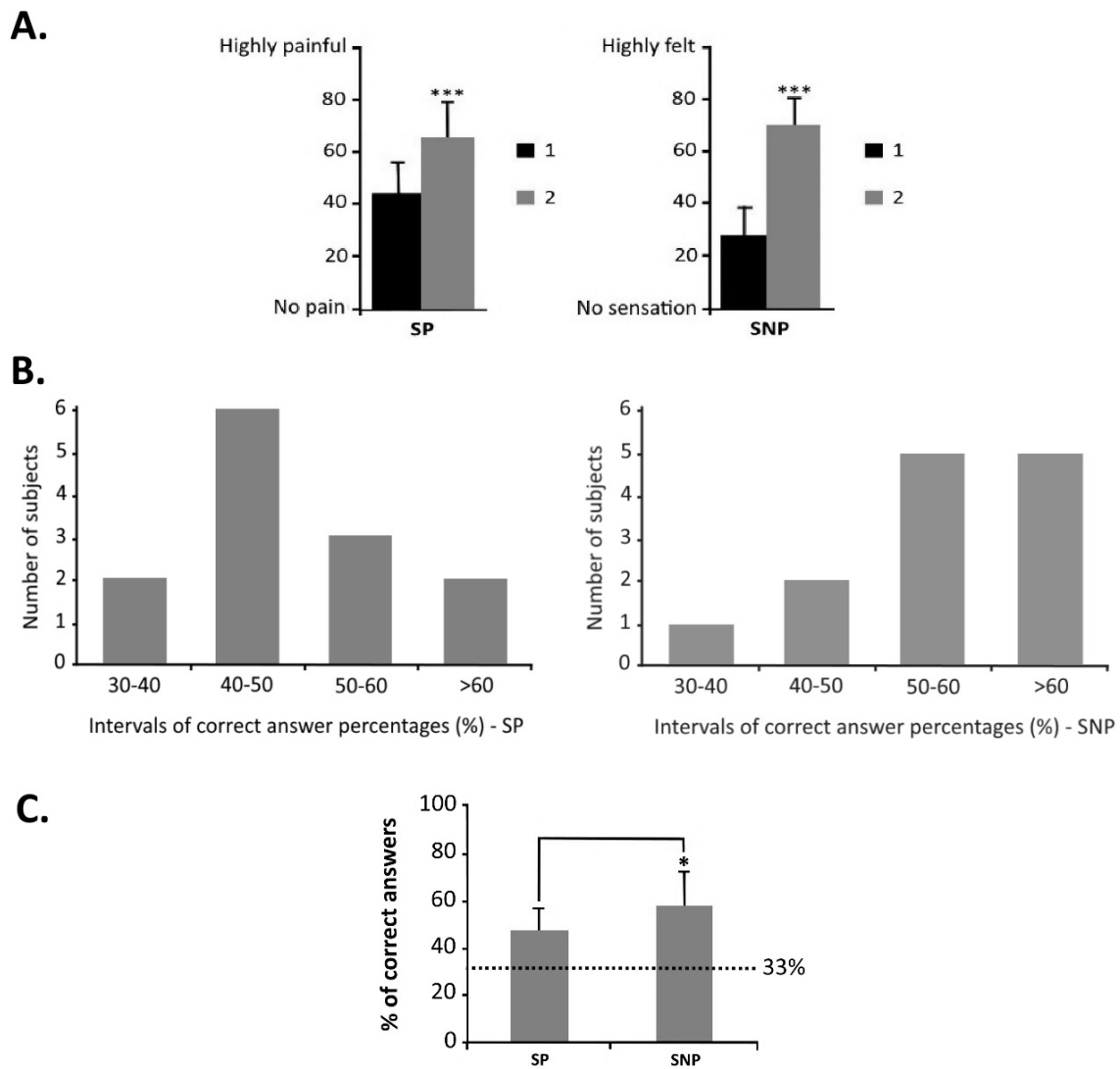


Figure 3 A. Average ratings of low (1) and high (2) intensities for the SP stimuli with a scale rating from “non-pain” to ‘highly painful” and the SNP stimuli with a scale rating from “no sensation” to “highly felt”. B. Number of subjects per interval of correct answer percentages for SP and SNP stimuli. The highest number of subjects was in the 40 to 50% of correct answers percentages for SP stimuli and above 50 % of correct answers percentages for SNP stimuli. C. Percentage of correct answers for SP and SNP conditions above chance rate (33%). * $p < 0.05$; * $p < 0,001$; SP: somatosensory painful; SNP: somatosensory non-painful**

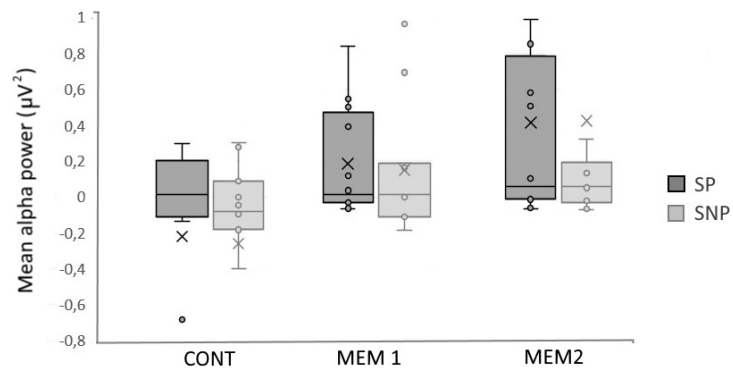


Figure 4 Mean alpha power (μV^2) for the painful (SP) and the non-painful (SNP) conditions during the control period (CONT) and in the memorization periods (MEM1 and MEM2). For each period and condition, the Standard error of means is represented (SEM)

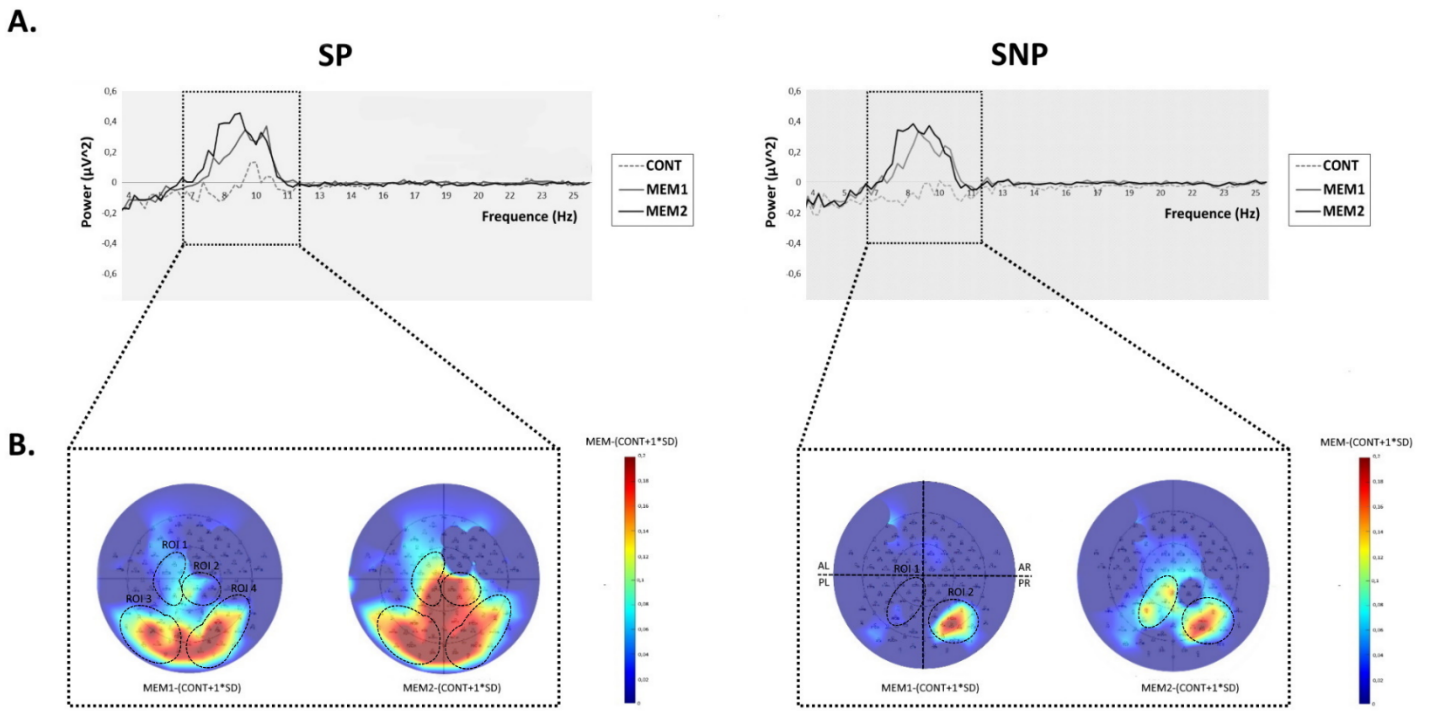


Figure 5 A. Spectral graphs between 0 and 25 Hz for the painful (SP) and the non-painful (SNP) conditions during the first phase of memorization (MEM1- grey line), the second phase of memorization (MEM2- black line) and the control task (CONT-dashed grey line). Note that since temporal segments (MEM1, MEM2, CONT) last 2750 ms only, the delta band was excluded from analyses as frequencies under 4Hz complete one cycle or less under such time length. The rectangle in black dotted line shows the frequency bands for which the power values appeared different for the memory periods (MEM1 and MEM2) compared to the control period (CONT). **B. Observational analysis per electrode:** comparison of averages for which the spectral power during the memory conditions (MEM1, MEM2) exceeded by at least 1 standard deviation the data during the control condition for non-painful stimuli (SNP) and painful stimuli (SP). The color scale represents the difference between the memory condition (MEM1, MEM2) and the control condition + 1SD (CONT+1SD) with zero corresponding to no difference between the two conditions. **ROI: Region of interest.** AL: Anterior-Left; AR: Anterior-Right; PL: Posterior-Left; PR: Posterior-Right. **C. Mean alpha power (μV^2)** for the painful (SP) condition in ROI4 during the control period (CONT) and the first memorization period for TRUE segments (MEM1_{TRUE}) and FALSE segments (MEM1_{FALSE}). * $p < 0.05$

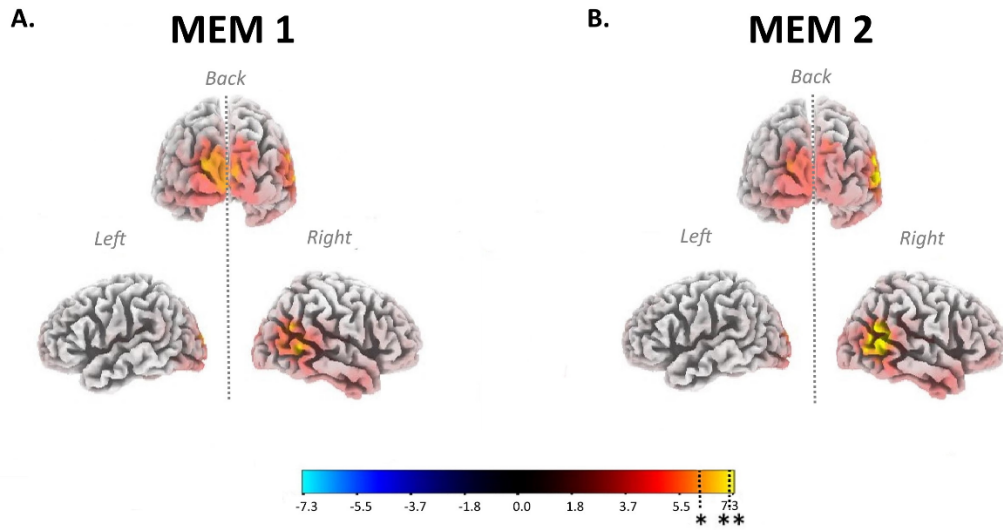


Figure 6 Current density increase in the lower alpha frequency band during memorization of a painful stimulus vs. during control task. For each memorization period (MEM 1 and MEM2), 3 views are represented: first row: back; second row: left, right. **A.** First period of memorization (MEM1), significant effect in 61 voxels of the occipital lobe (bilateral cuneus and bilateral middle occipital gyri) and 26 voxels of the right temporal lobe (superior and middle temporal gyri). Threshold $t=5.714$ for $p<0.05$. **B.** Second period of memorization (MEM2), significant to highly significant effect in 57 voxels of the right temporal lobe (superior and middle temporal gyri, supramarginal gyri). Threshold $t=5.813$ for $p<0.05$, $t=7.232$ for $p<0.01$. * $p<0.05$ ** $p<0.01$

| | ROI 1 | ROI 2 | ROI 3 | ROI 4 |
|------------|--------|-------|--------|--------|
| SP | FFC1h | Cz | TPP9h | TPP10h |
| | FC1 | C2 | TPP7h | TPP8h |
| | FCz | C4 | P7 | CPP6h |
| | FCC3h | CCP2h | P5 | TP8 |
| | FCC1h | CP2 | P3 | P8 |
| | C1 | CP4 | P9 | P6 |
| | Cz | CPP2h | PPO9h | P4 |
| | CCP3h | CPP4h | PO7 | PPO2 |
| | CP1 | P2 | PPO5h | PPO6h |
| | CPP3h | Pz | PO5 | PO4 |
| | CPP1h | | PO3 | PO6 |
| | P1 | | PPO1 | PO8 |
| | Pz | | POO3h | PPO10h |
| | | | PO9 | PO10 |
| | | | POO9h | POO4h |
| | | | O1 | O2 |
| | | O11h | POO10h | |
| | | I1 | I2 | |
| | | | O12h | |
| SNP | PO6 | Cz | | |
| | PPO6h | CPP1h | | |
| | P6 | CPz | | |
| | P8 | CP1 | | |
| | TPP8h | CPP1h | | |
| | PPO10h | Pz | | |
| | PO8 | P1 | | |
| | O2 | CPP3h | | |
| | POO10h | P3 | | |
| | POO4h | PPO5h | | |
| | PPO2 | PO5 | | |
| | P4 | PO3 | | |
| | CPP6h | | | |
| | P2 | | | |

Table 1: ROIs defined by selection of electrode clusters for which the spectral power during the memory consolidations (MEM1, MEM2) exceeded by at least 1 standard deviation the data during the control condition for painful (SP) and non-painful (SNP) stimulation.

| | Frequency bands Range (Hz) | Brain Region (Brodmann area B) | | | Local Maximum | | | |
|-------------|----------------------------|--------------------------------|---------------------------------------------|------------------------------------------------------------|--------------------------------|----------|------------|--------|
| | | <i>Left</i> | <i>Bilateral</i> | <i>Right</i> | <i>Brain Area</i> | X | Y | Z |
| MEM1 | Alpha 1 8.5 – 10.0 | | Cuneus (B17) Middle occipital gyri (B19) | Middle temporal gyri (B21) Superior temporal gyri (B22) | Middle temporal gyri Cuneus | 65 -5 | -50 -90 | 5 5 |
| MEM2 | | | | Middle temporal gyri (B21) Superior temporal gyri (B22) | Superior temporal gyri | 65 | -50 | 10 |

Table 2: MNI coordinates of each cluster’s most significant voxel for the alpha frequency band during memorization of a painful stimulus.