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Original article

EEG changes reflecting pain: is alpha suppression better than gamma enhancement?

Running title: Looking for a pain marker in EEG spectrum

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Abstract

Objective

Suppression of alpha and enhancement of gamma electroencephalographic (EEG) power have both been suggested as objective indicators of cortical pain processing. While gamma activity has been emphasized as the best potential marker, its spectral overlap with pain-related muscular responses is a potential drawback. Since muscle contractions are almost universal concomitants of physical pain, here we investigated alpha and gamma scalp-recorded activities during either tonic pain or voluntary facial grimaces mimicking those triggered by pain.

Methods

High-density EEG (128 electrodes) was recorded while 14 healthy participants either underwent a cold pressor test (painful hand immersion in 10°C water) or produced stereotyped facial/nuchal contractions (grimaces) mimicking those evoked by pain. The scalp distribution of spectral EEG changes was quantified via vector-transformation of maps and compared between the pain and grimacing conditions by calculating the cosine of the angle between the two corresponding topographies.

Results

Painful stimuli significantly enhanced gamma power bilaterally in fronto-temporal regions and decreased alpha power in the contralateral central scalp. Sustained cervico-facial contractions (grimaces) gave also rise to significant gamma power increase in fronto-temporal regions but did not decrease central scalp alpha. While changes in alpha topography significantly differed between the pain and grimace situations, the scalp topography of gamma power was statistically indistinguishable from that occurring during grimaces.

Conclusion

Gamma power induced by painful stimuli or voluntary facial-cervical muscle contractions had overlapping topography. Pain-related alpha decrease in contralateral central scalp was less disturbed by muscle activity and may therefore prove more discriminant as an ancillary pain biomarker.

Keywords: Alpha, Electroencephalography, Gamma, Muscle Artifact, Pain Perception

Introduction

Pain is a subjective experience, accessible to others only through verbal reports. The development of objective measures reflecting the existence of painful states appears therefore as an essential step to improve pain management in a number of clinical situations, ranging from the management of non-communicating or cognitively-impaired patients to the detection of simulation and malingering, as well as the development of analgesic drugs [2,3,6,11]. In this respect, electroencephalographic (EEG) activations have been described as cortical concomitants of pain processing, including both a focal decrease in alpha EEG rhythms (8–12 Hz) and an increase in fast EEG activity (gamma power: 25–100 Hz) in fronto-central brain regions [8,14,18,19,32,33,39,42,44,47,50]. Recent studies suggested a progression in the magnitude of gamma power over somatosensory areas from non-painful to painful stimuli [18,26] and such magnitude has been reported to be closely related to pain intensity regardless of the saliency of the stimulations [50]. These and other encouraging results have led a number of investigators to consider that gamma band enhancement could represent a genuine indicator of the presence of pain, applicable in clinical conditions [24].

Notwithstanding these significant advances, the recording and interpretation of gamma band power may be also subject to important limitations, not the least the fact that gamma activity overlaps entirely with the spectral bandwidth of muscle contractions [31,35]. It is likely that muscle-related gamma power (EMG) will display larger amplitudes than any other high-frequency brain signal reaching the scalp: for instance, pharmacological blockade (curarization) of muscle activity in humans resulted in a reduction of EEG gamma power by factors of between 10 and 200, leading the authors to conclude that most of the scalp EEG recording above 20Hz is of electromyographic (EMG) origin [49]. Indeed, the increase in EMG

activity has been identified as a source of contamination of pain-related brain responses [14], but the extent to which muscle activity may have contaminated previous reports on the relevance of gamma as a marker of pain perception remains unknown.

In the present work we specifically assessed with high-density EEG the magnitude and distribution of alpha- and gamma-band changes during a tonic nociceptive stimulus (the “cold pressor” test) and compared them with those induced by voluntary contraction of neck and face muscles mimicking pain-related grimaces.

Methods

Participants

Fourteen healthy subjects (aged 23.5 ± 3.8 years, 8 women) participated in the experiment. All subjects gave written informed consent. They were recruited via poster advertisements at various Faculties and departments of the Université Claude Bernard Lyon 1 (France). Inclusion criteria were a history free of chronic pain or neurological, psychiatric, or sleep disorders. No medication was allowed during the study, except for contraceptive pills. The study was approved by the Regional Ethics Committee (2013-A01636-39, CCP Loire, France) and was conducted in accordance with the Declaration of Helsinki.

Experimental protocol

Each subject participated in two consecutive conditions (‘grimace’ and ‘pain’) in a randomized order, during a single session. This session was preceded by explanations of the protocol and signature of the written informed consent. Inter-condition time was maintained around 90 seconds and each experimental block was preceded by a quiet baseline period (Figure 1).

In condition 1 (muscle activation), subjects were asked to “mimic the facial response

to pain” by performing a grimace of moderate intensity, entailing the contraction of muscles of neck and face for 10 seconds. The contracture was stereotyped and combined frowning, teeth clenching and neck contraction (corresponding to activities mainly in corrugator, orbicularis oris and trapezius muscles), but subjects were allowed to perform a ‘wincing of their own’ mimicking a pain grimace.

In condition 2 (cold pressor test) subjects placed their left hand in a bucket of ice water at the beginning of the testing (ThermoFisher Scientific, USA). Water remained in movement, and its temperature was maintained at 10°C, to induce a continuous but bearable pain sensation during the testing block [5,25], which lasted on average 88.3 ± 22.1 seconds. Subjects were allowed to take their hand out of the water if the pain became intolerable before the end of the testing block. At the end of the test, they put their hand next to the box in a towel to allow rapid rewarming.

For comparison purposes, each condition was preceded by a 20s baseline during which the subjects remained eyes open and calm, were asked to relax, and did not receive somatosensory stimulation.

Pain ratings

Continuous assessment of subjective pain intensity was obtained using an electronic 10 cm visual analog scale (VAS) [40] via a potentiometer that the participants manipulated with their free (right) hand. VAS pain intensity was rated on a scale from “no sensation” (0/10) to “most intense pain imaginable” (10/10) with the pain threshold set at 4/10, which the subject could feel manually as a salient in the potentiometer, without the need to look at it. The meaning, importance and manipulation of the potentiometer were explained to the subjects at the beginning of the session.

Data analysis

EEG recordings

The EEG signal was continuously recorded using an EEG cap (Waveguard Cap[®], ANT) with 128 electrodes placed in accordance with the 10–10 extended international system [22], referenced to the nose, grounded between AFz and Fz, sampled at 1024 Hz and band-pass filtered between 0.263 and 512 Hz. (ASA software[®] and ANT[®] amplifiers). The impedance was kept below 5 k Ω , using a conductive gel (ElectroCap[®]).

EEG pre-processing

EEG data were preprocessed using BrainVision[®] Analyzer software (Brain Products, Munich, Germany). The EEG signal was down-sampled to 512 Hz and filtered off-line between 0.5–125 Hz, (Butterworth Filter, 48 dB/oct), with a notch at 50 Hz. Independent component analysis (ICA) [21] was used to remove artifacts from eye movements in semi-manual mode. Channels contaminated by other artifacts (bad contact, electrode instability, etc.) were interpolated offline using 4th order spherical splines which took account of all scalp potentials [16]. The number of electrodes subject to interpolation never exceeded 10 out of the 128 electrodes of the montage.

In order to test whether muscle-derived gamma could be separated from pain-related gamma based on advanced topographic discrimination, a second ICA analysis was applied to the same down-sampled and filtered EEG data in both conditions. To this aim, we used an automatic Infomax algorithm [1,13], devoted to correct all artifacts including eye movements and muscle artifacts. Muscle-related independent components were then excluded to obtain EEG spectra “ICA-cleansed” from EMG and other artifacts.

EEG spectral analysis

Spectral analysis of EEG power during each experimental condition was carried out using BrainVision Analyzer[®] software (Brain Products, Munich, Germany). Frequency analysis was

performed for each subject and condition by calculating the fast Fourier transform (FFT) in each experimental condition compared to its corresponding baseline period. The FFT associated to a sliding Hamming window was used with a spectral resolution of 0.25 Hz. Spectral power was computed from 0.5 to 100 Hz but only the alpha (8–12.5 Hz) and gamma (25–100 Hz) bands were considered for analysis. Since recent studies have suggested a specific link between pain, alpha band and a restricted part of the gamma band (the 70-90 Hz sub-gamma band, [26,42,44,50]), our analysis was further focused on this sub-band. Nine regions of interest (ROIs) were defined to parcel the whole scalp EEG activity, as follows: mid-frontal (Fz, F1, F2), right frontal (F4, F6, F8), left frontal (F3, F5, F7), mid-central (Cz, C1, C2), right centro-temporal (C4, C6, CP6, T8, TP8, FT8), left centro-temporal (C3, C5, CP5, T7, TP7, FT7), mid-parieto-occipital (Pz, P1, P2, Oz, O1, O2), right parieto-occipital (P4, P6, P8, PO4, PO8, PO10), left parieto-occipital (P3, P5, P7, PO3, PO7, PO9) areas. The average of gamma and alpha powers of the electrodes in each ROI was computed for further analyses. Data were normalized by calculating the percentage of change during each experimental condition relative to their respective baseline ($\% \text{ change} = 100 * \text{parameter value} / \text{baseline average}$). To this aim, we compared the 10 seconds of grimace vs. 20 seconds of the most painful perception (the last 20 seconds of the CPT). In order for the comparison to be balanced, we also compared 10 seconds basal vs. 20 seconds basal respectively.

Topographical comparisons

Differences in the topographic scalp distribution of alpha and gamma powers were quantified with an estimator of distributional similitude that is independent of spectral power [12,17]. This procedure considers magnitude and spatial distribution of each spectral power band as a vector in an n-dimensional space (where n is the number of electrodes, in our case n=128). The magnitude of a given spectral power distribution is therefore given by

the length of the resultant vector, while the distribution shape determines the vector's orientation [28]. The topographical similitude of two distributions (maps) can then be estimated from the angle between the corresponding two vectors, or, as proposed by Desmedt and Chalklin (1989) by the cosine of that angle (their z-estimator), both of which are independent of the vectors' magnitude [12]. The cosine (z-estimator) may adopt any value between +1 (the angle is 0 and the distributions are the same) and -1 (the angle is 180°, and the distributions are mirror images).

Statistical analysis

Statview® software (SAS Institute, Inc., Cary, NC, USA) was used for statistical purposes. Mean pain reports (VAS ratings) were submitted to repeated-measures analyses of variance (RM-ANOVA) with two within factors: *time* (before vs during tests) and *condition* (tonic pain vs. grimace). Changes in alpha and gamma power values (expressed in percentage) were submitted to RM-ANOVA with three within factors: *time* (before vs during tests), *condition* (tonic pain vs grimace) and *topography* (ROIs defined above). Greenhouse–Geisser correction of degrees of freedom was applied when appropriate. To minimize the number of *post-hoc* analyses, predefined contrasts were tested between a ROI and the other regions only when the mean value of this ROI differed by more than one SD from the mean value of all pooled ROIs. The association between the subjective pain sensation and each of these variables was tested by regression analyses (linear, polynomial or logarithmic as appropriate) for continuous variables.

To control for potential differences in pre-processing on alpha and gamma power spectrum density, we added an additional analysis based on ICA pre-processing specifically devoted to excluding muscle and other artifact-related components. As in the previous condition, we submitted changes in alpha and gamma power values to RM-ANOVA with an

additional within-factor *ICA* (with and without *ICA* pre-processing). The same corrections and predefined contrasts were used.

To compare topographic differences between whole-scalp distributions, the vector-transformed map corresponding to each frequency change (gamma and alpha) in each subject was compared with a template vector corresponding to a 'flat map', i.e. a map with the same amplitude across all electrodes. Therefore, a single z-value estimating the difference between gamma or alpha maps and the template was obtained for each subject and condition [12,17], according to the following formula:

$$z = \frac{\sum_{i=1}^{128} f_i g_i}{(\sum_{i=1}^{128} f_i^2)^{1/2} (\sum_{i=1}^{128} g_i^2)^{1/2}}$$

Where f_i ($i=1, \dots, 128$, for 128 electrodes) is the measure of interest (gamma- or alpha-vectors, for 'grimace' or 'pain' conditions) and g_i ($i=1, \dots, 128$, for 128 electrodes) is the template vector. The mean z-values were then compared statistically to determine if the gamma- and alpha-vectors (i.e. their topographies) significantly differed between the 'grimace' and the 'pain' conditions using Wilcoxon tests for non-parametric data.

P-values were considered as significant at $p < 0.05$ for RM-ANOVAs, Wilcoxon, simple regression and post-hoc tests and data were presented as mean \pm SD.

Results

Immediate pain perception

As expected, subjects did not report any physical pain or somatosensory input to the hand before and during grimace conditions (VAS 0/10 in both cases). In contrast, they reported pain at moderate – to high intensities during the cold pressor test (VAS: 6.0 ± 1.3). Two-way RM-ANOVA revealed significant effects of *condition* ($F(1, 13) = 273.91, p < 0.001$); *time* ($F(1,$

13) = 273.91, $p < 0.001$), as well as a *condition* x *time* interaction ($F(1, 13) = 273.91, p < 0.001$) reflecting that pain was felt exclusively during the cold pressor condition.

Gamma power during painful and grimace conditions

There was a significant effect of *time* on the distribution of gamma EEG power spectrum density, gamma power being higher during the tests than before ($F(1, 13) = 13.31, p = 0.0030$), as well as a significant effect of condition, changes in gamma power being higher during the *grimace* than the painful test ($F(1, 13) = 13.11, p = 0.0031$), and a significant effect of topography ($F(8, 13) = 3.24, p = 0.0025$) (Figures 2 and 3). Significant interactions were observed between time and condition ($F(1, 13) = 13.11, p = 0.0031$), time x topography ($F(8, 13) = 3.24, p = 0.0025$), and condition x topography interaction ($F(8, 13) = 3.22, p = 0.0026$). Pre-defined contrasts between ROIs where changes in gamma activity exceeded by at least one SD the mean ROI value indicated that changes in gamma power of bilateral right and left frontal ROIs was significantly higher than those observed in other regions during the pain (contrast $F(1, 13) = 4.98, p = 0.0278$) and grimace conditions (contrast $F(1, 13) = 13.612, p = 0.0004$).

Linear regression analyses showed no significant association between the pain sensation, and changes in gamma activity of right ($t = 0.48; p = 0.5001$ and $r = 0.20$), nor left ($t = 0.17; p = 0.5735$ and $r = 0.17$) frontal ROIs during the pain condition.

Quantitative topographical comparisons between the distribution of gamma activity in painful and grimace conditions was performed via Chalklin's Z-estimator of distributional similitude (see Experimental procedure). The topography of gamma power increase was very similarly distributed over the frontal regions in the two conditions, without significant topographical differences: the angles of the vector-transformed gamma topography vs. flat

maps in the pain and grimace conditions did not differ (grimace: $\Delta Z = 0.85 \pm 0.14$, pain: $\Delta Z = 0.89 \pm 0.15$, $z = -1.609$, $p = 0.1077$) (Figure 4).

Alpha power during painful and grimace conditions

A 3-way RM-ANOVA with *time*, *condition* and *topography* as within factors was also computed for the alpha power spectrum (Figures 2 and 3). There were significant effects of *time* ($F(1, 13) = 14.20$, $p = 0.0023$) and *condition* ($F(1, 13) = 13.22$, $p = 0.0025$), changes in alpha power being significantly lower during the pain than the grimace experiments. The factor topography yielded a significant effect too, ($F(8, 13) = 12.32$, $p < 0.0001$), suggesting a strong influence of region on alpha spectral changes. Pre-defined contrasts between ROIs where alpha spectral power exceeded by at least one SD the mean value indicated that during pain, the alpha power of the mid- and right centro-temporal ROIs (i.e. contralateral to pain) was significantly lower than that recorded from other regions (contrast $F(1, 13) = 4.14$, $p = 0.0445$), whereas during the grimace conditions the alpha power in bilateral right and left frontal ROIs was significantly higher than that observed in other regions (contrast $F(1, 13) = 16.98$, $p = 0.0012$).

There were also interactions between these effects with a *time* x *condition* interaction ($F(1, 13) = 14.00$, $p < 0.0001$), a *time* x *topography* interaction ($F(8, 13) = 12.32$, $p < 0.0001$), a *condition* x *topography* interaction ($F(8, 13) = 12.11$, $p < 0.0001$). Furthermore, the angles of the vector-transformed alpha topographies in the painful and grimace conditions differed significantly (*Pain*: $\Delta Z = 0.96 \pm 0.07$, *Grimace*: $\Delta Z = 0.67 \pm 0.29$, $z = -4.67$, $p = 0.0004$).

Linear regression analyses revealed a near-significant trend in the association between the pain sensation and changes in alpha activity of the centro-temporal ROIs contralateral to pain ($t = 1.99$; $p = 0.0699$, $r = 0.50$). No significant correlation was found

between pain sensation and alpha activity in mid- ($t = 0.87$; $p = 0.4014$ and $r = 0.24$) and left (ipsilateral to pain) centro-temporal ROIs ($t = 0.63$; $p = 0.5397$ and $r = 0.18$).

These results illustrate a decrease in alpha power during painful conditions but not during grimace conditions, in mid- and right centro-temporal regions, contralateral to the painful stimulation. Direct comparison of the alpha and gamma topographies demonstrated significant differences in their respective scalp distribution during pain ($z = -2.28$, $p = 0.0228$; Figure 4).

Effect of independent component analysis (ICA) pre-processing

The addition to our statistical model of a level of analysis as a function of the presence or absence of ICA pre-processing had no significant effect on gamma EEG power spectrum density ($F(1, 13) = 1.67$, $p = 0.2185$), nor any interaction with *time* ($F(1, 13) = 1.67$, $p = 0.2185$) and *condition* ($F(1, 13) = 1.60$, $p = 0.2281$) and *ICA x time x condition* interaction ($F(1, 13) = 1.60$, $p = 0.2281$). However, there were significant interactions between *ICA* and *topography* ($F(8, 13) = 2.81$, $p = 0.0074$), *ICA x topography x condition* ($F(8, 13) = 2.80$, $p = 0.0076$), *ICA x topography x time* ($F(8, 13) = 2.81$, $p = 0.0074$) with an overall interaction ($F(8, 13) = 2.80$, $p = 0.0076$). Pre-defined contrasts indicated that, as expected, changes in gamma power of bilateral frontal ROIs were significantly higher without ICA artifact rejection pre-processing than following such pre-processing (contrast $F(1, 13) = 10.79$, $p = 0.0059$). This was the case for both pain and grimace conditions and did not change the overall results and similarity between gamma distribution in the two conditions. These results are summarized in Figure 5.

Regarding alpha power, RM-ANOVA with *ICA* revealed significant difference between with and without ICA pre-processing on the alpha EEG power spectrum density ($F(1, 13) = 6.44$, $p = 0.0248$), with a significant *ICA x time* interaction ($F(1, 13) = 6.44$, $p = 0.0248$), a

trend for ICA x condition interaction ($F(1, 13) = 3.91, p = 0.0696$), and no ICA x topography interaction ($F(8, 13) = 0.34, p = 0.9467$). There was also a significant trend in ICA x time x condition interaction ($F(1, 13) = 3.90, p = 0.0696$), but again this did not concern topography (ICA x topography x condition interaction ($F(1, 13) = 0.40, p = 0.9186$) and ICA x topography x time interaction ($F(1, 13) = 0.34, p = 0.9467$). Finally, condition x time x topography interaction was still significant ($F(8, 13) = 18.00, p = 0.0010$) as well as topography x condition interaction ($F(8, 13) = 2.33, p = 0.0242$), condition x time interaction ($F(1, 13) = 19.48, p = 0.0007$) with a trend in topography x time interaction ($F(8, 13) = 2.03, p = 0.0501$) showing that although alpha spectral power decreased with ICA pre-processing whatever the topography and conditions, the alpha power still changed differentially according to the experimental conditions. These results are summarized in Figure 5.

These results illustrate that both alpha and gamma power were decreased by ICA pre-processing, during both experimental conditions, but that ICA removal of muscle artifact did not modify the dissimilar effects of pain and grimaces on alpha and gamma amplitude and topographies.

Discussion

The present work showed a similar topography between gamma power evoked by pain and that arising from muscular activity during a simple grimace. Conversely, the decrease in alpha EEG power during painful stimulations did not match the EEG oscillatory changes induced by facial muscular activity. These results underscore the limits of gamma power to approach clinical pain perception, and the necessary caution needed before interpreting them as a brain marker of pain processing. EEG alpha power appeared more resistant to muscle activity and as such potentially more promising to approach clinical pain.

Gamma power reflecting central pain processing

Since the pioneering work of [30] indicating that stimulation of the brainstem reticular formation increases fast, and decreases slow EEG power, these ‘activation-related’ changes have been associated with an extensive array of brain processes, from elementary perceptions to complex attention, learning and memory tasks [23,30,37]. Interest in this area has been further enhanced by the notion that cortical information processing may be subserved by synchronization of oscillatory networks [9,46].

In this vein, frequency EEG analysis has highlighted changes in oscillatory EEG responses to phasic [8,18,19,39,44,50] and tonic [14,26,32,42] painful stimulations, the most consistent results being an increase in gamma power, concomitant with a decrease in alpha power in centro-temporal regions (also called ‘alpha desynchronization’). Although long recognized [48], these pain-related gamma oscillatory responses have recently inspired a number of publications. Zhang and colleagues (2012) attempted to dissociate stimulus painfulness from “sensory salience”, which is a common confounding factor, using laser stimuli which are both salient and specific for nociceptive pathways. By reducing the time interval between successive painful laser pulses, which reduces stimulus salience but increases pain, they showed a specific increase in gamma power correlated with both pain perception and stimulus intensity [50]. Using a tonic stimulus closer than laser pulses to clinical pains, Schulz and colleagues (2015) reported a good correlation between mid-frontal gamma power and the subjective pain perception to a continuous thermal stimulus, suggesting that this approach could be relevant to pain assessment in clinical conditions including non-communicating patients or patients suspected of malingering [42].

In contradistinction, our results illustrate a serious difficulty limiting the clinical application of a gamma-band approach to clinical pain, namely its spectral and topographical

overlap with pain-related muscle activity.

Gamma power, pain and muscle activity

Pain is commonly accompanied by muscle reactivity [10], including facial and cervical components that contaminate the EEG in a large spectral band. Although this contamination includes the theta, alpha, beta and gamma EEG bands, the two clearly dominant peaks correspond to the beta and gamma bands [4,31] (see Figure 3). While healthy subjects can voluntarily minimize muscular responses “on demand”, this remains hardly possible in clinical situations, where muscle activation can result not only from pain, but also from anxiety or stress [20]. Our quantitative topographical assessment shows that muscle artefact evoked by grimaces not only has similar spectral range as pain-induced cortical gamma, but also closely matches its scalp topography. This is likely to induce interpretation uncertainty if gamma changes were to be used as a clinical reflection of central pain processing. Although a growing number of techniques are available for the reduction of muscle artifacts, such as surface Laplacian processing or independent component analysis [40, 41] as used in this study, these methods remain controversial [36], especially in absence of testing methods assessing their reliability in case of small sample sizes [20]. Also, in the case of spatio-temporal overlap of muscle and neural signals, both may be rejected together. Our attempt to improve specificity by reducing EMG-related contamination via ICA, although it reduced gamma spectral power overall, did not change gamma overlapping in the pain and grimace conditions. It is to be hoped that continuous improvement in signal separation methods, including muscle activity modeling, might be able to overcome these difficulties in the future, and succeed in separating muscle activity from that related to the encoding of the stimulus [31,34]. However, this may be of limited interest in the clinics, not only because it would require significant longer data processing, but also because, since muscle activity is

different in each patient, it would first be necessary to obtain and model its own muscle activity in order to be able to "detach" it from brain activity. EMG electrodes on the face and neck can be added, improving the techniques of EEG signal pre-processing [34]. However, additional EMG electrodes and the lengthening of the EEG data analysis process are likely to limit the usefulness of this strategy in clinical conditions.

Alpha power reflecting central pain processing

Most EEG pain studies conducted to date used highly focused laser or electric stimuli lasting only several milliseconds, which can hardly model clinical pain. Experimental pain models inducing widespread sensations of longer duration and enhanced unpleasantness may better mimic the pain observed in the clinics [7,41], and indeed, a decrease in alpha power was more frequently reported when using tonic [14,26,32] than phasic stimulation [8,18,29,43,44,50]. The pain-related decrease in alpha in these studies predominated over centro-temporal regions contralateral to the pain stimulus. This was also the case in the present experiments (Figures 2, 3 and 4), which also show that the alpha response, contrary to evoked gamma power, is less –if at all– perturbed by muscle activity. The mechanisms underpinned by pain-related alpha decrease remain, however, very incompletely understood, and this may also hamper clinical application. A variety of processes can determine a decrease in alpha power, including sensory-discriminative, affective-motivational, attentional and cognitive modulations [19,38] all of which can contribute to the pain experience. In particular, prominent alpha modulation occurs during attentional processing [9]: May and colleagues (2012) [50] showed that alpha reductions similar to those evoked by pain could be obtained when attention was focused on a body region other than the one receiving painful stimuli [27]. Future mechanistic studies are needed to provide a comprehensive understanding of the processes underlying this alpha EEG response. While it

is clear that changes in alpha activity should *not* be considered as a specific and univocal marker of pain sensation, the potential clinical importance of modulating this activity has been recently underscored by results showing that nociception can be reduced by visual alpha-band entrainment in the human brain [15].

Limitations, perspectives and conclusion

The relatively small number of subjects in this work can limit the statistical power of results. For example, while previous studies highlighted the relationship between pain sensation and contralateral changes in alpha activity [19,33], here this relation remained as a near-significant trend. Notwithstanding, the head-to-head quantitative comparison of pain- and grimace-related spectral changes reported here rely on the largest electrode density and subject sample published to date. The message of this study is that gamma band power should be interpreted with caution when using EEG to infer the existence of subjective pain, while changes in the alpha band appear as a more robust tool to approach pain in clinical settings.

Conclusions

Pain-related gamma enhancement might be used as a physiological pain marker only in situations where muscle contraction can be removed or minimized (sedation, anesthesia). Conversely, in common clinical situations where muscle activity accompanies pain, focal decrease in alpha appears as a more robust EEG marker to approach pain perception, largely independent from muscle-related activity.

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Conflicts of interest

The authors declare no conflict of interest.

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Figure

Figure 1: Time course of experimental events: (A) Each subject participated in consecutive ‘grimace’ and ‘pain’ conditions in a single session, **(B)** during which we recorded 128 EEG electrodes placed in accordance with the 10–10 extended international system [22], referenced to the nose, grounded between AFz and Fz (G: Ground).

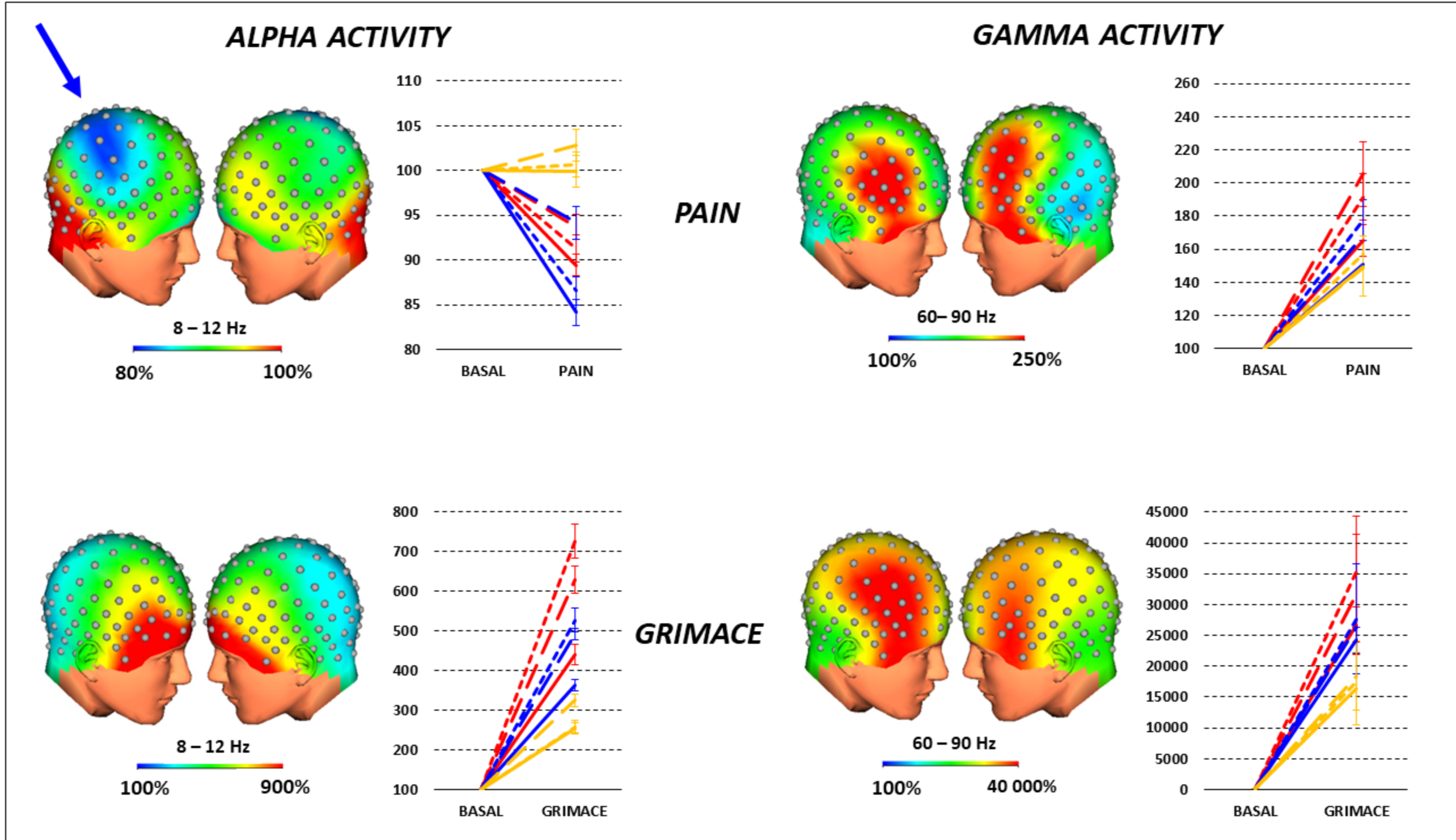
Figure 2: Gamma (right) and alpha (left) power during painful tests (top) and grimaces (down) according to ROIs in 14 healthy subjects. Gamma activity of bilateral right and left frontal and centro-temporal ROIs was significantly higher than that observed in other regions; alpha activity of the mid-central and right centro-temporal ROIs during pain was significantly lower than those recorded from other regions. The blue arrow shows the decrease in alpha power.

Figure 3: Grand-average spectrum on the bands of interest Alpha (8-12 Hz) and Gamma (70-90 Hz) according to the experimental conditions ‘Pain’ and ‘Grimace’.

Figure 4: Topographic comparisons using the z estimator for gamma (right) and alpha (left) power during painful tests (top) and grimaces (down). Center: flat topographic map representing the unitary (template) vector. Angles of the vector-transformed alpha topographies relative to the flat map in the painful and grimace conditions differed significantly (left maps), as well as alpha and gamma topographies during painful conditions (top left vs. top right maps). Conversely, gamma topographies in the painful and grimace conditions did not differ (right upper vs. *right* lower map).

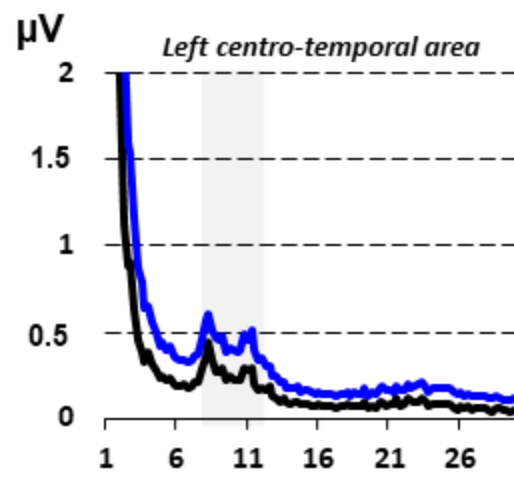
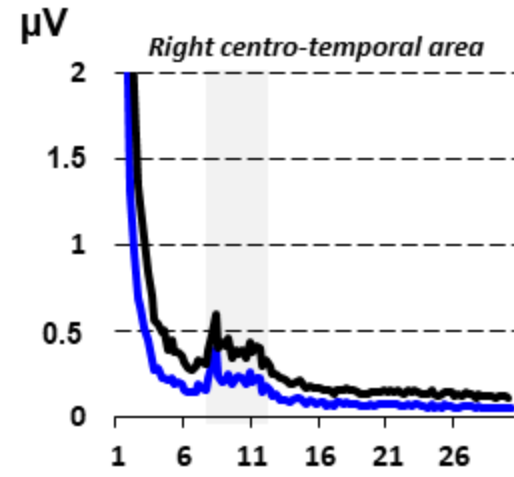
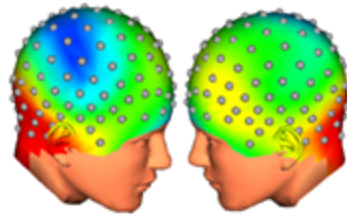
Figure 5: Gamma (right) and alpha (left) power during painful tests (top) and grimaces (down) according to ROIs following independent component analysis pre-processing.

Gamma powers in frontal regions were mainly decreased by ICA pre-processing, but in both cases, frontal gamma power increased in pain and grimace conditions. Alpha power was decreased by ICA pre-processing especially during both experimental conditions.

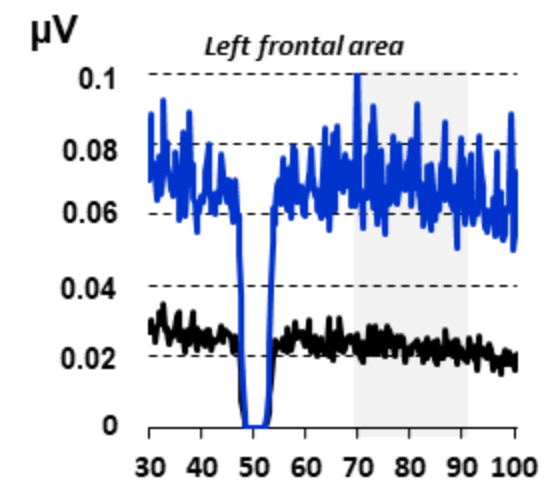
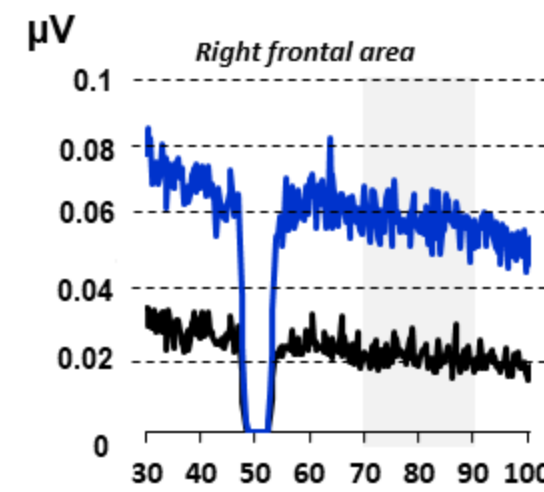
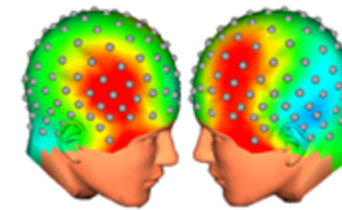


- | | | | | | |
|--|-----------------------|--|------------------------|--|-------------------------|
| | Mid-Frontal | | Left frontal | | Right frontal |
| | Central | | Left centro-temporal | | Right centro-temporal |
| | Mid-parieto-occipital | | Left parieto-occipital | | Right parieto-occipital |

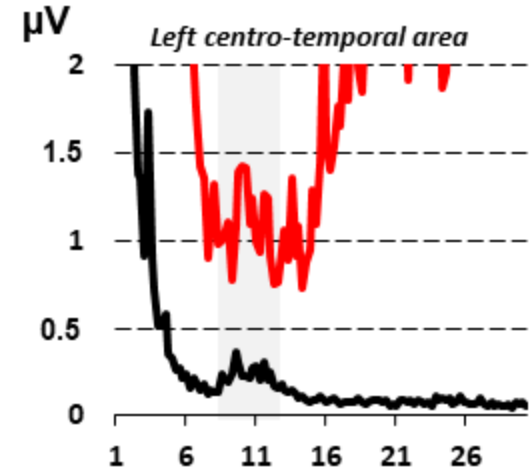
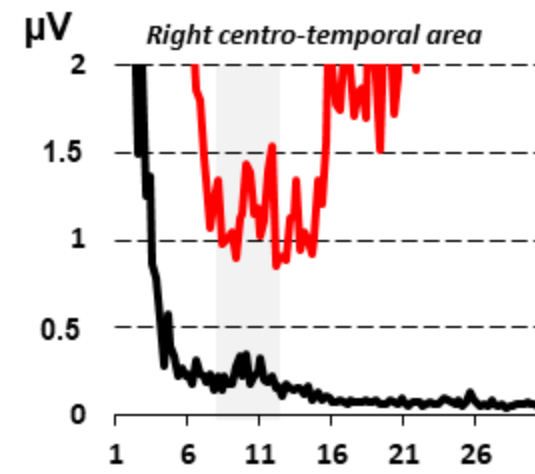
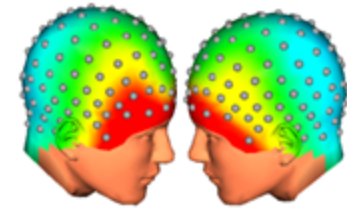
ALPHA ACTIVITY



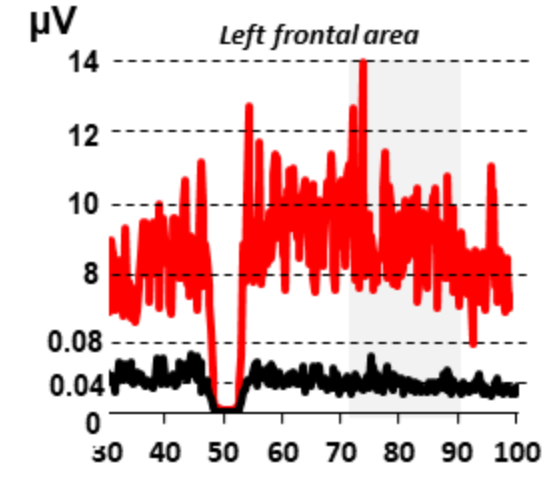
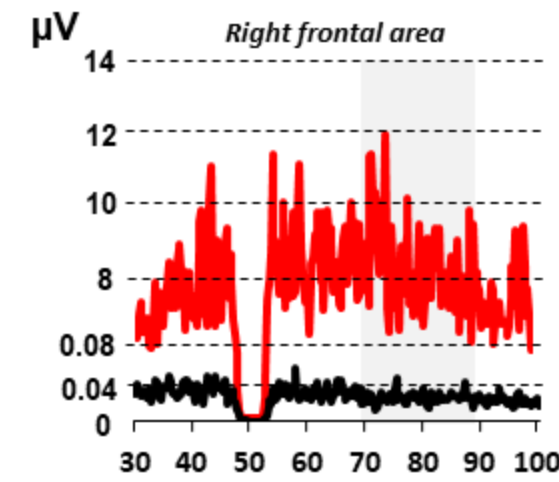
GAMMA ACTIVITY



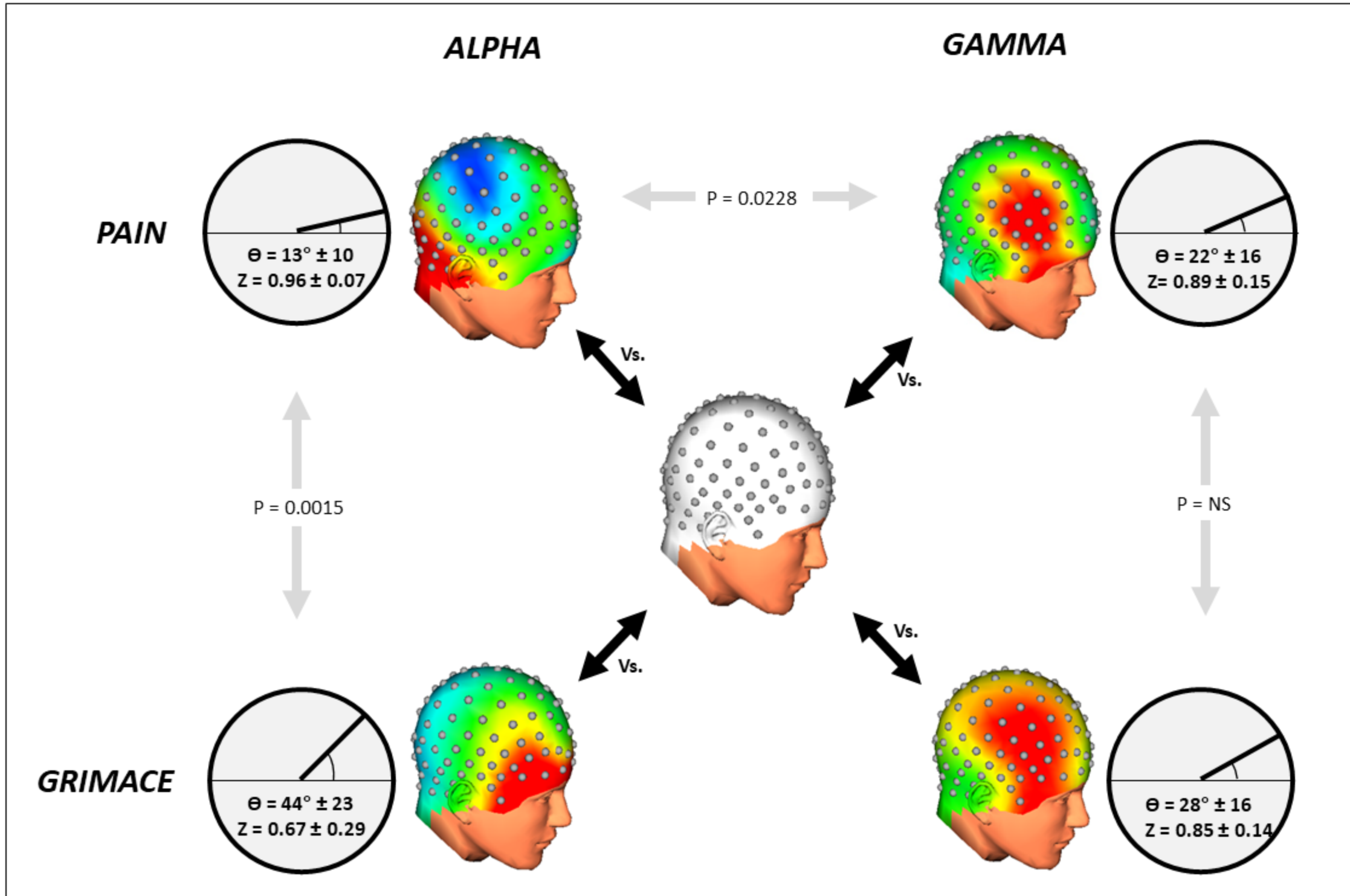
PAIN



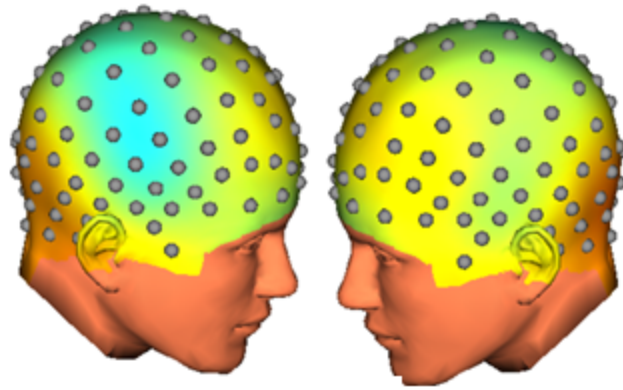
GRIMACE



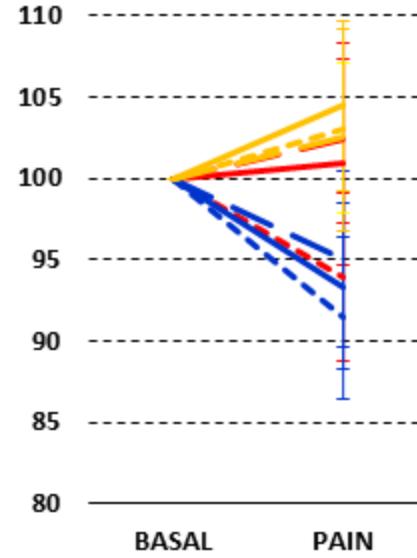
— Basal — Pain — Grimace



ALPHA ACTIVITY

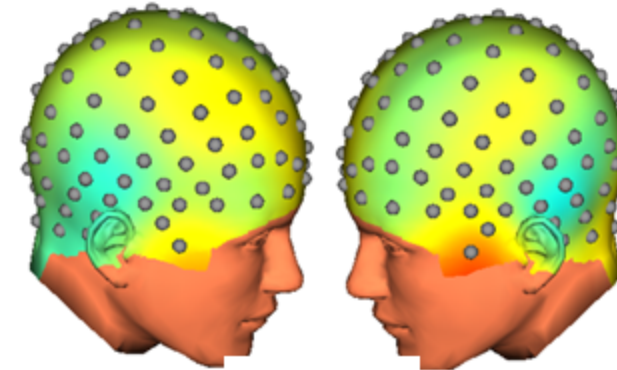


8 – 12 Hz
80% 100%

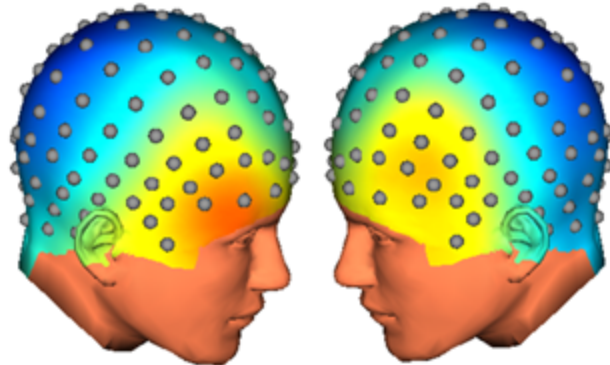
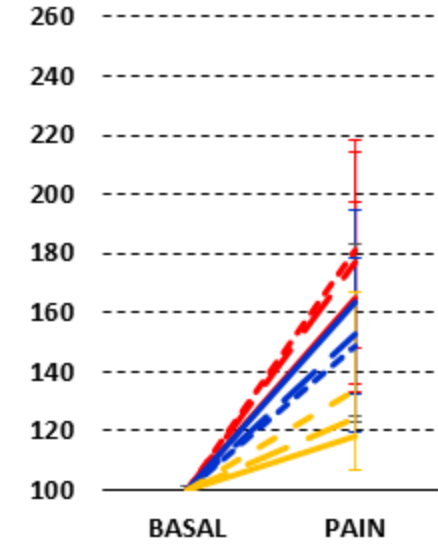


PAIN

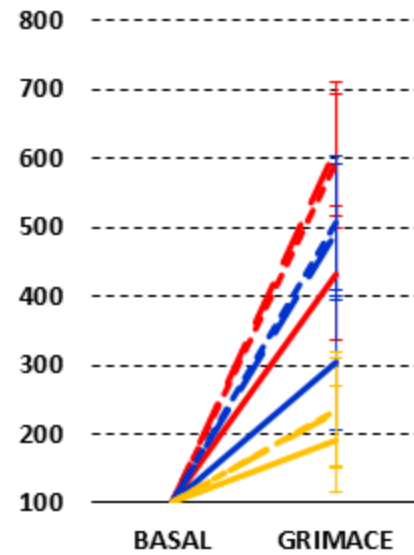
GAMMA ACTIVITY



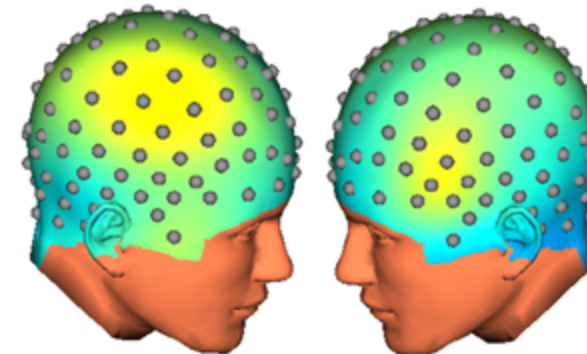
60– 90 Hz
100% 250%



8 – 12 Hz
100% 900%



GRIMACE



60 – 90 Hz
100% 40 000%

