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Abbreviated Title: Peak Alpha Frequency and Pain Sensitivity

Cerebral Peak Alpha Frequency Predicts Individual Differences in Pain Sensitivity

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Abstract

The identification of neurobiological markers that predict individual predisposition to pain are not only important for development of effective pain treatments, but would also yield a more complete understanding of how pain is implemented in the brain. In the current study using electroencephalography (EEG), we investigated the relationship between the peak frequency of alpha activity over sensorimotor cortex and pain intensity during capsaicin-heat pain (C-HP), a prolonged pain model known to induce spinal central sensitization in primates. We found that peak alpha frequency (PAF) recorded during a pain-free period preceding the induction of prolonged pain correlated with subsequent pain intensity reports: slower peak frequency at pain-free state was associated with higher pain during the prolonged pain condition. Moreover, the degree to which PAF decreased between pain-free and prolonged pain states was correlated with pain intensity. These two metrics were statistically uncorrelated and in combination were able to account for 50% of the variability in pain intensity. Altogether, our findings suggest that pain-free state PAF over relevant sensory systems could serve as a marker of individual predisposition to prolonged pain. Moreover, slowing of PAF in response to prolonged pain could represent an objective marker for subjective pain intensity. Our findings potentially lead the way for investigations in clinical populations in which alpha oscillations, and the brain areas contributing to their generation are used in identifying and formulating treatment strategies for patients more likely to develop chronic pain.

Highlights

- Relationship between EEG peak alpha frequency and prolonged pain is examined
- PAF during pain-free state correlated with prolonged pain intensity 40 minutes later
- PAF change from pain-free to prolonged pain correlated with reported pain intensity
- PAF and PAF changes could represent distinct mechanisms predicting pain sensitivity

Introduction

Pain is a salient, multidimensional experience that varies widely between individuals in both intensity and duration. Identifying biomarkers that can determine individual susceptibility for the development of chronic pain is a fundamental step for improved pain treatments. One approach to this problem has been to investigate the role that neural oscillations like the alpha rhythm play in the individual pain experience (Peng et al., 2015; Ploner, Sorg, Gross, 2016).

The alpha rhythm represents the predominant oscillatory activity in the EEG which is chiefly observed in primary sensory regions (e.g. vision, auditory). Although previously considered a signature of cortical "idling," significant evidence now suggests that alpha activity plays a top-down role in gating information in sensory cortices depending on task demands (Foxe et al., 1998; Foxe & Snyder, 2011; Jensen & Mazaheri, 2010; Klimesch, 2012, Pfurtscheller et al., 1996).

The peak frequency of alpha activity (i.e the frequency within the 8-12Hz, that has the maximal power) has been found to change across the life span, increasing from childhood to adulthood, and subsequently decreasing with age (Aurlien et al., 2004; Lindsley, 1939,Hashemi et al., 2016; Bazanova & Vernon, 2014). There is evidence that the frequency of alpha activity is positively correlated to measures such as working performance (reviewed in Klimesch, 1999). More recently, it has been demonstrated that individuals with higher alpha frequencies in the occipital cortex are able to perceive visual information with a finer temporal resolution (Samaha et al., 2015). Peak alpha frequency has been found to be reliable in test-retest studies (Grandy et al., 2013), and appears to be a heritable phenotypic trait (Posthuma et al., 2001; Smit et al., 2006). Taken together, these studies suggest that peak alpha frequency (PAF) could be viewed as a 'state' variable with its subtle fluctuations within an individual reflecting shifts in the excitability of the underlying cortex and its capacity to process information. Alternatively PAF can be viewed as a 'trait' variable with its variability across individuals reflecting cognitive ability.

In recent years, the variability of alpha frequency has been studied in the context of characterizing disease states in clinical populations, and the subjective experience of pain in the typical population. In patients suffering from central, visceral, and neuropathic pain conditions, PAF was slowed relative to matched, healthy controls (Sarnthein et al., 2005; Walton et al., 2010; de Vries et al., 2013, Lim et al., 2016). It has been hypothesized, that the slowing of PAF and that the

increased power of slower alpha rhythms (8-9.5 Hz) contributes to the generation of pathological pain, perhaps reflecting thalamocortical dysrhythmia (Llinas et al., 2005).

In contrast to the slowing of PAF associated with chronic pain, exposure to acute, painful stimuli in healthy subjects has been found to increase the frequency of alpha activity (Nir, et al 2010). Furthermore, PAF collected from healthy individuals either during or, perhaps more importantly, prior to stimulation were positively correlated with pain intensity (Nir et al., 2010), suggesting that PAF reflects processes related to both ongoing pain and individual vulnerability.

These findings together suggest a rather complex relationship between types of pain and variations in PAF: transient acute pain, increases alpha frequency in the healthy population, whereas alpha frequency is slowed down in patients with chronic pain. The slowing of alpha frequency in chronic pain populations could reflect changes in the brain's neural architecture brought about by the constant experience of pain. Supporting this view is a finding that PAF had an inverse relationship with duration of chronic pancreatitis (de Vries et al., 2013). An alternative explanation could be that individuals with slower alpha frequency are more prone to develop chronic pain. Why some people will go on to develop chronic pain following an injury that would normally heal and not lead to persistent pain remains a major question in the field, and cerebral functional connectivity might be one way to predict this transition from acute to chronic pain (Baliki et al., 2012).

Here we investigated the relationship between PAF and sensitivity to prolonged pain. The prolonged pain model we used – the capsaicin-heat pain model – lasts for hours to days and recapitulates cardinal sensory aspects of chronic neuropathic pain (Culp et al., 1989; LaMotte RH, et al,1992; Baron 2009; Lotsch et al., 2015). The prolonged pain model might thus be more similar to chronic pain – or the early transition period from acute to chronic pain – than acute pain, where there is no central sensitization, and the pain disappears as soon as the stimulus is removed. The personal experience of pain is highly variable among individuals even if the underlying noxious stimulation is similar. The objective of our study was to systematically investigate the relationship between PAF prior to and during prolonged pain and the subjective experience of pain. We recorded EEG activity during pain-free and prolonged pain states, which allowed us to determine the relationship of PAF and pain intensity, as well as how PAF shifts (i.e. change in PAF between

states) relate to individual pain intensity. We tested the hypothesis that PAF slowing reflects the intensity of prolonged pain.

Materials and Methods

Participants

Forty-four pain-free, neurotypical adult participants (22 males, mean age = 28.4, age range = 19 – 42) took part in the experiment. Twenty-seven participants were randomly assigned to the Pain group (would be administered topical capsaicin), while seventeen were assigned to the Non-Pain group (not administered topical capsaicin). The Non-Pain group served as a control to confirm that prolonged pain was a result of the capsaicin application and not only the warm thermode, as well as to control for effects of ongoing stimulation and attention. More participants were assigned to the capsaicin group to account for the variability in response to topical capsaicin (Liu et al., 1998). This study was approved by the University of Maryland, Baltimore Institutional Review Board, and informed written consent was obtained from each participant prior to any study procedures.

EEG

Scalp EEG was collected from an EEG cap housing a 64 channel Brain Vision actiCAP system (Brain Products GmbH, Munich, Germany) labeled in accord with an extended international 10–20 system (Oostenveld and Praamstra, 2001). All electrodes were referenced online to an electrode placed on the right earlobe and a common ground set at the FPz site. Electrode impendences were maintained below 5kΩ throughout the experiment. Brain activity was continuously recorded within .01 to 100 Hz bandpass filter, and with a digital sampling rate of 1000 Hz. The EEG signal was amplified and digitized using a BrainAmp DC amplifier (Brain Products GmbH, Munich, Germany) linked to Brain Vision Recorder software (version 2.1, Brain Products GmbH, Munich, Germany).

Prolonged pain induced by the Capsaicin-Heat Pain model

Thermal stimuli were delivered to the volar surface of participant's left forearm using a thermal-contact heat stimulator (30 × 30 mm Medoc Pathway ATS Peltier device; Medoc Advanced Medical Systems Ltd., Ramat Yishai, Israel). Prior to the beginning of the experiment all participants underwent a brief sensory testing session in which they were asked to report when they felt a change in temperature (for warmth detection threshold (WDT)) or when the temperature first

became painful (heat pain threshold (HPT)). For WDT and HPT three and four trials were presented, respectively, and the average across trials, rounded down to the nearest integer, was used.

Prolonged pain was modelled following a procedure modified from previous studies (Anderson et al., 2002). We applied ~1g 10% capsaicin paste (Professional Arts Pharmacy, Baltimore, MD) topically to the volar surface of the left forearm, fixing it in place with a Tegaderm bandage. After 15 fifteen minutes of exposure, we placed the thermode over top of the Tegaderm bandage at a temperature that was greater than the WDT and at least 1°C below the HPT. We term this model the capsaicin-heat pain model (C-HP).

To ensure that the capsaicin produced a stable, long-lasting pain, participants were asked to provide pain intensity ratings every minute for the first five minutes following thermode placement. The thermode temperature was adjusted during this time to achieve a consistent pain intensity above 20 on a 0-100 point scale (i.e. if pain was intolerable, the temperature was lowered slightly, and if there was no pain, the temperature was increased closer to the HPT). Once this five minute period elapsed, the temperature was held in place for 25 minutes. Participants were asked to rate pain intensity every 5 minutes. This procedure does not cause lasting tissue damage (Moritz and Henriques, 1947). Previous work has found that topical capsaicin evokes no pain or hypersensitivity in some participants (Liu et al., 1998; Walls et al., 2017). Therefore, we excluded participants who did not develop moderate pain, which we set at a reported pain intensity level of 20 (details of the scale provided below).

Procedure

A summary of the order of procedures is described in Figure 1. Once the EEG set-up was complete, participants were seated in a comfortable chair and underwent a brief sensory testing session to establish their individual HPT. Participants were then trained on and performed a simple cognitive task which will be detailed elsewhere. The total duration of this task was approximately thirty minutes. While performing this task, participants rate their current pain intensity every five minutes on a 0-100 scale, with the anchors 0, not at all painful and 100, most intense pain imaginable. In total participants provided six pain intensity ratings during this testing session. Ratings were always given during a rest period. At the conclusion of this testing session, and immediately following the final pain intensity rating, all lights in the testing room were turned off and participants were instructed to close their eyes, remain still, and relax

without falling asleep. Continuous EEG was recorded during this pain-free resting state for three minutes in both the Pain and Non-Pain groups.

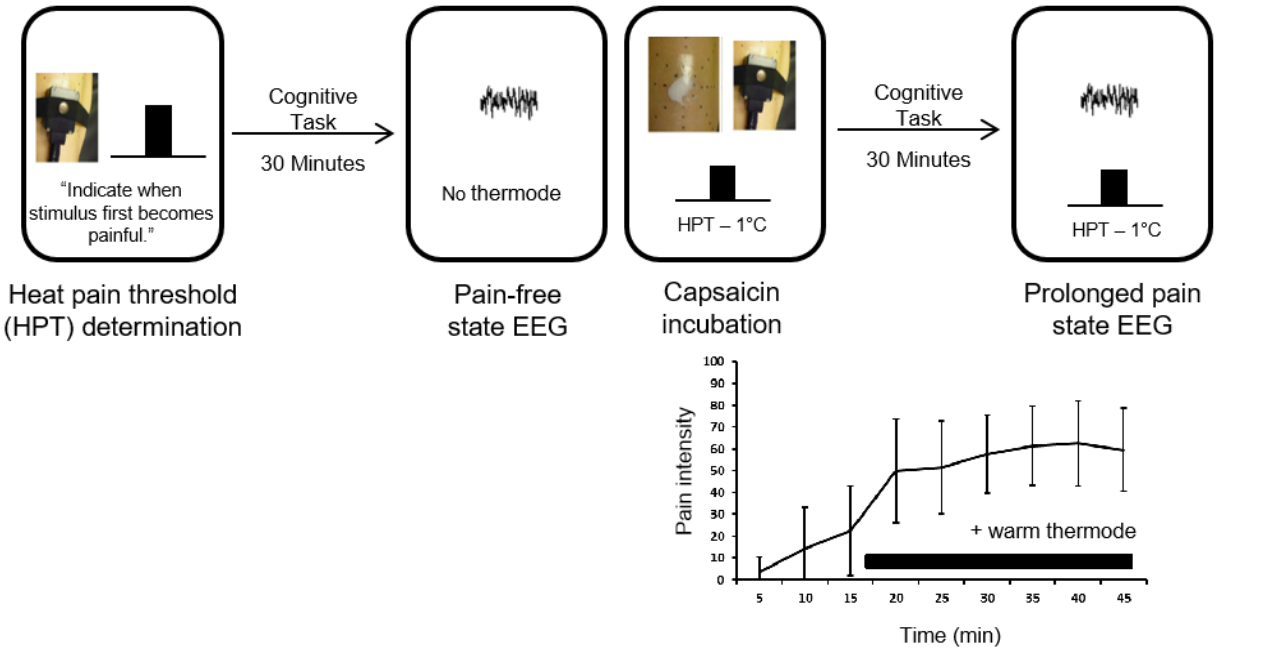

Figure 1. Outline of the experimental procedure. Participants first underwent sensory testing to determine their Heat Pain Threshold (HPT). After a 30 minute cognitive task, EEG was collected while participants completed a 3-minute eyes closed session in the absence of any thermal stimulus (pain-free state). Next, capsaicin was applied (Pain group) to the forearm and a temperature no more than one degree below their HPT was introduced fifteen minutes later. Five minutes later, when pain in response to the model has stabilized, the same cognitive task from earlier in the experiment was repeated. Following this task, EEG was collected while participants completed a 3-minute eyes closed session in the presence of capsaicin and warm thermode (prolonged pain state). Subjects in the Non-Pain group underwent identical procedures, but without capsaicin application.

After finishing this pain-free state EEG recording, the lights in the testing room were turned on, capsaicin was applied to the participant's left forearm, as described above, and the thermode was placed directly on top of the capsaicin application. During this incubation period participants were instructed to relax without falling asleep. The thermode was kept at 32°C, and participants provided a pain intensity rating every three minutes over a total of fifteen minutes. For

participants in the Non-Pain group, this process was identical, including thermode placement, except there was no capsaicin application.

Following this incubation period, the thermode temperature increased to a warm temperature 3°C below the previously determined HPT. Every minute, for the next five minutes, participants were asked to provide a pain intensity rating. If the participant did not report feeling any sensation from the capsaicin, the temperature was adjusted in 1°C increments with the requirement that the final testing temperature be at least 1°C below their HPT. For Non-Pain group participants, adjustments were only made to lower the temperature in the event that pain was reported. When this five minute period had elapsed, the full twenty-five minute cognitive task from earlier in the experiment was performed once more. As before, participants were asked to provide a total of 6 pain intensity ratings during this testing. Immediately after the last rating was provided, a three minute "stimulation" resting state EEG was collected. For the Pain group, this "prolonged pain" resting state was collected with the capsaicin and warm thermode placed on the forearm. For the Non-Pain Group, this "nonpainful warmth" resting state was collected with the warm thermode placed on the forearm without capsaicin.

Data Processing

The primary data of interest in this study were the within-subject resting state EEG acquired prior to and during prolonged capsaicin pain. For the primary set of analyses the preprocessing of EEG data was done using EEGLAB 13.6.5b (Delorme and Makeig, 2004) using an approach similar to that used previously (Scheeringa et al., 2011a; Scheeringa et al., 2011b). Here, the first step involved band-pass filtering the EEG between 5 and 16 Hz using the function 'eegnewfilt' after which Infomax (extended) independent component analysis (ICA) was performed (Bell and Sejnowski, 1995). It should be noted that the ICA was performed on resting state EEG data combined across the pain-free and prolonged pain states. The obtained unmixing matrix was applied to the unfiltered data resulting in components that retained broadband spectral content. A Fourier transform was done on the time series of each component to obtain a frequency-power spectra for each component. Next for each participant we visually inspected the frequency-spectra of the components, and identified components that had a clear alpha peak (8-14 Hz) and a scalp topography that suggested a

source predominately over the sensorimotor cortices. This component is referred to as the "central component" for the remainder of the manuscript.

Quantification of PAF

The frequency decomposition of the sensorimotor component data was done using the routines in FieldTrip (Oostenveld et al., 2011). The data was segmented into 5-second epochs and power spectral density in the 2-40 Hz range was derived for each epoch in 0.2 Hz bins using the 'ft_freqanalysis_mtmfft' function. A Hanning taper was applied to the data prior to calculating the spectra to reduce any edge artifacts (Mazaheri et al., 2010; Mazaheri et al., 2009; Mazaheri 2014). The peak alpha frequency for each 5 second epoch was estimated using a center of gravity (CoG) method (Jann et al., 2012; Jann et al., 2010; Klimesch, Schimke, & Pfurtscheller, 1993). We defined CoG as follows:

$$CoG = \frac{\sum_{i=1}^{n} f_i * a_i}{\sum_{i=1}^{n} a_i}$$

where f_i is the ith frequency bin including and above 9 Hz, n is the number of frequency bins between 9 and 11 Hz, and a_i the spectral amplitude for f_i. PAF, as well as power at the PAF bin (PAF Power), were estimated for the central alpha components for every 5 second epoch and then averaged.

Statistical analysis

We first investigated whether capsaicin led to heightened pain intensity using an independent samples t-test. We determined average pain intensity ratings to capsaicin for each participant by averaging the six ratings during the prolonged pain state. Average pain intensity ratings were compared between Pain and Non-Pain groups using an independent samples t-test. This test was performed separately for the whole sample and the sample that excluded subjects in the Non-Pain group who developed pain and subjects in the Pain group who had <20/100 pain.

In order to investigate if central component PAF during pain-free and prolonged pain states were related to pain intensity, we correlated each Pain group participant's central component PAF during the pain-free state (i.e. before the administration of capsaicin) and during prolonged pain with their averaged pain intensity. In order to account for the possibility that the relationship between PAF and pain intensity ratings could be confounded by the temperature of the thermal device, we performed a partial correlation between PAF and pain controlling for thermode temperature. Due to

technical error, thermode temperatures were missing for two participants in the Pain Group and one participant in the Non-Pain Group.

For all correlational analyses, Pearson's correlation coefficients were used to test the relationship between variables. Analyses were also conducted using Spearman's rank order correlations, but these did not change any of the results and are therefore not reported.

As an additional test to investigate whether alpha frequency was related to pain sensitivity, we separated our Pain group participants into "high" and "low" pain sensitive groups by performing a median split based on pain intensity. Here, a 2x2 Repeated Measures ANOVA with group (high pain sensitive vs low pain sensitive vs Non-Pain) x state (pain-free vs prolonged pain state) serving as between- and within-subject factors, respectively, was used to assess how central PAF differed amongst groups and how it changes in response to C-HP.

Next, we investigated if changes in central PAF from baseline to prolonged pain state were related to the pain intensity reported by the participants. This PAF shift (ΔPAF) was calculated by subtracting pain-free state PAF from the prolonged pain state PAF. We then correlated ΔPAF with pain intensity, and, as above, we also performed a partial correlation to control for the impact of thermode temperature.

Hierarchical multiple regression was used to test the independent contributions of baseline resting state PAF and ΔPAF. In this model, pain intensity was the dependent variable and baseline resting state PAF and ΔPAF were the independent variables entered sequentially in the model.

We followed this multiple regression with a leave one out regression approach to formally evaluate the ability of baseline PAF and ΔPAF to predict C-HP model sensitivity. To do so, we generated a series of regression models using central baseline PAF and central ΔPAF from all but one Pain group individual. The resulting model intercept and unstandardized beta coefficients were used to generate a pain prediction for the single individual withheld from model building. This procedure was repeated iteratively so that each individual served as the test participant for exactly one regression model. The accuracy of these pain predictions were then tested by calculating the Pearson correlation between actual pain intensity and the pain intensity predicted by the leave one out models. To test the significance of

this prediction, the aforementioned procedure was repeated 10,000 times using randomly shuffled pain and PAF measures to bootstrap a null distribution of r values. The 95% of the null distribution was used as a significance cutoff for assessing the predictive ability of PAF and ΔPAF. To ensure that results generalized beyond this maximally sized training set, we repeated the above analysis with training set sizes ranging from 3 individuals to 19 individuals. For each training set size, a separate regression model was generated for each possible unique combination of a given training size and the overall correlation between all predictions and observed pain intensity was assessed with a Pearson correlation.

Results

Pain Intensity and the C-HP model

Prolonged pain was evoked using C-HP model on the forearm. Six participants in the Pain group were excluded for failing to develop moderate pain to the capsaicin (consistent with previous observations that about 25% of people are insensitive to capsaicin (Liu et al., 1998; Walls et al. 2017) and three participants in the Non-Pain group were excluded for developing pain that was rated as greater than 10 on average. For the remaining 21 participants in the Pain group, mean pain intensity was 56.01 (s.d. ±16.96). For the Non-Pain group, which underwent identical procedures without capsaicin exposure, mean pain was 1.99 (s.d. ±2.68). As a manipulation check, an independent samples t-test comparing these two groups confirmed that the presence of capsaicin led to heightened pain in response to a warm stimulus, $t(36) = 11.86$, $p < .01$. (This test was also performed for the entire sample (i.e. including subjects who did not respond to the C-HP model and subjects who reported pain with just the warm stimulus): $t(42) = 6.78$, $p < .01$). This difference appears to be a result of the capsaicin rather the heat stimulus given that applied temperatures were not significantly different between the group (Pain Group: mean = 38.52, std = 2.71, range = 32-41; Non-Pain group: mean = 38.25, std = 1.57, range = 37-41; $t(33) = .36$, $p = .72$). Furthermore, there was no difference between the groups in terms of HPT (Pain Group: mean = 43.67, std = 2.22, range = 39 – 47; Non-Pain group: mean = 43.52, std = 2.74, range = 39 – 50; $t(36) = .86$, $p = .17$) or difference between HPT and thermode temperature (Pain Group: mean = 5.21, std = 2.16, range = 1-9; Non-

Pain Group: mean = 5.44, std = 2.13, range = 2-9; t(33) = .75, p = .31) .In addition, there was no relationship between thermode temperature and pain intensity in the Pain group (r = -0.25, p =0 .30) or Non-Pain group (r = -.02, p = .94).

PAF at pain-free and prolonged pain states correlated with pain intensity

The topography of the central alpha component used in our analysis, averaged across Pain group participants can be seen in Figure 2A.

We first set out to investigate if central component PAF recorded during the pain-free state correlated with pain intensity. We found that pain-free state central component PAF correlated negatively with pain intensity (r = -.57, p = .01); that is, the lower an individual's average central PAF, the greater their pain (Figure 2B). This provides initial evidence that an individual's central PAF in the absence of a noxious stimulus may play a role in determining an individual's vulnerability to a prolonged pain. There was not a significant relationship between the pain-free state power estimate of the central component PAF (PAF power) and subsequent pain intensity ratings (r = .23, p = .32).

Next, we assessed whether central component PAF during the prolonged pain state was related to pain intensity. We found central PAF during prolonged pain correlated negatively with pain intensity (r = -.73, p < .01); i.e., slower PAF was associated with greater pain intensity (Figure 2C). The relationship between prolonged pain state central component PAF and pain intensity remained significant when controlling for thermode temperature using a partial correlation (r = -.72, p < .01), suggesting that this relationship is driven by factors other than the magnitude of the sensory stimulus alone. Again we did not observe a significant relationship between central component PAF power during prolonged pain and pain intensity (r = 0.10, p = .67), highlighting the importance of PAF rather than PAF power in prolonged pain.

PAF can distinguish between high and low pain sensitive individuals

The foregoing correlations suggest that the frequency of central alpha activity at baseline and during pain is related to the pain intensity an individual experiences. To investigate this relationship further we performed a median split of our Pain group participants into high and low pain sensitivity groups based on their reported pain intensity.

The difference in central PAF between Non-Pain (control), high pain sensitive, and low pain sensitive groups was statistically assessed using a 2x2 Repeated Measures ANOVA with group (controls vs high pain sensitive vs low pain

sensitive) x state (pain-free vs prolonged pain state) serving as between- and within-subject factors. The main effect of group was significant, $F(2,32) = 3.48$, $p = .04$. As can be seen qualitatively in Figure 2D, the low pain sensitive group displayed the fastest central PAF across both states, the high pain sensitive group displayed the slowest central PAF across both states, and the control group displayed PAF somewhere in between the two; this last observation likely reflects that the Non-pain group contains some combination of high and low pain sensitive individuals. Critically, neither the main effect of state $F(2,32) = .127$, $p = .72$, nor the group x state interaction $F(2,32) = .397$, $p = .68$ were significant.

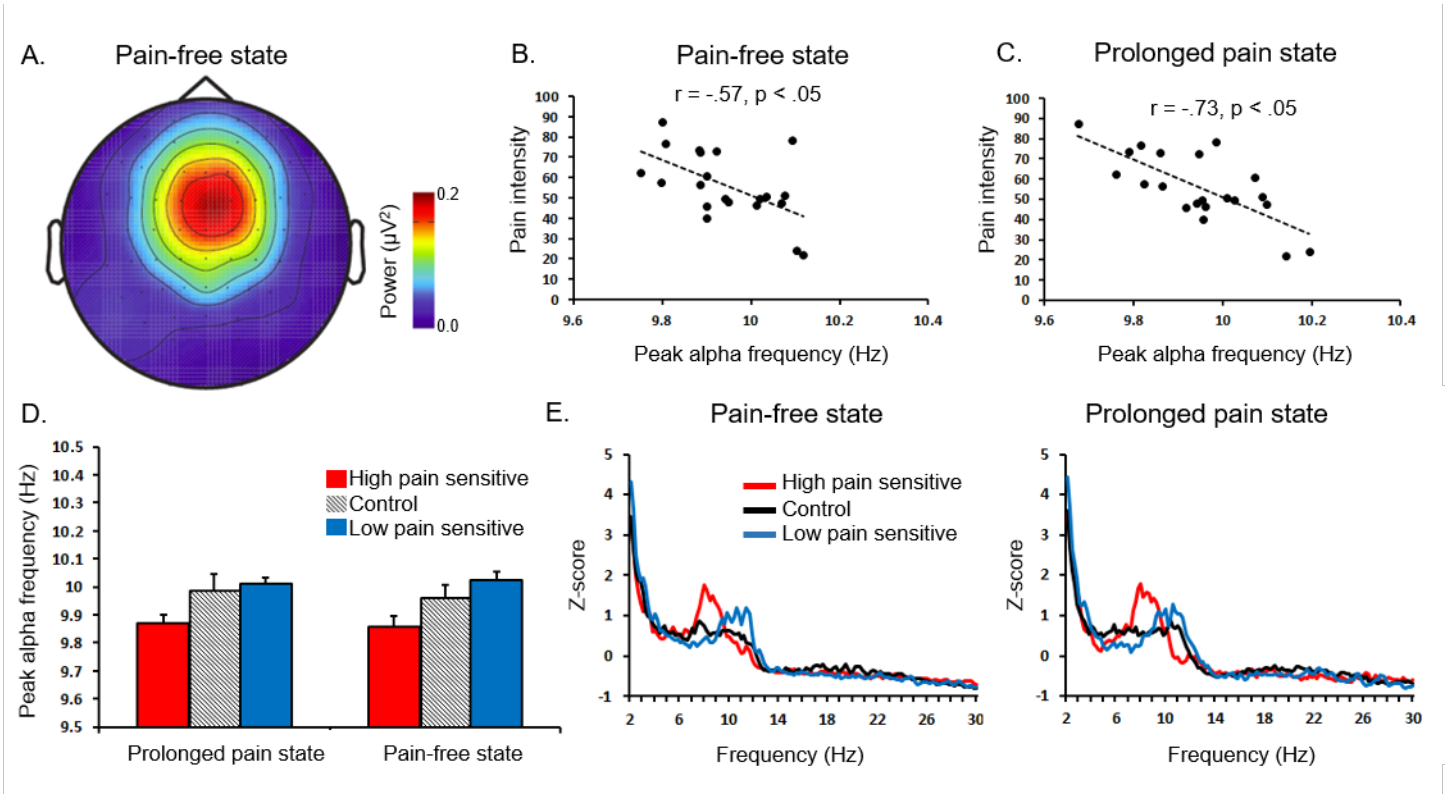

Figure 2. The relationship between PAF and prolonged pain. (A) The topography of the 'central' alpha component selected for peak frequency analysis averaged across Pain group participants during the pain-free state. (B) Central component PAF during the pain-free state was plotted against future pain-intensity ratings (pain during the prolonged pain state). There was a negative correlation between PAF and pain intensity. (C) Central component PAF during the prolonged pain state and pain intensity, showing a similar negative relationship. (D-E) Pain group subjects were divided into low- and high-pain sensitive groups based on a median split of pain intensity ratings in response to the capsaicin-heat pain model. (D) High pain sensitive subjects demonstrated significantly slower central PAF across both pain-free and prolonged pain states than low pain

sensitive subjects. Error bars reflect ± SEM. (E) High pain sensitive subjects show a selective increase in power at slower alpha frequencies relative to low pain sensitive subjects. The frequency spectra was normalized across participants by transforming the data into z-scores from the total mean amplitude of the frequency spectra in each 5 second epoch.

Bonferroni corrected pair-wise comparisons revealed a significant difference in PAF between high and low pain sensitive groups in the pain-free state, $p = .026$. Visual inspection of the central component power spectra revealed differences between groups were largely restricted to the alpha frequency domain, further highlighting the specific importance of alpha in our model of prolonged pain (Figure 2E).

PAF shift from pain-free to prolonged pain states (ΔPAF) was associated with pain intensity

Central component PAF in the pain-free and prolonged pain states were strongly correlated ($r = 0.86$, $p < .05$, Figure 3A). While this suggests PAF is largely stationary, it does not rule out the possibility that small changes in PAF also play a role in the experience of pain.

To investigate this we calculated the PAF shift (ΔPAF) as the difference between central alpha component PAF during prolonged pain and pain-free states). ΔPAF negatively correlated with pain intensity ($r = -0.50$, $p = .02$, Figure3B), indicating that PAF slowing is associated with increased pain. The average, absolute PAF shift across individuals was .05 Hz (s.d. = .05).

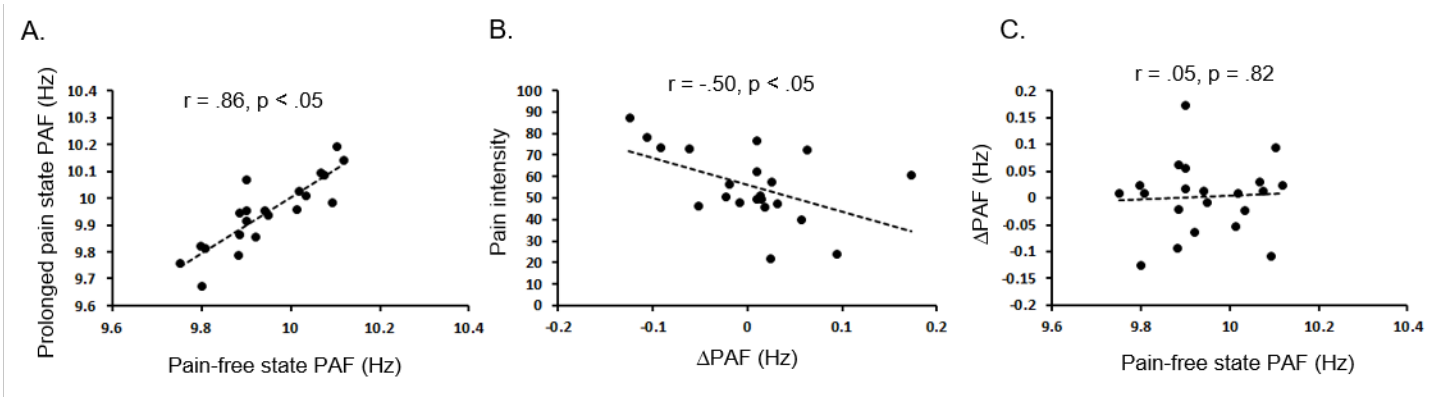

Figure 3. The relationship between PAF shifts (ΔPAF) from pain-free to prolonged pain states and pain intensity. (A) Central component PAF at pain-free state was highly correlated with central component PAF during

prolonged pain, suggesting PAF is a relatively stable measure. (B) ΔPAF correlated with pain intensity. I.e., individuals whose PAF slowed during the prolonged pain state relative to pain-free state reported greater pain intensity. (C) There was no relationship between an individual's pain-free state PAF and ΔPAF, suggesting that these two metrics independently predict pain sensitivity.

PAF and* ΔPAF *provide distinct information about pain intensity

Despite showing quantitatively similar relationships to pain intensity, central component ΔPAF and pain-free state central component PAF were uncorrelated (r = .05, p = .82, Figure 3C), suggesting that pain-free state PAF and ΔPAF represent distinct elements of pain sensitivity.

To formally test the degree to which pain-free state central PAF and central ΔPAF independently predict pain sensitivity, we performed a hierarchical regression using pain sensitivity as the dependent variable and pain-free state, central component PAF and central component ΔPAF as independent variables entered first and second, respectively, into the model. The full regression model significantly predicted pain intensity ($F(2,18) = 10.72$, $p < .01$) with an adjusted R^2 of .493, indicating that pain-free state central PAF and ΔPAF accounted for nearly 50% of the variance in pain intensity. Importantly, addition of pain-free state PAF ($\beta = -.543$, $p < .01$) and ΔPAF ($\beta = -.47$, $p < .01$) each yielded significant changes to the R^2 of the regression model (Pain-free state $\Delta R^2 = .323$, $\Delta F = 9.065$, $p < .01$; Shift $\Delta R^2 = .221$, $\Delta F = 8.70$, $p < .01$). Taken together, this analysis provides evidence that PAF characteristic to an individual, indexed by pain-free state central component PAF, and the extent to which PAF is modulated by prolonged pain, indexed by central component ΔPAF, are distinct mechanisms whose action play an important role in determining pain sensitivity.

PAF and ΔPAF can be used to predict pain intensity

To further assess the robustness of our finding that pain-free state central component PAF and its changes in response to the C-HP model are predictive of pain sensitivity, we performed a leave one out regression analysis. In brief, we generated a series of regression models using pain-free state PAF and ΔPAF from 20 of the 21 individuals (training set) and then used the resulting model to generate a pain prediction for the withheld test individual. Each individual served as the test for exactly one regression model, yielding a total of 21 regression models and 21 predictions. The Pearson correlation between predicted pain intensity and actual pain intensity was r = .55 (Figure 4A). This observed relationship

surpassed the 95th percentile of a null distribution of *r* values generated using permuted PAF measures and pain intensity (r = .22), indicating that the two PAF measures can be used to predict pain intensities at a level greater than chance (Figure 4B).

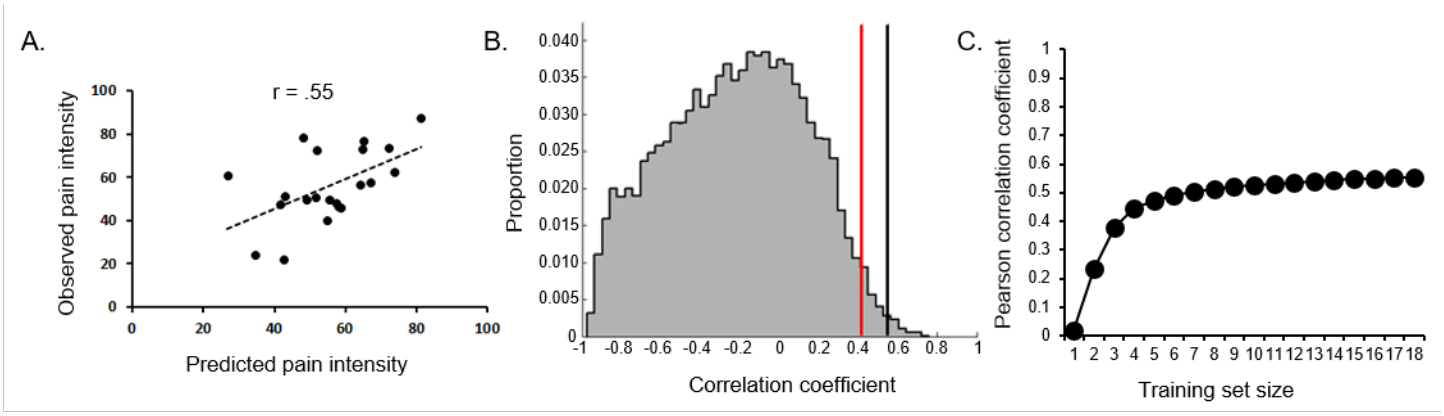

Figure 4. Individual pain sensitivity can be predicted. (A) Correlation between actual pain intensity and the pain intensity predicted by the leave one out regression approach using pain-free state central component PAF and ΔPAF. (B) Histogram of correlation values for a null distribution of pain and PAF indices. Correlation values were obtained by randomly assigning PAF indices to pain intensity and then performing the same leave one out approach as before. The red line indicates the 95th percentile of the null distribution and the black line indicates the correlation value obtained in the actual leave out approach. (C) Correlation between predicted and observed pain scores obtained using a regression approach with a range of training set sizes ranging from three to twenty individuals. The model stabilizes with a training set of about 6, supporting the robustness of the prediction.

To ensure that the apparent ability of pain-free state central component PAF and central component ΔPAF to predict pain intensity was not specific to this leave one out approach, we repeated the above analysis with training set sizes that ranged from 3 individuals to 20. Within a training set size, separate regression models were generated for all the unique combinations of participants; models were then evaluated together as the Pearson correlation between all predicted pain intensity and all observed pain intensity. As can be seen in Figure 4C, prediction became stable around a training set size of 6 (r = .49) and increased a relatively small amount to the maximum training size of 20 (.55). This suggests that our ability to predict future pain intensity from pain-free state PAF and ΔPAF to predict pain intensity is robust and not altered by the cross-validation procedures we employed.

Discussion

The personal experience of pain is highly variable, even when the underlying tissue damage is identical. While previous research has found some genetic and psychological factors influencing pain susceptibility, methods to reliably predict pain intensity consequent to medical intervention are lacking. Here we report that the peak alpha frequency and its shifts over time, measured using EEG, were negatively related to the subjective pain intensity experience during induced prolonged pain. Specifically, slower PAF during the pain-free state and a shift to slower PAF (ΔPAF) during the prolonged pain state were independently associated with higher pain intensity. Using these two metrics, we could predict individual pain sensitivity. These observations taken together suggest that PAF could represent a brain biomarker of an individual's predisposition to pain, which would have useful clinical applications.

PAF has previously been suggested as a putative biomarker for individual differences in the experience of pain (Nir et al., 2010; Bazanova & Vernon, 2014). For healthy individuals, acute pain intensity is related to faster PAF both before and during exposure to a noxious stimulus. In contrast, studies of chronic pain conditions have repeatedly demonstrated slowing of PAF, but little is known about whether this change reflects disease severity, symptom severity, individual vulnerabilities, or an interaction amongst the three. In the current study, we tested the hypothesis that PAF slowing reflects the intensity of prolonged pain by measuring PAF from healthy individuals in response to the capsaicin-heat pain model, which involves central sensitization (LaMotte RH, et al.1992; Lotsch J, et al 2015). In support of this hypothesis, we demonstrated that PAF recorded from central components during pain-free or prolonged pain states are inversely related to pain intensity. Also in support of our hypothesis, we found an inverse relationship between ΔPAF and prolonged pain intensity, suggesting that slowing of the alpha rhythm promotes prolonged pain intensity.

Our finding that PAF recorded during pain-free and prolonged pain states are inversely related to pain intensity is notable for two reasons. First, the direction of this relationship is distinct from what has been previously reported for acute phasic pain (Nir et al., 2010; Nir et al., 2012), but consistent with reports of in chronic pain (Sarnthein et al., 2005; de Vries et al., 2013). This likely reflects the different nature of the prolonged pain model compared to acute phasic pain, with the CH-P model capturing at least some aspects of chronic pain (e.g. central sensitization), or the early

transition period to chronic pain (long lasting pain with peripheral nerve damage). Second, the ability of PAF recorded during the pain-free state to predict future prolonged pain intensity indicates that PAF indexes mechanisms that generate individual susceptibility sensitivity to prolonged pain. Our median split analyses provide strong support for this interpretation: the most sensitive individuals demonstrated PAF that were, on average, slower both before and during the pain state. In contrast, individuals with faster pain-free state PAF had a relatively less painful subsequent pain experience. We believe the median split analysis might have clinical relevance, since given identical injuries some individuals will develop persistent pain, while others will heal and be pain free. Taken together, we believe these findings suggest not only that PAF can predict the magnitude of future, prolonged pain but may also set the stage for PAF as a biomarker for distinguishing healthy and pathological pain. One intriguing implication of our findings is that the slowing of alpha frequency observed in chronic pain patients is not solely a reflection of the changes in the brain brought about by the constant experience of pain, but that slower alpha frequency might have represented sensitivity to develop chronic pain in the future.

We also observed that across individuals, changes in alpha frequency in the prolonged pain state relative to the pain free state (ΔPAF), were inversely related to the subjective pain experienced. This is the first study to our knowledge demonstrate a relationship between ΔPAF and pain. The magnitude of ΔPAF was small (~0.05 Hz) and future investigations are needed to determine how these shifts represent meaningful changes in behavior. We here speculate that the slowing of PAF reflects a maladaptive change in the alpha state leading these individual to experience more pain. Conversely, the stability or increasing of PAF might reflect an adaptive response leading to pain resiliency.

An important result from the current study was that ΔPAF is independent of pain-free state PAF. This finding suggests a potential new avenue for future pain treatments that use pain-free state PAF to identify high-risk individuals and generate interventions that aim to prevent injury induced changes in PAF. In fact, we believe that the current findings position PAF as a promising biomarker for treating and evaluating pain. Post-operative pain can sometimes lead to chronic pain, and one of the best predictors of chronicity is pain intensity immediately following surgery (Katz et al., 1996). Thus, by predicting pain sensitivity following surgery with a simple metric such as alpha activity, patients at greater risk of developing chronic pain could be identified before the procedure begins, and appropriate measures could

be taken (e.g. pre- and post-operative pain management, or in some cases avoiding surgical interventions). Shifting PAF through transcranial alternating current stimulation (tACS) has been shown to affect perceptual ability (Samaha et al. 2015; Cecere et al., 2015) and similar approaches could be used to modulate PAF for prophylactic and interventional pain treatments.

Although it is tempting to speculate that the central independent component indexes this cortical hyper-excitability, the precise anatomical localization identity of the neural substrate giving rise to this component cannot be stated with any certainty. Inferring the location of EEG dipoles is always hazardous as different combinations of generators can give rise to the same apparent source (the so called “inverse problem” of EEG). For example, while 8-14 Hz “mu” rhythms originating from somatosensory cortex are modulated by painful stimulation (Ploner et al., 2006) combined EEG-fMRI studies have also suggested a coupling between scalp recorded alpha power and blood-oxygenation levels in the anterior cingulate cortex (Goldman et al., 2002). At present, both neural sources seem like equally good candidates for generating the independent component used in this study. Ultimately, future studies incorporating techniques, such as fMRI, that are better equipped to resolve the spatial identity of the currently sample source will be needed to fully resolve this question.

It is important to acknowledge that the current study cannot determine whether PAF or PAF changes index the actual experience of pain as opposed to any process that may co-vary with it, such as the salience of the stimulus or the attention an individual pays to it. Importantly, our finding that PAF measured before capsaicin administration can reliably predict pain sensitivity provides some evidence that PAF does not index these confounding factors directly. Along similar lines, the pain intensity in our study and the Nir et al. (2010) study was relatively well matched, suggesting that potentially confounding factors such as stimulus saliency should be even across the studies and unable to account for the difference in findings.

In summary, we provide novel data supporting the hypothesis that slowing of PAF is associated with prolonged pain intensity. These results extend previous findings that linked PAF and chronic neuropathic pain conditions, and suggest that slowing of PAF can be used as a potential marker of prolonged pain sensitivity, as well as a possible mechanism for understanding transitions from acute to chronic pain. The distinct mechanism we identified – PAF and ΔPAF – could

provide a number of innovative approaches for understanding, diagnosing, and treating chronic pain. Finally, slow alpha rhythms appear to have a specific relationship to prolonged pain and interventions that directly manipulate these rhythms may represent a viable means to prevent the transition from acute to chronic pain. Future work directly elucidating the neural mechanisms underlying our observation could offer new fundamental insights into how changes in neural oscillations shape the pain experience.

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