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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.

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 et al., 2017).

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 and Snyder, 2011; Jensen and Mazaheri, 2010; Klimesch, 2012; Pfurtscheller et al., 1996; Van Diepen and Mazaheri, 2017).

The peak frequency of alpha activity (i.e the frequency within the 8–12 Hz, 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 and Vernon, 2014). There is evidence that the frequency

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of alpha activity is positively correlated to measures such as working memory 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 the increased power of slower alpha rhythms (8–9.5 Hz) contributes to the generation of pathological pain, perhaps reflecting thalamocortical dysrhythmia (Llinás 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 et al., 1992; Baron, 2009; Lötsch 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 5 kΩ throughout the experiment. Brain activity was continuously recorded within 0.01–100 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 ~1 g 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 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 5 min 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 5 min period elapsed, the temperature was held in place for 25 min. Participants were asked to rate pain intensity every 5 min. 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 Fig. 1. Once the