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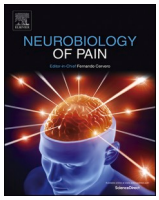

Cerebral peak alpha frequency: Associations with chronic pain onset and pain modulation

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ABSTRACT

Chronic pain is highly prevalent in the U.S. and leads to myriad negative sequalae and suffering. One way to address chronic pain is to identify who is at risk and intervene prior to symptom onset. Research suggests resting peak alpha frequency (PAF), the speed of alpha oscillations at rest, is slower in healthy individuals with greater pain sensitivity and in chronic pain patients. Thus, slower PAF may denote chronic pain vulnerability. Other research has shown that individuals at higher risk of chronic pain exhibit disrupted pain modulation, i.e., less efficient pain inhibition and increased pain facilitation. Currently, the ability of PAF to predict chronic pain and its relation to pain modulation is under-researched. This investigation aimed to address this gap by characterizing associations between PAF, onset of chronic pain, and pain modulation. Using archival data from three independent studies, this investigation assessed whether slower PAF is associated with prospectively-determined chronic pain onset, decreased pain inhibition (i.e., impaired conditioned pain modulation, impaired erotica-induced pain inhibition), and increased pain facilitation (i.e., increased temporal summation of pain, augmented mutilation-induced pain facilitation). Results show that slower PAF was associated with greater facilitation of spinal (i.e., nociceptive flexion reflex) and supraspinal (i.e., N2 potential) nociception in response to unpleasant pictures (i.e., human injury images). This suggests that slower PAF is associated with threat-enhanced spinal and supraspinal nociception and may be relevant for chronic pain conditions with disrupted threat systems. Slower PAF was not associated with any other pain outcome, including prospectively determined chronic pain onset. However, chronic pain onset could only be assessed in one study with a mixed eyes open/eyes closed recording, limiting the significance of this finding.

1. Introduction

Chronic pain is a major public health issue, with prevalence rates estimated to be around 20 % (Treede et al., 2015; Tunks et al., 2008; van Hecke et al., 2013) and rising (Dahlhamer et al., 2018; Von Korff et al., 2020). The impact for the individual as well as the community at large is staggering, encompassing increased rates of anxiety, depression, interference/disability, reduced quality of life, as well as higher unemployment and health care costs (Dorner, 2018; Gaskin and Richard, 2012; Goldberg and McGee, 2011; Smith et al., 2001; Tunks et al., 2008; van Hecke et al., 2013).

Identification of who is at risk for chronic pain is an important step towards primary prevention. One promising chronic pain risk marker has emerged from research on cortical correlates of pain sensitivity. Peak alpha frequency (PAF; speed of alpha oscillations at rest) is slower in individuals with chronic pain (Boord et al., 2008; de Vries et al., 2013; Sarnthein et al., 2006). Importantly, slower PAF has also been linked to higher pain sensitivity in healthy individuals with no chronic pain (Furman et al., 2019, 2018; Seminowicz et al., 2018). This suggests slower PAF might be present before chronic pain develops, leading to higher pain sensitivity and increased risk for chronic pain. However, the link between PAF and prospectively determined chronic pain onset has not yet been established.

Another marker associated with increased chronic pain risk is a pronociceptive pain modulation profile. This term refers to an individual's impaired endogenous pain inhibition ability as well as propensity towards pain signal amplification (Yarnitsky, 2015; Yarnitsky et al., 2014). Decreased pain inhibition and increased pain amplification

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may increase one's risk for chronic pain. For instance, research found that reduced efficiency of endogenous pain inhibition pre-surgery predicted chronic postthoracotomy pain (Yarnitsky et al., 2008). Additionally, less efficient pain inhibition and enhanced pain amplification was found in several different chronic pain conditions (Yarnitsky, 2015; Yarnitsky et al., 2014), such as fibromyalgia (Lautenbacher and Rollman, 1997), irritable bowel syndrome (Marcuzzi et al., 2019), migraine (Sandrini et al., 2006), and osteoarthritis (Arendt-Nielsen et al., 2010). It is reasonable to hypothesize that if individuals demonstrate slower PAF and higher pain sensitivity, it may be because their ability to inhibit pain is impaired, or ascending nociceptive input is amplified. Thus, a slower PAF might be associated with a pronociceptive pain modulation profile. However, research into this line of inquiry is sparse.

The present study used data from 3 independent archival datasets to determine whether (1) PAF predicts prospectively determined chronic pain onset and (2) there is relationship between PAF and three well-validated forms of pain modulation (i.e., temporal summation, conditioned pain modulation, emotion-induced modulation) assessed at 3 levels of the neuraxis (spinal, supraspinal, and perceptual). It was hypothesized that slower resting PAF in healthy individuals would be associated with 1) chronic pain onset at 2-years follow-up and 2) decreased pain inhibition and increased pain amplification.

2. Methods

2.1. Participants

All studies recruited healthy, chronic pain-free participants from the community. Recruitment methods included newspaper ads, Craigslist posts, community fliers, and email announcements. Study 2 also recruited undergraduate psychology students who received class credits for participating. Exclusion criteria for all studies included: <18 years of age, history of cardiovascular, neuroendocrine, musculoskeletal, or neurological disorders, type 1 or type 2 diabetes, current or acute chronic pain, kidney or liver problems, current psychotic symptoms, or substance/alcohol dependence, current pregnancy, being unable to read or write fluently in English, and current use of analgesic, stimulant, antidepressant, anticonvulsant, or anxiolytic medication. Study 1 also excluded for current use of statin medications and a Montreal Cognitive Assessment score < 26 (Nasreddine et al., 2005). Additionally, Studies 2 and 3 excluded for high blood pressure and antihypertensive medication as well as BMI > 35. Due to known hemispheric differences in cerebral anatomical and functional lateralization of emotion processing between left- and right-handers (Bourne, 2008), left-handed individuals were excluded from analyses of the emotion-induced modulation task in Studies 2 and 3. Participants were given information about study procedures before they provided written and verbal informed consent. Participants were informed that they were free to discontinue participation at any time. All procedures were approved by the University of Tulsa IRB. Studies 1 and 3 were also approved by the Cherokee Nation and Indian Health Service Oklahoma City Area Office IRBs due to the inclusion of Native Americans.

2.2. Power analysis

Based on the lowest effect sizes from the peak alpha frequency and pain literature ($r = -0.44$; (Furman et al., 2020, Furman et al., 2019, 2018)) power analysis suggested 40 healthy, pain-free individuals would provide power > 0.80 for correlational analyses between resting PAF and pain outcomes at alpha = 0.05. Given that all our sample sizes were > 40, we believe analyses are adequately powered.

2.3. Procedures

An overview of procedures for study 1, 2, and 3 are outlined in Fig. 1. Detailed information regarding study procedures can be found in the supplemental file. No data/results of study 1 and none of the EEG resting state data have been previously analyzed or published. However, main results from study 2 are published in (Toledo et al., 2024) and main outcomes from study 3 are published in (Rhudy et al., 2021, Rhudy et al., 2020). In brief, all studies entailed resting phases during which PAF was captured. Study 1 assessed temporal summation (TS) and conditioned pain modulation (CPM). Study 2 assessed emotion-induced modulation (emotional controls of nociception task, ECON). Study 3 assessed CPM, TS, ECON as well as chronic pain onset in a longitudinal design (i.e., every six months after enrollment participants were asked to complete a survey about their pain experiences, see section 2.10). All studies assessed perceptual and spinal outcomes during pain modulation tasks (i.e., pain report and nociceptive flexion reflex magnitudes). Studies 1 and 2 also captured event-related potentials in response to painful events, referred to here as pain-evoked potentials (PEPs) during CPM (study 1) and ECON (study 2). This was done to examine supraspinal nociceptive processing.

2.4. Apparatus and physiological recording

In all three studies, testing took place in sound-attenuated, electrically shielded rooms. During testing, participants sat in a reclining chair and were monitored from an adjacent room by video camera. Participants wore headphones to communicate with the experimenter and

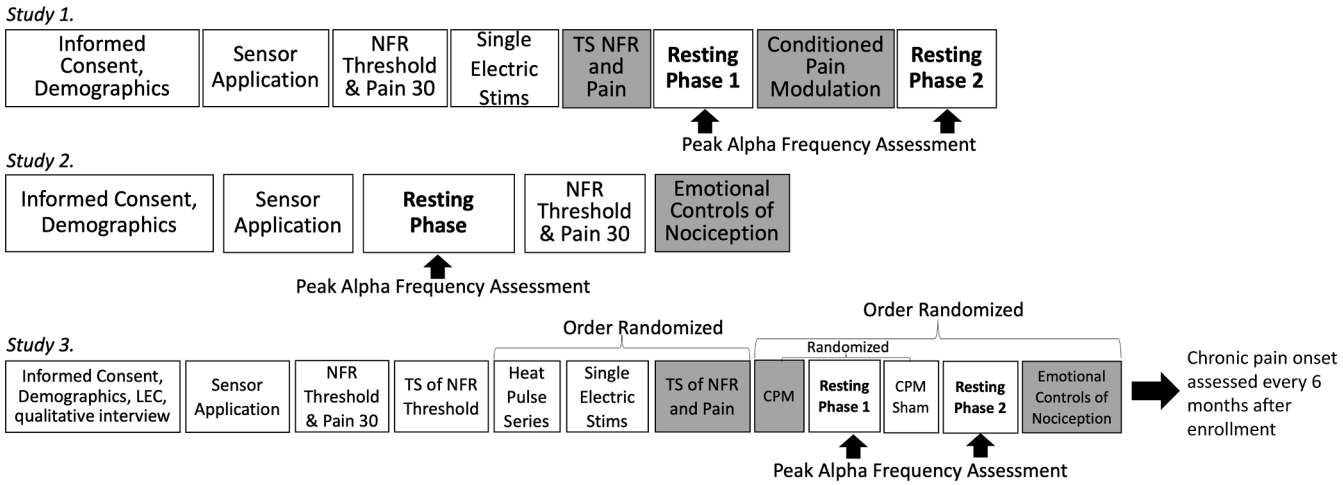

Fig. 1. Overview of procedures for study 1, 2, and 3. Peak alpha frequency was assessed from resting phases. Pain modulation tasks shaded in gray.

receive instructions. Participants submitted ratings with a computer mouse that was shared with the experiment computer screen. Procedures and data collection were computer-controlled using a PC with dual monitor capability, A/D board (USB-6212 BNC; National Instruments, Austin, TX), and LabVIEW software (National Instruments).

2.4.1. NFR recording

For all studies, electromyogram (EMG) was assessed over the biceps femoris muscle in the leg to measure nociceptive flexion reflex (NFR)-related muscle activity. NFR is a reflex that provides information about spinal nociception. Two active Ag-AgCl electrodes were applied over the biceps femoris of the left leg. A bipolar stimulating electrode was applied over the sural nerve at participants' left ankles to deliver electric stimulations over the retromalleolar pathway for select tasks, and a ground electrode was placed over the lateral epicondyle of the femur of the left leg to attenuate noise. Areas that EMG sensors were attached to were first cleaned using isopropyl alcohol and exfoliated using Nuprep cream (Weaver and Company, Aurora, CO) until the electrical impedance for each site was < 5 kΩ. Conductive gel was then placed on the sensors immediately prior to application. Electric stimuli were delivered in a train of 5 1-ms wave pulses (250 Hz) by an isolated Digitimer DS7A stimulator (Digitimer DS7A; Hertfordshire, England; max intensity = 50 mA). Timing of stimulation delivery was computer controlled. For Study 1, EMG signals were collected using the EMG100C BIOPAC amplifier (BIOPAC Systems, Inc., Goleta, CA). For studies 2 and study 3, EMG signals were collected, filtered, and amplified using a Grass Technologies (West Warwick, RI) Model 15LT amplifier with AC Module 15A54.

2.4.2. Electroencephalogram (EEG) and Electrooculogram (EOG) recording

EEG was recorded during CPM and ECON for analysis of pain-evoked potentials as well as during resting phase for PAF analysis. For studies 1 and 2, EEG and vertical electro-oculogram (EOG) data were collected using an acti32CHamp amplifier (BrainVision LLC, Morrisville, NC) and BrainVision Recorder Software (Version 1.21.0102; Brain Products, Germany). In these studies, EEG was measured from 32 electrodes embedded in an EEG cap that was placed on participants' heads (BrainVision ActiCap, cap and active electrodes). The 32 EEG locations were gently abraded with the blunted tip of a syringe and high viscosity electrolyte gel (SuperVisc 1000 g High Viscosity Electrolyte Gel for Active electrodes, Brain Products, Morrisville, NC). Signals were referenced to electrode Fz during recording. The electrode impedances were less than 25 kΩ, which is sufficient for good signal quality when using active electrodes. To capture blinks and eye-movement artifacts unrelated to brain activity, vertical EOG was measured using two Ag-AgCl sensors (one above the eye and one below the eye.) The sites of the EOG sensors were first cleaned using isopropyl alcohol and exfoliated using Nuprep cream (Weaver and Company, Aurora, CO) until an electrical impedance < 5 kΩ was achieved. For Study 3, EEG and vertical EOG were collected, filtered, and amplified using a Grass Technologies (West Warwick, RI) Model 15LT amplifier with AC Module 15A54. EEG was measured from a single electrode at the Cz location that was placed on participants' heads using a passive electrode. The reference electrode was placed on the center of the forehead. The location of Cz and the reference electrode were gently abraded using a Q-tip and exfoliation cream (Nuprep, Weaver and Company, Aurora, CO) and attached to the scalp using Ten20 electrode paste (Weaver and Company, Aurora, CO). Impedances were kept to < 5 kΩ which is sufficient for good signal quality for passive electrodes. Vertical EOG was applied using the same procedures as in studies 1 and 2.

2.5. Determination of stimulus intensity for electric stimulations

Three procedures were used to determine the intensity (in mA) of electric stimulations during subsequent pain tasks: NFR threshold, Pain30, and three-stimulation threshold. These procedures were administered prior to other pain tasks to ensure that the stimulations had sufficient intensity to reliably elicit pain and NFRs. After each electric stimulation, participants rated along a visual analogue scale (VAS) from 'no pain sensation' (0) to 'the most intense pain sensation imaginable' (100).

2.5.1. NFR threshold

To determine NFR threshold, electric stimuli were delivered over the sural nerve using a validated protocol (France et al., 2009; Rhudy and France, 2007). Stimulus intensity was increased from 0 mA in 2 mA increments until a reflex was detected (peak), and then decreased by 1 mA until reflex disappeared (trough). This so-called staircase procedure was done three times total. EMG activity of the biceps femoris of the left leg was recorded, and the NFR magnitude was measured in the 90–150 ms window after stimulation of the sural nerve. NFR magnitude was calculated in Cohen's d units as (mean rectified EMG of 90–150 ms of the post-stimulation interval minus mean rectified EMG of − 60 to 0 ms pre-stimulation interval) divided by average SD of both intervals (−60 to 0 ms pre-stimulation and 90–150 ms postimulation). The average intensity of the last two peaks and troughs was used to define NFR threshold. Stimulation intensity never exceeded 50 mA to ensure participant safety.

2.5.2. Pain30

If NFR threshold was achieved before participants rated their pain sensation at least 30 out of 100, stimulation intensity was increased in 2 mA increments until a VAS rating of 30 or higher was recorded.

2.5.3. Three-Stimulation threshold

For three-stimulation threshold, a series of three electric stimulations were delivered (0.5 s between stimuli), and stimulus intensity increased by 2 mA until NFR was elicited in response to the third stimulus in the series.

2.5.4. Calculation of stimulus intensity for each pain task

Stimulus intensity varied for each pain task according to established criteria (Huber et al., 2022; Rhudy et al., 2020; Terry et al., 2014). For TS, the stimulus intensity was the higher of 120 % NFR threshold or 120 % 3-stimulation threshold. For CPM, the highest of 120 % NFR threshold, 120 % 3-stimulation threshold, or 100 % Pain30 was used. The intensity of electric stimulations during ECON was the higher of 120 % NFR threshold and Pain30.

2.6. Assessment of endogenous facilitation: temporal summation (TS) of pain and NFR

An identical TS task, based on a previously validated protocol, was used for studies 1 and 3 (Rhudy et al., 2011; Terry et al., 2011). In this task, participants received a series of three identical suprathreshold electric stimulations to the sural nerve in rapid succession (interstimulus interval = 0.5 s). There were five series of stimulations for each participant, and the interval between each series varied randomly between 15 and 25 s. After each series of stimulations, a set of computer-presented pain rating scales was administered. Participants were asked to rate pain intensity for each of the three stimulations in the series individually using a computer-presented visual analog scale (VAS) ranging from 0 ("no pain sensation") to 100 ("the most painful sensation imaginable"). The rating of the third stimulus in the series was compared to the pain rating in response to a single suprathreshold electric stimulation of identical intensity. TS of pain was defined as change in pain rating of the third stimulus in the series from the rating of the single electric stimulus. TS of NFR was defined as change in average NFR magnitude from the third stimulus in the series to the first. Due to the high level of movement in response to a train of electric stimulations, recording/analysis of EEG activity in response to TS was not feasible.

2.7. Assessment of descending inhibition: conditioned pain modulation (CPM) of pain, NFR, and PEPs

CPM paradigms were used in studies 1 and 3 to assess endogenous descending inhibition of pain and nociception. For both studies, the CPM testing procedure was broken up into 2 phases: a baseline phase, during which participants received several suprathreshold electric stimulations over the left sural nerve, and a conditioning phase, during which participants received an identical number of suprathreshold electrical stimulations after submerging their right (contralateral) hand in a circulating, painfully cold (10 °C) water bath (Thermo Scientific; SC100-A10B). Interstimulus intervals ranged from 8 to 12 s. Although studies 1 and 3 employed identical test and conditioning stimuli, they varied in the number of electric stimuli delivered in each phase. In study 1, nine electric stimulations were delivered during the baseline and conditioning phases (18 stimulations total). In study 3, five electric stimulations were delivered during the baseline and conditioning phases (10 stimulations total). NFR magnitudes and pain-evoked potentials in response to each electric stimulation were recorded (PEPs only in study 1). Additionally, participants were asked to rate their pain intensity using a NRS that was constantly displayed on the computer screen with the following anchors: 0 = no pain, 20 = mild pain, 40 = moderate pain, 60 = severe pain, 80 = very severe pain, and 100 = worst possible pain (Hellman et al., 2018; Williams et al., 2019). Participants reported their pain rating verbally after each stimulation, which the experimenter in the adjacent room recorded. The amount of pain inhibition due to cold water (CPM pain) was defined as pain during conditioning minus pain during baseline. NFR inhibition due to the cold water (CPM NFR) was defined as NFR magnitude during conditioning minus NFR magnitude during baseline. The amount of inhibition of pain-evoked potentials due to cold water (CPM PEP) was defined as mean N2P2 amplitude during conditioning minus mean N2P2 amplitude during baseline (Granovsky et al., 2016). For analysis of PEPs during CPM, it is standard to compare N2P2 difference scores between baseline and conditioning to best capture the amount of inhibition during CPM.

2.8. Assessment of emotion-induced modulation of pain, NFR, and PEPs: emotional controls of nociception (ECON)

The emotional controls of nociception (ECON) task was administered in studies 2 and 3 to assess emotional modulation of pain, pain-evoked potentials (study 2 only), and NFR. Both studies used identical procedures for ECON. In the paradigm, 24 pictures from the International Affective Picture System (IAPS;(Lang et al., 2005)) were presented by the computer. The order of pictures was pseudorandomized (pictures of same content were not shown more than twice in a row). Each picture was presented for six seconds with a 12–22 s inter-picture interval. Eight mutilation pictures (e.g., injured bodies; negative content), eight erotica pictures (e.g., couples engaging in sexual acts; positive content) and eight neutral pictures (e.g., household objects; neutral content) were presented with 12 electric stimulations delivered during half of the pictures. These stimulations occurred three to five seconds after picture onset and were equally balanced across picture content. To reduce predictability and anticipation effects, six stimulations were delivered during inter-picture intervals (18 stimulations total). Participants were asked to rate subject valence and arousal to the pictures using a Self-Assessment Manikin (Lang et al., 2005).

Pain, NFR magnitude, and PEPs (i.e., N2, P2) were measured in response to the electric stimulations and were assessed by picture content to determine whether emotional modulation occurred. To assess pain, participants were asked to rate their pain intensity using a computer-presented visual analog scale (VAS) ranging from “no pain sensation” to “the most pain sensation imaginable.” Ratings were converted to values ranging from 0 to 100, with higher scores reflecting higher pain intensities. Next, the mean of each outcome was calculated for all three picture contents. After this, two change scores were created for each outcome variable: one change score measured inhibition in response to erotica content relative to neutral pictures (i.e., erotic − neutral), such that increasingly negative scores would indicate greater inhibition. The second change score measured facilitation in response to mutilation content relative to neutral pictures (i.e., mutilation − neutral), such that increasingly positive scores would indicate greater facilitation.

2.9. Assessment of resting peak alpha frequency (PAF)

2.9.1. Studies 1 and 2

In these studies, PAF was calculated using data collected while participants rested for 6-minutes. For study 1, PAF was collected before and after CPM. For study 2, PAF was collected prior to all other tasks, at the beginning of the study. During resting periods, participants remained relaxed and still, minimizing movements and blinks. Participants were instructed by an audio cue to open and close their eyes in alternating, 1-minute blocks. A fixation cross was presented on the computer screen to focus on during the eyes open condition. There were two resting periods in study 1 and one resting period in study 2.

2.9.2. Study 3

For Study 3, participants were asked to rest for 5 min. They did not receive any instructions about having their eyes open or closed. Resting EEG was assessed twice during study 3, once after CPM and once after a CPM “sham” condition, during which participants were instructed to put their hand in a warm water bath.

2.10. Assessment of chronic pain onset: follow-up surveys

Every six months after enrollment in study 3, participants were contacted by phone, mail, or email and asked to complete a survey about their pain experiences. Survey questions asked about pain at 19 different body sites and participants were asked if they had persistent, bothersome pain on more days than not for at least three months for each site (see more details here (Rhudy et al., 2021)). The sites included head, neck, face, shoulder, upper back, lower back, arms, elbows, wrists, hands, buttocks, hips, chest, abdomen/pelvis, legs, knees, ankles, feet and other. For chronic pain criteria to be met, pain had to be rated three or higher on an 11-point rating scale (0 = no pain, 10 = pain as bad as it could be). A dummy variable coded for chronic pain onset. If above mentioned criteria were met, participants were coded as 1 = chronic pain. If criteria for chronic pain were not met, participants were coded as 0 = no pain. If participants reported chronic pain during one survey, but this pain remitted at a subsequent follow up, this was not counted as chronic pain but was scored as “intermittent pain” and excluded from analyses. Data in this study corresponded to the 2-year follow-up. This approach was used previously by the research team to determine chronic pain onset in Native Americans (Rhudy et al., 2021).

2.11. EEG data Preprocessing and Scoring

2.11.1. Peak alpha frequency

EEG resting data were preprocessed in EEGlab (Delorme and Makeig, 2004) and analyzed in Fieldtrip (Oostenveld et al., 2010). First, experimenter notes were reviewed to determine if there were any notable influences on the EEG data or observations relevant to the EEG recording. Then, the EEG raw data were visually inspected to identify channel problems or other sources of noise that could impact the frequency spectrum. After filtering (between 0.2 and 100 Hz, linear FIR filter), eye blinks were corrected. Data was segmented into five second epochs. Fourier analysis was conducted on each five second epoch and a power distribution/spectrum for frequencies between 2–50 Hz was calculated in 0.2 Hz bins with the “ft_freqanalysis_mtmfft” function. A Hanning taper was applied to reduce edge artifacts. Next, the frequency spectrum of the entire trial was visually inspected to identify whether a

peak in the alpha band was present. Then, the frequency spectra of the 60 single trials (spectra of five second epochs) were examined. If no peak in the alpha range nor alpha activity in the raw data was visible, the participant was excluded (n = 1 in study 1, n = 1 in study 2, n = 59 in study 3). Peak alpha frequency was calculated for each five sec epoch using the center of gravity method (Furman et al., 2020; Klimesch et al., 1993) in the frequency range of 9–11 Hz. The 9–11 Hz range was chosen as it reduces the impact of 1/f EEG noise on PAF estimation (Furman et al., 2019, 2018). The calculation for the center of gravity method (CoG) is defined as

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

where f_i is the i^{th} frequency bin including and above 9 Hz (e.g., 9, 9.2, 9.4, 9.6…11 Hz), n is the number of frequency bins between 9 and 11 Hz and a is the spectral amplitude for the frequency bin. The output of this equation is the frequency bin (in Hz) where the center of spectral power is located in the 9- to 11-Hz range (Furman et al., 2019). The center of gravity method differs from the 'peak picking' method in several ways. First, instead of identifying the highest peak in the frequency range, CoG provides information on the distribution or shape of alpha power across the frequency range (Klimesch et al., 1993). In the case of several peaks being present in the alpha band, CoG takes both peaks into account by weighing each peak's contribution and returning a frequency bin in between these peaks. This is especially relevant considering that there are multiple alpha oscillators in the brain, and research suggests that there are at least 2 different alpha rhythms, a "lower" and an "upper alpha", each likely emerging from a different oscillator (Klimesch, 2018). Peak picking might therefore not be the ideal parameter to describe the alpha frequency: instead of arbitrarily choosing one of the peaks, CoG takes both peaks into account, and can be used to infer whether there is faster or slower alpha power in the range. Thus, CoG measures how balanced power is across the alpha range. After calculation of PAF via CoG for each 5-sec epoch, PAF estimates were averaged, such that a single mean PAF estimate was calculated for each channel. A grand mean sensorimotor PAF was averaged across channels C3, C4, and Cz for studies 1 and 2, and Cz only for study 3 given that this study only measured from Cz (in line with (Furman et al., 2020, Furman et al., 2019, 2018)).

2.11.2. Pain-evoked potentials (PEPs)

The evoked potentials recorded have been referred to in this manuscript as "pain-evoked potentials" instead of somatosensory-evoked, sural nerve-evoked, or cortical-evoked potentials. This decision was made due to the parameters of our studies, which lead us to expect nociceptive processing to significantly contribute to the averaged traces, in addition to activated innocuous somatosensation. Specifically, the intensity of electric stimulations were set at or above Pain30 (>30 is generally agreed upon to be mild to moderate pain (Boonstra et al., 2014)), and our median stimulation intensities were in the range of 22.5–25 mA. For more on this topic, see (Huber et al., 2022).

For analysis of PEPs during CPM and ECON, EEG data were preprocessed and analyzed in BrainVision Analyzer Software (Version 2.1.2.327). Eye movement and blink artifacts were removed using independent component analysis (Ocular Correction ICA, FastICA algorithm, BrainVision Analyzer Software). Sections with non-stereotypical artifacts, like body movements or bursts of EMG activity were excluded prior to ICA to ensure optimal results of ICA. A high-pass filter was applied (.05 Hz for ECON and 0.3 Hz for CPM, 12 db/octave, Butterworth Zero Phase Filters) as well as a Notch filter (60 Hz). After ICA, the data were visually inspected to confirm that the ICA was successful in removing eye movement and blink artifacts. Then, a common average reference was applied. For CPM and ECON analyses, the continuous EEG was segmented between −200 to 700 ms after electric stimulus onset. Epochs were corrected relative to a 200 ms pre-stimulus baseline. The PEPs of interest (i.e., the N2 and the P2 potential) were quantified as mean amplitudes calculated over time windows based on visual inspection and previous literature (Albu and Meagher, 2019; Goffaux et al., 2007; Kenntner-Mabiala et al., 2007; Kenntner-Mabiala and Pauli, 2005). For the N2 potential, the time window was specified as 90–140 ms post electric stimulus onset. For the P2 potential, the time window was specified as 280–350 ms post electric stimulus onset.

For subsequent CPM analysis of the relationship between resting PAF and PEPs a 'mean peak-to-peak' amplitude measure was used. Specifically, after quantifying N2 and P2 amplitudes as described above, the difference between N2 and P2 mean amplitudes was calculated and used for CPM analysis. For ECON analysis, N2 and P2 amplitudes were analyzed separately, due to the differences in how they are modulated in the context of emotion: while N2 is modulated in parallel with valence, P2 is modulated in parallel with arousal (Kenntner-Mabiala and Pauli, 2005).

2.12. Data analysis

Data analyses were conducted with SPSS v28 (Statistical Package for the Social Sciences; IBM Corp). All variables were first examined for non-normality. Non-normality was addressed with log10/squared transformations and outliers were identified with Wilcox's MAD-median procedure (threshold to identify outliers = 2.24) and winsorized. An alpha level of $p < 0.05$ was used in all analyses. Due to the influence of age on PAF (Kondacs and Szabó, 1999; Mierau et al., 2017), age was controlled for in the analyses. Given well-established sex differences in pain, sex was added as control variable as well (Rhudy and Williams, 2005). Due to known effects of socioeconomic status on chronic pain development, education and income were controlled for in the resting PAF-chronic pain onset analysis (Landmark et al., 2013). Given that stimulus intensity was individually calibrated to participants' reflex threshold, stimulation intensity was entered as covariate as well since this could have impacted pain modulation. All predictors were entered in a single step in the regression. Missing data were not imputed and excluded from analyses.

To establish the stability of resting PAF, test–retest reliability was assessed for studies 1 and 3, because both studies included two resting EEG periods. This is relevant to demonstrate stability of resting PAF, since participants in studies 1 and 3 underwent pain testing prior to resting PAF assessments. Study 2, however, started the experiment session with a resting state phase, prior to any pain testing, thereby providing a "true" resting state session. To estimate the impact of combined eyes-open/eyes-closed resting phase on PAF in study 3, the correlation of PAF during eyes open and PAF during eyes closed was calculated for study 1 (study 1 was more similar in procedure to study 3).

2.13. Public involvement statement

A community-engaged approach was used for studies 1 and 3. All procedures, presentations, and manuscripts from these data are reviewed and approved by the Cherokee Nation and Oklahoma City Area Indian Health Service IRBs. Only healthy participants were included this this study; therefore, no patients were involved.

3. Results

3.1. Sample and background characteristics

3.1.1. Study 1

The sample included 48 participants. Three participants decided to end the study early due to intensity of electric stimulations. One participant's data had to be excluded due to a technical error. One further participant was excluded due to lack of viable PAF value. Thus, 43 participants were included in the analyses. The sample's background

characteristics are described in supplementary Table 1.

3.1.2. Study 2

The sample included 62 participants. Nine individuals were left-handed and were excluded from further analysis. One additional participant was excluded due to lack of PAF value (see section *2.11.1*; remaining sample = 52). The sample's background characteristics as well as the excluded participants are described in supplementary Table 2.

3.1.3. Study 3

In all, 329 participants met inclusion criteria for the study. 59 participants ended the study early and 64 participants' data were excluded due to data quality concerns. Of those, 4 participants' data were excluded due to a faulty EEG channel. 1 participant's data were excluded because they fell asleep during the resting phase. The remainder (n = 59) were excluded due to lack of identifiable alpha activity in the raw data and frequency spectrum. This is a higher proportion than in study 1 and 2 due to the circumstances of data collection in study 3. Specifically, study 3 recorded data from only 1 electrode sensor which made assessment of data quality more difficult. Additionally, the electrode in study 3 was applied with a different technique that was not as robust to head movement. Therefore, a higher percentage of data was rejected for study 3 since (1) data quality was worse than in study 1 and 2 and (2) data of questionable quality could not be examined across other channels, leading to automatic rejection. Thus, for 206 participants a peak alpha frequency value was identified from at least 1 of the EEG recording sessions (i.e., final sample = 206). Study 3′s high test–retest reliability suggests that the strict EEG data cleaning procedures were successful in maintaining the quality of the data (see section 3.2). The sample's background characteristics are described in supplementary Table 3.

3.2. Peak alpha frequency

For study 1, Pearson's correlations of average PAF values across sites Cz, C3, C4 between the two phases was $r = 0.92$ ($p < 0.001$), suggesting high test–retest reliability. Study 2 only had 1 resting phase. For study 3, the correlation between the 2 sessions was $r = 0.90$ ($p < 0.001$; Cz sensory only). Distribution of PAF values per study (in absolute frequencies and as % frequencies) are depicted in supplementary Fig. 1. The correlation between eyes open and eyes closed PAF at sensor Cz was $r = 0.79$ for study 1. Given this high correlation and increased sample size of study 3, we believe relationships between mixed eyes open/closed PAF and chronic pain onset should still be able to be detected.

3.3. Chronic pain onset

A logistic regression analysis with peak alpha frequency predicting chronic pain status (yes = 1/no = 0) while controlling for age, sex, education, and income was not significant $\chi^2(5) = 1.44$, $p = 0.92$. This suggests that the predictors, as a set, did not significantly distinguish between participants who developed chronic pain or not. Further, none of the variables individually predicted chronic pain outcome per the Wald criterion (see Table 1).

Table 1
Logistic regression of chronic pain development yes/no ($n = 139$).

Predictors	*B*	*SE*	Wald χ^2	*p*-value	Odds Ratio	95 % CI L. CI	U. CI
PAF	−1.01	1.48	0.47	0.49	0.36	0.02	6.66
Age	0.003	0.02	0.02	0.89	1.00	0.96	1.04
Sex	−0.31	0.51	0.37	0.55	0.74	0.27	1.99
Education	−0.00002	0.32	0.00	0.99	1.00	0.53	1.89
Income	−0.09	0.11	0.67	0.41	0.91	0.73	1.14

Note. PAF = peak alpha frequency, assessed during mixed eyes open and closed periods at Cz. L. = lower, U. = upper. Sex = 1 if female, 0 if male. *$p < 0.05$.

3.4. Conditioned pain modulation

Neither PAF nor any control variables were a significant predictor of CPM of NFR or CPM of N2P2 across studies 1 & 3 (see supplementary Table 4). In the model predicting CPM of pain, stimulation intensity emerged as the only significant predictor in studies 1 ($p = 0.022$) and 3 ($p = 0.003$), with higher stimulation intensity being associated with less pain inhibition during CPM. Supplementary Fig. 2 presents the grand average EEG waveforms of the pain-evoked potentials for baseline and conditioning phases. Supplementary Table 4 presents regression results for CPM outcomes for studies 1 &3.

3.5. Temporal summation

Across studies 1 and 3, PAF was not significant for predicting TS of NFR and TS of pain. For study 3, only age ($p < 0.001$), stimulation intensity ($p = 0.001$) and sex ($p = 0.035$) emerged as significant predictors of TS of NFR. Higher stimulation intensity, older age, and being male was associated with greater temporal summation of NFR. In the model predicting TS of pain, only stimulation intensity emerged as significant predictor ($p = 0.046$), and only in study 3. Higher stimulation intensity was associated with greater temporal summation of pain. Supplementary Table 5 presents the regression results for the TS outcomes for both studies.

3.6. Emotional controls of nociception

Table 2 presents the regression results for the modulation of pain, NFR, N2, and P2 by erotica content for study 2. Neither resting PAF nor any of the control variables emerged as significant predictors. Table 2 also presents the regression output for the modulation of NFR and pain by erotica content for study 3. In the model predicting NFR modulation by erotica, only sex emerged as a significant predictor ($p = 0.03$). Being male was associated with less erotica-induced inhibition of NFR. In the model predicting pain modulation by erotica, only age emerged as significant ($p = 0.03$), with older age being associated with less erotica-induced inhibition of pain.

Table 3 presents the regression results for the modulation of NFR, pain, N2, and P2 by mutilation content for study 2. In the model predicting N2 modulation, resting PAF emerged as a significant predictor ($p = 0.045$), with higher PAF being associated with less mutilation-induced facilitation of N2. For all other models predicting modulation of NFR, pain and P2, neither resting PAF nor any of the control variables emerged as significant predictors. Fig. 2 depicts the grand average EEG waveforms of the pain-evoked potentials and Fig. 3 depicts the relationship between PAF and N2 change score (mutilation-neutral). Table 3 also presents the regression output for the modulation of NFR and pain by mutilation content for study 3. In the model predicting NFR modulation, peak alpha frequency ($p = 0.045$) and stimulation intensity ($p = 0.041$) emerged as significant. Higher PAF and higher stimulation intensity were associated with less mutilation-induced NFR facilitation. Fig. 4 depicts the relationship between PAF and NFR change score. In the model predicting pain modulation, neither resting PAF nor any of the control variables emerged as significant.

4. Discussion

This study examined the relationship between resting peak alpha frequency (PAF) and chronic pain onset at 2-years, as well as pain inhibitory and pain amplifying processes. Contrary to hypotheses, resting PAF was not associated with chronic pain onset or most pain/nociceptive outcomes. However, slower resting PAF was associated with greater mutilation-induced N2 facilitation in study 2 and with greater mutilation-induced NFR facilitation in study 3.

Table 2
Erotica-induced modulation of NFR, pain, N2 and P2 in studies 2 and 3.

Study 2												
	NFR ($n = 51$)			Pain ($n = 52$)			N2 ($n = 41$)			P2 ($n = 41$)		
Overall Model	$F(4,46) = 0.31$, $p = 0.87$ $R^2 = 0.026$			$F(4,47) = 0.43$, $p = 0.78$ $R^2 = 0.035$			$F(4,36) = 0.53$, $p = 0.71$ $R^2 = 0.056$			$F(4,36) = 1.15$, $p = 0.35$ $R^2 = 0.11$		
Predictors	B	*SEB*	*β*	B	*SEB*	*β*	B	*SEB*	*β*	B	*SEB*	*β*
PAF	−0.20	0.34	−0.09	−0.89	5.67	−0.02	4.85	4.53	0.18	2.25	4.87	0.07
Stim Int	0.003	0.005	0.11	0.04	0.07	0.09	−0.004	0.05	−0.01	0.003	0.06	0.01
Age	−0.02	0.05	−0.06	−0.55	0.80	−0.11	0.27	0.55	0.08	0.60	0.59	0.17
Sex	−0.001	0.12	−0.001	1.14	1.96	0.09	1.50	1.49	0.17	2.95	1.60	0.30

Study 3							
	NFR ($n = 173$)			Pain ($n = 176$)			No EEG during ECON
Overall Model	$F(4,168) = 1.51$, $p = 0.20$, $R^2 = 0.035$			$F(4,171) = 1.46$, $p = 0.22$, $R^2 = 0.033$			
Predictors	B	*SEB*	*β*	B	*SEB*	*β*	
PAF	0.14	0.15	0.07	1.52	2.79	0.04	
Stim Int	−0.001	0.002	−0.04	0.01	0.04	0.03	
Age	−0.0004	0.004	−0.01	**0.16***	0.07	**0.16***	
Sex	**−0.11***	**0.05***	**−0.17***	0.52	0.97	0.04	

Note. PAF = peak alpha frequency, for study 2 assessed during eyes closed periods (Cz, C3, C4 average), for study 3 assessed during mixed eyes open and closed periods (at Cz). Sex = 1 if female, 0 if male. *$p < 0.05$.

Table 3
Mutilation-induced modulation of NFR, pain, N2 and P2 in studies 2 & 3.

Study 2												
	NFR ($n = 51$)			Pain ($n = 52$)			N2 ($n = 38$)			P2 ($n = 38$)		
Overall Model	$F(4,46) = 1.13$, $p = 0.36$ $R^2 = 0.09$			$F(4,47) = 0.94$, $p = 0.45$ $R^2 = 0.07$			$F(4,33) = 1.34$, $p = 0.28$ $R^2 = 0.14$			$F(4,33) = 0.48$, $p = 0.75$ $R^2 = 0.055$		
Predictors	B	*SEB*	*β*	B	*SEB*	*β*	B	*SEB*	*β*	B	*SEB*	*β*
PAF	0.20	0.32	0.09	4.28	5.96	0.10	**8.30***	3.99	**0.34***	−1.02	6.39	−0.03
Stim Int	−0.01	0.004	−0.19	−0.02	0.08	−0.04	−0.01	0.05	−0.05	−0.03	0.07	−0.09
Age	−0.04	0.04	−0.13	−0.40	0.84	−0.07	0.14	0.48	0.05	−0.40	0.76	−0.10
Sex	0.18	0.11	0.24	3.78	2.06	0.26	−0.80	1.24	−0.11	−2.37	1.99	−0.20

Study 3							
	NFR ($n = 173$)			Pain ($n = 176$)			No EEG during ECON
Overall Model	$F(4,168) = 2.61$, $p = 0.037$, $R^2 = 0.059$			$F(4,171) = 0.80$, $p = 0.53$, $R^2 = 0.018$			
Predictors	B	*SEB*	*β*	B	*SEB*	*β*	
PAF	**−0.30***	0.15	**−0.15***	−3.45	3.24	−0.08	
Stim Int	**−0.004***	0.002	**−0.16***	−0.07	0.05	−0.11	
Age	−0.01	0.004	−0.11	0.04	0.09	0.03	
Sex	0.04	0.05	0.07	0.34	1.12	0.02	

Note. PAF = peak alpha frequency, for study 2 assessed during eyes closed periods (Cz, C3, C4 average), for study 3 assessed during mixed eyes open and closed periods (at Cz). Sex = 1 if female, 0 if male. *$p < 0.05$.

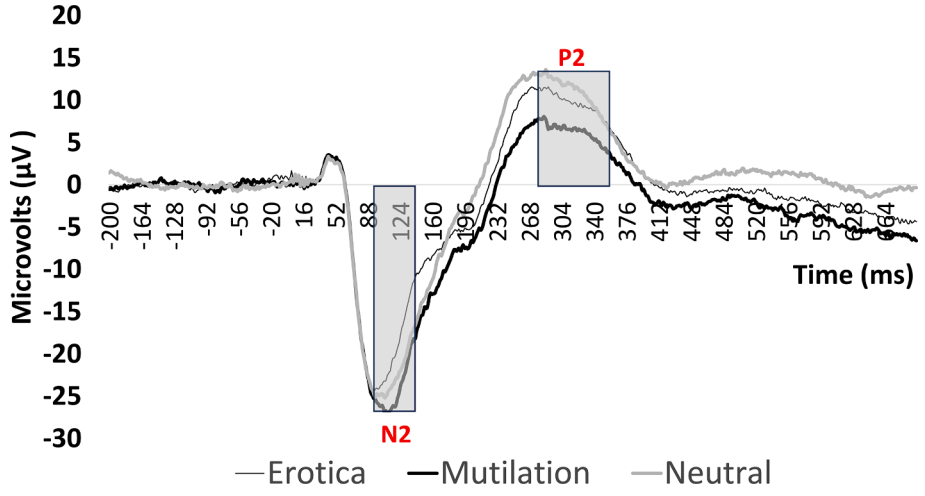

Fig. 2. Grand average EEG waveforms at Cz for ECON. Time windows used for analysis of N2 (90–140 ms) and P2 (280–350 ms) are shaded.

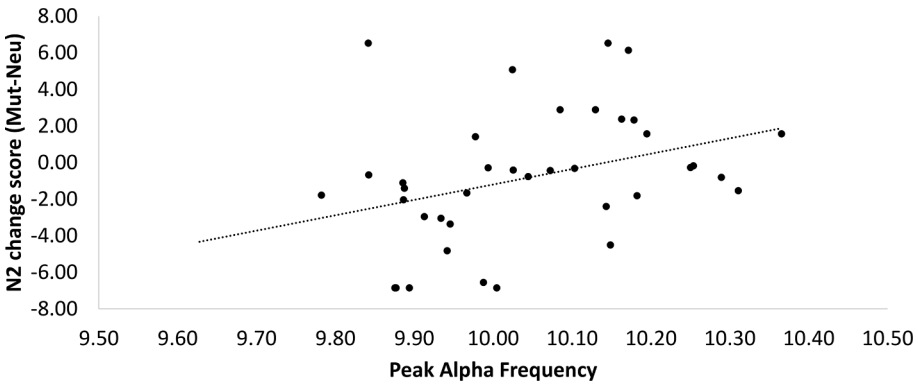

Fig. 3. Relationship between peak alpha frequency and N2 change score (mutilation-neutral). More positive N2 change score indicates less mutilation-induced facilitation.

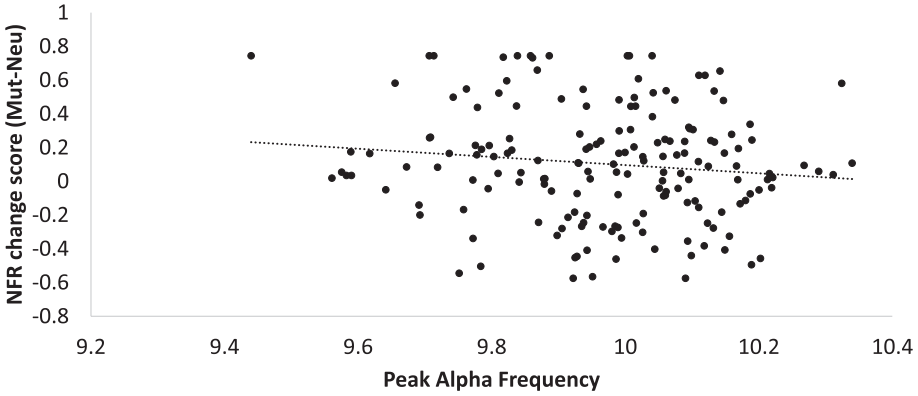

Fig. 4. Relationship between peak alpha frequency and NFR change score (mutilation-neutral). More negative NFR change score indicates less mutilation-induced facilitation.

4.1. PAF did not predict chronic pain onset

Surprisingly, resting PAF was not associated with chronic pain onset which is at odds with a previous study examining postsurgical pain (Millard et al., 2022) and research on slowed PAF in chronic pain conditions (Boord et al., 2008; de Vries et al., 2013; Sarnthein et al., 2006). One potential explanation regarding the finding from Millard et al. (2022) is that the sample consisted of lung cancer patients undergoing surgery. Thus, participants were already experiencing some level of pain pre-surgery, which may have resulted in slowed resting PAF. Therefore, instead of a pre-existing vulnerability marker, the resting PAF assessed may have been a result of pre-surgery pain. This is consistent with findings of slowed PAF in chronic pain conditions. By contrast, our study collected PAF from healthy individuals before pain onset to explore if PAF is a premorbid risk marker. Our results suggest this may not be the case, especially considering samples from studies 1 and 3 include Native American individuals, who are at the highest risk of chronic pain development among all racial/ethnic groups (Rhudy et al., 2021; Zajacova et al., 2022).

Another potential explanation is that slowed PAF is a risk factor for developing specific types of chronic pain. The chronic pain most common in the study 3 sample was located in the lower back, shoulders, and upper back (Rhudy et al., 2021). Thus, it is possible that slower PAF is not associated with development of musculoskeletal pain. A counterpoint to this explanation is that slower PAF has been associated with a model of musculoskeletal pain in healthy humans (Furman et al., 2019). Thus, more research is necessary to resolve whether slower PAF is relevant for musculoskeletal pain, or for chronic pain risk at all. Given the prior literature and our results, PAF may be more relevant as a marker for clinical pain, and this should be explored in future research. Alternatively, it is also possible that the EEG data in study 3 were limited by having a mixture of eyes open and eyes closed, and that an eyes-closed recording prior to experimental tasks may have led to different results.

4.2. Slower PAF is related to mutilation-induced facilitation of spinal and supraspinal nociception

Our findings suggest that slower PAF is associated with mutilation picture-induced facilitation of spinal and supraspinal nociception, but not facilitation of pain. Thus, PAF was associated with 2 out of 3 nociceptive/pain outputs that belong to the defensive system. This suggests a threat-specific role for PAF.

If an electric stimulation is presented after a mutilation picture, the defensive system – which is already primed by the picture – amplifies the additional threat, leading to greater NFR, greater N2, and greater pain perception (Rhudy, 2016). Previous fMRI research suggests that emotional modulation of NFR is mediated by circuitry including left medial thalamus, bilateral amygdala, left pons, subgenual cingulate and ventromedial prefrontal cortex (vmPFC), while emotional modulation of pain is mediated by circuitry including the right insula and bilateral lingual gyri (Roy et al., 2009). While the generators of N2 are known (S1, S2 (Dowman and Darcey, 1994)), the circuitry responsible for emotional modulation of N2 is not. This complicates interpretation.

One hypothesis of how PAF interacts with the defensive system is that slower PAF reflects brain properties that impact N2 and NFR circuitry responsible for nociceptive responding. In this hypothesis, slower PAF may reflect a brain with fewer synaptic connections and/or with greater propagation delays. This is supported by research indicating that PAF is associated with (1) the amount of synaptic contacts, white matter

density, membrane time constants, and propagation delays (David and Friston, 2003; Grandy et al., 2013a, 2013b; Jansen and Rit, 1995; Lopes da Silva et al., 1974) and (2) aging. (Kondacs and Szabó, 1999; Mierau et al., 2017) which is thought to be due to loss of white matter integrity (Coelho et al., 2021). Thus, slower PAF could reflect a less connected brain or having greater propagation delays, resulting in greater mutilation-induced N2 and NFR facilitation. The exact brain areas responsible for this are subject to speculation, but given that the thalamus and thalamocortical connections play an important role in alpha rhythm (da Silva, 2013), connections to the thalamus may be affected by slower PAF. This could have downstream effects on the amygdala-thalamus-PFC connectivity that is part of NFR modulation circuitry and perhaps N2 modulation circuitry as well (Roy et al., 2009).

Functionally, the thalamus and amygdala are both targets of ascending nociceptive pathways: the amygdala is involved in detection and orienting towards nociceptive stimuli, as well as the degree of emotional arousal (Bradley et al., 2001; Pessoa, 2010; Roy et al., 2009), whereas the thalamus plays a role in transmission of nociceptive signals to prefrontal cortex (Roy et al., 2009). The mPFC contributes to affective evaluation and meaning attribution (Roy et al., 2009). Slower PAF could impact connectivity to and from mPFC and result in overinterpretation of threat (by mPFC) and subsequent increased representation of the stimulus in S1 (indexed by greater N2) and mobilization for defense, reflected in reduced descending inhibition and greater NFR magnitude. The connection between amygdala, thalamus, and mPFC is the lynchpin of this explanation; that pain is unaffected could be explained by lack of amygdala, thalamic, and mPFC involvement in the circuitry responsible for emotional modulation of pain (Roy, 2015).

4.3. Linking threat to chronic pain

Our results suggest that slowed PAF is associated with enhanced nociceptive responding in response to threat. This relationship might be especially relevant for development of chronic pain conditions that have a disrupted threat system, such as fibromyalgia (Pinto et al., 2023). In a recent review, Pinto et al (2023) postulate fibromyalgia is associated with a heightened threat system coupled with an underactive soothing-affiliative system. They propose this imbalance leads to a persistent activation of the salience network which then leads to amplification of negative input (such as pain). In this model, slowed PAF could either be part of a heightened threat system or a result of persistent activation of the salience network. A recent study examining PAF and resting state fMRI activity provides preliminary support for PAF being closely connected to salience network activity (i.e., a positive relationship between PAF and salience network activity (McLain et al., 2022)). Additionally, a recent study (Ho et al., 2024) has found that PAF was slowed in those with high fear of movement and chronic low back pain, and that pain intensity, disability, and fear of movement in combination predicted PAF. These results are consistent with our results such that slower PAF may be associated with enhanced nociceptive responding to movement in chronic low back pain, essentially interpreting any movement as threatening. Future studies should test these hypotheses.

4.4. Non-significance of PAF and other pain modulation

In contrast to emotional modulation results, PAF was not associated with temporal summation (TS) of NFR or TS-pain. This suggests slower PAF is not associated with increased TS-associated spinal sensitization/hyperexcitability or its perceptual correlate. Temporal summation is thought to assess mechanisms associated with central sensitization (Eide, 2000; Woolf, 1996) and enhanced TS has been found in chronic pain patients (Eide, 2000; Eide and Rabben, 1998; Maixner et al., 1998; Yarnitsky, 2015). Our findings suggest slower PAF is unrelated to enhanced central sensitization associated with repetitive peripheral nociceptive input.

PAF was also not associated with inhibition of pain or nociception in two different supraspinally-mediated pain modulation tasks, CPM and ECON. Previous research has found a lack of association between PAF and another supraspinally-mediated pain modulation – placebo analgesia, i.e., ability of sham "analgesic" to reduce pain (Raghuraman et al., 2019). Additionally, prior studies found no association between CPM efficiency and power in the alpha band (Simis et al., 2022; Teixeira et al., 2022). Given that CPM and placebo analgesia are most likely mediated by opioidergic pathways, combined findings suggest PAF does not reflect the function of endogenous opioid systems (Tan and Kuner, 2021). Further studies are necessary to assess whether our null results generalize to other forms of supraspinally-mediated inhibition (e.g., hypnosis, mindfulness).

4.5. Implications

Our results have several implications. First, although resting PAF appears to be reliable across testing sessions (suggesting a trait), the relationship between PAF and chronic pain risk and onset is not a direct one. Rather, slower PAF appears to impact systems (amygdala, thalamus, PFC) that have a multitude of functions, one of which includes nociceptive responding (e.g., facilitation of N2/NFR). Second, resting PAF does not appear predictive of onset of musculoskeletal pain. However, given our findings, additional research with other chronic pain populations, especially fibromyalgia, is needed. The potential of PAF as an objective clinical pain marker should be explored as well.

4.6. Limitations

Although this investigation has several strengths (data from 3 samples, several pain tasks, different levels of neuraxis) there are also several limitations. First, only one study (study 1) had a true resting period for assessment of resting PAF prior to pain testing, thus carry-over effects of pain tasks in study 2 and 3 may have influenced results. Additionally, assessment of PAF in study 3 was based on 1 electrode (Cz) only and the recording contained a mixture of eyes open/eyes closed which perhaps impacted integrity of the data. Because of this, a conservative approach to rejecting data was taken, resulting in a higher exclusion rate than the other 2 studies.

4.7. Summary

In conclusion, resting PAF was not associated with chronic pain onset and was also not associated with descending inhibition and pain/NFR facilitation, with one exception. Specifically, slower PAF was associated with increased threat facilitation of N2 and NFR response resulting from viewing pictures of mutilated/injured bodies. This suggests slower PAF affects N2 and NFR modulation in response to threat. This could be due to greater attribution of threat to electrical stimulation by the mPFC, leading to enhanced NFR and N2. Thus, resting PAF may be relevant for chronic pain disorders associated with disrupted threat responding. Given how few of our outcomes were associated with resting PAF, it is unlikely that PAF could be used as a vulnerability marker for a wide variety of chronic pain conditions.

Notice of previous presentation

Aspects of this research have been presented at the 2021 United States Association for the Study of Pain. Parts of this work have been submitted in partial fulfillment of the requirements for the degree of Ph. D. at The University of Tulsa.

CRediT authorship contribution statement

Felicitas A. Huber: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Parker A. Kell:**

Writing – review & editing, Investigation, Data curation. **Joanna O. Shadlow:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization. **Jamie L. Rhudy:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments and Conflict of Interest

The authors would like to thank Dr. Andrew Furman for advice on analysis of peak alpha frequency and sharing EEGlab/Fieldtrip processing scripts. This research was supported by the National Institute on Minority Health and Health Disparities of the National Institute of Health under Award No. R01MD007807, the Oklahoma Center for the Advancement of Science and Technology (OCAST) Health award number HR18-039, and faculty and student research grants from The University of Tulsa Office of Research and Sponsored Programs. The content is solely the responsibility of the authors, and does not necessarily reflect the views of the University of Tulsa, National Institutes of Health, Indian Health Service, or the Cherokee Nation. Aspects of this research have been presented at the 2021 United States Association for the Study of Pain. Parts of this work have been submitted in partial fulfillment of the requirements for the degree of Ph.D. at The University of Tulsa. The authors report no conflicts of interest. Data and analytic codes will be made available on request from the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynpai.2025.100180.

Data availability

The data for this manuscript are available from the PI (Jamie Rhudy) upon reasonable request and after Cherokee Nation & Oklahoma City Area Indian Health Service IRBs.

References

Albu, S., Meagher, M.W., 2019. Divergent effects of conditioned pain modulation on subjective pain and nociceptive-related brain activity. Exp. Brain Res. 237, 1735–1744. https://doi.org/10.1007/s00221-019-05545-8.

Arendt-Nielsen, L., Nie, H., Laursen, M.B., Laursen, B.S., Madeleine, P., Simonsen, O.H., Graven-Nielsen, T., 2010. Sensitization in patients with painful knee osteoarthritis. Pain 149, 573–581. https://doi.org/10.1016/j.pain.2010.04.003.

Boonstra, A.M., Schiphorst Preuper, H.R., Balk, G.A., Stewart, R.E., 2014. Cut-off points for mild, moderate, and severe pain on the visual analogue scale for pain in patients with chronic musculoskeletal pain. Pain 155, 2545–2550. https://doi.org/10.1016/j.pain.2014.09.014.

Boord, P., Siddall, P.J., Tran, Y., Herbert, D., Middleton, J., Craig, A., 2008. Electroencephalographic slowing and reduced reactivity in neuropathic pain following spinal cord injury. Spinal Cord 46, 118–123. https://doi.org/10.1038/sj.sc.3102077.

Bourne, V.J., 2008. Examining the relationship between degree of handedness and degree of cerebral lateralization for processing facial emotion. Neuropsychology 22, 350–356. https://doi.org/10.1037/0894-4105.22.3.350.

Bradley, M.M., Codispoti, M., Cuthbert, B.N., Lang, P.J., 2001. Emotion and motivation I: Defensive and appetitive reactions in picture processing. Emotion 1, 276–298.

Coelho, A., Fernandes, H.M., Magalhães, R., Moreira, P.S., Marques, P., Soares, J.M., Amorim, L., Portugal-Nunes, C., Castanho, T., Santos, N.C., Sousa, N., 2021. Signatures of white-matter microstructure degradation during aging and its association with cognitive status. Sci. Rep. 11, 4517. https://doi.org/10.1038/s41598-021-83983-7.

Dahlhamer, J., Lucas, J., Zelaya, C., Nahin, R., Mackey, S., DeBar, L., Kerns, R., Von Korff, M., Porter, L., Helmick, C., 2018. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016. Morb. Mortal. Wkly. Rep. 67, 1001–1006. https://doi.org/10.15585/mmwr.mm6736a2.

da Silva, L.F., 2013. EEG and MEG: Relevance to Neuroscience. Neuron 80, 1112–1128. https://doi.org/10.1016/j.neuron.2013.10.017.

David, O., Friston, K.J., 2003. A neural mass model for MEG/EEG: coupling and neuronal dynamics. NeuroImage 20, 1743–1755. https://doi.org/10.1016/j.neuroimage.2003.07.015.

de Vries, M., Wilder-Smith, O.H., Jongsma, M.L., van den Broeke, E.N., Arns, M., van Goor, H., van Rijn, C.M., 2013. Altered resting state EEG in chronic pancreatitis patients: toward a marker for chronic pain. J. Pain Res. 6, 815–824. https://doi.org/10.2147/JPR.S50919.

Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J. Neurosci. Methods 134, 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009.

Dorner, T.E., 2018. Pain and chronic pain epidemiology: Implications for clinical and public health fields. Wien. Klin. Wochenschr. 130, 1–3. https://doi.org/10.1007/s00508-017-1301-0.

Dowman, R., Darcey, T.M., 1994. SEP topographies elicited by innocuous and noxious sural nerve stimulation. III. Dipole source localization analysis. Electroencephalogr. Clin. Neurophysiol. Potentials Sect. 92, 373–391. https://doi.org/10.1016/0168-5597(94)90014-0.

Eide, P.K., 2000. Wind-up and the NMDA receptor complex from a clinical perspective. Eur. J. Pain 4, 5–15. https://doi.org/10.1053/eujp.1999.0154.

Eide, P.K., Rabben, T., 1998. Trigeminal Neuropathic Pain: Pathophysiological Mechanisms Examined by Quantitative Assessment of Abnormal Pain and Sensory Perception. Neurosurgery 43, 1103.

France, C.R., Rhudy, J.L., McGlone, S., 2009. Using normalized EMG to define the Nociceptive Flexion Reflex (NFR) threshold: Further evaluation of standardized scoring criteria. Pain 145, 211–218.

Furman, A.J., Meeker, T.J., Rietschel, J.C., Yoo, S., Muthulingam, J., Prokhorenko, M., Keaser, M.L., Goodman, R.N., Mazaheri, A., Seminowicz, D.A., 2018. Cerebral peak alpha frequency predicts individual differences in pain sensitivity. NeuroImage 167, 203–210. https://doi.org/10.1016/j.neuroimage.2017.11.042.

Furman, A.J., Prokhorenko, M., Keaser, M.L., Zhang, J., Chen, S., Mazaheri, A., Seminowicz, D.A., 2020. Sensorimotor Peak Alpha Frequency Is a Reliable Biomarker of Prolonged Pain Sensitivity. Cereb. Cortex 30, 6069–6082. https://doi.org/10.1093/cercor/bhaa124.

Furman, A.J., Thapa, T., Summers, S.J., Cavaleri, R., Fogarty, J.S., Steiner, G.Z., Schabrun, S.M., Seminowicz, D.A., 2019. Cerebral peak alpha frequency reflects average pain severity in a human model of sustained, musculoskeletal pain. J. Neurophysiol. 122, 1784–1793. https://doi.org/10.1152/jn.00279.2019.

Gaskin, D.J., Richard, P., 2012. The Economic Costs of Pain in the United States. J. Pain 13, 715–724. https://doi.org/10.1016/j.jpain.2012.03.009.

Goffaux, P., Redmond, W.J., Rainville, P., Marchand, S., 2007. Pain 130, 137.

Goldberg, D.S., McGee, S.J., 2011. Pain as a global public health priority. BMC Public Health 11, 770. https://doi.org/10.1186/1471-2458-11-770.

Grandy, T.H., Werkle-Bergner, M., Chicherio, C., Lövdén, M., Schmiedek, F., Lindenberger, U., 2013a. Individual alpha peak frequency is related to latent factors of general cognitive abilities. NeuroImage 79, 10–18. https://doi.org/10.1016/j.neuroimage.2013.04.059.

Grandy, T.H., Werkle-Bergner, M., Chicherio, C., Schmiedek, F., Lövdén, M., Lindenberger, U., 2013b. Peak individual alpha frequency qualifies as a stable neurophysiological trait marker in healthy younger and older adults. Psychophysiology 50, 570–582. https://doi.org/10.1111/psyp.12043.

Granovsky, Y., Anand, P., Nakae, A., Nascimento, O., Smith, B., Sprecher, E., Valls-Solé, J., 2016. Normative data for Aδ contact heat evoked potentials in adult population: a multicenter study. Pain 157, 1156–1163.

Hellman, N., Kuhn, B.L., Lannon, E.W., Payne, M.F., Sturycz, C.A., Palit, S., Shadlow, J. O., Rhudy, J.L., 2018. Emotional Modulation of Pain and Spinal Nociception in Sexual Assault Survivors. Psychosom, Med.

Ho, R.L.M., Park, J., Wang, W., Thomas, J.S., Cruz-Almeida, Y., Coombes, S.A., 2024. Lower individual alpha frequency in individuals with chronic low back pain and fear of movement. PAIN 165, 1033. https://doi.org/10.1097/j.pain.0000000000003098.

Huber, F.A., Toledo, T.A., Newsom, G., Rhudy, J.L., 2022. The relationship between sleep quality and emotional modulation of spinal, supraspinal, and perceptual measures of pain. Biol. Psychol. 171, 108352. https://doi.org/10.1016/j.biopsycho.2022.108352.

Jansen, B.H., Rit, V.G., 1995. Electroencephalogram and visual evoked potential generation in a mathematical model of coupled cortical columns. Biol. Cybern. 73, 357–366. https://doi.org/10.1007/BF00199471.

Kenntner-Mabiala, R., Pauli, P., 2005. Affective modulation of brain potentials to painful and nonpainful stimuli. Psychophysiology 42, 559–567.

Kenntner-Mabiala, R., Weyers, P., Pauli, P., 2007. Independent effects of emotion and attention on sensory and affective pain perception. Cogn. Emot. 21, 1615–1629. https://doi.org/10.1080/02699930701252249.

Klimesch, W., 2018. The frequency architecture of brain and brain body oscillations: an analysis. Eur. J. Neurosci. 48, 2431–2453. https://doi.org/10.1111/ejn.14192.

Klimesch, W., Schimke, H., Pfurtscheller, G., 1993. Alpha frequency, cognitive load and memory performance. Brain Topogr. 5, 241–251. https://doi.org/10.1007/BF01128991.

Kondacs, A., Szabó, M., 1999. Long-term intra-individual variability of the background EEG in normals. Clin. Neurophysiol. 110, 1708–1716. https://doi.org/10.1016/S1388-2457(99)00122-4.

Landmark, T., Romundstad, P., Dale, O., Borchgrevink, P.C., Vatten, L., Kaasa, S., 2013. Chronic pain: One year prevalence and associated characteristics (the HUNT pain study). Scand. J. Pain 4, 182–187. https://doi.org/10.1016/j.sjpain.2013.07.022.

Lang, P.J., Bradley, M.M., Cuthbert, B., 2005. The International Affective Picture System (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-6. University of Florida, Gainesville, FL.
Lautenbacher, S., Rollman, G.B., 1997. Possible deficiencies of pain modulation in fibromyalgia. Clin. J. Pain 13, 189.
Lopes da Silva, F.H., Hoeks, A., Smits, H., Zetterberg, L.H., 1974. Model of brain rhythmic activity. Kybernetik 15, 27–37. https://doi.org/10.1007/BF00270757.
Maixner, W., Fillingim, R., Sigurdsson, A., Kincaid, S., Silva, S., 1998. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: evidence for altered temporal summation of pain. Pain 76, 71–81.
Marcuzzi, A., Chakiath, R.J., Siddall, P.J., Kellow, J.E., Hush, J.M., Jones, M.P., Costa, D. S.J., Wrigley, P.J., 2019. Conditioned Pain Modulation (CPM) is Reduced in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of CPM and the Role of Psychological Factors. J. Clin. Gastroenterol. 53, 399. https://doi.org/10.1097/MCG.0000000000001181.
McLain, N.J., Yani, M.S., Kutch, J.J., 2022. Analytic consistency and neural correlates of peak alpha frequency in the study of pain. J. Neurosci. Methods 368, 109460. https://doi.org/10.1016/j.jneumeth.2021.109460.
Mierau, A., Klimesch, W., Lefebvre, J., 2017. State-dependent alpha peak frequency shifts: Experimental evidence, potential mechanisms and functional implications. Neuroscience 360, 146–154. https://doi.org/10.1016/j.neuroscience.2017.07.037.
Millard, S.K., Furman, A.J., Kerr, A., Seminowicz, D.A., Gao, F., Naidu, B.V., Mazaheri, A., 2022. Predicting postoperative pain in lung cancer patients using preoperative peak alpha frequency. Br. J. Anaesth. 128, e346–e348. https://doi.org/10.1016/j.bja.2022.03.006.
Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc. 53, 695–699.
Oostenveld, R., Fries, P., Maris, E., Schoffelen, J.-M., 2010. FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. Comput. Intell. Neurosci. 2011, e156869. https://doi.org/10.1155/2011/156869.
Pessoa, L., 2010. Emotion and cognition and the amygdala: From "what is it?" to "what's to be done?". Neuropsychologia 48, 3416–3429. https://doi.org/10.1016/j.neuropsychologia.2010.06.038.
Pinto, A.M., Geenen, R., Wager, T.D., Lumley, M.A., Häuser, W., Kosek, E., Ablin, J.N., Amris, K., Branco, J., Buskila, D., Castelhano, J., Castelo-Branco, M., Crofford, L.J., Fitzcharles, M.-A., López-Solà, M., Luís, M., Marques, T.R., Mease, P.J., Palavra, F., Rhudy, J.L., Uddin, L.Q., Castilho, P., Jacobs, J.W.G., da Silva, J.A.P., 2023. Emotion regulation and the salience network: a hypothetical integrative model of fibromyalgia. Nat. Rev. Rheumatol. 19, 44–60. https://doi.org/10.1038/s41584-022-00873-6.
Raghuraman, N., Wang, Y., Schenk, L.A., Furman, A.J., Tricou, C., Seminowicz, D.A., Colloca, L., 2019. Neural and behavioral changes driven by observationally-induced hypoalgesia. Sci. Rep. 9, 19760. https://doi.org/10.1038/s41598-019-56188-2.
Rhudy, J.L., 2016. Emotional Modulation of Pain, in: Neuroscience of Pain, Stress, and Emotion.
Rhudy, J.L., France, C.R., 2007. Defining the nociceptive flexion reflex (NFR) threshold in human participants: A comparison of different scoring criteria. Pain 128, 244–253.
Rhudy, J.L., Huber, F.A., Toledo, T.A., Kell, P.A., Street, E.N., Shadlow, J.O., 2021. Psychosocial and cardiometabolic predictors of chronic pain onset in Native Americans: serial mediation analyses of 2-year prospective data from the Oklahoma Study of Native American Pain Risk. PAIN. https://doi.org/10.1097/j.pain.0000000000002458.
Rhudy, J.L., Lannon, E.W., Kuhn, B.L., Palit, S., Payne, M.F., Sturycz, C.A., Hellman, N., Güereca, Y.M., Toledo, T.A., Huber, F., Demuth, M.J., Hahn, B.J., Chaney, J.M., Shadlow, J.O., 2020. Assessing peripheral fibers, pain sensitivity, central sensitization, and descending inhibition in Native Americans: main findings from the Oklahoma Study of Native American Pain Risk. PAIN 161, 388–404. https://doi.org/10.1097/j.pain.0000000000001715.
Rhudy, J.L., Martin, S.L., Terry, E.L., France, C.R., Bartley, E.J., DelVentura, J.L., Kerr, K. L., 2011. Pain catastrophizing is related to temporal summation of pain, but not temporal summation of the nociceptive flexion reflex. Pain 152, 794–801.
Rhudy, J.L., Williams, A.E., 2005. Gender differences in pain: Do emotions play a role? Gend. Med. 2, 208–226.
Roy, M., 2015. Cerebral and Spinal Modulation of Pain by Emotions and Attention. In: Pickering, G., Gibson, S. (Eds.), Pain, Emotion and Cognition: A Complex Nexus. Springer International Publishing, Cham, pp. 35–52. https://doi.org/10.1007/978-3-319-12033-1_3.
Roy, M., Piche, M., Chen, J.-I., Peretz, I., Rainville, P., 2009. Cerebral and spinal modulation of pain by emotions. PNAS Proc. Natl. Acad. Sci. u. s. Am. 106, 20900–20905. https://doi.org/10.1073/pnas.0904706106.
Sandrini, G., Rossi, P., Milanov, I., Serrao, M., Cecchini, A.P., Nappi, G., 2006. Abnormal modulatory influence of diffuse noxious inhibitory controls in migraine and chronic tension-type headache patients. Cephalalgia 26, 782.
Sarnthein, J., Stern, J., Aufenberg, C., Rousson, V., Jeanmonod, D., 2006. Increased EEG power and slowed dominant frequency in patients with neurogenic pain. Brain 129, 55–64. https://doi.org/10.1093/brain/awh631.
Seminowicz, D.A., Thapa, T., Furman, A.J., Summers, S.J., Cavaleri, R., Fogarty, J.S., Steiner, G.Z., Schabrun, S.M., 2018. Slow peak alpha frequency and corticomotor depression linked to high pain susceptibility in transition to sustained pain. bioRxiv 278598. https://doi.org/10.1101/278598.
Simis, M., Pacheco-Barrios, K., Uygur-Kucukseymen, E., Castelo-Branco, L., Battistella, L. R., Fregni, F., 2022. Specific Electroencephalographic Signatures for Pain and Descending Pain Inhibitory System in Spinal Cord Injury. Pain Med. 23, 955–964. https://doi.org/10.1093/pm/pnab124.
Smith, B.H., Elliott, A.M., Chambers, W.A., Smith, W.C., Hannaford, P.C., Penny, K., 2001. The impact of chronic pain in the community. Fam. Pract. 18, 292–299. https://doi.org/10.1093/fampra/18.3.292.
Tan, L.L., Kuner, R., 2021. Neocortical circuits in pain and pain relief. Nat. Rev. Neurosci. 22, 458–471. https://doi.org/10.1038/s41583-021-00468-2.
Teixeira, P.E.P., Pacheco-Barrios, K., Uygur-Kucukseymen, E., Machado, R.M., Balbuena-Pareja, A., Giannoni-Luza, S., Luna-Cuadros, M.A., Cardenas-Rojas, A., Gonzalez-Mego, P., Mejia-Pando, P.F., Wagner, T., Dipietro, L., Fregni, F., 2022. Electroencephalography Signatures for Conditioned Pain Modulation and Pain Perception in Nonspecific Chronic Low Back Pain—An Exploratory Study. Pain Med. 23, 558–570. https://doi.org/10.1093/pm/pnab293.
Terry, E.L., France, C.R., Bartley, E.J., DelVentura, J.L., Kerr, K.L., Vincent, A.L., Rhudy, J.L., 2011. Standardizing procedures to study sensitization of human spinal nociceptive processes: Comparing parameters for temporal summation of the nociceptive flexion reflex (TS-NFR). Int. J. Psychophysiol. 81, 263–274.
Terry, E.L., Thompson, K.A., Rhudy, J.L., 2014. Experimental reduction of pain catastrophizing reduces pain perception and temporal summation of the nociceptive flexion reflex (NFR). Presented at the International Association for the Study of Pain, 15th World Congress on Pain.
Toledo, T.A., Vore, C.N., Huber, F.A., Rhudy, J.L., 2024. The effect of emotion regulation on the emotional modulation of pain and nociceptive flexion reflex. PAIN 165, 1266. https://doi.org/10.1097/j.pain.0000000000003127.
Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M.I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N.B., First, M.B., Giamberardino, M.A., Kaasa, S., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., Smith, B.H., Svensson, P., Vlaeyen, J.W.S., Wang, S.-J.,, 2015. A classification of chronic pain for ICD-11. Pain 156, 1003–1007. https://doi.org/10.1097/j.pain.0000000000000160.
Tunks, E.R., Crook, J., Weir, R., 2008. Epidemiology of Chronic Pain with Psychological Comorbidity: Prevalence, Risk, Course, and Prognosis. Can. J. Psychiatry 53, 224–234. https://doi.org/10.1177/070674370805300403.
van Hecke, O., Torrance, N., Smith, B.H., 2013. Chronic pain epidemiology and its clinical relevance. Br. J. Anaesth. 111, 13–18. https://doi.org/10.1093/bja/aet123.
Von Korff, M., DeBar, L.L., Krebs, E.E., Kerns, R.D., Deyo, R.A., Keefe, F.J., 2020. Graded chronic pain scale revised: mild, bothersome, and high impact chronic pain. Pain 161, 651–661. https://doi.org/10.1097/j.pain.0000000000001758.
Williams, A.E., Miller, M.M., Bartley, E.J., McCabe, K.M., Kerr, K.L., Rhudy, J.L., 2019. Impairment of Inhibition of Trigeminal Nociception via Conditioned Pain Modulation in Persons with Migraine Headaches. Pain Med. 20, 1600–1610. https://doi.org/10.1093/pm/pny305.
Woolf, C.J., 1996. Windup and central sensitization are not equivalent. Pain 66, 105–108.
Yarnitsky, D., 2015. Role of endogenous pain modulation in chronic pain mechanisms and treatment. Pain 156, S24–S31.
Yarnitsky, D., Crispel, Y., Eisenberg, E., Granovsky, Y., Ben-Nun, A., Sprecher, E., Best, L.-A., Granot, M., 2008. Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. Pain 138, 22–28. https://doi.org/10.1016/j.pain.2007.10.033.
Yarnitsky, D., Granot, M., Granovsky, Y., 2014. Pain modulation profile and pain therapy: between pro-and antinociception. Pain 155, 663–665.
Zajacova, A., Grol-Prokopczyk, H., Fillingim, R., 2022. Beyond black vs white: racial/ethnic disparities in chronic pain including Hispanic, Asian, Native American, and multiracial US adults. PAIN 163, 1688. https://doi.org/10.1097/j.pain.0000000000002574.