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RESEARCH ARTICLE | *Sensory Processing*

Cerebral peak alpha frequency reflects average pain severity in a human model of sustained, musculoskeletal pain

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Furman AJ, Thapa T, Summers SJ, Cavaleri R, Fogarty JS, Steiner GZ, Schabrun SM, Seminowicz DA. Cerebral peak alpha frequency reflects average pain severity in a human model of sustained, musculoskeletal pain. *J Neurophysiol* 122: 1784–1793, 2019. First published August 7, 2019; doi:10.1152/jn.00279.2019.—Heightened pain sensitivity, the amount of pain experienced in response to a noxious event, is a known risk factor for development of chronic pain. We have previously reported that pain-free, sensorimotor peak alpha frequency (PAF) is a reliable biomarker of pain sensitivity for thermal, prolonged pains lasting tens of minutes. To test whether PAF can provide information about pain sensitivity occurring over clinically relevant timescales (i.e., weeks), EEG was recorded before and while participants experienced a long-lasting pain model, repeated intramuscular injection of nerve growth factor (NGF), that produces progressively developing muscle pain for up to 21 days. We demonstrate that pain-free, sensorimotor PAF is negatively correlated with NGF pain sensitivity; increasingly slower PAF is associated with increasingly greater pain sensitivity. Furthermore, PAF remained stable following NGF injection, indicating that the presence of NGF pain for multiple weeks is not sufficient to induce the PAF slowing reported in chronic pain. In total, our results demonstrate that slower pain-free, sensorimotor PAF is associated with heightened sensitivity to a long-lasting musculoskeletal pain and also suggest that the apparent slowing of PAF in chronic pain may reflect predisease pain sensitivity.

NEW & NOTEWORTHY Pain sensitivity, the intensity of pain experienced after injury, has been identified as an important risk factor in the development of chronic pain. Biomarkers of pain sensitivity have the potential to ease chronic pain burdens by preventing disease emergence. In the current study, we demonstrate that the speed of pain-free, sensorimotor peak alpha frequency recorded during resting-state EEG predicts pain sensitivity to a clinically-relevant, human model of prolonged pain that persists for weeks.

biomarker; EEG; nerve growth factor; pain sensitivity

INTRODUCTION

Chronic pain is a pervasive and debilitating disease that is often frustratingly treatment resistant. One avenue to overcome this treatment resistance is to prevent chronic pain incidence by identifying, and prescribing interventions to, those individuals at high risk for its development. Unfortunately, currently available biomarkers of chronic pain risk are either reliant on subjective report or apply to situations where pain is already present. Behavioral predictors of pain sensitivity, such as reported anxiety before surgery (i.e., Masselin-Dubois et al. 2013) or psychophysical tests of descending pain modulation (i.e., Yarnitsky et al. 2008), have promise but may be difficult to collect in cases where the patient cannot provide feedback (i.e., patient is nonverbal). Similarly, existing neurophysiological markers of chronic pain risk, such as functional and structural changes that occur to the brain in the presence of acute pain (Hashmi et al. 2013; Mansour et al. 2013), may be available too late in the transition to chronic pain to provide time for intervention. As a result, biomarkers that can predict chronic pain risk before pain onset and without requiring patient feedback are needed.

We have previously hypothesized that pain-free, electroencephalographic (EEG) sensorimotor peak alpha frequency (PAF), the frequency band within the 8- to 12-Hz range displaying maximal power, is a biomarker of prolonged pain sensitivity. Pain-free, sensorimotor PAF is negatively related to the intensity of a prolonged pain, capsaicin heat pain, occurring 45 min later (Furman et al. 2018): namely, slower PAF is associated with greater pain intensity. This relationship between pain-free PAF and prolonged pain sensitivity is reliable across multiple testing sessions, generalizes to a second test of prolonged pain, and can be used to make predictions about pain sensitivity across short (i.e., minutes) and long (i.e., weeks) timescales (Furman et al. 2019).

To date, the relationship between pain-free, sensorimotor PAF and prolonged pain has only been explored with painful thermal tests that last brief periods of time (i.e., minutes to hours; Furman et al. 2018; Nir et al. 2010). Pain in the clinic, however, is not restricted to a single type of pain and occurs

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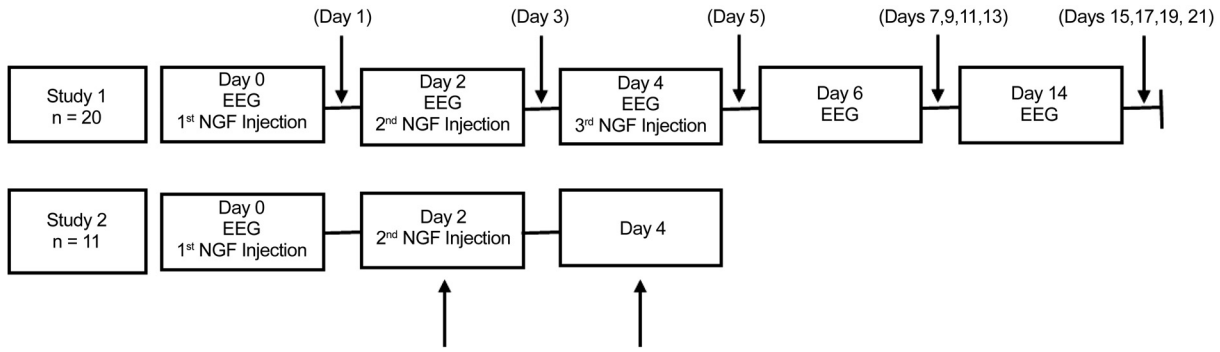

Fig. 1. Timeline of experimental events for both studies. EEG was always collected before nerve growth factor (NGF) injection. Arrows and associated dates indicate time points where pain ratings were collected. For *Study 1*, pain ratings were collected for 21 days on every other day following the first NGF injection (i.e., *days 1*, *3*, ..., *21*). For *Study 2*, pain ratings were collected on *days 2* and *4*.

over much longer periods of time. As such, determining whether pain-free, sensorimotor PAF is relevant for temporally sustained, nonthermal pain is a crucial step in evaluating its potential as a pain sensitivity biomarker.

In this study we use a novel human pain model, repeated intramuscular injection of nerve growth factor (NGF), to induce a progressively developing muscle pain that lasts for up to 21 days (Hayashi et al. 2013; Schabrun et al. 2016). By recording sensorimotor PAF before NGF injection, we were able to test whether pain-free PAF could predict the intensity of musculoskeletal pain occurring over a clinically relevant period of time. We elected to focus on sensorimotor regions given our previous findings (Furman et al. 2018). Additionally, we collected sensorimotor PAF after NGF injection to determine whether PAF is altered following the onset of pain. Chronic pain patients display abnormally slow PAF (e.g., Kim et al. 2019; Sarnthein et al. 2006), and this slowing has been hypothesized to be a result of disease development and persistence (i.e., de Vries et al. 2013; Llinás et al. 1999). By recording sensorimotor PAF before and after NGF injection, we were able to directly test whether the presence of weeks-long NGF pain is sufficient to induce PAF slowing. We demonstrate that pain-free, sensorimotor PAF is negatively associated with average NGF pain and that PAF slowing is not a necessary consequence of NGF pain. In sum, our data demonstrate that pain-free, sensorimotor PAF is a promising metric for predicting clinically relevant pain sensitivity.

MATERIALS AND METHODS

Participants

Thirty-one healthy, right-handed individuals participated. Twenty individuals participated in *Study 1* (11 men, mean age = 23.20 yr, SD = 4.30), and 11 individuals participated in *Study 2* (5 men, mean age = 24.30 yr, SD = 6.90). Handedness was assessed using the Edinburgh handedness questionnaire (Oldfield 1971). Participants with a history of neurological, psychiatric, musculoskeletal, or upper limb conditions were excluded, and a transcranial magnetic stimulation (TMS) safety screen was completed before study enrollment (Keel et al. 2001). All participants provided written informed consent consistent with the Declaration of Helsinki. Experimental procedures were approved by the institutional ethics committee (H10184) at Western Sydney University.

Procedure

We used available data from two studies involving the same pain model and resting-state EEG acquired at baseline. An overview of procedures for *Study 1* and *Study 2* is shown in Fig. 1.

Study 1. Participants visited the laboratory on five occasions: *days 0*, *2*, *4*, *6*, and *14*. *Day 0* outcome measures included eyes-closed resting-state EEG, pressure pain thresholds, TMS-derived motor cortical maps, and a number of questionnaires related to affect and pain (i.e., Pain Catastrophizing Scale; Sullivan et al. 1995); data regarding TMS maps and questionnaires is not reported in this article. The time of the day in which testing occurred varied between subjects but was held constant within subject across the study. EEG recordings lasted a total of 3 min, during which participants were instructed to sit quietly with their eyes closed. EEG, pressure pain thresholds, and motor cortical maps were also collected at the beginning of visits occurring on *days 2*, *4*, *6*, and *14*. NGF was injected into the belly of the right extensor carpi radialis brevis (ECRB) muscle immediately following the collection of outcome measures on *days 0*, *2*, and *4*. Electronic pain diaries (described below) were administered on each alternative day from *day 1* to *day 21*.

Study 2. Participants visited the laboratory on three occasions: *days 0*, *2*, and *4*. Collected outcome measures were identical to those performed on *days 0*, *2*, and *4* in *Study 1* except EEG (3 min of eyes-closed resting state) was only collected on *day 0*. NGF was injected into the belly of the right ECRB immediately following collection of all outcome measures on *days 0* and *2*. Electronic pain diaries were administered on *days 0*, *2*, and *4*. The length of *Study 2* was shortened because of the presence of an intervention occurring after *day 4*. After *day 4*, a repetitive TMS (primary motor cortex, 10 Hz, 1,200 stimuli) intervention was applied for 5 consecutive days to modulate pain. Given that data collection for the current study was completed well before intervention, we expect there to be minimal impact of this intervention on current study aims. The results of this intervention are published elsewhere (Cavaleri et al. 2019; Summers et al. 2019).

Although *Studies 1* and *2* differed in their protocols, we include data from both, since the relationship between pain-free PAF and NGF pain sensitivity should be stable regardless of these differences.

NGF-Induced Muscle Pain

NGF is an endogenous neuromodulator that is essential for the development and maintenance of the nervous system (Lewin et al. 1992). Intramuscular injection of NGF in humans has been shown to induce progressively developing muscle pain that is sustained for up to 21 days and is accompanied by hyperalgesia, movement-evoked pain, and reduced function (Bergin et al. 2015). After the skin was cleaned with alcohol, a dose of 5 μg (0.2 mL) of sterile, recombinant human NGF was given as a bolus injection in the ECRB muscle belly

using a 1-mL syringe with a 27-gauge disposable needle (Schabrun et al. 2016).

Electronic Pain Diary

Pain was assessed using an 11-point numerical rating scale anchored with "no pain" at 0 and "worst imaginable pain" at 10. Pain diary information was collected through an internet website. Participants were given midday reminders to complete diaries and were allowed to submit ratings at any time on the queried day.

EEG

EEG data were recorded continuously from direct current (DC) to 70 Hz from 19 scalp sites (Fp1, Fp2, F3, Fz, F4, F7, F8, C3, Cz, C4, P3, Pz, P4, P7, P8, T7, T8, O1, and O2) and M2 with an electrode cap using sintered Ag-AgCl electrodes. M1 was used as the active reference, and the cap was grounded by an electrode located between AF3 and AF4. Electrooculogram (EOG) was recorded using sintered Ag-AgCl electrodes placed 2 cm above and below the left eye for vertical movements and on the outer canthus of each eye for horizontal movements. Data were acquired at 1,000 Hz from DC to 70 Hz with the default gain setting and a 50-Hz notch filter using a Neuroscan SynAmps 2 digital signal-processing system and Neuroscan 4.3.1 Acquire software. Impedances were <5 kΩ for cap, EOG, and reference electrodes.

Data Processing

The EEG data of interest were the resting-state EEG sessions collected at the beginning of *days 0*, *2*, *4*, *6*, and *14* in *Study 1* and at the beginning of *day 0* in *Study 2*. EEG collected at *day 0* represents a pain-free estimate of activity. Initial processing of EEG data was performed using EEGLAB 13.6.5b (Delorme and Makeig 2004). Processing began by downsampling the data to 500 Hz and filtering between 2 and 100 Hz using a linear finite impulse response bandpass filter. Principal components analysis was performed, and components with spatial topographies and time series resembling blinks and/or saccades were removed from the data. Channel data were then visually inspected, and overtly noisy channels were removed from further analysis. Removed channels were not interpolated. On average, very few channels were removed per subject: 0.52 (range: 0–3), 0.30 (range: 0–2), 0.45 (range: 0–2), 0.15 (range: 0–1), and 0.25 (range: 0–2) channels were removed for *day 0*, *2*, *4*, *6*, and *14* data sets, respectively. Data from remaining channels were re-referenced to the common average reference (i.e., mean across all remaining channels).

For channel-level analyses, we focused on channels that most strongly contributed to the sensorimotor component from our first study on sensorimotor PAF (Furman et al. 2018). Thus the sensorimotor region of interest (ROI) included only the C3, Cz, and C4 channels. Across all data sets, no participant had one of these three channels rejected due to noise.

Quantification of Sensorimotor PAF

The frequency decomposition of the sensorimotor ROI data was performed using routines in FieldTrip (Oostenveld et al. 2011). The data for each resting-state session were segmented into 5-s epochs. Next, power spectral density in the 2- to 50-Hz range was derived for each epoch in 0.2-Hz bins using the default settings in the "ft_freqanalysis_mtmfft" function with a Hanning taper to reduce any edge artifacts (e.g., Mazaheri et al. 2014).

PAF for each 5-s epoch at every sensor was estimated using a center of gravity (CoG) method (Klimesch et al. 1993). We defined CoG as follows:

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

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. This equation returns the frequency bin (in Hz) where the center of spectral power is located in the 9- to 11-Hz range. From our previous work, we have determined that this narrow analysis band reduces the influence of $1/f$ EEG noise on the estimation of PAF (Furman et al. 2018). Epoch-level PAF estimates were averaged to yield a single mean PAF estimate for each channel, and mean estimates from sensorimotor ROI sensors (C3, Cz, C4) were further averaged to yield a grand mean sensorimotor PAF estimate for each participant at each visit.

Statistical Analyses

All analyses were performed using custom scripts implemented in the MATLAB environment (version R2013A). Statistical tests were conducted in MATLAB or SPSS (version 25).

We first sought to determine the periods of time when pain was present following NGF injection. For each study and on each day, pain scores were compared against 0 using one-sample t tests. Given that detection of pain on each diary day was an a priori analysis of interest, we elected not to apply corrections for multiple comparisons in this instance.

To determine whether pain-free, sensorimotor PAF is associated with pain sensitivity, we first determined the maximum and average pain experienced across the days in which pain was statistically present for each study (*days 1–17* for *Study 1*; *days 2–4* for *Study 2*). *Day 0* pain-free, sensorimotor PAF was then related to the maximum and average pain using separate Spearman correlations. To examine the unique relationship of sensorimotor PAF to each pain metric, we performed a pair of partial correlations between PAF and one pain metric while controlling for the influence of the other pain metric.

To investigate how PAF speed is associated with NGF pain over time, we median-split our data according to *day 0* sensorimotor PAF to yield "slow" and "fast" PAF groups. Pain scores were then analyzed using a linear mixed model with subjects as random effects (intercept modeled) and group (fast vs. slow), day (repeated measures; *days 1–17*), and the group $\times$ day interaction as fixed effects.

Next, we investigated whether sensorimotor PAF changes in response to the presence of NGF-induced pain. Sensorimotor PAF estimates were submitted to a linear mixed-effects model with subjects as random effects (intercept included) and day (*0*, *2*, *4*, *6*, and *14*) as a fixed effect. We further investigated the effect of day using a planned, a priori linear contrast comparing *day 0* PAF with all remaining post-NGF PAF estimates. In cases where we could not find a significant effect, we tested for the likelihood of the null hypothesis using Bayes factor analysis (Rouder et al. 2009). Bayes factor analysis provides a method for assessing the relative evidence in favor of either the null or alternative hypothesis. A Bayes factor <0.33 or >3 is taken as strong evidence in favor of the null and alternative hypotheses, respectively; Bayes factor scores in between these values are considered to provide no evidence in favor of either hypothesis.

To further test the stability of sensorimotor PAF, we performed Spearman correlations between all possible pairs of PAF estimates. Corrections for multiple tests (10 possible pairs) were made according to the Bonferroni method, yielding a significance threshold of $P = 0.005$. Additionally, we investigated the reliability of sensorimotor PAF using Cronbach's α.

To test whether changes in sensorimotor PAF after NGF injection (ΔPAF) are related to average pain sensitivity, we first calculated ΔPAF by subtracting pain-free, sensorimotor PAF from the average, post-NGF sensorimotor PAF recorded on *days 2*, *4*, *6*, and *14*. We

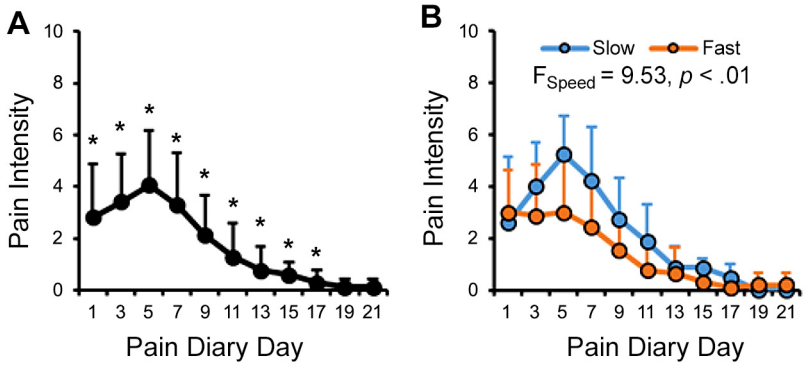

Fig. 2. Peak alpha frequency (PAF) affects the magnitude, but not the pattern, of pain development. *A*: daily diary pain ratings for *Study 1*. *$P < 0.05$, time points where pain was found to be significantly greater than 0. *B*: *cohort 1* median split based on the speed of pain-free, sensorimotor PAF (F_{speed}) reveals that "slow" PAF individuals experience greater pain at almost all time points.

then performed a Spearman correlation between ΔPAF and average pain.

RESULTS

Three participants were removed from *Study 1* for failing to develop pain in response to NGF injection. Two of these participants did not report pain in any diary entries, whereas a third only reported pain on a single diary entry. All of the remaining 17 participants in *Study 1* reported pain in at least three pain diary entries (mean = 6 pain days, SD = 3.15). One participant was removed from *Study 2* after developing extreme pain (average rating = 9), leaving 10 subjects in the *Study 2* analyses. This value was 2.85 standard deviations above the average pain calculated from the comparable time frames of *days 3–7* in *Study 1* and *days 2* and *4* in *Study 2* (group average = 3.48, SD = 1.93, range = 0.67–7.00).

For *Study 1*, pain was present on *days 1–17*, with the highest levels of pain reported on *day 5* [mean = 4.06, SD = 2.11, $t_{(16)} = 7.95$, $P < 0.01$], and ceased on *day 19* [mean = 0.12, SD = 0.33, $t_{(16)} = 1.46$, $P = 0.16$; Fig. 2*A*]. For *Study 2*, pain was present on both days that pain ratings were recorded [*day 2*: mean = 2.72, SD = 2.12, $t_{(9)} = 4.07$, $P < 0.01$; *day 4*: mean = 2.79, SD = 1.48, $t_{(9)} = 5.95$, $P < 0.01$; see APPENDIX, Fig. A1*A*).

Pain-Free Sensorimotor PAF is Associated with Average Experienced Pain

We first assessed whether pain-free, sensorimotor PAF is related to NGF pain sensitivity by computing the maximum and average pain experienced over *days 1–17* for *Study 1* and *days 2–4* for *Study 2*. Across both studies, *day 0* pain-free sensorimotor PAF was significantly correlated with average pain [$\rho = -0.47$ (*Study 1* $\rho = -0.39$; *Study 2* $\rho = -0.69$), $P = 0.01$; Fig. 3*B*]. We could not detect any relationship between PAF and maximum pain (see APPENDIX, Fig. A2). The correlation between *day 0* pain-free, sensorimotor PAF and average pain did not change when we only included *days 3*, *5*, and *7*, for *Study 1* to best match the time frame available for *Study 2* [$\rho = -0.40$ (*Study 1* $\rho = -0.35$; *Study 2* $\rho = -0.69$), $P = 0.04$]. This relationship was observed at nearly all EEG channels (see APPENDIX, Fig. A3*A*).

Average pain scores were not correlated with pain-free, sensorimotor PAF power (i.e., the estimated power at the PAF) [$\rho < 0.01$ (*Study 1* $\rho = 0.16$; *Study 2* $\rho = -0.12$), $P > 0.99$]. Thus it appears that the speed of the alpha rhythm before NGF injection is more relevant than power for predicting pain sensitivity.

"Slow" Sensorimotor PAF Individuals Consistently Experience More NGF Pain Over Time

We separated *Study 1* participants into "fast" and "slow" PAF groups on the basis of a median split of pain-free, sensorimotor PAF. This yielded 8 slow PAF individuals (mean = 9.79, SD = 0.16, range = 9.50–9.98) and 9 fast PAF individuals (mean = 10.15, SD = 0.12, range = 9.98–10.31).

A linear mixed model with subjects as random effects and day (repeated measures; 1, 3, 5, 7, 9, 11, 13, 15, and 17), speed (fast vs. slow), and the day × speed interaction as fixed effects revealed a significant effect of day [$F_{(8,22.99)} = 27.78$, $P < 0.01$] and a significant effect of speed [$F_{(1,38.48)} = 9.53$, $P < 0.01$], but no significant effect of day × speed [$F_{(8,22.98)} = 1.58$, $P = 0.19$]. As can be seen in Fig. 2*B*, the significant effect of speed reflects the fact that pain scores were almost universally greater for slow PAF individuals on each day following NGF injection. Failure to find a significant day × speed interaction reinforces the idea that PAF distinguishes individuals with high and low pain sensitivity consistently over time.

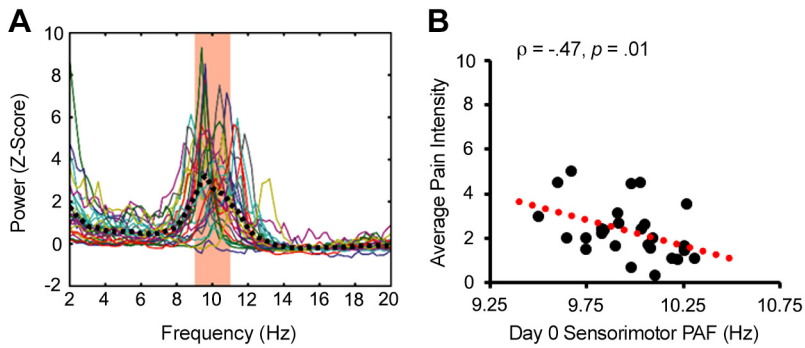

Fig. 3. Pain-free, sensorimotor peak alpha frequency (PAF) is correlated with average NGF pain. *A*: spectra collected from all participants on *day 0*. Colored lines reflect individual participants, and black dashed line reflects the average spectra across all participants. Red zone reflects the area used to calculate PAF according to the center of gravity method. The alpha peak for the group average, and for most participants, falls within this zone. *B*: *day 0* pain-free, sensorimotor PAF was negatively correlated with the average pain intensity reported from *days 1–17*. Red dotted line reflects the linear regression line of best fit.

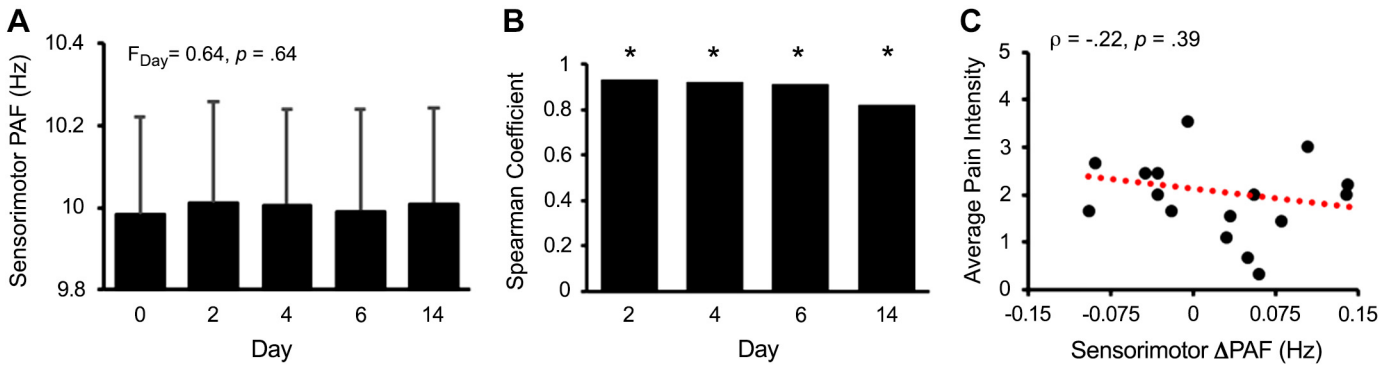

Fig. 4. Sensorimotor peak alpha frequency (PAF) remains stable after nerve growth factor (NGF) injection. *A*: mean (SD) of sensorimotor PAF estimates at each testing day (F_{Day}). *B*: *Study 1* sensorimotor PAF collected at *day 0* is significantly correlated with sensorimotor PAF collected at all other time points. *$P < 0.005$. *C*: shifts in sensorimotor PAF (ΔPAF; average post-NGF PAF – *day 0* PAF) are not related to average NGF pain. Red dotted line reflects the linear regression line of best fit.

A median split applied to *Study 2* participants produced slow ($n = 5$ participants, mean = 9.75, SD = 0.13, range: 9.60–9.91) and fast groups ($n = 5$ participants, mean = 10.11, SD = 0.09, range: 10.02–10.22) characteristically similar to what we found for *Study 1*. Slow PAF individuals from *Study 2* reported higher pain only at *day 2*, however (see APPENDIX, Fig. A1*B*).

Sensorimotor PAF Does Not Slow After NGF Injection

In contrast to our expectation that NGF injection would alter sensorimotor PAF, a linear mixed model with subjects as random effects and day (*0*, *2*, *4*, *6*, *14*) as fixed effects revealed no significant main effect of day [$F_{(1,4)} = 0.64$, $P = 0.64$; Fig. 4*A*]. Similarly, a planned contrast comparing *day 0* PAF (mean = 9.98, SD = 0.23) with all post-NGF PAF estimates (mean = 10.00, SD = 0.23) was not significant ($t = 1.27$, $P = 0.22$). Finally, Bayesian analysis comparing *day 0* PAF with average post-NGF PAF supported the null hypothesis of no difference (Bayes factor = 0.01).

As an alternative method to confirm the stability of PAF across the experiment, correlations for all possible day pairs reached significance with no ρ value falling below 0.81 (see Fig. 4*B* for all *day 0* correlations). In agreement with the idea that PAF is stable over time, PAF estimates were nearly perfectly reliable with a Cronbach's $\alpha = 0.98$. In total, these results demonstrate that despite the presence of pain, PAF is incredibly stable over the 2 weeks in which EEG was recorded.

Sensorimotor PAF Shifts Are Unrelated to NGF Pain Sensitivity

The preceding results indicate that slowing of sensorimotor PAF does not necessarily occur during an extended period of pain. Instead, it is equally likely that an individual's PAF will speed up ($n = 9$) or slow down ($n = 8$) during NGF exposure. This seems to rule against the idea that PAF shifts are markers for the presence of pain. An alternative interpretation is that shifts in PAF represent processes that serve to modify the intensity of the pain experience (i.e., Furman et al. 2018). To test this idea, we first calculated the difference between the average post-NGF PAF and *day 0* pain-free PAF (ΔPAF; positive value = faster PAF after NGF). As in our earlier work, pain-free PAF and ΔPAF were not correlated ($\rho = -0.17$, $P = 0.52$), suggesting that ΔPAF may exert unique influence on pain sensitivity. However, unlike our previous study, we could not find a relationship between ΔPAF and average pain ($\rho = -0.22$, $P = 0.39$; Fig. 4*C*). This finding was not restricted to our sensorimotor ROI, however, since the relationship between ΔPAF and pain was relatively small at all channels (see APPENDIX, Fig. A3*C*).

DISCUSSION

Musculoskeletal pain disorders are particularly treatment resistant, representing one of the largest contributors to global years lived with disability (Vos et al. 2016). One possible means of combatting this treatment resistance is to deploy interventions to those at risk for developing chronic musculoskeletal pain. This requires a means for identifying high-risk individuals in the first place.

In the current study, we set out to determine whether pain-free, sensorimotor PAF could predict individual sensitivity to a novel model of prolonged musculoskeletal pain, NGF injection (Hayashi et al. 2013). Indeed, we found that pain-free, sensorimotor PAF could predict the intensity of NGF pain; increasingly slower pain-free, sensorimotor PAF was associated with increasingly greater NGF pain at multiple time points. More specifically, our results demonstrate that pain-free, sensorimotor PAF is related to the average, but not the maximum, NGF pain experienced over a two-and-a-half-week period. This suggests that PAF provides relevant information about the entire time course of pain. In line with this interpretation, our median-split analysis demonstrated that slow PAF individuals experience greater pain than fast PAF individuals at almost all post-NGF time points. It is worth pointing out that the pain time course pattern did not vary between the slow and fast PAF groups, indicating that PAF modulates the overall level of pain but not how it progresses.

The relationship between PAF and NGF pain was not restricted to our sensorimotor ROI but could be observed at almost all scalp EEG sensors. Although we elected to focus on the sensorimotor region given our previous results, it is now becoming clear that our findings are not restricted to this region. It therefore seems unlikely that PAF's influence on pain sensitivity is a purely sensorimotor process. The widespread nature of our results may reflect the fact that PAF is controlled by a central generator, such as the thalamus (Lörincz et al. 2008), that interacts with multiple cortical sites. Although a common hypothesis is that the speed of PAF modulates perception by altering inhibitory and excitatory

cycle timing in primary sensory cortices (i.e., Samaha and Postle 2015), little is known about the topology or relevance of PAF speed across the brain except that it slows in the posterior-to-anterior direction (Chiang et al. 2008). Thus reference to sensorimotor PAF in this article should be taken as an indicator of where PAF was explicitly measured as opposed to a declaration of a particular process.

The consistent association between pain sensitivity and PAF across EEG channels likely suggests that cognitive processes linked to widespread cortical networks, such as attention, play an important role in mediating this relationship. Processes such as top-down attention seem well positioned to impact pain sensitivity given that self-reported attention to pain is a strong predictor of pain sensitivity (Baum et al. 2011) and directing attention away from pain and toward a cognitive task can reduce pain perception and pain-related brain activity (i.e., Malloy and Milling 2010; Seminowicz et al. 2004). Along similar lines, factors that affect both attentional control and pain sensitivity, such as sleep quantity (Lim and Dinges 2008; Onen et al. 2001), may be useful in understanding how individual differences in PAF arise in the first place. Ultimately, use of multimodal imaging, such as simultaneous EEG-functional MRI, alongside relevant questionnaires will be needed to resolve the identity of the PAF-related processes involved in determining pain sensitivity.

The current work extends prior work on PAF that has focused exclusively on relatively short-duration thermal pain (Furman et al. 2018). The current findings provide important evidence that PAF's relationship to pain extends to musculoskeletal pain and, perhaps more importantly, to a duration of pain (weeks) that far exceeds the length of tests used previously (minutes/hours). This provides important evidence that PAF has real potential for predicting pain sensitivity to noxious events that occur over clinically relevant timescales. Postsurgical pain at these timescales has been shown to be relevant for determining chronic pain vulnerability (e.g., Katz et al. 1996), with one recent study demonstrating a strong, positive association between the magnitude of pain reported over the 10 days immediately following invasive surgery and pain persistence (Hah et al. 2019). Furthermore, the collection of pain ratings outside of the laboratory (i.e., by electronic diary) provides the best evidence to date that PAF can reflect real-world pain and is not confounded by factors associated with laboratory collection of pain ratings (i.e., participant alertness). It is also notable that an upcoming TMS intervention in *Study 2*, which could have affected pain ratings through expectation of analgesia (Goffaux et al. 2009), did not appear to impact the relationship between PAF and NGF pain. Investigating if and how participant expectation impacts the PAF-pain sensitivity relationship is an important future direction because expectations appear to play a critical role in the variability of clinical pain outcomes (e.g., Kalauokalani et al. 2001).

We additionally demonstrate that sensorimotor PAF slowing does not necessarily occur as a result of a long-lasting pain experience. Quite simply, sensorimotor PAF remained extremely stable over a 14-day period despite the presence of ongoing NGF pain. What is more, participants were just as likely to experience increases or decreases in PAF speed after NGF injection. Unlike our prior study, the small PAF shifts that did occur were not related to pain sensitivity. One possible explanation for this lack of effect is that we did not account for the speed of pain-free, sensorimotor PAF. For example, ΔPAF may only have an impact on pain sensitivity for those individuals with pain-free PAF that is neither particularly fast nor slow (i.e., ~10 Hz). Exploratory analyses provided preliminary evidence in favor of this explanation (see APPENDIX, Fig. A5). A larger study is currently underway to better examine this possible interaction.

These results do not appear to support the hypothesis that PAF slowing in chronic pain is a marker of pain's persistence (i.e., de Vries et al. 2013). Instead, our data suggest that slow, pain-free PAF may reflect a heightened risk for developing chronic pain; that is, slowing of PAF in chronic pain may not reflect a result of active disease, but instead a heightened pain sensitivity that predates disease onset. Caution should be urged, however, given that the length of pain in the current study may not have been sufficient to induce PAF slowing. Ultimately, prospective studies in populations at risk for developing chronic pain will be needed to determine the role PAF slowing plays in disease development and persistence.

To our knowledge, PAF reflects the first brain-based biomarker of prolonged pain sensitivity that is available before pain onset. Whereas a number of studies have identified neural signatures that can be used to predict different intensity level of a noxious stimulus (i.e., high vs low; Iannetti et al. 2005; Wager et al. 2013), PAF provides information about individual variability in pain resulting from the same stimulus. An interesting avenue of future research would be to see how well these pain intensity tools can be applied to questions of pain sensitivity. Given that pain sensitivity has been identified as a positive predictor of chronic pain development (i.e., Hah et al. 2019), this would suggest PAF can offer a window into identifying chronic pain risk that was previously inaccessible. Previous research on brain-based markers of chronic pain risk have largely focused on instances where pain is already present (i.e., acute low back pain; Baliki et al. 2012). Although useful, such biomarkers may be accessible too late in the transition to chronic pain to allow for full prophylaxis. Unlike these markers, however, PAF can be accessed in the pain-free

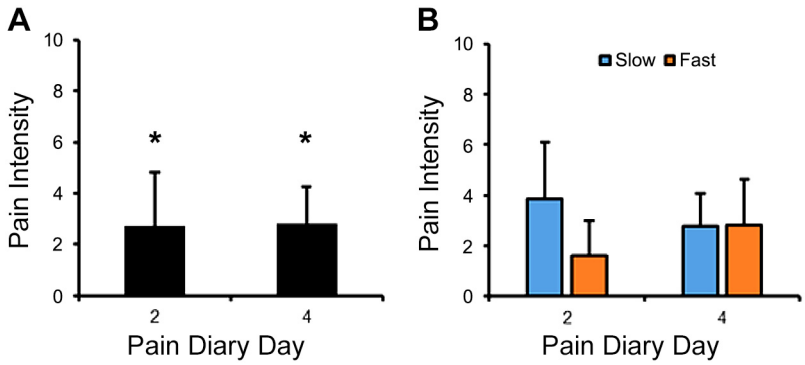

Fig. A1. *A*: daily diary reports for *Study 2*. *$P < 0.05$, pain scores significantly different from 0. *B*. *cohort 1* median split based on pain-free, sensorimotor peak alpha frequency (PAF) reveals that "slow" PAF individuals experienced greater pain on *day 2* but not *day 4*.

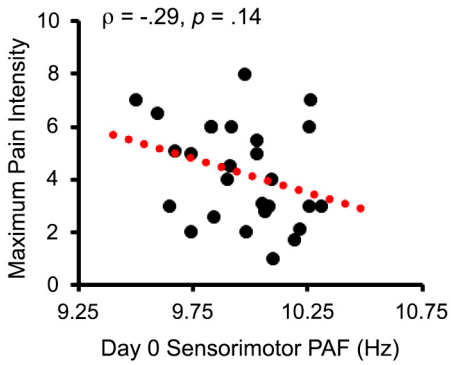

Fig. A2. *Day 0* pain-free, sensorimotor peak alpha frequency (PAF) is not correlated with the maximum pain reported from *days 1–21*. Red dotted line reflects the linear regression line of best fit.

state and could be used by clinicians to intervene before injury (e.g., surgery). To begin realizing this potential, future studies determining whether PAF can provide accurate information about chronic pain risk is needed.

In summary, we provide new evidence that pain-free, sensorimotor PAF reflects pain sensitivity to a clinically relevant model of musculoskeletal pain. We also provide initial evidence that the presence of pain for more than 2 wk is not sufficient to slow PAF, suggesting that PAF slowing in chronic pain may reflect heightened pain sensitivity that predates disease onset. These results highlight the important role pain-free, sensorimotor PAF can play in the clinical identification of those at high risk for developing chronic pain. Although these results are important and have important clinical potential applications, large-scale validation studies of PAF as a marker of clinical pain sensitivity are required.

APPENDIX

PAF Speed Impacts Day 2 Pain in Study 2

A median-split applied to *Study 2* participants produced five "slow" (mean = 9.75, SD = 0.13, range: 9.60 – 9.91) and five "fast" individuals (mean = 10.11, SD = 0.09, range: 10.02 – 10.22). Pain ratings on *day 2* were qualitatively greater for slow (mean = 3.84, SD = 2.25, range = 1.00 – 6.50) than for fast individuals (mean = 1.60, SD = 1.37, range = 0 – 3.50; Fig. A1). Pain ratings on *day 4* did not distinguish slow (mean = 2.78, SD = 1.29, range = 1.80 – 5.00) and fast individuals (mean = 2.80, S.D. = 1.81, range = 0.50 – 5.50).

Pain-Free Sensorimotor PAF Is Not Associated with Maximum Experienced Pain

Across both studies, *day 0*, pain-free sensorimotor PAF was not correlated with maximum pain [$\rho = -0.29$ (*Study 1* $\rho = -0.25$; *Study 2* $\rho = -0.54$), $P = 0.14$; Fig. A2). It is important to note, however, that pain-free, sensorimotor PAF's relationship to average pain was not significantly different than its relationship to maximum pain (Fisher r-to-$z = -0.73$, $P = 0.47$). As further evidence that PAF better describes average than maximum pain, the relationship between PAF and average pain remained significant when maximum pain was controlled for with a partial correlation ($\rho = -0.41$, $P = 0.04$), whereas its relationship to maximum pain when average pain was controlled for remained nonsignificant ($\rho = 0.15$, $P = 0.47$). The difference between these two correlations was significant (Fisher r-to-$z = -2.02$, $P = 0.04$), indicating that PAF is a better correlate of average NGF pain. In line with this idea, pain-free, sensorimotor PAF was correlated with pain reports at multiple post-NGF time points in *Study 1* (see Fig. A4).

Relationship Between Pain-Free PAF and Average Pain Is Similar Across Channels

To determine the topographic pattern of the relationship between PAF and NGF pain, we investigated the Spearman correlations of average NGF pain and pain-free PAF at each channel. As can be seen in Fig. A3, *A* and *B*, the relationship between pain-free PAF and average NGF pain was similarly represented across all channels with a mean $\rho = -0.43$, an absolute maximum $\rho = -0.57$ (channel O2), and an absolute minimum $\rho = -0.33$ (channel P7).

Pain-Free PAF Is Correlated with Reported Pain at Multiple Time Points in Study 1

Separate Spearman correlations between pain-free, sensorimotor PAF and pain reports from *days 1–17* (i.e., days where pain was statistically present) revealed sizable relationships at many time points, beginning with the first pain diary, *day 5*, occurring after the final NGF injection (Fig. A4*A*). Across all time points, the average correlation between PAF and reported pain was $\rho = -0.27$ (SD = 0.26) with the largest magnitude correlation occurring on *day 15*, $\rho = -0.56$. This pattern was well preserved across all scalp EEG channels (Fig. A4, *B* and *C*).

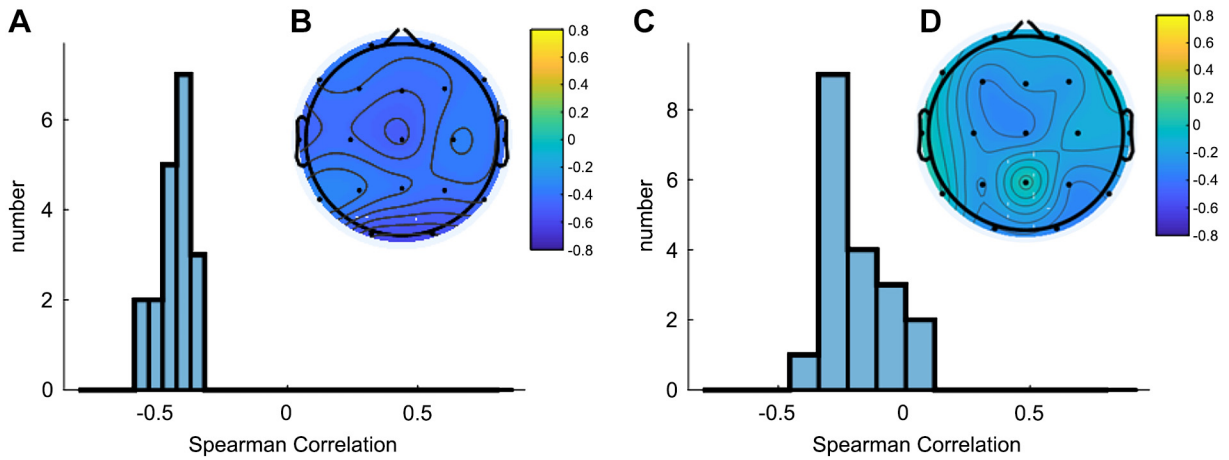

Fig. A3. *A* and *B*: relationship of peak alpha frequency (PAF) to average pain is consistent across channels. *C* and *D*: relationship of post-nerve growth factor PAF shifts (ΔPAF) to average pain is also consistent across channels. Topoplot (topogaphical map) colors reflect Spearman coefficients.

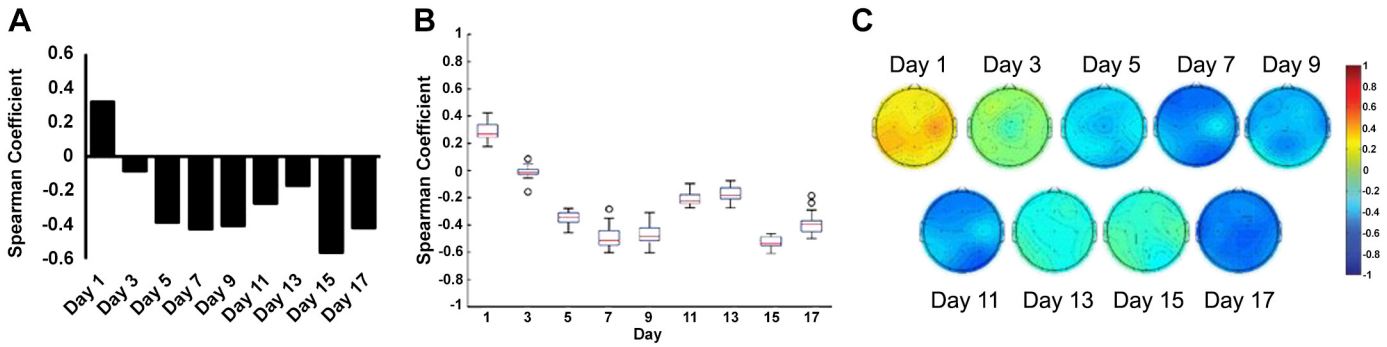

Fig. A4. Pain-free, sensorimotor peak alpha frequency (PAF) is correlated with multiple pain diary days. *A*: the relationship appears to first become stable at *day 5*, the first available diary report following the final nerve growth factor injection. *B*: box and whisker plots of Spearman coefficients (ρ) for pain-free PAF calculated from each EEG channel and pain reported on each day. The pattern of results is nearly identical to what was found for the sensorimotor region of interest. Red lines reflect medians, box edges reflect the 25th and 75th percentiles, and circles reflect outliers. *C*: topoplots (topographical maps) of ρ coefficients for pain-free, PAF calculated at each EEG channel and daily pain reports. Coefficients obtained for each day's pain diary for consistent across channels.

Relationship of PAF Shifts and Average Pain Does Not Vary by Channel Location

To determine the topographic pattern of the relationship between ΔPAF and NGF pain, we investigated the Spearman correlations of average NGF pain and ΔPAF at each channel. As can be seen in Fig. A3, *C* and *D*, the relationship between ΔPAF and average NGF pain was small at all channels with a mean $\rho = -0.19$, an absolute maximum $\rho = -0.36$ (channel O2), and an absolute minimum $\rho = 0.05$ (channel T7).

The Relationship of Sensorimotor PAF Shifts to NGF Pain May Depend on Pain-Free PAF

The range of recorded PAF values in the current study, 9.50–10.31, is larger than what we found in the prior study, 9.75–10.12. This raises the possibility that extreme pain-free PAF values may mitigate the impact of ΔPAF on pain; for example, ΔPAF may only have an impact on pain sensitivity for those individuals with pain-free PAF that is neither particularly fast nor slow (i.e., ~10Hz). To test this idea, we performed exploratory correlations between ΔPAF and average pain for the 10 individuals with PAF values in the range of our prior study (current study range = 9.83–10.10). This yielded an estimated relationship between ΔPAF and pain that trended toward significance ($\rho = -0.59$, $P = 0.07$; Fig. A5*A*). In comparison, the relationship between ΔPAF and pain for individuals with more extreme PAF values was smaller and in the opposite direction to what we have found previously ($\rho = 0.10$, $P = 0.67$; Fig. A5*B*). In an attempt to normalize ΔPAF based on the extremity of pain-free, sensorimotor PAF, we calculated a normed ΔPAF, $\widehat{\Delta PAF}$, using the following equation:

$$\widehat{\Delta PAF} = \frac{\Delta PAF}{\left|PAF - 10\right| \times \frac{1}{0.05}}.$$

This normalization process scales the original ΔPAF by the absolute distance of pain-free PAF from 10 Hz, expressed in ceilinged units of 0.05. For example, a pain-free PAF of 9.50 Hz is 10 units from 10 Hz, thereby resulting in a $\widehat{\Delta PAF}$ that is a 10-fold reduction of the original ΔPAF.

Using $\widehat{\Delta PAF}$ in place of ΔPAF yielded a relationship with average pain that was more in line with what we have found previously ($\rho = -0.44$, $P = 0.08$; Fig. A5*C*). Varying the scaling factor from 0.01 to 0.20 Hz did not greatly alter the magnitude of the relationship between $\widehat{\Delta PAF}$ and average pain (range = −0.47 to −0.35, mean = −0.40; Fig. A5*D*).

Finally, to ensure that $\widehat{\Delta PAF}$ is generalizable, we reanalyzed the relationship between $\widehat{\Delta PAF}$ and pain from previously published data (Furman et al. 2018). In doing so, we found a relationship between $\widehat{\Delta PAF}$ and pain ($\rho = -0.48$) that was nearly identical to what we found using ΔPAF ($\rho = -0.50$).

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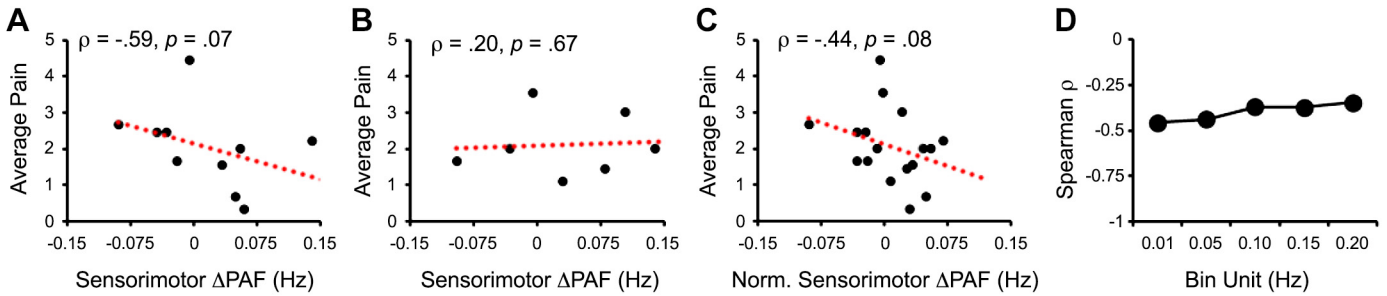

Fig. A5. Relationship of post-nerve growth factor (NGF) peak alpha frequency (PAF) shifts (ΔPAF) to pain sensitivity depend on pain-free, sensorimotor PAF. *A*: for individuals with pain-free PAF close to 10 Hz, ΔPAF is negatively correlated with average pain. *B*: for individuals with pain-free PAF not close to 10 Hz, ΔPAF is not related to average pain. *C*: changes in PAF after NGF, normalized (Norm.) to pain-free PAF, are moderately related to average NGF pain. *D*: relationship between normalized ΔPAF and pain is not dependent on the scaling factor. Red dotted lines reflect linear regression lines of best fit.

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DISCLOSURES

D. A. Seminowicz and A. J. Furman have a patent pending for "A Simple and Portable Biomarker for Pain Sensitivity." No conflicts of interest, financial or otherwise, are declared by the remaining authors.

AUTHOR CONTRIBUTIONS

G.Z.S., S.M.S., and D.A.S. conceived and designed research; T.T., S.J.S., R.C., and J.S.F. performed experiments; A.J.F. analyzed data; A.J.F. and D.A.S. interpreted results of experiments; A.J.F. and D.A.S. prepared figures; A.J.F. drafted manuscript; G.Z.S., S.M.S., and D.A.S. edited and revised manuscript; G.Z.S., S.M.S., and D.A.S. approved final version of manuscript.

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