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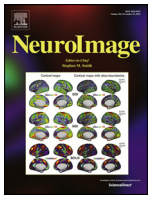

Peak alpha frequency as a candidate biomarker of pain sensitivity: the importance of distinguishing slow from slowing

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A B S T R A C T

The study by Valentini et al. (2022) observed that the peak alpha frequency (PAF) of participants became slower after they were exposed to painful, as well as non-painful but unpleasant stimuli. The authors interpreted this as a challenge to our previous studies which propose that the speed of resting PAF, independently of pain-induced changes to PAF, can be a reliable biomarker marker for gaging individual pain sensitivity. While investigations into the role that PAF plays in pain perception are timely, we have some concerns about the assumptions and methodology employed by Valentini et al. Moreover, we believe the authors here have also misrepresented some of our previous work. In the current commentary, we detail the critical differences between our respective studies, with the ultimate aim of guiding future investigations.

Dear editor

In our 2018 Neuroimage paper (Furman et al., 2018) we observed across healthy individuals, the peak frequency of alpha activity (PAF, aka individual alpha frequency or IAF) obtained during a pain-free rest period was negatively correlated with the degree of pain they would go on to report during induction of thermal hyperalgesia. Moreover, the degree to which alpha frequency slowed between pain-free and pain states was also independently correlated with pain intensity.

Chronic pain patients are known to display alterations in alpha rhythms compared to control subjects, specifically a relatively slower PAF (Sarnthein et al., 2006). Moreover, the degree of alpha slowing is shown to be correlated with disease duration (de Vries et al., 2013) suggesting that the frequency (i.e., speed) of an individual's alpha rhythm may not only index ongoing pain but also disease progression. This apparent slowing of PAF in chronic pain has been interpreted to reflect pathological changes within the brain that occur during the chronification of pain (Llinas et al., 1999). However, it should also be noted that the observation of a slow PAF in chronic pain patients is not entirely unequivocal, with a number of studies failing to report slower PAF in patients than controls (e.g. Schmidt et al. 2012, Ta Dinh et al. 2019, Witjes et al., 2021).

We have suggested based on our findings that chronic pain is not necessarily associated with PAF slowing but instead that pre-existing PAF slowness reflects a predisposition for developing chronic pain. Our hypothesis is based on the observation that heightened pain sensitivity is a risk factor for developing chronic pain (Hah et al., 2019).

The recent article by Valentini et al. (2022) claims to challenge our conclusions by testing "pain-specificity of EEG alpha oscillations against neutral and perceptually matched unpleasant non-painful stimulation". The authors found that alpha frequency slowed during experimental pain induction. However, they also observed similar phenomena during an unpleasant presentation of auditory stimuli. They interpreted this result as being contrary to our previous conclusions and suggested this demonstrates "an absence of the causal role of PAF in the generation of acute pain experience in healthy individuals."

Although investigations into the role that alpha activity play in pain perception are very timely, the study by Valentini et al. has the potential to introduce confusion to the fledgling field of oscillations and pain perception. We here argue for the importance of distinguishing between an individual's resting pain-free PAF and the modulation of alpha frequency in response to pain.

In the current article, we aim to clarify some key methodological differences between our respective studies to provide clarity and guide further investigations of PAF and pain perception. We begin by summarizing recent developments in the area of alpha oscillations and pain perception before addressing these key issues.

Alpha oscillations, the gate-keeper of information flow

The alpha rhythm (8–12 Hz) is the predominant oscillatory activity observed in the scalp-recorded EEG (electroencephalogram) of the primary sensory cortices (e.g., occipital and somatosensory), while an individual is quietly resting. A prevalent hypothesis of the alpha rhythm

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is that it gates the perception of sensory input by inhibiting sensory processing when power is high (Van Diepen et al., 2019). Across individuals, there is considerable variability in the alpha band frequency (i.e. speed) from which the greatest EEG power is recorded (Haegens et al., 2014). This frequency, often labelled the Peak Alpha Frequency (PAF) or Individual Alpha Frequency (IAF), has been found to contribute to individual differences in multiple psychological and physiological processes (Cecere et al., 2015; Haegens et al., 2014; Ramsay et al., 2021).

Resting alpha frequency and its relationship to pain sensitivity

In our 2018 Neuroimage paper, we found that PAF obtained from healthy individuals during a pain-free rest period was negatively correlated with the degree of pain experienced during an experimental model of thermal hyperalgesia. Specifically, we induced pain in 21 healthy participants (mean age 28.4 years) using a 10% capsaicin paste (topically applied, not intradermally as reported by Valentini et al.). Topical capsaicin exposure induces robust thermal hyperalgesia, a common symptom in chronic neuropathic pain. We found that those who had a slower PAF in the pain-free state one hour before pain induction reported more subsequent pain than those who had faster PAF.

We replicated this finding (Furman et al., 2020) in a pre-registered study (NCT02796625) using a larger sample of participants ($n = 61$ (a larger sample than in Valentini 2022, despite their claim that they used "the largest sample size ($n = 36$)," mean age 27 years) and found that PAF could predict sensitivity to two models of prolonged pain, even up to eight weeks later. We also replicated this finding (slower PAF = higher pain sensitivity) in a completely different muscle pain model that induces pain lasting days to weeks (Furman et al., 2019).

Most recently we directly investigated if PAF can be used as a clinical tool to stratify pain-sensitive patients and found that pre-operative (pain-free) PAF of patients correlated with pain severity during the 72 h period after surgery (Millard et al., 2022). These studies taken together support the idea that PAF is a reliable and robust biomarker of an individual's sensitivity to pain and could serve to identify patients who are at risk for severe post-surgical pain. The identification of these patients would allow for pre-emptive pain management strategies which could reduce patient suffering, reliance on post-operative opioid use, and potentially minimize chronic pain development. In some cases, alternatives to elective surgeries might be sought for patients assessed to be high risk for developing chronic post-surgical pain.

The important distinctions between our work and Valentini et al

Simply put, Valentini et al. mistakenly assert that the basis of our claim of PAF being a reliable biomarker pertains to PAF slowing, rather than slow PAF. Indeed, in Furman 2018, we demonstrated these two things are independent.

The investigation by Valentini et al., which also used healthy participants, focused on PAF changes (i.e. PAF slowing) in response to pain induced by hand immersion into hot-water, with 'warm-water' immersion as well as an unpleasant (but not painful) auditory stimulus presentation condition serving as control conditions. They observed that PAF slowed during the painful hot hand immersion compared with warm stimulation. However, they did not observe significant differences between the painful hot and unpleasant auditory conditions. They interpreted this as being contrary to our previous work by suggesting a causal role of PAF in the generation of acute pain experience in healthy individuals.

We have never suggested that PAF plays a causal role in the generation of painful experiences. Rather, our data across multiple experiments suggests that slow PAF is a trait-like marker that is predictive of individual sensitivity to acute pain, either induced experimentally or by surgery. The causal versus predictor distinction here is crucial.

As mentioned earlier, the alpha rhythm is the predominant rhythm of our sensory cortices and PAF has been shown to contribute to individual differences in multiple psychological and physiological processes (Cecere et al., 2015; Haegens et al., 2014; Ramsay et al., 2021; Torralba Cuello et al., 2022). Moreover, diverse populations have been found to show a slow alpha frequency, including school-aged children born very premature (Doesburg et al., 2011), people with schizophrenia (Ramsay, 2021 and elderly adults with earlier dementia (Garcés et al., 2013). One view of alpha activity is that each cycle reflects a pulse of phasic inhibition (Haegens et al., 2011; Van Diepen et al., 2019) which is capable of inhibiting incoming sensory information (noxious and innocuous). Faster PAF could reflect a greater capacity to modulate sensory input.

We would like to further note that factors that predispose an individual to high pain sensitivity need themselves not be specific to pain; for example, attention – a fundamental core cognitive process that enables us to selectively focus on one aspect of our environment while ignoring the other – has been repeatedly shown to play an important role in determining pain susceptibility (Baum et al., 2011). While we feel that it is unlikely that PAF is exclusively tied to pain, both our work and findings of Valentini et al. suggest that its modulation in response to pain bears a relationship to individual pain sensitivity.

Finally, in addition to the slow versus slowing of PAF, there are some key distinct methodological differences between our investigations and those of Valentini et al. which need to be discussed and scrutinized to avoid ambiguity in future research.

The state of participants when PAF was estimated

Our investigations have used 'pain-free', eyes-closed peak alpha frequency as the predictor of an individual's sensitivity to induced pain (experimental or surgical). We reason that having participants close their eyes increases the amplitude of the PAF, making it easier to detect, and reducing ocular artefacts that can distort its estimation. Valentini et al. obtained the participants' eyes-open PAF while they were experiencing pain. Obtaining PAF during a pain state makes it very hard to assess it as a trait marker for pain sensitivity. In fact, our 2018 study failed to find a systematic slowing of PAF after pain induction across participants, but rather the pain resulted in speeding of PAF in some participants and a slowing in others. Indeed, other groups have reported a lack of association between PAF slowing and pain sensitivity (De Martino et al., 2021), suggesting that while pain-free PAF is a reliable pain sensitivity biomarker, the association between the change in PAF speed during ongoing pain and pain sensitivity is more complex.

The sensory modality of stimulation

Valentini et al. claim that their experiment shed light on the functional significance of PAF with regards to pain by including a condition (an auditory stimulus) that while not painful is unpleasant. While we believe this to be an interesting line of inquiry, the choice of having the unpleasant stimuli and painful stimuli being two different modalities does confound this line of investigation. Previous research has shown both the visual, auditory, and somatosensory cortex each have respective alpha generators (often with different PAF frequencies) which are modulated by perceptual demands (Banerjee et al., 2011; Haegens et al., 2011; Mazaheri et al., 2014; Whitmarsh et al., 2022).We speculate that it is likely that even though the unpleasantness of the sound and heat conditions were matched, being different sensory modalities meant that they were impacting different alpha sources (possibly with different resting PAFs).

Nevertheless, if non-painful unpleasant stimuli are found to modulate individual PAF similar to painful ones, it would suggest the modulation of PAF reflects a general aversion response. This would be in line with previous work has found a shared somatosensory representation between unpleasant emotional stimuli and somatic pain (Kross et al., 2011) as well as the observation that brain areas such as the midcingulate cortex, thalamus, amygdala, and lateral orbital frontal cor-

tex encode a general aversion signal irrespective of stimulus modality (Čeko et al., 2022).

Experimental design to assess pain

Valentini et al. appear to implicitly claim that their investigation is more 'reliable and robust' than previous investigations looking at the relationship between PAF and pain perception. They claim to employ a data-driven cluster-analysis approach to spatially select alpha oscillations at 'rest and only rest'… "while avoiding selective analysis and double-dipping."

We are unsure here if the authors are (wrongly) suggesting that previous investigations looking at the impact of pain on PAF have used the same data set for selection and selective analysis. Nevertheless, we suggest that the best way to reliably and robustly assess the relationship of PAF with pain sensitivity is to (1) Use different pain models within the same study (2) Include test and re-test (3) Incorporate cross-validation. We should note that all of these were employed in our recent investigation cited by the authors (Furman et al., 2020).

In conclusion, PAF remains a viable and promising biomarker of pain sensitivity and in our opinion the work by Valentini et al. 2022 generally supports that literature. We are encouraged that multiple labs (De Martino et al., 2021; Fauchon et al., 2021; McLain et al., 2022; Seminowicz et al., 2020) are now working on this emerging field. In future studies, we need to be precise about *what we are measuring* and *what we are predicting* before making claims of refuting others' work.

There is no code or data contained in this commentary

Declarations of Competing Interest

DS, AF, and AM have a patent pending (PCT/US2018/058889) for "A Simple and Portable Biomarker for Pain Sensitivity." AF and AM are shareholders and DS, AF, and AM serve as advisors to Empower Therapeutics, a University of Maryland/University of Birmingham spin-out company commercializing this IP to create pain management technology.

Data Availability

No data was used for the research described in the article.

References

Banerjee, S., Snyder, A.C., Molholm, S., Foxe, J.J., 2011. Oscillatory alpha-band mechanisms and the deployment of spatial attention to anticipated auditory and visual target locations: supramodal or sensory-specific control mechanisms? J. Neurosci. 31, 9923–9932.

Baum, C., Huber, C., Schneider, R., Lautenbacher, S., 2011. Prediction of experimental pain sensitivity by attention to pain-related stimuli in healthy individuals. Percept. Mot. Skills 112, 926–946.

Cecere, R., Rees, G., Romei, V., 2015. Individual differences in alpha frequency drive crossmodal illusory perception. Curr. Biol. 25, 231–235.

Čeko, M., Kragel, P.A., Woo, C.-.W., López-Solà, M., Wager, T.D., 2022. Common and stimulus-type-specific brain representations of negative affect. Nat. Neurosci. 25, 760–770.

De Martino, E., Gregoret, L., Zandalasini, M., Graven-Nielsen, T., 2021. Slowing in peak-alpha frequency recorded after experimentally-induced muscle pain is not significantly different between high and low pain-sensitive subjects. J. Pain 22, 1722–1732.

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.

Doesburg, S.M., Ribary, U., Herdman, A.T., Moiseev, A., Cheung, T., Miller, S.P., Poskitt, K.J., Weinberg, H., Whitfield, M.F., Synnes, A., Grunau, R.E., 2011. Magnetoencephalography reveals slowing of resting peak oscillatory frequency in children born very preterm. Pediatr. Res. 70, 171–175.

Fauchon, C., Kim, J.A., El-Sayed, R., Osborne, N.R., Rogachov, A., Cheng, J.C., Hemington, K.S., Bosma, R.L., Dunkley, B.T., Oh, J., Bhatia, A., Inman, R.D., Davis, K.D., 2021. Exploring sex differences in alpha brain activity as a potential neuromarker associated with neuropathic pain. Pain 163, 1291–1302.

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.

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.

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.

Garcés, P., Vicente, R., Wibral, M., Pineda-Pardo, J., López, M.E., Aurtenetxe, S., Marcos, A., de Andrés, M.E., Yus, M., Sancho, M., Maestú, F., Fernández, A., 2013. Brain-wide slowing of spontaneous alpha rhythms in mild cognitive impairment. Front. Aging Neurosci. 5, 100.

Haegens, S., Cousijn, H., Wallis, G., Harrison, P.J., Nobre, A.C., 2014. Inter- and intra-individual variability in alpha peak frequency. Neuroimage 92, 46–55.

Haegens, S., Händel, B.F., Jensen, O., 2011. Top-down controlled alpha band activity in somatosensory areas determines behavioral performance in a discrimination task. J. Neurosci. 31, 5197–5204.

Hah, J.M., Cramer, E., Hilmoe, H., Schmidt, P., McCue, R., Trafton, J., Clay, D., Sharifzadeh, Y., Ruchelli, G., Goodman, S., Huddleston, J., Maloney, W.J., Dirbas, F.M., Shrager, J., Costouros, J.G., Curtin, C., Mackey, S.C., Carroll, I., 2019. Factors associated with acute pain estimation, postoperative pain resolution, opioid cessation, and recovery: secondary analysis of a randomized clinical trial. JAMA Netw. Open 2, e190168.

Kross, E., Berman, M.G., Mischel, W., Smith, E.E., Wager, T.D., 2011. Social rejection shares somatosensory representations with physical pain. Proc. Natl. Acad. Sci. 108, 6270–6275.

Llinas, R.R., Ribary, U., Jeanmonod, D., Kronberg, E., Mitra, P.P., 1999. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc. Natl. Acad. Sci. U. S. A. 96, 15222–15227.

Mazaheri, A., van Schouwenburg, M.R., Dimitrijevic, A., Denys, D., Cools, R., Jensen, O., 2014. Region-specific modulations in oscillatory alpha activity serve to facilitate processing in the visual and auditory modalities. Neuroimage 87, 356–362.

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.

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.

Ramsay, I.S., Lynn, P.A., Schermitzler, B., Sponheim, S.R., 2021. Individual alpha peak frequency is slower in schizophrenia and related to deficits in visual perception and cognition. Sci. Rep. 11, 17852.

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.

Schmidt, S., Naranjo, J.R., Brenneisen, C., Gundlach, J., Schultz, C., Kaube, H., Hinterberger, T., Jeanmonod, D., 2012. Pain ratings, psychological functioning and quantitative eeg in a controlled study of chronic back pain patients. PLoS One 7, e31138.

Seminowicz, D.A., Bilska, K., Chowdhury, N.S., Skippen, P., Millard, S.K., Chiang, A.K.I., Chen, S., Furman, A.J., Schabrun, S.M., 2020. A novel cortical biomarker signature for predicting pain sensitivity: protocol for the PREDICT longitudinal analytical validation study. Pain Rep. 5, e833.

Ta Dinh, S., Nickel, M.M., Tiemann, L., May, E.S., Heitmann, H., Hohn, V.D., Edenharter, G., Utpadel-Fischler, D., Tölle, T.R., Sauseng, P., Gross, J., Ploner, M., 2019. Brain dysfunction in chronic pain patients assessed by resting-state electroencephalography. Pain 160, 2751–2765.

Torralba Cuello, M., Drew, A., Sabaté San José, A., Morís Fernández, L., Soto-Faraco, S., 2022. Alpha fluctuations regulate the accrual of visual information to awareness. Cortex 147, 58–71.

Valentini, E., Halder, S., McInnerney, D., Cooke, J., Gyimes, I.L., Romei, V., 2022. Assessing the specificity of the relationship between brain alpha oscillations and tonic pain. Neuroimage 255, 119143.

Van Diepen, R.M., Foxe, J.J., Mazaheri, A., 2019. The functional role of alpha-band activity in attentional processing: the current zeitgeist and future outlook. Curr. Opin. Psychol. 29, 229–238.

Whitmarsh, S., Gitton, C., Jousmäki, V., Sackur, J., Tallon-Baudry, C., 2022. Neuronal correlates of the subjective experience of attention. Eur. J. Neurosci. 55, 3465–3482.

Witjes, B., Baillet, S., Roy, M., Oostenveld, R., Huygen, F.J.P.M., de Vos, C.C., 2021. Magnetoencephalography reveals increased slow-to-fast alpha power ratios in patients with chronic pain. Pain Rep. 6, e928.