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Commentary

The independence and predictivity of resting pain-free slow alpha frequency as a biomarker of pain: A reply to Mazaheri et al.

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ABSTRACT

In response to Mazaheri et al.'s critique, we revisited our study (Valentini et al., 2022) on the relationship between peak alpha frequency (PAF) and pain. Their commentary prompted us to reassess our data to address the independence between slow and slowing alpha brain oscillations, as well as the predictivity of slow alpha oscillations in pain perception. Bayesian correlation analyses revealed mixed support for independence. Investigating predictivity, we found inconsistent associations between pre-PAF and unpleasantness ratings. We critically reflected on methodological and theoretical issues on the path to PAF validation as a pain biomarker. We emphasized the need for diversified methodology and analytical approaches as well as robust findings across research groups.

Dear Editor,

we read Mazaheri et al.'s letter (Mazaheri et al., 2022) with much interest. The authors went to great lengths to question the assumptions and methodology of our recent study (Valentini et al., 2022), as well as expressing doubts about our interpretation of their previous work (Furman et al., 2018, 2020). We appreciated the breath of their commentary, which extended beyond specific criticism of our work to foster future research on the relationship between peak alpha frequency (PAF) and pain. In our reply we will attempt to resolve what remained unaddressed in our original study while also providing further constructive reflection for researchers working in the field.

In Valentini et al. (2022) we showed slower PAF during painful hot compared with innocuous warm stimulation; however PAF recorded during an affectively matched unpleasant sound decreased in frequency similarly to the hot condition. In addition, we could not prove a strong predictive effect of frequency variation on participants' affective experience (i.e., unpleasantness ratings), thus leading us to endorse the absence of a causal role of PAF in the generation of acute pain experience in healthy individuals. We would like to highlight that we explicitly acknowledged that our findings were consistent with the notion of slowing of alpha oscillations over the central and parietal region of the scalp as observed in Furman et al., 2018 (i.e., ΔPAF findings), and that our approach was different from our Colleagues' (page 9 in Valentini et al., 2022). Therefore, although we used a different approach to calculate ΔPAF, we deemed the differences between findings to be explained by significant differences in methodology (e.g., laboratory pain model) rather than by a mechanistic interpretation of the PAF effect, as instead highlighted by our Colleagues in their rebuttal.

Specifically, in Mazaheri et al.'s words, we neglected "*the importance of distinguishing between an individual's resting pain-free PAF and the modulation of alpha frequency in response to pain*", a distinction that they otherwise referred to as the difference between slow and slowing PAF. We agree in principle with our colleagues that slowing PAF might be functionally dissociated from slow PAF. Here, we argue that this interpretation is not yet substantiated enough for us to conclude that the two phenomena may be i) independent from each other and ii) able to predict increased pain sensitivity.

In their reply, Mazaheri et al. acknowledged that there is no universal evidence of slow alpha in chronic pain patients. This implies that the evidence originated from laboratory models of pain may not be sufficient for electing slow alpha (or any other physiological response for the matter) as a biomarker of pain (Mouraux and Iannetti, 2018).

Mazaheri et al. stated that we "*obtained the participants' eyes-open PAF while they were experiencing pain*". We would like to clarify that we recorded resting alpha *without* any sensory stimulation *during* eyes-open and eyes-closed conditions, and we did it both before and after we recorded the sensory stimulation conditions, according to a pre-post design (see Fig. 1 in Valentini et al., 2022). Perhaps, our Colleagues referred to the fact that we studied the PAF obtained during the hot painful condition as function of the resting state PAF, thus mirroring their ΔPAF analysis in Furman et al., 2018. This choice implied that our

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findings did not allow any conclusion on the predictive role of slow alpha frequency. In fact, we measured both the ΔPAF (i.e., slowing) and pain-free state PAF (i.e., slow), but our analysis and interpretation focused on the ΔPAF. We also noted that our Colleagues disagreed with our approach of recording pain-free resting state alpha after the experience of pain. Indeed, they might have hypothesized that both eyes-open and eyes-closed PAF recorded *only before* the sensory stimulation blocks (pre-PAF) would negatively correlate with the unpleasantness reported during the hot painful recording. This is something we considered in our re-analysis of the data (please see the supplementary file for details on the data analysis approach).

In the next two sections we will present new analyses of our previous work that will i) address the property of independence (i.e., the hypothesis that ΔPAF and pain-free state PAF are not correlated, as per Furman et al., 2018) and ii) investigate the issue of predictivity (i.e., the hypothesis that pain-free state PAF can predict the affective changes reported during the painful condition). We will then provide a final summary to integrate this latest information.

1. On the independence between slow and slowing alpha brain oscillations

Concerning the property of independence, we noted that our Colleagues reported a lack of correlation between the ΔPAF (i.e., slowing) and pain-free state PAF (i.e., slow) in Furman et al., 2018, thus hinting at a dissociation. We therefore set out to investigate this question using a Bayesian correlational approach to quantify the bidirectional element of this relationship in our dataset.

The analysis of the relationship between ΔPAF (i.e., PAF during hot pain condition expressed as a function of the preliminary resting state baseline) and pre-PAF during both eyes-open and eyes-closed (i.e., resting state PAF recorded *only before* the sensory stimulation blocks) displayed anecdotal to moderate support for the H0 (i.e., lack of correlation) except for one correlation that instead revealed extreme evidence in support of the H1 (Table 1). That is, we found very robust evidence (as also highlighted by the sensitivity analysis reported in supplementary material) in support of a positive relationship between PAF recorded during the hot painful condition in the Parietal-Occipital (PO) region of interest and resting PAF during eyes-open condition (compared to H0). This is at odds with the other correlations supporting the notion of a lack of a strong association between the two variables as per Furman et al.'s findings (Furman et al., 2018).

2. On the predictivity of slow alpha brain oscillations in the generation of pain

It is noteworthy that colleagues in the statistics (e.g., Shmueli, 2010) and biomedical (e.g., Emmert-Streib et al., 2021) communities have expressed the need for a distinction between *causal* and *predictive* models because the two terms are not interchangeable. Additionally, even when the biomarker (i.e., slow PAF) lies in a causal pathway of the disease process (i.e., burning pain), the clinical efficacy of a therapeutic intervention (i.e., analgesic drug) may be jeopardised by side/unspecific effects (Fleming and Powers, 2012). Nonetheless, we will here refer to predictive as the term of choice to indicate the main property of a desirable *diagnostic pain perception biomarker*.

Furman et al. 2018 reported that while PAF and ΔPAF did not correlate, they could both predict pain intensity, thus suggesting the co-existence of distinct but functionally similar responses. This difference is important because they argued that PAF recorded during a painful state may lead to both speeding and slowing across participants. In their letter, they cited the work by De Martino et al., 2021 as a further example of it. Crucially though, De Martino et al. reported a trend towards higher PAF also when high pain sensitive participants were resting at day zero of their longitudinal design, and without any earlier exposure to pain (their Fig. 5, A). We shall add that, at variance with these previous findings, we found both PAF decrease and increase at different regions of the scalp within the same sample. This evidence, together with Mazaheri et al.'s evidence of ΔPAF being able to predict pain intensity, would need to be accommodated into the interpretation of PAF mechanisms.

Our second analysis will address the predictive power of pre-PAF on perception (i.e., PAF recorded *only before* the sensory stimulation blocks, which is the equivalent of Furman et al., 2018 pain-free condition). We assessed the hypothesis that pre-PAF would negatively correlate with the unpleasantness recorded during the hot painful condition. We investigated this question using again a Bayesian approach. Crucially, in doing so we could implement the informed priors of a negative relationship as reported by Mazaheri et al.'s (see supplementary file for details). Out of the original seventy-seven Independent component analysis (ICA) clusters we selected those with at least eighteen components, thus delivering forty-two clusters whereas in our previous analysis we screened only clusters with at least twenty components (see methods section in Valentini et al., 2022 for details and Furman et al., 2018 for a similar analysis in ICA space). Because different number of ICs and participants contributed to different clusters, we analysed each cluster separately. For each cluster we computed a correlation between the eyes-closed pre-PAF and unpleasantness ratings during the hot pain condition (in keeping with our Colleagues' approach, and to reduce the number of tests, we excluded the eyes-open pre-PAF). Only three out of forty-two clusters displayed an anecdotal to moderate evidence for a significant negative correlation of pre-PAF with unpleasantness (Fig. 1).

3. Final summary and critical reflections

To summarise, we failed to assess the property of independence in Valentini et al. (2022), that is we did not investigate i) the relationship between the ΔPAF (i.e., slowing) and pain-free state PAF (i.e., slow) and ii) the relationship between pain-free state PAF and the unpleasantness reported during hot painful condition. We attempted to fill this gap with the present work.

Our data only partly supported the property of independence, raising the question of whether there is no single alpha activity to be considered relevant during resting state activity. We agree with Mike Cohen (2017) that "*The lack of convergence on a single cellular mechanism of alpha suggests multiple distinct mechanisms*". Based on the current understanding of alpha neuronal oscillations generators, it is entirely possible that different generators may perform different functions during rest and pain (Halgren et al., 2019). We believe more light should be shed on the relationship between ΔPAF (i.e., slowing) and pain-free state PAF (i.e., slow).

Regarding the issue of predictivity, if we assumed that our pre-PAF would be considered a fair measure of pre-existing slow alpha "trait", then we must conclude that, albeit present, the negative relationship identified with a more liberal investigation of the ICA clusters did not seem to be consistent and well represented in the ICA space. Although our re-analysis did not fully address predictivity, taken together with the

Table 1
Bayesian Pearson's Correlation between ΔPAF and pre-PAF during both eyes-open and eyes-closed.

ΔPAF Vs	pre-PAF	R	BF_{10}	95 % Credible interval Lower	Upper
CP_O	Pre_O	0.183	0.359	−0.150	0.466
PO_O	Pre_O	0.645***	1175.743	0.380	0.792
	tau	0.486	953	0.232	0.655
CP_C	Pre_C	0.207	0.421	−0.126	0.485
PO_C	Pre_C	−0.043	0.214	−0.353	0.279

*** BF10 >100. CP: bilateral central-parietal. PO: bilateral parietal-occipital. O: open eyes. C: closed eyes. Pre: resting state recorded at the beginning of the experiment (see Fig. 1 in Valentini et al., 2022).

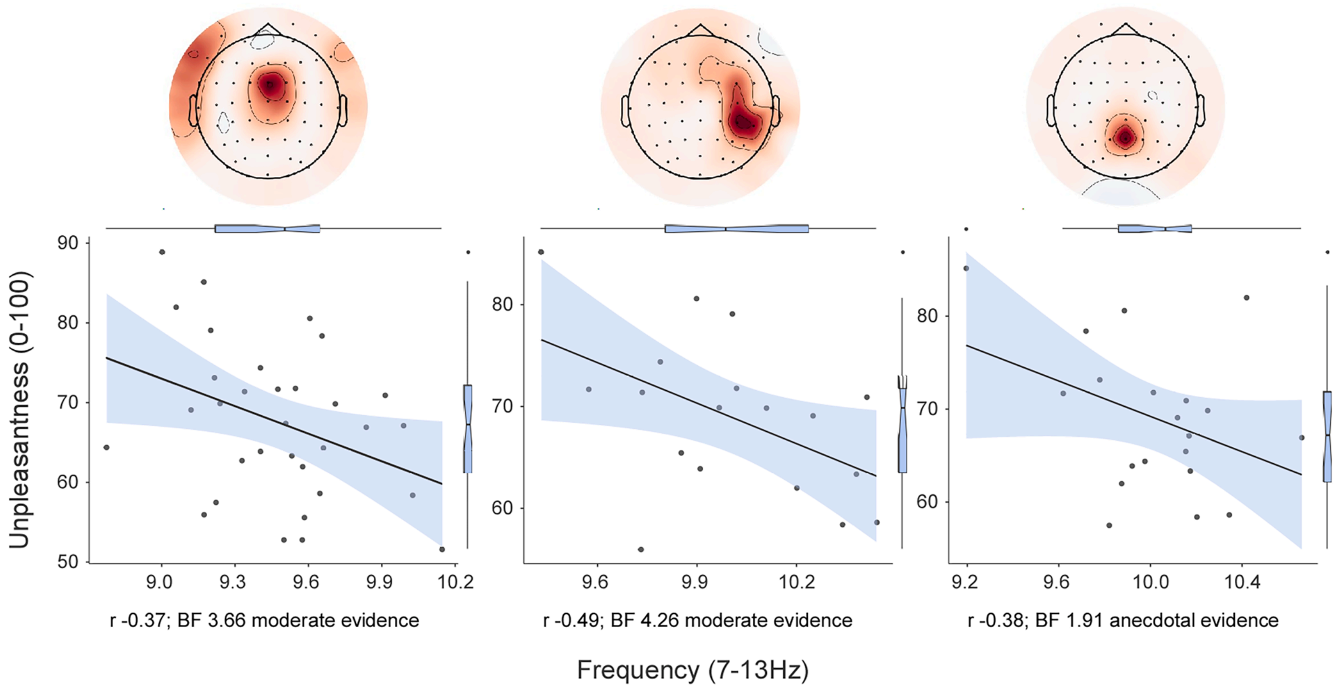

Fig. 1. Three clusters that revealed a credible negative relationship between unpleasantness ratings reported during the hot painful condition and PAF during eyes-closed at the beginning of the experiment (from left to right: fronto-central, right centro-parietal, posterior parietal). The confidence band around the linear regression line represents the standard error. The side boxplots show the distribution for both variables. Note how the lower the baseline eyes-closed PAF extracted from these clusters the greater the unpleasantness reported in the hot pain condition.

results of our earlier mediation analysis using ΔPAF (Valentini et al., 2022), we conclude that at present, we have not gathered enough evidence to support a predictive role of either ΔPAF or pain-free PAF. Letting aside possible issues of power and statistical robustness, there might be several reasons why we did not replicate Mazaheri et al.'s findings.

We are aware that our Colleagues replicated their original findings in follow-up publications with different pain models, analytical tools, and temporal lags. We simply highlight that we could not achieve the same interpretation based on our own sample characteristics, methodology, pain model, and analytical approach. These study features may be quite important in explaining why other groups cannot confirm the effects observed by Mazaheri et al. We argue that these differences may better explain the lack of conceptual replication, at least in our study, rather than an invalid interpretation of the functional mechanism underpinning the PAF biomarker. The new analyses presented in our reply should address either theoretical and empirical concerns, support the validity of our previous conclusions, and foster further research into PAF as a candidate neural marker of pain sensitivity.

Interestingly, a very recent paper from the same research group failed to identify a robust relationship between PAF and pain (Millard et al., 2023). While current evidence seems to lean towards a promising predictive role of PAF in pre-clinical models of pain, we feel that more effort involving diverse methodology and analytical tools, across different research groups, as well as multi-lab projects, will be beneficial to advance the field.

Data availability

Data and analyses will be uploaded on the first author's Open Science Foundation repository at the following link: https://osf.io/r5zns/?view_only=7779b40fb85d42a693f1bdc10314f979

CRediT authorship contribution statement

Elia Valentini: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sebastian Halder:** Data curation, Formal analysis, Methodology, Validation, Writing – review & editing. **Vincenzo Romei:** Writing – review & editing.

Declaration of competing interest

The authors report no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2024.120681.

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