Neural biomarkers of pain:

Defining perspectives and limitations of peak alpha frequency

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Identifying reliable neural biomarkers of pain remains a critical challenge in both basic research and clinical practice, with significant implications for diagnostic accuracy and treatment optimization [11,15]. Such biomarkers offer the potential to stratify pain conditions based on underlying mechanisms, predict treatment responses, and implement individualized therapeutic interventions [11]. Peak alpha frequency (PAF) – the dominant oscillatory frequency within 8-13 Hz – has recently emerged as a promising candidate for predicting pain sensitivity in both healthy [2,3] and clinical [9,13] populations. This evidence is particularly relevant, given that individual pain sensitivity has been repeatedly associated with chronic pain development and maintenance [6,12]. Consequently, PAF could constitute a valuable electrophysiological biomarker to guide individualized treatments, with particular relevance for brain stimulation and other neuromodulatory interventions targeting neural oscillations [10,14].

The recent study by May et al. [7], published in the current issue of PAIN, provides a timely and methodologically rigorous assessment of PAF's generalizability as a biomarker of pain sensitivity. Using a large sample of 159 participants tested across two sessions, and employing brief thermonociceptive stimuli, the authors investigated whether PAF measured through scalp electroencephalography (EEG) could predict both inter-individual differences in pain sensitivity and intra-individual variations in pain perception. The study's methodological innovation lies in its comprehensive "multiverse" analysis, which systematically tests hypotheses across multiple analytical choices – an unprecedented approach in PAF research. Despite its complexity, this method is particularly valuable given the large diversity of analytical procedures in the field [8]. This approach not only enables to assess the impact of different analytical choices but also

demonstrates the robustness of the findings, enhancing their reliability and transparency.

The findings reported by May et al. [7] reveal that PAF does not consistently predict sensitivity to brief experimental pain, either between or within individuals – a result that held true whether examining PAF from somatosensory electrodes specifically or globally across the scalp. These findings were replicated across sessions and remained consistent when controlling for potential confounds, such as age, time effects and stimulation intensity. These results suggest that PAF's relationship with pain is not universally generalizable but may be specific to certain pain types or contexts. Specifically, while PAF holds potential as a valid biomarker for sensitivity to long-lasting pain [2–4,9], these findings indicate that it does not function effectively as a biomarker for sensitivity to brief experimental pain. A possible explanation for this discrepancy is that PAF might better reflect cognitive-affective aspects of pain processing that become more prominent during sustained pain states [1], rather than the immediate sensory processing of brief nociceptive stimuli.

The study by May et al. [7] highlights critical gaps in our understanding of PAF's role in pain processing, pointing toward important next steps in the field. Rather than diminishing PAF's value, their results help define its scope of application and guide future research toward more targeted investigations. First, pain researchers should conduct systematic investigations to examine how PAF correlates with acute versus chronic pain, and its relationship to various pain qualities, durations, and contextual factors. Such comprehensive assessments would help clarify which neural mechanisms of pain

processing are captured by PAF measurements, enabling more tailored clinical applications. For instance, PAF could prove particularly valuable for assessing and monitoring sustained or chronic pain conditions where cognitive-affective aspects play a prominent role [1]. Identifying patient subgroups in which PAF strongly correlates with pain sensitivity could enable more precise selection for interventions targeting alpha oscillations, thereby advancing individualized treatment strategies.

Additionally, developing more advanced methods to isolate functionally specific alpha components could enhance signal selectivity and improve the reliability of findings. While current approaches focused on somatosensory alpha by analyzing central electrodes [7], scalp EEG provides limited spatial selectivity, and the measured signals likely reflect a mixture of different alpha generators, potentially obscuring more specific somatosensory contributions. Advanced source separation techniques might help isolate more functionally specific alpha components [5]. This refined selectivity could substantially increase PAF's utility in clinical settings by enabling practitioners to identify patients most likely to benefit from PAF-guided interventions, including neuromodulatory therapies targeting alpha oscillations such as transcranial alternating current stimulation (tACS) [10,14].

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