Neurotherapeutics 23 (2026) e00929

Contents lists available at ScienceDirect

Neurotherapeutics

journal homepage: www.sciencedirect.com/journal/neurotherapeutics

Commentary

Alpha oscillations in pain neuromodulation: From resting rhythms to reactive networks

Giulia Liberati [a,b,*]

[a] Institute of Neuroscience (IoNS), Université Catholique de Louvain, Brussels, Belgium
[b] Psychological Sciences Research Institute, Université Catholique de Louvain, Louvain-la-Neuve, Belgium

ARTICLE INFO

Keywords:
pain
alpha oscillations
transcranial magnetic stimulation (TMS)

Chronic pain remains a major clinical challenge. Pharmacological treatments, while central to current care, often provide only partial and unsatisfactory relief [1]. This therapeutic gap has fueled increasing interest in non-invasive brain stimulation approaches, particularly repetitive transcranial magnetic stimulation (rTMS) [1–3]. In this context, a central goal is to identify neurophysiological processes that mediate analgesia. Alpha oscillations are prominent candidates, with resting-state power and peak frequency consistently linked to pain sensitivity [4–6]. Yet, a key question persists: are alpha rhythms merely a marker of ongoing pain states, or are they mechanistically relevant targets for neuromodulation?

In this issue of Neurotherapeutics [7], Chowdhury and colleagues advance this debate by moving beyond resting-state measures to perturbation-evoked alpha dynamics. Using combined transcranial magnetic stimulation and electroencephalography (TMS-EEG) in a capsaicin-induced tonic pain model, they tracked event-related spectral perturbations (ERSP) and inter-trial coherence (ITC) before and after posterior insula–proximal rTMS. In this perspective, alpha oscillations are not static features of brain state, rather they are dynamic, perturbation-sensitive properties of neural systems.

Chowdhury et al. [7] re port that posterior insula–proximal rTMS – shown to produce analgesia in their prior study [8], was associated with a more positive pre-to-post change in frontocentral alpha ERSP following active compared to sham stimulation, although within-session changes were not significant. This pattern reflects a difference-in-differences interaction rather than a clear increase after active rTMS, pointing to a relative modulation of evoked alpha power and suggesting that perturbation-evoked alpha responses may track aspects of the analgesic process. Bayesian analysis and a substantial interaction effect size support the interpretation that this modulation is meaningful. This interaction, however, does not fully disambiguate the underlying pattern: it could reflect a decline in the sham condition, a modest increase after active stimulation, or both. As such, the data do not establish whether the effect reflects true enhancement, sham-related decrease, or relative preservation of alpha reactivity. Unlike prior work from the same group [9], no significant reduction in frontocentral ERSP from baseline to the pre-rTMS assessment during ongoing capsaicin-induced pain was observed in this dataset, possibly because recordings did not capture peak pain. Consequently, the rTMS-related relative increase cannot be interpreted as a restoration of a suppressed alpha state, but rather as a state-dependent modulation whose relationship to ongoing pain intensity remains to be clarified.

Importantly, this effect should be interpreted alongside the complementary – though exploratory – ITC findings. At the group level, parietal–occipital alpha ITC did not show a significant rTMS-related modulation, a null result that may reflect insufficient power rather than a true absence of effect. Exploratory analyses nonetheless revealed that lower pre-rTMS ITC predicted greater analgesic response in the active condition, a finding consistent with prior work from the same group in patients with chronic pain [10]. This pattern raises the possibility that power- and phase-based measures of alpha reactivity capture

DOI of original article: https://doi.org/10.1016/j.neurot.2026.e00915.
* Institute of Neuroscience (IoNS), Université catholique de Louvain, Brussels, Belgium.
E-mail address: giulia.liberati@uclouvain.be.

https://doi.org/10.1016/j.neurot.2026.e00929
Received 8 May 2026; Accepted 9 May 2026

distinct aspects of the analgesic process – ERSP potentially reflecting a state-dependent shift in cortical excitability, and ITC potentially capturing individual characteristics of network organization that constrain responsiveness to stimulation. Whether ERSP and ITC genuinely reflect separable functional dimensions – and whether this distinction has practical implications for biomarker development – is an open question that adequately powered, prospective studies will need to address. If this dissociation holds in larger samples, it would suggest that neuromodulation may act primarily on one dimension of alpha dynamics (power/excitability), while clinical response is partly constrained by another (phase stability).

This distinction aligns with a broader conceptual shift toward reactive network dynamics. As pain arises from the interaction between endogenous brain dynamics and external perturbations [11], the most informative biomarkers may not be static features such as baseline power or peak frequency alone, but rather how neural systems respond to perturbation. Within this framework, ERSP and ITC capture complementary aspects of reactivity: amplitude modulation and temporal alignment. If this dissociation holds in larger samples, it would suggest that neuromodulation may act primarily on one dimension of alpha dynamics (power/excitability), while clinical response is partly constrained by another (phase stability/synchronization). Such a perspective naturally extends toward individualized interventions, in which distinct features are used for prediction, stratification, and real-time control of stimulation parameters [12].

An interesting aspect of this work by Chowdhury et al. [7] is the pr oposal that TMS-evoked responses at M1 may provide an indirect window onto distributed network dynamics. The modulation of frontocentral ERSP following posterior insula–proximal rTMS raises the possibility that these responses reflect interactions within a broader insular–opercular–thalamocortical system. This is a compelling hypothesis, given that M1 is densely interconnected with premotor and somatosensory regions and embedded within networks linking motor, insular, and thalamocortical systems involved in action control and pain processing [13]. Through these pathways, perturbations at M1 can engage widespread cortical and subcortical circuits, making its evoked responses a plausible remote readout of distributed network state. While the present data remain indirect, this framework provides a useful conceptual bridge between local perturbations and large-scale network dynamics.

Several aspects of the study also point to clear directions for future work. First, as a secondary analysis of a dataset originally powered for TMS-evoked potentials, the findings would benefit from confirmation in studies specifically designed and powered for time–frequency measures. In particular, replication will help refine estimates of ERSP effects and clarify the role of ITC at the group level. Second, the use of the Fast-PSI method without individual MRI-based neuronavigation reflects a pragmatic approach [14], but likely engages a broader insular–opercular network rather than the posterior insula in isolation – an aspect that future studies could address with more precise targeting. Finally, the predictive ITC results, while compelling, remain exploratory and call for validation in larger, independent cohorts. Taken together, these considerations reinforce the promise of the ERSP/ITC framework, while highlighting the importance of prospective, adequately powered studies to establish its robustness and clinical utility.

The present findings also point toward concrete methodological directions. If ERSP signals state-dependent excitability, it could in principle inform *when* a network is in a modifiable state – directly relevant to state-dependent TMS paradigms, which have shown that stimulation effects depend critically on ongoing oscillatory activity at delivery [15]. Real-time EEG-triggered TMS already exploits this logic at the level of instantaneous alpha phase [16], and extending such approaches to pain-relevant networks is a natural next step. ITC, by contrast, is not directly translatable into a real-time signal, but related measures – instantaneous phase or short-window phase stability – could serve as proxies for the network susceptibility that it appears to index. Together, ERSP and ITC point toward a closed-loop framework in which stimulation timing is guided by state-dependent excitability, while individual responsiveness is predicted from phase-based network metrics [17].

If the proposed dissociation between ERSP and ITC holds – one tracking the analgesic process, the other predicting individual responsiveness – it would suggest that moving toward multidimensional oscillatory profiles, in which different measures serve distinct functions, is crucial to enable state monitoring, responder stratification, and real-time guidance of stimulation. Chowdhury et al. give this vision a concrete direction to build upon.

Funding

Giulia Liberati is funded by F.R.S.-FNRS and by the Fondation Médicale Reine Elisabeth (F.M.R.E.).

Author contributions

Giulia Liberati was the sole author and contributor to the invited commentary titled “Alpha oscillations in pain neuromodulation: from resting rhythms to reactive networks” commenting on the accepted article by Chowdhury et al. “Modulation of Evoked Alpha Oscillatory Activity in the Frontocentral Region during Analgesia by Non-Invasive Brain Stimulation”.

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.

References

[1] Soliman N, Moisset X, Ferraro MC, de Andrade DC, Baron R, Belton J, et al. Pharmacotherapy and non-invasive neuromodulation for neuropathic pain: a systematic review and meta-analysis. Lancet Neurol 2025;24(5):413–28.
[2] Spagna A, Attal N. Pharmacotherapy and noninvasive neurostimulation for neuropathic pain. Presse Med 2024;53(2):104233.
[3] Garcia-Larrea L. Non-invasive cortical stimulation for drug-resistant pain. Curr Opin Support Palliat Care 2023;17(3):142–9.
[4] Nir RR, Sinai A, Moont R, Harari E, Yarnitsky D. Tonic pain and continuous EEG: prediction of subjective pain perception by alpha-1 power during stimulation and at rest. Clin Neurophysiol 2012;123(3):605–12.
[5] Furman AJ, Meeker TJ, Rietschel JC, Yoo S, Muthulingam J, Prokhorenko M, et al. Cerebral peak alpha frequency predicts individual differences in pain sensitivity. Neuroimage 2018;167:203–10.
[6] Chowdhury NS, Bi C, Furman AJ, Chiang AKI, Skippen P, Si E, et al. Predicting individual pain sensitivity using a novel cortical biomarker signature. JAMA Neurol 2025;82(3):237–46.
[7] Chowdhury NS, Millard SK, de Martino E, Larsen DB, Seminowicz DA, Schabrun SM, et al. CNSe. Modulation of evoked alpha oscillatory activity in the frontocentral region during analgesia by non-invasive brain stimulation. Neurotherapeutics 2026.
[8] Chowdhury NS, Millard SK, de Martino E, Larsen DB, Seminowicz DA, Schabrun SM, et al. Posterior-superior insula repetitive transcranial magnetic stimulation reduces experimental tonic pain and pain-related cortical inhibition in humans. Pain 2025;166(6):1314–27.
[9] De Martino E, Casali A, Casarotto S, Hassan G, Couto BA, Rosanova M, et al. Evoked oscillatory cortical activity during acute pain: probing brain in pain by transcranial magnetic stimulation combined with electroencephalogram. Hum Brain Mapp 2024;45(6):e26679.
[10] De Martino E, Bach MM, Jakobsen A, Couto BN, Chowdhury NS, Ingemann-Molden S, et al. Lower pre-treatment TMS-Evoked cortical reactivity and alpha-band oscillatory dynamics predict efficacy of primary motor cortex neuromodulation for chronic pain. Neuroimage 2026;333:121931.
[11] Ploner M, Sorg C, Gross J. Brain rhythms of pain. Trends Cogn Sci 2017;21(2):100–10.
[12] Ciampi de Andrade D, Garcia-Larrea L. Beyond trial-and-error: individualizing therapeutic transcranial neuromodulation for chronic pain. Eur J Pain 2023;27(9):1065–83.

[13] Gordon EM, Chauvin RJ, Van AN, Rajesh A, Nielsen A, Newbold DJ, et al. A somato-cognitive action network alternates with effector regions in motor cortex. Nature 2023;617(7960):351–9.
[14] da Cunha PHM, Tanaka H, Lapa J, Dongyang L, Boa Sorte AAJ, Pereira TMR, et al. The fast-posterior superior insula (Fast-PSI): a neuronavigation-free targeting method for non-invasive neuromodulation. Brain Stimul 2022;15(5):1178–80.
[15] Zrenner C, Belardinelli P, Ziemann U. Oscillatory brain state-dependent stimulation with transcranial magnetic stimulation combined with electroencephalography. Nat Protoc 2026. https://doi.org/10.1038/s41596-025-01309-7. Epub ahead of print. PMID: 41760982.
[16] Stefanou MI, Baur D, Belardinelli P, Bergmann TO, Blum C, Gordon PC, et al. Brain state-dependent brain stimulation with real-time electroencephalography-triggered transcranial magnetic stimulation. J Vis Exp 2019;150.
[17] Zrenner C, Ziemann U. Closed-loop brain stimulation. Biol Psychiatry 2024;95(6):545–52.