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Comment on: Frontal HD-tACS enhances behavioral and EEG biomarkers of vigilance in continuous attention task

Dear Editor,

The recent work by Gebodh et al., titled: *Frontal HD-tACS enhances behavioral and EEG biomarkers of vigilance in continuous attention task* [1] is a welcomed and advancing study which furthered our understanding of how transcranial electrical stimulation (tES) might modulate vigilance behaviours and their associated physiological markers. In two successive experiments, they present findings which indicate that 30Hz HD-tACS delivered in a frontal montage, as opposed to motor montage, modulates behavioural and neurophysiological markers of vigilant attention, without associated somatic arousal (e.g., cardiovascular and sleepiness). These findings are important, and not without commendation, particularly for the publication of an impressive brain stimulation dataset which can be used to pursue novel, and reproducible, advances in the field of brain stimulation. We wish to comment, however, on the secondary claims of this paper, which state that despite behavioural and neurophysiological modulation, there is no evidence for a peripheral or transcutaneous mechanism.

The authors used a crossover design, comparing a series of markers between conditions within individuals. This included performance on a behavioural compensatory tracking task, sleepiness, heart-rate variability (RMSSD), and EEG markers (Delta/Theta ratio, Alpha/Theta ratio). Here we focus on arousal measures to discuss a significant claim of the paper: that given a lack of differences between motor and frontal montage stimulation on arousal measures, the effects are not mediated via a peripheral mechanism. We intend to discuss how the authors provide little direct evidence to support this claim.

Our first observation was that although the increase in RMSSD did not differ significantly between groups, using the author's data set, we note that there was in fact an increase in RMSSD from pre-to-during in the F30 montage, as calculated by a one-sample Wilcoxon signed-rank test[1] with a test value of 0 % change (F30: median = 0.097, Z = 44.00, $p = 0.008$). However, there was no significant difference from 0 % change in the M30 montage: median = 0.036, Z = 32.00, $p = 00.301$ (data retrieved from Ref. [2]). It may be that inter-individual variability were driving these seemingly contradictory results. However, if we follow the reasoning that RMSSD is a reliable measure of sympathetic arousal (which itself is difficult to attribute entirely to vagal function [3]), the above analysis is evidence of autonomic modulation in the frontal montage, during which behavioural modulation was reported.

This observation was similarly shown with vagus nerve stimulation (VNS) [4], and in effect, describes the non-specific peripheral effect which the authors conclude is *not* driving the observed behavioural and electrophysiological changes. We reason that the behavioural changes (and subsequent arousal change) were not observed in the M30 montage due to electrode placement, given that innervation of cranial nerves in the scalp is prevalent in the forehead, coinciding with AF3 electrode placement. Conversely, the motor montage has less overlap with nerve innervation that has been previously associated with modulation (i.e., trigeminal, occipital).

In parallel, however, the behavioural and neurophysiological differences could then be driven simply by the task pairing. By this, we mean to describe the importance of domain-specific pairing which elicits changes mediated by arousal based on task demand. Animal models have shown indeed that stimulation and task temporal pairing is essential for driving peripheral effects, drawing attention to the concept of targeted plasticity [5]. As an example, rats receiving VNS paired with auditory tones resulted in reorganization of the auditory cortex [5], while rats receiving VNS paired with a motor task resulted in reorganization of the motor cortex [6]. In both instances, the same intervention produced neural changes which were domain specific. Thus, we agree with the authors that there is no evidence of montage-specific arousal when compared to each-other, but caution that the lack of differences between stimulation montages does not indicate against a peripheral hypothesis.

Instead, we suggest that this arousal effect simply becomes apparent in areas and domains in which there is engagement, in this case, regions driving vigilance performance in frontal, but not motor, areas. Furthermore, more sensitive and time-specific measures of arousal such as pupillometry [7] could provide further support, in favour of, or against, a peripheral mechanism. In future, in order to effectively argue against a peripheral mechanism, more direct evidence where the peripheral mechanism is experimentally blocked, or placebo/sham stimulation groups are compared are necessary. Indeed, prior work has blocked peripheral mechanisms in rodents [8] and humans [9] and in fact demonstrated that stimulations' effects were consequently impacted.

We commend the authors on the creation of an important database, but caution that in absence of a sham or placebo-controlling groups or more direct mechanistic approaches, it is difficult to conclude that peripheral mechanisms are not at play based strictly on non-specific arousal.

CRediT authorship contribution statement

Gabriel Byczynski: Writing – original draft, Writing – review & editing. **Elva Arulchelvan:** Writing – original draft, Writing – review & editing. **Sven Vanneste:** Writing – original draft, Writing – review &

[1] Due to violations of assumptions of normality via Shapiro-Wilk $p < 0.001$.

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Declaration of competing interest

None.

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