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

1. Background

Dear Editor,

We published the GX dataset; one of the largest (>4340 hours) open-source, concurrent brain stimulation (HD-tES; 3 brain regions x 3 waveforms), EEG, ECG, and behavioral datasets [1]. The GX dataset supports democratized, reproducible, and transparent data-driven analysis of HD-tES effects on performance in a vigilant attention task and whether biomarkers either predict or explain behavioral changes [2]. Here we use the GX dataset to show preliminary evidence that frontal 30 Hz HD-tACS enhances acute vigilant attention and associated EEG biomarkers, compared to motor 30 Hz HD-tACS. Absence of effects between stimulation conditions on sleepiness or cardiovascular biomarkers (heart rate variability-HRV) argue against non-specific (peripheral stimulation) arousal effects.

The GX experiment (open dataset, as described in Ref. [1]) was designed to assess the effects of acute noninvasive transcranial Electrical Stimulation (tES) on continuous vigilance with behavioral and neuro/-physiological markers. The GX dataset was collected in two repeated measures crossover design experiments. In Experiment 1, nine doses were selected for their potential to enhance vigilant attention; frontal (Dorsolateral prefrontal cortex- DLPFC, ascending reticular activating system- ARAS), parietal (downstream attention network), or motor (motor cortex excitability/function) and spanning three stimulation waveforms [3–9]. Experiment 2 down selected two tES doses based on results from Experiment 1, with increased trials per condition. Experiments 1 and 2 were designed without any *a priori* superiority between the tested conditions.

Within the GX dataset, Experiment 2 consisted of two active experimental arms (30 sessions total; Fig. 1c): frontal 30 Hz HD-tACS (F30), and motor 30 Hz HD-tACS (M30). Participants (N = 9, Female: 4, mean: 29 ± 5 years, range: 20–36 years) underwent 70 min experimental sessions for each arm (Fig. 1a–b), where they performed a compensatory tracking task (CTT) [10]. After a 20 min task acclimation period, F30 or M30 stimulation was applied intermittently with 20 trials of 30 sec of stimulation (see Ref. [1]). Acclimation periods prior to each experiment accommodated participants' transition to lowered vigilant states to avoid potential ceiling effects. Prior to the start of each session, using brief test doses, participants reported no significant discomfort (VAS pain) and absence of phosphenes. Here we directly compare the effects of frontal versus motor 30 Hz tACS on behavioral and physiological vigilance outcomes.

To quantify the effects of frontal and motor 30 Hz tACS on vigilant attention, we accessed behavioral (CTT, Karolinska Sleepiness Scale-KSS), cardiac HRV (ECG-based root mean square of successive differences -RMSSD; and low frequency high frequency ratio -LF/HF ratio), and neurophysiological (EEG-based parieto-occipital alpha/theta and delta/theta ratios) markers of vigilance.

The CTT assessed continuous vigilance performance without salient interruptions or interactions with inherent vigilance decrement over time [10,11]. KSS measured subjective sleepiness, to assess prolonged changes in vigilance [12,13]. Time (RMSSD) and frequency (LF/HF ratio) cardiac measures assessed changes in acute autonomic function (in regard to vigilance); and to control for non-condition-specific changes with peripheral stimulation [14,15]. Parieto-occipital EEG frequency band ratios (delta/theta, alpha/theta) were selected as neurophysiological markers of vigilance [11,16–21].

2. Methods

All outcomes were calculated as the percent change for each 30 sec stimulation from immediately pre to either during (taken over 30 sec; CTT, ECG outcomes) or immediately post (taken over 30 sec; CTT, EEG outcomes) stimulation (e.g. Fig. 1d). Except KSS which was calculated pre session to post session. Data from participants who repeated sessions were aggregated (see Ref. [1]).

Behavioral data (CTT deviation) was resampled to 100 Hz and smoothened with a 5-sec moving average filter, prior to computing the percent change in CTT deviation. EEG data were baseline corrected (between 1 and 25 secs after the start of each session), bandpass filtered (0.35–40 Hz, 2nd order Butterworth filter), and partitioned using trial-wise trigger codes (Fig. 1b). Power spectral density (PSDs) calculations were performed on each 30-sec EEG data segment using the Welch's power spectral density estimate and EEG band power was calculated as the area under the PSD curve [22]. EEG outcomes were calculated from the aggregate of electrodes P8, P4, O2, P7, P3, and O1. EEG data during stimulation was not examined in order to avoid nonlinear artifacts [23,24]. ECG data were similarly processed, with data down sampling to 1k Hz followed by ECG R-peak detection and calculations of time (RMSSD) and frequency metrics (LF/HF ratio) [25].

Paired outcomes for F30 and M30 were compared directly (two tailed *t*-test or Wilcoxon signed-rank test) under the null hypothesis of no difference between groups (α = 5 %) with multiple comparison correction (Benjamini & Hochberg procedure [26]) and effect size calculation (Robust Cohen's *d* [27] or matched-pairs rank biserial correlation coefficient *r* [28]). Analyses were performed using MATLAB (2019b, 2022b) and Python (3.11.0). Analysis code and processed data can be found here: https://github.com/ngebodh/GX_tES_EEG_Physio_Behavior/tree/master/GX_F30vM30 [29].

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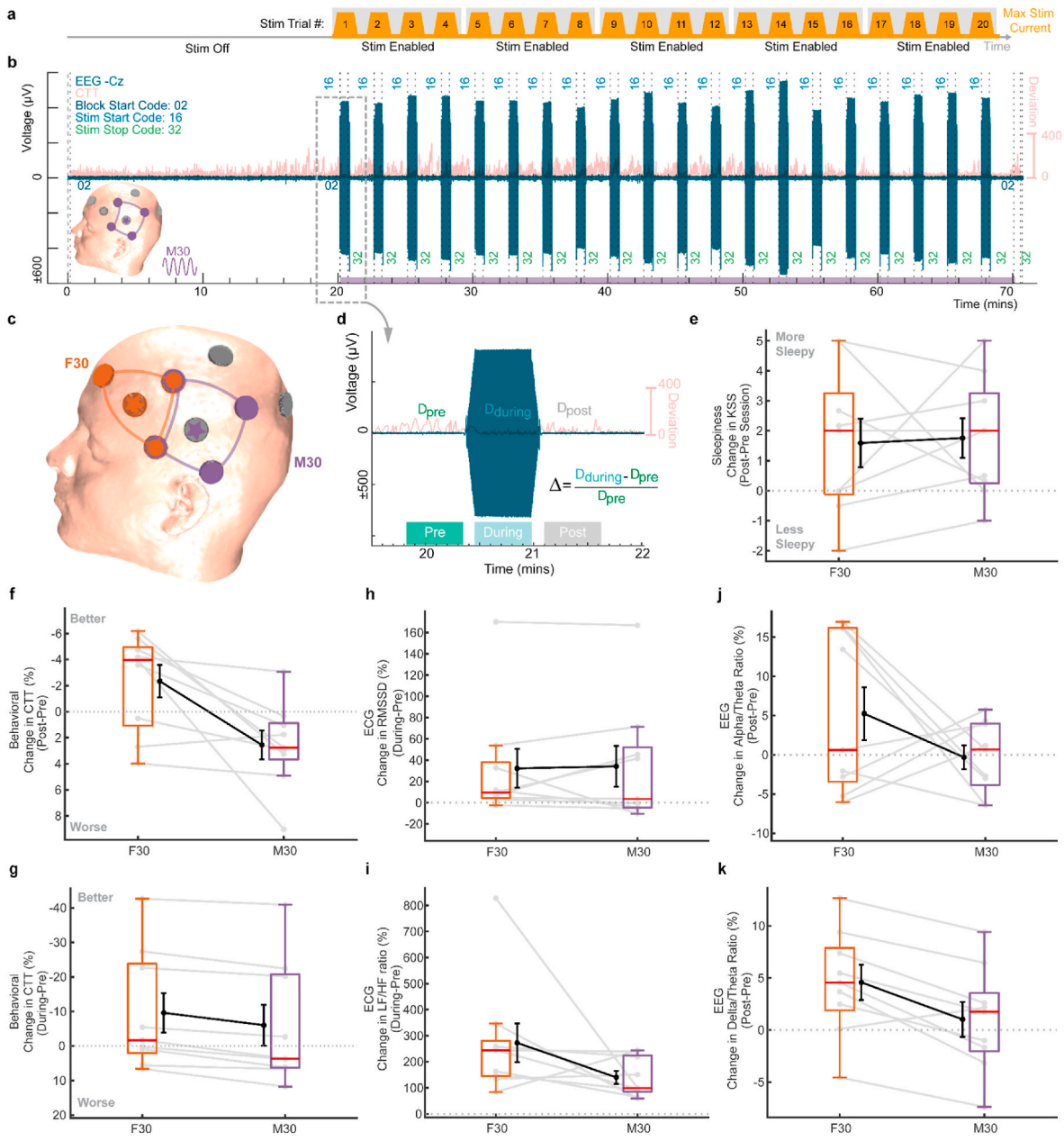

Fig. 1. Comparing effects of F30 and M30 stimulation on vigilance/attentional outcome measures. a) GX dataset Experiment 2 session timeline with 20 min acclimation period followed by 20 trials of stimulation (either F30 or M30 per session). **b)** Example session where M30 stimulation was applied with concurrent EEG and CTT data (concurrent ECG not shown). **c)** MRI-derived head model used to visualize stimulation electrode placement for F30 (3X1 HD-tES) and M30 (4X1 HD-tES). **d)** Example stimulation trial segmented into 30 sec pre, during, and post stimulation. All percent changes were calculated in regard to each trials' pre-stimulation period (i.e. see inset); except for the KSS (difference from pre to post session). **e)** Change in subjective sleepiness before and after each session quantified with the KSS. **f)** Behavioral change in CTT deviation from pre to post stimulation. **g)** Behavioral change in CTT deviation from pre to during stimulation. **h)** Change in RMSSD-based HRV from pre to during stimulation. **i)** Change in LF/HF ratio-based HRV from pre to during stimulation. **j)** EEG change in alpha/theta ratio from pre to post stimulation. **k)** EEG change in delta/theta ratio from pre to post stimulation. **f-k** depict the average over 20 trials for each participant with group means and standard error of the mean as error bars as well as medians within each boxplot.

3. Results

Subjective sleepiness/general arousal (**KSS**) was assessed at the beginning and end of each session (Fig. 1e). Sleepiness increased, however, there was no significant difference between F30 (median: 2, IQR: 2.88) and M30 (median: 2, IQR: 3.25); $z = -0.36$, $p = 0.72$, $r = 0.16$. This suggested that neither stimulation types had prolonged effects on reducing (KSS assessed) sleepiness or at increasing prolonged vigilance.

Acute changes in vigilant attention was quantified with the **CTT**. There was a significant difference in the change in mean CTT task performance (during minus pre stimulation) between F30 (mean: 9.61 ± 17.18) and M30 (mean: 6.01 ± 17.74); $t(8) = -6.50$, $p < 0.001$, $d = 0.16$ ($p = 0.001$, BH correction; Fig. 1f). Thus, F30 improved acute behavioral vigilant attention as compared to M30. These improvements carried over to post stimulation periods with a significant difference in the change in mean CTT task performance (post minus pre stimulation) between F30 (mean: 2.34 ± 3.75) and M30 (mean: 2.56 ± 3.30); $t(8) = -3.20$, $p = 0.013$, $d = 1.21$ ($p = 0.029$, BH correction; Fig. 1g). This suggested that F30 had immediate enhancement effects on acute

behavioral vigilant attention, which persisted up to 30 secs after stimulation cessation, as compared to M30.

There were no significant differences in acute **ECG**-derived measures of HRV, namely in RMSSD (during minus pre stimulation) between F30 (median: 9.68, IQR: 33.84) and M30 (median: 3.61, IQR: 56.79); z = 0.18, p = 0.86, $r = 0.07$; or LF/HF ratio (during minus pre stimulation) between F30 (median: 243.94, IQR: 134.87) and M30 (median: 99.11, IQR: 138.32); z = 1.60, p = 0.11, $r = 0.60$ (Fig. 1h–i). This refuted the notion that non-specific (e.g. peripheral/cranial nerve stimulation) effects were responsible for driving relative task performance changes due to the lack of relative change in HRV markers [15,30–32].

The **EEG** alpha/theta ratio increased from pre to post stimulation with F30; indicating increases in arousal, and vigilant attention (with decreased theta activity) with increased mental effort (associated with alpha increases) [20,33–35]; however, there was no significant difference in the change in alpha/theta ratios (post minus pre stimulation) between F30 (median: 0.60, IQR: 19.59) and M30 (median: 0.66, IQR: 7.85); z = 1.13, p = 0.26, $r = 0.42$ (Fig. 1j). There was a significant difference in the change in delta/theta ratios (post minus pre stimulation) between F30 (mean: 4.57 ± 5.07) and M30 (mean: 1.01 ± 5.05); t (8) = 4.19, p = 0.003, $d = 0.69$ (p = 0.01, BH correction; Fig. 1k). This suggested a relative enhancement in vigilant attention by decreased theta activity with concurrent fatigue inhibition driven by increases in delta activity for F30, as compared to M30 [17,19–21,33,36].

4. Conclusion

Using the open-source GX dataset we present preliminary evidence that frontally applied HD-tACS at 30 Hz (F30) can produce behavioral (CTT) and neurophysiological (delta/theta ratio) vigilant attention enhancement without associated cardiovascular (HRV) or prolonged subjective sleepiness (KSS) changes, as compared to motor HD-tACS at 30 Hz. These findings are consistent with frontal 30 Hz HD-tACS enhancing acute vigilance and attention during continuous task performance, and generally for the role of the frontal cortex in mediating vigilant attentional activity.

CRediT authorship contribution statement

Nigel Gebodh: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Vladimir Miskovic:** Writing – review & editing, Resources, Methodology, Conceptualization. **Sarah Laszlo:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Abhishek Datta:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Conceptualization. **Marom Bikson:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

The authors declare no competing non-financial interests but the following competing financial interests. Nigel Gebodh has consulted for HUMM and been employed by Soterix Medical Inc. Vladimir Miskovic and Sarah Laszlo have been employed by Alphabet Inc. Abhishek Datta and Marom Bikson and have equity in Soterix Medical Inc. The City University of New York holds patents on brain stimulation with Marom Bikson as inventor. Marom Bikson consults, received grants, assigned inventions, and/or serves on the SAB of SafeToddles, Boston Scientific, GlaxoSmithKline, Biovisics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Humm, Allergan (AbbVie), Apple, Ybrain, Ceragem, Remz.

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