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Occipital nerve stimulation selectively modulates top-down inhibitory control

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Dear Editor,

Modulating executive function using transcranial electrical stimulation (tES) is a difficult feat with an inconsistent track record of success [1]. One methodological approach is to use direct (tDCS) or alternating (tACS) current stimulation to modulate neural plasticity, improving behaviour via either bottom-up or top-down mechanisms [2]. However recent research suggests that tES methods possess discrepancies between the current needed to induce changes, and those which are actually achieved in typical stimulation experiments [3].

Novel approaches to modulating neural activity via peripheral nerve stimulation have been developed, including non-invasive stimulation of the greater occipital nerve (NITESGON). Using NITESGON, research has successfully modulated neural activity governing memory processes, with evidence toward a norepinephrine-driven mechanism through the Locus Coeruleus (LC-NE) [4]. Following this evidence, we chose to pursue a series of two experiments which investigate if attentional control can be modulated using NITESGON. Two pathways of modulation, either via top-down goal directed processes or bottom-up stimulus driven processes, could be selectively modulated via the peripheral nerve through subcortical activity.

47 participants with no tES contraindications nor psychiatric diagnoses were recruited to participant in 1 of 2 experiments. In both experiments, participants completed training blocks while either receiving 40Hz (selected as opposed to tDCS due to mechanism in previous work [5]) NITESGON at 1.5mA for the duration of the task (stimulation group), or sham 1Hz NITESGON for 30 seconds before beginning the training (control group), and then returned after a period of time of the testing blocks without stimulation. Thus, we endeavoured to determine if pairing NITESGON with training would induce plasticity and improve/sustain behaviour (Fig. 1A). Alternating-current occipital nerve stimulation was delivered using a DC-Stimulation Plus device from NeuroConn (Germany). Saline-soaked electrodes (35 cm^2) were placed on the C2 nerve dermatome equidistant from each ear and each-other, with cathode place on left hemisphere, and anode placed on right [4,5].

In Experiment 1 (Fig. 1B), 23 participants (9 female, 14 male; Mean age = 21.8, SD = 0.9) were randomly allocated to the stimulation group (n = 12) or the control group (n = 11). Participants completed 4 blocks of a sustained-attention task (Sust-att-RT) in which they were asked to respond only when shown a specific letter, and to withhold responding for any other letter. 1 hour later, participants returned to complete 4 blocks of the same task, with modified character stimuli (e.g., size) to alter task demands. We chose 1 hour to allow participants a break, but short enough that sustained attention may still be impacted.

In Experiment 2 (Fig. 1C and D), 24 participants (23 female, 1 male; Mean age = 22.0, SD = 4.6) were randomly allocated to the stimulation group (n = 12) or the control group (n = 12). Participant completed 2 blocks of a stop-signal reaction time task (Stop-sign-RT) in which they were asked to respond by pressing the arrow key in the direction indicated by the arrow on the screen. In some trials (25 %), the arrow would change to red after 200 ms, and participants were asked to withhold responding (Fig. 1C). During the day 2 testing session, participants were given a similar task (Stop-change-RT; stop-change reaction time), in which instead of a colour change, participants heard an auditory stimulus 150 ms after initial presentation, which indicated to participants they should withhold the initial response, and redirect to the up-arrow (Fig. 1D).

In both experiments participants completed a modified version of the task to probe the same domain (e.g., attention), but prevent task-specific effects from obscuring cognitive modulation. Participants reported a group-guess and completed a follow-up tES questionnaire to gauge discomfort.

In experiment 1, there were no significant differences in NoGo accuracy between active and control groups during either training ($F(1,20) = 0.02$, $p = 0.88$, $\eta_p^2 = 0.001$) or testing ($F(1,20) = 0.19$, $p = 0.67$, $\eta_p^2 = 0.01$) (Fig. 1E). There was no significant difference in reaction time between groups during training ($F(1,20) = 0.08$, $p = 0.77$, $\eta_p^2 = 0.004$) or testing $F(1,20) = 0.24$, $p = 0.63$, $\eta_p^2 = 0.01$) (Fig. 1F). We therefore found that NITESGON did not improve or sustain inhibitory ability in the sustained attention task, even after a 1 hour recovery period.

In experiment 2, day 1 training revealed that Stop-sign-RT did not differ between groups in reaction time ($F(1,19) = 0.594$, $p = 0.45$, $\eta_p^2 = 0.03$), nor accuracy ($F(1,19) = 0.594$, $p = 0.45$, $\eta_p^2 = 0.03$) (Fig. 1G).

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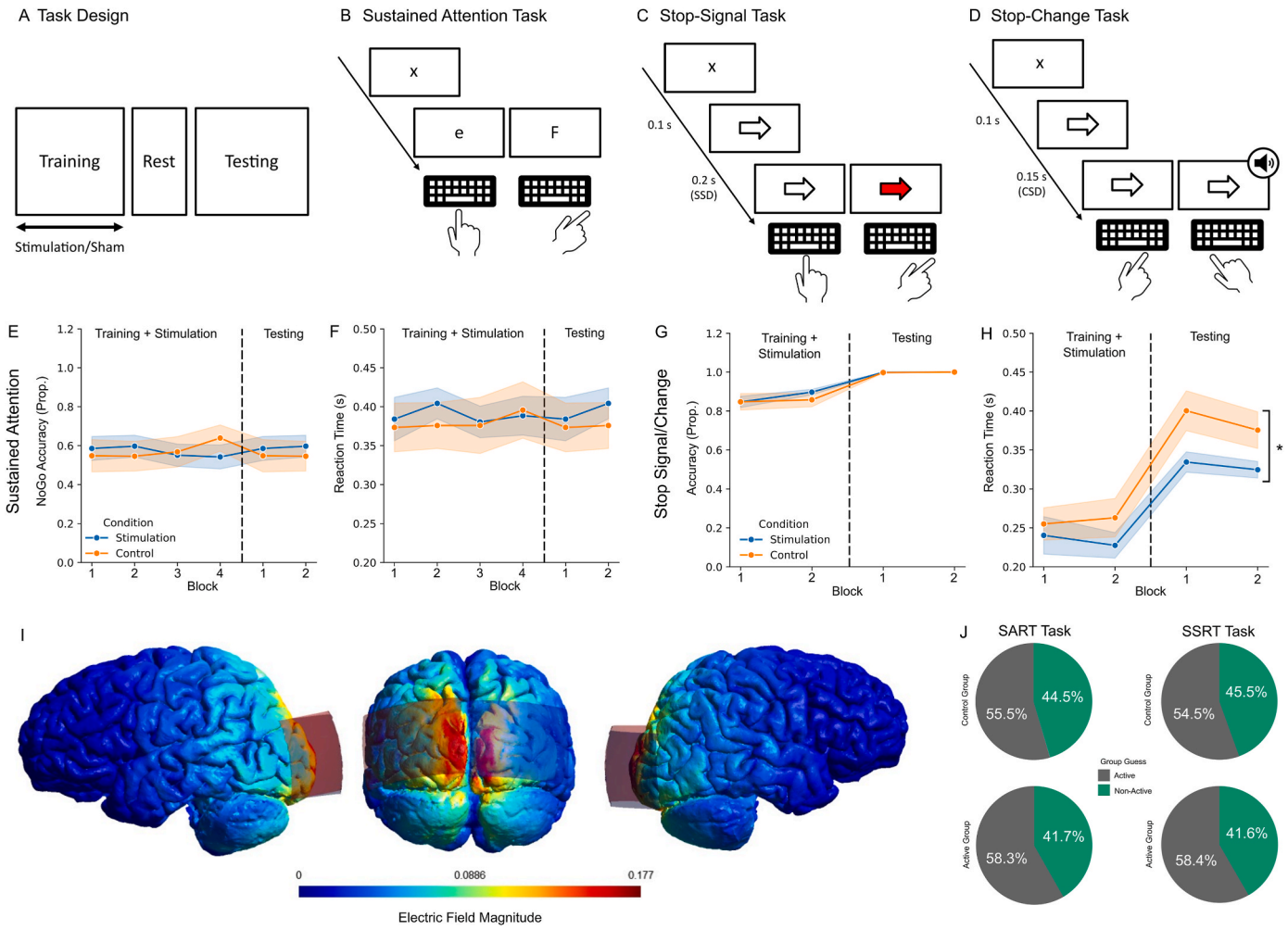

Fig. 1. A) Task design for experiment 1 and 2. B) Experiment 1 (Sust-att-RT)) study design. C) Experiment 2, day 1 (Stop-sign-RT) study design. D) Experiment 2, day 2 (Stop-change-RT) study design. E) NoGo accuracy during the training and testing sections of the Sust-att-RT) (1 hour break between training and testing). F) Reaction time during the training and testing sections of the Sust-att-RT). G) Accuracy in the training and testing sections of the Stop-sign-RT/Stop-change-RT. H) Reaction time in the training and testing sections of the Stop-sign-RT/Stop-change-RT. *$p < 0.05$. I) Current modelling for NITESGON. J) Group guess for Sust-att-RT and Stop-sign-RT experiments. The Sust-att-RT refers to the response time from stimulus to response. In experiment 2, the reaction time refers to the calculated values of Stop-sign-RT/Stop-change-RT (i.e., mean [RT] – stop-signal delay (SSD)).

Interestingly, 24 hours later, the Stop-change-RT was significantly faster (corrected threshold for both accuracy and reaction time analysis: $p_{corr} < 0.025$) ($F(1,20) = 5.835$, $p = 0.02$, $\eta_p^2 = 0.23$), in the group that received 40 Hz stimulation (mean Stop-change-RT = 0.33s, SD = 0.04s) compared to the sham group (mean Stop-change-RT = 0.39s, SD = 0.08s) (Fig. 1H). There was no significant difference in accuracy between groups ($F(1,19) = 0.157$, $p = 0.696$, $\eta_p^2 = 0.008$) (Fig. 1G).

Current modelling was performed in SimNIBS [6] using 1.5mA current intensity, 5 × 7 cm electrode pads placed over the C2 dermatome at approximately ear-height, equidistant from each ear and each-other, with cathode place on left hemisphere, and anode placed on right, identical to our stimulation parameters. (Fig. 1I). This illustrates the theoretical current distribution using NITESGON placement if it were driven by a primarily transcranial mechanism. Here, previous work has shown that gamma stimulation to the occipital region can modulate selective attention [7], however the task-specificity of our effect suggests against a general attentional improvement. There was no significant difference in group guess in either experiment, suggesting against a placebo-driven effect in either the Sust-att-RT task ($X^2 = 0.016$, $df = 1$, $p = 0.90$), or Stop-sign-RT task ($X^2 = 0.034$, $df = 1$, $p = 0.85$) (Fig. 1J)[1].

Previous work [8] has found that LC-NE stimulation increased goal-directed attention and response inhibition, fitting with our findings that NITESGON improved performance on the Stop-change-RT task compared to the control group. Additionally Bari et al. [8] reported that inhibition of the LC neurons increased impulsivity, akin to a stimulus-driven mode, thus following this interpretation, NITESGON stimulation in theory would not improve Sust-att-RT performance, given that the present interpretation is that Sust-att-RT performance is in-part predicted by stimulus-driven attention and bottom-up inhibition. Therefore, concurrent with the dual control mechanisms evidenced in previous work [8], NITESGON could be activating the LC [4], increasing top-down goal-directed processes without changing stimulus-driven, bottom-up processes, although additional neuroimaging and arousal measures are necessary to exclude other subcortical contributions due to the non-specific input to numerous brain centers.

CRediT authorship contribution statement

Gabriel Byczynski: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Roisin Farrelly:** Writing – review & editing, Software, Methodology, Investigation, Conceptualization. **Elias Dempsey:** Writing – review & editing, Software,

Methodology, Investigation, Conceptualization. **Iulia-Mara Scarlat:** Writing – review & editing, Validation, Methodology, Investigation. **Sven Vanneste:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Consent

This study was approved by the Trinity College Dublin ethics committee and carried out in accordance with declaration of Helsinki and EU GDPR. Written informed consent was obtained before the start of the first session.

Data availability

Behavioural data generated and used in this manuscript are published as the following dataset, made freely available.

Byczynski, G., Farrelly, R., Dempsey, E., Scarlat, I.-M., & Vanneste, S. (2024). Occipital Nerve Stimulation Selectively Modulates Top-down Inhibitory Control (1.0.0) [Data set]. Zenodo. https://doi.org/10.5281/zenodo.11046014.

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Declaration of competing interest

The authors report no declaration of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2025.01.004.

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