Novelty-dependent enhancement of sustained attention and electrophysiological signatures via transcutaneous auricular vagus nerve stimulation.

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Abstract

Background: Sustained attention, the ability to remain focused during a task relies on Locus coeruleus - Noradrenaline (LC-NA) activity with tonic activity regulating arousal and phasic responses facilitating stimulus processing. In animals, phasic LC activity also depends on novelty of situations, yet human evidence is missing.

Objective: We investigate how noninvasive vagus nerve stimulation affects behavioral and electrophysiological parameters of sustained attention during first exposure to a Go-Nogo task.

Methods: Transcutaneous auricular vagus nerve stimulation (taVNS) was used to noninvasively modulate activity in the LC-NA system in forty-four healthy participants (36 female) while they completed a gradual-onset Go-Nogo task on two days ≥ 24 hours apart while EEG was recorded. 500 ms taVNS was applied with each stimulus onset either in the first, novel or second, familiar session while sham stimulation was applied in the remaining session.

Results: When delivered during the first, novel session, taVNS accelerated reaction times, reduced response variability, and attenuated the typical block-wise decline in subjective focus. Concurrently, fronto-central P1-N1 and parietal N1-P2 amplitudes were enhanced, and larger P1-N1 amplitudes predicted faster responses, linking early cortical gain to behavioral performance. Improvements persisted into the next-day sham session, whereas taVNS applied only during the familiar second session was ineffective.

Conclusion: These results support a mechanistic account in which taVNS selectively enhances novelty-dependent phasic LC activity, underscoring context as critical for taVNS effects.

Introduction

Sustained attention refers to the ability to maintain focus on a task over time [1–3]. Go-Nogo paradigms, where participants respond to frequent "Go" stimuli while withholding a response to infrequent "Nogo" stimuli, are commonly employed to assess sustained attention. Failures in response inhibition (commission errors) indicate lapses of attention. Esterman and colleagues [1] refined this classical paradigm, noting that the abrupt stimulus onsets may exogenously capture attention while periods between trials provide unintended breaks, thereby reducing attentional demands. They developed the *gradual-onset Continuous Performance Task* (gradCPT) [1] where naturalistic images constantly transition into each other without clear on- and offset. Despite this continuous nature, the task retains a Go-Nogo structure: Frequent city scenes (Go) require a button press while infrequent mountain scenes (Nogo) require response inhibition, allowing the investigation of intra- and interpersonal fluctuations in sustained attention [1].

Neurophysiologically, sustained attention during discrimination tasks (i.e., Go-Nogo tasks) engages right-lateralized prefrontal regions like the right dorsolateral and medial prefrontal cortex (PFC), the right postcentral gyrus and the left posterior ventromedial PFC [4]. Additionally, the dorsal attention network, involving bilateral intraparietal sulcus and frontal eye fields [5], provides top-down control [6]. Optimal attentional performance further depends on cortical arousal, as both hypo- and hyperarousal impair attention [7].

A key regulator for arousal is the Locus coeruleus - Noradrenaline (LC-NA) system [8]. The LC, a small brainstem nucleus and main source of cortical noradrenaline [9], projects widely to cortical and subcortical areas, including prefrontal regions, implicated in attentional control [10]. It exhibits two distinct activity modes: A tonic background activity is strongly related to arousal [11] with low tonic activity during hypoarousal and high tonic activity during hyperarousal [8]. Intermediate tonic activity is associated with optimal task performance [12]. An additional phasic activity mode is triggered by behaviorally salient or novel stimuli and transiently increases cortical NA levels [7]. This mode is particularly relevant for attentional engagement, as it selectively amplifies processing in prefrontal and parietal regions critical for attentional control [13]. Studies in rodents suggest that phasic LC activity is also evoked by novel situations and that this response habituates over time [14]. Thus, tonic and phasic LC activity form a dynamic neuromodulatory system that enables flexible adaptation of attention to internal states and external demands [8].

Pharmacological studies further emphasize NA's role in sustained attention [15]. NA-reuptake inhibitors improved sustained attention in animal models [16] and humans [17] (but see Chamberlain et al. [18] for conflicting results) while a reduction in NA levels impaired sustained attention [19,20]. Notably, LC-NA activity decreases with age [21] and large-scale behavioral data confirm that the ability to sustain attention declines in older adults [2]. Together, these findings underscore the role of the LC–NA system in

sustained attention and raise the possibility that external activation of this system may improve attentional performance.

Transcutaneous auricular vagus nerve stimulation (taVNS) is a promising, non-invasive stimulation technique to modulate activity in the LC-NA system. Brief electric pulses are delivered to regions of the auricle innervated by the auricular branch of the vagus nerve (ABVN)[22]. The ABVN projects centrally to the nucleus tractus solitarius (NTS), which then projects to several areas including the LC [23,24]. Invasive vagus nerve stimulation in animals increased LC firing and cortical NA release [25–27]. Correspondingly, human imaging studies have demonstrated increased activation along the vagal afferent path, including the NTS and LC, following taVNS [28]. Optimal stimulation parameters are still under debate but recent studies showed higher effectiveness of short, phasic stimulation trains over tonic or continuous stimulation to engage the LC-NA system [29]. Especially taVNS applied in parallel with stimulus onset appears to effectively modulate LC-NA activity [30], suggesting that stimulation may be more effective when it coincides with ongoing neural activity.

These findings underscore the potential of taVNS to enhance sustained attention during the gradCPT. However, several important questions remain. The gradCPT has been extensively studied in behavioral [2,31] and neuroimaging studies [1,32]. Electrophysiological investigations, on the other hand, are scarce and have predominantly relied on intracranial recordings in clinical populations [33,34]. To date, no study has systematically examined EEG correlates of the gradCPT in healthy adults. TaVNS applications in Go-Nogo paradigms are also limited. Camargo et al. [35], for example, reported taVNS specific increases in N2 amplitudes during Nogo trials after controlling for handedness, mood and fatigue levels but found no modulation of the P3. In contrast, taVNS related reductions of the N2 amplitude in an Executive Reaction Time Test [36] and a Simon conflict task [37], both requiring cognitive control and response inhibition, have been reported. For the P3, increased amplitudes following taVNS in oddball paradigms [38–40] are reported although null findings also exist [37,41]. Behavioral results from Go-Nogo tasks during taVNS are likewise rare. While some studies report improved accuracy following taVNS [42,43], others found no effect [35] or even impaired performance [44]. Studies employing other paradigms demonstrated faster reaction times during an auditory oddball [38] and a visual dot probe task [39] as well as improved accuracy in an emotional Stroop task [30].

Here we investigate whether canonical event-related potential (ERP) components associated with response inhibition, namely the N2 [45] and the P3 [46], can be reliably elicited during the gradCPT despite its continuous stimulus transition. Furthermore, we examined whether taVNS modulates these electrophysiological markers as well as behavioral performance in a context-dependent manner. Based on the involvement of phasic LC–NA activity in sustained attention and the effects of taVNS on noradrenergic signaling, we hypothesized that taVNS would improve behavioral performance during the gradCPT, particularly when stimulation is applied during first task exposure. Behaviorally, we expected

faster and more stable reaction times; electrophysiologically, we anticipated robust, early ERP components, including N2 and P3 responses, that would be modulated by trial type (Nogo > Go) and enhanced under taVNS relative to sham stimulation, especially during initial task engagement.

Materials and Methods

Study sample

A total of 44 participants (36 female) aged between 18 and 30 (M = 21.7, SD = 3.2) took part in this study. Sample size was determined to match previous taVNS studies where behavioral and electrophysiological data were recorded [30,41]. All participants were right handed, had normal or corrected to normal vision and reported no history of neurological or psychological disorders. Exclusion criteria were the following: electrically active implants (e.g. pacemaker , cochlear implants), head injuries within the past 6 months, history of psychological or neurological disorders, psychoactive medication, arrhythmia, pregnancy. Written informed consent was obtained prior to participation. Recordings took place at the Otto-von-Guericke University, Magdeburg and the study was approved by the local ethics committee ('Ethical committee of the Otto-von-Guericke University Magdeburg'; Az:95/18). Participation was reimbursed with course credit or money.

Experimental procedure and task

We employed a single-blind, within-subject, counterbalanced design consisting of two sessions. In each session, participants performed the gradual-onset continuous performance task (gradCPT; adapted from Kucyi et al. [33]) while receiving either active taVNS or sham stimulation. The order of stimulation (taVNS first and sham first) was pseudo-randomized and balanced across participants. Sessions were spaced at least 24h and at most 7 days apart (M = 2.98, SD = 2.03, range: 1-7 days) with no significant difference between both order groups (t_{42} = -0.81, p = 0.42).

Following EEG and stimulation setup, participants performed four blocks of the gradCPT per session (Fig. 1A). Stimuli were presented using Matlab R2018b (The MathWorks, Inc., Natick, Massachusetts, United States) and the Psychtoolbox 3 [47–49]. Each block lasted approximately 9 minutes (Fig. 1B) and consisted of 375 trials. Stimuli were round, greyscale images of city scenes (Go trials, 90%) and mountain scenes (Nogo trials, 10%) adapted from the SUN database [50]. Images gradually faded into each other over a 1.3 s transition (Fig. 1C). Participants were instructed to press the space bar with their left index finger in response to city scenes and to withhold a response for mountain scenes. TaVNS or sham stimulation (see below) was applied at the onset of each new stimulus, i.e., when a new scene started to fade in (Fig. 1C). Each session started with two training runs of 1 min duration to familiarize participants with the task. In the first training run, transition time between stimuli was double (i.e. 2.6 s) while the second training run used the same transition duration as the actual experimental blocks. No stimulation was applied during these training runs.

Each block contained 9 thought probes presented approximately once per minute (Fig. 1B). During these thought probes, participants were first asked to rate the extent to which their attention was focused on the

task or elsewhere. A visual rating scale (VRS) was displayed, anchored with “only task” and “only something else”. Participants moved a cursor along the scale using arrow keys and confirmed their selection with the space key. A second question then assessed meta-awareness (i.e., to what extent they were aware about their focus of attention) using a similar VRS anchored with “completely aware” and “completely unaware”. Responses on both VRS were recorded on a 0-100 scale, though values were not displayed to participants. The task resumed immediately after the second response. Participants were allowed self-paced breaks between blocks.

At the end of each session, participants completed two questionnaires. The first assessed potential adverse effects of stimulation (e.g. headache, nausea, dizziness, skin irritation) on a 4-point scale from 0 (none) to 3 (strong). The second questionnaire asked participants to rate their confidence in monitoring their attentional focus during the thought probes, followed by ratings of how often periods of reduced task focus were due to external distractions, internal task-related thoughts (e.g., about performance or strategy), or task-unrelated thoughts (e.g., mind-wandering). These items were rated on a 7-point scale from 1 (completely not confident / never) to 7 (completely confident / always).

Electrical stimulation

Stimulation was applied as trains of monophasic, 200 μs long square wave pulses at 30 Hz for 500 ms coinciding with the onset of each picture as in recent studies [30,51]. For taVNS, electrodes were attached to the cymba conchae of the left auricle. For the sham stimulation, electrodes were attached to the scapha of the left auricle (Fig. 1D). In both cases, Ag/AgCl surface electrodes (Ambu Neuroline 700, Ambu, Germany), cut to a size of 4x4 mm and placed ca. 1 cm apart, were used. Prior to electrode placement, the skin was cleaned using disinfectant alcohol. A small amount of conductive paste (lic2 low impedance cream, www.cnsac-medshop.com) was used to assure proper conductance. Pulses were delivered by a Digitimer DS7A (Welwyn Garden City, UK) connected to the two electrodes. The Digitimer was controlled via custom Matlab scripts using the Data Acquisition Toolbox and a digital/analog converter (DAC; NI USB-6212, National Instruments, Austin, TX, USA). Stimulation intensity was set to 2 mA for all participants and tested before starting. If 2 mA felt uncomfortable, the intensity was reduced in 0.1 mA steps until no longer uncomfortable. The average stimulation intensity was 1.96 mA for sham (*SD:* 0.15) and 1.91 mA for taVNS (*SD* = 0.27). There was no statistical difference between conditions (t_{43}: 1.2, p = 0.24).

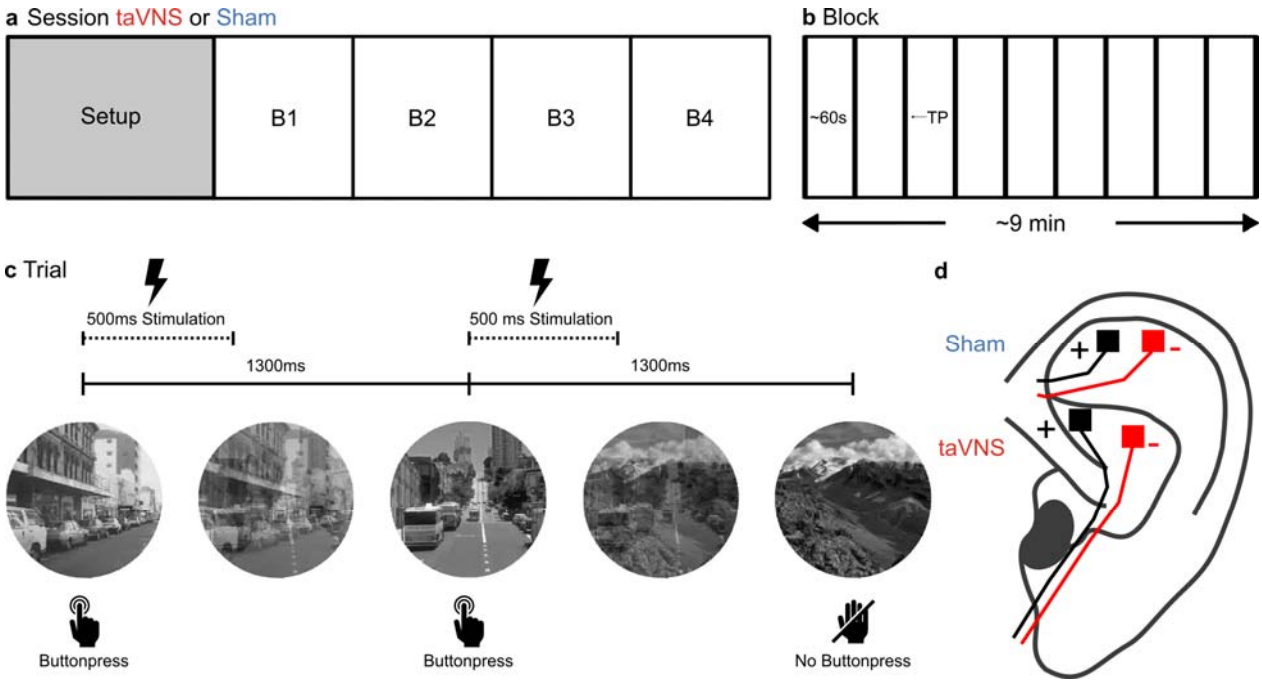

Fig. 1. Experimental design and stimulation protocol. *A) Session structure: Each participant completed two sessions in pseudorandomized order, receiving either transcutaneous auricular vagus nerve stimulation (taVNS) or sham stimulation. Following EEG setup, each session comprised four consecutive blocks of the gradual-onset continuous performance task (gradCPT). B) Block structure: Each block lasted ~9 minutes and contained 375 trials and 9 intermittent thought probes (TP) assessing subjective task focus. C) Task trial timeline: Stimuli consisted of round grayscale city (frequent Go) and mountain (rare Nogo) scenes that gradually transistioned every 1300 ms. Participants pressed a button for city scenes and withheld a response for mountain scenes. A 500 ms train of electrical stimulation was administered time-locked to each each stimulus onset in both, the taVNS and sham condition. D) Stimulation montage: For taVNS, electrodes were placed on the cymba conchae of the left ear. For sham, electrodes were placed on the scapha of the same ear, avoiding vagal innervation.*

EEG recording and processing

The EEG was continuously recorded throughout the task from 34 Ag/AgCl electrodes, placed according to the international 10-10 system, via a BrainAmp amplifier (www.brainproducts.com) with 1000 Hz sampling frequency. The online reference was placed on the nose, the ground electrode at AFz. Impedance for all electrodes was kept below 10 k . A salt free, abrasive, conductive paste (Abralyt 2000, Brain Products, Gilching, Germany) was used to ensure conductivity. A vertical electrooculogram (EOG) was recorded from below the right eye. Remaining electrodes were Fpz, Fp1, Fp2, F1, F2, F3, F4, F7, F8, FT9, FT10, FCz, Cz, C3, C4, CP5, CP6, T7, T8, TP9, TP10, Pz, P7, P8, POz, PO3, PO4, PO8, PO9, O1, O2, Iz, left and right mastoid.

Offline, the stimulation artifacts were removed from the EEG by applying a spatial filter derived via generalized eigendecomposition (GED) [52–54], implemented in Python using MNE, SciPy, and NumPy. GED, similar to ICA, extracts multivariate components from the data, but here we contrasted covariances around stimulation pulses with baseline periods, allowing for an a priori tuning of the decomposition

towards artifact components. In the present data, 1–3 components were sufficient to attenuate the artifact. The remaining preprocessing of the EEG data was performed in Matlab R2024b using the Fieldtrip toolbox [55]. Continuous data were filtered between 1 and 30 Hz using a bidirectional infinite impulse response Butterworth filter. An additional Band-Stop filter between 49 and 51 Hz was applied to suppress line noise. Data were then downsampled to 200 Hz and remaining artefacts, e.g. from blinks, were removed using an ICA approach (Infomax algorithm). Afterwards the continuous EEG signal was segmented into epochs from -500 to 1200 ms relative to stimulus onset. Epochs exceeding absolute amplitudes of 200 µV peak-to-peak in a 200 ms window were automatically excluded. One subject was excluded from the analysis due to more than 50% of removed trials. In the remaining participants, an average number of 5.69 Go-trials (*SD:* 8.23, range: 0-38) and an average number of 0.65 Nogo-trials (*SD:* 1.17, range: 0-7) was excluded. The amount of excluded trials between sessions did neither differ for go-trials (t_{42} = -0.75, p = 0.46) nor for nogo-trials (t_{42} = 0.97, p = 0.34).

Event related potentials (ERPs) were computed from correct Go trials for each block, stimulation condition and session. For the correct Nogo condition, blocks 1 and 2 as well as 3 and 4 were combined. For the incorrect Nogo condition, all 4 blocks were combined. No baseline correction was performed, since the gradCPT does not provide a suitable stimulus free period immediately prior to each stimulus onset. Peak-to-peak amplitudes were instead extracted as they are independent of a baseline correction [56]. In the Go condition, the Grand Average ERP across all blocks, sessions and stimulation conditions showed an early positive as well as a later negative deflection primarily at fronto-central electrodes FCz and Cz (Fig. 2A). The first positive peak ("P1") was defined as the most positive local maximum between 200 and 600 ms after stimulus onset. The subsequent negative peak ("N1") was defined as the most negative local minimum occurring within 400 ms after the P1 peak. The peak-to-peak amplitude was calculated as the difference between these two peaks. In addition, a second prominent positive deflection was observed, particularly at electrode Pz (Fig. 2C). The peak-to-peak amplitude was calculated as difference between the most negative peak occurring between 300 and 700 ms post-stimulus and the most positive peak occurring within 500 ms after this negative peak. In the grand average ERP of the Nogo condition (Fig. 3A), we observed pronounced negative and positive deflections with a more parietal distribution centered around electrode Pz. As with the Go condition, peak-to-peak amplitudes between the negative and positive deflections at electrode Pz were computed for each stimulation condition, session, and the combined block pairs (blocks 1+2 and blocks 3+4). For the incorrect Nogo trials the N1-P2 amplitude was determined in the same way for both sessions and stimulation conditions.

Behavioral parameters

Reaction times (RTs) were calculated as in previous studies [1,33] relative to onset of each image transition and used to define trials into *in the zone* and *out of the zone* based on the variance time course

[1]. A detailed description can be found in the supplementary material. The *Reaction time coefficient of variation (RT-CoV)* was calculated as additional marker of sustained attention [31] as the standard deviation from correct Go trials divided by their mean for each block and session. As an index of *discriminatory ability*, *d'* was computed based on hit rate and false alarm rate [2,32] for each block and session. As a complementary marker of discriminatory ability, the parameter *A* was calculated as it does not depend on the artificial insertion of errors and an underlying normal distribution [57]. A detailed description, including the formulas used for calculation, can be found in the supplementary material. We also determined the number of *in the zone* trials based on the variance time course of both concatenated sessions. This allowed us to analyze whether taVNS affected task engagement within participants.

Statistical Analyses

Statistical analyses were performed using R 4.3.3 [58] and RStudio 2021.09.1 [59]. Linear mixed effect models (LMMs) and generalized linear mixed effect models (GLMMs) were fitted with the *lme4*-package [60]. For each model, we initially specified the maximal random effects structure justified by the design [61]. Random slopes were retained only if they improved model fit or convergence, resulting in the most parsimonious random effects structure supported by the data. Model comparisons were performed using the *anova()* function which tests whether the inclusion of a parameter significantly improves model fit using a likelihood-ratio test ($\alpha = 0.05$). Significance of predictors in the final models were estimated using the *Anova()* function from the *car*-package [62] which calculates F-tests for fixed effects and returns χ^2 statistics. Post-hoc tests were conducted with the *emmeans* package [63], using pairwise comparisons and applying a False Discovery Rate (FDR) correction based on the Benjamini–Hochberg procedure to account for multiple comparisons. Model assumptions were assessed using graphical residual diagnostics. Histograms and QQ-Plots were used to assess normality and residuals vs. fitted values as well as standardized residuals were used to assess homoscedasticity and potential outliers.

End-of-session questionnaire responses were analyzed using Wilcoxon signed-rank tests to compare taVNS and sham conditions. For all other dependent measures, the main predictor of interest was *stimulation* (taVNS vs. sham). *Block* (1–4) and *session* (1 vs. 2) were included to account for potential effects of e.g. tiredness or training within and across sessions. Interactions included all two- and the three-way interaction. For behavioral data, the categorical covariate *zone* (in the zone vs. out of the zone) was included to account for different task engagement. RTs were analyzed using a GLMM with gamma distribution and identity link function [64] while for the RT-CoV a GLMM with gamma distribution and log-link function was used. The number of *in the zone* trials across sessions was analyzed using a negative binomial GLMM due to overdispersion. Subjective task focus as measured by the thought probes, discriminatory ability parameters (*d'*, *A*), and ERP peak-to-peak amplitudes were analyzed using LMMs.

Random effects in all models included random intercepts across participants. Final model formulas are provided in the supplementary material.

Results

Our findings demonstrate that brief, stimulus-locked taVNS selectively enhances sustained attention when delivered in a cognitively novel context. Participants who received taVNS during their first exposure to the task exhibited faster reaction times (Fig. 2A), reduced response variability, and a slower decline in self-reported focus (Fig. S1), relative to sham stimulation. These behavioral effects were absent when taVNS was applied during the second, familiar session, reinforcing the context dependency of stimulation efficacy. Notably, the RT improvement persisted into the next-day sham session (Fig. 2B), suggesting a lasting functional impact beyond immediate neuromodulation. Electrophysiological markers closely paralleled this pattern: fronto-central P1–N1 and parietal N1–P2 amplitudes were significantly increased during the first, taVNS-stimulated session (Fig. 3), but not in the second. Furthermore, the parietal N1–P2 amplitude continued to increase across blocks only when taVNS was applied in the novel session (Fig. 4), suggesting accelerated development of inhibitory control. Critically, larger ERP amplitudes were associated with faster reaction times, particularly in the taVNS-first group (Fig. S2), linking early cortical modulation to behavioral gain. Together, these results support a mechanistic account in which taVNS selectively potentiated novelty-gated sensory–attentional processing via early cortical dynamics.

Adverse stimulation effects

Participants did not report any serious adverse effects in response to either taVNS or sham stimulation. Ratings of minor side effects (e.g., tingling, headache, dizziness) were low and did not differ significantly between stimulation conditions (all p's > 0.24). Additionally, mind wandering was reported more often as cause for distraction, although no differences between taVNS and sham were observed. Details can be found in tables S1 and S2.

General characteristics of the gradCPT

We first report general effects of the gradCPT on behavioral and ERP parameters. Behavioral analyses on reaction time (RT) and discriminatory ability (*d'* and *A*) aimed to replicate and extend the original work [1]. We also analyzed the *reaction time coefficient of variation* (RT-CoV) as additional marker of sustained attention [31]. Predictors include the *block* and *session* number as well as the *zone* of attention, estimated from the response time variability [1]. ERP parameters focus on early, fronto-central and later parietal components defined from the Grand Average ERP (see Methods section). In accordance with the original work [1], *RTs* were significantly modified by the *zone* of attention ($\chi^2_{(1)} = 151.1$, $p < 0.001$). Participants responded faster during *in the zone* trials (M = 992 ms, SE = 18 ms) compared to *out of the zone* trials (M = 1057 ms, SE = 18 ms). An additional main effect of *session* was observed ($\chi^2_{(3)} = 39.607$, $p < 0.001$) with shorter RTs in the second (M: 1002 ms, SE: 20 ms) than during the first session (M: 1046

ms, *SE:* 17 ms). A *block - session* interaction ($^{2}_{(3)}$ = 8.487, p = 0.037) indicated longest RTs in block 1 of session 1 which declined in block 2 ($p_{corrected}$ = 0.01), 3 ($p_{corrected}$ < 0.001), and 4 ($p_{corrected}$ < 0.001) but no differences between blocks in the second session (p's > 0.57). For the RT-CoV, we observed no main effect of *block* (p = 0.09) or *session* (p = 0.93) but a significant *block - session* interaction ($^{2}_{(3)}$ = 11.1, p = 0.01) due to a non-linear increase in the first session for the sham-first group (see Fig. S1A). The discriminatory parameters *d'* and *A* were only modulated by the *zone* of attention (*d'*: $^{2}_{(1)}$ = 80.44, p < 0.001; *A*: $^{2}_{(1)}$ = 47.18, p < 0.001). While being *in the zone*, *d'* was higher (*M:* 3.8, *SE:* 0.08) than during *out of the zone* (*M:* 3.12, *SE:* 0.1). Similarly, *A* was higher *in the zone* (*M:* 0.97, *SE:* 0) than *out of the zone* (*M:* 0.93, *SE:* 0.01). Finally, Subjective task focus significantly declined from block 1 (*M:* 76.15, *SE:* 2.71) to block 4 (*M:* 61.2, *SE:* 2.71, $^{2}_{(3)}$ = 166.39, p < 0.001, see Fig. S1B).

For the ERP components during correct Go trials, the parietal (Pz) N1-P2 amplitude was modulated by the predictor *session* ($^{2}_{(1)}$ = 7.03, p = 0.01) with higher amplitudes in the second (*M:* 3.15, *SE:* 0.13) compared to the first session (*M:* 3.08, *SE:* 0.13). For the correct Nogo trials, ERP amplitudes were considerably larger than during Go trials (Fig. 4A). Apart from that, N1-P2 amplitudes at Pz were not modulated by a general *session* or *block* effect (p's > 0.11). N1-P2 amplitudes from incorrect Nogo trials were significantly lower compared to correct Nogo trials ($^{2}_{(1)}$ = 109.76, p < 0.001) and followed a more central topography similar to the Go trials (Fig. 3A for comparison). Interestingly, we also observed an early positive deflection peaking at around 340 ms after stimulus onset at central electrodes, resembling the P1 peak during Go trials (Fig. 4C). No effect of *stimulation*, *session*, or an interaction between these two (all p's > 0.38) was observed. However, as the number of trials available for this ERP was small, these results need to be interpreted with care.

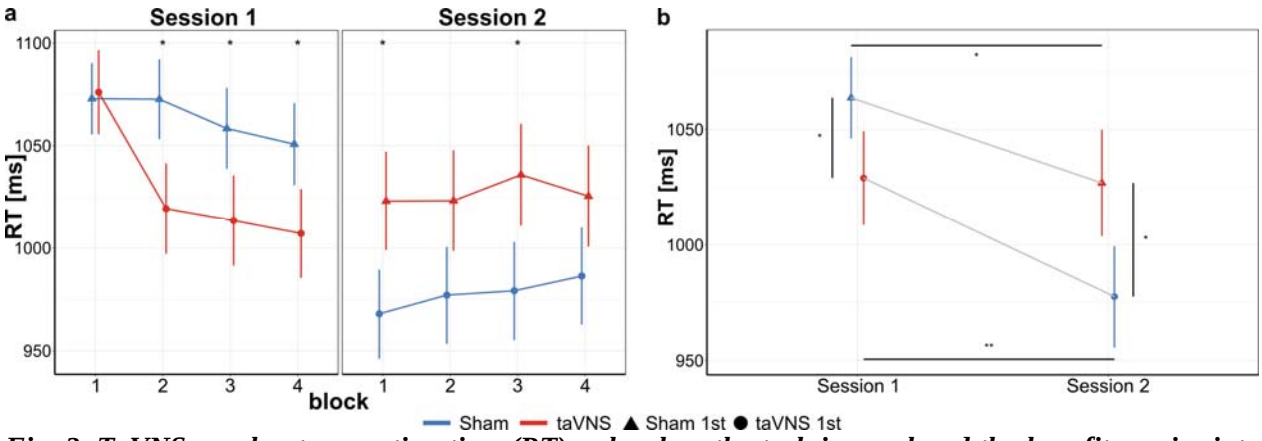

Fig. 2. TaVNS accelerates reaction time (RT) only when the task is novel and the benefit carries into the next day. *A) During the first exposure to the gradCPT (Session 1, left panel) taVNS (red) produced a rapid RT drop after Block 1, whereas sham (blue) showed no change; both groups started with identical baseline RTs in Block 1. When the same participants returned ≥24 h later (Session 2, right panel) the taVNS-first group retained faster RTs during sham stimulation (Blocks 1 and 3), indicating a persistent benefit, while the sham-first group still showed no improvement. B) RT gains within Sessions and from*

*Session 1 to Session 2 were larger for the taVNS-first group (circles) than for the sham-first group (triangles). error bars denote s.e.m.; *P < 0.05, **P < 0.01 (FDR-corrected)*

Stimulation specific effects on gradCPT characteristics

Next, we focus on stimulation specific effects during the gradCPT. Visual inspection of the RT data (Fig. 2A) suggested that taVNS only had an effect when applied in the first session. The corresponding GLMM indicated that RTs were indeed modulated by a *stimulation-block-session* interaction ($\chi^2_{(3)}$ = 13.037, p = 0.005, Fig. 2A and table S3). Post-hoc comparisons between sham and taVNS per block and session revealed significant differences during block 2 ($p_{corrected}$ = 0.02), 3 ($p_{corrected}$ = 0.03), and 4 ($p_{corrected}$ = 0.03) of the first session as well as during block 1 ($p_{corrected}$ = 0.02) and 3 ($p_{corrected}$ = 0.03) of the second session. During block 2 of the second session, we observed a trend towards statistical significance between taVNS and sham ($p_{corrected}$ = 0.06). Importantly, no differences in RT were observed during the first block of the first session when all participants were naive to the task. These results suggest that the effect of taVNS depended on whether it was applied during the first, novel session. This was further demonstrated by the significant *stimulation-session* interaction ($\chi^2_{(3)}$ = 4.727, p = 0.03, Figure 2B). RTs differed between taVNS and sham in both, session 1 ($p_{corrected}$ = 0.02) and session 2 ($p_{corrected}$ = 0.02). The more interesting aspect of this interaction is the effect within the taVNS-first and the sham-first group. Participants receiving taVNS in the first session had lower RTs (M = 1029, SE = 20) compared to participants receiving sham stimulation (M = 1064, SE = 18). These participants also showed shorter RTs in the second session (M = 978, SE = 22), where they then received sham stimulation, compared to participants receiving taVNS in the second session (M = 1027, SE = 23). The RT improvement from the first to the second session was stronger for the taVNS-first group (-51 ms, $p_{corrected}$ = 0.002) than for the sham-first group (-37 ms, $p_{corrected}$ = 0.047, Figure 2B). Importantly, the significant *stimulation - session* interaction reflects a reversal of the direction of the taVNS - sham contrast across sessions, which in turn results from the different orders of stimulation. Since taVNS and sham were each applied in both sessions but to different subject groups, this statistical interaction should not be interpreted as a within-subject interaction effect. Instead, it reflects a main effect of stimulation order that manifests as a crossover in the taVNS–sham contrast between sessions.

No stimulation-specific effects on the discriminatory ability parameters *d'* and *A* were observed (all p's > 0.22), indicating that accuracy did neither improve nor decline despite faster RTs. Further analyses revealed significant three-way interactions for RT-CoV and subjective task focus. However, post-hoc comparisons between taVNS and sham yielded no statistically significant result after correction for multiple comparisons. A more comprehensive description of these results is provided in the supplementary material.

Finally, the number of *in-the-zone* trials was affected by the stimulation ($^{2}_{(1)}$ = 5.38, p = 0.02). During taVNS subjects spent an average of 189 trials per block *in the zone* (*SE* = 3.17) compared to 185 (*SE* = 3.1) during sham stimulation. No other significant main effect or interaction was observed (all *p's* > 0.08).

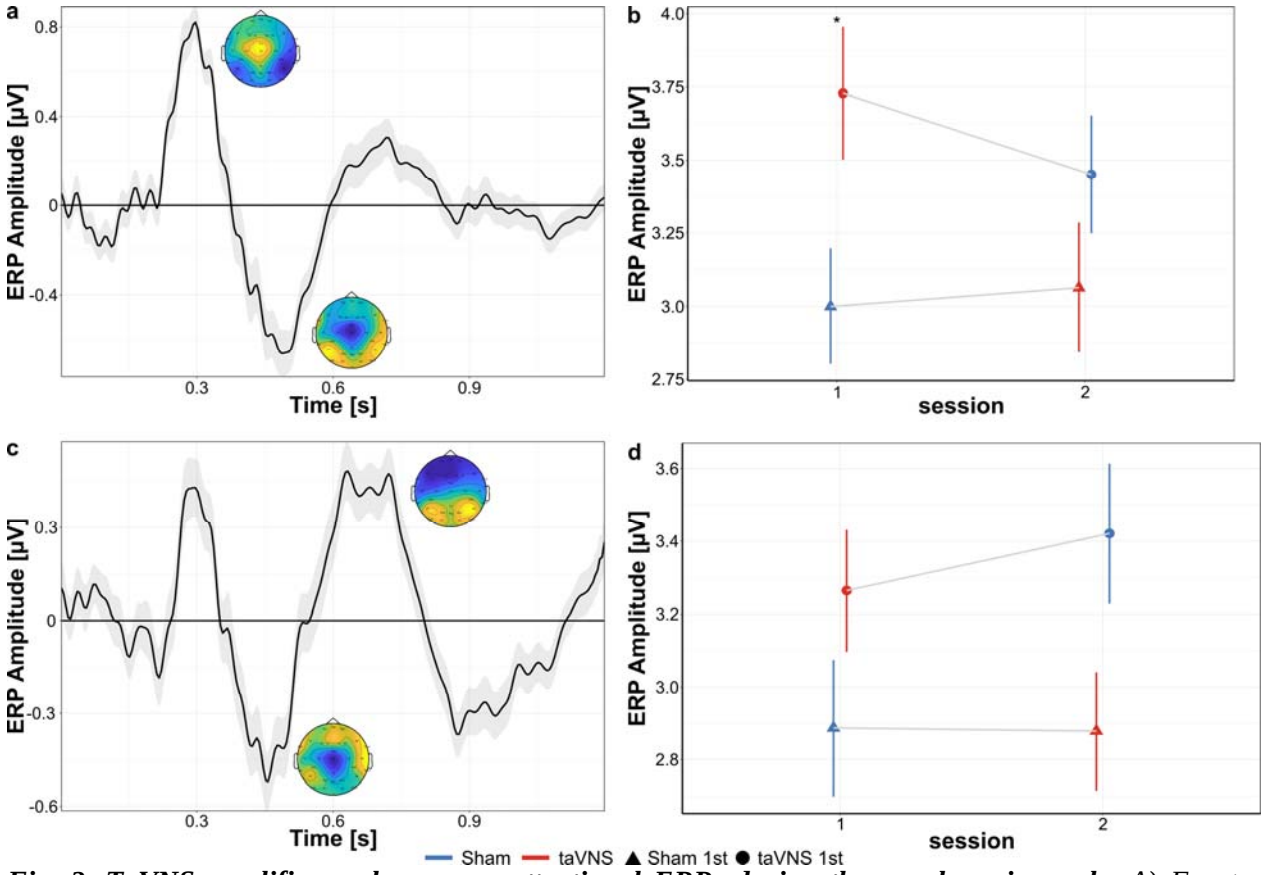

Fig. 3. TaVNS amplifies early sensory–attentional ERPs during the novel session only. *A) Fronto-central waveform. Grand-average event-related potential (ERP) for correct Go trials at FCz + Cz shows an initial positive peak (~300 ms) followed by a negative deflection (~500 ms); insets depict scalp voltage at each peak. B) P1–N1 amplitude (FCz + Cz). A significant stimulation - session interaction revealed larger peak-to-peak amplitudes when taVNS was delivered in Session 1 (red) relative to sham (blue); no difference emerged in Session 2. C) Parietal waveform. Grand-average ERP at Pz exhibits a pronounced second positive peak. D) N1–P2 amplitude (Pz). The same stimulation - session interaction was observed, although post-hoc contrasts did not reach FDR-corrected significance. Shaded areas (A, C) and error bars (B, D) denote s.e.m.; P < 0.05, **P < 0.001 (FDR-corrected).*

Behavioral effects were mirrored in the electrophysiological data. The fronto-central P1-N1 amplitude during Go trials (Fig. 3A), was modulated by the *stimulation* ($^{2}_{(1)}$ = 5.72, p = 0.02) which was driven by a *stimulation-session* interaction ($^{2}_{(1)}$ = 4.94, p = 0.03; Fig. 3B): In the first session, taVNS was associated with higher amplitudes (*M* = 3.73, *SE* = 0.23) compared to sham (*M* = 3, *SE* = 0.2, *t-ratio* = -2.43, $p_{corrected}$ = 0.036). In the second session, this difference between taVNS and sham was absent ($p_{corrected}$ = 0.202), indicating again a differential effect of the stimulation depending on whether taVNS or sham was applied in the first, novel session. The parietal N1-P2 amplitude at Pz exhibited a similar *stimulation-session*

interaction ($\chi^2_{(1)}$ = 6.49, p = 0.01). However, here we observed no difference between taVNS and sham in the first session ($p_{corrected}$ = 0.139) and only a weak trend towards a difference in the second session (*t-ratio* = 2.15, $p_{corrected}$ = 0.072) with higher amplitudes during sham (M = 3.42, SE = 0.19) than during taVNS (M = 2.88, SE = 0.16). Additional GLMMs were fitted to test whether P1-N1 and N1-P2 amplitudes during correct Go trials can serve as predictor of RTs. Results indicate that P1-N1 amplitude but not N1-P2 amplitude significantly predicted RTs but only across both sessions and order groups (Fig. S2). When repeating the analysis separately for the taVNS-first and sham-first group, results are no longer conclusive, indicating potential loss of statistical power. More detailed information is provided in the supplementary material.

The N1-P2 amplitude for correct Nogo trials was also modulated by a significant 3-way interaction ($\chi^2_{(1)}$ = 9.54, p = 0.002). Post-hoc comparisons between taVNS and sham stimulation for the different block-session combinations, however, failed to reach significance (all p's > 0.5). Nevertheless, participants receiving taVNS in the first session showed a significant increase in N1-P2 amplitudes from the first (M = 9.87, SE = 1.05) to the second half of the session (M = 12.67, SE = 1.05, *t-ratio* = -4.39, $p_{corrected}$ < 0.001). Participants receiving sham stimulation in the first session, on the other hand, showed no difference between the first (M = 11.17, SE = 1.12) and second half of session 1 (M = 11.35, SE = 1.12, *t-ratio* = -0.28, $p_{corrected}$ = 0.78, Fig. 4B). In the second session, N1-P2 amplitudes did not differ between taVNS and sham stimulation or the first and second half within a stimulation condition (all p's > 0.34) Nevertheless, as for the RTs and the fronto-central P1-N1 amplitude, we see evidence of differential modulations depending on whether participants received taVNS or sham in the first session.

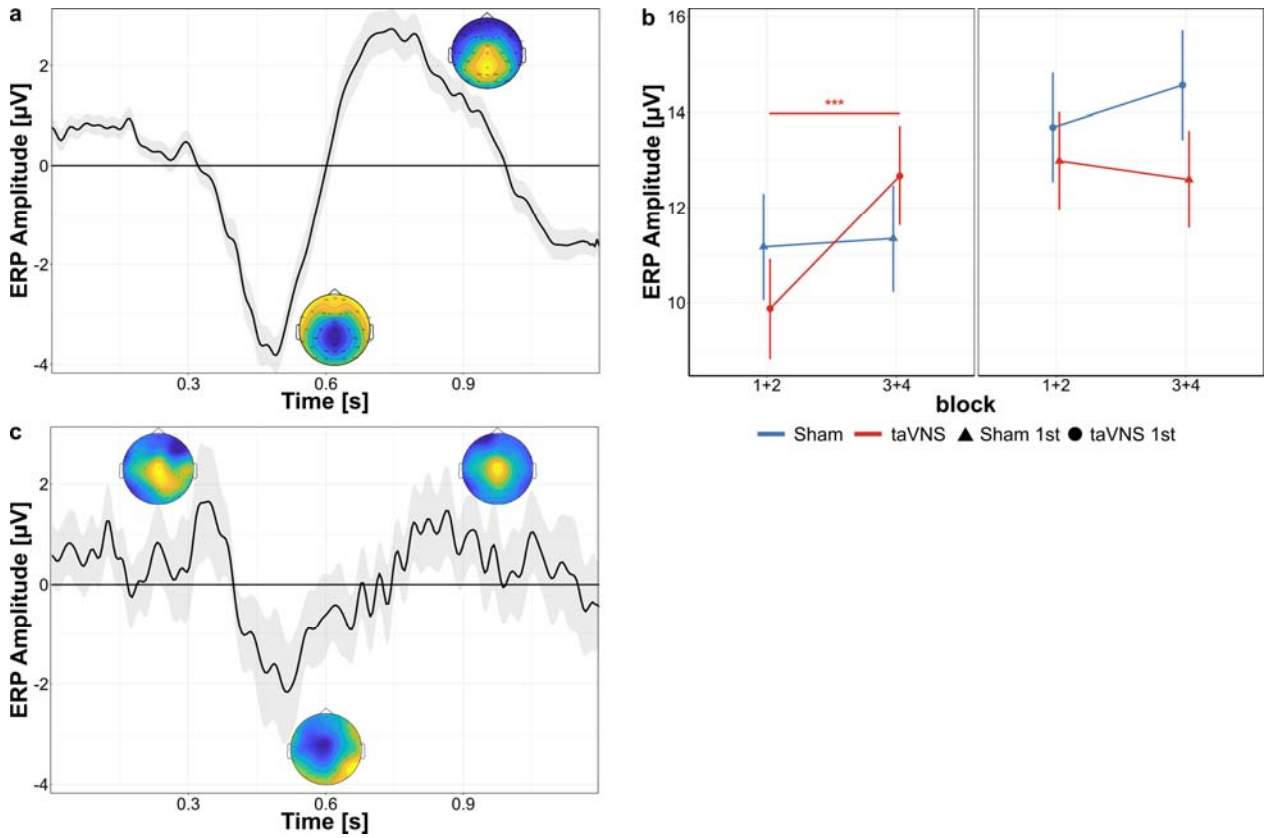

Fig. 4. TaVNS modulates parietal Nogo ERPs during the novel session. *A) Parietal waveform. Grand-average event-related potential (ERP) for correct Nogo trials (electrode Pz) shows a large negative peak (~650 ms) followed by a broad positive deflection (~800–900 ms); insets depict scalp voltage at these extrema. B) Block-wise N1–P2 amplitude (Pz). A three-way stimulation - session - block interaction revealed that participants who received taVNS in Session 1 (red) exhibited a pronounced increase in N1–P2 amplitude from the first half of the session (blocks 1 + 2) to the second half (blocks 3 + 4). No within-session change was observed in the sham-first group (blue), and direct taVNS-vs-sham contrasts were not significant in either half. C) Fronto-central waveform. For completeness, the grand-average Nogo ERP at FCz + Cz is displayed; no stimulation effect emerged here. Shaded areas (A, C) and error bars (B) denote s.e.m.; ***P < 0.001 (FDR-corrected).*

Discussion

In the first electrophysiological characterization of the gradCPT, we demonstrate that ERP components resembling the N2 and P3 component can be observed during both the Go and Nogo conditions, despite the continuously transitioning stimuli in the gradCPT. The Go condition was further characterized by a positive deflection preceding the N2 and P3 components. On the behavioral level, we replicate previous observations [1–3] that reaction time and discriminatory ability during the task were modulated by the zone of attention (e.g., in the zone vs. out of the zone). More importantly, we demonstrate that the cognitive effects of taVNS appear to be shaped by the context in which the stimulation occurs. The observed improvements in reaction time, stability of performance, and subjective focus were specific to the initial task exposure under taVNS and did not reappear when stimulation was applied during a second, familiar session (Fig. 2A, Fig. S1). Importantly, these improvements were not transient: Participants who received taVNS during their first session continued to perform better during sham testing ≥ 24 hours later (Fig. 2B), suggesting a lasting modulation of attentional function. Electrophysiological results mirrored this pattern, with enhanced early sensory–attentional ERP components (P1–N1 and N1–P2; Fig. 3) and block-wise increases in Nogo-related amplitudes (Fig. 4) supporting the interpretation that taVNS facilitates early cortical processes related to both stimulus engagement and inhibitory control.

The decrease of RT through taVNS in the first session suggests improved stimulus processing, given that the overall accuracy did not decline. Critically, this facilitation was dependent on task novelty. Participants that were already familiar with the task (i.e., the sham-first group in the second session) did no longer show a taVNS induced behavioral benefit. Studies in rodents suggests that novel situations also evoke strong phasic LC activity. The first exposure to novel environments increased phasic LC activity whereas familiar situations no longer evoked such a response [14,65]. Our results can be interpreted to reflect a similar process in humans. Both participant subgroups likely experienced increased phasic LC activity in the first, novel session. In the taVNS-first group this activity was amplified by the matching, coinciding stimulation, resulting in improved attention and earlier detection of Go stimuli. Accordingly, this would also suggest, that the stimulation is effective when it coincides with a naturally occurring phasic LC activation. This assumption is in accordance with the concept of state dependency [66], which suggests that the effectiveness of non-invasive brain stimulation depends on the current state of the targeted neural system [67]. This attentional modulation was effective already in the second block of the session, whereas participants receiving the sham stimulation showed a slight, numerical decrease in RT only in block 3 of the task. The fact, that the taVNS group also reported numerically higher, subjective focus on the task (Fig. S1B) and increased the number of *in the zone* trials indicates that taVNS successfully modulated attentional processes necessary to optimize performance. Especially the PFC plays an important role in regulation of attention and executive control [68] and increased NA signaling has

been shown to increase excitability in the PFC [69]. In the second, familiar session, phasic LC activity to stimuli was not as strong as during the first session, due to the familiar situation. Therefore, the applied taVNS was not as effective and the sham-first group could no longer benefit. The general RT improvement across sessions, which was stronger for the taVNS-first group, also fits with this interpretation. Phasic LC responses occurred in both groups in session 1 and facilitated performance improvements over time. The amplification of the phasic LC response in the taVNS-first group enhanced this facilitation and provided a performance benefit up to the second session. The fact that we did not observe changes in behavioral accuracy could be attributed to our young and healthy sample. Overall performance was high which causes ceiling effects and reduces variability in our data. Thus, it remains unclear whether a sample with impaired executive function would show behavioral improvements through the stimulation.

Regarding the ERP results, both, Go and Nogo stimuli in our study elicited a negative and a subsequent positive deflection, resembling the canonical N2 and P3 components typically observed in Go-Nogo tasks [70]. Due to the gradual fade-in of the stimuli, these components occurred later in time compared to traditional paradigms with abrupt stimulus onsets. Across participants, the components appeared relatively stable, as indicated by the low variance in the grand average ERP. Moreover, the finding that Nogo trials elicited larger amplitudes is consistent with previous research demonstrating that N2 and P3 amplitudes tend to increase when Nogo stimuli are less frequent [70]. The N2 component is associated with the monitoring of response conflicts between the Go and Nogo conditions [70] and its generator is typically located in the anterior and mid-cingulate cortex [70]. The P3 component, especially the more parietal located P3b, on the other side is typically associated with attention and decision making [46] with broader neural generators including the temporo-parietal junction [71]. Due to its close connection to the LC-NA system [46,71], the P3 component has been investigated as potential biomarker for taVNS effects [22]. Apart from these two components, we also observed an earlier, positive deflection in correct Go trials that preceded the N2 and P3 component, similar to the Go-P2 observed by Gajewski and Falkenstein [72]. However, as most Go-Nogo studies focus on the N2 and P3 component, comparable results are sparse. In previous studies the P2 component has been linked to stimulus evaluation [73–75] with positive correlations between P2 amplitude and reaction time variability and mean reaction time [76]. It has been linked to activity in the prefrontal and orbitofrontal cortex [74,75]. The fact that we observed a P2 peak in the ERP for incorrect Nogo trials (commission errors) but not for correct Nogo trials (correct omissions, Fig. 3) indicates a possible missclassification into *Go* already at this early stage, as the P2 is larger for trials requiring an overt response [75].

Due to the nature of the gradCPT we decided to analyze peak-to-peak amplitudes, which do not depend on a baseline correction. For the Go trials we observed increased P2-N2 amplitudes only in session 1 for the taVNS-first group. In session two, these participants still exhibited numerically larger amplitudes although

this difference was no longer statistically significant, mirroring in part our RT results. The association of the P2-N2 complex with stimulus evaluation and response selection [75] is consisted with our observation that the P2-N2 amplitude was a significant predictor of RT. The N2-P3 complex on the other hand was, as expected, larger for the Nogo condition reflecting enhanced inhibitory control and response monitoring. Here we also observed novelty dependent effects on peak-to-peak amplitudes only in the taVNS-first group. This could be due to an increase in the P3 component as previous studies observed taVNS specific effects on P3 amplitude [38,40]. However, these ERP changes did not manifest in a behavioral effect which could indicate that this modulation was not sufficient to improve task performance in our sample. Taken together, these results indicate a noradrenergic modulation of cortical brain regions involved in attention and sensory discrimination that lasted for at least 24 hours. However, more research is needed to replicate our results and to better understand the temporal dynamics of brain activity during the gradCPT.

One limitation of our design is that we cannot differentiate between first exposure to the task and first exposure to the stimulation. Nevertheless, we would speculate that, if the first exposure to the stimulation is the driving novelty factor, the sham-first group should show similar improvements in the first session as well. Future studies that aim to replicate our results therefore need to assess participants prior experiences with taVNS to control for this factor. Additionally, further information about LC activity during the task (e.g., from pupillometry) would provide additional insights into novelty dependent taVNS effects. Regardless of whether one considers the driving factor to be the novelty of stimulation or the novelty of the task, we see that taVNS enhances this effect and that this enhancement persists for at least 24h. Another limiting factor is the inherently low number of Nogo trials per block, which may constrain the statistical power for detecting effects specific to response inhibition. Designs with slightly more Nogo trials (e.g., 20% Nogo instead of 10%) could help to better understand the temporal dynamics of brain activity while still eliciting a prepotent Go response. Further, as mentioned above, our sample consisted of young, healthy adults who performed with overall high accuracy. This might have limited the behavioral potential of the stimulation due to ceiling effects. More research is needed to investigate whether participants with attentional deficits could benefit more from the stimulation. Another limitation relates to the temporal stability of the observed effects. Although our design allowed us to show that effects were stable for at least 24 hours, more research is needed to understand the temporal stability over a longer period of time. In future studies, follow up session e.g., after two weeks could help to understand the long-term effects.

To conclude, our findings demonstrate that phasic, stimulus-locked taVNS likely selectively modulates behavioral and electrophysiological markers of sustained attention in a novelty-dependent manner. When delivered during initial task exposure, taVNS accelerated reaction times and stabilized performance without compromising accuracy, and these benefits persisted into the following day's sham session. Early fronto-central ERP components linked to stimulus evaluation and conflict monitoring were similarly

enhanced, mirroring behavioral improvements. Together, these results indicate that taVNS potentiates novelty-gated phasic LC-NA activity, amplifying early cortical gain to optimize attentional processing. This work establishes a mechanistic basis for state-dependent vagal neuromodulation and underscores the critical role of novelty when designing within-subject crossover studies in participants naive to a task.

Author contributions

Conceptualization: TZ, CW; Data curation: CW; Formal analysis: CW, JPW; Funding acquisition: TZ, AG; Investigation: CW; Methodology: CW, TZ; Project administration: CW, TZ; Resources: TZ, AG; Software: CW, JPW; Supervision: TZ; Validation: CW, TZ; Visualization: CW, TZ; Writing - original draft: CW, JPW, AG, TZ;

Data availability

EEG data and analysis code are available on OSF at osf.io/znasf/

References

[1] Esterman M, Noonan SK, Rosenberg M, DeGutis J. In the Zone or Zoning Out? Tracking Behavioral and Neural Fluctuations During Sustained Attention. Cereb Cortex 2013;23:2712–23.

[2] Fortenbaugh FC, DeGutis J, Germine L, Wilmer JB, Grosso M, Russo K, et al. Sustained Attention Across the Life Span in a Sample of 10,000: Dissociating Ability and Strategy. Psychol Sci 2015;26:1497–510. https://doi.org/10.1177/0956797615594896.

[3] Fortenbaugh FC, DeGutis J, Esterman M. Recent theoretical, neural, and clinical advances in sustained attention research: Sustained attention. Ann Ny Acad Sci 2017;1396:70–91. https://doi.org/10.1111/nyas.13318.

[4] Langner R, Eickhoff SB. Sustaining attention to simple tasks: A meta-analytic review of the neural mechanisms of vigilant attention. Psychol Bull 2013;139:870–900. https://doi.org/10.1037/a0030694.

[5] Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proceedings of the National Academy of Sciences 2006;103:10046–51. https://doi.org/10.1073/pnas.0604187103.

[6] Vossel S, Geng JJ, Fink GR. Dorsal and Ventral Attention Systems. The Neuroscientist 2014;20:150–9. https://doi.org/10.1177/1073858413494269.

[7] Huang R, Clewett D. The locus coeruleus: Where cognitive and emotional processing meet the eye. Modern Pupillometry, Zurich, Switzerland: Springer Nature; 2024, p. 3–75.

[8] Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: Adaptive gain and optimal performance. Annu Rev Neurosci 2005;28:403–50. https://doi.org/10.1146/annurev.neuro.28.061604.135709.

[9] Sara SJ. The locus coeruleus and noradrenergic modulation of cognition. Nat Rev Neurosci 2009;10:211–23. https://doi.org/10.1038/nrn2573.

[10] Szabadi E. Functional neuroanatomy of the central noradrenergic system. J Psychopharmacol 2013;27:659–93. https://doi.org/10.1177/0269881113490326.

[11] Rajkowski J, Kubiak P, Aston-Jones G. Locus coeruleus activity in monkey: Phasic and tonic changes are associated with altered vigilance. Brain Res Bull 1994;35:607–16. https://doi.org/10.1016/0361-9230(94)90175-9.

[12] Murphy PR, Robertson IH, Balsters JH, O'connell RG. Pupillometry and P3 index the locus coeruleus-noradrenergic arousal function in humans: Indirect markers of locus coeruleus activity. Psychophysiology 2011;48:1532–43. https://doi.org/10.1111/j.1469-8986.2011.01226.x.

[13] Devoto P, Flore G, Saba P, Fa M, Gessa GL. Stimulation of the locus coeruleus elicits noradrenaline and dopamine release in the medial prefrontal and parietal cortex. J Neurochem 2005;92:368–74. https://doi.org/10.1111/j.1471-4159.2004.02866.x.

[14] Vankov A, Hervé-Minvielle A, Sara SJ. Response to Novelty and its Rapid Habituation in Locus Coeruleus Neurons of the Freely Exploring Rat. Eur J Neurosci 1995;7:1180–7. https://doi.org/10.1111/j.1460-9568.1995.tb01108.x.

[15] Chamberlain SR, Robbins TW. Noradrenergic modulation of cognition: Therapeutic implications. J Psychopharmacol 2013;27:694–718. https://doi.org/10.1177/0269881113480988.

[16] Marshall CA, Brodnik ZD, Mortensen OV, Reith MEA, Shumsky JS, Waterhouse BD, et al. Selective activation of Dopamine D3 receptors and norepinephrine transporter blockade enhances

sustained attention. Neuropharmacology 2019;148:178–88. https://doi.org/10.1016/j.neuropharm.2019.01.003.

[17] Crockett MJ, Clark L, Hauser MD, Robbins TW. Serotonin selectively influences moral judgment and behavior through effects on harm aversion. Proceedings of the National Academy of Sciences 2010;107:17433–8. https://doi.org/10.1073/pnas.1009396107.

[18] Chamberlain SR, Müller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ. Neurochemical Modulation of Response Inhibition and Probabilistic Learning in Humans. Science 2006;311:861–3. https://doi.org/10.1126/science.1121218.

[19] Coull JT, Middleton HC, Robbins TW, Sahakian BJ. Clonidine and diazepam have differential effects on tests of attention and learning. Psychopharmacology 1995;120:322–32. https://doi.org/10.1007/BF02311180.

[20] Smith A, Nutt D. Noradrenaline and attention lapses. Cah Rev The 1996;380:291–1. https://doi.org/10.1038/380291a0.

[21] Liu KY, Acosta-Cabronero J, Cardenas-Blanco A, Loane C, Berry AJ, Betts MJ, et al. In vivo visualization of age-related differences in the locus coeruleus. Neurobiol Aging 2019;74:101–11. https://doi.org/10.1016/j.neurobiolaging.2018.10.014.

[22] Farmer AD, Strzelczyk A, Finisguerra A, Gourine AV, Gharabaghi A, Hasan A, et al. International Consensus Based Review and Recommendations for Minimum Reporting Standards in Research on Transcutaneous Vagus Nerve Stimulation (Version 2020). Front Hum Neurosci 2021;14:568051. https://doi.org/10.3389/fnhum.2020.568051.

[23] Butt MF, Albusoda A, Farmer AD, Aziz Q. The anatomical basis for transcutaneous auricular vagus nerve stimulation. J Anat 2020;236:588–611. https://doi.org/10.1111/joa.13122.

[24] Ruffoli R, Giorgi FS, Pizzanelli C, Murri L, Paparelli A, Fornai F. The chemical neuroanatomy of vagus nerve stimulation. J Chem Neuroanat 2011;42:288–96. https://doi.org/10.1016/j.jchemneu.2010.12.002.

[25] Manta S, El Mansari M, Debonnel G, Blier P. Electrophysiological and neurochemical effects of long-term vagus nerve stimulation on the rat monoaminergic systems. Int J Neuropsychop 2013;16:459–70. https://doi.org/10.1017/S1461145712000387.

[26] Hulsey DR, Riley JR, Loerwald KW, Rennaker RL, Kilgard MP, Hays SA. Parametric characterization of neural activity in the locus coeruleus in response to vagus nerve stimulation. Exp Neurol 2017;289:21–30. https://doi.org/10.1016/j.expneurol.2016.12.005.

[27] Raedt R, Clinckers R, Mollet L, Vonck K, El Tahry R, Wyckhuys T, et al. Increased hippocampal noradrenaline is a biomarker for efficacy of vagus nerve stimulation in a limbic seizure model: VNS, noradrenaline and seizure suppression. J Neurochem 2011;117:461–9. https://doi.org/10.1111/j.1471-4159.2011.07214.x.

[28] Borgmann D, Rigoux L, Kuzmanovic B, Edwin Thanarajah S, Münte TF, Fenselau H, et al. Technical Note: Modulation of fMRI brainstem responses by transcutaneous vagus nerve stimulation. Neuroimage 2021;244:118566. https://doi.org/10.1016/j.neuroimage.2021.118566.

[29] Pervaz I, Thurn L, Vezzani C, Kaluza L, Kühnel A, Kroemer NB. Does transcutaneous auricular vagus nerve stimulation alter pupil dilation? A living Bayesian meta-analysis. Brain Stimul 2025;18:148–57. https://doi.org/10.1016/j.brs.2025.01.022.

[30] Wienke C, Grueschow M, Haghikia A, Zaehle T. Phasic, Event-Related Transcutaneous Auricular Vagus Nerve Stimulation Modifies Behavioral, Pupillary, and Low-Frequency Oscillatory Power Responses. The Journal of Neuroscience 2023;43:6306–19. https://doi.org/10.1523/JNEUROSCI.0452-23.2023.

[31] Yamashita A, Rothlein D, Kucyi A, Valera EM, Germine L, Wilmer J, et al. Variable rather than extreme slow reaction times distinguish brain states during sustained attention. Scientific Reports 2021;11:14883. https://doi.org/10.1038/s41598-021-94161-0.

[32] Fortenbaugh FC, Rothlein D, McGlinchey R, DeGutis J, Esterman M. Tracking behavioral and neural fluctuations during sustained attention: A robust replication and extension. Neuroimage 2018;171:148–64. https://doi.org/10.1016/j.neuroimage.2018.01.002.

[33] Kucyi A, Esterman M, Riley CS, Valera EM. Spontaneous default network activity reflects behavioral variability independent of mind-wandering. Proceedings of the National Academy of Sciences 2016;113:13899–904. https://doi.org/10.1073/pnas.1611743113.

[34] Akkol S, Kucyi A, Hu W, Zhao B, Zhang C, Sava-Segal C, et al. Intracranial Electroencephalography Reveals Selective Responses to Cognitive Stimuli in the Periventricular Heterotopias. The Journal of Neuroscience 2021;41:3870–8. https://doi.org/10.1523/JNEUROSCI.2785-20.2021.

[35] Camargo L, Pacheco-Barrios K, Gianlorenço AC, Menacho M, Choi H, Song J-J, et al. Evidence of bottom-up homeostatic modulation induced taVNS during emotional and Go/No-Go tasks. Exp Brain Res 2024;242:2069–81. https://doi.org/10.1007/s00221-024-06876-x.

[36] Pihlaja M, Failla L, Peräkylä J, Hartikainen KM. Reduced Frontal Nogo-N2 With Uncompromised Response Inhibition During Transcutaneous Vagus Nerve Stimulation—More Efficient Cognitive Control? Front Hum Neurosci 2020;14:561780. https://doi.org/10.3389/fnhum.2020.561780.

[37] Fischer R, Ventura-Bort C, Hamm A, Weymar M. Transcutaneous vagus nerve stimulation (tVNS) enhances conflict-triggered adjustment of cognitive control. Cognitive, Affective, & Behavioral Neuroscience 2018;18:680–93. https://doi.org/10.3758/s13415-018-0596-2.

[38] Gurtubay IG, Perez-Rodriguez DR, Fernandez E, Librero-Lopez J, Calvo D, Bermejo P, et al. Immediate effects and duration of a short and single application of transcutaneous auricular vagus nerve stimulation on P300 event related potential. Front Neurosci 2023;17:1096865. https://doi.org/10.3389/fnins.2023.1096865.

[39] Chen Y, Yang H, Wang F, Lu X, Hu L. Modulatory effects of transcutaneous auricular vagus nerve stimulation (taVNS) on attentional processes. General Psychiatry 2023;36:e101176. https://doi.org/10.1136/gpsych-2023-101176.

[40] Giraudier M, Ventura-Bort C, Weymar M. Effects of Transcutaneous Auricular Vagus Nerve Stimulation on the P300: Do Stimulation Duration and Stimulation Type Matter? Brain Sciences 2024;14. https://doi.org/10.3390/brainsci14070690.

[41] D'Agostini M, Burger AM, Jelinčić V, Von Leupoldt A, Van Diest I. Effects of transcutaneous auricular vagus nerve stimulation on P300 magnitudes and salivary alpha-amylase during an auditory oddball task. Biol Psychol 2023;182:108646. https://doi.org/10.1016/j.biopsycho.2023.108646.

[42] Keute M, Barth D, Liebrand M, Heinze H-J, Kraemer U, Zaehle T. Effects of Transcutaneous Vagus Nerve Stimulation (tVNS) on Conflict-Related Behavioral Performance and Frontal Midline Theta Activity. Journal of Cognitive Enhancement 2020;4:121–30. https://doi.org/10.1007/s41465-019-00152-5.

[43] Zhu S, Liu Q, Zhang X, Zhou M, Zhou X, Ding F, et al. Transcutaneous auricular vagus nerve stimulation enhanced emotional inhibitory control via increasing intrinsic prefrontal couplings. Int J Clin Hlth Psyc 2024;24:100462. https://doi.org/10.1016/j.ijchp.2024.100462.

[44] Bömmer T, Schmidt LM, Meier K, Kricheldorff J, Stecher H, Herrmann CS, et al. Impact of Stimulation Duration in taVNS—Exploring Multiple Physiological and Cognitive Outcomes. Brain Sciences 2024;14:875. https://doi.org/10.3390/brainsci14090875.

[45] Folstein JR, Van Petten C. Influence of cognitive control and mismatch on the N2 component of the ERP: A review. Psychophysiology 2008;45:152–70. https://doi.org/10.1111/j.1469-8986.2007.00602.x.

[46] Polich J. Updating P300: An integrative theory of P3a and P3b. Clin Neurophysiol 2007;118:2128–48. https://doi.org/10.1016/j.clinph.2007.04.019.

[47] Brainard DH. The Psychophysics Toolbox. Spatial Vision 1997;10:433–6. https://doi.org/10.1163/156856897X00357.

[48] Kleiner M, Brainard D, Pelli D, Ingling A, Murray R, Broussard C, et al. What's new in Psychtoolbox-3? Perception 2007;36.

[49] Pelli DG. The VideoToolbox software for visual psychophysics: Transforming numbers into movies. Spatial Vision 1997;10:437–42. https://doi.org/10.1163/156856897X00366.

[50] Xiao J, Hays J, Ehinger KA, Oliva A, Torralba A. SUN database: Large-scale scene recognition from abbey to zoo. 2010 IEEE Computer Society Conference on Computer Vision and Pattern Recognition, San Francisco, CA, USA: IEEE; 2010, p. 3485–92. https://doi.org/10.1109/CVPR.2010.5539970.

[51] Rufener KS, Wienke C, Salanje A, Haghikia A, Zaehle T. Effects of transcutaneous auricular vagus nerve stimulation paired with tones on electrophysiological markers of auditory perception. Brain Stimul 2023;16:982–9. https://doi.org/10.1016/j.brs.2023.06.006.

[52] Cohen MX. A tutorial on generalized eigendecomposition for denoising, contrast enhancement, and dimension reduction in multichannel electrophysiology. Neuroimage 2022;247:118809. https://doi.org/10.1016/j.neuroimage.2021.118809.

[53] Haslacher D, Nasr K, Robinson SE, Braun C, Soekadar SR. Stimulation artifact source separation (SASS) for assessing electric brain oscillations during transcranial alternating current stimulation (tACS). Neuroimage 2021;228:117571. https://doi.org/10.1016/j.neuroimage.2020.117571.

[54] Woller JP, Menrath D, Gharabaghi A. EEG denoising during transcutaneous auricular vagus nerve stimulation across simulated, phantom and human data 2024. https://doi.org/10.1101/2024.05.13.593884.

[55] Oostenveld R, Fries P, Maris E, Schoffelen J-M. FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. Computational Intelligence and Neuroscience 2011;2011:1–9. https://doi.org/10.1155/2011/156869.

[56] McClaskey CM, Dias JW, Dubno JR, Harris KC. Reliability of Measures of N1 Peak Amplitude of the Compound Action Potential in Younger and Older Adults. Journal of Speech, Language, and Hearing Research 2018;61:2422–30. https://doi.org/10.1044/2018_jslhr-h-18-0097.

[57] Zhang J, Mueller ST. A note on ROC analysis and non-parametric estimate of sensitivity. Psychometrika 2005;70:203–12. https://doi.org/10.1007/s11336-003-1119-8.

[58] R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2024.

[59] RStudio Team. RStudio: Integrated development environment for R. Boston, MA: RStudio, PBC; 2021.

[60] Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using Lme4. J Stat Softw 2015;67:1–48. https://doi.org/10.18637/jss.v067.i01.

[61] Barr DJ, Levy R, Scheepers C, Tily HJ. Random effects structure for confirmatory hypothesis testing: Keep it maximal. J Mem Lang 2013;68:255–78. https://doi.org/10.1016/j.jml.2012.11.001.

[62] Fox J, Weisberg S. An R companion to applied regression. 3rd ed. Thousand Oaks CA: Sage; 2019.

[63] Lenth RV. Emmeans: Estimated marginal means, aka least-squares means. 2022.

[64] Lo S, Andrews S. To transform or not to transform: Using generalized linear mixed models to analyse reaction time data. Frontiers in Psychology 2015;6. https://doi.org/10.3389/fpsyg.2015.01171.

[65] Kitchigina V, Vankov A, Harley C, Sara SJ. Novelty-elicited, Noradrenaline-dependent Enhancement of Excitability in the Dentate Gyrus. Eur J Neurosci 1997;9:41–7. https://doi.org/10.1111/j.1460-9568.1997.tb01351.x.

[66] Silvanto J, Muggleton N, Walsh V. State-dependency in brain stimulation studies of perception and cognition. Trends Cogn Sci 2008;12:447–54. https://doi.org/10.1016/j.tics.2008.09.004.

[67] Bergmann TO. Brain State-Dependent Brain Stimulation. Frontiers in Psychology 2018;9:2108. https://doi.org/10.3389/fpsyg.2018.02108.

[68] Friedman NP, Robbins TW. The role of prefrontal cortex in cognitive control and executive function. Neuropsychopharmacol 2022;47:72–89. https://doi.org/10.1038/s41386-021-01132-0.

[69] Barth AMI, Vizi ES, Zelles T, Lendvai B. A_2-Adrenergic Receptors Modify Dendritic Spike Generation Via HCN Channels in the Prefrontal Cortex. J Neurophysiol 2008;99:394–401. https://doi.org/10.1152/jn.00943.2007.

[70] Nieuwenhuis S, Yeung N, Van Den Wildenberg W, Ridderinkhof KR. Electrophysiological correlates of anterior cingulate function in a go/no-go task: Effects of response conflict and trial type frequency. Cognitive, Affective, & Behavioral Neuroscience 2003;3:17–26. https://doi.org/10.3758/CABN.3.1.17.

[71] Nieuwenhuis S, Aston-Jones G, Cohen JD. Decision making, the P3, and the locus coeruleus–norepinephrine system. Psychol Bull 2005;131:510–32. https://doi.org/10.1037/0033-2909.131.4.510.

[72] Gajewski PD, Falkenstein M. Effects of task complexity on ERP components in Go/Nogo tasks. Int J Psychophysiol 2013;87:273–8. https://doi.org/10.1016/j.ijpsycho.2012.08.007.

[73] Falkenstein M, Hoormann J, Hohnsbein J, Kleinsorge T. Short-term mobilization of processing resources is revealed in the event-related potential. Psychophysiology 2003;40:914–23. https://doi.org/10.1111/1469-8986.00109.

[74] Potts GF. An ERP index of task relevance evaluation of visual stimuli. Brain Cognition 2004;56:5–13. https://doi.org/10.1016/j.bandc.2004.03.006.

[75] Gajewski PD, Stoerig P, Falkenstein M. ERP—Correlates of response selection in a response conflict paradigm. Brain Res 2008;1189:127–34. https://doi.org/10.1016/j.brainres.2007.10.076.

[76] Karamacoska D, Barry RJ, De Blasio FM, Steiner GZ. EEG-ERP dynamics in a visual Continuous Performance Test. Int J Psychophysiol 2019;146:249–60. https://doi.org/10.1016/j.ijpsycho.2019.08.013.