

## REGULAR RESEARCH ARTICLE

# Auricular Transcutaneous Vagus Nerve Stimulation Diminishes Alpha-Band-Related Inhibitory Gating Processes During Conflict Monitoring in Frontal Cortices

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## Abstract

**Background:** Pursuing goals is compromised when being confronted with interfering information. In such situations, conflict monitoring is important. Theoretical considerations on the neurobiology of response selection and control suggest that auricular transcutaneous vagus nerve stimulation (atVNS) should modulate conflict monitoring. However, the neurophysiological-functional neuroanatomical underpinnings are still not understood.

**Methods:** AtVNS was applied in a randomized crossover study design (n=45). During atVNS or sham stimulation, conflict monitoring was assessed using a Flanker task. EEG data were recorded and analyzed with focus on theta and alpha band activity. Beamforming was applied to examine functional neuroanatomical correlates of atVNS-induced EEG modulations. Moreover, temporal EEG signal decomposition was applied to examine different coding levels in alpha and theta band activity. **Results:** AtVNS compromised conflict monitoring processes when it was applied at the second appointment in the crossover study design. On a neurophysiological level, atVNS exerted specific effects because only alpha-band activity was modulated. Alpha-band activity was lower in middle and superior prefrontal regions during atVNS stimulation and thus lower when there was also a decline in task performance. The same direction of alpha-band modulations was evident in fractions of the alpha-band activity coding stimulus-related processes, stimulus-response translation processes, and motor response-related processes.

**Conclusions:** The combination of prior task experience and atVNS compromises conflict monitoring processes. This is likely due to reduction of the alpha-band-associated inhibitory gating process on interfering information in frontal cortices. Future research should pay considerable attention to boundary conditions affecting the direction of atVNS effects.

**Keywords:** Auricular transcutaneous vagus nerve stimulation (atVNS), conflict monitoring, EEG, theta band, alpha band, beamforming

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## Significance Statement

Goal-directed behavior is particularly demanding when being confronted with interfering information. Methods thought to enhance cognitive functions in such demanding situations through the modulation of specific neurotransmitter systems, such as transcutaneous vagus nerve stimulation (atVNS), have reached an astonishing activity in recent years. We provide evidence that atVNS can compromise behavioral performance and neurophysiological processes during interference control. The results highlight that research will intensify efforts to examine boundary conditions affecting the direction of atVNS effects.

## Introduction

We encounter tremendous amounts of information in our everyday life, and not all of this is relevant to guide goal-directed behavior and response selection. Cognitive control mechanisms are mostly needed when encountering conflicting situations, often characterized by multiple simultaneously active response options from which one is correct (Botvinick et al., 2001; Kim et al., 2010; Keye et al., 2013). Considering neuroanatomical and neurobiological processes, fronto-striatal loops (Alexander and Brown, 2010; Silvetti et al., 2014) and the dopamine system play a role in signaling and resolving conflict (Holroyd and Coles, 2002; Botvinick, 2007). However, it is unlikely that dopamine is the only modulator during conflict monitoring (Jocham and Ullsperger, 2009).

Various computational frameworks have implied that increased GABAergic system activity in prefrontal-striatal circuits plays a role in response selection (Humphries et al., 2006; Beste et al., 2014), probably via the suppression of competing response alternatives (Schroll and Hamker, 2013; de la Vega et al., 2014). Nevertheless, the GABAergic system is modulated by the glutamatergic system and catecholamines, including norepinephrine (NE) activity (Redgrave et al., 2011). NE is particularly relevant for response selection and control because proper response selection is affected by the signal-to-noise ratio in neural circuits (Aston-Jones and Cohen, 2005; Nieuwenhuis et al., 2005). NE increases the signal-to-noise ratio (SNR) in neural circuits (Aston-Jones and Cohen, 2005) by modulating the ability of neural networks to differentiate relevant and irrelevant information and is therefore necessary for conflict monitoring (Aston-Jones and Cohen, 2005; Verguts and Notebaert, 2008, 2009; Mückschel et al., 2017a). Consequently, increases in catecholamine system activity have been linked to enhanced conflict monitoring processes (Bensmann et al., 2018). Considering this, an increased GABAergic and NE system activity might enhance response selection and conflict monitoring.

One method to concomitantly increase GABAergic and NE-system activity is administering auricular transcutaneous vagus nerve stimulation (atVNS). In contrast to cervical tVNS and invasive VNS, which activate both afferent and efferent fibers (Clancy et al., 2013; Colzato and Beste, 2020), atVNS activates only afferent fibers to the brain (Colzato and Beste, 2020). Whereas afferent fibers (the thick-myelinated A $\beta$  fibers) stimulated by atVNS are noradrenergic and GABAergic (Colzato and Beste, 2020), the efferent fibers are related to other neurotransmitter systems such as, among others, the cholinergic anti-inflammatory system (Bonaz et al., 2016). According to a recent review (Colzato and Beste, 2020), several lines of evidence support the notion that the atVNS technique works by increasing GABA/NE-system activity and affects NE and GABA-related cognitive performance. Indeed, the application of atVNS has been shown to enhance various cognitive control functions (Beste et al., 2016a; Jongkees et al., 2018; Borges et al., 2020), and very recent evidence supports the strong modulatory effects of atVNS particularly on NE system activity (Sharon et al., 2021). A recent

meta-analysis (Ridgewell et al., 2021) suggested that atVNS can profoundly modulate cognitive control functions. Therefore, it is reasonable to hypothesize that atVNS can enhance response selection processes. This should mainly be the case in conflicting situations because mechanisms associated with GABAergic and NE system activity (i.e., suppressing competing response alternatives) are essential. However, considering that atVNS may unfold its effect on cognitive control processes via the modulation of gain control processes, it is crucial to keep in mind that such processes are also central for learning and plasticity processes (Doshier and Lu, 1998; Gold et al., 1999). Several pharmacological studies targeting the NE system have shown that effects of the pharmacological stimulation can be modulated by prior experience (learning) with the task at hand to examined cognitive control (Bensmann et al., 2019; Mückschel et al., 2020a, 2020b; Eggert et al., 2021). Interestingly, it has been shown that prior task experience can eliminate effects of catecholaminergic modulations in cognitive control contexts (Mückschel et al., 2020b) and even reverse intended expected cognitive enhancement effects of catecholaminergic modulation (Mückschel et al., 2020a). Because atVNS also partly modulates portions of the catecholaminergic systems (i.e., the NE system) (Colzato and Beste, 2020), it cannot be ruled out that the order of stimulation in a cross-over study design (as applied here) may affect modulatory effects of atVNS during conflict monitoring and that atVNS effects are not visible or even worsen conflict monitoring.

However, the question is also what neurophysiological processes are associated with the hypothesized atVNS effects during conflict monitoring?

Conflict monitoring and cognitive control processes are associated with increased medial frontal theta band activity in the EEG (Cohen and Cavanagh, 2011; Nigbur et al., 2011; Cavanagh and Frank, 2014; Cohen, 2014; Chmielewski et al., 2016). Considering that theta band activity-related cognitive control processes are modulated by the GABA (Quetscher et al., 2015) and the NE systems (Dippel et al., 2017; Adelhöfer et al., 2019b), it is likely that atVNS effects on conflict monitoring manifest via theta band activity associated with medial prefrontal cortices. However, especially during conflict monitoring, adjustments in attentional selection processes play an essential role (Reynolds and Chelazzi, 2004; Gazzaley and Nobre, 2012). Interestingly, alpha-band activity is linked to attentional processing and cognitive control mechanisms (Lu et al., 2017; Clements et al., 2021) in that they are relevant for the suppression of irrelevant/interfering information (von Stein et al., 2000; Palva and Palva, 2007; Klimesch, 2012; Kostandov and Cheremushkin, 2013; Suzuki et al., 2018). Studies have shown that alpha activity modulates behavioral conflicts in congruency tasks (Tang et al., 2013; Wu et al., 2015). It has been suggested that the brain adapts to conflict via the modulation of the alpha-band magnitude (Tang et al., 2013) and that neural correlates of conflict processing involve posterior parietal alpha-band oscillations (Jiang et al., 2018). Therefore, theta-band activity and alpha-band activity may reflect the

effects of atVNS during conflict monitoring. On a functional neuroanatomical level, these modulations are likely to be associated with activity modulations in superior and middle frontal as well as superior and inferior parietal cortices because these regions were previously associated with modulations of theta (Cavanagh and Frank, 2014; Cohen, 2014) and alpha-band activity (Zhao and Wang, 2019; Mamashli et al., 2020) during response selection. However, concerning these modulatory effects, it has to be considered that different aspects of information are coded in this activity (Mückschel et al., 2017b). During conflict monitoring, stimulus-related information and information detailing the response selection are concomitantly coded (Folstein and Petten, 2008), as revealed by studies applying a temporal EEG signal decomposition method: residue iteration decomposition (RIDE) (Dippel et al., 2017; Mückschel et al., 2017b; Adelhöfer et al., 2019a, 2019b; Giller et al., 2020). The RIDE method decomposes the EEG into 3 clusters of dissociable functional relevance. These 3 clusters involve the S-cluster, which pertains to stimulus-related processes such as perception and attention; the R-cluster reflects the response-related processes such as motor preparation and response execution; and the C-cluster, which reflects stimulus-response mapping processes (Ouyang et al., 2011). Depending on the paradigm to examine conflicts, conflict monitoring processes are reflected by activity modulations in the S-cluster and the R-cluster and less in the C-cluster (Mückschel et al., 2017a, 2017b; Adelhöfer et al., 2018; Giller et al., 2020; Pscherer et al., 2020; Adelhöfer et al., 2021). To summarize, the study aims to provide an in-depth analysis of neurophysiological processes associated with atVNS effects on conflict monitoring.

## METHODS

Detailed information on all methodological procedures can be found in the [supplemental Material](#). All data presented in this publication and custom code can be accessed from [https://osf.io/fn7br/?view\\_only=ff66410be4e14b018f1068d7c7404098](https://osf.io/fn7br/?view_only=ff66410be4e14b018f1068d7c7404098).

### Participants

The final sample for the data analysis consisted of  $n=45$  participants (female=37; age:  $23.57 \pm 0.51$  years). Before their participation, the participants were screened individually using a structured questionnaire that examined the history of psychological disorders, brain injury, drug use, and background information. None of the participants had prior experience with the atVNS brain stimulation technique. Written informed consent for the experiment was obtained from all participants, and the ethics committee approved the applied procedures of the Technical University of Dresden.

### Design and Procedure

The current study employed a cross-over (within-subject) design. All participants took part in the experiment twice, with approximately 1 week between the sessions. One-half of the participants received active atVNS stimulation at the first session and sham stimulation at the second session, and the other one-half received active atVNS stimulation at the second session and sham stimulation at the first session. After each appointment, participants filled out an atVNS aversive effects questionnaire (data shown in the Results section). The participants were stimulated approximately 20 minutes before the start of the experiment, like other studies (Beste et al., 2016b), and they continued to be stimulated throughout the experiment.

## Auricular Transcutaneous Vagus Nerve Stimulation

We used a Cerbomed atVNS device (CM02, Cerbomed, Erlangen, Germany). Based on the recent consensus statements (Farmer et al., 2021), the stimulation intensity of the instrument was set to 0.5 mA delivered with a pulse of 200–300 seconds at 25 Hz (Dietrich et al., 2008). The participants received either active atVNS or sham atVNS. In both experimental conditions (i.e., active and sham), the stimulation was active for 30 seconds after a pause of another 30 seconds. That is, the only difference between the active and sham condition was the location of the electrode. In the case of the active condition, the electrode was placed in the outer ear where the innervation of the auricular branch of the vagus nerve is positioned (Colzato and Beste, 2020). In contrast, in the case of the sham condition the electrode was placed on the earlobe, which is free from vagal afferents (Colzato and Beste, 2020). Hence, even if in both conditions the electrode sent electrical impulses, only in the active condition was the vagus nerve really stimulated. By doing so, the participants hardly disentangle the active from the sham condition, assuring the effectivity of our blinding procedure. Previous research studies have indicated that atVNS is considered safe when applied in the left but not in the right ear to avoid cardiac side effects (Kreuzer et al., 2012; Sperling et al., 2010). Therefore, atVNS was placed only in the left ear of the participants. In the active stimulation condition, atVNS was placed in the cymba conchae, which is considered to be the ideal location of stimulation because it induces the strongest activation of nucleus of the solitary tract and locus coeruleus (Yakunina et al., 2017). In the sham condition, the electrodes were applied on the center of the left ear lobe (Kraus et al., 2007), which is free of cutaneous vagal innervation (Peuker and Filler, 2002) and thus should not produce any activation in the cortex or brain stem (Frangos et al., 2015).

### Eriksen Flanker Task

To investigate response selection in conflict and non-conflicting situations, a Flanker task was used (Kopp et al., 1996; Mückschel et al., 2017a). In the task, a target stimulus (arrowhead pointing to the left or right in the center of the screen) was preceded by 2 flanking stimuli (arrowhead pointing to the left of right above and below the target stimulus) by 200 ms. Flanker and target stimuli were switched off simultaneously. Participants were asked to respond in the direction of the target stimulus arrowhead. When the target stimulus was pointing to the left, they had to press the left Ctrl-button, and when it was pointing to the right, they had to press the right Ctrl-button (see Fig. 1 in the [supplemental Material](#)).

### EEG Recording and Analysis

The EEG data were recorded in TU Dresden Cognitive Neurophysiology Lab premises with 60 Ag/AgCl electrodes. After data pre-processing, the data were segmented (stimulus-locked) regarding congruent and incongruent trials. Only trials with correct responses were included in the EEG data analysis. The single-trial EEG data were then used for the RIDE (Ouyang et al., 2011, 2015) to dissociate coding levels in EEG data. The RIDE-decomposed data (S-cluster, C-cluster, and R-cluster) were then subjected to a time-frequency decomposition step applying Morlet wavelets to examine theta- (4–7 Hz) and alpha-band activities (8–12 Hz) in each of the clusters (i.e., S-cluster, C-cluster, and R-cluster). To examine which functional neuroanatomical

regions were associated with alpha-band activity in these clusters, a Dynamical Imaging of Coherent Sources beamformer was utilized (Gross et al., 2001).

## RESULTS

### Participants' Reports on atVNS Effects

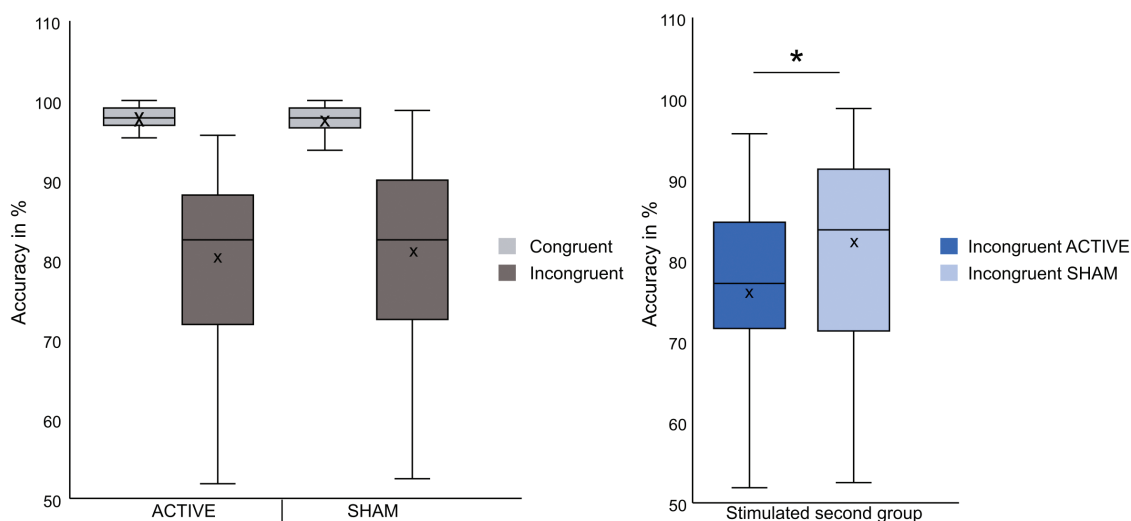
We examined the side effects reported from the participants. For all descriptive statistics, the mean and the SEM are reported. Bonferroni-correction was used throughout. The paired samples *t* test for "headache" did not reveal any significant difference for sham stimulation ( $1.40 \pm 0.10$ ) or active stimulation ( $1.37 \pm 0.10$ ) ( $t[44] = -0.19$ ;  $P > .9$ ), and likewise for "neck pain" sham stimulation ( $1.37 \pm 0.09$ ) or active stimulation ( $1.26 \pm 0.08$ ) ( $t[44] = -1.15$ ;  $P > .9$ ) and for "nausea" active ( $1.06 \pm 0.03$ ) and sham ( $1.04 \pm 0.03$ ) ( $t[44] = 0.44$ ;  $P > .9$ ). Similarly, there was no difference for "stinging sensation under the electrodes" between the active stimulation ( $2.15 \pm 0.18$ ) and the sham condition ( $1.75 \pm 0.15$ ) ( $t[44] = 1.86$ ;  $P = .547$ ). Also, for "muscle contraction in face and/or neck" no difference between active atVNS ( $1.28 \pm 0.08$ ) and sham atVNS ( $1.28 \pm 0.08$ ) was evident ( $t[44] < 0.01$ ;  $P > .9$ ). On average there was a difference in the "burning sensation," with the active stimulation condition showing higher impact ( $1.86 \pm 0.14$ ) than the sham condition ( $1.53 \pm 0.12$ ) ( $t[44] = 2.01$ ;  $P = .397$ ) that did not yield significance after Bonferroni correction. For "uncomfortable generic feelings," there were no differences between active atVNS ( $1.60 \pm 0.10$ ) and sham atVNS ( $1.60 \pm 0.13$ ) ( $t[44] < 0.01$ ;  $P > .9$ ). The same was the case for "other sensations and/or aversive effects" between active atVNS ( $1.24 \pm 0.09$ ) and sham atVNS ( $1.42 \pm 0.13$ ) ( $t[44] = -1.27$ ;  $P > .9$ ). The participants were asked to guess in which session they thought they received active stimulation. It is shown that guesses did not differ from chance level ( $\chi^2 = 1.089$ ,  $P = .297$ ), suggesting that the blinding was successful.

### Behavioral Data (Flanker Task)

The mean and SEM is reported for all descriptive statistics. The repeated-measures ANOVA for accuracy revealed a significant main effect of congruency ( $F[1,43] = 136.00$ ;  $P < .001$ ;  $\eta_p^2 = .760$ ), as participants revealed higher accuracy in the

congruent condition ( $97.5 \% \pm 0.26$ ) than in the incongruent condition ( $79.6 \% \pm 1.58$ ). Furthermore, there were significant interaction effects of stimulation\*order of stimulation ( $F[1,43] = 4.42$ ;  $P = .041$ ;  $\eta_p^2 = .093$ ) and a threefold interaction effect of stimulation\*congruency\*order of stimulation ( $F[1,43] = 7.27$ ;  $P = .010$ ;  $\eta_p^2 = .145$ ). Therefore, we conducted post-hoc tests for the highest interaction that we obtained. Separate post-hoc repeated-measures ANOVAs were conducted for each stimulation order group. The ANOVA for the group stimulated at the first appointment revealed only a main effect of congruency ( $F[1,21] = 70.68$ ;  $P < .001$ ;  $\eta_p^2 = .771$ ), reflecting higher accuracy for congruent trials ( $97.83 \% \pm 0.28$ ) than for the incongruent trials ( $81.01 \% \pm 2.03$ ), but no other main or interaction effects. ( $F[1,21] < 1.24$ ;  $P > .276$ ). Opposed to this, the ANOVA for the group that was stimulated at the second appointment showed a main effect of congruency ( $F[1,22] = 67.37$ ;  $P < .001$ ;  $\eta_p^2 = .754$ ) and an interaction of stimulation\*congruency ( $F[1,22] = 6.23$ ;  $P = .021$ ;  $\eta_p^2 = .221$ ). Further post-hoc paired *t* tests were applied to investigate the interaction of stimulation and congruency. The post-hoc paired *t* test revealed that for the group stimulated at the second appointment, there was a significant difference in accuracy for the incongruent trials in the active stimulation appointment ( $75.57 \% \pm 2.71$ ) compared with the sham stimulation appointment ( $80.81 \% \pm 2.66$ ) ( $t[22] = -2.22$ ;  $P = .037$ ) (see Fig 1). For the group stimulated at the first appointment, there were no differences in accuracy for incongruent trials in the active stimulation appointment ( $82.38 \% \pm 2.22$ ) compared with the sham stimulation appointment ( $79.63 \% \pm 2.42$ ) ( $t[21] = 1.20$ ;  $P = .243$ ). For both groups, there were no significant differences for the congruent trials ( $P > .05$ ).

Reaction times were determined relative to the onset of the target stimulus. The repeated-measures ANOVA was also run for the reaction times and revealed a main effect of congruency ( $F[1,43] = 569.38$ ;  $P < .001$ ;  $\eta_p^2 = .930$ ), showing that participants displayed faster reaction times in the congruent condition ( $299.75 \text{ ms} \pm 3.87$ ) than the incongruent condition ( $373.82 \text{ ms} \pm 3.78$ ) (see supplemental Fig. 2). Moreover, there was an interaction effect of stimulation\*order of stimulation ( $F[1,43] = 48.33$ ;  $P < .001$ ;  $\eta_p^2 = .529$ ). To explore this 2-way interaction, we conducted post-hoc paired *t* tests. For the group stimulated at the first session, there were significant differences



**Figure 1.** Box plots of the obtained mean accuracy in percent for each task condition and the post-hoc tests revealing a significant difference in the stimulated second group for the incongruent trials for stimulation and sham sessions. \* $P < .05$ .



in reaction times for the congruent trials in the active stimulation session ( $306.59\text{ ms} \pm 6.95$ ) and the sham stimulation session ( $287.95\text{ ms} \pm 5.19$ ) ( $t[21] = 3.487$ ;  $P = .002$ ). The same group had significant differences in reaction times for the incongruent trials in the active stimulation session ( $375.75\text{ ms} \pm 6.24$ ) and sham stimulation session ( $358.40\text{ ms} \pm 4.68$ ) ( $t[21] = 3.69$ ;  $P = .001$ ). Similarly, the group stimulated at the second session had significant differences for reaction times in congruent trials in the active stimulation session ( $291.59\text{ ms} \pm 5.58$ ) and sham stimulation session ( $312.83\text{ ms} \pm 5.68$ ) ( $t[22] = -6.90$ ;  $P < .001$ ). Likewise, the incongruent trials reaction times were faster in the active stimulation session ( $372.02\text{ ms} \pm 5.96$ ) than the sham stimulation session ( $389.08\text{ ms} \pm 5.81$ ) ( $t[22] = -4.91$ ;  $P \leq .001$ ).

### Neurophysiological Data (Flanker Task)

Power differences of the sham and the active stimulation condition were compared using cluster-based permutation tests (CPTs) for the theta- and alpha-frequency bands. The contrast that we computed for the neurophysiological analysis of the data was sham-active. The analysis was confined to the significant stimulation effect observed for incongruent trials in the behavioral data (i.e., the group stimulated second). The reason is that repeated-measures ANOVAs are not appropriate to run in CPTs and beamforming analysis because they need to fulfill the requirement of the assumption of exchangeability under the null hypothesis and that is not fulfilled in the context of CPTs (Frossard and Renaud, 2018). More specifically, the random effects associated with subjects and their interaction with fixed effects pose a complex structure in regards to the covariance matrix of observations. The results of the time frequency analysis for the RIDE S-cluster, R-cluster, and C-cluster data are shown in Figure 2.

The CPT did not reveal any significant differences in modulations of theta-band activity of incongruent trials between active stimulation and sham stimulation, regardless of the information coding level (i.e., S-, C-, and R-cluster). Crucially, however, the CPTs revealed significant differences in alpha-band activity for S-, C- and R-cluster. Due to the lack of a priori hypotheses for a time window of interest for alpha-band power modulations, the initial CPTs were conducted for the time window of 0 to 1000 ms relative to flanker stimulus onset. Significant power differences were found for the S-, C-, and R-clusters, as indicated by negative clusters of mostly central electrodes from approximately 300 to 1000 ms ( $P < .048$ ). A negative cluster suggests that the alpha power was larger in the active stimulation condition than in the sham condition, whereas a positive cluster suggests smaller alpha power in the active condition. To back these alpha-band power difference findings, we computed additional CPTs for the mean power within 400 to 600 ms, encompassing the average time window for behavioral responses in relation to the Flanker onset. As can be seen in Figure 3A, significant alpha-band differences were found for the S-cluster, as indicated by a negative cluster of central electrodes (Cz, FCz, FC1, CP1, F1, FC2, CP2, CPz, FC4;  $P = .007$ ) and a positive cluster at left hemisphere frontal electrodes (F5, Fp1, AF7, FT7, T7, FT9;  $P = .026$ ). For the frontal positive cluster, the increase from the sham condition to active stimulation condition on average was  $63.3 \pm 22.8$ , and for the central negative cluster an average decrease of  $-50.9 \pm 13.8$  was observed. For the C-cluster, significant alpha-band modulations could be shown, as indicated by a negative cluster of central electrodes (Cz, FC1, FC2, CP2;  $P = .041$ ) and a positive cluster at left hemisphere frontal electrodes (F5, Fp1, AF7, FT7, FT9;  $P = .044$ ). The average power change for the frontal positive

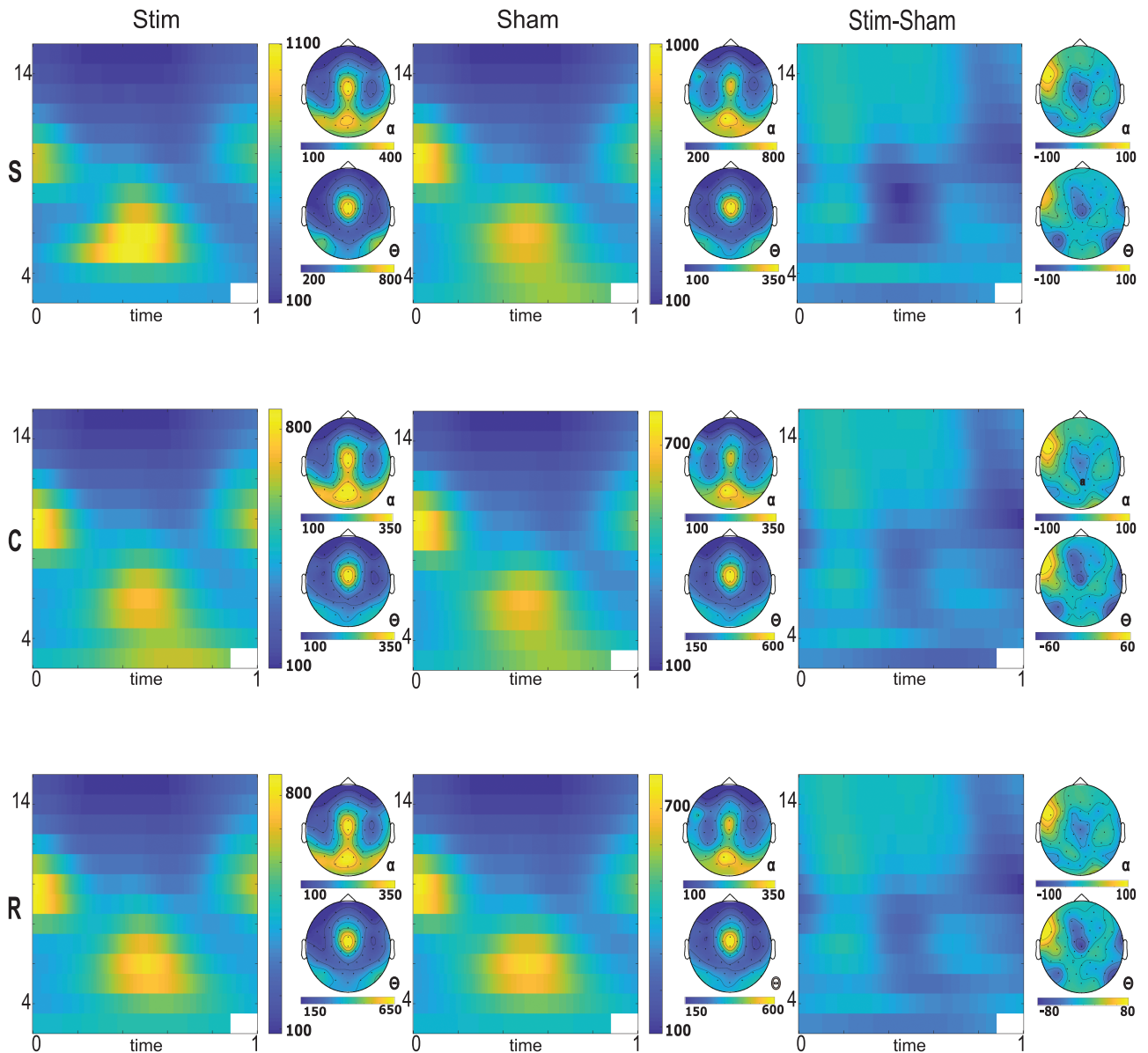
cluster was  $61.5 \pm 22.4$ , and for the central negative cluster it was  $-43.1 \pm 12.2$ . Finally, significant alpha-band power differences were also found for the R-cluster, as indicated by a negative cluster of central electrodes (Cz, FC1, FC2, CP2;  $P = .040$ ) and a positive cluster at left hemisphere frontal electrodes (F5, Fp1, AF7, FT7, FT9;  $P = .033$ ). Here, alpha-band power in the active condition increased by 61.4 at the frontal positive cluster and decreased by  $-44.1 \pm 11.6$  in the central negative cluster. The power of alpha-band activity is depicted in Figure 3B. The alpha-band power differences of S-, C-, and R-clusters did not correlate significantly with the stimulation effect observed in the behavioral data for either the frontal electrode clusters or for the central electrode clusters ( $P \geq .125$ ;  $r \leq .329$ ).

The Dynamical Imaging of Coherent Sources beamformer source reconstruction for the stimulation effect in incongruent trials revealed positive source activity differences in the middle frontal region and the superior frontal region. Negative alpha power differences were associated with the superior parietal cortex (compare Fig. 4). This pattern was the same for all 3 clusters.

### Discussion

In the current study, we examined the effects of atVNS on conflict-monitoring processes, emphasizing the neurophysiological processes associated with atVNS effects. To this end, we examined theta- and alpha-band activity and examined whether atVNS affects specific aspects of information coded in theta- and alpha-band activity. This was combined with an EEG-beamforming approach to delineate the functional neuro-anatomical correlates of the atVNS modulations during conflict monitoring.

The behavioral data revealed that atVNS vs sham-atVNS modulated the response accuracy but not the response speed in the incongruent condition and not in the congruent condition. This modulation, however, was also shown to be dependent on the time point at which atVNS or sham-atVNS was applied in the cross-over study design. Performance differences between atVNS and sham atVNS were only evident when atVNS was applied in the second session of the cross-over study design. In this case, performance was worse (i.e., response accuracy lower) during atVNS compared with the sham stimulation appointment. This shows that atVNS can compromise conflict monitoring and cognitive control performance. Likely, these effects may have emerged due to concomitant effects of neural mechanisms being modulated by prior task experience and by atVNS. The pattern of findings shows striking parallels with findings on the effects of methylphenidate (MPH: Bensmann et al., 2019; Mückschel et al., 2020a, 2020b), which is a dopamine and NE reuptake inhibitor (Faraone, 2018). Administering moderate doses of MPH it was shown that prior task experience could eliminate and even compromise task performance (Bensmann et al., 2019; Mückschel et al., 2020a, 2020b). This has been attributed to an overshoot in the modulation of NE system activity (Bensmann et al., 2019; Mückschel et al., 2020a, 2020b). Increased NE-system activity can increase gain control of the SNR in neural circuits (Aston-Jones and Cohen, 2005). However, the inter-relation of NE-system activity and task performance obeys the Yerkes-Dobson Principle (i.e., an inverted U-shaped function). Therefore, increases in NE system activity beyond a specific point can worsen task performance. Because learning also modulates the SNR (Doshier and Lu, 1998; Gold et al., 1999), it is possible that the combination of previous task experience and atVNS (Colzato and Beste, 2020) worsens performance. The similarities

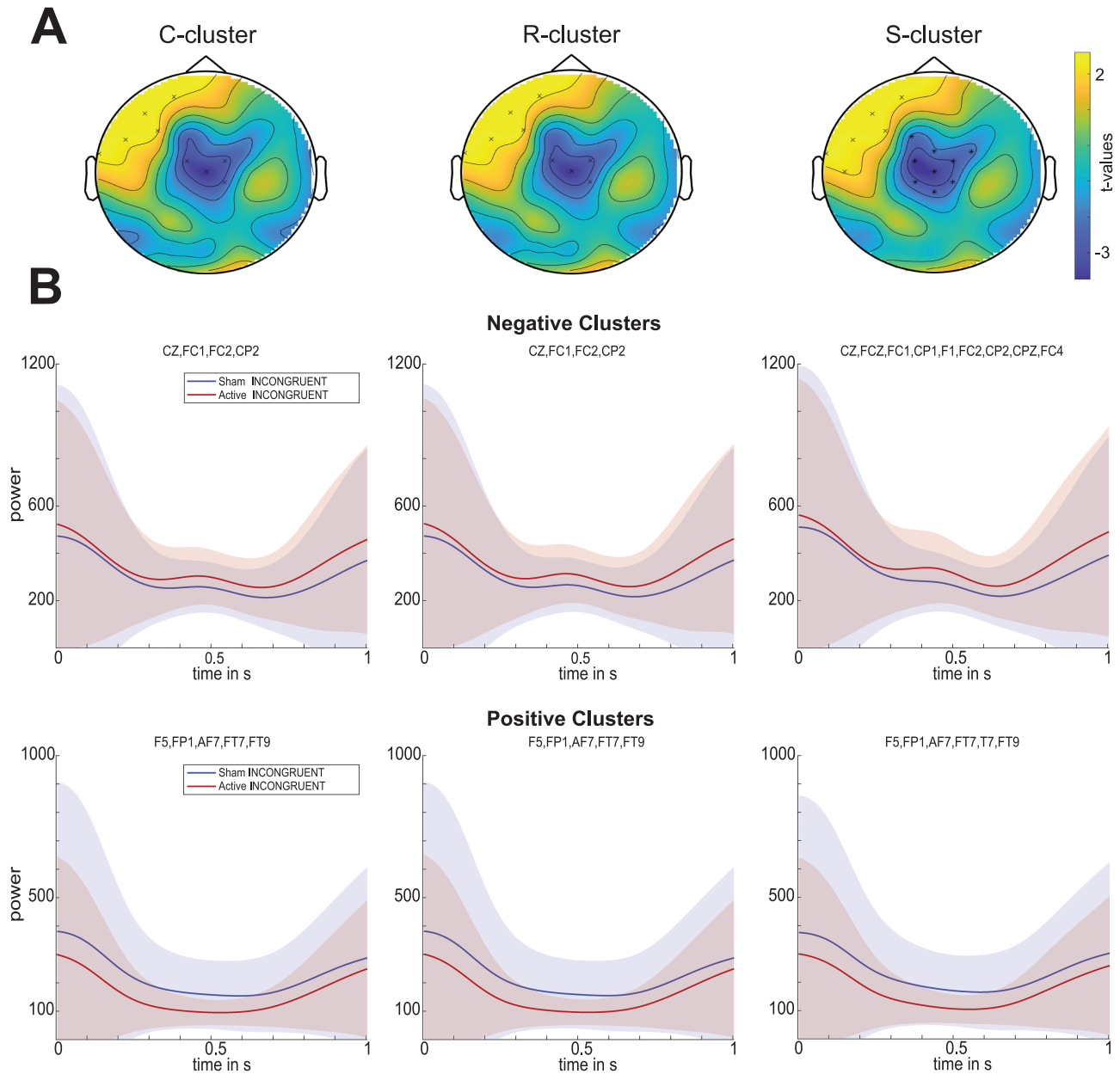


**Figure 2.** A schematic illustration of the time frequency analysis depicting alpha and theta band frequency in S-, C- and R-clusters for sham stimulation and for active stimulation sessions. The difference between the sham stimulation and active stimulation for the incongruent trials is shown in the right part of the picture. Power is indicated by color. Moreover, the topographic figures for both alpha and theta band activity are presented next to each plot.

in terms of task experience-dependent effects between studies examining MPH effects and the current study on atVNS effects provide hints which neurobiological system is presumably most important for the overshoot effect to emerge. MPH modulates the dopamine and the NE system (Faraone, 2018). Several lines of research indicate that stimulation of afferent fibers of the vagus nerve by means of atVNS modulate the NE system and also the GABAergic system. In light of the similarities and the neurobiological modulation profile of MPH and atVNS, it is likely that it is the overshooting stimulation of the NE system that can impair task performance. For the current study, it is possibly an overshoot in the NE system resulting in worsened task performance when demands on response selection were high, that is, in conflict situations.

The EEG data provide further insights into the neurophysiology of the observed effects. No atVNS-dependent effects explaining task performance were observed for the theta-band

activity. However, alpha-frequency band activity revealed modulatory effects at all investigated coding levels as revealed by RIDE of the EEG alpha signal (i.e., in the S-, C-, and R-clusters). This suggests that stimulus-related processes, stimulus-response translation processes, and motor response-related processes coded in alpha-band activity are modulated by atVNS effects. Interestingly, positive and negative activity modulations were observed depending on the electrode site. Negative activity differences (i.e., alpha power active stimulation > sham stimulation) were associated with superior parietal regions. Positive activity differences (i.e., alpha power active stimulation < sham stimulation) were associated with middle and superior frontal regions. Thus, alpha-band activity was lower in prefrontal regions during atVNS stimulation and lower when there was also a decline in task performance. Alpha-band activity is linked to attentional processing and cognitive control mechanisms (Lu et al., 2017; Clements et al., 2021) in that they are relevant for

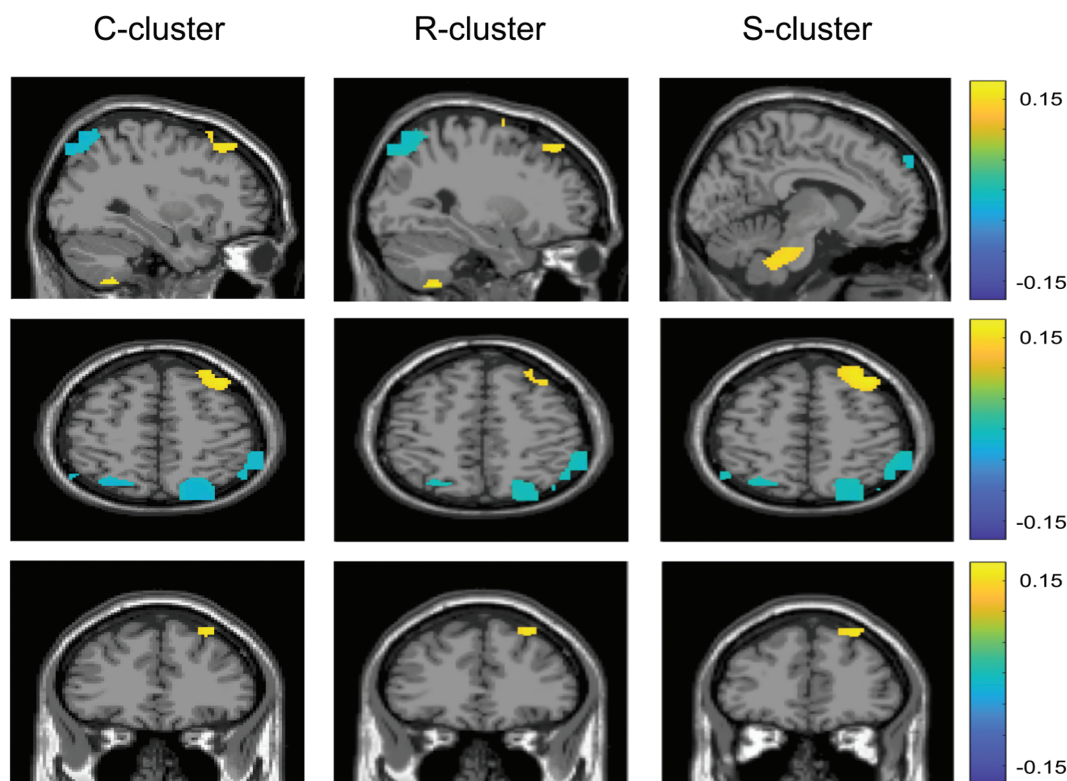


**Figure 3.** Topographical projection of the cluster based permutation tests depicting the positive and negative clusters for alpha band activity for S-, C-, and R-clusters (A). The colors denote cluster-level summed t values. The power of alpha-band activity is presented in the second part of the figure (B). The shaded bands indicate the SDs.

the suppression of irrelevant/interfering information (von Stein et al., 2000; Palva and Palva, 2007; Klimesch, 2012; Kostandov and Cheremushkin, 2013; Suzuki et al., 2018). Mainly prefrontal regions are critically involved in such top-down control processes (Miller and Cohen, 2001). It thus seems that atVNS has reduced the property of alpha-band activity to suppress the interfering effects of irrelevant flanker information in prefrontal cortices. The finding that all decomposed RIDE clusters reveal the same effect suggests that the lowered ability to suppress interfering effects of irrelevant flanker information affects stimulus-related processes, stimulus-response translation processes, and motor response-related processes. These effects can plausibly explain the decrease in responding in conflicting trials. Previous findings have shown that especially superior frontal areas process stimulus-related stimulus-response translation processes and

motor response-related codings (Mückschel et al., 2017a, 2017b). The current results extend this for alpha-band activity. However, concomitant with prefrontal regions, alpha-band activity was increased during atVNS stimulation in superior parietal regions compared with sham stimulation. Considering that increase in alpha-band activity may reflect inhibitory gating processes (Klimesch, 2012), the modulatory pattern reflected by superior parietal regions indicates that inhibitory gating is enhanced in these areas for all analyzed aspects of information decoded using RIDE in alpha-band activity. This is plausible considering that parietal regions are involved in processing stimulus information, stimulus-response translation processes, and motor response programming (Andersen and Buneo, 2002; Gottlieb, 2007; Andersen and Cui, 2009). Because the behavioral data show an apparent decline in performance as an effect of atVNS, the





**Figure 4.** Representations of the Dynamical Imaging of Coherent Sources (DICS) beamformer source reconstruction for the stimulation effect in incongruent trials showing activity differences in the frontal middle region, frontal superior region, and superior parietal cortex (B). The colors denote the difference of source-power estimate ratios between the contrasted conditions (incongruent sham-incongruent active).

observed increase in superior parietal cortex-associated inhibitory gating is not as substantial as the observed decrease in inhibitory gating processes in frontal regions.

However, considering the broader literature on atVNS effects, it needs to be noted that other data revealed beneficial effects of atVNS in a conflict-monitoring experiment (Fischer et al., 2018). While this may be regarded as at odds with the current findings, several differences between methodological procedures are essential. First, in Fischer et al. (2018), atVNS stimulation intensity was adjusted individually and varied considerably between participants (i.e., mean 1.3 mA; range 0.4–3.3 mA), which was not done in the current study. Second, the study by Fischer et al. (2018) used a different task (i.e., a Simon task) known to measure different aspects of conflict monitoring (Verbruggen et al., 2006; Keye et al., 2013). Both factors can explain the differences between findings. However, the first aspect (individualized vs non-individual stimulation intensity) may be most important because this is probably most critical for possible overshoot effects in the NE system. Future research should pay considerable attention to boundary conditions affecting the direction of atVNS effects. Moreover, future studies should directly model Bayesian prior to investigating the atVNS effects and its interaction with previous experience, providing more insights regarding the atVNS modulation effects. A limitation of our study is that we used the MRI template (MNI brain) instead of the individual MRI of the participant to construct the head model, which might cause the source localization to not be as precise. Additionally, most of the participants tested in this study were female. Based on animal studies (for a review, see Bangasser et al., 2016), it should be remembered that female participants are more susceptible to atVNS-induced locus coeruleus (LC)-NE activation.

This might be the case for 2 reasons. First, as hypothesized by Bangasser and colleagues (2016), female rats, compared with male rats, have an anatomically bigger locus coeruleus (LC) and display an extended complexity in terms of dendritic trees, and this could cause an increase in afferent information coming from the NTS. Second, atVNS might affect the neurochemistry of the LC-NE system more in females than males by virtue of the fact that NE synthesis and degradation are influenced by estrogen release, and they are higher in female rats (Vathy and Etgen, 1988). Related to that, it seems likely the estrous cycle in rats directly modulates NE levels (Selmanoff et al., 1976). Notwithstanding these findings in rats, it is unclear whether they can directly translate to humans. Accordingly, future studies will be needed to determine whether atVNS affects women differently from men. Finally, Flanker paradigms such as that used here require an imbalance in the probability of congruent and incongruent condition trials. An imbalance of trial numbers may be related to signal-to-noise ratio differences, which may affect congruency-related effects. These effects should be stronger when trial numbers are quite low. We used many trials for the less frequent incongruent condition (160 trials) to reduce possible adversary effects.

In summary, we provide evidence that atVNS effects on conflict monitoring are modulated by prior task experience. The combination of prior task experience and atVNS compromises conflict monitoring processes compared with sham atVNS stimulation. On a neurophysiological level, atVNS exerted specific effects because only alpha-band activity was modulated. Alpha-band activity was lower in prefrontal regions during atVNS stimulation and lower when there was also a decline in task performance. atVNS likely reduces the ability to suppress



the interfering effects of irrelevant flanker information in prefrontal cortices. The finding that all decomposed RIDE clusters reveal the same effect suggests that the lowered ability to suppress interfering effects of irrelevant flanker information affects stimulus-related processes, stimulus-response translation processes, and motor response-related processes.

## Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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