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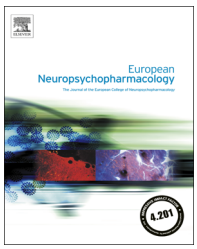

Transcutaneous vagus nerve stimulation (tVNS) enhances response selection during action cascading processes

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Abstract
The ever-changing environment we are living in requires us to apply different action control strategies in order to fulfill a task goal. Indeed, when confronted with multiple response options it is fundamental to prioritize and cascade different actions. So far, very little is known about the neuromodulation of action cascading. In this study we assessed the causal role of the gamma-aminobutyric acid (GABA)-ergic and noradrenergic system in modulating the efficiency of action cascading by applying transcutaneous vagus nerve stimulation (tVNS), a new non-invasive and safe method to stimulate the vagus nerve and to increase GABA and norepinephrine concentrations in the brain. A single-blind, sham-controlled, between-group design was used to assess the effect of on-line (i.e., stimulation overlapping with the critical task) tVNS in healthy young volunteers (n=30)–on a stop-change paradigm. Results showed that active, as compared to sham stimulation, enhanced response selection functions during action cascading and led to faster responses when two actions were executed in succession. These findings provide evidence for the important role of the GABA-ergic and noradrenergic system in modulating performance in action cascading.

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1. Introduction

The ever-changing environment we are living in requires us to apply different action control strategies in order to fulfill a task goal. Indeed, when confronted with multiple response options it is fundamental to prioritize and cascade different actions (Mückschel et al., 2014). So far, very little is known about the neuromodulation of action cascading, although there is evidence showing that dopaminergic and the gamma-aminobutyric acid (GABA)-ergic system are important (Stock et al., 2014a, 2014b; Beste and Saft, 2013). Concerning the GABA-ergic system, recent findings using magnetic resonance spectroscopy (MRS) showed that superior performance in action cascading was associated with increased concentrations of striatal GABA (Yildiz et al., 2014a). Given the correlational nature of MRS studies, it is, however, hard to infer the exact role of GABA in mediating action cascading. There is also evidence showing that stress modulates action cascading processes (Yildiz et al., 2014b). Stress is known to affect the noradrenergic system (Glavin, 1985). So there is tentative evidence for the idea that norepinephrine (NE), playing an important role in stress responses, may affect functions during action cascading and lead to slowing of responses when two actions are executed in succession.

In this study we assessed the causal role of the GABA-ergic and noradrenergic system in modulating the efficiency of action cascading by applying transcutaneous vagus nerve stimulation (tVNS), a new non-invasive method to stimulate the vagus nerve, introduced for the first time by Ventureyra (2000); for a recent review see Vonck et al. (2014). tVNS stimulates the afferent auricular branch of the vagus nerve located medial of the tragus at the entry of the acoustic meatus (Kreuzer et al., 2012). tVNS is safe and is accompanied only by minor side effects such as a burning or itching sensation under the electrodes. Very recently, it has been suggested that tVNS may be a useful tool to further investigate the neuromodulation of cognitive processes related to NE and GABA, two of the main neurotransmitters targeted by VNS (van Leusden et al., 2015). In rats, it has been demonstrated that VNS leads to an intensity-dependent increase in brain NE in response to stimulation of the left vagus nerve (Raedt et al., 2011; Roosevelt et al., 2006). These increases in NE are transient and return to baseline levels when the stimulation is stopped and the vagus nerve is no longer being stimulated (Roosevelt et al., 2006). Besides NE, the other main neurotransmitter targeted by VNS is GABA. So far, tVNS has mainly been used to treat patients with epilepsy (Vonck et al., 2014), who suffer from an abnormal reduction of GABA-ergic function (Treiman, 2001). Indeed, VNS seems to increase the levels of free GABA in the cerebrospinal fluid (Ben-Menachem et al., 1995). Moreover, in epileptic patients receiving VNS for a year, GABA-A receptor density was significantly increased as compared to controls (Marrosu et al., 2003).

Given the available, correlational evidence that action cascading is modulated by the GABA-ergic system, we tested whether tVNS, via GABA and NE release, ameliorates the efficiency of action cascading. This hypothesis is supported by the fact that, from an anatomical point of view, action cascading efficiency is related to a neural network that includes the anterior cingulate cortex (ACC; Mückschel et al., 2014). Importantly, the vagal nerve is connected to the ACC (Mayer, 2011), and the ACC is a crucial area for the execution of multi-component behavior (Duncan, 2010, 2013). We assessed action cascading by means of a well-established stop-change paradigm (Verbruggen et al., 2008), in which we varied the interval between "stopping" and "changing" (stop-change delay; SCD) and hence varied the time available for preparation before executing the change response (Mückschel et al., 2014). Given the idea that GABA and NE impact action selection (Yildiz et al., 2014a; Yildiz et al., 2014b), we expected the active tVNS to ameliorate the action cascading processes (i.e. decrease reaction times on the change stimuli) when (i) an interruption, i.e. stopping a response, and a change toward an alternative response are required simultaneously (SCD0), and when (ii) the change to another response is required once the stopping process has already finished (SCD300).

2. Experimental procedures

2.1. Participants

Thirty undergraduate students of the Leiden University (26 females, 4 males, mean age=19.8 years, range 18–27) participated in the experiment. Participants were recruited via an on-line recruiting system and were offered course credit for participating in a study on the effects of brain stimulation on cognition. Once recruited, participants were randomly assigned to one of the two following experimental groups: sham stimulation (N=15; 2 male; mean age=20.2, SD=3.0), or active stimulation (N=15; 2 male; mean age=19.3, SD=1.4). Groups did not differ in terms of age, $t(28)=1.0$, $p=.32$, or gender, $\chi^2<.01$, $p>.9$. All participants were naïve to tVNS. Participants were screened individually via a phone interview by the same lab-assistant using the Mini International Neuropsychiatric Interview (M.I.N.I.). The M.I.N.I. is a short, structured, interview of about 15 minutes that screens for several psychiatric disorders and drug use, often used in clinical and pharmacological research (Sheehan et al., 1998; Colzato et al., 2008, 2010). Participants were considered suitable to participate in this study if they fulfilled the following criteria: (i) age between 18 and 30 years; (ii) no history of neurological or psychiatric disorders; (iii) no history of substance abuse or dependence; (iv) no history of brain surgery, tumor or intracranial metal implantation; (v) no chronic or acute medications; (vi) no pregnancy; (vii) no susceptibility to seizures or migraine; (viii) no pacemaker or other implanted devices.

All participants were naïve to tVNS. Prior to the testing session, they received a verbal and written explanation of the procedure and of the typical adverse effects (i.e., itching and tingling skin sensation, skin reddening, and headache). No information was provided about the different types of stimulation (active vs. sham) or about the hypotheses concerning the outcome of the experiment. The study conformed to the ethical standards of the declaration of Helsinki and the protocol was approved by the local ethical committee (Leiden University, Institute for Psychological Research).

2.2. Apparatus and procedure

Single-blinded, sham-controlled, randomized two-arms trials were used to assess the effect of on-line (i.e., stimulation overlapping with the critical task) tVNS in healthy young volunteers in a stop-change paradigm. All participants were tested individually. After having read and signed the informed consent, heart rate (HR) was collected from the non-dominant arm with an OSZ 3 Automatic Digital Electronic Wrist Blood Pressure Monitor (Spiedel & Keller). Immediately after,

participants performed the stop-change paradigm, which included a practice phase (about 20 minutes) and a testing phase (about 25 minutes). Thus, tVNS was applied throughout the whole task. Once finished, participants had their HR measured for the second time.

After completion of the session, participants were debriefed and asked to complete a tVNS adverse effects questionnaire requiring them to rate, on a five-point (1–5) scale, how much they experienced: (1) headache, (2) neck pain, (3) nausea, (4) muscles contraction in face and/or neck, (5) stinging sensation under the electrodes, (6) burning sensation under the electrodes, (7) uncomfortable (generic) feelings, (8) other sensations and/or adverse effects. None of the participants reported major complains or discomfort during or after tVNS.

2.2.1. tVNS

We used a tVNS instrument consisting of two titan electrodes mounted on a gel frame and connected to a wired neurostimulating device (CM02, Cerbomed, Erlangen, Germany). Following the suggestions by Dietrich et al. (2008) for optimal stimulation, the tVNS® device was programmed to a stimulus intensity at .5 mA, delivered with a pulse width of 200–300 μs at 25 Hz. Stimulation was active for 30 seconds, followed by a break of 30 seconds. Following Kraus et al. (2007), in the sham condition, the stimulation electrodes were attached to the center of the left ear love instead of the outer aditory canal. Indeed, the ear lobe has been found to be free of cutaneous vagal innervation (Peuker and Filler, 2002; Fallgatter et al., 2003) and a recent fMRI study showed that this sham condition produced no activation in the cortex and brain stem (Kraus et al., 2013).

None of the participants were able to determine whether or not they received real or sham stimulation. Since efferent fibers of the vagus nerve modulate cardiac function, cardiac safety has always been a concern in the therapeutic use of vagus nerve stimulation (Cristancho et al., 2011). Efferent vagal fibers to the heart are supposed to be located on the right side (Nemeroff et al., 2006). In order to avoid cardiac side effects, electrodes were always placed on the left ear (Nemeroff et al., 2006). While placing electrodes on the left side, a clinical trial showed no arrhythmic effects of tVNS (Kreuzer et al., 2012).

2.2.2. Stop-change paradigm

The experiment was controlled by an Asus laptop running on an Intel Core i3-3217U processor, attached to a LG Flatron 776FM 16 in. monitor (refresh rate of 60 Hz). Stimulus presentation and data collection were controlled using the Presentation software system (Neurobehavioral Systems, Inc., Berkeley, CA). The stop-change (SC) paradigm was adapted from Yildiz et al. (2014b), see Figure 1. Responses were given using the index and middle fingers of the right hand during the GO trials and those of the left hand for the SC trials.

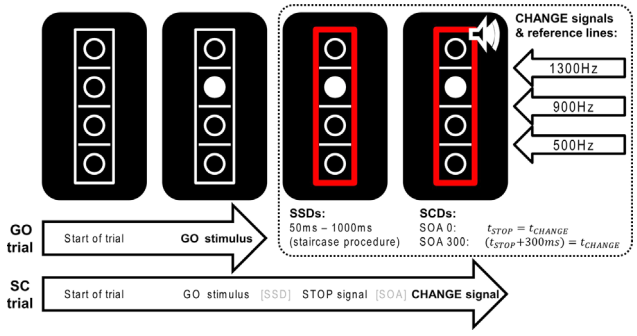

Figure 1 Schematic illustration of the stop-change paradigm. GO1 trials end after the first response to the GO1 stimulus (bold). In contrast, SC trials end after the first response to the CHANGE signal (bold). The stop-signal delay (SSD) between the onset of the GO1 stimulus and the STOP signal was adjusted using a staircase procedure described in Section 2. The stimulus onset asynchrony (SOA) between the onset of the STOP and CHANGE stimuli was set to either 0 or 300 ms. As indicated in the upper right corner, the three CHANGE stimuli were associated with one of the three reference lines.

Throughout each trial, a white rectangle of 55 × 16 mm was displayed on a black background in the center of the screen. Within this rectangle, three horizontal reference lines (line thickness 1 mm, width 13 mm) separated four vertically aligned circles (diameter 7 mm). At 250 ms after trial onset, one of the circles was filled white, thus becoming the GO target stimulus. In the GO condition (67% of all trials), participants were expected to indicate whether this target was located above or below the middle reference line. Responses were given by pressing the outer right key with the right middle finger ("above" judgment) or by pressing the inner right key with the right index finger ("below" judgment). All stimuli remained visible until either the participant responded or 2500 ms had elapsed. When RTs were longer than 1000 ms, the word "Quicker" was presented above the box until the participant responded.

The remaining 33% of trials were SC trials. The SC condition began with the presentation of a white GO stimulus. After a variable stop signal delay (SSD), which was adjusted using a staircase procedure, a STOP signal (a red rectangle replacing the previous white frame) was presented. This STOP signal remained on the screen until the end of the trial and requested the participant to try to inhibit the response to the GO stimulus. The SSD was initially set to 250 ms and was adapted to each participant's performance by means of a staircase procedure to yield a 50% probability of successfully inhibited GO responses. This procedure ensured that motor actions were successfully inhibited on about half of the stop trials, which yields accurate estimates of the stop-signal reaction time (SSRT), a quantitative estimate of the duration of the covert response-inhibition process (Logan and Cowan, 1984). In the case of a completely correct SC trial (no response to GO stimulus, no response prior to the CHANGE stimulus in the SCD300 condition (explained below) and a correct left hand response to the CHANGE stimulus), the SSD of the following SC trial was adjusted by adding 50 ms to the SSD of the evaluated trial. In the case of an erroneous SC trial (if any of the above criteria were not met), the SSD was adjusted by subtracting 50 ms from the SSD of the evaluated trial. Limiting this procedure, the SSD values were set to not fall below a value of 50 ms nor exceed a value of 1000 ms. Irrespective of the stopping performance/inhibition, every stop signal was combined with one of the three possible CHANGE stimuli. The CHANGE stimulus was a 100 ms sine tone presented via headphones at 75 dB SPL and could be high (1300 Hz), medium (900 Hz) or low (500 Hz) in pitch. The tone assigned a new reference line in relation to which the CHANGE stimulus (the previous white GO target circle on the screen) had to be judged. The high tone represented the highest of the three lines as the new reference, the medium tone represented the middle line and the low tone represented the lowest line (see Figure 1). All three reference lines were used with equal frequency. The required CHANGE response had to be performed with the left hand. For this response, the reaction time (RT2) was measured. If the target was located above the newly assigned reference line, an outer left key press (left middle finger) was required; if the target circle was located below the newly assigned reference line, a left inner key press (left index finger) was required. In half of the SC trials, there was a stop change delay (SCD) with a stimulus onset asynchrony (SOA) of 300 ms between the STOP and the CHANGE signals (SCD300 condition); in the other half of SC trials, the two stimuli were presented simultaneously (SOA of 0 ms, SCD0 condition). In the case of RT2s longer than 2000 ms, the English word "Quicker" was presented above the box until the participant responded. During the inter-trial interval (ITI; fixed duration of 900 ms), a fixation cross was presented in the center of the screen. Participants first received explanation and practiced the task, whereafter they were presented with 864 test trials, which in total took the participants approximately 45 minutes to finish.

Table 1 Behavioral parameters (reaction times; RTs and error rates) separated for the active (tVNS) and sham group (mean ± SEM).

	Active tVNS		Sham	
	RTs (in ms)	Error rates (in %)	RTs (in ms)	Error rates (in %)
GO	542 ± 30	4.8 ± .7	539 ± 30	4.7 ± .7
SCD 0	977 ± 52	40.3 ± 1.8	1139 ± 52	42.9 ± 1.8
SCD 300	802 ± 60	17.3 ± 2.4	1000 ± 60	17.9 ± 2.4
SSRT	255 ± 13		270 ± 13	

2.3. Statistical analyses

HR was analyzed by means of repeated-measures analyses of variance (ANOVAs) with group (active vs. sham) as between-subjects factor and effect of time (first vs. second measurement) as within-subjects factor. The effect of tVNS on action cascading was assessed by means of repeated-measures ANOVAs with condition (Go, SCD0, and SCD300) as within-subject factor and group (active vs. sham) as between-subject factor. The effect of tVNS on SSRT was assessed by independent samples *t*-tests. LSD-Fisher post-hoc tests were performed to clarify mean differences in case of significant interactions. Trials with errors were excluded from the reaction times (RTs) analysis. A significance level of $p < .05$ was adopted for all statistical tests.

3. Results

3.1. Stop-change paradigm

Table 1 shows the behavioral parameters for the Stop-Change paradigm separately for the active and sham group.

There was a main effect of group, $F(1,28) = 4.97$, $p = .034$, $\eta_p^2 = .151$, indicating that RTs where faster in the active group (774 ms) as compared to the sham group (893 ms). There was also a main effect of condition, $F(2,56) = 98.22$, $p < .001$, $\eta_p^2 = .778$. LSD-Fisher post-hoc tests showed that RTs were longer in the SCD0 condition (1058 ± 37), as compared to the SCD300 (901 ± 42) and the Go condition (541 ± 21) (both $p < .001$). The latter conditions (i.e., SCD300 and Go) differed significantly from each other too, $p < .001$. Most importantly, the two-way interaction involving condition and group was significant, $F(2,56) = 4.00$; $p = .024$; $\eta_p^2 = .125$. LSD-Fisher post-hoc tests revealed a difference in RTs between groups in the SCD0 condition, $p = .02$, and in the SCD300 condition, $p = .006$, but not in the GO condition, $p = .96$. Specifically, for the SCD0 and the SCD300 conditions, the sham group had longer RTs (SCD0 1139 ms ± 52; SCD300 1000 ms ± 60) than the active group (SCD0 977 ms ± 52; SCD300 802 ms ± 60). The error rate analysis revealed a main effect of condition, $F(2,56) = 448.558$ $p < .001$, $\eta_p^2 = .94$: the SCD0 condition (41.6% ± 1.3) produced more errors as compared to the SCD300 (17.6% ± 1.7) and the Go conditions (4.8% ± .5) (both $p < .001$), which differed significantly from each other too ($p < .001$). The main effect of group and the two-way interaction between group and condition were not significant, $F_s < 1$, $p_s \geq .55$ (see Table 1). Analyzing SSRTs, as calculated after Logan and Cowan (1984), did not reveal differences between the active and sham groups ($t_{28} = .75$, $p > .45$).

3.2. HR measurements

ANOVA showed a main effect of time, $F(1,27) = 11.27$, $p < .002$, $\eta_p^2 = .295$, indicating that heart rate decreased during the experiment (85 vs. 75 BPM). However, HR did not significantly differ between groups (85 vs. 75 and 85 vs. 75 in the active and sham group, respectively), $F(1,27) < .001$, $p = .98$. This suggests that we can rule out an account of our results in terms of physiological changes.

4. Discussion

Our findings show that tVNS, likely via GABA and NE release and because of connections between the vagus nerve and the ACC, modulates the efficiency of action cascading as measured by a stop-change paradigm. The observation that tVNS boosts performance on a well-established diagnostic index of action cascading (Verbruggen et al., 2008) provides considerable support for the idea of a crucial role of GABA-ergic and noradrenergic pathways in action cascading (Yildiz et al., 2014a, 2014b). tVNS modulates action cascading processes when (i) an interruption, i.e. stopping a response, and a change toward an alternative response are required simultaneously (SCD0 condition) and when (ii) the change to another response is required once the stopping process has already finished (SCD300 condition). As revealed by the lack of tVNS effects on the stop-signal reaction time (SSRT), tVNS did not modulate the efficiency to stop an ongoing response. This is not surprising given that SSRT seems to be affected, instead, by dopaminergic manipulations (Colzato et al., 2013, 2014; but see Stock et al., 2014a, 2014b).

Our results are partially inconsistent with a previous study by Yildiz et al. (2014a) in which airplane pilot trainees (associated with increased GABA concentrations) were better than controls only in the SCD0 condition, when participants were confronted with stop and change stimuli at the same time. Given that tVNS, besides GABA, also targets NE it may be possible that the noradrenergic release contributed to ameliorating action cascading in the SCD300 condition, when participants have enough time to prepare for the change response. Indeed, a previous study showed that stress, a factor known to affect the noradrenergic system (Galvin, 1990), impacted the SCD300 but not the SCD0 condition (Yildiz et al., 2014b). As the data pattern is hence more consistent to what was found for stress responses, the results suggest that in the SCD300 condition the impact of tVNS is stronger on the NE-system than on the GABA-ergic system.

Future studies require a more systematic examination of this issue. Further investigations testing acute neuromodulatory effects of highly selective GABA and NE agonists on the efficiency of action cascading are necessary to determine the precise role of the GABA-ergic and noradrenergic system in modulating response selection processes. Of particular interest would be also to look into the genetic variability associated with GABA (Mulligan et al., 2012) and NE (Stöber et al., 1996), which may predict individual differences in the efficiency of action cascading.

Even though VNS, besides GABA and NE, is also associated with acetylcholine (ACh) release (Borovikova, et al., 2000), previous literature suggests that it is less plausible that ACh is responsible for our results. Indeed, animal literature proposes that ACh is responsible for, more than action selection processes, the proper development of action *coordination* in rats (e.g., Watanabe et al., 1990) and that it plays an essential role in neural communication in brain networks implicated in movements and actions (Bartus et al., 1985). That is, if ACh would have significantly contributed to our results, we would have found an improvement in action accuracy; however, in the current study, we failed to found such evidence in the Go trials.

The present study has some limitations that deserve discussion. First, we did not explicitly assess participants' blinding by asking them if they could guess the stimulation received. Second, it would have been ideal to have the application of tVNS accompanied by appropriate physiological assays, such as the vagus-evoked potentials (See Bestmann et al., 2015 for a related discussion).

In sum, the available observations provide converging evidence for the idea that GABA and NE-related processes only affect the change to an alternative response, once an ongoing response has stopped. Taken altogether, our results support the idea that tVNS is a promising non-invasive brain stimulation technique to enhance cognitive processes.

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Contributors

Authors LSC and CB designed the study and wrote the protocol. Authors AKS, BV and LS managed the literature searches and analyses. Authors RS and AKS undertook the statistical analysis, and Authors LSC, CB and LS wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors have declared that no competing interests exist.

Acknowledgments

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2015.03.015.

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