

Transcutaneous Vagus Nerve Stimulation Enhances Post-error Slowing

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Abstract

■ People tend to slow down after they commit an error, a phenomenon known as post-error slowing (PES). It has been proposed that slowing after negative feedback or unforeseen errors is linked to the activity of the locus coeruleus–norepinephrine (LC–NE) system, but there is little direct evidence for this hypothesis. Here, we assessed the causal role of the noradrenergic system in modulating PES by applying transcutaneous vagus nerve stimulation (tVNS), a new noninvasive and safe method

to stimulate the vagus nerve and to increase NE concentrations in the brain. A single-blind, sham-controlled, between-group design was used to assess the effect of tVNS in healthy young volunteers ($n = 40$) during two cognitive tasks designed to measure PES. Results showed increased PES during active tVNS, as compared with sham stimulation. This effect was of similar magnitude for the two tasks. These findings provide evidence for an important role of the noradrenergic system in PES. ■

INTRODUCTION

People tend to slow down their task performance after they make an error, a phenomenon called post-error slowing (PES). Particularly, PES is reflected by longer RTs on trials following an error than on trials following a correct response (Rabbitt, 1966). PES has been noticed in a broad range of tasks (Danielmeier & Ullsperger, 2011), comprising the flanker task (Krämer et al., 2007; Debener et al., 2005), the Stroop task (Gehring & Fencsik, 2001), and the Simon task (Danielmeier, Eichele, Forstmann, Tittgemeyer, & Ullsperger, 2011; King, Korb, Von Cramon, & Ullsperger, 2010).

PES has been proposed to reflect distinct mechanisms, depending on the duration of the response stimulus interval (RSI) (Jentsch & Dudschig, 2009; see also Laming, 1979). In tasks with long RSIs, PES is often accompanied by a post-error increase in accuracy. This pattern is thought to reflect a post-error strategic adjustment of the decision threshold, resulting in more cautious behavior on the subsequent trial (Botvinick, Braver, Carter, Barch, & Cohen, 2001). In contrast, in tasks with short RSIs, PES is often accompanied by a post-error decrease in accuracy. According to the orienting account of PES (Notebaert et al., 2009), this happens because unexpected errors evoke a transient process that temporarily disturbs task-related information processing and therefore results in disrupted performance on the post-error trial (van den Brink, Wynn, & Nieuwenhuis, 2014). As the RSI increases and more time passes since the error, the influence of this disruption gradually declines,

while participants have more time to adjust the decision threshold.

Interestingly, it has been proposed that slowing after negative feedback or unforeseen errors is linked to the activity of the locus coeruleus–norepinephrine (LC–NE) system (Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010). Preliminary evidence in favor of this hypothesis comes from a recent study by Colzato, van den Wildenberg, and Hommel (2013), suggesting that an individual's magnitude of PES is predicted by the DBH5'-ins/del polymorphism—a variation in the DBH gene that is linked with the synthesis of the enzyme dopamine beta-hydroxylase and is responsible for the conversion of dopamine into NE. Increased PES was found in DBH5'-ins/del heterozygotes (linked to average level of plasma DβH activity) in contrast to del/del and ins/ins homozygous individuals (linked to low and high levels of plasma DβH activity, respectively). However, given the correlational nature of genetic studies and the modest sample size of the study by Colzato et al., evidence supporting the possible role of NE in mediating PES is still indirect and rather weak.

In this study, we assessed the causal role of the noradrenergic system in modulating the size of PES by applying transcutaneous vagus nerve stimulation (tVNS). This is a new noninvasive method to stimulate the vagus nerve, presented for the first time by Ventureyra (2000; see also 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 associated with only minor side effects such as a burning or itching sensation under the electrodes. Very recently, it has been suggested that tVNS

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may be a valuable instrument to further investigate in healthy humans the neuromodulation of cognitive processes driven by NE and GABA, two of the main neurotransmitters targeted by VNS (van Leusden, Sellaro, & Colzato, 2015). Indeed, the afferent auricular branch of the vagus nerve ends in the nucleus of the solitary tract, which directly innervates the LC (Van Bockstaele, Peoples, & Telegan, 1999)—the noradrenergic supply center of the brain (Aston-Jones et al., 1991). Given this anatomical connection between the vagus nerve and the LC, it is reasonable to expect VNS to stimulate the release of NE by altering LC activity (George & Aston-Jones, 2010). Consistent with that, there is evidence that acute VNS increases not only firing rates in the rat LC (Dorr & Debonnel, 2006) but also the release of cortical and hippocampal NE (Raedt et al., 2011; Follesa et al., 2007; Roosevelt, Smith, Clough, Jensen, & Browning, 2006; Hassert, Miyashita, & Williams, 2004). Moreover, two fMRI studies in healthy humans have found that active tVNS increased activation in the brainstem region including the LC and nucleus of the solitary tract, indicating that tVNS also results in effective stimulation of the vagal afferents (Frangos, Ellrich, & Komisaruk, 2014; Dietrich et al., 2008). Given the available correlational evidence that PES is modulated by the noradrenergic system and the aforementioned evidence suggesting a link between VNS and NE release, we tested whether tVNS, possibly via NE release, enhances PES.

We assessed the effect of online tVNS on PES in a flanker task and an auditory four-choice RT (CRT) task previously used to study error processing (van den Brink et al., 2014; Yordanova, Falkenstein, Hohnsbein, & Kolev, 2004). The two cognitive tasks differed from each other in several regards, but the most critical difference with regard to PES was the RSI, which was relatively short in the flanker task and long in the CRT task. In case we found task-specific effects of tVNS on PES, this could provide a clue as to whether NE levels influence the error-related transient disturbance in task processing or are involved in strategic adjustment of the decision threshold. In case we would find a consistent effect of tVNS on PES in both tasks, this would suggest a more generic role of the noradrenergic system in PES.

METHODS

Participants

Forty undergraduate students of Leiden University participated in the experiment. Participants were recruited via an online recruiting system and were compensated with 15 € for participating in a study on the effects of brain stimulation on cognition. Once recruited, participants were randomly assigned to one of two experimental groups: sham stimulation ($n = 20$; 2 male; mean age = 20.65, $SD = 1.7$), and active stimulation ($n = 20$; 3 male; mean age = 20.30, $SD = 2.5$). Groups did not

differ in terms of age, $t(28) < 1$, $p = .65$, or sex, $\chi^2 < 1$, $p = .63$.

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; and (viii) no pacemaker or other implanted devices.

All participants were naive to tVNS. Before the testing session, they received a verbal and written explanation of the procedure and of the typical possible 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 medical ethical committee of the Leiden University Medical Center.

Apparatus and Procedure

A single-blind, sham-controlled, randomized, between-subject design was used to assess the effect of online (i.e., stimulation overlapping with the critical task) tVNS in healthy young volunteers in modulating PES. All participants took part in a single session and were tested individually. Upon arrival, after participants read and signed the informed consent, the tVNS electrodes were applied and the stimulation was started. Immediately after, participants were asked to rate their mood on a 9×9 Pleasure \times Arousal grid (Russell, Weiss, & Mendelsohn, 1989), with values ranging from -4 to 4 . Heart rate (HR) was measured from the nondominant hand with a finger-type pulse oximeter (Contec CMS50D+, Hebei Province, China; accuracy = 2 bpm/2%). Fifteen minutes after the onset of the stimulation, participants performed the flanker task, which lasted for about 30 min. Then participants again rated their mood, and HR was measured for the second time. Immediately after that, participants performed the CRT task for 30 min. Upon completion of this task, the participants' HR, pleasure, and arousal were measured once more. tVNS was applied throughout the duration of the tasks.

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

Transcutaneous Vagus Nerve Stimulation

We used a tVNS wired neurostimulating device connected with two titan electrodes fastened on a gel frame (CM02, Cerbomed, Erlangen, Germany). Following the suggestions by Dietrich et al. (2008) and Steenbergen et al. (2015) for optimal stimulation, the tVNS device was programmed to a stimulus intensity of 0.5 mA, delivered with a pulse width of 200–300 μ sec at 25 Hz. Stimulation alternated between on and off periods every 30 sec. In the sham condition, the stimulation electrodes were placed on the center of the left ear lobe instead of the outer auditory canal. Indeed, the ear lobe has been found to be free of cutaneous vagal innervation (Fallgatter et al., 2003; Peuker & Filler, 2002), and a recent fMRI study showed that this sham condition produced no activation in the cortex and brainstem (Kraus et al., 2013).

Importantly, following safety criteria to avoid cardiac side effects, the stimulation was always applied to the left ear (Cristancho, Cristancho, Baltuch, Thase, & O'Reardon, 2011; Nemeroff et al., 2006). Indeed, although efferent fibers of the vagus nerve modulate cardiac function, such a modulation seems to relate only to the efferent vagal fibers connected to the right ear (Nemeroff et al., 2006). Consistently, a clinical trial showed no arrhythmic effects of tVNS when applied to the left ear (Kreuzer et al., 2012).

Flanker Task

Participants performed a modified version of the flanker task (Eriksen & Eriksen, 1974), adapted from van den Brink et al. (2014). In each trial, participants were presented with a target letter (“H,” “K,” “C,” or “S”), flanked on each side by four letters different from the target, but belonging to the same set (“H,” “K,” “C,” or “S”) and identical to each other. Participants were to classify the target letter by pressing one of two left-hand responses or one of two right-hand responses. To guarantee comparable difficulty across trials and a sufficiently high error rate, the flanker letters were always incongruent with the target letter (e.g., SSSSHSSS or KKKKCKKKK) and mapped to a finger of the hand opposite to the hand associated with the correct response.

Stimuli were shown in black on a white background for 200 msec. The intertrial interval, in which a black fixation cross was shown, varied randomly between 1000 and 1300 msec in steps of 50 msec, resulting in relatively short RSIs. The response had to be made within 1000 msec after stimulus offset. The task comprised 10 blocks of 104 trials each and was preceded by a practice block of 120 trials. At the end of each task block, participants received RT and accuracy feedback and were pressed for speed.

CRT Task

Participants also performed an auditory four-CRT task, adapted from Yordanova and colleagues (2004). Four au-

ditory stimuli, the letters A, E, I, and O, served as targets and were presented via external speakers. A black fixation cross was displayed continuously on a gray background during experimental blocks. Participants were instructed to respond to the letters A, E, I, and O with the left middle, left index, right index, and right middle finger, respectively. Each target stimulus lasted approximately 300 msec and was followed by a 1200-msec time window during which the response had to be made. Afterwards, an additional 2000-msec time window followed, thus resulting in a total intertrial interval of 3.5 sec and relatively long RSIs. The task consisted of four experimental blocks of 100 trials each, preceded by a 20-trial practice block. At the end of each task block, feedback on RT and accuracy was provided, and participants were pressed for speed.

Statistical Analyses

To calculate PES for both tasks, we used the method proposed by Dutilh et al. (2012), according to which only error trials that are preceded and followed by at least one correct trial are considered. For each triplet, a single-trial value of PES was computed by performing a pairwise comparison of correct trials around each error ($RT_{\text{post-error}} - RT_{\text{pre-error}}$). The mean PES was computed by averaging these differences. This method ensures that post-error and post-correct trials originate from the same time periods in the data set and thus controls for global fluctuations in motivation and attention (Dutilh et al., 2012). In both tasks, all trials were of roughly equal difficulty, which ensured an unfounded comparison of correct pre- and post-error trials.

The effect of tVNS on mean correct RT, error rate, PES, and the post-error change in accuracy (post-error accuracy minus post-correct accuracy) was assessed by means of repeated-measures ANOVAs with Stimulation group (active vs. sham) as between-subject factor and Task (flanker vs. CRT) as within-subject factor.

Mood (i.e., pleasure and arousal scores) and HR were analyzed separately by means of repeated-measures ANOVAs with Stimulation group (active vs. sham) as between-subject factor and Time (first vs. second vs. third measurement) as within-subject factor.

A significance level of $p < .05$ was adopted for all statistical tests.

RESULTS

Cognitive Tasks

Table 1 summarizes performance in the two tasks, along with post-error changes in speed and accuracy. Main effects of Task were found for RT [$F(1, 38) = 243.88, p < .001, \eta_p^2 = .87$] and post-error change in accuracy [$F(1, 38) = 7.04, p < .05, \eta_p^2 = .16$], but not for error rates and PES [$F_s \leq 2.3, p_s \geq .14$]. RTs were faster in the flanker task (448 msec) than in the CRT task (684 msec). More interestingly, post-error

Table 1. Mean Correct RTs, Error Rates (in %), PES, Post-error Accuracy, Post-correct Accuracy, and Post-error Change in Accuracy (Post-error Accuracy Minus Post-correct Accuracy) as a Function of Stimulation Group (Active and Sham) and Task (Flanker and CRT)

	<i>Active</i>	<i>Sham</i>
<i>Flanker Task</i>		
RT (msec)	441 (17.2)	456 (17.2)
Error rates (%)	13.7 (1.1)	15.3 (1.1)
PES (msec)	58 (5.5)	42 (5.5)
Post-error accuracy (%)	81.1 (2.2)	81.9 (2.2)
Post-correct accuracy (%)	87.3 (0.9)	85.4 (0.9)
Post-error change in accuracy	-6.3 (1.8)	-3.5 (1.8)
<i>CRT Task</i>		
RT (msec)	683 (23.4)	684 (23.4)
Error rates (%)	12.8 (1.3)	12.9 (1.3)
PES (msec)	57 (11.7)	35 (11.7)
Post-error accuracy (%)	86.4 (2.1)	87.0 (2.1)
Post-correct accuracy (%)	87.6 (1.2)	87.2 (1.2)
Post-error change in accuracy	-1.3 (1.4)	-0.2 (1.4)

Standard errors are shown in parentheses.

accuracy (81.5%) was lower than post-correct accuracy (86.4%) in the flanker task, which had relatively short RSIs, whereas post-error accuracy (86.7%) and post-correct accuracy (87.4%) were comparable in the CRT task, which had long RSIs.

We were primarily interested in performance differences between active and sham tVNS. Mean RT, error rate, and post-error change in accuracy did not reliably differ between stimulation groups ($F_s \leq 1.3$, $p_s \geq .26$). However, as we expected, the two groups differed significantly in terms of PES, with participants who received active tVNS showing more pronounced PES than participants who received sham tVNS [57 msec vs. 38 msec; $F(1, 38) = 4.55$, $p < .05$, $\eta_p^2 = .11$]. The effect of tVNS on PES was of comparable magnitude in the flanker task

(16 msec) and the CRT task (22 msec), as indicated by the absence of a Stimulation group \times Task interaction ($F < 1$, $p = .78$). Similarly, no interactions were observed for the other dependent variables ($F_s < 1$, $p_s \geq .52$).

Physiological and Mood Measurements

Table 2 provides an overview of the outcomes for physiological and mood measurements. ANOVAs showed a main effect of Time for pleasure [$F(2, 76) = 14.07$, $p < .001$, $\eta_p^2 = .27$] and arousal [$F(2, 76) = 27.8$, $p < .001$, $\eta_p^2 = .42$], but not for HR ($F < 1$, $p = .6$). Pleasure and arousal levels decreased during the experiment, whereas HR did not vary across time. Importantly, HR, pleasure, and arousal scores did not significantly differ between the two groups. Indeed, no significant main effects of Group nor Time \times Stimulation group interactions were found ($F_s \leq 2.8$, $p_s \geq .10$). This suggests that we can rule out an account of our results in terms of physiological and/or mood changes.

DISCUSSION

Our findings show that tVNS increases PES, without having a clear effect on basic performance measures. This effect was of a similar magnitude in the two tasks, despite the large difference between the tasks in RSI, a factor thought to determine the primary mechanism underlying PES (Jentzsch & Dudschig, 2009). Given the excitatory effect of tVNS on LC activity and NE release (Raedt et al., 2011; Follesa et al., 2007; Roosevelt et al., 2006; Hassert et al., 2004; Van Bockstaele et al., 1999), these findings offer substantial support for the idea of an important role of the noradrenergic system in PES (Colzato et al., 2013; see also Ullsperger et al., 2010). In the flanker task, PES was accompanied by an error-related decrease in accuracy. This finding is consistent with previous studies using relatively short RSIs in which PES was generally accompanied with a decrease in accuracy, a pattern diagnostic of an error-related transient disturbance in information processing (van den Brink et al., 2014; Dudschig & Jentzsch, 2009; Notebaert et al., 2009). The error-related decrease in accuracy was about twice as large in the active tVNS group than in the sham tVNS group, but this group difference was not significant.

Table 2. Mean Heart Rate Values (in Beats per Minute), Pleasure and Arousal Scores as a Function of Time (First [T1] vs. Second [T2] vs. Third [T3] Measurement; See Text for More Details) for Active tVNS and Sham tVNS Groups

	<i>T1</i>		<i>T2</i>		<i>T3</i>	
	<i>Active</i>	<i>Sham</i>	<i>Active</i>	<i>Sham</i>	<i>Active</i>	<i>Sham</i>
HR	75.6 (3.0)	72.1 (3.0)	73.7 (3.9)	68.9 (3.9)	73.3 (3.5)	72.6 (3.5)
Arousal	0.6 (0.3)	0.2 (0.3)	0.6 (0.4)	-0.4 (0.4)	-1.2 (0.4)	-1.6 (0.4)
Pleasure	1.9 (0.3)	1.3 (0.3)	1.4 (0.3)	1.0 (0.3)	1.0 (0.3)	0.1 (0.3)

Standard errors are shown in parentheses.

Future studies should attempt to elucidate the precise mechanism by which NE levels regulate PES. For example, pharmacological studies using selective NE agents may determine if the relationship between NE and post-error adjustments is mediated by a specific receptor type. One pharmacological study has found no effect on PES of the noradrenergic alpha-2 receptor antagonist yohimbine (Riba, Rodriguez-Fornells, Morte, Munte, & Barbanj, 2005). Future studies may investigate the effects on PES of propranolol, a noradrenergic drug acting on β_1 and β_2 adrenergic receptors, or the selective NE reuptake inhibitor atomoxetine.¹ Although VNS, besides NE, is also associated with increased GABA release (Marrosu et al., 2003; Ben-Menachem et al., 1995), to the best of our knowledge there is no indication in the literature that changes in GABA might have been responsible for our results.

The current study has some limitations that warrant discussion. First, in this study, short and long RSIs were compared only indirectly—that is, by using two tasks that differed from each other in several aspects other than the RSI. The use of a single task with varying RSI conditions would have allowed for a more straightforward comparison. Second, and related to the previous point, we did not counterbalance the order of the two tasks, so that the CRT task was always performed roughly 30 min after the beginning of the flanker task. Therefore, a comparison of PES in the two tasks was potentially confounded with temporal changes in the effectiveness of tVNS. The size and direction of this potential confound are hard to estimate, given that so little is known about the time course of tVNS effects on brain and behavior. The aforementioned two limitations imply that the conclusion that NE plays a generic role in PES requires further research, preferably using a single task with different RSIs presented in counterbalanced order. Third, we used a between-subject design to avoid possible practice effects on task performance. Although practice effects are not expected to affect post-error adjustment processes, they might substantially reduce the number of errors, resulting in less reliable estimates of PES. However, a between-subject design can be sensitive to differences between the individuals in the two groups. Therefore, follow-up studies should determine whether our findings can be replicated using more difficult tasks, allowing a within-subject comparison. Fourth, it would have been optimal to have linked the implementation of tVNS with appropriate physiological assays, such as vagus-evoked potentials (see Bestmann, de Berker, & Bonaiuto, 2015, for a related discussion). Moreover, useful scalp EEG measures to include might be the P300 (Nunez Castellar, Kuhn, Fias, & Notebaert, 2010) and EEG alpha power, two cortical correlates of the orienting response and increased LC–NE activity (Nieuwenhuis, de Geus, & Aston-Jones, 2011; Swick, Pineda, & Foote, 1994; Swick, Pineda, Schacher, & Foote, 1994). Finally, we did not explicitly assess participants' blinding by asking them if they could guess the type of stimulation they received.

Notwithstanding these limitations, our observations provide preliminary direct evidence for the idea that NE plays an important role in PES. Therefore, the present findings may represent an important step in stimulating research to further extend our understanding of the specific role of NE and other neuromodulators (Danielmeier et al., 2015) in PES. More in general, our results support the idea that tVNS is a promising noninvasive brain stimulation technique for modulating cognitive processes in healthy humans (Steenbergen et al., 2015; van Leusden et al., 2015).

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Note

1. Recently, Bari and Robbins (2013) examined, in rats, the effect of three different adrenergic receptor agents on PES during a stop-signal task and failed to find evidence supporting the role of NE in PES. Notably, their subjects showed post-error speeding instead of PES, presumably because stop signals were rare (20%), so rats may have perceived the probability of occurrence of two consecutive stop trials to be low, or because there was a 5-sec time-out period after each error (see Orr & Hester, 2012, for a related discussion). Therefore, the pharmacological effects reported by Bari and Robbins are not informative with regard to PES.

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