# Modulatory Mechanisms of Transcutaneous Vagus Nerve Stimulation on Inhibitory Control

**Authors:** Wang Rong, Chen Xiaoyi, Du Xue, Jiang Jun, Nationalist army

**Date:** 2022-03-30T00:00:00+00:00

## Abstract

Numerous recent studies have demonstrated that transcutaneous vagus nerve stimulation (tVNS), as a novel non-invasive neuromodulation technique, exerts positive modulatory effects on individuals' inhibitory control functions. Existing research has found that the modulatory effects of tVNS on inhibitory control may be achieved by regulating the activity of the locus coeruleus-norepinephrine system (LC-NE) and the concentration of the neurotransmitter GABA. However, numerous questions regarding the neural mechanisms through which tVNS modulates inhibitory control remain unclear. Future research, after further optimizing the stimulation parameters of tVNS, can conduct in-depth exploration into the regulatory effects and mechanisms of tVNS on populations with impaired inhibitory control abilities, as well as how to achieve and enhance the long-term positive effects of tVNS.

## Full Text

## The Regulatory Mechanism of Transcutaneous Vagus Nerve Stimulation on Inhibitory Control

**WANG Rong[1], CHEN Xiaoyi[1], DU Xue[1], JIANG Jun[2]** [1]College of Education Science, Chongqing Normal University, Chongqing 401331, China [2]Department of Basic Psychology, School of Psychology, Army Medical University, Chongqing 400038, China

### Abstract

In recent years, numerous studies have demonstrated that transcutaneous vagus nerve stimulation (tVNS), as a novel non-invasive neuromodulation technique, exerts positive regulatory effects on individuals' inhibitory control functions.

Existing research suggests that tVNS may modulate inhibitory control by regulating activity in the locus coeruleus-norepinephrine system (LC-NE) and altering concentrations of the neurotransmitter GABA. However, many questions regarding the neural mechanisms through which tVNS regulates inhibitory control remain unresolved. Future research should optimize tVNS stimulation parameters and further investigate its regulatory effects and mechanisms in populations with impaired inhibitory control abilities, as well as explore how to achieve and enhance the long-term positive effects of tVNS.

**Keywords:** transcutaneous vagus nerve stimulation, inhibitory control, LC-NE system, GABA, biomarkers

The vagus nerve, as the tenth cranial nerve and a crucial component of the parasympathetic nervous system, primarily functions to transmit information between the brain and various organs to maintain homeostasis (Butt et al., 2020). Given its vital role in regulating physical and mental health, invasive vagus nerve stimulation (iVNS) has been widely applied since the mid-1980s for treating epilepsy, depression, primary headaches, and other conditions, demonstrating favorable therapeutic outcomes (Aaronson et al., 2017; Henssen et al., 2019; Toffa et al., 2020). However, because iVNS requires invasive surgical implantation of stimulation devices, it entails high costs and often produces side effects, limiting its large-scale application (Ellrich, 2019). Consequently, Ventureyra proposed transcutaneous vagus nerve stimulation (tVNS) in 2000 as a novel, safe, and non-invasive brain neuromodulation technique (Ventureyra, 2000). Its fundamental principle involves delivering intermittent pulsed electrical stimulation to the auricular branch of the vagus nerve in the external ear, allowing signals to be transmitted non-invasively to the brain via vagal pathways to induce changes in cortical activity and related neurochemical markers, thereby achieving neuromodulatory effects (Badran et al., 2018; Borges et al., 2020). Research has shown that tVNS activates the same neural pathways as iVNS (Assenza et al., 2017) while offering advantages of simpler operation, greater cost-effectiveness, and enhanced safety (Redgrave et al., 2018). In recent years, beyond its applications in regulating neurological, immune, and endocrine systems for treating various physical and mental disorders, tVNS has also been employed to modulate cognitive functions such as inhibitory control (Yap et al., 2020).

Numerous studies have found that tVNS positively regulates individuals' inhibitory functions (Beste et al., 2016; Fischer et al., 2018; Keute et al., 2020). Inhibitory control, as a core component of executive functions, primarily serves to suppress task-irrelevant endogenous and exogenous stimuli, enabling individuals to make adaptive changes when facing complex and dynamic environmental challenges (Diamond, 2013). Neuroimaging evidence indicates that inhibitory control is associated with activation in the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), left anterior insula, and locus coeruleus (LC) (Dores et al., 2017; Hung et al., 2018; Tomassini et al., 2021). Laboratories typically employ Flanker, Stroop, Simon,

Go/No-go, and Stop-signal tasks to investigate inhibitory control abilities and mechanisms. The first three tasks require participants to suppress interference from task-irrelevant information to successfully complete target tasks (cognitive inhibition), while the latter two require response inhibition—participants must withhold responses or suppress initiated response tendencies according to task demands (Diamond, 2013). Notably, researchers have increasingly applied the two-choice Oddball task to inhibitory control studies in recent years (Ventura-Bort et al., 2018; Warren et al., 2020). Unlike traditional single-choice Oddball tasks that require responses only to infrequent deviant stimuli, the two-choice Oddball paradigm requires participants to make binary responses to both frequent standard stimuli and infrequent deviant stimuli. Due to the different probabilities of these stimuli, participants must suppress habitual response tendencies toward dominant standard stimuli (Yuan et al., 2017). Consequently, behavioral indices and event-related potential (ERP) N2 and P3 component changes evoked by the two-choice Oddball paradigm can effectively reflect alterations in individuals' inhibitory control abilities (Wang & Dai, 2020; Zhao et al., 2018).

Investigating tVNS regulation of inhibitory control not only enhances our comprehensive understanding of its underlying neural mechanisms but also positions tVNS as a promising intervention for restoring or enhancing inhibitory function in populations with impaired or declining control abilities. Therefore, this review first summarizes behavioral and physiological manifestations of tVNS regulation of inhibitory control, elaborates on the associated neurochemical mechanisms, identifies existing research limitations, and finally discusses future research directions and approaches to address current shortcomings.

## 2. Behavioral and Physiological Manifestations of tVNS Regulation of Inhibitory Control

Existing research has demonstrated that tVNS produces significant modulatory effects on inhibitory control. Beste et al. (2016) found that compared to sham tVNS, participants receiving verum stimulation showed lower false alarm rates on high-difficulty No-go trials in a mental rotation Go/No-go task. Studies using cued Go/No-go tasks have similarly found that tVNS improved task accuracy across all experimental conditions compared to sham stimulation (Keute et al., 2020). These findings indicate that tVNS enhances response inhibition capabilities. Fischer et al. (2018) recorded physiological and behavioral data including heart rate and blood pressure while participants performed a Simon task under different tVNS conditions (verum vs. sham) and time phases (pre- vs. post-stimulation). Although no significant differences in heart rate or blood pressure were observed between verum and sham groups across time, participants in the verum condition demonstrated better conflict adaptation performance, suggesting that tVNS enhances the ability to suppress irrelevant information interference and thereby facilitates conflict resolution. However, it is noteworthy that one study employing Flanker and spatial Stroop tasks found no behavioral

effects of tVNS on inhibitory control (Borges et al., 2020).

These inconsistent results may stem from two factors. First, previous research has typically examined only one aspect of inhibitory control without systematically investigating different subtypes, yet inhibitory control comprises cognitive inhibition and response inhibition (Diamond, 2013), and tVNS effects may differ across these subfunctions. Second, due to limited sensitivity of behavioral measures, tVNS modulatory effects may be weakly expressed behaviorally. This is supported by ERP studies using more sensitive measures that have precisely captured tVNS effects on inhibitory control. For example, Pihlaja et al. (2020) examined EEG changes in healthy participants during a Go/No-go task with tVNS and found smaller N2 amplitudes on No-go trials in the verum stimulation group compared to sham. Another study investigating tVNS effects on inhibitory control using the Simon task similarly found reduced N2 amplitudes in incongruent (conflict) trials with verum tVNS compared to sham (Fischer et al., 2018). These ERP studies provide direct evidence that tVNS enhances individuals' inhibitory control abilities.

## 3. Neural and Biochemical Mechanisms of tVNS Regulation of Inhibitory Control

Current theories propose two primary mechanisms through which tVNS regulates inhibitory control: one suggests that tVNS modulates the locus coeruleus-norepinephrine (LC-NE) system, whose activity directly regulates task performance (Tomassini et al., 2021); the other posits that tVNS promotes release of the neurotransmitter gamma-aminobutyric acid (GABA), whose concentration changes importantly regulate inhibitory function (Beste et al., 2016).

### 3.1 LC-NE System-Mediated tVNS Regulation of Inhibitory Control

Neuroimaging studies have revealed that LC-NE system activity can regulate functional connectivity among nodes in the prefrontal inhibitory control network, thereby influencing inhibitory control abilities (O' Callaghan et al., 2021; Passamonti et al., 2018; Tomassini et al., 2021). Additionally, neuroimaging research has demonstrated that tVNS activates the LC region (Sclocco et al., 2020). Therefore, tVNS regulation of inhibitory control may occur through activation of the LC (the primary source of NE), promoting NE release (George & Aston-Jones, 2010; Sellaro et al., 2015) and subsequently modulating inhibitory control (Beste et al., 2016; Fischer et al., 2018). Studies have shown that compared to pre-treatment baseline, adult ADHD patients receiving methylphenidate (which promotes NE release) exhibited significantly reduced stop-signal reaction times (SSRT) in the Stop-signal task (Aron et al., 2003). O' Callaghan et al. (2021) found that treatment with atomoxetine (a drug that restores NE levels) significantly reduced SSRT and improved behavioral performance in Parkinson' s patients with low LC integrity. Tomassini et al. (2021) used magnetization transfer magnetic resonance imaging to demonstrate that

LC integrity is closely associated with better inhibitory control performance in older adults. These findings indicate that inhibitory control abilities are directly regulated by LC-NE system activity. Furthermore, studies on iVNS regulation of inhibitory control have found significant differences between iVNS and control groups in SSRT and Stop-P3 amplitudes (Schevernels et al., 2016), and event-related potential P3 changes can serve as indirect indicators of LC-NE system activity (Pineda et al., 1989; Warren et al., 2020), supporting the notion that the LC-NE system plays an important role in inhibitory control processing.

Currently, two methods exist for evaluating tVNS regulation of LC-NE system activity: direct measurement via implanted devices, which may cause pain or injury, and indirect measurement through observation of biomarkers including pupil size, salivary alpha-amylase, and event-related potential P300 (Burger et al., 2020; Farmer et al., 2021).

**3.1.1 Pupil Size Changes** Initial animal studies established a link between pupil size and LC-NE system activity (Rajkowski et al., 1994), subsequently confirmed in humans by Murphy et al. (2014) who demonstrated that pupil diameter changes correlate with LC activation. These findings indicate that pupil size changes not only reflect differences in cognitive processing but also indirectly mirror LC-NE system activity (Montefinese et al., 2018). Consequently, pupil size changes can serve as an explicit, observable measure in tVNS research, indirectly assessing tVNS effects on the LC-NE system. Capone et al. (2021) investigated tVNS effects on pupil size under different lighting conditions and stimulation intensities, finding that stimulation at 2mA under 0.4Lux illumination induced pupil dilation compared to baseline and control stimulation. Another study similarly found that tVNS affected pupil size changes, demonstrating pupil dilation at rest that peaked 4.25 seconds after stimulation onset (Sharon et al., 2021). However, some studies have failed to find tVNS effects on pupil size. Borges et al. (2021) examined tVNS cognitive effects using the Flanker task with pupil size as an LC-NE system activity probe and found no effect of tVNS on pupil changes. Similarly, a study investigating tVNS effects on pupil size during facial emotion recognition eye-tracking tasks found no significant differences in resting-state pupil size between verum and sham stimulation in healthy university students (Zhu et al., 2021).

These discrepant results may relate to tVNS stimulation parameters. For instance, Sharon et al. (2021) used short tVNS stimulation (3.4 seconds), whereas other studies employed on/off cycles of 30s/30s or continuous stimulation. This suggests that parameter settings may influence pupil size changes, with short-duration transcutaneous vagus nerve stimulation potentially being more effective at inducing pupil dilation. Additionally, pupil size changes have been associated with multiple neuromodulatory systems (e.g., LC-NE, cholinergic systems) (Larsen & Waters, 2018). Future research should conduct comparative studies of different tVNS stimulation modes while employing more advanced techniques to disentangle the independent role of the LC-NE system in pupil size changes.

**3.1.2 Salivary Alpha-Amylase** Salivary alpha-amylase (sAA) is a digestive enzyme secreted by salivary glands that reflects autonomic nervous system function changes (Nater & Rohleder, 2009). Previous research has validated sAA as an indicator of NE level changes (Chatterton et al., 1996; Nielsen et al., 2013). One study examining tVNS effects on response conflict in healthy university students collected saliva samples before and after Simon task performance under verum and sham conditions. Analysis revealed significantly increased sAA concentrations compared to baseline in the tVNS condition, with no significant changes observed in the sham group (Fischer et al., 2018). Similar results were obtained in another study using a two-choice Oddball task to investigate tVNS effects on the LC-NE system (Ventura-Bort et al., 2018).

These findings suggest that sAA may be a reliable target indicator for assessing LC-NE system activity through tracking its concentration changes. However, limitations exist: observed tVNS effects on sAA concentration were based solely on comparisons with baseline, without direct confirmation of tVNS effects compared to sham stimulation. Therefore, conclusions should be interpreted cautiously and require more rigorous investigation in future studies.

**3.1.3 Event-Related Potential P300** The event-related potential P300 component, occurring approximately 300ms post-stimulus, comprises P3a and P3b subcomponents, both closely related to inhibitory control functions (Nguyen et al., 2016; Waller et al., 2021). Pharmacological studies have shown that clonidine (a drug that modulates NE levels) affects P300 amplitudes (Brown et al., 2016), indicating that LC-NE system activity can induce corresponding changes in the P300 component. Based on these findings, researchers have begun using P300 as an EEG indicator of tVNS regulation of the LC-NE system. Ventura-Bort et al. (2018) employed a two-choice visual Oddball task to investigate the tVNS-LC-NE relationship, using P300 as an evaluation metric for neurophysiological changes. Results showed that although P3a amplitude differences between verum and sham conditions were not significant, P3b amplitudes in the easy task condition (requiring no mental rotation) were significantly increased in the tVNS group. Other studies have also observed tVNS effects on P3b amplitudes. Warren et al. (2020) examined P3b changes in healthy participants performing a two-choice visual Bayesian Oddball task and found that tVNS enhanced P3b amplitudes. However, Pihlaja et al. (2020) found no significant P3b amplitude differences between verum and sham conditions in their ERP study using a Go/No-go task to examine tVNS effects on cognitive control in healthy university students. These inconsistencies may relate to tVNS parameter settings or differential effects on distinct cognitive processing mechanisms. Researchers generally agree that information processing involves both top-down and bottom-up mechanisms, with P3a primarily related to bottom-up attentional processing and P3b reflecting top-down memory processing (Bachiller et al., 2015; Polich, 2007). Most studies support positive tVNS effects on the P3b component, suggesting that tVNS may primarily influence proactive control processes in inhibitory

control. Future research should adopt a dual cognitive control framework to evaluate tVNS effects on both proactive control (related to top-down processing) and reactive control (related to bottom-up processing) to further elucidate relationships among tVNS, inhibitory control, and P300 components.

In summary, although evidence suggests tVNS modulates the LC-NE system, inconsistent findings exist. These discrepancies may arise from two sources: first, the type and difficulty of inhibitory control tasks used, as different paradigms assess different inhibitory subtypes and differentially affect the LC-NE system. For example, Beste et al. (2016) found that tVNS did not affect backward inhibition but significantly influenced response inhibition under high working memory load. Second, differences in tVNS devices and stimulation parameters—including stimulation location, current intensity, frequency, pulse width, and duty cycle —may importantly affect results (Farmer et al., 2021). Future research should investigate effects of different tVNS stimulation modes on physiological, behavioral, and electrophysiological activity to identify effective biochemical markers of the tVNS-LC-NE relationship and provide robust support for understanding tVNS mechanisms in regulating inhibitory control.

### 3.2 GABA-Mediated tVNS Regulation of Inhibitory Control

Research has shown that the vagal neural network is associated not only with the LC-NE system but also with the neurotransmitter GABA, and both importantly influence cortical excitability and neuroplasticity (Colzato & Beste, 2020; Ziemann et al., 2015). Studies using magnetic resonance spectroscopy (MRS) have investigated GABAergic relationships with inhibitory control, finding that older adults with lower GABA levels exhibited longer SSRT in the Stop-signal task (Hermans et al., 2018). Murley et al. (2020) demonstrated that individuals' SSRT decreased as GABA levels in the inferior frontal gyrus increased. These findings indicate that GABA, as an inhibitory neurotransmitter that enhances cortical inhibitory control functions, directly affects inhibitory performance. Di Lazzaro et al. (2004) found that six months of iVNS clinical intervention in epilepsy patients not only reduced seizure frequency but also modulated GABA-mediated neural inhibition, increasing short-interval intracortical inhibition (SICI), an effective indicator for tracking GABA-A receptor inhibitory circuit activity in motor cortex (Ziemann et al., 2015). Empirical studies have also revealed potential or direct positive effects of tVNS on GABA. Capone et al. (2015) used transcranial magnetic stimulation (TMS) to assess tVNS effects on cortical excitability and found that tVNS induced inhibition in the right motor cortex (stimulation was applied to the left inner tragus). Specifically, participants exhibited higher SICI under tVNS compared to sham stimulation. Additionally, research has shown that compared to sham tVNS, verum stimulation significantly shortened reaction times during motor imagery tasks (high-difficulty condition), indicating enhanced action planning ability. By suppressing responses irrelevant to the target, tVNS facilitated target behavior execution and action plan completion (Chen et al., 2021). Since GABA levels

are associated with individuals' ability to suppress irrelevant stimulus interference (Sumner et al., 2010), tVNS may regulate inhibitory control by enhancing GABAergic system function in the cerebral cortex.

In summary, although most studies support that tVNS positively regulates inhibitory control via modulation of the LC-NE system and neurotransmitter GABA, the mechanisms are complex and several issues remain incompletely understood, warranting further in-depth investigation.

## 4.1 Further Optimization of tVNS Parameter Settings

Although previous studies have preliminarily investigated mechanisms through which tVNS regulates inhibitory control, inconsistent results and difficulties in cross-study comparison have arisen from variations in experimental tasks, stimulation modes, and participant populations. Future research should standardize tVNS operational procedures and systematically investigate stimulation parameter settings.

First, stimulation location differs across studies, with some placing electrodes on the left cymba conchae (Keute et al., 2020; Keute et al., 2019) and others on the left inner tragus (Capone et al., 2015; Pihlaja et al., 2020). Neuroanatomical research indicates that although both the cymba conchae and tragus are innervated by the auricular branch of the vagus nerve (ABVN), the tragus receives only 45% ABVN innervation whereas the cymba conchae receives 100% (Ellrich, 2019; Peuker & Filler, 2002). Furthermore, Yakunina et al. (2017) compared brainstem activation across different tVNS locations and found that electrical stimulation of the cymba conchae, but not the tragus, produced statistically significant LC activation. These findings suggest that the cymba conchae may be the more ideal stimulation target for transcutaneous vagus nerve stimulation. Future research should further identify optimal stimulation sites to provide effective guidance for tVNS research and interventions.

Second, stimulation intensity varies considerably, with some studies employing low-intensity tVNS (e.g., 0.5mA) (Chen et al., 2021; Sellaro et al., 2015) while others have safely used intensities up to 3mA or 8mA without adverse effects (Capone et al., 2015; Keute et al., 2019), demonstrating that higher-intensity tVNS can maintain good safety profiles. Moreover, intensity settings differ not only numerically but also across participants. Some studies use fixed-intensity modes where all participants receive identical stimulation (Chen et al., 2021; Keute et al., 2019), whereas others employ flexible settings where individual tolerance is assessed before formal experiments, and stimulation intensity is selected based on each participant' s tolerance under safety constraints (Borges et al., 2020; Sharon et al., 2021). Because different inhibitory control tasks may vary in their stimulation intensity requirements and sensitivity, insufficient intensity that fails to reach response thresholds may produce ceiling effects. Therefore, future research should investigate optimal stimulation intensity settings across different participant populations and experimental tasks to

ensure both safety and efficacy.

Third, regarding other parameter settings, most previous studies have employed pulse widths of 0.2-1ms, frequencies of 20Hz or 25Hz, and duty cycles of 30s on/30s off, though some have used alternative parameter configurations (Yap et al., 2020). S. Li et al. (2020) used animal experiments to investigate antidepressant effects of different tVNS frequencies and found that after 28 days of intervention, 20Hz tVNS produced more pronounced improvements in depressive-like behaviors compared to 5Hz and 100Hz stimulation. Another fMRI study examining effects of 2Hz, 10Hz, 25Hz, and 100Hz tVNS on brainstem activity in healthy participants found that 100Hz tVNS induced more robust LC-NE activity (Sclocco et al., 2020). These results suggest that different tVNS parameter settings may influence research outcomes, and future studies should conduct comparative experiments to examine effects of different parameter configurations.

In summary, future research should conduct comparative studies using different parameter settings while ensuring participant safety. Researchers should also provide detailed descriptions of study designs and procedures to standardize and normalize reporting, facilitating cross-study comparisons and helping to identify optimal tVNS stimulation protocols.

## 4.2 Investigating tVNS Effects on Inhibitory Control Across Different Populations

Current research on tVNS effects on inhibitory control has primarily focused on healthy populations, with relatively few studies examining populations with impaired or declining inhibitory control. Research has shown that major depressive disorder (MDD) impairs inhibitory control function (Hoffmann et al., 2019), and tVNS, as a non-invasive, non-pharmacological intervention, demonstrates good efficacy for MDD (Kong et al., 2018). However, most assessments of its effects have focused on emotional and somatic symptoms, with few studies addressing cognitive symptom improvement. As tVNS has become a novel clinical intervention for depression, supplementing traditional behavioral and pharmacological treatments, it holds considerable potential for alleviating MDD cognitive symptoms. Therefore, investigating tVNS effects on restoring impaired inhibitory function carries significant clinical importance.

Additionally, numerous studies have found that inhibitory control levels correlate with age, with task performance gradually declining as individuals age (T. Li et al., 2020). However, no studies have directly examined tVNS effects on inhibitory control function in older adults. Future research should therefore investigate tVNS effects on inhibitory function across different populations.

## 4.3 Attention to Long-Term Positive Effects of tVNS

As both a scientific research tool and a promising intervention technique, investigating the long-term positive effects of tVNS on inhibitory control holds important clinical value for delaying cognitive aging, promoting cognitive development, and intervening in neurological and psychiatric disorders. Although research has shown that the LC-NE system and neurotransmitter GABA enhance neural activity (Lee et al., 2018), most existing studies have focused on short-term tVNS effects, with few investigating long-term effects. We can hypothesize that tVNS achieves its long-term effects by influencing LC-NE system activity and GABA concentration (Colzato & Beste, 2020). Future research should emphasize long-term positive effects of tVNS on inhibitory function and investigate influencing factors and methods for maintaining or enhancing these effects.

As a novel brain neuromodulation technique, tVNS positively influences individuals' inhibitory control function. Although most studies support that tVNS regulates inhibitory control via effects on LC-NE system activity and GABA concentration, differences in stimulation parameters, experimental tasks, and participant populations across studies have left many questions about tVNS regulatory mechanisms incompletely resolved. Therefore, future research should conduct comparative studies to optimize tVNS stimulation parameters, further clarify tVNS regulatory effects and mechanisms on inhibitory control, and provide reliable theoretical foundations and data support for both basic research and clinical applications of tVNS.

**Yuan, J., Xu, M., Yang, J., & Li, H. (2017). Application of the two-choice oddball paradigm in behavioral inhibitory control research. Science China: Life Sciences, 47(10), 1065-1073.**

Aaronson, S. T., Sears, P., Ruvuna, F., Bunker, M., Conway, C. R., Dougherty, D. D., . . . Zajecka, J. M. (2017). A 5-year observational study of patients with treatment-resistant depression treated with vagus nerve stimulation or treatment as usual: Comparison of response, remission, and suicidality. *The American Journal of Psychiatry, 174*(7), 640-648.

Aron, A. R., Dowson, J. H., Sahakian, B. J., & Robbins, T. W. (2003). Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry, 54*(12), 1465-1468.

Assenza, G., Campana, C., Colicchio, G., Tombini, M., Assenza, F., Di Pino, G., & Di Lazzaro, V. (2017). Transcutaneous and invasive vagal nerve stimulations engage the same neural pathways: In-vivo human evidence. *Brain Stimulation, 10*(4), 853-854.

Bachiller, A., Romero, S., Molina, V., Alonso, J. F., Mañanas, M. A., Poza, J., & Hornero, R. (2015). Auditory P3a and P3b neural generators in schizophrenia: An adaptive sLORETA P300 localization approach. *Schizophrenia Research, 169*(1-3), 318-325.

Badran, B. W., Dowdle, L. T., Mithoefer, O. J., LaBate, N. T., Coatsworth, J., Brown, J. C., . . . George, M. S. (2018). Neurophysiologic effects of transcutaneous auricular vagus nerve stimulation (taVNS) via electrical stimulation of the tragus: A concurrent taVNS/fMRI study and review. *Brain Stimulation, 11*(3), 492–500.

Beste, C., Steenbergen, L., Sellaro, R., Grigoriadou, S., Zhang, R., Chmielewski, W., . . . Colzato, L. (2016). Effects of concomitant stimulation of the GABAergic and norepinephrine system on inhibitory control - a study using transcutaneous vagus nerve stimulation. *Brain Stimulation, 9*(6), 811–818.

Borges, U., Knops, L., Laborde, S., Klatt, S., & Raab, M. (2020). Transcutaneous vagus nerve stimulation may enhance only specific aspects of the core executive functions. A randomized crossover trial. *Frontiers in Neuroscience, 14*, 523.

Borges, U., Pfannenstiel, M., Tsukahara, J., Laborde, S., Klatt, S., & Raab, M. (2021). Transcutaneous vagus nerve stimulation via tragus or cymba conchae: Are its psychophysiological effects dependent on the stimulation area? *International Journal of Psychophysiology, 161*, 64–75.

Brown, S. B. R. E., Slagter, H. A., van Noorden, M. S., Giltay, E. J., van der Wee, N. J. A., & Nieuwenhuis, S. (2016). Effects of clonidine and scopolamine on multiple target detection in rapid serial visual presentation. *Psychopharmacology, 233*(2), 341–350.

Burger, A. M., D' Agostini, M., Verkuil, B., & Van Diest, I. (2020). Moving beyond belief: A narrative review of potential biomarkers for transcutaneous vagus nerve stimulation. *Psychophysiology, 57*(6), e13571.

Butt, M. F., Albusoda, A., Farmer, A. D., & Aziz, Q. (2020). The anatomical basis for transcutaneous auricular vagus nerve stimulation. *Journal of Anatomy, 236*(4), 588–611.

Capone, F., Assenza, G., Di Pino, G., Musumeci, G., Ranieri, F., Florio, L., . . . Di Lazzaro, V. (2015). The effect of transcutaneous vagus nerve stimulation on cortical excitability. *Journal of Neural Transmission, 122*(5), 679–685.

Capone, F., Motolese, F., Di Zazzo, A., Antonini, M., Magliozzi, A., Rossi, M., . . . Di Lazzaro, V. (2021). The effects of transcutaneous auricular vagal nerve stimulation on pupil size. *Clinical Neurophysiology, 132*(8), 1859–

Chatterton, R. T., Jr., Vogelsong, K. M., Lu, Y. C., Ellman, A. B., & Hudgens, G. A. (1996). Salivary alpha-amylase as a measure of endogenous adrenergic activity. *Clinical Physiology, 16*(4), 433–448.

Chen, L., Zhang, J., Wang, Z., Zhang, X., Zhang, L., Xu, M., . . . Ming, D. (2021). Effects of transcutaneous vagus nerve stimulation (tVNS) on action planning: A behavioural and eeg study. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 1–1.

Colzato, L., & Beste, C. (2020). A literature review on the neurophysiological underpinnings and cognitive effects of transcutaneous vagus nerve stimulation: Challenges and future directions. *Journal of Neurophysiology, 123*(5),

Di Lazzaro, V., Oliviero, A., Pilato, F., Saturno, E., Dileone, M., Meglio, M., . . . Tonali, P. (2004). Effects of vagus nerve stimulation on cortical excitability in epileptic patients. *Neurology, 62*(12), 2310–2312.

Diamond, A. (2013). Executive functions. *Annual Review of Psychology, 64*, 135–168.

Dores, A. R., Barbosa, F., Carvalho, I. P., Almeida, I., Guerreiro, S., da Rocha, B. M., . . . Castro Caldas, A. (2017). An fMRI paradigm based on Williams inhibition test to study the neural substrates of attention and inhibitory control. *Neurological Sciences, 38*(12), 2145–2152.

Ellrich, J. (2019). Transcutaneous auricular vagus nerve stimulation. *Journal of Clinical Neurophysiology, 36*(6),

Farmer, A. D., Strzelczyk, A., Finisguerra, A., Gourine, A. V., Gharabaghi, A., Hasan, A., . . . Majid, A. (2021). International consensus based review and recommendations for minimum reporting standards in research on transcutaneous vagus nerve stimulation (version 2020). *Frontiers in Human Neuroscience, 14*, 409.

Fischer, R., Ventura-Bort, C., Hamm, A., & Weymar, M. (2018). Transcutaneous vagus nerve stimulation (tVNS) enhances conflict-triggered adjustment of cognitive control. *Cognitive, Affective & Behavioral Neuroscience, 18*(4), 680–693.

George, M. S., & Aston-Jones, G. (2010). Noninvasive techniques for probing neurocircuitry and treating illness: Vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology, 35*(1), 301–316.

Henssen, D., Derks, B., van Doorn, M., Verhoogt, N., Van Cappellen van Walsum, A. M., Staats, P., & Vissers, K. (2019). Vagus nerve stimulation for primary headache disorders: An anatomical review to explain a clinical phenomenon. *Cephalalgia, 39*(9), 1180–1194.

Hermans, L., Leunissen, I., Pauwels, L., Cuypers, K., Peeters, R., Puts, N. A. J., . . . Swinnen, S. P. (2018). Brain GABA levels are associated with inhibitory control deficits in older adults. *The Journal of Neuroscience, 38*(36),

Hoffmann, A., Ettinger, U., Montoro, C., Reyes Del Paso, G. A., & Duschek, S. (2019). Cerebral blood flow responses during prosaccade and antisaccade preparation in major depression. *European Archives of Psychiatry and Clinical Neuroscience, 269*(7), 813–822.

Hung, Y., Gaillard, S. L., Yarmak, P., & Arsalidou, M. (2018). Dissociations of cognitive inhibition, response inhibition, and emotional interference: Voxelwise

ALE meta-analyses of fMRI studies. *Human Brain Mapping, 39*(10), 4065-4082.

Keute, M., Barth, D., Liebrand, M., Heinze, H.-J., Kraemer, U., & Zaehle, T. (2020). Effects of transcutaneous vagus nerve stimulation (tVNS) on conflict-related behavioral performance and frontal midline theta activity. *Journal of Cognitive Enhancement, 4*(2), 121-130.

Keute, M., Boehrer, L., Ruhnau, P., Heinze, H. J., & Zaehle, T. (2019). Transcutaneous vagus nerve stimulation (tVNS) and the dynamics of visual bistable perception. *Frontiers in Neuroscience, 13*, 227.

Kong, J., Fang, J., Park, J., Li, S., & Rong, P. (2018). Treating depression with transcutaneous auricular vagus nerve stimulation: State of the art and future perspectives. *Front Psychiatry, 9*, 20.

Larsen, R. S., & Waters, J. (2018). Neuromodulatory correlates of pupil dilation. *Frontiers in Neural Circuits, 12*,

Lee, T. H., Greening, S. G., Ueno, T., Clewett, D., Ponzio, A., Sakaki, M., & Mather, M. (2018). Arousal increases neural gain via the locus coeruleus-norepinephrine system in younger adults but not in older adults. *Nature Human Behaviour, 2*(5), 356-366.

Li, S., Wang, Y., Gao, G., Guo, X., Zhang, Y., Zhang, Z., . . . Rong, P. (2020). Transcutaneous auricular vagus nerve stimulation at 20 Hz improves depression-like behaviors and down-regulates the hyperactivity of HPA axis in chronic unpredictable mild stress model rats. *Frontiers in Neuroscience, 14*, 680.

Li, T., Wang, L., Huang, W., Zhen, Y., Zhong, C., Qu, Z., & Ding, Y. (2020). Onset time of inhibition of return is a promising index for assessing cognitive functions in older adults. *The Journals of Gerontology: Series B, 75*(4),

Montefinese, M., Vinson, D., & Ambrosini, E. (2018). Recognition memory and featural similarity between concepts: The pupil' s point of view. *Biological Psychology, 135*, 159-169.

Murley, A. G., Rouse, M. A., Jones, P. S., Ye, R., Hezemans, F. H., O'Callaghan, C., . . . Rowe, J. B. (2020). GABA and glutamate deficits from frontotemporal lobar degeneration are associated with disinhibition. *Brain: a Journal of Neurology, 143*(11), 3449-3462.

Murphy, P. R., O'Connell, R. G., O'Sullivan, M., Robertson, I. H., & Balsters, J. H. (2014). Pupil diameter covaries with bold activity in human locus coeruleus. *Human Brain Mapping, 35*(8), 4140-4154.

Nater, U. M., & Rohleder, N. (2009). Salivary alpha-amylase as a non-invasive biomarker for the sympathetic nervous system: Current state of research. *Psychoneuroendocrinology, 34*(4), 486-496.

Nguyen, A. T., Moyle, J. J., & Fox, A. M. (2016). N2 and P3 modulation during partial inhibition in a modified go/nogo task. *International Journal of Psychophysiology, 107*, 63–71.

Nielsen, S. E., Segal, S. K., Worden, I. V., Yim, I. S., & Cahill, L. (2013). Hormonal contraception use alters stress responses and emotional memory. *Biological Psychology, 92*(2), 257–266.

O' Callaghan, C., Hezemans, F. H., Ye, R., Rua, C., Jones, P. S., Murley, A. G., . . . Rowe, J. B. (2021). Locus coeruleus integrity and the effect of atomoxetine on response inhibition in Parkinson' s disease. *Brain: a Journal of Neurology, 144*(8), 2513–2526.

Passamonti, L., Lansdall, C. J., & Rowe, J. B. (2018). The neuroanatomical and neurochemical basis of apathy and impulsivity in frontotemporal lobar degeneration. *Current Opinion in Behavioral Sciences, 22*, 14–20.

Peuker, E. T., & Filler, T. J. (2002). The nerve supply of the human auricle. *Clinical Anatomy, 15*(1), 35–37.

Pihlaja, M., Failla, L., Peräkylä, J., & Hartikainen, K. M. (2020). Reduced frontal Nogo-N2 with uncompromised response inhibition during transcutaneous vagus nerve stimulation-more efficient cognitive control? *Frontiers in Human Neuroscience, 14*, 561780.

Pineda, J. A., Foote, S. L., & Neville, H. J. (1989). Effects of locus coeruleus lesions on auditory, long-latency, event-related potentials in monkey. *The Journal of Neuroscience, 9*(1), 81–93.

Polich, J. (2007). Updating P300: An integrative theory of P3a and P3b. *Clinical Neurophysiology, 118*(10), 2128–

Rajkowski, J., Kubiak, P., & Aston-Jones, G. (1994). Locus coeruleus activity in monkey: Phasic and tonic changes are associated with altered vigilance. *Brain research bulletin, 35*(5-6), 607–616.

Redgrave, J., Day, D., Leung, H., Laud, P. J., Ali, A., Lindert, R., & Majid, A. (2018). Safety and tolerability of transcutaneous vagus nerve stimulation in humans; a systematic review. *Brain Stimulation, 11*(6), 1225–1238.

Schevernels, H., van Bochove, M. E., De Taeye, L., Bombeke, K., Vonck, K., Van Roost, D., . . . Boehler, C. N. (2016). The effect of vagus nerve stimulation on response inhibition. *Epilepsy & Behavior, 64*, 171–179.

Sclocco, R., Garcia, R. G., Kettner, N. W., Fisher, H. P., Isenburg, K., Makarovsky, M., . . . Napadow, V. (2020). Stimulus frequency modulates brainstem response to respiratory-gated transcutaneous auricular vagus nerve stimulation. *Brain Stimulation, 13*(4), 970–978.

Sellaro, R., van Leusden, J. W., Tona, K. D., Verkuil, B., Nieuwenhuis, S., & Colzato, L. S. (2015). Transcutaneous vagus nerve stimulation enhances post-error slowing. *Journal of Cognitive Neuroscience, 27*(11), 2126–2132.

Sharon, O., Fahoum, F., & Nir, Y. (2021). Transcutaneous vagus nerve stimulation in humans induces pupil dilation and attenuates alpha oscillations. *The Journal of Neuroscience, 41*(2), 320-330.

Sumner, P., Edden, R. A., Bompas, A., Evans, C. J., & Singh, K. D. (2010). More GABA, less distraction: A neurochemical predictor of motor decision speed. *Nature Neuroscience, 13*(7), 825-827.

Toffa, D. H., Touma, L., El Meskine, T., Bouthillier, A., & Nguyen, D. K. (2020). Learnings from 30 years of reported efficacy and safety of vagus nerve stimulation (VNS) for epilepsy treatment: A critical review. *Seizure, 83*, 104-123.

Tomassini, A., Hezemans, F. H., Ye, R., Cam-CAN, Tsvetanov, K. A., Wolpe, N., & Rowe, J. B. (2021). Prefrontal cortical connectivity mediates locus coeruleus noradrenergic regulation of inhibitory control in older adults. *BioRxiv*, 2021.2006.2029.450427.

Ventura-Bort, C., Wirkner, J., Genheimer, H., Wendt, J., Hamm, A. O., & Weymar, M. (2018). Effects of transcutaneous vagus nerve stimulation (tVNS) on the P300 and alpha-amylase level: A pilot study. *Frontiers in Human Neuroscience, 12*, 202.

Ventureyra, E. C. G. (2000). Transcutaneous vagus nerve stimulation for partial onset seizure therapy. *Child' s Nervous System, 16*(2), 101-102.

Waller, D. A., Hazeltine, E., & Wessel, J. R. (2021). Common neural processes during action-stopping and infrequent stimulus detection: The frontocentral P3 as an index of generic motor inhibition. *International Journal of Psychophysiology, 163*, 11-21.

Wang, J., & Dai, B. (2020). Event-related potentials in a two-choice oddball task of impaired behavioral inhibitory control among males with tendencies towards cybersex addiction. *Journal of Behavioral Addictions, 9*(3), 785-

Warren, C. V., Maraver, M. J., de Luca, A., & Kopp, B. (2020). The effect of transcutaneous auricular vagal nerve stimulation (taVNS) on P3 event-related potentials during a Bayesian oddball task. *Brain Sciences, 10*(6), 404.

Yakunina, N., Kim, S. S., & Nam, E. C. (2017). Optimization of transcutaneous vagus nerve stimulation using functional MRI. *Neuromodulation: Journal of the International Neuromodulation Society, 20*(3), 290-300.

Yap, J. Y. Y., Keatch, C., Lambert, E., Woods, W., Stoddart, P. R., & Kameneva, T. (2020). Critical review of transcutaneous vagus nerve stimulation: Challenges for translation to clinical practice. *Frontiers in Neuroscience, 14*, 284.

Zhao, X., Liu, X., & Maes, J. H. R. (2018). Male smokers' behavioral and brain responses to deviant cigarette-related stimuli in a Two-choice oddball paradigm. *Journal of Psychophysiology, 32*(4), 172-181.

Zhu, S., Zhang, X., Qing, Y., Zhang, Y., Yao, S., Kendrick, K., & Zhao, W. (2021). Transcutaneous auricular vagus nerve stimulation increases eye-gaze to salient facial features and oxytocin release. *Brain Stimulation, 14*(6), 1639.

Ziemann, U., Reis, J., Schwenkreis, P., Rosanova, M., Strafella, A., Badawy, R., & Müller-Dahlhaus, F. (2015). TMS and drugs revisited 2014. *Clinical Neurophysiology, 126*(10), 1847–1868.

*Note: Figure translations are in progress. See original paper for figures.*