THE IMPACT OF PERSON-BASED FACTORS ON VAGUS NERVE STIMULATION INTENSITY AND RESPONSIVENESS

by

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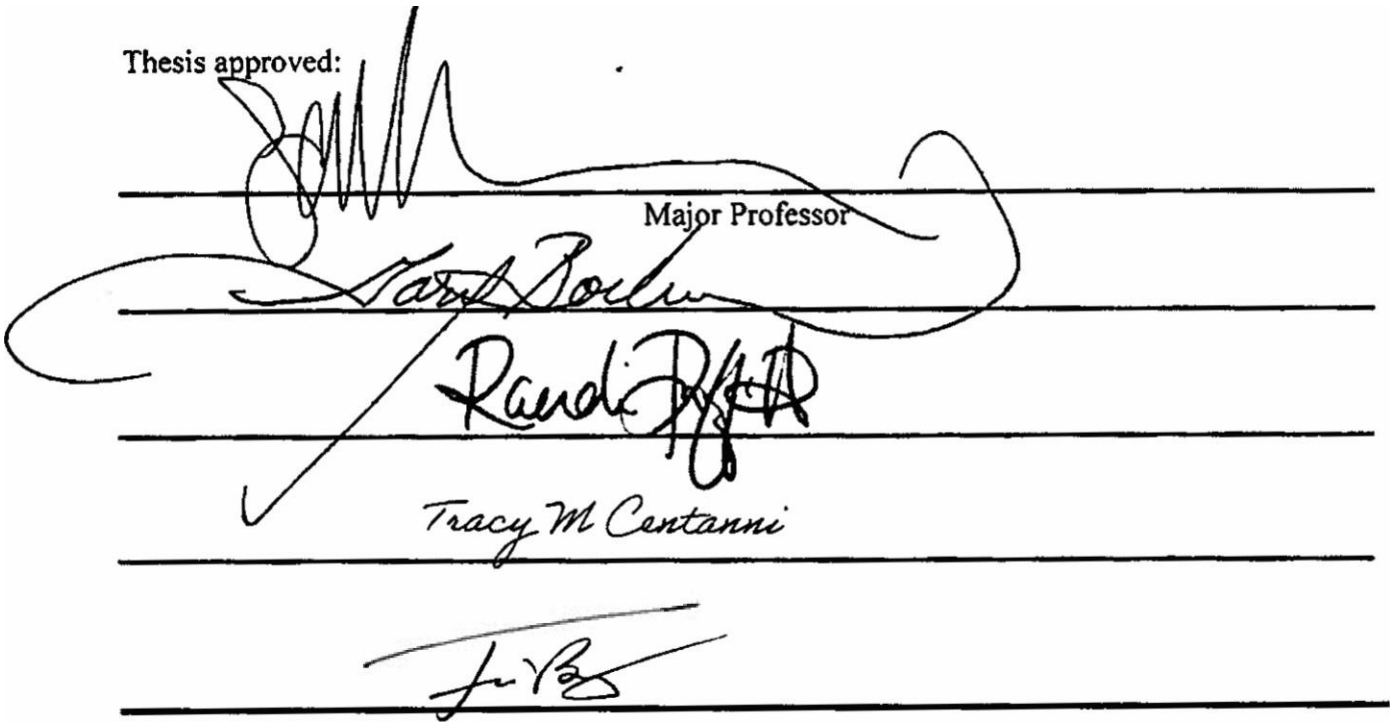

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The vagus nerve is involved in a plethora of functions, including parasympathetic nervous system function, autonomic nervous system balance, response to a stressor, and appropriate immune response to a pathogen. Given the far-reaching impact of the vagus nerve, researchers in the past 100 years began exploring whether stimulating vagus nerve fibers has therapeutic benefits. Indeed, Vagus Nerve Stimulation (VNS), a neuromodulation tool in which cranial nerve X is electrically stimulated to target the central nervous system (CNS), was first approved as a therapeutic in 1997 (Olsen et al., 2023). Since then, it has been adapted from its original invasive form into noninvasive forms, such as stimulation of afferent vagus nerve fibers through the skin. Further, VNS has now been FDA approved to treat epilepsy, treatment-resistant depression, cluster headaches and migraines, stroke rehabilitation, and opioid withdrawal (Grazzi et al., 2016; Mandalaneni & Rayi, 2023; Olsen et al., 2023; Spark Biomedical, Inc., 2024). Preliminary research also suggests that vagus nerve stimulation (VNS) may be therapeutic for metabolic, neurological, psychiatric, cardiovascular, and immunological conditions (Machetanz et al., 2021; Redgrave et al., 2018). Some specific examples include the therapeutic effect of VNS for those with elevated inflammation (Breit et al., 2018; Johnson & Wilson, 2018), and the positive impact of transcutaneous auricular vagus nerve stimulation (taVNS) on working memory (Thakkar et al., 2023). In addition, a recent study demonstrated that taVNS has the potential to treat COVID19-induced acute respiratory distress syndrome (Kaniusas et al., 2020). Thus, researchers have likely only scratched the surface of what VNS can be utilized for therapeutically.

One way that VNS research can continue to make strides is by identifying reasons for variation in VNS efficacy. Despite the success of VNS in treating several conditions, there is a great variability in outcomes. For example, not all patients with epilepsy demonstrate improvement after treatment with VNS. In fact, one-quarter were found to receive no benefit (reviewed in Englot et al., 2011). Inconsistencies such as these have been thought to be the result of variation in stimulation parameters including intensity, frequency, and duration of stimulation (Olsen et al., 2023). This is a reasonable explanation given that these stimulation parameters change depending on the method of VNS being used and the individual patient or participant (Olsen et al., 2023). For example, for noninvasive forms of VNS, stimulation intensity changes according to the individual receiving the treatment (Olsen et al., 2023). Additionally, characteristics such as sex and socioeconomic status impact baseline vagal tone (Lampert et al., 2005; Olsen et al., 2023), and existing research suggests that baseline vagal tone impacts responsiveness to VNS (Geng et al., 2022). Thus, differences in stimulation parameters such as intensity, *and* individual differences such as patient sex and socioeconomic status likely work together to lead to the observed variability in VNS treatment efficacy.

In the current research, I examined the impact of several person-based variables, specifically sex, body awareness, preterm birth, childhood socioeconomic status, childhood unpredictability, and childhood adverse experiences (ACES), on the effectiveness of VNS. Specifically, I examined variability in responses to taVNS, a type of noninvasive VNS that applies electrical impulses to the left tragus to stimulate the auricular branch of the vagus nerve (Forte et al., 2022). Each of these person-based factors were selected because they are related to baseline vagal tone, autonomic nervous system function, pain tolerance,

interoceptive-ness or sensitivity, or any processes that are closely related to or regulated by the vagus nerve.

The taVNS outcomes that we will focus on in the study at hand include intensity of stimulation and responsiveness to stimulation. The intensity variable represents the participant's sensitivity and tolerance to the physical experience of the stimulation. The responsiveness variable, on the other hand, quantifies the degree to which participant's nervous system responds to the stimulation.

Vagus Nerve Background

The vagus nerve is involved in several complex processes and has far-reaching effects on the brain and body. For example, the vagus nerve is involved in responding to threats in the environment whether they are pathogens or external threats (reviewed in Breit et al., 2018). Additionally, the vagus nerve plays a large role in function of the parasympathetic nervous system (reviewed in Breit et al., 2018), regulating blood pressure, heart rate, respiration, digestion, and the immune response (Olsen et al., 2023). Vagal nerve activity plays an essential role in autonomic nervous system balance and is essential for maintaining health (reviewed in Breit et al., 2018; reviewed in Liu et al., 2019). In particular, vagal activity is critical for an appropriate response to stress and pathogens, and when withdrawn, is greatly implicated in disease states. For example, when the vagus nerve is withdrawn, meaning that sympathetic nervous system activity is dominant and parasympathetic nervous system activity is decreased, risk of heart diseases and all-cause mortality increases (Thayer & Lane, 2007). Below, I review the form and function of the vagus nerve, and its role on the brain and body.

The vagus nerve has far-reaching effects on the brain and body because it has both efferent and afferent fibers. Specifically, eighty percent of the vagus nerve is composed of fibers carrying information from the body to the brain (afferent), and twenty percent is composed of fibers carrying information from the brain to the body (efferent) (Olsen et al., 2023). The vagus nerve efferent projections exit the medulla oblongata of the brainstem and innervate (a) the pharynx and larynx, which are responsible for swallowing and speech, (b) the heart, where the vagus nerve is essential for reduction in heart rate, (c) the esophagus, stomach, and intestines, where the vagus nerve contracts smooth muscle and secretes hormones, and (d) the liver and pancreas, where the vagus nerve has sensory endings (Olsen et al., 2023).

Afferent pathways of the vagus nerve project to the nucleus tractus solitarii (NTS), which conveys sensory information to the CNS, such as the locus coeruleus (LC), the nucleus basalis (NB), the amygdala, and the thalamus (reviewed in Breit et al., 2018; Hulsey et al., 2016). The NTS is the integration center in the brain where information about the body from the vagus nerve is processed (Olsen et al., 2023). The NTS projects to the LC, which is the norepinephrine (NE) center of the brain. The LC then projects to (a) the amygdala and the hippocampus which are associated with emotional and episodic memory, (b) the thalamus and hypothalamus which are involved in sensory processing, the stress response, and wakefulness, (c) the basal forebrain, which is important in alertness and arousal, and (d) the prefrontal cortex, which regulates attention and is involved in higher order processes like decision making, and (e) the midbrain and dorsal raphe nucleus, which is involved in dopamine (DA) and serotonin (5HT) signaling (Olsen et al., 2023).

The afferent pathways of the vagus nerve that carry information to the brain from the body are some of the most vital. In particular, information from the gut, heart, liver, and lungs is carried to the brain (reviewed in Breit et al., 2018). Additionally, the vagus nerve is highly involved in one's response to a stressor. A neural circuit made up of the vagus nerve, NTS, and locus coeruleus is involved in memory storage after an emotionally arousing event by controlling norepinephrine release within the amygdala (McIntyre et al., 2012). Afferent fibers of the vagus nerve are also involved in activating the Hypothalamic Pituitary Adrenal (HPA) axis, such as in the presence of environmental stress and when systemic proinflammatory cytokine levels are elevated (reviewed in Breit et al., 2018; Howland, 2014). It is this afferent vagal nerve pathway from the body to the brain that most VNS therapies target (Howland, 2014).

Balance of the ANS is incredibly important for health. Decreased vagal nerve activity, and by extension decreased parasympathetic activity, is associated with inflammation, oxidative stress, and pathological states (reviewed in Geng et al., 2022). For example, an overactive sympathetic nervous system has been shown to be associated with hypertension, heart failure, and mortality (Dekker et al., 1997; Singh et al., 1998). Furthermore, sufficient vagal activity is required in order to have an appropriate immune response to a pathogen.

Specifically, a properly active vagus nerve leads to controlled cytokine release in response to an immune threat, via the cholinergic anti-inflammatory pathway (CAIP) (Leitzke, 2020). Cytokines are small secreted proteins that are released by cells and may act on the cell that released them or other cells (Daroff & Aminoff, 2014). In particular, cytokines are involved in the inflammatory response in the peripheral and central nervous systems (Zhang & An, 2007). Without the CAIP, the immune response is unregulated and

instead of producing a controlled cytokine release, a “cytokine storm” is produced (Leitzke, 2020). This can lead to increased vulnerability to pathogen threat (Leitzke, 2020). For instance, COVID-19 poses more of a risk to individuals with an underrepresentation of the parasympathetic nervous system, such as elderly individuals, people with cardiovascular, respiratory, or metabolic disorders, and patients with cancer (Leitzke, 2020).

Vagus Nerve Stimulation Background

Given the ability of the vagus nerve to modulate brain activity, VNS has been adopted in clinical work to help activate the parasympathetic nervous system and modulate neuronal activity (Fan et al., 2019; Howland, 2014). For example, in 1997, VNS was approved as an implantable device to treat refractory epilepsy (Schachter, 2002). VNS is thought to treat epilepsy by modifying neuronal activity in the central nervous system, specifically in the amygdala and hippocampus (Fan et al., 2019). In 2005, VNS was approved by the FDA to treat drug-resistant depression (Olsen et al., 2023). VNS treats depression by stimulating areas of the brain that are important for affective regulation, in turn modulating neurotransmitters such as serotonin and norepinephrine (Young et al., 2020). Further, VNS has been approved to treat migraines since 2018 (American Headache Society, 2025). VNS is thought to treat migraines is by inhibiting the brainstem trigeminal nervous system, disrupting pain signals to the brain (Frangos & Komisaruk, 2017; Song et al., 2023). Finally, VNS was approved to treat opioid withdrawal in 2017, and works to activate the parasympathetic nervous system, decreasing sympathetic nervous system activation, as well as anxiety, pain, and reward circuits that are associated with opioid withdrawal (reviewed in Bremner et al., 2023).

Ongoing research has discovered other uses for vagus nerve stimulation, such as tagging salient stimuli and decreasing inflammation. In particular, the cognitive impacts of invasive vagus nerve stimulation, including enhanced attention, arousal, short-term memory, verbal memory recognition, working memory, memory consolidation, and decision-making has received much attention (Broncel et al., 2022; Clark et al., 1999; Ghacibeh et al., 2006; Klinkenberg et al., 2013; Martin et al., 2004; Olsen et al., 2023; Sackeim et al., 2001; Sun et al., 2017; Vonck et al., 2014). VNS has such impacts on memory because the vagus nerve regulates the stress response and tags memories associated with stressors. More specifically, the vagus nerve is involved in the memory consolidation of emotional experiences (Ventura-Bort et al., 2021). Proximally, VNS increases expression of brain derived neurotrophic factor (BDNF) and adrenergic receptors, facilitating long term potentiation (LTP) in the hippocampus and changes in memory (Olsen et al., 2023). Further, VNS has been identified as a potential treatment for conditions that have high levels of inflammation, such as endometriosis, although more research is still needed (Breit et al., 2018; Hao et al., 2021). Researchers have shown that VNS attenuates inflammatory response to endotoxin, (reviewed in Breit et al., 2018) and reduces inflammation in peripheral tissues (Borovikova et al., 2000). Preliminary research on the clinical relevance of this anti-inflammatory effect of VNS demonstrates promising results for a myriad of chronic inflammatory disorders such as sepsis, rheumatoid arthritis, Crohn's disease, irritable bowel syndrome, fibromyalgia, diabetes, and lung injury (Johnson & Wilson, 2018).

There are both invasive and noninvasive forms of VNS. When used chronically, invasive VNS can lead to side effects due to coincidental stimulation of efferent and afferent fibers in the cervical vagus nerve (Ellrich, 2011), such as cough, hoarseness, voice alteration,

and paresthesia (Ben-Menachem, 2001). However, noninvasive VNS has been found to improve creativity, alertness, and associative memory without producing these side effects (Olsen et al., 2023).

Within the category of noninvasive VNS, transcutaneous vagus nerve stimulation involves applying electrical stimulation to the skin at the ear (taVNS) or the neck (tVNS). It is effective at stimulating afferent vagus nerve fibers (Ellrich, 2011). Research has demonstrated that transcutaneous VNS leads to increased activation in the insula, precentral gyrus, and thalamus, and decreased activation in the amygdala, hippocampus, parahippocampal gyrus, and middle and superior temporal gyrus (Ellrich, 2011). TaVNS has been found to have anti-epileptic, anti-depressant, cardiac and pain-modulating effects (Machetanz et al., 2021; Yap et al., 2020; Sinko vec et al., 2021; von Wrede and Surges, 2021). Further, researchers find that in healthy individuals, taVNS increased recall of previously read material in comparison to controls who did not receive taVNS (Thakkar et al., 2023). Future applications of this work will include testing noninvasive forms of VNS in those who need memory aid. VNS will continue to be researched as a potential therapeutic for several conditions due to the important role of the vagus nerve in brain-body interaction and many physiological processes.

Although VNS is approved for several conditions and will be approved for more in the future, there are some individuals who receive no benefit from the treatment. As mentioned previously, a quarter of individuals who receive VNS for epilepsy do not experience improvements (reviewed in Englot et al., 2011). Additionally, previous research has found a response rate of 42% among those with treatment resistant depression after 2 years of VNS therapy (n = 59) (O'Reardon et al., 2006). More recent research found a

response rate of 83% after 1 year of VNS therapy in those with treatment resistant depression, although the sample size in this study was small (n = 6) (Kucia et al., 2019). Thus, we consider factors that may influence efficacy.

Vagus Nerve Intensity Background

A potential contributor to variation in VNS efficacy is individual differences in sensitivity and tolerance to VNS intensity (Olsen et al., 2023). Both an individual's tolerance to the stimulation, and their sensitivity to the stimulation is utilized to determine the intensity level in milliamps at which non-invasive VNS is applied. Specifically, stimulation intensity differs depending on the individual receiving the treatment. It is adjusted based on when the individual first detects stimulation, referred to as the sensory threshold or lower threshold, and when they begin to find the stimulation uncomfortable or painful, referred to as sensory tolerance or upper threshold. An average of these numbers is the intensity level at which VNS is applied (Thakkar et al., 2023). Thus, there is much variation in intensity level utilized between subjects, and it is not well understood how this impacts efficacy (Thakkar et al., 2025).

Some research suggests that there is an optimal intensity required in order for VNS to lead to a CNS effect. For example, in preclinical work, researchers found that moderate intensity stimulation is most effective at enhancing motor cortex plasticity, whereas high and low intensity are not as effective (Morrison et al., 2019). However, this effect was found in an animal model of invasive VNS. It is still unknown whether there is an optimal intensity for taVNS, which is noninvasive by definition. In particular, the intensity at which taVNS can be applied is limited by pain receptors in the outer ear (Thakkar et al., 2025). Some researchers have hypothesized that there may be a maximum effective level of taVNS

intensity in which increasing it beyond a certain threshold does not continue to increase its effectiveness (Geng et al., 2022). However, if all individuals cannot tolerate such an intensity, we predict that treatment will be differentially effective. Thus, in the present study, we examine several factors that may influence sensitivity to VNS intensity.

Vagus Nerve Responsiveness Background

In addition to variability in VNS intensity, there is also individual variability in the neurocardiac response to VNS. This is referred to as VNS responsiveness. For example, research suggests that those with lower baseline vagal tone were more responsive to Vagus Nerve Stimulation than those with higher baseline vagal tone (Geng et al., 2022). Specifically, lower vagal tone predicted greater vagal activation due to VNS. This suggests that one's existing vagal tone when they seek VNS treatment may factor into clinical efficacy. Thus, in the present study, we examine several factors that may influence vagal tone, and thus VNS responsiveness by extension. VNS responsiveness is defined methodologically as the change in participant's heart rate variability (HRV) from baseline to stimulation due to taVNS, while controlling for VNS intensity.

In the following, we will examine multiple factors that may impact our outcomes of (a) intensity of VNS applied and (b) responsiveness to VNS (while controlling for intensity). The factors to be explored in the study at hand are participant sex, body awareness, preterm birth, childhood socioeconomic status, childhood unpredictability, and childhood adverse experiences. Again, each of these factors were selected because they are related to baseline vagal tone, autonomic nervous system function, pain tolerance, interoceptive-ness or sensitivity, or any processes that are closely related to or regulated by the vagus nerve (i.e., inflammation). Specifically, we hypothesize that factors that are related to pain tolerance or

general physical sensitivity in the existing literature will predict the stimulation intensity that is utilized in VNS. Further, we hypothesize that the factors that are related to vagal tone or autonomic nervous system function will predict one's responsiveness to VNS. We describe our hypotheses and corresponding rationale below.

Hypotheses: Overarching Predictions

Responsiveness

In the present study, VNS responsiveness is defined as the change in HRV from baseline to stimulation due to taVNS, while controlling for intensity. Each of the predictions about VNS responsiveness in this section are based on the flowing rationale: research has found individuals who have greater sympathetic activity (i.e., lower vagal tone) to be the ones who are most affected by taVNS (Geng et al., 2022). Put another way, lower vagal tone at baseline predicted the greatest increase in vagal tone due to VNS (Geng et al., 2022), i.e., greater responsiveness. This finding demonstrates the success of VNS in those who may need the treatment the most.

Hypothesis 1a: Baseline vagal tone and responsiveness to VNS will be negatively correlated, such that lower baseline vagal tone is associated with greater responsiveness to VNS (Geng et al., 2022).

Hypothesis 1b: Factors that tend to be associated with lower vagal tone (low SES, being male, etc.) will be associated with greater responsiveness to VNS.

Intensity

The intensity variable, measured in milliamps (mA), is the average of the participants' upper and lower thresholds: the lower threshold being the intensity at which the participant is first able to detect the stimulation, and the upper threshold being the intensity at which the

stimulation becomes uncomfortable or distracting (see **Methods** for more detail). Each of the predictions about VNS intensity are based on the understanding that VNS intensity is dependent on participants' general sensitivity and pain tolerance. The physical experience of receiving taVNS is a warm or tingly sensation in the tragus. However, some participants first feel this sensation at a lower current than others. Likewise, some participants begin to find it uncomfortable at a lower current than others. This differential experience is worth investigating, as researchers have hypothesized that the variation in intensity between patients receiving VNS impacts its efficacy (Olsen et al., 2023).

Hypothesis 2: Individuals with traits that are associated with greater general sensitivity and/or lower pain tolerance (e.g., early life stress, preterm birth) will receive VNS at a lower intensity in the study at hand.

Hypotheses: Specific Predictions

Sex

Participant sex (i.e., assigned male at birth or assigned female at birth), has been an important variable of interest in studies on pain tolerance, sensitivity, vagal tone, and vagus nerve stimulation outcomes, leading us to predict that it may influence our VNS outcomes in the study at hand. To start, there are sex differences in vagal tone. Compared to men, women have higher vagal parasympathetic activity (Olsen et al., 2023), despite having greater average heart rate (Koenig & Thayer, 2016). This is of significance because greater vagal activity is cardioprotective and associated with wellbeing and longevity (reviewed in Koenig & Thayer, 2016). Additionally, VNS has been shown to reduce heat pain perception in men, but not women (Olsen et al., 2023). Given that Geng et al. (2022) found that those with lower baseline vagal tone were more responsive to treatment, we predict that men, given their lower

average vagal activation, will be more responsive to the stimulation than women (See Table 1 for full list of predictions).

Furthermore, research has uncovered sex differences with regards to pain tolerance. Existing experimental research demonstrates that women have lower pain thresholds, meaning that they have greater pain sensitivity, than men (Osborne & Davis, 2022). However, one study found that these sex differences in pain tolerance are due to differences in trait anxiety between the sexes (Goffaux et al., 2011). Additionally, a systematic review concluded that the existing research on sex differences in pain tolerance was not conclusive (Racine et al., 2011). Given the available evidence, though limited, we predict that female participants receive VNS during the experiment at a lower intensity than male participants, due to increased pain sensitivity.

Childhood SES, Unpredictability, and ACES

Variables related to life in early childhood have been found to be associated with pain tolerance, health outcomes, and vagal tone, leading us to predict that they may influence our VNS outcomes in the study at hand. Early life stress can lead to chronic elevation of the sympathetic nervous system (i.e., a decrease in parasympathetic nervous system function), which is a recipe for increased inflammation, decreased efficacy of the immune response, and increased likelihood of disease state (Deuchars et al., 2018; Leitzke, 2020). Indeed, researchers have shown that individuals from environments of early life stress such as poverty, maltreatment, or unpredictability, have increased risk of mortality from disease and illness (Cuijpers et al., 2011; Kittleson et al., 2006). In particular, those with an adverse childhood experiences (ACEs) score of at least four have a small to moderate increased risk of physical inactivity, being overweight or obese, and having diabetes; a moderate increased

risk of smoking, heavy alcohol use, poor self-perceived health, cancer, heart disease, and respiratory disease; and a strong increased risk of sexual risk taking, mental health issues, and problematic alcohol use (Hughes et al. 2017). As demonstrated by immunology, neurology, and psychology research, early life stress has a significant impact on health and behavior throughout the course of adult life. Finally, individuals from low SES environments have been shown to have depressed autonomic nervous system function relative to those from higher SES environments (Lampert et al., 2005). Overall, childhood environment greatly impacts one's physiology, including autonomic nervous system function and immunological function.

Given the impact of childhood SES, a marker of early life stress, on autonomic nervous system function, we predict that childhood SES, unpredictability, and ACES will influence responsiveness to vagus nerve stimulation. Specifically, since individuals from lower SES backgrounds have lower vagal tone (Lampert et al., 2005), and individuals with lower vagal tone have been shown to be responsive to VNS (Geng et al., 2022), we predict that individuals with markers of early life stress may be more responsive to vagus nerve stimulation.

Further, research demonstrates that early life stress is associated with pain sensitivity. In particular, those from environments of family dysfunction in the first three years of life were found to have greater pain sensitivity to a cold pressor task, but only if they were already experiencing frequent and/or chronic pain at age 22 (Waller et al., 2020). Similarly, others found that early life disadvantage, particularly low socioeconomic status, was associated with higher perceived pain sensitivity and higher pain catastrophizing later in life (Simon et al., 2022). Interestingly, this was mediated by unpredictability and body

awareness (Simon et al., 2022). Likewise, others have found that those from high-adversity backgrounds had greater sensitization to pain than those from low-adversity backgrounds (You & Meagher, 2016). Thus, we expect that our measures of early life stress including childhood SES, unpredictability, and ACES may influence the VNS intensity utilized in the experiment. For example, we predict that those from lower SES backgrounds will have lower VNS intensity in the experiment at hand, indicating higher sensitivity and lower pain tolerance.

Body Awareness

Body awareness, one's awareness of their internal cues and needs, has been found to be related to heart rate variability, a proxy for vagal tone, and pain tolerance, leading us to predict that it may influence our VNS outcomes in the study at hand. First, we predict that body awareness will impact responsiveness to VNS. Researchers have found heart rate variability is positively associated with interoceptive ability (Lischke et al., 2021). Interoceptive ability was quantified by having researchers determine the accuracy with which participants counted their own heart beats in a specific time frame (Lischke et al., 2021). They found that higher HRV (i.e., higher vagal tone) was associated with greater interoceptive ability, or a greater ability to accurately count their own heart beats (Lischke et al., 2021). Further, both parasympathetic nervous system activation (i.e., vagal activity) and bodily awareness are important elements of emotional regulation, suggesting that they are closely related (Pinna & Edwards, 2020). As previously mentioned, baseline vagal tone has been shown to impact responsiveness to VNS, such that lower vagal tone is associated with increased VNS responsiveness (Geng et al., 2022). Specifically, we predict that greater body awareness will be associated with greater baseline vagal tone and lower VNS responsiveness.

Additionally, attunement to bodily states has been shown to be low in those with markers of early life stress (Proffitt Leyva & Hill, 2018). Specifically, researchers have found that (a) low SES during childhood is associated with greater unpredictability which in turn is linked to low body awareness and (b) that individuals that have an unpredictability schema, or a belief that the world is unpredictable, were found to have lower body awareness and less mindful eating (Proffitt Leyva & Hill, 2018). As previously mentioned, childhood environment is related to vagal tone, such that those from lower childhood SES have depressed autonomic nervous system function (Lampert et al., 2005). Thus, since body awareness is closely related to childhood SES, we predict that both variables will predict VNS responsiveness.

Second, we predict that body awareness will be associated with the taVNS intensity level utilized in the experiment. Researchers have found that the insula, one of the many brain structures that the vagus nerve projects to (Paciorek & Skora, 2020), to be important for body awareness, self-awareness (Chen et al., 2021; Critchley & Harrison, 2013), and pain sensation (Craig, 2011). Some research suggests that maladaptive body awareness, such as excessive worrying about bodily sensations, or on the other hand, distracting oneself from bodily sensations, may increase chronic pain (Colgan et al., 2021). Alternatively, in an experimental pain paradigm, body awareness was positively associated with pain thresholds (Minev et al., 2017). Specifically, we predict that body awareness and VNS intensity levels will be positively related, such that individuals with greater body awareness will have greater intensity levels in the experiment, reflecting lower sensitivity and higher pain tolerance.

Pre-term Birth

Pre-term birth has been found to be associated with general sensitivity and responsiveness to the environment, leading us to predict that it may influence our VNS outcomes in the study at hand. First, we predict that those who were born early may be more responsive to VNS due to their enhanced responsiveness to their environment. For example, preterm infants demonstrate a greater emotional benefit from positive parenting than full-term birth infants at 12-months (reviewed in Lionetti et al., 2021). Additionally, at 3 years of age, preterm infants demonstrated a higher cognitive score and emotional benefit than later preterm infants (reviewed in Lionetti et al., 2021). Second, we predict that those who are born early will receive VNS at a lower intensity in the experiment due to greater general sensitivity. For example, researchers found that at age eighteen, subjects who were born prematurely demonstrated lower pain tolerance than subject who were born at term via a cold pressor task, although pre-term males accounted for most of the difference (Vederhus et al., 2012).

Table 1

Summary of Hypotheses & Factors to Be Examined – Responsiveness

Factor	**Predicted impact on VNS outcomes**	**Reasoning**
Overarching predictions	Hypothesis 1a: Individuals with low vagal tone will be more responsive to VNS. Hypothesis 1b: Factors that tend to be associated with lower baseline vagal tone (low SES, being male, etc.) will be associated with greater responsiveness to VNS.	Lower vagal tone at baseline predicted the greatest increase in vagal tone due to VNS (Geng et al., 2022).

Sex	Men will demonstrate greater responsiveness to VNS.	Compared to men, women have higher vagal parasympathetic activity (Olsen et al., 2023).
Childhood SES Childhood unpredictability Childhood ACEs	Those who experienced low SES during childhood, or other markers of early life stress, will have greater responsiveness to VNS.	Individuals from low SES environments have been shown to have depressed ANS function relative to those from higher SES environments (Lampert et al., 2005).
Body awareness	Lower body awareness will be associated with greater VNS responsiveness.	Greater body awareness is associated with greater baseline vagal tone (Lischke et al., 2021)
Pre-term birth	Those who were born prematurely will demonstrate greater responsiveness to VNS.	Individuals who are born prematurely are more responsive to their environment (e.g., Lionetti et al., 2021)

Table 2

Summary of Hypotheses & Factors to Be Examined - Intensity

Factor	**Predicted impact on sensitivity to VNS**	**Reasoning**
Overarching prediction	Hypothesis 2: Individuals with traits that are associated with lower pain tolerance or higher general sensitivity will receive VNS at a lower intensity level in the study at hand.	VNS intensity is adjusted based on one's sensitivity and tolerance. We expect that their personalized VNS intensity can be predicted by trait pain tolerance and general sensitivity.
Sex	Women will receive VNS at a lower intensity than men.	Compared to men, women have lower pain thresholds (Osborne & Davis, 2022)
Childhood SES	Individuals with a greater number of markers of early life stress will	Those from high-adversity backgrounds had greater sensitization

Childhood unpredictability Childhood ACEs	receive VNS at a lower intensity, relative to those with fewer markers of early life stress.	to pain than those from low-adversity backgrounds (You & Meagher, 2016).
Body awareness	Individuals with higher body awareness will receive VNS at a higher intensity in the study at hand than those with lower body awareness.	Body awareness was positively associated with pain tolerance in an experimental study (Colgan et al., 2021).
Pre-term birth	Those who were born prematurely will receive VNS at a lower intensity than those who were not born prematurely.	Research suggests adults who were born prematurely have lower pain tolerance than those who were not born prematurely (Vederhus et al., 2012).

Current Project

In the project at hand, participants will undergo a survey procedure and taVNS procedures with periods of rest, baseline, stimulation, and recovery. We will do a confirmation analysis to confirm a significant difference in HRV at baseline, stimulation, and recovery time points. Further, we will examine the impact of sex, body awareness, preterm birth, childhood socioeconomic status, childhood unpredictability, and childhood adverse experiences on (a) baseline vagal tone, (b) intensity of VNS utilized in the experiment, (c) responsiveness to VNS while controlling for intensity, and (d) responsiveness to VNS while controlling for intensity and baseline vagal tone. These outcomes have large implications for VNS therapeutic efficacy, for instance, if results indicate that women do not demonstrate as much responsiveness to VNS as men, this will inform future intervention strategies.

Methods

Participants

Participants were recruited from TCU's sona pool ($N = 87$). Upon their lab session, participants completed a consent form, took a survey, and participated in the taVNS procedures. A between-subject study design was utilized, and individuals participated in the study only once. The study at hand consisted of male and female participants, but female participants were only scheduled on certain days. To account for fluctuation in vagal activity across the menstrual cycle, female participants were scheduled to participate between days 4 to 8 of their ovulatory cycle, during their early follicular phase (Schmalenberger et al., 2019). Individuals were not able to participate if they (a) have a heart condition of any kind, (b) have a tragus piercing, (c) have an implanted device, such as a pacemaker (Thakkar et al., 2023), (d) are on any type of hormonal birth control or any type of IUD in the last 3 months, (e) are pregnant or breastfeeding.

Upon the end of data collection, $N = 87$ participant had been collected. However, $N = 9$ individuals were excluded. Individuals were filtered out if they failed either of the attention checks. The attention check questions included, "In general, did you pay attention when responding to each item in this survey?" and "We were interested in analyzing your responses for research purposes. Would you recommend we use your data?" ($n = 2$). Further, individuals were screened out if they reported taking allergy medication or anti-inflammatory medication like Advil within the 24 hours prior to study participation ($n = 6$). Further, one participant was screened out because the research assistant noted that this individual attended the research session despite obviously being sick with a cold, which could influence study results ($n = 1$) given the vagus nerve is involved in the immune response. We initiated data analysis with $N = 78$ participants.

Of these N = 78 participants, n = 32, or 41% of the sample, were male, and n = 46, or 59% of the sample, were female. Further, participant age ranged from 18 to 31, with the majority of participants (90% of the sample) spanning ages 18 to 21. Further, n = 53 participants reported being White/European American, or 68% of the sample, n = 4 participants reported being Black / African American, or 5% of the sample, n = 17 participants reported being Hispanic/Latino(a), or 22% of the sample, n = 2 participants reported being Native American, or 3% of the sample, n = 2 participants reported being Middle Eastern / Arab American, or 3% of the sample, and n = 9 participants reported being Asian/Pacific Islander, or 12% of the sample. Further, n = 63 individuals reported English as their native language, or 81% of the sample, while n = 15 individuals reported that English was not their native language, or 19% of the sample.

Procedure

Participants were required to avoid the following behaviors 5 hours before participation to prevent any influence on their autonomic nervous system: exercise, smoking, or taking any drugs such as alcohol or caffeine (Geng et al., 2022). They will also be encouraged to avoid medication 24 hours prior to participation, with the exception of necessary and/or prescription medication. Following consent, but prior to the experimental procedure, participants reported their current stress and mood levels. The research session began with a survey, where participants were asked about birth control use (current and past), cycle phase, and childhood environment, including socioeconomic status, unpredictability, and adverse experiences. Further, participants were asked to report any medications or chronic conditions (Geng et al., 2022; Shaffer & Ginsberg, 2017). Several control variables were tested for including state stress level, change in stress and mood levels before and after

the procedure, and BMI. The research session ended with the taVNS procedure, a second assessment of stress and mood, and a debrief.

Measures

Childhood Measures

Subjective childhood SES will be measured by asking participants to respond to three statements and indicate the degree to which they agree or disagree (1 = *Strongly Disagree*, 7 = *Strongly agree*). The three statements are, "I grew up in a relatively wealthy neighborhood.", "My family usually had enough money for things when I was growing up.", and "I felt relatively wealthy compared to other kids at my school." Childhood Unpredictability will be measured by asking participants to respond to three statements and indicate the degree to which they agree or disagree (1 = *Strongly Disagree*, 7 = *Strongly agree*). The three statements are, "Things were often chaotic in my house.", "People often moved in and out of my house on a pretty random basis.", and "I had a hard time knowing what my parent(s) or other people in my house were going to say or do from day-to-day.' Adverse Childhood Experiences will be measured with the original ACEs that assesses childhood experiences before age eighteen scale (Felitti et al., 1998).

Body Awareness

The Body Awareness Questionnaire (BAQ) will be used to measure participant's attunement to their internal state (Shields et al., 1989). This scale has 18 items, including items such as "I notice differences in the way my body reacts to various foods.", "I know in advance when I'm getting the flu.", "There seems to be a "best" time for me to go to sleep at night." Participants will respond on a 7-point scale and indicate the degree to which the statements are like them (1= *Not at all true of me*, to 7= *Very true of me*).

Stress and Mood Scale

The Stress and Mood Scale will measure participants state stress and mood levels with single-item questions before and after the experiment. The stress question asks, "How stressed are you right now?" Participants will respond on a 7-point scale and indicate their current stress levels (1 = *Not at all stressed,* 7 = *Extremely stressed*). The mood question asks, "What is your current mood?" Participants respond on a 7-point scale, indicating how positive or negative their current mood is (1 = *Extremely bad/negative*, 7 = *Extremely positive*).

taVNS Device, Settings, and Procedures

Following survey participation, all participants will receive taVNS from the Parasym device which delivers stimulation via a one-quarter inch diameter gold-plated copper electrode. It will be utilized to stimulate the auricular branch of the vagus nerve and thus positioned at the posterior tragus of the left ear. Intensity level (mA) will be customized based on the participant's threshold sensitivity and tolerance. All other parameters will be standardized; participants will receive square, biphasic pulses with a 200 μs pulse width, and 25 Hz frequency. The frequency was set to 25Hz due to its clinical relevance (Musselman et al. 2019; Thompson et al. 2021).

Prior to the taVNS procedure, participants will put on a Polar H10 heart rate monitor. The monitor is located on an adjustable strap and is placed on the sternum, where the ribs meet. This allows heart rate data to be collected during the experiment. Next, participants will clean their inner left ear with an alcohol wipe, on and around where the device will be placed on their tragus. Once the device is set up and the participant is ready, we will collect four measures as part of the thresholding procedure. A graduate student will manually

increase the current. The participant will be instructed to let us know when they initially feel the current and again when the current begins feeling uncomfortable and distracting, but not painful. Both of these values will be recorded. Next, the researcher will decrease the current and ask the participant to let them know when they will no longer feel the sensation. Again, this value will be recorded. Next, the graduate student will increase the current again and mark down when it becomes uncomfortable and distracting but not painful and again record this value. Researchers will average the four measurements and round down to the nearest whole number in order to arrive at the stimulation intensity that will be utilized in the experiment.

The stimulation will be broken up into periods of stimulation and periods of rest. Upon entering the lab, participants will rest for 10 minutes, have their baseline HRV recorded for 5 minutes, receive 5 minutes stimulation, and have 10 minutes of recovery time (Geng et al., 2022). During the 30 minutes of the taVNS experiment, participants are instructed to watch a nature video of fish swimming without sound. They are instructed to remain awake, to use this time as a designating "chill time" or relaxation period for the day, and to avoid talking, utilizing devices, or thinking about anything that may be stressing them out. During the procedure, the researcher sits next to them with the parasym device hidden behind a binder.

Kubios software will allow us to store and analyze HRV data. HRV, a measure of the variation over time of the space between consecutive heartbeats, is a tool utilized to evaluate autonomic nervous system balance (ANS) (reviewed in Breit et al., 2018; Geng et al., 2022). VNS responsiveness will be measured with HRV. HRV reflects the sympathetic-parasympathetic activation ratio (Yugar et al., 2023). At rest, vagal activity is dominant over

sympathetic activity. During arousal, such as stress or exercise, sympathetic nervous system activity increases and this ratio decreases (Yugar et al., 2023). Alternatively, during VNS, the parasympathetic nervous system is activated (Machetanz et al., 2021). In the present study, Kubios software will be utilized to measure HRV.

We are utilizing Kubios software because it calculates the root mean square of successive differences between normal heartbeats (RMSSD), which is the primary time-domain HRV parameter utilized to estimate changes in HRV that are vagally mediated (reviewed in Shaffer & Ginsberg, 2017). Researchers have documented that RMSSD was significantly higher in a taVNS group relative to controls (Geng et al., 2022). A higher RMSSD indicates greater parasympathetic nervous system activity and vagal activity, and is associated with better emotional regulation (Sakaki et al., 2016). Kubios software also calculates LF/HF ratio, which is a frequency-domain HRV parameter that has been thought to represent the ratio of parasympathetic to sympathetic activity. We will utilize this metric to contextualize our work with respect to previous research (e.g., Geng et al., 2022). However, this method has faced some criticism (Billman et al., 2013) and thus any analyses with this metric will be secondary. A lower LF/HF ratio indicates greater parasympathetic nervous system activity and greater vagal activity (Shaffer & Ginsberg, 2017).

Data analysis and Expected Results

To understand the relationship between our person-based variables and our VNS outcomes, we will perform several t-tests to determine whether participant sex, or preterm-birth has a significant impact on (a) vagal tone i.e., baseline HRV, (b) VNS intensity, (c) VNS responsiveness, while controlling for intensity, and (d) VNS responsiveness, while controlling for intensity and baseline vagal tone. Additionally, we will perform correlations to

capture the associations between the person-based variables of childhood SES, childhood unpredictability, ACEs, and body awareness with (a) vagal tone i.e., baseline HRV, (b) VNS intensity, (c) VNS responsiveness, while controlling for intensity, and (d) VNS responsiveness, while controlling for intensity and baseline vagal tone

Further, we will examine the association between various VNS outcomes. First, we will examine whether VNS intensity is correlated with responsiveness. Second, we will examine whether baseline HRV is correlated with responsiveness. Finally, we will utilize a one-way repeated measures ANOVAs to determine if there is a significant difference in HRV at baseline, stimulation, and recovery timepoints among our participants.

Finally, exploratory analyses will be conducted. We will conduct two moderated regressions to examine whether participant sex and preterm birth, respectively, moderate the relationship between each of the continuous factors (childhood SES, childhood unpredictability, ACES, body awareness) and our VNS outcomes, (a) vagal tone i.e., baseline HRV, (b) VNS intensity, (c) VNS responsiveness, while controlling for intensity, and (d) VNS responsiveness, while controlling for intensity and baseline vagal tone. Next, we expect that one's sensitivity to VNS correlates with their state pain tolerance. We will run a correlation to confirm or deny this.

In order to understand how many participants we would need to conduct our correlations and t-tests of interest, a priori power analyses were calculated for this experiment using G*Power 3 (Faul et al., 2007). Previously, researchers have found that one's baseline HRV predicts degree of HRV increase due to VNS with a large effect, $R^2 = 0.459$, or Pearson's $r = 0.677$ (Geng et al., 2022). I aimed to be more conservative than this because the effect of person-based factors on VNS sensitivity has not been studied extensively. With

a small-medium effect size, $r = 0.2$, I would need to collect $N = 193$ participants in order to conduct our correlations of interest. With a small-medium effect size, $d = 0.35$, I would need $N = 260$ participants in order to conduct our t-tests of interest (i.e., sex, preterm birth). Thus, I aimed to recruit at least 260 participants. However, in the present write up, results are preliminary and participant sample is limited. Due to time limitations, only $N = 87$ participants were collected.

Results

First, VNS outcome variables were cleaned and computed. The VNS outcomes include VNS intensity, or the intensity at which VNS stimulation was applied, baseline HRV, and change in HRV from baseline to stimulation. In the current study we measured HRV with both RMSSD and LF/HF ratio. Thus, baseline HRV and change in HRV were represented by two variables each.

HRV change scores were computed in order to examine whether an increase in vagal/parasympathetic activity had occurred between the baseline and stimulation period. The LF/HF ratio or RMSSD value from the baseline timepoint was subtracted from the LF/HF ratio or RMSSD value from the VNS timepoint (i.e., change in HRV = VNS HRV value – baseline HRV value). Given that a higher RMSSD and a lower LF/HF ratio value indicates higher parasympathetic activity and higher vagal activation, the change scores have meaning in opposite directions (Shaffer & Ginsberg, 2017). Specifically, for RMSSD values, a more positive / higher change score is associated with an increase in vagal activity from baseline to stimulation. Alternatively, for LF/HF ratio values, a more negative / lower change score is associated with an increase in vagal activity. The results discussed in the study at hand were interpreted with this in mind.

Next, data cleaning involved testing for outliers and checking for normality. As per the Open Science Framework preregistration (https://osf.io/2cxrp), values for each of our outcome variables that were three standard deviations above or below the mean were removed. Even after removing outliers, baseline HRV was positively skewed, both for RMSSD and LF/HF ratio variables. Each of these baseline variables was then square root transformed. VNS intensity and change in HRV had a normal distribution and were therefore not square root transformed.

Next, a series of manipulation checks were conducted. One-way repeated measure analysis of variances (ANOVAs) were performed to compare HRV between baseline, VNS, and recovery. Specifically, we aimed to confirm that there was a significant difference in HRV between the three timepoints. According to existing work, RMSSD should increase during the VNS timepoint and be lower during the baseline and recovery timepoints (Shaffer & Ginsberg, 2017). Alternatively, LF/HF ratio would be expected to be lower during the VNS timepoint than during the baseline and recovery timepoints (Shaffer & Ginsberg, 2017). For this analysis only, untransformed baseline HRV values were utilized in order to maintain scale consistency between the variables. Two one-way repeated measures ANOVAs were conducted, one for RMSSD HRV variables, and one for LF/HF ratio HRV variables.

The first one-way repeated measures ANOVA, utilizing LF/HF ratio, revealed a within-subjects effect of timepoint, $F(1,59) = 5.60$, $p = .021$. A Bonferroni correction was utilized to provide a more detailed look at pairwise comparisons. No significant differences were found in HRV between the baseline period ($M = 2.16$, $SE = .24$) and the VNS period ($M = 2.19$, SE = .24), $p = 1.000$. However, there was a marginally significant difference between the baseline period and the recovery period, $p = .064$, such that baseline LF/HF ratio ($M =$

2.16, *SE* = .24) was lower than recovery LF/HF ratio (*M* = 2.79, *SE* = .33). Additionally, there was a significant difference between the VNS period and the recovery period, $p = .008$, such that the LF/HF ratio during the VNS period (*M* = 2.19, *SE* = .24) was lower than during the recovery period (*M* = 2.79, *SE* = .33). This suggests that at least when compared to recovery, the VNS manipulation successfully activated the parasympathetic nervous system. However, when the ANOVA was repeated for RMSSD, no significant within-subject difference was found between timepoints, *p*s > .743.

Next, we tested for correlations between our outcome variables of interest. Possible associations between VNS intensity, baseline HRV, and change in HRV from baseline to stimulation were examined. No significant correlation between VNS intensity and baseline HRV was found, neither for RMSSD, $r = .003$, $p = .979$, nor LF/HF ratio, $r = -.001$, $p = .993$. Similarly, there was no significant correlation between VNS intensity and change in HRV via RMSSD, $r = .097$, $p = .452$, or LF/HF ratio, $r = -.163$, $p = .204$. However, a significant negative association between baseline HRV and change in HRV was found when utilizing LF/HF ratio data, $p < .001$, $r = -.422$. Such that a lower baseline LF/HF ratio was associated with a more positive value for change in LF/HF ratio. This suggests that individuals with a lower baseline LF/HF ratio, or a more dominant parasympathetic nervous system at baseline (Shaffer & Ginsberg, 2017), demonstrated less responsiveness to VNS. Put another way, individuals with a higher baseline LF/HF ratio, or lower parasympathetic nervous system activity, were more responsive to VNS. The same significant result was not found for RMSSD data, $r = -.080$, $p = .515$.

Following, we examined the impact of participant sex (male v. female) on our VNS outcomes, starting with VNS intensity. No significant difference was found between males

and females with respect to VNS intensity, $F(1,67) = 2.30$, $p = .134$, $\eta^2_p = .033$. A marginally significant difference between male and female participants on baseline HRV, measured via LF/HF ratio, was found, $F(1, 69) = 3.17$, $p = .080$, $\eta^2_p = .044$. Such that males ($M = 1.49$, $SD = .63$) had a greater LF/HF ratio than females ($M = 1.25$, $SD = .54$), indicating greater sympathetic nervous system activity at baseline. However, this did not hold true for RMSSD, $F(1, 69) = 1.15$, $p = .288$, $\eta^2_p = .016$.

Further, possible sex differences in change in HRV from baseline to stimulation were examined. No significant difference was found between males and females on change in HRV when utilizing change in LF/HF ratio from baseline to stimulation, $F(1,67) = .86$, $p = .356$, $\eta^2_p = .013$. This held true even when controlling for VNS intensity, $F(1,59) = .844$, $p = .362$, $\eta^2_p = .014$, and when controlling for both VNS intensity and baseline HRV, $F(1,58) = 2.24$, $p = .140$, $\eta^2_p = .037$. Similarly, no significant effect of participant sex on change in HRV via RMSSD was detected, $F(1,68) = 1.509$, $p = .224$, $\eta^2_p = .022$. This held true even when controlling for VNS intensity, $F(1,59) = 3.09$, $p = .084$, $\eta^2_p = .050$, and when controlling both for VNS intensity and baseline HRV, $F(1,57) = 3.66$, $p = .061$, $\eta^2_p = .060$. Although nonsignificant, the final iteration of this analysis was marginal, $p = .061$. Specifically, trending results suggest that males ($M = 2.41$, $SD = 8.63$) had a more positive change in RMSSD than females ($M = -.894$, $SD = 7.05$), which would suggest that males were more responsive to the VNS stimulation than females.

Next, we planned to examine differences in whether or not someone was born prematurely influenced their VNS outcomes. However, due to unequal sample size, we were unable to compare those with and without preterm birth on these outcomes (Preterm birth, $N = 6$; No preterm birth, $N = 57$).

Further, we examined correlations between our person-based variables of interest (i.e., childhood SES, childhood unpredictability, ACES, and body awareness) and our VNS outcomes. There was no significant correlation between childhood SES, childhood unpredictability, ACES, or body awareness, and VNS intensity *p*s > .181. Similarly, we did not find that childhood SES, childhood unpredictability, ACES, or body awareness were associated with baseline HRV either via RMSSD or LFHF ratio, *p*s > .154. Finally, we did not find that childhood SES, childhood unpredictability, ACES, or body awareness were associated with change in HRV either via RMSSD or LFHF ratio, *p*s > . 129. The same held true when controlling for intensity, *p*s > .087. Similarly, when controlling for intensity *and* baseline HRV, there were no significant associations between body awareness or childhood SES with change in HRV, *p*s > .141. However, we did find that childhood unpredictability, $r = -.336$, $p = .034$, and ACES score, $r = -.304$, $p = .056$, were negatively associated with change in HRV (via LF/HF ratio, but not RMSSD, *p*s > .239), such that a greater score on the unpredictability and ACES measures, respectively, were associated with more negative / lower change scores for LF/HF measures. This suggests that these individuals had a greater VNS responsiveness, or greater increase in vagal activity due to the stimulation.

Covariate analyses and Spotlight Analyses

Covariate Analyses

Next, several covariates were considered. Possible covariates included participant age (reviewed in Shaffer & Ginsberg, 2017), state stress level, change in stress and mood levels before and after the procedure, and BMI. These variables were tested for their possible associations with our outcome variables of interest. If significant, covariates were included in corresponding follow up analyses.

To prepare for the covariate analyses, state stress and mood levels, which were examined before and after the procedure, were examined. There were no significant differences in mood before and after the experiment, $F(1,59) = 3.58$, $p = .064$, $\eta^2_p = .057$. Due to its lack of significant, change in mood was not included as a possible covariate. However, there was a significant difference in stress before and after the experiment, $F(1,59) = 4.08$, $p = .048$, $\eta^2_p = .065$, such that stress was lower after the experiment ($M = 2.42$, $SE = .18$) than before ($M = 2.73$, $SD = .19$). A change score for change in stress was computed and included as a possible covariate to test for.

In order to determine whether they should be included as covariates, BMI, age, trait stress level, and change in stress due to the experiment were tested for their association with VNS outcomes. Results revealed a negative correlation between BMI and VNS intensity, $r = -.259$, $p = .031$. None of the other variables of interest were correlated with the VNS outcomes, ps > .206, and thus they were not included as covariates in follow-up analyses. Accordingly, analyses with VNS intensity as the outcome variable were rerun with BMI as a covariate. Results did not deviate from those previously reported. Specifically, controlling for BMI did not change that there was no difference in VNS intensity based on sex, $F(1,66) = 1.16$, $p = .285$, $\eta^2_p = .017$. Similarly, none of our person-based factors were found to be associated with VNS intensity while controlling for BMI, ps > .091.

Spotlight Analyses

Due to previous research suggesting that chronic conditions such as autoimmune or neurological conditions, and medications containing neurotransmitters such as acetylcholine or norepinephrine may interfere with VNS data, we conducted a reiteration of analyses excluding these individuals. In particular, we excluded individuals who reported either (a)

taking prescription medications in the 24 hours prior to participation or (b) chronic conditions. These analyses were a reiteration of the analyses geared towards examining the relationship(s) between person-based factors and VNS outcomes, with a larger number of participants were filtered out.

Overall, results were aligned with previous analyses. To start, associations between our VNS outcomes of interest were conducted. No significant correlation was found between VNS intensity and baseline HRV, including both RMSSD and LF/HF ratio, *p*s > .945. Similarly, no significant correlation was found between VNS intensity and change in HRV from baseline to stimulation, including both RMSSD and LF/HF ratio, *p*s > .256. Further, no significant correlation was found between baseline HRV (RMSSD) and change in HRV from baseline to stimulation (RMSSD), $p = .732$, $r = .051$. However, a significant correlation was found between baseline HRV (LF/HF ratio) and change in HRV from baseline to stimulation (LF/HF ratio), $p < .001$, $r = -.532$, such that lower baseline LF/HF ratio is associated with a more positive value for change in LF/HF ratio. This suggests that those with greater baseline parasympathetic nervous system activity were less responsive to VNS. These results are consistent with the original analysis.

Next, we examined the impact of participant sex (male v. female) on our VNS outcomes. Overall, results remained consistent. No significant difference was found between males and females in VNS intensity, $F(1,46) = .30$, $p = .589$, $\eta^2_p = .006$. Similarly, no significant difference was found between males and females in baseline HRV, measured via RMSSD, $F(1,48) = 2.05$, $p = .159$, $\eta^2_p = .041$. However, a marginally significant difference was found between males and females in baseline HRV, measured via LF/HF ratio, $F(1,47) = 3.52$, $p = .067$, $\eta^2_p = .070$. Results were trending in such a way that suggest that males (*M* =

1.41, *SD* = .61) have higher LF/HF ratio at baseline than females (*M* = 1.15, *SD* = .37), suggesting greater sympathetic nervous system activation at baseline in males. These results are consistent with what was previously reported.

Following, spotlight analyses examining the impact of participant sex on change in HRV were conducted. There was no significant difference between males and females in change in HRV from baseline to stimulation, measured via RMSSD, $F(1,46) = 1.05$, $p = .311$, $\eta^2_p = .022$. This held true when controlling for VNS intensity, $F(1,39) = 1.33$, $p = .257$, $\eta^2_p = .033$, and when controlling for VNS intensity and baseline HRV, $F(1,38) = 1.16$, $p = .289$, $\eta^2_p = .030$. Although the original analysis showed a marginally significant difference at the final iteration of this analysis (impact of sex on change in RMSSD when controlling for both VNS intensity and baseline HRV), this is no longer the case in this spotlight analysis. Further, as is consistent with results discussed previously, there was no significant difference between males and females in change in HRV from baseline to stimulation, measured via LF/HF ratio, $F(1,45) = .22$, $p = .640$, $\eta^2_p = .005$. This held true when controlling for VNS intensity, $F(1,39) = .07$, $p = .792$, $\eta^2_p = .002$, and when controlling for VNS intensity and baseline HRV, $F(1,38) = .19$, $p = .669$, $\eta^2_p = .005$.

Next, spotlight analyses examining the relationship between our continuous person-based factors and our VNS outcomes were conducted. As is consistent with our previously discussed results, there was no significant correlation between ACES, childhood unpredictability, childhood SES, body awareness, or hypochondriasis, and VNS intensity, *p*s > .321. Similarly, there was no significant correlation between childhood unpredictability, childhood SES, ACES, body awareness, or hypochondriasis, and baseline HRV (RMSSD and LF/HF ratio), *p*s > .255. Again, this is consistent with previous analyses.

We then examined the relationship between our continuous person-based variables and change in HRV from baseline to stimulation. Consistent with previous analyses, childhood SES, body awareness, and hypochondriasis were not associated with change in HRV, *p*s> .288. However, inconsistent with previous analyses, there was a significant negative correlation between change in LF/HF ratio and ACES, r = -.387, p = .008, and between change in LF/HF ratio and childhood unpredictability, r = -.318, p = .030 (the same was not true for these variables and RMSSD, *p*s > .348). This effect was not present in the main analysis, and it suggests that in this pristine sample, individuals with higher ACES and childhood unpredictability have greater VNS responsiveness, or greater vagal activation due to VNS.

Additionally, when controlling for VNS intensity, none of the person-based variables of interest were found to be significantly associated with change in HRV, *ps* > .150. An exception being that ACES was marginally significantly associated with change in LF/HF ratio, p = .060, r = -.373. This was not present in the wider analysis.

Finally, when controlling for VNS intensity and baseline HRV, all variables remained non-significantly correlated with change in HRV measured via RMSSD, *p*s > .280. This is consistent with previous analyses. However, when controlling for both VNS intensity and baseline HRV, ACES, p = .021, r = -.451, childhood unpredictability, p = .042, r = -.402, and childhood SES, p = .055, r = .381, were all significantly correlated with change in HRV from baseline to stimulation, measured via LF/HF ratio, such that lower SES, higher unpredictability, and higher ACES, were associated with lower/more negative LF/HF ratio values. This suggests that higher ACES, higher childhood unpredictability, and lower SES were associated with greater change in vagal activation due to stimulation, i.e., greater VNS

responsiveness. The same was not true for body awareness or hypochondriasis, *p*s > .475. This is largely consistent with previous analyses. However, in the original analysis, childhood SES was not significant.

Overall, nothing that had previously been found to be significant was found to be nonsignificant in this narrower sample. However, a few additional effects were found.

Exploratory analyses

Exploratory analyses included (a) examining whether there was a relationship between VNS intensity and pain tolerance, and (b) conducting moderated regressions to see if participant sex moderated any of the detected effects.

First, participant trait pain tolerance (reported measure, subjective) was examined. Trait pain tolerance was not found to be correlated with VNS intensity, *ps* > .119 in either the original sample, $p = .425$, or the spotlight sample, $p = .119$. Thus, either participants are not accurate at estimating their own pain tolerance, and/or VNS intensity is not a metric of pain tolerance as much as it is a metric of something else, perhaps general sensitivity to stimulation.

Next, moderated regression analyses were run to see if sex moderated the observed relationship between (a) baseline HRV (LF/HF ratio) and change in HRV from baseline to stimulation (LF/HF ratio) and (b) SES, childhood unpredictability, and ACES with change in HRV measured via LF/HF ratio. Note, regression analyses were only run on specific analyses, those for which we had found a significant relationship between X and Y. This is because an assumption of regression is that linearity has been detected between X and Y (Casson & Farmer, 2014). The PROCESS MACRO was utilized to conduct these analyses.

In order to be meaningful in the regression, participant sex was dummy coded, 0 = male, 1 = female. Analyses were run first with the original filter and then with the spotlight filter.

A moderated regression was run to determine whether participant sex moderates the relationship between baseline HRV, measured via LF/HF ratio, and change in LF/HF ratio from baseline to stimulation. The continuous predictor baseline HRV was not centered, given that it has a meaningful zero. The model was significant, $r = .54$, $r^2 = .29$, $F(3,65) = 8.75$, $p < .0001$. Although the main effects of baseline HRV and participant sex were nonsignificant, *p*s > .110, a significant interaction was detected, $b = -1.38$, $SE = .54$, $t = -2.56$, $p = .013$, R^2 change = .072. Follow up analyses revealed, that for males, the relationship between baseline HRV and change in HRV (all measured via LF/HF ratio), is nonsignificant, $b = -.41$, $SE = .40$, $t = -1.03$, $p = .306$. For females, the effect is significant such that higher baseline LF/HF ratio is associated with more negative change in LF/HF ratio, $b = -1.79$, $SE = .36$, $t = -4.90$, $p < .001$. This suggests that female participants are driving the main effect detected. In particular, for female participants, higher LF/HF ratio at baseline, indicating dominant sympathetic activity, is associated with greater VNS responsiveness. Alternatively, female participants who had a lower LF/HF ratio at baseline, indicating dominant parasympathetic activity, demonstrated less responsiveness to VNS.

Next, the same moderation analysis was repeated while excluding participants who had any kind of chronic conditions or had taken any prescription medication in the last 24 hours. This is our spotlight analysis, a follow up on a more pristine sample of participants. The model was significant, $r = .56$, $r^2 = .31$, $F(3,43) = 6.45$, $p = .001$. However, in this iteration of the analysis, a significant main effect of baseline HRV (LF/HF ratio) was

detected, b = -1.18, SE = .42, t = -2.82, p = .007, such that lower LF/HF ratio at baseline was associated with more positive HRV change values, indicating less VNS responsiveness. There was no significant main effect of participant sex, b = .92, SE = .96, t = .96, p = .343. Further, there was no significant interaction between sex and baseline HRV, b = -.91, SE = .75, t = -1.21, p = .233, R^2 *change* = .024.

Next, a moderated regression was conducted to determine whether there was a significant interaction between participant sex and childhood SES on change in HRV (LF/HF ratio). Given that childhood SES is a continuous predictor without a meaningful zero, it was centered prior to analyses. The model was not significant, r = .20, r^2= .04, F(3,65) = .88, p = .457. Further, no main effects were significant, ps > .242, neither was the interaction, b = .33, SE = .26, t = 1.28, p = .204, R^2 *change* = .024.

Interestingly, when participants who had taken medications in the last 24 hours and/or who had any kind of chronic conditions were excluded, the model became significant, R = .423, r^2= .18, F(3,43) = 3.12, p = .036. There was no significant main effect of childhood SES, b = -.22, SE = .17, t = -1.32, p = .192. There was also no significant main effect of participant sex, b = .23, SE = .35, t = .65, p = .517, but a significant interaction between participant sex and childhood SES emerged, b = .76, SE = .26, t = 2.93, p = .005, R^2 *change* = .164. Follow up analyses revealed that the association between childhood SES and change in HRV (LF/HF ratio) was not significant for males, b = -.22, SE = .17, t = -1.32, p = .192. However, it was significant for females, b = .54, SE = .20, t = 2.71, p < .01, suggesting that females are driving the effect. This suggests that for female participants, higher childhood SES is associated with more positive LF/HF ratio change values, indicating less VNS responsiveness in these individuals. Put another way, for female participants, lower

childhood SES is associated with more negative LF/HF ratio change values, indicating more VNS responsiveness in these individuals.

Next, a moderated regression was conducted to examine whether sex moderated the relationship between childhood unpredictability and change in HRV from baseline to stimulation (LF/HF ratio). Given that childhood unpredictability is a continuous predictor without a meaningful zero, it was centered prior to analyses. The model was nonsignificant, r = .28, r^2 = .08, F(3, 65) = 1.82, p = .152. A significant main effect for childhood unpredictability was found, b = -.45, SE = .21, t = -2.13, p = .037. However, no significant effect of sex was found, b = -.35, SE = .35, t = -.99, p = .325. Further, no main effect of the interaction was detected, b = .43, SE = .28, t = 1.53, p = .130, R^2 *change* = .033.

This moderation was repeated again, excluding participants who had taken a prescription medication in the last 24 hours and participants who reported a chronic condition. The model was not significant, r = .32, r^2 = .10, F(3,43) = 1.63, p = .196. No significant main effects were detected, ps> .086. Similarly, the interaction was not significant, b = .04, SE = .31, t = .139, p = .890, R^2 *change* = .0004.

Next, a moderated regression was conducted in order to examine the impact of participant sex on the relationship between ACES and change in HRV from baseline to stimulation (LF/HF ratio). The continuous predictor ACES was not centered prior to analyses because it has a meaningful zero. The model was not significant, R = .27, R^2 = .07, F(3,64) = 1.61, p =.195. A significant main effect of ACES was detected, b = -.33, SE = .17, t = -1.94, p = .056, such that higher ACES is associated with more negative change in LF/HF ratio, or more VNS responsiveness. No significant main effect of sex was detected, b = -.55, SE = .41,

t = -1.34, p = .184. Similarly, no interaction was detected, b = .28, SE = .20, t = 1.38, p = .173, R^2 *change* = .03.

This moderation was repeated again, this time excluding all participants who reported a chronic condition and/or reported taking medication in the last 24 hours. This time, the model was significant, r = .41, r^2 = .17, $F(3,42)$ = 2.87, p = .047. Similar to the previous iteration, a significant main effect of ACES was found in the same direction, b = -.32, SE = .15, t = -2.12, p = .040. However, there was no significant effect of sex, b = .23, SE = .42, t = .55, p = .588. Further, no interaction was detected, b = .091, SE = .19, t = .47, p = .642, R^2 *change* = .004.

Discussion

Overall, we found mixed support for our hypotheses. We found no evidence to support the hypothesis that person-based factors would predict differences in VNS intensity. Further, we found no evidence to support the hypothesis that person-based variables influence baseline HRV. However, our results support our VNS responsiveness hypotheses. In particular, we found evidence that replicates what Geng et al., 2022 found, that those with lower vagal tone (i.e., a more activated sympathetic nervous system), were the most responsive to VNS stimulation. In the study at hand, these individuals had the greatest increase in vagal activation as a result of VNS stimulation (measured via change in HRV). Additionally, we found that traits typically associated with elevated sympathetic nervous system activity, including low SES, high childhood unpredictability, and high ACES score, were associated with greater VNS responsiveness. To our knowledge, we are the first to demonstrate such findings. Furthermore, we demonstrated that several of these findings, in particular the association between baseline LF/HF ratio and change in LF/HF ratio, and the

association between childhood SES and change in LF/HF ratio, were driven by female participants. These findings could have beneficial effects on both the scientific literature and clinical practice of Vagus Nerve Stimulation.

Future Research

Our finding that traits typically associated with low vagal tone, such as childhood unpredictability, are in fact associated with greater VNS responsiveness is something that both clinical and experimental researchers alike should be aware of. Our findings suggest that those who could benefit the most from VNS therapy, may be the most responsive to it. Future research should aim to replicate and extend this effect. In particular, researchers should extend these results to the realms of treatment and prevention.

First, future researchers should examine whether this translates into treatment efficacy. Specifically, it is possible that for any number of chronic conditions, VNS is more likely to be successful in individuals from early life stress backgrounds, than in individuals who do not have this same background. Alternatively, it is possible that for individuals from backgrounds of early life stress, VNS is a more effective therapy than other alternatives, such as medication. Future work is needed to support such predictions.

Further, future research should use these results to inform preventative measures. Given the increased health risk of individuals who come from backgrounds of early life stress, and the increased responsiveness to VNS in this population, researchers should start to explore whether VNS can be employed as a measure to mitigate health risk. For example, we hypothesize that VNS may serve as a powerful tool to reduce inflammation, activate the vagal nerve, and prevent negative health outcomes in individuals with early life stress.

Further, future research should examine why women were driving several of the detected effects. Specifically, female participants drove the effect for both of the following findings, (a) lower childhood SES is associated with greater VNS responsiveness, and (b) lower LF/HF ratio is associated with greater VNS responsiveness. Relative to men, women have been found to have greater parasympathetic nervous system activity, which has been found to be cardioprotective (reviewed in Koenig & Thayer, 2016). However, women are often at increased risk of stress, as well as risk of depression and anxiety when compared to men (Li & Graham, 2017), which can be counterproductive for heart health. Thus, despite their average elevated parasympathetic activity, many women may still benefit from VNS therapy. In particular, researchers should examine how person-based variables such as sex, childhood environment, and baseline vagal tone, interact to predict (a) VNS treatment efficacy and (b) the health benefits that VNS may offer, particularly with regards to preventative medicine (e.g., decreased inflammation). Further, future researchers should consider age, hormonal birth control status, and menstrual cycle phase when studying female participants.

Future Research: Incorporating the Menstrual Cycle and Hormonal Birth Control

In the current study, women participated during the early follicular phase and were naturally cycling, meaning that they were not using hormonal birth control. Future research should extend the current results by examining VNS outcomes in women both on and off hormonal birth control, and in all phases of the menstrual cycle.

Menstrual cycle phase has been found to be associated with ANS activity by researchers who were measuring HRV. In particular, researchers have reported greater sympathetic activity during the luteal phase (Guasti et al., 1999; Yildirir et al., 2001) and

greater vagal activity and HRV in the follicular phase (Sato et al., 1995; Saeki et al., 1997). Further, a 2019 review found a significant decrease from the follicular to the luteal phase in participant cardiac vagal activity (CVA) (Schmalenberger et al., 2019; but see Hamidovic et al., 2023). Cardiac vagal activity is heart rate variability that is mediated by the parasympathetic nervous system, primarily the vagus nerve (Schmalenberger et al., 2019). More specifically, their review found decreases in CVA both from the menstrual to premenstrual and from the mid-to-late follicular to the premenstrual phase (Schmalenberger et al., 2019). This suggests a general decrease in CVA across the menstrual cycle. Thus, future research should focus on examining intensity and responsiveness to VNS across the menstrual cycle.

Further, we expect that women on hormonal birth control (HBC) may have a difference in sensitivity to VNS when compared to naturally cycling women. Hormonal contraception impacts the hormonal milieu that women are exposed to by introducing synthetic hormones and lowering production of endogenous hormones (reviewed in Alvergne & Lummaa, 2010). Research has shown that change in concentration of endogenous sex hormone across the cycle is related to vagal activity (Schmalenberger et al., 2020), suggesting that a change in hormonal milieu may translate to a change in vagal activity. Additionally, researchers have found that women who take HBC have a blunted cortisol response to stress (Nielsen et al., 2013). This indicates that the HPA axis, which is activated by the vagus nerve, is operating differently in these women. Women, especially adolescents, who begin hormonal birth control use also have an increased risk of being diagnosed with depression (Skovlund et al., 2016), which may suggest an increase in inflammatory activity which the vagus nerve, when functioning properly, is involved in attenuating (reviewed in

Breit et al., 2018). Future studies may predict that women on hormonal birth control will have low average vagal activation than naturally cycling women, and thus will be more responsive to vagus nerve stimulation.

Limitations

There were several limitations to the current research. In particular, we found results primarily with the LF/HF ratio variable, and not with the RMSSD variable. This is of note, because as previously mentioned, RMSSD is a more robust measurement of HRV than the LF/HF ratio (Shaffer & Ginsberg, 2017). It could be that we will see significant results emerge with the RMSSD variable once we have more participants. As previously mentioned, the current dataset is preliminary. Further, it is worth noting that although LF/HF ratio and RMSSD both measure HRV, they capture different elements of it. LF/HF ratio focuses on the balance of the parasympathetic nervous system to the sympathetic nervous system, while RMSSD measures short-term variability in heart rate, or cardiac activity (Wang & Huang et al., 2012).

Further, no significant difference between the baseline and stimulation periods were detected. This was an assumption of the present analysis and although it does not render our detected results incorrect (we did still find significant associations between person-based variables and change in HRV), it is likely that our findings would have been more robust (i.e., detected stronger effects) if there had been a significant difference in participant HRV between each timepoint. Despite the lack of difference between the baseline and stimulation periods, there was a significant difference detected between the VNS period and the recovery period, using LF/HF ratio, such that more parasympathetic activity was detected during the VNS period than the recovery period, which is to be expected. In order to increase the

likelihood of HRV differences between the timepoints, future studies may consider altering the length of the timepoints, and/or stimulating the vagus nerve multiple times in one research session, in order to properly capture the effect.

A final limitation of the study is power. Despite the limited sample size, several significant effects were still detected in the study at hand. Although our participant sample of $N = 78$ is far below that of our target $N = 250$, there is a difference between being underpowered to detect an effect and being underpowered but still detecting an effect. Thus, we hypothesize that with more participants, the detected effects will remain and increase in strength.

Conclusion

In conclusion, we found support for our VNS responsiveness hypotheses. In particular, we found that those with lower vagal tone (higher LF/HF ratio) were more responsive to VNS stimulation. A moderation analysis revealed that this effect was driven by women. Further, we found that lower childhood SES, higher childhood unpredictability, and higher ACES were associated with increased responsiveness to VNS stimulation in the study at hand. For the association between childhood SES and responsiveness, women drove this effect. Future research should aim to replicate and extend this effect. In particular, researchers should examine whether these effects extend to clinical efficacy. Is VNS a more effective therapy for individuals from backgrounds of early life stress than from individuals without this background? Further, these results can also be applied to preventative medicine. Individuals from backgrounds of early life stress may be well suited to receive preventative VNS treatment, such as for high inflammation, before such inflammation progresses to a disease state. Finally, researchers should examine why several of these effects were driven by

women, and continue to examine how participant sex influences VNS responsiveness and efficacy in future research.

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VITA

Savannah Hastings was born on March 4, 2000 in Bellevue, Washington. She graduated from Monroe High School in Monroe, Washington in 2018. In 2022 she earned a Bachelor of Science degree from Western Washington University, with a major in Behavioral Neuroscience and a minor in Chemistry. In 2022, she started graduate school at Texas Christian University under the advisement of Dr. Sarah E. Hill.

ABSTRACT

THE IMPACT OF PERSON-BASED FACTORS ON VAGUS NERVE STIMULATION INTENSITY AND RESPONSIVENESS

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Transcutaneous auricular vagus nerve stimulation (taVNS) is a therapy used to treat conditions like epilepsy and treatment-resistant depression. TaVNS works by stimulating the afferent fibers of the vagus nerve, activating the central nervous system. This study examines person-based factors, such as sex, childhood experiences, and body awareness, that influence one's response to stimulation. Specifically, we will assess (a) sensitivity to taVNS intensity, or the current in milliamps that is applied transcutaneously at the tragus, and (b) responsiveness to stimulation, measured by neurocardiac response, or change in heart rate variability (HRV) from baseline to stimulation, while controlling for intensity. Results revealed greater VNS responsiveness in individuals with lower vagal tone, lower childhood SES, higher childhood unpredictability, and higher ACES score. Several of these effects were driven by female participants. Future research should examine whether this translates to clinical efficacy, and evaluate whether it can be utilized to prevent certain conditions.