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Hitting the right nerve: effects of transcutaneous vagus nerve stimulation on symptoms of anxiety

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Chapter 1

General Introduction

Anxiety disorders constitute the most prevalent class of mental disorders in Western society, affecting close to 30% of the population at some point in their lifetime [1,2]. As such, anxiety does not only place a large burden of disease on individuals and their immediate social environments [3], but also places a large economic burden on society (ie. direct and indirect costs of anxiety disorders in Europe totaled 74 billion euros in 2010 [4]). Cognitive-behavioral therapy (CBT) is the first-line intervention for anxiety disorders, with exposure therapy being its cardinal component. Despite CBT being a 'gold standard' treatment for anxiety disorders, a substantial proportion of patients do not remit after therapy (between 20 and 67%, [5]). Additionally, as exposure therapy relies on the inherently stressful process of testing one's appraisal of what situations are dangerous, dropout is a very commonly occurring problem (up to 50% drop out of treatment, [5,6]). As such, there is a clear need to either improve currently existing treatment protocols, or develop alternative treatments that may tackle these problems.

Meta-analyses have provided mixed evidence for an augmentation of treatment efficacy when CBT is combined with pharmacotherapy [7–9]. Moreover, the interactions, contra-indications, and side-effects of these pharmacological agents should be considered when using medications as add-on therapy. Alternatively, recent technological advances, as well as increased understanding in the neurobiological underpinnings of anxiety, have sparked an interest in findings ways to augment the effects of CBT by using neurostimulation (e.g. through the use of deep brain stimulation or transcranial magnetic stimulation, [10]). One of the most recent developments in the area of neurostimulation is that of transcutaneous vagus nerve stimulation, a non-invasive technique designed to stimulate the auricular branch of the vagus nerve. In this thesis, we aim to assess whether this technique has the potential to ameliorate symptoms of anxiety, either as an add-on treatment for exposure therapy, or as a stand-alone treatment.

The Vagus Nerve

The vagus nerve is the tenth cranial nerve and owes its name - vagus is Latin for 'wandering' - to its length and complexity: travelling from the brain stem to the abdomen and branching out to innervate most visceral organs, the vagus nerve is the largest cranial nerve in the body. Broadly speaking, the vagus nerve sprout from four nuclei in the medulla and form two nerve trunks (left and right) before entering the jugular foramen and passing through the superior and inferior ganglia. In the superior ganglion, the auricular branch of the vagus nerve arises and innervates the external auditory canal and parts of the external ear. After exiting the cranium via the jugular foramen, the main branch of the vagus nerve travels down and branches out to innervate the lungs, heart, spleen, kidneys, liver, stomach, small intestines and colon [11–14]. The distinction between the left and right vagus nerves is of critical importance for the stimulation of the nerve, because of differential innervation of either

nerve with the sinoatrial node of the heart. Specifically, the right vagus nerve is known to innervate the sinoatrial node – the heart's pacemaker – more strongly than the left vagus nerve, which primarily terminates on the atrioventricular node [15]. For this reason, invasive vagus nerve stimulation is preferably applied to the left vagus nerve to avoid severe bradycardia [16,17].

The vagus nerve consists of different fibers that can be broadly categorized into A-, B- and C fibers, ranging from large, myelinated, fast-conducting A fibers to small, unmyelinated and slow-conducting C fibers. The majority of all fibers within the vagus nerve are part of this last category of afferent unmyelinated C-fibers. These fiber types each have a specific physiological role: large A fibers carry somatic afferent or efferent information, small A fibers carry visceral afferent information, B fibers carry efferent sympathetic and parasympathetic information, and small unmyelinated C fibers carry afferent visceral information. Recent studies conducted in anesthetized dogs revealed different activation thresholds for these fiber types; 0.4mA for A-fiber, 3.8mA for B-fiber and 17mA for C-fibers. Given the similarities in fiber thickness between dog and human vagal nerves, the human vagus nerves may follow the same pattern.

Due to the central role of the vagus nerve in the parasympathetic activation of peripheral organs, the vagus nerve is often mistakenly described as a parasympathetic nerve. However, the vagus nerve also has a sympathetic function via the peripheral chemoreceptors, which trigger a vasoconstrictor response and increase blood pressure. Additionally, approximately 80% of the fibers of the vagus nerve are afferent fibers that transfer sensory information from peripheral organs to the brainstem [18,19], a process that is neither parasympathetic nor sympathetic [20].

The Auricular Branch of the Vagus Nerve

The auricular branch of the vagus nerve (ABVN) – the target for most tVNS interventions – appears to be a phylogenic remnant of nerves that supply the lateral line organs in amphibians and fish to sense vibrations and movements in the surrounding water [21,22]. In mammals, the ABVN is an exclusively afferent sensory nerve that innervates part of the skin of the outer ear as well as the ear canal. Research on the anatomical distribution of the auricular branch of the vagus nerve is scarce. In an anatomical study performed on macaques in 1897 [23], Sherrington noted that the ABVN innervates the cavum and cymba conchae and the antitragus, and also part of the tragus and the antihelix. In 1927, a case study was published concerning a patient suffering from severe pain in the ear and throat. In an initial procedure, Fay performed a resection of the trigeminal nerve supplying the area of the tongue and throat. This initial surgical procedure resulted in complete analgesia of the tragus, indicating that although the ABVN may also innervate this part of the ear, it is not the only nerve to provide sensory feedback from this part of the ear. In a subsequent procedure, the ABVN was sectioned, resulting in complete anesthesia in the cymba concha, and to a lesser degree the antihelix

and antitragus [24] (see figure 1). Finally, a study performed on human cadavers showed that the ABVN is the only nerve to stimulate the cymba concha [25]. Additionally, the ABVN may innervate the tragus, antihelix and cavum concha, although the study reports contradictory innervation percentages in the main text and the corresponding table, making it impossible to assess whether and to what extent the ABVN innervates these areas of the outer ear [26].

The afferent fibers of the ABVN terminate in the nucleus of the solitary tract – similarly to the thoracic vagus nerve – as well as the spinal trigeminal nucleus [27,28]. The ABVN seems to be innervated predominantly by the large, myelinated A-fibers [29]. Given that stimulation intensities of VNS and tVNS typically vary between 0.3-3mA, it seems likely that these techniques almost exclusively recruit A-fibers of the vagus nerve, and thus it seems unlikely that tVNS will have efferent cardiac effects.

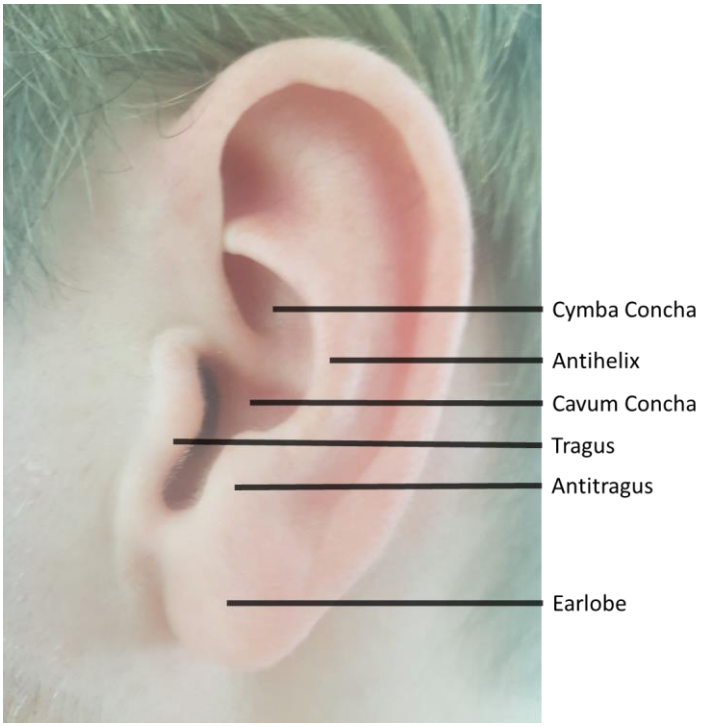

Figure 1. Picture of the author's ear. The ABVN innervates the cymba concha of the ear, and to a lesser degree may also innervate the antihelix, antitragus and tragus.

Stimulating the vagus nerve

Although vagus nerve can be activated through chemical [30,31], mechanical [31], and electric means [32], research on vagus nerve stimulation has mainly focused on the therapeutic effects of electrical stimulation of the vagus nerve. This may have been due to the relative ease of controlling the frequency and the intensity of stimulation through electric means compared to chemical or mechanical means. Additionally, prolonged chemical or mechanical stimulation may lead to fiber damage and

increased fibrotic tissue compared to electric stimulation. As such, electric stimulation provides a relatively safe and controllable means of activating the vagus nerve.

The first reports of electrical vagus nerve stimulation are as early as 1884, and describe a technique of transcutaneous vagus nerve stimulation (tVNS) in the neck as a treatment for seizures [33]. This initial 'electrocompressor' combined compression of both carotid arteries with simultaneous electrical stimulation of the vagus nerve and the cervical sympathetic nerves. This technique was not widely adopted by Corning's contemporaries due to a lack of consistent positive results, and the technique was abandoned for over a century [34]. In 1990, Penry and Dean first described a technique of invasive vagus nerve stimulation (VNS) in humans, again as a treatment for intractable seizures in epilepsy patients [35]. During invasive VNS, the vagus nerve is electrically stimulated by two electrodes that have been surgically implanted and sutured around the vagus nerve at the level of the neck. The electrodes are connected to a battery that is also surgically implanted, and the vagus nerve is typically stimulated with a '30 seconds on, 5 minutes off' duty cycle. Due to the invasiveness of the procedure as well as its costs, VNS is not a commonly used intervention, and not a lot of research has been done on VNS in humans.

Ten years after the development of invasive VNS, the concept of a non-invasive, transcutaneous vagus nerve stimulation (tVNS) method of the ABVN was proposed by Ventureyra [36]. During tVNS, two electrodes are attached to the surface of the outer ear at a location that is believed to be innervated by the ABVN. Typically, tVNS aims to stimulate either the cymba concha or the tragus of the ear, based on the anatomical distribution of the ABVN [25]. Unfortunately, parametric research on tVNS is scarce, and stimulation parameters are mainly based on preclinical and clinical research on invasive VNS (e.g. [37–44]). Specifically, electrical stimulation during tVNS typically consists of an alternating current (usually 250-500μs stimulation wavelength delivered at 25Hz) delivered intermittently (30 seconds on, 30 seconds off). To stimulate the vagus nerve, electrical pulses must penetrate the skin and the nerve's epineurium, and exceed the excitation threshold of fibers in the vagus nerve [29]. The stimulated fibers fire action potentials that propagate through the vagus nerve to the nucleus of the solitary tract in the brain stem, which in turn affects other cortical and subcortical brain structures.

tVNS as an add-on for exposure therapy

The central afferent projections of the vagus nerve suggest that tVNS could play an important role in the treatment of anxiety disorder. Notably, the indirect projections to the locus coeruleus-noradrenaline (LC-NA) network, reflect its integral role in the encoding and consolidation of memory traces. Indeed, during stressful or threatening situations, peripheral adrenaline binds to beta-adrenergic receptors of the vagus nerve, which triggers action potentials in the afferent vagus nerve

and subsequently increases memory encoding and consolidation through enhanced activity in brain areas including the LC-NA system [45]. Preclinical studies show that when the peripheral beta-adrenergic receptors of the vagus nerve are blocked, or when the afferent fibers of the vagus nerve are cut entirely, encoding and consolidation of emotional memory is strongly attenuated [46–48]. These findings suggest that direct stimulation of the vagus nerve may strengthen learning and memory through activation of the LC-NA network. Moreover, since stimulation of the vagus nerve circumvents the necessity of peripheral adrenergic receptor binding, VNS may also strengthen non-emotional learning and memory [49]. This suggests that tVNS could be used as an adjunct to exposure-based therapy, a learning-dependent psychological treatment that is currently considered the gold-standard for anxiety disorders.

A series of preclinical fear conditioning studies repeatedly and consistently demonstrated that invasive VNS strengthened the extinction of auditory conditioned fear [50–53]. Although these animal studies confirm the importance of vagal nerve activity during extinction learning and highlight a potential role for VNS in augmenting exposure therapy, it remains unclear to what extent these preclinical findings can be translated to humans [54–56]. Apart from this translational issue, it also remains unclear whether the effects of VNS can be achieved through non-invasive, transcutaneous means of stimulating the vagus nerve. Therefore, a main goal of this dissertation is to assess whether tVNS accelerates extinction learning and strengthens the consolidation of extinction memories in humans. This could have clear implications for the utility of tVNS as an add-on for exposure therapy.

Learning and Memory in Anxiety Disorders

To understand the importance of learning and memory in the treatment of anxiety disorders, we should first discuss their roles in the etiology and maintenance of anxiety disorders. Specifically, according to the Learning Theory of anxiety [57,58], individuals are thought to acquire fear of a certain stimulus or context through a Pavlovian associative learning process. For example, when an aversive event unfolds (e.g. a traffic accident) in a neutral context (e.g. when driving a car), the initially neutral context may come to elicit fear or anxiety due to its association with the aversive event. Apart from this direct learning, fear can also arise vicariously through verbal instructions or visual observations of responses of others [59,60]. Exposure-based treatments are reliant on a similar associative learning process: patients undergo prolonged and repeated exposure to the feared stimulus or context (e.g. driving a car) in absence of the expected aversive event (e.g. a traffic accident). During this process, the propositional expectancies of the original fear memory are repeatedly violated, since the feared stimulus or context is not followed by an aversive event. As such, a new, inhibitory memory is created, which competes with the fear memory for activation upon being presented with the feared stimulus. Successful exposure therapy relies on this expectancy violation of the original fear memory, leading to

the creation of a strong inhibitory memory capable of being preferentially activated upon presentation of the once-feared stimulus or context.

Fear learning and exposure therapy have been studied extensively using the fear conditioning framework, which provides a valid experimental analogue for a range of processes relevant to studying the etiology, maintenance, generalization, treatment, and reinstatement of fear [61–63]. Typically, during experimental fear acquisition, participants are presented with a conditioned stimulus (the CS+, often a geometrical shape or a tone) that is repeatedly paired with an aversive unconditioned stimulus (the US, often a loud noise or an electric shock), and a different conditioned stimulus (the CS-), which is never followed by the US and serves as a safety cue. Participants learn that the presentation of the CS+ predicts the occurrence of a US, and thus the presentation of the CS+, even in absence of the US, will elicit a fear response. During subsequent extinction learning, as an analog for exposure therapy, participants are presented repeatedly with the CS in absence of a US, which will eventually extinguish the fear response to the CS+.

An alternative approach: targeting worry

Alongside preclinical studies that point towards tVNS as a potential add-on treatment for exposure therapy, there are also indications that tVNS may be used as a stand-alone treatment. Specifically, stimulating the vagus nerve may affect anxiety disorders by targeting one of their cardinal symptoms: perseverative cognition.

According to the neurovisceral integration model, individual differences in vagus nerve activity at rest – as indexed by heart rate variability (HRV) - underlie differences in worrying [64–67]. HRV is a reliable indicator of efferent vagal tone [68] and is predominantly affected by the inhibitory control of the vagus nerve on the heart's sinoatrial node. High HRV (i.e., greater vagal tone) at rest reflects prefrontal inhibitory control over subcortical emotional areas in the brain, allowing the organism to respond to environmental challenges in a controlled and adaptive manner [69]. In contrast, a chronically low HRV represents a breakdown of these inhibitory influences, allowing subcortical brain areas to become hyperactive. This facilitates an excitatory positive feedback loop, reflected at the psychological level by hypervigilance and worry (cf. [67]).

In support of this model, many studies have found lower baseline HRV in GAD patients compared to healthy participants (for a meta-analysis, see [70]). The severity of worry – and not the diagnosis of an anxiety disorder – was associated with the most robust negative correlations with HRV [71]. These results also extend to non-clinical samples, where high dispositional worry has been found to be related to lower average HRV [72]. Experimental inductions of worry lead to a strong reduction in HRV (for a meta-analysis see [73]), and this reduction is more pronounced and slower to recover in chronic worriers [72,74–78]. Together, these studies indicate that low vagal activity could be a

vulnerability factor for chronic worrying. In summary, both the chronically low HRV of dispositional worriers, and the acute decrease of HRV during induced worry episodes are well established. Studies that have examined the relation between HRV and worrying have only examined this association on a cross-sectional basis or through worry inductions, but have never experimentally manipulated HRV to test its effects on worry. It remains unknown whether low vagus nerve activity is a mere reflection of the breakdown of prefrontal inhibitory control on subcortical areas, or is playing a causal, role in maintaining worry.

Although it remains unclear to what extent these associations between efferent vagus nerve activity and perseverative cognitions are predictive of the effects of tVNS – which is believed to activate primarily afferent fibers of the vagus nerve –, there are indications that tVNS may strongly affect central processes and cognitive functions thought to underlie perseverative cognition and stress-related cognition. Crucially, fMRI studies have shown that tVNS directly promotes activity in brain areas that reduce worry, including the prefrontal cortex and the anterior cingulate (for a review, see [79]). Furthermore, tVNS increases the functional connectivity between the amygdala and the prefrontal cortex in depressed patients [80]. Decreased functional connectivity between the amygdala and the prefrontal cortex has repeatedly and robustly been demonstrated as a function of anxiety [81], and has also been linked to self-reported worry intensity in patients suffering from GAD [82–84].

Previous studies have indicated that invasive VNS affects cognitive functions that rely on prefrontal activity, e.g. cognitive flexibility, decision making, and memory formation and consolidation (for a review, see [85]). Similarly, tVNS affects cognitive functions that rely on prefrontal activity, e.g. enhanced associative memory formation and consolidation [86] and action control [87]. Critically, tVNS promotes the ability to inhibit task-irrelevant processing [88,89], a process which is strongly compromised in patients suffering from GAD [90]. Finally, the potential effects of tVNS on worrying are further illustrated in a non-randomized study that showed positive effects of tVNS on symptoms of depression and anxiety in patients suffering from a major depressive disorder [80,91,92], a condition that is characterized by perseverative cognitions including worrying and rumination [93]. Thus, it could be worthwhile to assess whether tVNS could affect perseverative cognition, and thereby could also ameliorate anxiety symptoms by targeting one of the core symptoms of stress related psychopathology. Thus, a second aim of this thesis is to test whether tVNS affects perseverative cognition, one of the cardinal symptoms underlying anxiety disorders.

Working Mechanisms

The working mechanisms underlying tVNS are currently poorly understood. One of the most important working mechanisms hypothesized to underlie the effects of tVNS on psychological and neurological disorders is an increased activity of the locus coeruleus – norepinephrine (LC-NE) network. Specifically,

afferent fibers of the vagus nerve are known to terminate in the nucleus of the solitary tract, from which there are direct and indirect routes that can both activate and inhibit neurons in the LC [94]. Indeed, animal studies that tested the effects of invasive VNS have repeatedly found that rats receiving VNS, compared to those that had undergone sham surgery, show increased firing rates in LC neurons both acutely [45,95–98] as well as over a longer timespan (after a period of 90 days: [95]; after 14 and 90 days: [99]). In line with these findings, several studies found increased concentrations of NE in brain areas that the LC projects to, including the hippocampus [11,12], basolateral amygdala [13], and medial PFC [14].

Although the effects of VNS on LC-NE activity is well established in animals, studies on the noradrenergic effects of (t)VNS in humans are lacking. Direct measurement of NE in humans requires an invasive procedure and suffers from poor reliability and sensitivity [100]. Therefore, measuring NE in humans relies on assessing biomarkers that are related to LC – NE activity. Common biomarkers used as a proxy of NE include pupil diameter, the P300 component of event related potentials, and salivary alpha amylase. Several studies performed in small samples of patients wearing invasive vagus nerve stimulators provided some preliminary indications that LC-NE activity is increased when the stimulator is turned on compared to when it is turned off. Specifically, patients showed increased P300 amplitudes to visual cues [101], and increased resting pupil diameters [102], when VNS was turned on compared to when it was turned off. However, other studies were unable to find effects of VNS and auditory P300 [101,103], resting pupil diameter [104] and pupillary light reflexes [102]. As such, the working mechanisms underlying invasive and transcutaneous VNS remain unclear, and there's a clear need to assess whether the effects of VNS on LC-NE activity found in animals can be replicated using tVNS in humans. Thus, a final aim of this thesis is to assess whether tVNS increases LC-NE activity in humans, thereby testing the central working mechanism underlying the effects of tVNS.

Aims and Outline

To summarize, this thesis aims to study the potential for tVNS as a stand-alone or add-on treatment for stress-related disorders through a series of experimental studies focusing on stress-related cognition. Specifically, we examine how tVNS affects extinction learning, the experimental surrogate of exposure therapy. Additionally, we assess the effects of tVNS on worry frequency in a population of high worriers, since worrying is thought to underlie most stress-related psychopathology. Finally, we assess the hypothesized working mechanisms of tVNS in a series of studies that measure the effects of tVNS on noradrenergic activity.

In **Part I**, *Extinction of Fear*, we examine whether tVNS facilitates the extinction of fear. In **chapter 2**, we test whether tVNS accelerates the extinction of fear and strengthens the consolidation of immediate extinction memories (i.e. extinction occurring on the same day as acquisition). In **chapter**

3, we attempt to replicate these findings using a delayed extinction protocol (i.e. extinction occurring one day after fear acquisition). **Chapter 4** describes a conceptual replication attempt of these studies, where we studied the effects of tVNS on the immediate extinction of prepared fear in a highly arousing environment. Finally, **chapter 5** describes an experiment where we tested whether tVNS decreases the generalization of fear memories, which is believed to be one of the main contributing factors in the development and maintenance of anxiety disorders.

In **Part II**, *Negative Thought Intrusions*, we assess whether tVNS can decrease the number of negative thought intrusions in a population of high worriers (**chapter 6**).

In **Part III**, *Working Mechanisms*, we point out several critical inconsistencies in a cornerstone anatomical publication on the nerve supply in the human ear, thereby questioning the validity of the tragus as a target site for tVNS (**chapter 7**). Furthermore, in **chapter 8**, we describe a series of three studies are described, wherein the main working mechanism hypothesized to underlie the effects of tVNS is tested. Specifically, we tested whether tVNS increases activity in the LC-NE network by measuring the effects of tVNS on resting pupil diameter, task-related pupil dilation, and task performance on an Attentional Blink task.

To conclude, an overview of the results found in chapters 2 to 7 is provided in a general discussion (**chapter 9**). The theoretical and practical implications of the results, as well as directions for future research, are discussed.