

The Compassionate Vagus: effects of transcutaneous vagal nerve stimulation on cognition,
emotion and heart rate variability during compassionate mind training

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Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:



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Date: 19.07.20

Overview

This clinical psychology doctoral thesis is structured into three chapters. The first chapter presents a systematic review of the cognitive and emotional domains affected by transcutaneous vagus nerve stimulation (tVNS). It also aims to present an overview of the experimental designs, psychological tasks, outcome measures, participant groups and stimulation parameters used in the field of tVNS. The second chapter is an empirical paper investigating the potential facilitatory effects of tVNS as an adjunct to compassionate mind training (CMT). The study investigates the effect of tVNS and CMT on state affect, self-compassion/criticism, vagally mediated heart rate variability and emotional face processing in healthy participants. The third chapter is a critical appraisal of the research process of chapter 1 and 2.

Impact Statement

The results from the systematic review in this doctoral thesis will benefit academia through a systematic review and overview of the psychological and emotional domains that can be affected by transcutaneous vagus nerve stimulation (tVNS). This is a relatively new, non-invasive stimulation technique being used as a neuromodulator tool in research and a clinical intervention for mental health problems. The systematic review of the literature also highlights the methodology being used in the tVNS field. This information will be a useful resource to guide future tVNS research towards a coherent application of tVNS as a clinical and experimental tool.

The empirical study of this doctoral thesis expands the potential use of tVNS into the new cognitive, affective and clinical area of compassionate mind training (CMT), a key component of Compassion Focused Therapy. It also provides a potential new adjunct to CMT that may facilitate cultivation of self-compassion for people that find this particularly difficult. The results of this study also further confirm the evolutionary and developmental theory that underpins CMT.

The benefits of this research outside academia are in its potential to influence better quality and patient informed clinical interventions. Furthermore, facilitatory adjuncts to therapy, like the one investigated in the empirical study, can make certain therapies more accessible and effective for clinical groups that would otherwise find therapy challenging.

The impact of these results could reach an international academic and industry audience. tVNS and CMT research is conducted globally. The area of tVNS as an adjunct to clinical intervention could provide potential new avenues of research, research funding and research student scholarships. In the future, the results of this thesis could impact individuals accessing a psychological treatment that would have otherwise been challenging for them to engage with.

The results of this thesis will be disseminated through peer-reviewed journals and international conferences. The research has relevance for clinical and basic science in the fields of psychology, physiology, engineering and industry, and may result in multi-disciplinary collaborations in the future.

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Dedication

Hazel
(Mum)
1964 – 2017

For all that is good in me

Chapter 1 – Literature Review

A systematic review of the cognitive and emotional effects of non-invasive vagus nerve stimulation

Abstract

Background: Transcutaneous vagus nerve stimulation (tVNS) is a non-invasive tool used as a neuromodulator in cognitive neuroscience research and as a potential therapeutic intervention for mental health problems. There has been a rise in tVNS research in the last decade and the aim of this systematic review was to assess the domains of cognition and emotion that are affected by tVNS. Furthermore, we wanted to provide an overview of the types of experimental designs, psychological tasks, outcome measures, participant groups, and stimulation protocols used in tVNS research. This review will be an initial attempt to guide future research towards a coherent application of tVNS as a clinical and experimental tool.

Methods: A systematic review of several literature databases was conducted for research involving tVNS and at least one psychological task or outcome measure. The psychological task and outcome measures related to a variety of cognitive and emotional processes and various mental health diagnoses were also included in the search terms.

Results: Thirty-six unique publications were identified, covering cognitive domains such as memory, emotional face processing, inhibitory control, attention, creativity, decision making, flow experience, worry, and fear extinction learning. Several clinical populations were examined including individuals with depression, post-traumatic stress disorder and schizophrenia. tVNS effects were varied. The most consistent results were a facilitation of extinction memory and reductions in depression symptoms. There was also some evidence that tVNS improves attention, creativity, inhibitory control and emotional face processing. However, these results often stem from a small number of studies and with only partial effects from those originally hypothesised. The variety in domains investigated is similarly reflected in the variety of stimulation protocols, including a wide range of stimulation amplitudes, locations and durations. There were two main theories put forward as the potential underlying mechanism of tVNS change: Porges' Polyvagal Theory and the locus coeruleus-norepinephrine system.

Conclusions: The domains of cognition and emotion studied in tVNS research is vast. While there are some consistent positive results in fear extinction learning, depression symptoms, attention and inhibitory control, tVNS effects in other domains remain unclear and understudied. This review of tVNS evidence and methodology will assist future research design and contribute to a coherent approach in using tVNS as a research tool and therapeutic intervention.

Introduction

Direct vagus nerve stimulation (dVNS) is an invasive neuromodulation technique harnessed in the 1990s for the treatment of refractory epilepsy (Dario, Edward, & Kurtis, 2011) and chronic depression (Martin & Martín-Sánchez, 2012). In addition to evidence for the mood and quality of life enhancing effects (Cimpianu, Strube, Falkai, Palm, & Hasan, 2017), dVNS was shown to positively influence cognition, such as verbal memory and, in later trials, sustained cognitive status in Alzheimer's patients (Vonck et al., 2014). However, the medically risky and costly nature of invasive dVNS has limited extensive research and clinical application. Nevertheless, advances in technology has given rise to the non-invasive, low risk and inexpensive use of *transcutaneous* vagus nerve stimulation (tVNS; stimulation of the vagus nerve through the skin). This has reignited investigations into the therapeutic potential of vagus stimulation, as well as its use as a non-invasive, non-pharmacological neuromodulation approach in cognitive neuroscience research. In particular, the last decade has seen a rise in the use of tVNS for the treatment of mental health problems, including depression, post-traumatic stress disorder (PTSD) and schizophrenia (Cimpianu et al., 2017; Lamb, Porges, Lewis, & Williamson, 2017). It has also been used to explore the neural basis of cognitive processes such as learning and memory (Hansen, 2019), emotion recognition (Colzato, Sellaro, & Beste, 2017) and inhibitory control (Beste et al., 2016). These diverse areas of investigation are similarly matched by the diversity of methods of tVNS research, and inconsistent results. Considering this, the aim of current systematic review is to examine the evidence-base of tVNS modulated cognition and emotion, and methods of stimulation. It is hoped that this will enable future experimental studies to proceed in a more informed and effective way, and positively contribute to the application of tVNS as an experimental tool for neuromodulation and, potentially, a therapeutic intervention or adjunctive treatment for psychological disorders.

The vagus nerve is the tenth and largest of the cranial nerves. While it innervates many peripheral structures, it has a predominant role in the parasympathetic regulation of the heart, lungs and gut. The vagus nerve is a complex, evolved structure with descending efferent fibres to regulate peripheral organs and the sympathetic nervous system, and ascending afferent fibres conveying sensory and visceral information to the brain via the nucleus tractus solitarius (NTS) in the brainstem. Secondary projections lead to the locus coeruleus, raphe nuclei, pre-frontal cortex, limbic system and cerebellum (Nemeroff et al., 2006). Connection to the raphe and locus coeruleus give rise to the potential for widespread central neuromodulation via noradrenergic and serotonergic projections.

Transcutaneous stimulation activates afferent fibers of the vagus nerve via small electrical currents through the skin. This is predominantly done at the outer ear, stimulating the auricular branch of the vagus nerve (ABNV: Peuker & Filler, 2002; Sherrington, 1898). More rarely, cervical stimulation of the vagus nerve is also used as a non-invasive VNS (Goadsby et al., 2018; Gurel et al., 2020). The ABNV innervates the cymba concha, antitragus, tragus and antihelix of the ear (Sherrington, 1898) (*see Figure 1*). There are lateral differences with the right branch of the vagus nerve innervating the sinoatrial node of the heart more than the left branch, which preferentially innervates the atrioventricular node. Similar to invasive dVNS, fMRI studies have shown that tVNS activates the pre-frontal cortex, locus coeruleus, limbic system, and cingulate cortex (Dietrich et al., 2008; Frangos, Ellrich, & Komisaruk, 2015; Kraus et al., 2007; Kraus et al., 2013), and alters connectivity between the default mode network, insula cortex and limbic system, and between the amygdala and pre-frontal context (Fang et al., 2017; Fang et al., 2016; Liu et al., 2016).

Although not mutually exclusive, there are two primary rationales that guide the use of tVNS in psychological research. The first is Porges' polyvagal theory (Porges, 2009, 2011), which implicates the vagus nerve in social interaction, care-giving and emotional and

physiological regulation. The second concerns the locus coeruleus-norepinephrine (LC-NE) system, which is the sole source of noradrenaline in the forebrain and plays an important role in a variety of cognitive and emotional processes (Aston-Jones, Rajkowski, & Cohen, 1999; Berridge & Waterhouse, 2003; Mather & Harley, 2016; Sara, 2009; Sara & Bouret, 2012) and is activated through vagus afferent termination on NTS.

Porges' polyvagal theory (Porges, 2007, 2009, 2011) states that mammals evolved two vagal branches that perform distinct evolutionary processes. The more primitive, dorsal vagal pathway is hypothesised to regulate visceral functions and initiates immobilisation behaviour (e.g. freezing in instances of threat) via an unmyelinated part of the nerve. The more evolutionarily recent, ventral vagal system regulates the heart and lungs via myelinated fibers, and signals a state of calm, safety and soothing to counteract sympathetic "fight/flight" emotions and behaviours. The ventral vagal system is thought to give rise to, in part, mammalian care-giving motivations whereby the mother is attuned to the needs and distress of her young and can effectively meet, remedy and regulate those to the benefit of infant survival (Depue & Morrone-Strupinsky, 2005; Di Bello et al., 2020; Kirby, Doty, Petrocchi, & Gilbert, 2017; Petrocchi & Cheli, 2019; Porges, 2007). This care-giving capacity is thought to have evolved alongside the myelination of the ventral vagal pathway. Furthermore, connections between the myelinated vagal nerve and other cranial nerves potentially influence social orienting and exchanges through control of the facial nerves and throat, adjusting facial expressions, eye contact and voice tone (Petrocchi & Cheli, 2019; Porges, 2017). In light of this, research studies investigating the vagus nerve and social and interpersonal phenomena cite the polyvagal theory as a potential mechanisms of vagal involvement (e.g. Sellaro, de Gelder, Finisguerra, & Colzato, 2018).

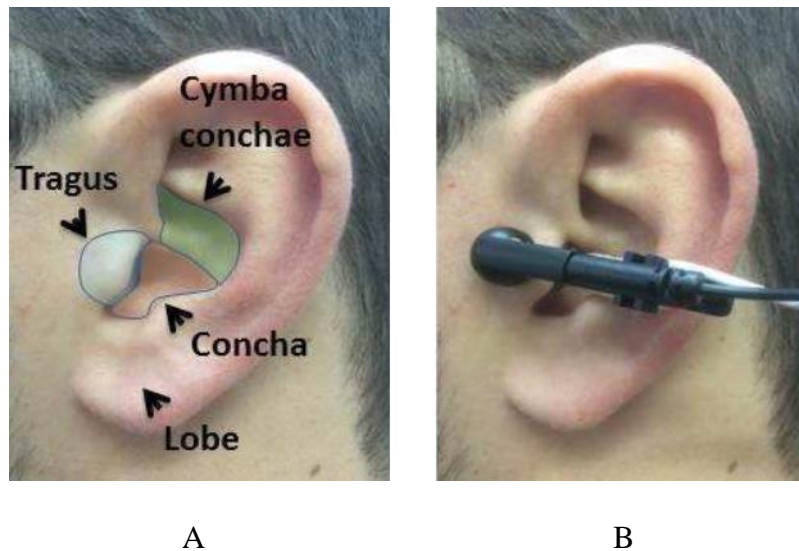


Figure 1. Anatomy of the outer ear (a) and positioning of tVNS electrode clip to the Tragus (B)

Although tVNS potentially modulates a variety of neurotransmitter systems via brainstem nuclei and wide projections to cortical and subcortical regions, (Van Leusden, Sellaro, & Colzato, 2015) many studies have focused on tVNS activation of the LC-NE system, which has a well-documented role in cognitive processes such as attention, memory and perception (Sara, 2009; Sara & Bouret, 2012), and its role in psychiatric disorders such as depression (Grimonprez, Raedt, Baeken, Boon, & Vonck, 2015), PTSD (Mueller & Cahill, 2010), and schizophrenia (Yamamoto & Hornykiewicz, 2004). There are several proposed noradrenergically-mediated mechanisms that underlie normative affective-cognitive processes, which are dysregulated in psychiatric disorders. For example, LC-NE activation can increase the functional connectivity of brain regions involved in attention and working memory (Coull, Büchel, Friston, & Frith, 1999; Sara & Bouret, 2012). Noradrenaline release also facilitates synaptic excitation and plasticity (long term potentiation) in hippocampal neurons, a process essential for memory consolidation and extinction (Mueller & Cahill, 2010; Sara & Bouret, 2012). tVNS has increasingly been used as a non-invasive, non-pharmacological tool for neuromodulation of the LC-NE system. VNS-based strategies have also been tested as potential

corrective neuromodulatory treatments targeting the LC-NE system in psychiatric disorders (e.g. Genheimer, Andreatta, Asan, & Pauli, 2017; Grimonprez et al., 2015).

Given the broad areas of investigation and the underlying theories explored above, this systematic review will address the broad question: *which domains of cognition and emotion are affected by tVNS?* Furthermore, due to the emerging field of tVNS as a non-invasive brain stimulation tool for research and a potential adjunct in the treatment of mental health problems, we address the following questions as an initial attempt to guide future research towards a coherent application of tVNS as a clinical and experimental tool:

1. What psychological tasks have been used in tVNS studies?
2. What measures (e.g. subjective questionnaire and objective behavioural data) of cognition and emotion have been used?
3. What populations (e.g. clinical, healthy, young, old) have been investigated?
4. What stimulation protocols have been employed (e.g. laterality, intensity, duration, frequency, type of stimulator)?
5. What comparators (i.e. control conditions) have been used?

Methods

Inclusion Criteria

Included studies had to be published in peer reviewed English language journals and describe the effects of non-invasive, transcutaneous VNS on at least one established psychological paradigm (e.g. task or manipulation such as fear conditioning) or one quantitative outcome measure (e.g. mood questionnaire).

Exclusion Criteria

Studies were excluded if *invasive* VNS was used, if they tested the effects of tVNS in animals, were not peer-reviewed or were non-empirical papers (e.g. reviews).

Search Strategy

The following databases were searched for studies published prior to 3rd February 2020: Web of Science (Thomson Reuters), PsycInfo, ProQuest and Medline. Searches included appropriate key words associated with non-invasive VNS (e.g. “transcutaneous vagus nerve stimulation” and “non-invasive vagus nerve stimulation”), cognition and emotion (e.g. “decision making” and “fear”) and mental health disorders (e.g. “depression” and “post-traumatic stress disorder”). A full list of key word and search syntax is presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist (Liberati et al., 2009) in Appendix 1.

Study processing and data extraction

Literature found in the database searches were downloaded for further processing. Once duplicates were removed the remaining titles and abstracts were reviewed. Literature that did not meet eligibility criteria were excluded at this stage and the remaining literature was read to further establish eligibility. The remaining reference lists were also checked for additional, eligible studies missed from the search. This process and the number of studies at each stage are presented in **Figure 2**.

All eligible studies were read in full, with any uncertainties regarding inclusion discussed between CJF and supervisor (SK). Data extraction for eligible studies was conducted by CJF using a template. This included information about the study design, psychological paradigm used, cognition and/or emotion of interest, comparators, inclusion and exclusion

criteria, sample size, participant characteristics (e.g. age and gender), primary and secondary outcome measures, stimulation parameters, key findings and the reporting of adverse events.

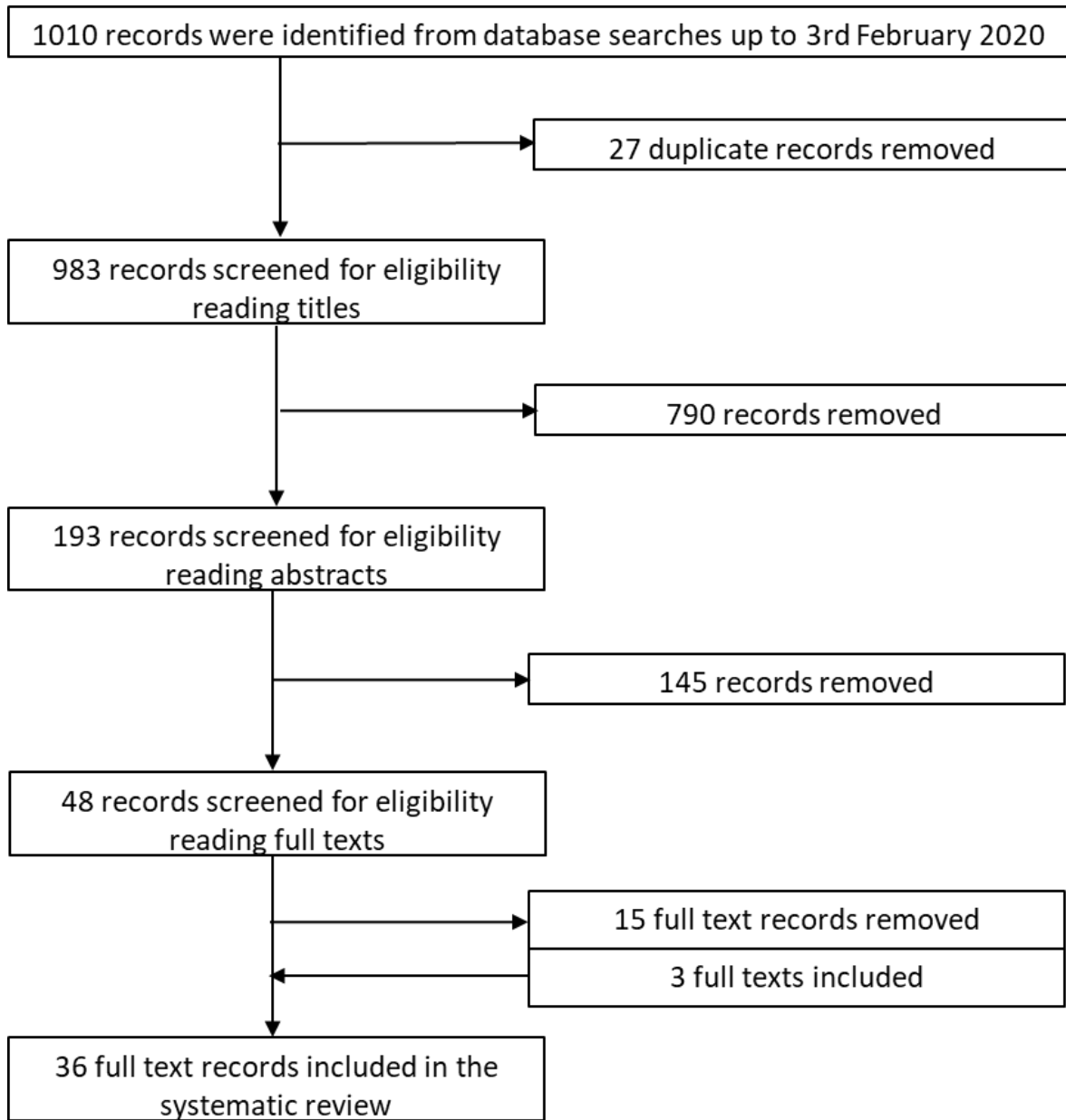


Figure 2. Flow chart showing study selection for systematic review

Results

The literature search identified 1010 publications. This was reduced to 983 after the removal of 27 duplicates. There were 193 publications left after inspection of the title for eligibility and 48 after reading the abstracts. After full text and reference list inspections, 36 publications met inclusion criteria, including three identified from study reference lists. The publications cover a wide range of cognitive and emotional domains and were grouped according to these domains. **Table 1.** provides a summary of the participant characteristics, experimental design, cognitive and emotional domains of interest, and stimulation parameters. **Table 2** provides a summary of the study paradigms, measures and outcomes. An extended table summary is available as an Excel table in Supplementary Material. The following results sections will be organised by discussing the psychological paradigm, measures of cognition and emotion, the participant group, study design and comparators, and stimulation protocols used. This will then be followed by a summary of the effects of tVNS in each section.

Fear extinction learning

Fear conditioning is the predominant model of anxiety disorder onset in humans. Relatedly, subsequent extinction following repeated unreinforced trials with the conditioned stimulus is an experimental parallel for (exposure) therapy (McNally, 2007).

Six studies investigated the effects of tVNS during extinction learning in a conditioned fear paradigm, with the primary outcome variables of startle blink response (non-declarative fear memory) and expectancy ratings (declarative fear memory) of an aversive, unconditioned stimulus (e.g. electric shock) (Burger et al., 2018; Burger, Van Diest, et al., 2019; Burger et al., 2017; Burger et al., 2016; Genheimer et al., 2017; Szeska, Richter, Wendt, Weymar, & Hamm, 2020). All studies investigated a healthy, predominantly young, student population. Five of these studies used a between-subjects design while one study (Szeska et al., 2020) employed a

between- and within-subjects design comparing extinction learning during tVNS or Sham stimulation. All studies report blinding, namely participants, and all participants were randomised to stimulation condition (tVNS v sham). Stimulation was applied to the left ear in all studies. tVNS was applied to the cymba concha in all studies, while sham stimulation was applied to the ear lobe in five studies and to the cymba concha in one study (Genheimer et al., 2017) with the stimulator turned off. Four of the six studies originated from the same (Burger et al) lab. All four studies by Burger et al., used a fixed stimulation threshold of 0.5mA while the two other studies used a perceptual threshold whereby stimulation amplitude was set at perceptive but not-uncomfortable level (range of 1.2mA - 2.5mA). The frequency of stimulation was consistent across all fear conditioning studies at 25Hz and the pulse width ranged between 200-300 μ s. The duration of tVNS and sham stimulation varied from 10 to 40 minutes, with two studies not reporting stimulation duration (Burger et al., 2017; Burger et al., 2016). The duration of any baseline period of stimulation applied before behavioural tasks began was unclear from description of methods.

The effects of tVNS during extinction learning are mixed. Three out of six studies found that expectancy ratings were significantly reduced during tVNS compared to sham stimulation (Burger, Van Diest, et al., 2019; Burger et al., 2016; Szeska et al., 2020). This indicated an accelerated extinction of declarative fear memory. Three studies (Burger et al., 2018; Burger et al., 2017; Szeska et al., 2020), showed a reduction in expectancy ratings that was most notable at the early stages of the extinction phase. However, the two Burger et al studies found these results only after exploratory analysis as there was no outright effect of tVNS on extinction. Only Szeska et al. (2020) found a significant reduction in startle reflex responses during tVNS, indicating an accelerated extinction of non-declarative fear memory. The extinction effects observed by Szeska et al. (2020) in participants who received tVNS were sustained, with evidence for reduced expectancy and startle response at 28 days after initial

extinction. While Burger et al. (2017) found no overall effect of tVNS on startle response, they did find a reduction in startle response during the initial segment of the extinction session in an exploratory analysis. This was also the case for startle responses on day 3 of their paradigm which assessed extinction memory retention. Finally, Genheimer et al. (2017) tried to replicate and extend the findings of Burger et al. (2016) by investigating the effects of tVNS in a contextualised, conditioned fear paradigm in virtual reality. The use of virtual reality and contextualised (e.g. a whole room as a conditioned stimulus) conditioning was thought to have closer parallels to exposure therapies for anxiety disorders and thus positive results would take the field a step further in the use of tVNS as a clinical adjunct. However, despite successful fear conditioning there were no differences between tVNS and Sham conditions on any outcome measures, including expectancy ratings or startle responses.

Psychological stress and PTSD

Two studies investigate the effects of tVNS in participants with current PTSD or recovered from PTSD. Firstly, Lamb et al. (2017), used a startle-blink paradigm whereby participants were exposed to emotionally laden images and, on some trials, received an acoustic startle stimulus during image presentation. Participants also rated the valence and arousal elicited by the images. Startle blink responses were measured using electromyography (EMG). Participants were combat veterans with a diagnosis of PTSD and traumatic brain injury. They were compared against healthy veteran controls in a within- and between-subjects design employing both tVNS and sham stimulation. Participants were randomised to stimulation condition and the study was double blind (i.e. participants and testing researcher). Stimulation was applied to the left tragus for both tVNS and sham stimulation, but the stimulator was turned off for the sham condition. Stimulation was set at 80% of participants' subjective comfort level. The average amplitude was 5.6mA, with a frequency of 20Hz and a pulse width of 100 μ s. The total duration of stimulation was not reported, nor was the stimulator brand, or whether a

minimum, baseline period of stimulation occurred before the behavioural tasks. tVNS significantly reduced features of the startle blink response for both patients and healthy participants. tVNS also increased heart rate variability for all participants compared to sham stimulation. The study did not report whether tVNS had any effect on the valence and arousal ratings of the emotional images.

Secondly, Gurel et al. (2020) aimed to establish acute bio-markers of cervical tVNS beyond basic HRV in healthy volunteers with a history of PTSD. Over three days participants completed several psychologically stressful tasks. The first was to listen to an audio recording of their past traumatic experience and neutral (albeit positive) narratives (e.g. nature descriptions). The second task involved preparing and delivering a public defence to an accusation of theft. The third task involved a math exercise with negative feedback. In the between-subjects, double-blind (i.e. participants and testing researchers) design, participants were randomly allocated to tVNS or Sham stimulation conditions. Stimulation was set at a perceptible but not painful level. The average amplitude was 18V, with a frequency of 25Hz and a pulse width of 5kHz. Stimulation was applied for 2 minutes after each stressful event. The results revealed a reduction in sympathetic responses during the trauma audio and stressful tasks for the cervical tVNS condition, compared to sham. Cervical tVNS also resulted in reduced parasympathetic activity (heart rate variability - HRV) during the trauma audio task and the stress induction tasks.

Depression and Low Mood

Eight studies investigated the effects of a course of tVNS on depression symptoms (Fang et al., 2017; Fang et al., 2016; Hein et al., 2013; Li et al., 2019; Liu et al., 2016; Rong et al., 2016; Tu et al., 2018; Wang et al., 2018). None of these studies used a psychological task or behavioural outcome. All studies used subjective measures of depression symptoms as their

primary psychological outcome measures. The Hamilton Depression Rating Scale (HAM-D: Hamilton, 1960) was used in all studies and the Beck Depression Inventory (BDI: Beck, Steer, & Brown, 1996) was used as an additional measure by Hein et al. (2013). All studies used a clinical population with a verified diagnosis of depression. Six of these studies appear to be based on the same sample of participants, but reported different outcomes (Fang et al., 2017; Fang et al., 2016; Liu et al., 2016; Rong et al., 2016; Tu et al., 2018; Wang et al., 2018). Seven studies used both within- and between-subject designs with tVNS and Sham stimulation conditions. Li et al. (2019) was a single case-study design. Only one study (Hein et al., 2013) randomly allocated participants to stimulation condition. All participants were reported as blind to the experimental hypotheses and stimulation conditions. Treatment regimens varied from 2 – 12 weeks of, predominantly, twice daily 30-minute stimulation sessions. Stimulation was self-administered at home, except for Hein et al. (2013) which occurred in an inpatient setting. tVNS was applied to the Concha of both ears in seven studies, with no indication of laterality in or Fang et al. (2017); Fang et al. (2016) and no anatomical location specified in Hein et al. (2013). Sham stimulation was applied to the superior scapha in six studies while Hein et al. (2013) did not report sham location. All eight studies used a subjective stimulation threshold that was either the sensory threshold or a perceptual threshold that was not uncomfortable. Stimulation amplitude ranged from 1.3mA – 8mA. Frequency of stimulation was 20Hz in five studies, 25Hz in two studies and 1.5Hz in one study. Pulse width varied between 100-200 μ s with four studies stating it was “< 1ms”.

The eighth study, Li et al.’s (2019), was case report of a treatment-resistant depressed patient receiving tVNS twice a day for 8 weeks in combination with a selective serotonin reuptake inhibitor (SSRI), showed a significant reduction in HAM-D score. The six studies that were based on the same sample of participants used the following intervention schedule: a first cohort of patients was recruited to receive tVNS for 12 weeks; the second cohort then received

sham stimulation for 4 weeks and tVNS for 8 weeks. Comparisons between the first 4 weeks of the first cohort (active tVNS) and the first 4 weeks of the second cohort (sham stimulation) revealed a significant reduction in HAM-D scores for those receiving tVNS (Fang et al., 2017; Fang et al., 2016; Liu et al., 2016; Rong et al., 2016; Tu et al., 2018; Wang et al., 2018). In addition, Rong et al. (2016) report a greater level of symptom reduction and remission rates in tVNS patients than sham patients after 4 weeks of tVNS treatment. The effects of tVNS continued in this cohort of participants until week 12 of treatment. Hein et al. (2013) was the only study not to find significant changes in the HAM-D after their treatment schedule of two weeks but they did find a significant reduction in BDI for tVNS patients compared to sham patients.

Further comparisons in the six studies based on the same sample also investigated the relationship between changes in brain function and depression symptoms after tVNS. Functional magnetic resonance imaging (fMRI) was used to investigate the effects of acute tVNS, as well as the sustained effects of prolonged tVNS treatment. Fang et al. (2016) found reduced functional connectivity between the Default Mode Network (DMN) and the anterior insula and parahippocampus of patients after 4 weeks of tVNS treatment. Reductions in HAM-D scores were associated with an increase in functional connectivity between the DMN and the Anterior Cingulate Cortex (ACC), as well as with a decrease in functional connectivity with the Orbito-Prefrontal Cortex (OPFC). In a subsequent paper, Fang et al. (2017) report BOLD signal increases in the left anterior insula *during* tVNS compared to sham stimulation, with a more active insula associated with lower scores on the HAM-D at week 4 of treatment. Liu et al. (2016) found an increased resting state functional connectivity (rsFC) between the right amygdala and left Dorsolateral Prefrontal Cortex (dlPFC) after 4 weeks of tVNS treatment. The increase in rsFC was negatively associated with symptom reduction on the HAM-D. Similarly, Tu et al. (2018) report finding a decrease in functional connectivity between the

medial hypothalamus and the rostral ACC (rACC) during continuous tVNS. This change was associated with symptomatic improvement measured by the HAM-D. Lastly, Wang et al. (2018) found tVNS significantly increased functional connectivity between left nucleus accumbens (NAc) and bilateral medial PFC or rACC when compared to sham stimulation. This increase was associated with symptom severity changes on the HAM-D.

Finally, Kraus et al. (2007) investigated the mood enhancing effects of different intensities of tVNS. In a within-subjects design, healthy participants were randomly allocated to either tVNS or sham stimulation. They then received low and high intensity, which were preceded and followed by the Adjective Mood Scale (ASM: Bobon, Lapierre, & Lottin, 1981) to assess mood. The same procedure was also subsequently conducted during fMRI. The left tragus was stimulated during tVNS and the ear lobe during sham stimulation. Stimulation amplitude was set at the participants sensory threshold (i.e. just noticeable) for low intensity condition and perceptible but tolerable for the high intensity condition. Average amplitude of low and high intensities were 4.0mA and 5.0mA, respectively. Frequency was set at 8 Hz with a pulse width of 20 μ s. Stimulation duration was 7.5 minutes and then 18 minutes during the fMRI session. There was a significant decrease in Adjective Mood Scale during tVNS, indicating improved mood, and significant increase during sham stimulation, indicated a decline in positive mood. The study also showed a decrease of blood oxygen level dependant (BOLD) signal during tVNS in limbic and temporal regions, and an increase of BOLD signal in the insula, precentral gyrus, right thalamus and right anterior cingulate. Results were comparable for high and low intensity stimulation.

Table 1. Summary of systematic review studies

Study Number	Citation	Experimental Design; Trail Arm Conditions; Randomisation; Blindness	Cognitive and Emotion Domains	Participant Characteristics (Age = mean or count)	Stimulation Configuration (Anatomy, Parameters, Duration)
1	Beste et al (2016)	Between-subjects design; Active and Sham conditions; Randomised; Participant Blind:	Inhibitory Control	Age: 23.6 years; Sample size: 51; Females: 37; Healthy	Left inner ear (tVNS) and earlobe (sham); Perception Level: Fixed for all, Amplitude: 0.5mA, Frequency: 25Hz, Pulse width: 200-300µs; Stimulation duration: 60 minutes
2	Bretherton et al (2019)	Within-subjects design; Active; Non-Randomised; Participant Blind	Quality of life & Mood	Age: 64.1 years; Sample size: 26; Females: 17; Healthy	Tragus (tVNS & Sham: laterality not reported); Perception Level: sensory threshold, Amplitude: 2-4 mA, Pulse Width: 200µs, Frequency: 30 Hz; Stimulation duration: 15 minutes daily for 2 weeks
3	Burger, Van der Does et al (2019)	Between-subjects design; Active and Sham conditions; Randomised; Unsure of Blinding	Worry (spontaneous & induced worrying thoughts) & Anxiety	Age: 21 years; Sample Size: 97; Females: 78; Healthy, High Worriers	Left cymba concha (tVNS) & earlobe (Sham); Perception Level: Fixed for all, Amplitude: 0.5mA, Frequency: 25Hz, Pulse width: 250µs; Stimulation duration: 35 minutes
4	Burger et al (2018)	Between-subjects design; Active and Sham conditions; Randomised; Participant Blind	Fear extinction learning	Age: 18-24 years; Sample Size: 85; Females: 71; Healthy	Left cymba concha (tVNS) & earlobe (Sham); Perception Level: Fixed for all, Amplitude: 0.5mA, Frequency: 25Hz, Pulse width: 250µs; Stimulation duration: 25 minutes
5	Burger, Van Dies et al (2019)	Between-subjects design; Active and Sham conditions; Randomised; Participant Blind	Fear generalisation and extinction learning	Age: 22 years; Sample Size: 58; Females: 48; Healthy	Left cymba concha (tVNS) & earlobe (Sham); Perception Level: Fixed for all, Amplitude: 0.5mA, Frequency: 25Hz, Pulse width: 250µs; Stimulation duration: 29 minutes

6	Burger et al (2017)	Between-subjects design; Active and Sham conditions; Randomised; Unsure of Blinding	Fear extinction learning and retention	Age: 20-36years; Sample Size: 39; Females: 26; Healthy	Left cymba concha (tVNS) & earlobe (and Sham); Perception Level: Fixed for all (7 participants found this too painful and had the amplitude reduced to between 0.1 -0.4mA), Amplitude: 0.5mA, Frequency: 25Hz, Pulse width: 250µs; Stimulation duration: not reported
7	Burger et al (2016)	Between-subjects design; Active and Sham conditions; Randomised; Participant Blind	Fear extinction learning and retention	Age: 21 years; Sample Size: 31; Females: 24; Healthy	Left cymba concha (tVNS) & earlobe (Sham); Perception Level: Fixed for all, Amplitude: 0.5mA, Frequency Hz: 25Hz, pulse width: not reported; Stimulation duration: no reported
8	Colzato, Sellaro and Beste (2017)	Within-subjects design; Active and Sham conditions; Randomised; Participant Blind	Facial Emotion Recognition	Age: 22.3 years; Sample Size: 38; Females: 30; Healthy	Left cymba concha (tVNS) & earlobe (Sham); Perception Level: Fixed for all, Amplitude: 0.5mA, Frequency: 25Hz, Pulse width: 200-300µs; Stimulation duration: 35 minutes
9	Colzato, Ritter and Steenbergen (2018)	Between-subjects design; Active and Sham conditions; Randomised; Participant & Researcher Blind	Creative Thinking (divergent and convergent thinking)	Age: 21.4 years; Sample Size: 80; Females: 50; Healthy	Left cymba concha (tVNS) & earlobe (Sham); Perception Level: Fixed for all, Amplitude: 0.5mA, Frequency: 25Hz, Pulse width: 200-300µs; Stimulation duration: 40 minutes
10	Colzato, Wolters and Peifer (2018)	Within-subjects design; Active and Sham conditions; Randomised; Participant Blind	Flow experience	Age: 21.3 years; Sample Size: 32; Females: 22; Healthy	Left outer auditory canal (tVNS) & earlobe (Sham); Perception Level: Fixed for all, Amplitude: 0.5mA, Frequency: 25Hz, Pulse width: 200-300µs; tasks duration: 50 minutes
11	Eren et al (2018)	Between- & within-subjects design; Active and TAU conditions; Randomised; Unsure of Blinding	QoL, Depression & Anxiety	Age: 39 years; Sample Size: 16; Females: 11; Clinical	Right ear (anatomy not specified); stimulation configuration not reported; Stimulation duration: 3x90 seconds twice daily for 4 weeks

12	Fang et al (2017)	Between- & within-subjects design; Active and Sham conditions; Randomised; Participant Blind	Depression	Age: 40.4years; Sample Size: 38; Females: 26; Clinical	Cymba concha (tVNS) & superior scapha (sham; Laterality not reported); Perception Level: perceptible but not painful, Amplitude: 4 - 6mA, Frequency: 25Hz, Pulse width: 100µs; Stimulation duration: 2x30 minutes daily for 4 weeks
13	Fang et al (2016)	Between- & within-subjects design; Active and Sham conditions; Non-randomised; Participant Blind	Depression & Anxiety	Age: 39.2 years; Sample Size: 34; Females: 24; Clinical	Cymba concha (tVNS) & superior scapha (Sham; Laterality not reported); Perception Level: perceptible but not painful, Amplitude: 4 - 8mA, Frequency: 25Hz, Pulse width: 200µs; Stimulation duration: 2x30 minutes daily for 4 weeks
14	Fischer et al (2018)	Within-subjects design; Active and Sham conditions; Randomised; Participant Blind	Conflict Processing	Age: 20.3 years; Sample Size: 21; Females: 18; Healthy	Left cymba concha (tVNS) & earlobe (Sham); Perception Level: perceptible tingling but, not painful Amplitude: 0.4 - 3.3mA, Frequency: 25Hz, Pulse width: 250µs; Stimulation duration: 36 minutes
15	Genheime et al (2017)	Between-subjects design; Active, Sham & No Stimulation conditions; Randomised; Participant Blind	Contextualised Fear Conditioning	Age: 24.6 years; Sample Size: 75; Females: 41; Healthy	Left cymba concha (tVNS), Helix (Sham), cymba concha (No stimulation); Perception Level: perceptible but not painful, Amplitude: average of 1.2mA, Frequency: 25Hz, Pulse width: 200-300µs; Stimulation duration: 40 minutes
16	Gurel et al (2020)	Between-subjects design; Active and Sham conditions; Randomised; Participant & Researcher Blind	Psychological Stress response	Age: 31 years; Sample Size: 24; Females: 12; Healthy with Trauma History	Cervical tVNS applied to the left neck (tVNS & Sham); Perception Level: perceptible but not painful, Amplitude: average of 18 V (4.8), Frequency: 25Hz, Pulse width: 5 kHz sine; Stimulation duration: 28 minutes
17	Hasan, et al (2015)	Between- & within-subjects design; Active and Sham conditions;	Positive and Negative Symptoms of Schizophrenia	Age: 37.6 years; Sample Size: 19; Females: 9; Clinical	Left, outer auditory canal (tVNS) & earlobe (sham); Perception Level: highest tolerable; Amplitude: not reported, Frequency: 25Hz, Pulse width: 250µs;

		Randomised; Participant & Researcher Blind			Stimulation duration: "on throughout the day" for 26 weeks
18	Hein,et al (2013)	Between- & within-subjects design; Active and Sham conditions; Randomised; Participant Blind	Depression	Age: Not Reported; Sample Size: 22; Females: 13; Clinical	Left & right outer auditory canal (tVNS & Sham); Perception Level: just below perceptual threshold in study 1 but fixed in study ;, Amplitude: study 1 not reported; 1.30µA (study 2), Frequency: 1.5Hz, Pulse width: not reported; Stimulation duration: 15 minutes daily for 2 week (study 1) & 2x15 minutes daily for 2 weeks
19	Jacobs et al (2015)	Within-subjects design; Active and Sham conditions; Randomised; Participant and Researcher Blind	Association Memory	Age: 60.6 years; Sample Size: 30; Females: 15; Healthy	Left tragus (tVNS), earlobe (Sham); Perception Level: Fixed for all; Amplitude: 5mA, Frequency: 8Hz, Pulse width: 200-300µs; Stimulation duration: 17 stimulation
20	Jongkees et al (2018)	Between-subjects design; Active and Sham conditions; Randomised; Participant Blind	Sequential Action Control	Age: 22.3 years; Sample Size: 40; Females: 32; Healthy	Left outer auditory canal (tVNS) & earlobe (Sham); Perception Level: Fixed for all, Amplitude: 0.5mA, Frequency: 25Hz, Pulse width: 200-300µs; Stimulation duration: 45 minutes
21	Koenig et al (2019)	Between- & within-subjects design; Active and Sham conditions; Randomised; Unsure of Blinding	Facial Emotion Recognition & Depression	Age: 14-17 years; Sample Size: 63; Females: 51; Clinical	Left concha (tVNS) & earlobe (Sham); Perception Level: Fixed for all, Amplitude: 5mA, Frequency 1 Hz; Pulse width: 5mA; Frequency 1, Pulse width: 250µs; categorising duration: 30 minutes

22	Kraus et al (2007)	Within-subjects design; Active and Sham conditions; Randomised; Participant Blind	Subjective Mood	Age: 20-37 years; Sample Size: 22, 8, 6; Females: 23; Healthy	Left tragus (tVNS) and earlobe (Sham); Perception Level: sensory threshold (strong, but tolerable for high & just noticeable for low stimulation conditions); Amplitude: 4.0 mA (low intensity), 5.0 mA (high intensity), Frequency: 8Hz, Pulse width: 20µs; Stimulation duration: 7.5 minutes (study 1), 18 minutes (study 2 & 3)
23	Lamb et al (2017)	Between- & within-subjects design; Active and Sham conditions; Randomised; Participant & Researcher Blind	PTSD & Fear	Age: 30.4 years; Sample Size: 22; Females: 0; Clinical	Left tragus (tVNS & Sham); Perception Level: 80% of subjective comfort level for tVNS condition and 0% for sham condition), Amplitude: 5.6 mA; Frequency: 20 Hz; Wave width: 100µs; Stimulation duration: not reported
24	Li et al (2019)	Case Report; Active condition; non-randomised; No Blinding	Depression	Age: 55 years; Sample Size: 1; Females: 0; Clinical	Right & left concha (tVNS); Amplitude: 4-6 mA; Frequency: 20 Hz; Wave width: < 1ms; Stimulation duration: 2x30 minutes daily for 8 weeks
25	Liu et al (2016)	Between- & within-subjects design; Active and Sham conditions; Non-randomised; Participant Blind	Depression	Age: 37.8 years; Sample Size: 34; Females: 23; Clinical	Right & left concha (tVNS) and superior scapha (sham); Perception level: sensory threshold; Amplitude: 4-6mA; Frequency: 20 Hz; Wave width < 1ms; Stimulation duration: 2x30 minutes daily for 4 weeks
26	Rong et al (2016)	Non-randomised clinical trial; Active and Sham conditions; Non-randomised; Participant Blind	Depression	Age: 40.1 years; Sample Size: 148; Females: 117; Clinical	Right & left concha (tVNS) & superior scapha (Sham); Perception level: sensory threshold; Amplitude: 4-6mA; Frequency: 20 Hz; Wave width: 0.2ms; Stimulation duration: 2x30 minutes daily for 4 and 8 weeks

27	Rufener et al (2018)	Within-subjects design; Active and Sham conditions; Randomised; Participant Blind	Auditory Selective Attention	Age: 24.9 years; Sample Size: 20; Females: 10; Healthy	Left cymba concha (tVNS & Sham); Perception Level: Fixed for all; Amplitude: 0.5mA Frequency: 25Hz; Pulse width: 250µs; Stimulation duration: 100 minutes
28	Sellaro et al (2018)	Within-subjects design; Active and Sham conditions; Unclear of randomisation; Participant Blind	Emotion Recognition	Average Age: 20.7 years; Sample Size: 24; Females: 15; Healthy	Left concha (tVNS) & earlobe (Sham); Perception Level: Fixed for all, Amplitude: 0.5mA, Frequency: 25Hz; Pulse width: 200-300µs; Stimulation duration: 35 minutes
29	Steenbergen, Colzato and Maraver (2020)	Within-subjects design; Active and Sham conditions; Randomised; Participant Blind	Delay Discounting & Positive & Negative State Affect	Average Age: 22.3 years; Sample Size: 84; Females: 52; Healthy	Left cymba concha & earlobe (Sham); Perception Level: Fixed for all, Amplitude: 0.5mA, Frequency: 25Hz; Pulse width: 200-300µs; Stimulation duration: 75 minutes
30	Steenbergen et al (2015)	Between-subjects design; Active and Sham conditions; Randomised; Participant Blind	Action cascading	Age: 19.8 years; Sample Size: 30; Females: 26; Healthy	Left outer auditory canal (tVNS) and earlobe (Sham); Perception Level: Fixed for all; Amplitude: 0.5mA Frequency: 25Hz; Pulse width: 200-300µs; Stimulation duration: 45 minutes
31	Szeska et al (2020)	Between- & within-subjects design; Active and Sham conditions; Randomised; Unsure of Blinding	Fear extinction learning	Age: 22.8 years; Sample Size: 80; Females: 57; Healthy	Left cymba concha (tVNS) & Earlobe (Sham); Perception level: sensory threshold with no discomfort; Amplitude: 2.28mA; Frequency: 25 Hz; Pulse width: 200-300µs; Stimulation duration: 10 minutes
32	Tu et al (2018)	Between- & within-subjects design; Active and Sham conditions; Non-randomised; Participant Blind	Depression	Age: Not Reported; Sample Size: 41; Females: Not Reported; Clinical	Right (fMRI only) & left concha (tVNS) & superior scapha (Sham); Perception level: sensory threshold; Amplitude: 4-6mA; Frequency: 20 Hz; Wave width < 1ms; Stimulation duration: 6 minutes (fMRI), 20 hours (treatment)

33	Ventura-Bort et al (2018)	Within-subjects design; Active and Sham conditions; Randomised; Participant Blind	Selective Attention	Age: 20.3 years; Sample Size: 21; Females: 18; Healthy	Left cymba concha (tVNS) & earlobe (Sham); Perception level: sensory threshold; Amplitude: 0.4-3.3; Frequency: 25 Hz; Pulse width: 200-300µs; Stimulation duration: 35 minutes
34	Verkuil and Burger (2019)	Between-subjects design; Active and Sham conditions; Randomised; Participant Blind	Attentional bias	Age: 18-25 years; Sample Size: 94; Females: Not Reported; Healthy, High Worriers	Left cymba concha (tVNS) & earlobe; Perception level: fixed for all; Amplitude: 0.5 mA; Frequency: 25 Hz; Pulse width: 250µs; Stimulation duration: Unclear
35	Wang et al (2018)	Between- & within-subjects design; Active and Sham conditions; Non-randomised; Participant Blind	Depression	Age: 40.9 years; Sample Size: 37; Females: 25; Clinical	Right (fMRI only) & left concha (tVNS) & superior scapha (Sham); Perception level: sensory threshold; Amplitude: 4-6mA; Frequency: 20 Hz; Wave width < 1ms; Stimulation duration: 6 minutes (fMRI), 20 hours (treatment)
36	Warren et al (2019)	Within-subjects design; Active and Sham conditions; Randomised; Participant Blind	Selective Attention	Age: 22.5 years; Sample Size: 24, 20, 17; Females: 18, 9, 0; Healthy	Left cymba concha (tVNS) & earlobe (Sham); Perception level: fixed for all, Amplitude: 0.5 mA; Frequency: 25 Hz; Pulse width: 200-300µs; Visual duration: 80 minutes

NB: reports of blinding will indicate only the levels of blinding included in the study (e.g. “participant blind” and/or “researcher blind” or “unsure of blinding” or “no blinding”).

Quality of Life

Two studies report the effects of tVNS on quality of life (QoL). Bretherton et al. (2019) used a two week, tVNS treatment schedule for older adults in a within-subjects pre-/post-design. The Healthy Survey-Short Form (SF-36: Ware et al., 1998) was used as a QoL measure. Stimulation was applied to the tragus for 15 minutes daily for two weeks. The laterality of ear was not reported. tVNS was applied at sensory threshold with an amplitude range of 2 – 4 mA. The frequency was 30Hz, with a pulse width of 200µs. The only effect of the tVNS was a significant improvement in the role limitations factor of the QoL questionnaire. Bretherton et al. (2019) also used the Profile of Mood States (POMS: Boyle, 1987) questionnaire as a secondary outcome measure. There were significant improvements in the vigour, disturbance, tension and depression scores after 2 weeks of stimulation.

The other study, by Eren et al. (2018), investigated the effects of tVNS on QoL in patients suffering from Persistent Postural Perceptual Dizziness (PPPD). The primary outcome measure was the QoL scale EQ-5D-3L (Janssen et al., 2013). The hospital anxiety and depression scale (HADS: Zigmond & Snaith, 1983) was used as a secondary outcome measure. In a between and within-subjects design, PPPD patients were randomised to either treatment as usual (TAU) or TAU plus tVNS. Stimulation was applied prophylactically using three 90 second sessions daily for four weeks. This was the briefest of stimulation procedures. Stimulation was also applied during acute attacks of dizziness/vertigo using three 90 second sessions. The right ear was stimulated but there was no report of ear anatomy or the stimulation protocol. tVNS significantly improved the QoL of PPPD patients. tVNS also significantly reduced depression scores. Regression analysis revealed that depression, anxiety and reductions in postural sway severity accounted for 42% of the variance of QoL improvement.

Worry

Two studies investigated the effects of tVNS on cognitive processes relevant to worry, namely negative intrusive thoughts. Both studies used a healthy but high worry population in a between-subjects design. Participants were randomly assigned to either tVNS or sham stimulation and were blind to the study hypotheses. Both studies used a fixed stimulation amplitude of 0.5mA applied to the left cymba concha for tVNS and the ear lobe for sham stimulation. The frequency was set at 25Hz with a pulse width of 250 μ s. Stimulation duration was 35 minutes for one study (Burger, Van der Does, Thayer, Brosschot, & Verkuil, 2019) but was unclear for the second study (Verkuil & Burger, 2019). Both studies came from a larger, pre-registered study investigating the attentional bias effects of tVNS.

Burger, Van der Does, et al. (2019) investigated the frequency of intrusive, worrying thoughts during tVNS or sham stimulation. These thoughts were measured with and without a pre-worry induction task and represent induced or spontaneous worrying thoughts, respectively. Spontaneous worry was significantly lower for participants who received tVNS. Negative thoughts intrusions increased significantly after the worry induction for tVNS participants, but not sham participants. There were no significant stimulation group differences in worrying thoughts after worry induction

Verkuil and Burger (2019) investigated the attention bias of high worriers to emotional faces during tVNS or sham stimulation. Neutral or fearful faces cued the location of a stimulus and participants were required to respond to the location of the cued stimulus. An inhibition of return response (i.e. whereby participants are slower to return to an area where a previous, irrelevant stimulus was presented) was observed but this was not significantly influenced by the valence of the facial cues or the stimulation condition.

Attention

In addition to Verkuil and Burger (2019) described in the *Worry* section above, three other studies investigated aspects of attention. In all three studies, the P3 event related potential (ERP) of the electroencephalogram was used as the primary outcome variable. The P3 reflects the time an individual requires to categorise a stimulus and is thus used as a marker in selective attention paradigms. All three studies used healthy participants and an Oddball Task in their within-subjects design. The Oddball Task assesses participants' reactions to a stimulus that interrupts a sequence of repetitive stimuli. tVNS and sham stimulation order was randomised, and participants were blind to the study hypotheses and stimulation. The left cymba concha and ear lobe was stimulated for tVNS and sham stimulation, respectively in all studies. Two studies (Rufener, Geyer, Janitzky, Hans-Jochen, & Zaehle, 2018; Warren et al., 2019) used a fixed stimulation amplitude of .05mA, with a frequency of 25Hz and a pulse width of 200-300 μ s and 250 μ s, respectively. Ventura-Bort et al. (2018) used a sensory threshold tVNS amplitude ranging from 0.4 – 3.3mA, with a frequency of 25Hz and a pulse width of 200-300 μ s. Stimulation durations were 80 minutes (Warren et al., 2019), 35 minutes (Ventura-Bort et al., 2018) and 100 minutes (Rufener et al., 2018).

Warren et al. (2019) and Ventura-Bort et al. (2018) found no overall effect of tVNS on P3. However, tVNS did significantly increase alpha-amylase in Warren et al. (2019) study and Ventura-Bort et al. (2018), in an exploratory analysis, found tVNS increase P3b amplitude to easy targets and significantly increased alpha-amylase. Alpha amylase was also positively correlated with P3b amplitudes for easy targets. Rufener et al. (2018) found that tVNS significantly increased P3 amplitudes and reduced P3 latencies.

Inhibitory Control

Four studies have investigated the effects of tVNS on facets of inhibitory control. Various behavioural measures of inhibitory control were used across the studies. Steenbergen et al. (2015) investigated action cascading using a Stop-Change task where participants were required to respond to a stimulus on Go trials, which, on some trials, were accompanied by an inhibitory rule. In addition to this, change trials were introduced where inhibitory rules changed. Jongkees, Immink, Finisguerra, and Colzato (2018) investigated sequential action control using a serial reaction time task where participants were required to press a button corresponding to a position of a stimulus. Implicit learning of sequenced trials was then interspersed with random trials. Reaction times in response to changes in sequence, and therefore inhibition of previously learned sequences, were the primary outcome variable. Fischer, Ventura-Bort, Hamm, and Weymar (2018) investigated response conflict using a number version of the Simon task, whereby laterally presented numbers were categorised as being smaller or larger than the number 5. A “response conflict” occurs during the processing of a number that does not correspond to the laterality (i.e. left or right) of the correct button response (e.g. when the number 7 is presented on the left of the screen and requires a right-handed response). Finally, Beste et al. (2016) investigated inhibitory control using a backward inhibition paradigm, whereby task responses are cued and then changed in the presence of a different cue (i.e. task switching requires the inhibition of previous instructions) and Go/NoGo task completed with extra mental load (i.e. using mental rotation to establish the cue). All studies used healthy participants in a between-subjects design, except Fischer et al. (2018) who used a within-subjects design. Participants were randomised to stimulation condition and were blind to the study hypotheses. The left ear lobe was stimulated in each study’s sham condition. Two report tVNS stimulation of the “outer auditory canal” (Jongkees et al., 2018; Steenbergen et al., 2015), one the cyma concha (Fischer et al., 2018) and one study is not clear as to the

stimulation site (Beste et al., 2016). Stimulation amplitude was fixed at 0.5mA for three studies (Beste et al., 2016; Jongkees et al., 2018; Steenbergen et al., 2015) and one (Fischer et al., 2018) at perceptible threshold ranging for 0.4 – 3.3mA. All stimulation was set at a frequency of 25Hz with a pulse width of 200 – 300 μ s. Stimulation duration varied from 36 minutes (Fischer et al., 2018), 45 minutes (Jongkees et al., 2018; Steenbergen et al., 2015), and 60 minutes (Beste et al., 2016).

Steenbergen et al. (2015) found that tVNS significantly decreased reaction times to change trials, thereby improving action cascading performance. Jongkees et al. (2018) found that tVNS did not significantly enhance sequential learning but did significantly improve response selection. While Beste et al. (2016) found no effects of tVNS in the backward inhibition task, there was a significant reduction in false alarms in the mental rotation Go/NoGo task during tVNS. However, this was only found for trials that were higher in working memory load. Finally, Fischer et al. (2018) found a reduced Simon Effect during tVNS. Reaction times to incongruent trials, particularly after a conflict trial, were reduced. Furthermore, tVNS also reduced the phenomenon of post-conflict slowing. Fischer et al. also employed EEG during the task and found a reduced N2 component under tVNS in response to incongruent trials that proceeded a conflict trial. However, they did not find any tVNS effects of the P3 component.

Schizophrenia

Hasan et al. (2015) investigated whether treatment schedule of tVNS would influence the positive and negative symptoms of schizophrenia. The Positive and Negative Symptom Scale (PANSS) total score was used as the primary outcome variable of change. In a between and within-subjects design, individuals with a diagnosis of Schizophrenia were randomly allocated to tVNS or sham stimulation. Participants in the tVNS condition received 26 weeks of stimulation. Participants in the sham condition received 12 weeks of sham and then crossed

over to 14 weeks of tVNS. The stimulation duration was noted as occurring “throughout the day (from morning to bedtime)”. Both participants and researchers were blind to the stimulation condition. Stimulation was applied to the left “outer auditory canal” for tVNS and the ear lobe for sham stimulation. Stimulation amplitude was set at the “highest, tolerable level”. The frequency was 25Hz with a pulse width of 250 μ s. Average or range of stimulation amplitude was not provided but the device was configured to deliver intensities between 0.1mA and 10mA.

The results concluded with no significant effect of tVNS on PANSS. However, a proportion of participants (4/19) failed to complete the intervention up to the 12-week time point and only 53% were compliant with the stimulation protocol (which was undefined in the publication).

Memory

Jacobs, Riphagen, Razat, Wiese, and Sack (2015) investigated the effects of tVNS on associative memory performance in healthy older individuals. In a within-subjects design, participants learned face-name pairings during tVNS and sham stimulation. The different stimulations were conducted two weeks apart, the order of first session stimulation type was randomised and participants and researchers were blind to the stimulation condition. tVNS was applied to the left tragus and sham stimulation the left ear lobe. Stimulation intensity was fixed for all participants with an amplitude of 5mA, a frequency of 8Hz and a pulse width of 200-300 μ s. Stimulation or sham each lasted for 17 minutes. The results revealed a significant increase in the number of correct responses to face-name pairings during tVNS.

Emotion Recognition

Three studies investigated the effects of tVNS on facial emotion recognition. In a between- and within-subjects cross-over design using an adolescent clinical and non-clinical

population, Koenig et al. (2019) investigated the effects of tVNS or Sham on reaction times and error rates during three emotion recognition tasks: dynamic facial emotion recognition, static emotion recognition, and emotional Go/No Go task (response inhibition task). tVNS was applied to the left concha while sham stimulation was applied to the left ear lobe. Stimulation amplitude was fixed for all participants at 5mA, with a frequency of 1 Hz and a pulse width of 250 μ s. Performance (inhibition control) on the emotional Go/NoGo tasks improved for depressed adolescents during tVNS. Correct responses to sad faces in this decreased during stimulation, showing a reduction of negative bias for depressed adolescents. Non-depressed controls were found to make more omission errors and more incorrect responses to all emotional faces during tVNS. There were no overall effects of tVNS on the dynamic and static emotion recognition tasks. Additional analysis also revealed a significant negative association between tVNS correct responses and depression severity, and a significant positive association between tVNS omission errors and depression severity.

Colzato et al. (2017) investigated emotion recognition using the Reading the Mind in the Eye Test (RMET). Participants are required to select the appropriate emotion from a list that corresponds to the presented eye region photo. Participants were randomly allocated in a within-subjects design to tVNS or sham stimulation in the first session. The alternative stimulation was applied in session two, two weeks after the first. Participants were blind to the study hypotheses and stimulation conditions. tVNS was applied to the left cymba concha and sham stimulation to the ear lobe. Stimulation intensity was fixed for all participants with an amplitude of 0.5mA, frequency of 25Hz and pulse width of 200-300 μ s. Stimulation was applied for a duration of 35 minutes per session. tVNS was found to significantly increase the accuracy of facial emotion recognition for easy trials on the RMET. There was also no effect of tVNS on state mood assessments (using a pleasure-arousal grid) or physiological measures (i.e. heart rate and blood pressure).

Sellaro et al. (2018) investigated whether tVNS could influence the recognition of emotion displayed on faces and expressed through the body. Healthy participants had to choose from four labels (happy sad, angry, fear) the one that best described the emotion being expressed in the photos of faces and bodies. In a within-subjects design, participants were allocated (unclear if this was randomised) to tVNS or sham stimulation in the first session. The alternative stimulation was applied in session two, two weeks after the first. Participants were blind to the study hypotheses. tVNS was applied to the left cymba concha and sham stimulation to the ear lobe. Stimulation intensity was fixed for all participants with an amplitude of 0.5mA, frequency of 25Hz and pulse width of 200-300 μ s. Stimulation was applied for a duration of 35 minutes per session. Compared to sham stimulation, tVNS enhanced the emotion recognition for faces but not bodies. There was no evidence that tVNS improvements were specific to any particular emotion.

Decision Making

Steenbergen, Colzato, and Maraver (2020) used a delay discounting task to investigate the effects of tVNS on decision making. Healthy participants had to make decisions about accepting an immediate, but lower value, reward or a delayed, but higher value, reward. The reward value that a participant is willing to hold out for was calculated and used as the dependant variable (k-value: the higher the k value the greater devaluation of the reward based on the duration of waiting. This represents a greater rate of discounting of the higher value reward). Positive and negative affect was also measured to investigate the effects of tVNS on mood and its interaction with the k-value. Using a within-subjects design, participants were randomly allocated to either tVNS or sham stimulation first. Participants were also blind to the study hypothesis and stimulation conditions. tVNS was applied to the left cymba concha and sham stimulation to the ear lobe. Stimulation intensity was fixed for all participants with an amplitude of 0.5mA, frequency of 25Hz and pulse width of 200-300 μ s. Stimulation was applied

for a duration of 75 minutes per session. The results revealed that tVNS significantly increased the k-value for those experiencing low positive affect. This means that the discounting of a higher value reward, based on the delay time of receiving that reward, became steeper (quicker) for those with low positive affect.

Creativity

Colzato, Ritter, and Steenbergen (2018) investigated the effects of tVNS on creativity. In this study, creativity was operationalised via performance on divergent and convergent thinking tasks. Divergent thinking was assessed with Alternative Uses Task (AUT) whereby participants were asked to name as many possible uses of a brick. A score was calculated by two independent scorers based on the number of listed uses (fluency), uses in different categories (flexibilities), creativity, originality and usefulness. Convergent thinking was assessed via 1) Idea Selection Task (IST: choosing the most creative items from a list in response to a societal problem and scored against an expert rating), 2) Remote Association Test (RAT: generating a word that connects three presented word cues), 3) Creative Problem Solving task (CPS: two illustrated rooms are presented with a specific problem solving task. Scores correspond to complete, partial or no solution). Using a between-subjects design, participants were randomly allocated to either tVNS or sham. Participants were also blind to the study hypothesis and stimulation conditions. tVNS was applied to the left cymba concha and sham stimulation to the ear lobe. Stimulation intensity was fixed for all participants with an amplitude of 0.5mA, frequency of 25Hz and pulse width of 200-300 μ s. Stimulation was applied for a duration of 40 minutes per session. The results revealed that, compared to sham stimulation, participants receiving tVNS showed increases in divergent thinking. They were able to generate more alternatives uses for the object, more categories of usage, and greater originality. No effects of stimulation condition were found for convergent thinking.

Flow

Colzato, Wolters, and Peifer (2018) investigated the effects of tVNS on the experience of Flow. Flow was described by the authors as the “pleasant psychological state that people experience when completely absorbed in an activity...A rise of concentration and attention, and an enhanced sense of control without keeping track of time”. Flow was assessed using the Flow Short-Scale (absorption (e.g. "I did not notice the time going by") and fluency (e.g. "I feel that everything is under control") subscales) that was completed after an emotion categorisation task, which was not analysed as part of the study. Using a within-subjects design, participants were randomly allocated to either tVNS or sham stimulation first. Participants were also blind to the study hypothesis and stimulation conditions. tVNS was applied to the left “outer auditory canal” and sham stimulation to the ear lobe. Stimulation intensity was fixed for all participants with an amplitude of 0.5mA, frequency of 25Hz and pulse width of 200-300µs. Stimulation was applied for a duration of 50 minutes per session. The results revealed that tVNS significantly reduced absorption scores as compared to sham stimulation. There was no effect of tVNS on fluency scores compared to sham stimulation.

Adverse Events Reporting

Of the 36 studies, 24 studies reported on side effects. However, this varied in terms of the recording and assessment of side effects. The most comprehensive assessment of adverse events was a rating scale of common side effects (e.g. headache, pain in the neck, nausea, muscle contractions in the face or neck, prickling sensation under the electrodes, burning sensation under the electrodes and a general feeling of discomfort: Burger et al., 2016). This was completed in 12 studies, the majority of which appear to come from the same research group (Burger, Van der Does, et al., 2019; Burger et al., 2018; Burger et al., 2016; Colzato et al., 2017; Colzato, Wolters, et al., 2018; Fischer et al., 2018; Jacobs et al., 2015; Jongkees et al., 2018; Sellaro et al., 2018; Steenbergen et al., 2020; Steenbergen et al., 2015; Ventura-Bort

et al., 2018). However, not all these studies provided the statistics data of their analysis of side effects. Some studies report the use of side effect diaries but no indicated of how these were analysed and no results were provided (Fang et al., 2017; Fang et al., 2016; Liu et al., 2016; Rong et al., 2016; Tu et al., 2018). Several studies merely stated that there were no side effects reported by participants or that no “major” side effects were reported (Colzato, Ritter, et al., 2018; Eren et al., 2018; Hasan et al., 2015; Hein et al., 2013; Kraus et al., 2007; Lamb et al., 2017). Burger et al. (2017) reported that the painfulness of tVNS resulted in the reduction of amplitude in 7 participants. However, no further assessment of side effects was taken. The most common side effects reported are low levels of stinging and burning from stimulation.

Table 2 Summary of results from systematic review studies

Study Number	Citation	Psychological Task	Primary Outcome Measure(s)	Primary Outcome(s)
1	Beste et al (2016)	Backward inhibition paradigm and mental workload response inhibition paradigm.	Behavioural responses: Reaction times, error rates and false alarms	No stimulation effects for backward inhibition. No stimulation effects for reaction times or error rates in the Go-NoGo memory loaded task. Significant reduction in False Alarms during tVNS in the Go-NoGo memory loaded task, but only for the block of trials that had higher working memory load.
2	Bretherton et al (2019)	No Task. Stimulation Only	Study 3: HRV/BRS, QoL (SF-36), Mood (POMS)	Study 3: visit two HRV markers significantly increased during stimulation and recovery compared to visit one. Only Role impingement of the QoL questionnaire significantly improved at visit 2. POMS (vigour, disturbance, tension, depression) significantly improved at visit 2.
3	Burger, Van der Does et al (2019)	Breathing Focus Task (BFT)	Negative Thought Intrusions (from BFT)	Pre-worry ("spontaneous" worry): tVNS participants reported significantly fewer intrusive negative thoughts compared to sham participants. Post-worry ("induced worry"): tVNS participants reported significantly more intrusive negative thoughts compared to the pre-worry phase but there were no between-group differences.
4	Burger et al (2018)	Fear conditioning paradigm. Stimulation during extinction phase only.	Expectation rating and startle response to electric shock (US)	Fear conditioning paradigm was successfully executed. There were no effects of tVNS on declarative fear extinction. Effect of tVNS on US expectancy ratings at the start of the extinction phase.

5	Burger, Van Dies et al (2019)	Fear conditioning paradigm. Stimulation during generalisation and extinction phases only.	Expectation rating and startle response to electric shock (US)	<p>Fear conditioning was successfully executed. Generalization: participants showed significant increase in expectancy ratings and startle response as a function of stimulus similarly (generalisation effect). There were no significant between condition differences in expectancy ratings or startle response. Extinction: expectancy ratings were significantly lower for conditioned stimuli during the tVNS condition however, for both conditions, extinction did not fully occur by the end of the extinction phase. Startle response significantly declined over the extinction phase but there were no between group differences in this decline.</p>
6	Burger et al (2017)	Fear conditioning paradigm. Stimulation during extinction phase only.	Expectation rating and startle response and skin conductance to electric shock (US)	<p>Extinction Phase: Fear conditioning was maintained in Day 2. Expectancy ratings significantly decreased over the extinction phase but there was no main effect of stimulation. However, tVNS was shown to significantly reduce the gap between ratings on CS+ and CS- trials. Early analysis of the extinction phase did indicate a significant reduction in expectancy ratings in the tVNS condition, indicating a potential acceleration of extinction during tVNS. There were also no significant effects of stimulation condition on psychophysiological responses, with the exception of initial accelerated decline in startle responses. Retention Phase: there were renewed declarative fear responses (expectancy rates) at the beginning of Day 3. There were no significant group differences of this renewed fear response. There was also no significant effect of tVNS on expectancy ratings during retention phase extinction. Physiological responses were similar to extinction phase; startle response showed an initial accelerated decline during tVNS.</p>
7	Burger et al (2016)	Fear conditioning paradigm. Stimulation during extinction phase only.	Expectation rating and startle response to human scream (US)	<p>Fear conditioning paradigm was successfully executed in 31 participants. tVNS facilitated declarative fear extinction compared to sham. There were no condition effects on physiological measures, indicating non-declarative fear extinction. There were no significant condition effects on fear extinction retention.</p>

8	Colzato, Sellaro and Beste (2017)	Reading the Mind in the Eye Test	Percentage of correct responses on the RMET	tVNS significantly increased the accuracy of facial emotion recognition for the easy trials of the RMET.
9	Colzato, Ritter and Steenbergen (2018)	Alternative Uses Task (AUT); Idea Selection Task; Remote Association Test; Creative Problem-Solving Task	Scores from the creative thinking tasks.	Compared to sham stimulation, participants receiving tVNS showed increases in divergent thinking whereby they were able to come up with more alternatives uses to the object, more categories of usage, and originality. No effects of stimulation condition were found for convergent thinking.
10	Colzato, Wolters and Peifer (2018)	No Task. Stimulation Only	Flow Short-Scale: absorption (e.g. "I did not notice the time going by" and fluency (e.g. "I feel that everything is under control") subscales	tVNS significantly reduced absorption scores as compared to sham stimulation. There was no effect of tVNS on fluency scores compared to sham stimulation.
11	Eren et al (2018)	No Task. Stimulation Only	Quality of Life Measure: EQ-5D-3L	tVNS significantly improved QoL scores. No significant change was experienced for TAU. The pooled tVNS data after cross over (n=16) this significant improvement in QoL was sustained. Regression analysis revealed that depression, anxiety and postural sway accounted for 42% of the variance of QoL improvement.
12	Fang et al (2017)	No Task. Stimulation Only	Bold Signal and Depression scores from Hamilton Depression Rating Scale (HAM-D)	Depression scores significantly reduced for both sham and tVNS stimulation, but an interaction effect showed that tVNS produced significantly greater decrease in depression scores compared to sham. fMRI results show that during tVNS there was significantly more activation of the left anterior insula compared to sham stimulation. Furthermore, activation of the insula during the first session was negatively correlated with depression scores for the tVNS condition only.

13	Fang et al (2016)	No Task. Stimulation Only	Functional Connectivity Bold Signal and Depression scores from Hamilton Depression Rating Scale (HAM-D)	Mood: HAM-D and self-reported anxiety and depression scores significantly reduced for those receiving tVNS. HAM-A showed a trend for improvement. DMN: The functional connectivity of the DMN and anterior insula and parahippocampus were significantly reduced after tVNS. Connectivity with Orbital Prefrontal Cortex was increased. Decreases in depression scores were associated with significant increased function connectivity between DMN and Anterior Cingulate Cortex, Medial Prefrontal Cortex and significant reductions in OPFC connectivity.
14	Fischer et al (2018)	Number version of the Simon Task	Behavioural: Reaction time responses of Simon Effect (when number and response location are congruent); EEG: N2 (AAC origins and signals conflict detection) and P3 (central parietal origins and signals response inhibition and attention allocation) event related potentials	Behavioural: The Simon Effect was replicated. During tVNS the Simon Effect was reduced. tVNS decreased reaction times to incongruent trials particularly after a previous conflict trial. tVNS also reduced post-conflict slowing of reaction times. EEG: Reduced N2 amplitude during tVNS for incongruent trials that proceeded a previous conflict trial. No significant effects of tVNS on P3 responses.
15	Genheime et al (2017)	Contextualised fear conditioning paradigm. Stimulation during extinction phase only.	Expectancy ratings for US, arousal, valence and anxiety ratings for each contextualisation room	There were no significant effects of tVNS on any of the primary outcome measures, despite the conditioned fear paradigm being successful.
16	Gurel et al (2020)	Trauma paradigm listening to trauma audio; Public Defence Task; Math task with negative feedback.	Electro-cardiograph (ECG), Seismocardiography (SCG), Photo plethysmography (PPG), Respiration (RSP), Electrodermal activity (EDA), Blood pressure (BP)	Cervical tVNS resulted in reduced peripheral and cardiac sympathetic nervous system responses. Reduction in sympathetic responses during trauma audio and stress inducing tasks for cervical tVNS compared to sham. Cervical tVNS also resulted reduced parasympathetic ECG withdrawal in responses to trauma audio and stress induction task
17	Hasan, et al (2015)	No Task. Stimulation Only	PANSS (Positive and Negative Symptom Scale) total score	No significant effect of stimulation on PANSS. 15 participants completed the study up to T1 (12 weeks stimulation). 53% of participants were compliant with stimulation protocol.

18	Hein et al (2013)	No Task. Stimulation Only	Hamilton Depression Rating Scale (HAMD), Beck's Depression Inventory (BDI)	Significant reduction in BDI scores for those receiving tVNS. No differences in stimulation condition for HDRS.
19	Jacobs et al (2015)	Face-name association memory task,	Correct responses and reaction times during recall	There was a significant increase in the number of "hits (correct responses" to face-name pairings during tVNS.
20	Jongkees et al (2018)	Serial reaction time tasks	Reaction times from Serial Reaction Time Task	tVNS did not significantly enhance sequential learning. tVNS did significantly enhance response selection.
21	Koenig et al (2019)	Emotion Recognition Tasks: categorising gradually changing facial expressions; categorising static facial expressions; Emotional Go/NoGo task	Response times, Correct responses, errors of omission and commission in 3 facial recognition tasks (dynamic and static facial recognition, emotional Go/No Go task)	Task 1 & 2: no main effect of condition (tVNS/sham). Emotional Go/NoGo: main effect of tVNS. Significant group x condition interaction: in MDD patients, correct responses to sad faces decreased under tVNS; in controls, correct hits on happy/ sad emotions decreased and omission errors increased under tVNS.
22	Kraus et al (2007)	The Adjective Mood Scale	Adjective Mood Scale (AMS), BOLD signal changes (fMRI)	Study 1: Significant decrease in Adjective Mood Scale during tVNS (improved mood) and significant increase during Sham. Study 2: Decrease of BOLD signal during tVNS in limbic and temporal regions, increase of BOLD signal in the insula, precentral gyrus, right thalamus and right anterior cingulate (comparable for high and low intensity stimulation). Study 3: "unspecific" activation patterns.
23	Lamb et al (2017)	Startle-Blink Paradigm	HRV and Electrodermal responses	HRV was increased for all participants during the tVNS condition compared to sham. tVNS reduced features of startle EDR for both participant groups. Sample size was too small for interactional effects.
24	Li et al (2019)	No Task. Stimulation Only	Hamilton Anxiety Scale (HAMA), self-rating Depression Scale (SDS), self-rating Anxiety Scale (SAS), Functional connectivity (fMRI) and concentrations of GABA and glutamate (MRS)	Symptoms of depression improved according to scores on HAMD, HAMA, SDS and SAS. No relapse after 3 months.

25	Liu et al (2016)	No Task. Stimulation Only	Hamilton Depression Rating Scale (HAMD), resting state functional connectivity (rsFC)	Scores for total Hamilton Depression Rating Scale and subscales of anxiety and retardation significantly decreased in the tVNS group compared to Sham. Increased rsFC between right amygdala and left DLPFC, associated with symptom severity changes.
26	Rong et al (2016)	No Task. Stimulation Only	Hamilton Depression Rating Scale	Decrease in Hamilton Depression Rating Scale scores significantly greater in tVNS group compared to Sham.
27	Rufener et al (2018)	Auditory Oddball Task	Reaction times from the Oddball task, P3 latency and amplitude from EEG	Both tVNS and transcranial random noise stimulation (tRNS) reduced P3 latencies. TVNS increased P3 amplitude and tRNS decreased target reaction times.
28	Sellaro et al (2018)	Emotion categorisation of face and body stimuli	Facial recognition accuracy	tVNS improved the accuracy of emotion categorisation for difficult displays of emotion, and only for facial stimuli. tVNS improvements were also not specific to any particular emotion.
29	Steenbergen, Colzato and Maraver (2020)	Delay Discounting Task	Delayed discounting (K value) and positive and negative affect as measured by PANAS	tVNS significantly increased the k value for those experiencing low positive affect. This means that the discounting of a higher value reward, based on the delay time of receiving that reward, became steeper (quicker).
30	Steenbergen et al (2015)	Stop-Change Paradigm	Reaction time (to go trials, stop trials, stop trials with simultaneous response change, stop trials plus delayed response change)	tVNS significantly decreased reaction times to change trials, thereby improving action cascading.

31	Szeska et al (2020)	Fear conditioning paradigm. Stimulation during extinction phase only.	Shock expectancy ratings; Startle eyeblink response;	tVNS reduced fear expectancy ratings compared to sham condition, which was most notable at the beginning of the extinction phase (session 2). tVNS also reduced potentiation of the startle reflex at the end of extinction training (session 2) compared to sham stimulation. Initial short-term extinction memory recall was unaffected by tVNS (session 3) however, subsequent trials showed that tVNS significantly reduced startle responses and expectancy ratings. tVNS did not affect the expectancy ratings during the reinstatement of learned fear in session 3 but did significantly reduce startle responses. Initial long-term recall of extinction memory was unaffected by tVNS (session 4). However, subsequent trials of extinction memory recall showed that tVNS did significantly reduced startle responses and expectancy ratings (session 4).
32	Tu et al (2018)	No Task. Stimulation Only	Hamilton Depression Rating Scale, fMRI (functional connectivity)	Real tVNS had significantly stronger treatment effects than Sham as measured by the Hamilton Depression Rating Scale at week 4 compared to baseline. Continuous tVNS significantly modulated the strength of medial hypothalamus - rostral anterior cingulate cortex functional connectivity. The strength of the connection was significantly associated with tVNS treatment effects.
33	Ventura-Bort et al (2018)	Visual Oddball Task	Reaction times, Accuracy (Oddball Task), P3a and P3b Amplitude (EEG), heart rate, blood pressure, salivary alpha-amylase (Autonomic measures)	No effects of stimulation on Autonomic measures, Reaction times and Accuracy (Oddball Task), P3a and P3b Amplitudes. Secondary, post-hoc, hypotheses-driven analyses revealed tVNS increased P3b amplitude for easy targets (compared to standard) and increased salivary alpha-amylase (compared to baseline). Changes in alpha-amylase levels correlated positively with P3b amplitudes for easy targets.
34	Verkuil and Burger (2019)	Exogenous Cueing Task	Reaction time	An inhibition of return response was observed but this was not significantly influenced by the valence of the facial cues or the stimulation condition.

35	Wang et al (2018)	No Task. Stimulation Only	Hamilton Depression Rating Scale, fMRI (functional connectivity)	Clinical outcomes: Scores on the Hamilton Depression Rating Scale decreased in the tVNS group from baseline to week 4. fMRI: Compared to sham, active tVNS significantly increased functional connectivity between left nucleus accumbens and bilateral medial prefrontal cortex / rostral anterior cingulate cortex in the slow-5 frequency band. This increase was negatively correlated with changes in symptom severity (HAMD) in the real tVNS group
36	Warren et al (2019)	Classic and Novelty Visual Oddball Task	Salivary cortisol and alpha-amylase, P3 amplitude, pupil size	The stimulation did not influence pupil size and P3 amplitude. TVNS increased salivary alpha-amylase and attenuated a decrease in salivary cortisol that was observed in the Sham stimulation.

Discussion

This systematic review aimed to determine the domains of cognition and emotion effected by tVNS, the type of psychological tasks and outcome measures used to assess these effects, the participant groups investigated, comparators used, and the stimulation protocols employed. Thirty-six studies were eligible after a systematic review of the literature. The areas of cognition and emotion reported were varied, including symptoms of depression, PTSD and schizophrenia, cognitive processes such as conditioned fear extinction, attention, memory, inhibitory control, creativity, decision making, emotion recognition, flow, worry, and quality of life. Effects on emotion were investigated predominantly via self-reported depression measures or state measures of affect.

Domains of Cognition

There was evidence of tVNS effects in every cognitive domain investigated. However, these were often only partially supportive of hypotheses, based on exploratory analysis or inconsistently replicated. The most promising evidence comes from investigations into fear extinction learning (Burger et al., 2018; Burger, Van Diest, et al., 2019; Burger et al., 2017; Burger et al., 2016; Genheimer et al., 2017; Szeska et al., 2020), inhibitory control (Beste et al., 2016; Fischer et al., 2018; Jongkees et al., 2018; Koenig et al., 2019; Steenbergen et al., 2015), and attention (Rufener et al., 2018; Ventura-Bort et al., 2018; Warren et al., 2019).

Fear extinction learning was facilitated for participants receiving tVNS as measured by reductions in declarative fear memory responses (expectancy ratings) (Burger, Van Diest, et al., 2019; Burger et al., 2016; Szeska et al., 2020). However, the same effect was not reliably found in two other studies (Burger et al., 2018; Burger et al., 2017). Nevertheless, during exploratory analysis these two studies, and another by Szeska et al. (2020), did find significant reductions in declarative fear memory for participants receiving tVNS at the early stages of

extinction. Only Szeska et al. (2020) found an overall reduction in non-declarative fear memory (startle response) during tVNS. Both declarative and non-declarative effects of tVNS were also present 28 days after the initial extinction phase. Szeska et al. (2020) state that their personalised stimulation amplitude for participants, compared to the standardised stimulation employed in the Burger et al. studies, and their simplified conditioning paradigm, may have contributed to both declarative and non-declarative effects. However, Burger et al. (2017) did find a reduction in non-declarative fear memory when they analysed the initial segment of the extinction phase, which was also the case for startle responses assessed on day three of their paradigm. Further research is required to investigate the ways in which researchers can capitalise on these initial phases of extinction learning to maximise tVNS effects. The more definitive results from the Szeska et al. (2020) study also suggest that personalised stimulation amplitudes may provide greater tVNS efficacy.

All of these studies cite the LC-NE as a potential underlying mechanism of change elicited by tVNS. More specifically, release of NE is thought to provide salience to specific cued learning during extinction and facilitate long term potentiation of the learned relationship in the hippocampus (Mueller & Cahill, 2010; Sara & Bouret, 2012). These studies also note the potential of tVNS as an adjunct to exposure therapy for anxiety disorders such as phobias and PTSD. Genheimer et al. (2017) tried to take this further in a tVNS virtual reality (VR) conditioned fear paradigm. The use of VR and a more contextualised conditioning paradigm using rooms was thought to offer greater fidelity to therapeutic exposure work. However, despite successful fear conditioning there were no differences between tVNS and sham conditions on any outcome measures.

In terms of cognitive control there were facilitatory effects in all studies reported despite the varied use of tasks (Beste et al., 2016; Fischer et al., 2018; Jongkees et al., 2018; Steenbergen et al., 2015). These studies also cite the role of NE and GABA neurotransmitters

in inhibitory control. They suggest that NE reduces response conflict by increasing cognitive flexibility and increased focus on task characteristics. This is also consistent with increased activation in the pre-frontal cortex and increased connectivity between limbic structures and the pre-frontal cortex (Fang et al., 2017; Fang et al., 2016; Liu et al., 2016; Tu et al., 2018; Wang et al., 2018). Interestingly, subjective reports of flow experience during tVNS were reduced. This was mainly characterised by a reduction in absorption scores. Colzato, Wolters, et al. (2018) propose that increases in phasic LC activation results in a “network reset” of attention, allowing cognitive flexibility and rapid behavioural adaptations (Sara, 2009; Sara & Bouret, 2012), which subsequently reduced the experience of flow in their study. However, this could also be a potential mechanism facilitating inhibitory control more generally.

The effects of tVNS on attention revealed mixed results. Warren et al. (2019) and Ventura-Bort et al. (2018) found no overall effect of tVNS on the P3, which is an ERP indicative of the time it takes someone to categorise a stimulus. However, Ventura-Bort et al. (2018), in an exploratory analysis, found tVNS increased P3b amplitude (P3b is thought to be NE mediated while P3a is thought to be dopaminergic) to easy targets and Ruffener et al. (2018) found that tVNS significantly increased P3 amplitudes and reduced P3 latencies. These results suggest that attention could be enhanced during tVNS. Verkuil and Burger (2019) further investigated tVNS’s role in attention by exploring attentional bias in high worriers to emotional faces. More specifically, they were interested in the effects on inhibition of return to fearful and neutral faces. However, tVNS did not affect any outcome measures.

While Verkuil and Burger (2019) found no effect of tVNS for emotion attentional bias, tVNS was found to improve emotion recognition and categorisation of faces (Colzato et al., 2017; Sellaro et al., 2018) but not bodies. This was the case for easy, partial face stimuli (Colzato et al., 2017) and for difficult whole face stimuli (Sellaro et al., 2018). However, Koenig et al. (2019) found no effect of tVNS during facial emotion recognition in depressed

adolescents or their non-depressed controls. They did however find an effect in an emotional Go NoGo task whereby depressed participants exhibited a reduction in correct responses to sad faces during tVNS. Control participants also displayed reductions in both happy and sad hits and increased omission errors during tVNS. These findings suggest tVNS resulted in an impairment in recognising negatively valenced emotional stimuli. The authors suggest that this may be the result of reduced attentional bias. However, this would be inconsistent with null results found for high worriers in the Verkuil and Burger (2019) study, but differences in participant characteristics and face stimuli could account for these discrepancies. Both Colzato et al. (2017) and Sellaro et al. (2018) cite the polyvagal theory (Porges, 2009, 2011) as a potential mechanisms underlying improved emotion recognition during vagus stimulation.

In terms of worry related cognition, Burger, Van der Does, et al. (2019) found that tVNS reduced the amount of *spontaneous*, intrusive negative thoughts in high worriers, but no effect was found for occurrence of *induced* negative thoughts. Burger, Van der Does, et al. (2019) suggest several possible explanations for these results. For example, stimulation of the vagus nerve results in increased connectivity between the prefrontal cortex and the amygdala (Liu et al., 2016), a pathway found to be attenuated for high worriers. Thus, improved prefrontal control over spontaneous thought could explain the results. Alternatively, changes in activation of the default mode network during tVNS (Yakunina, Kim, & Nam, 2017) could also influence self-referential processing and consequently negative self-referential intrusions.

Other, single study investigations into the effects of tVNS on cognition report numerous positive effects. In relation to the evidence of memory improvements during VNS in Alzheimer's patients (Vonck et al., 2014), Jacobs et al. (2015) found increases in associative memory accuracy in healthy older adults during tVNS. They suggest that activation of the hippocampus and NE release during tVNS may underlie these results. Colzato, Ritter, et al. (2018) found an increase in creativity (operationalised as divergent thinking). The authors

suggest that increased GABA and NE release during tVNS may facilitate selection processes under situations of high selection demand, which is crucial for divergent thinking. Finally, Steenbergen et al. (2020) found an increase in delayed discounting decision making during tVNS when participants experienced lower pleasant mood (as measured by the PANAS). They suggest these results are in line with the Somatic Marker Hypothesis (Damasio et al., 1996; Poppa & Bechara, 2018) whereby autonomic and somatic bodily states associated with the experience of emotions influences cognitive processes. They state that the tVNS can increase arousal to facilitate goal-relevant behaviour, which in this case was to choose immediate reward to maintain or improve their pleasant mood. However, these results should be interpreted with caution as the high and low pleasant mood states were derived from a median split of the positive affect factor on the PANAS, which is unusual. Furthermore, state affect was assessed only at the beginning of each session. It is not clear whether state affect can change during tVNS.

Emotion and Clinical Studies

The most consistent evidence for tVNS effects on mood come from studies of depressed participants. All eight studies reported significant improvements in self-reported depression scores, namely the HAM-D (Fang et al., 2017; Fang et al., 2016; Liu et al., 2016; Rong et al., 2016; Tu et al., 2018; Wang et al., 2018), with the exception of Hein et al. (2013) who found a reduction in symptoms on the BDI. While consistent with VNS studies, these results require caution as six report using the same sample of participants. Thus, further, better quality research, with greater sample sizes in randomised controlled trials is required. Consistent with these results are two studies that assessed quality of life. Bretherton et al. (2019) found that tVNS improved the quality of life domains of vigour, disturbance, tension and depression for healthy, older adults after two weeks of stimulation. This study suggested that tVNS may attenuate age related decline in autonomic functioning (a shift towards sympathetic

prevalence). Quality of life and depression scores also improved for individuals with Persistent Postural Perceptual Dizziness after four weeks of stimulation (Eren et al., 2018). The researchers suggested that activation of the cingulate cortex during tVNS may alleviate depression symptoms while NE release in the insular cortex during may account for improved postural control in these participants.

Only one study specifically investigated the effects of tVNS on state affect. As part of a tVNS fMRI study, Kraus et al. (2007) used the Adjective Mood Scale (adjectives representing different dimensions of affect) as a primary outcome measure. They found that tVNS improved these mood scores, while sham stimulation deteriorated mood. However, several other studies investigating state affect as a secondary outcome measure did not report any interactions with tVNS (Burger, Van der Does, et al., 2019; Burger et al., 2018; Burger, Van Diest, et al., 2019; Burger et al., 2017; Burger et al., 2016; Colzato et al., 2017; Genheimer et al., 2017; Koenig et al., 2019). It is worth noting that only three of these studies (Colzato et al., 2017; Genheimer et al., 2017; Koenig et al., 2019) assessed state affect before and after stimulation. This allows for an investigation into the causal role of tVNS in affect change. All other studies assessed state affect directly prior to or only after stimulation, using scores as covariates in analysis.

Finally, one study assessed the effects of tVNS on positive and negative symptoms for participants diagnosed with schizophrenia. No effect of tVNS was found for either positive or negative symptoms. While the study design was ambitious, there was no clear rationale for treatment length and the daily stimulation protocol. Perhaps a shorter study with patient involvement in the design could result in greater treatment completion rates and treatment fidelity.

Research design

Most studies used a sham-controlled condition in either a within- or between subjects' design. Single blindness (participants) was also reported for the majority of studies; however, this was rarely assessed, and when assessed never incorporated into the analysis. All studies investigating a cognitive domain employed a psychological task to assess their cognition of interest. It is unfortunate that studies investigating depression only reported depression symptoms as their outcome. There was a missed opportunity to assess cognitive and affective processes of depression beyond general symptomology. Psychological tasks could have helped address questions on the mechanisms of depression (e.g. attentional bias to negative information) (Everaert, Grahek, & Koster, 2017; Kube, Schwarting, Rozenkrantz, Glombiewski, & Rief, 2020). Koenig et al. (2019) was the only study to investigate cognitive processes of depressed participants, discovering a reduction in correct responses to negative faces in a Go NoGo trial during tVNS, potentially highlighting an effect of tVNS for negative attentional bias. Clinical trials were often long, with no clear rationale for treatment duration or stimulation protocols. Nevertheless, improvements in symptoms were obtained for all studies of depressed patients. Further work is required to investigate the mediating role of cognition in depression symptoms during tVNS, as well as further investigations into potential "dose response" curves.

Participants

The majority of participants were young, healthy students and, therefore, the extent to which results can be generalised to other demographic groups is unclear. Two studies investigated an older adult sample (Bretherton et al., 2019; Jacobs et al., 2015) and only one study has investigated adolescents (Koenig et al., 2019). Clinical groups included individuals with depression (Fang et al., 2017; Fang et al., 2016; Hein et al., 2013; Koenig et al., 2019; Li

et al., 2019; Liu et al., 2016; Rong et al., 2016; Tu et al., 2018; Wang et al., 2018), PTSD or history of trauma (Gurel et al., 2020; Lamb et al., 2017), and schizophrenia (Hasan et al., 2015). Both Verkuil and Burger (2019) and Burger, Van der Does, et al. (2019) studied healthy individuals with high worry traits, and Eren et al. (2018) explored the effects of tVNS in a group of individuals with persistent postural-perceptual dizziness, which is often comorbid with mood disorders.

Stimulation Protocols

Stimulation protocols were heterogeneous across studies. The most consistent protocols were from the Belgium and Netherlands research teams (Burger, Van der Does, et al., 2019; Burger et al., 2018; Burger, Van Diest, et al., 2019; Burger et al., 2017; Burger et al., 2016; Colzato, Ritter, et al., 2018; Colzato et al., 2017; Colzato, Wolters, et al., 2018; Steenbergen et al., 2020; Steenbergen et al., 2015). They used a fixed stimulation amplitude of 0.5mA with a frequency of 25Hz and a pulse width of 200-300 μ s. Stimulation was consistently applied to the Left cymba concha during tVNS and the left earlobe during sham. Despite evidence of other outer ear areas (e.g. tragus) having vagal afferents (Badran et al., 2018), these studies report that the cymba Concha has the most convincing evidence of vestibular afferent activation as well as evidence that no other cranial nerve innervates the area (Burger, D'Agostini, Verkuil, & Van Diest, 2020). Furthermore, the left ear is used to avoid potential cardiac effects due to efferent vagal fibers in the right ear (Kreuzer et al., 2012; Nemeroff et al., 2006).

Seventeen other studies report the use of personalised stimulation amplitudes at either a sensory threshold or a perceptible, but comfortable, threshold. Not all studies report on the method of setting thresholds, although Lamb et al. (2017) and Genheimer et al. (2017) provide explicit, replicable details of threshold setting. Average amplitudes for personalised settings ranged from 0.4mA to 8mA. Interestingly, Szeska et al. (2020), who used a personalised

amplitude setting in their conditioned fear paradigm, found more consistent and encompassing effects of tVNS on fear extinction learning than the Burger et al. studies, who used a fixed amplitude of 0.5mA. Of these 17 studies, the stimulation frequency was consistently set at 25Hz with a pulse width between 200-300 μ s, and four studies stimulated the tragus instead of the cymba concha.

The duration of stimulation varied across all studies. The range of stimulation duration in a single session was between 7.5 minutes to 100 minutes, although in some instances the duration was unclear or not reported. Longitudinal studies commonly report the use of between 15 and 30 minutes of stimulation twice daily across 2 to 26 weeks. There is little evidence concerning the temporal effects of tVNS (Biggio et al., 2009; Follesa et al., 2007; Frangos et al., 2015; Hassert, Miyashita, & Williams, 2004). However, Frangos et al. (2015) note a rise and plateau in hippocampal activation after 6 minutes of tVNS. As a result, some studies (e.g. Burger, Van der Does, et al., 2019; Burger, Van Diest, et al., 2019; Colzato, Wolters, et al., 2018) employ a pre-task or “ramp-up” stimulation period, however this could range from 5 minutes to 20 minutes and many studies do not report this period. This lack of methodological detail has serious consequences for interpreting published results and for planning of future studies, including independent replications. Additional neuroimaging studies and studies using other biophysiological markers of vagus stimulation such as heart rate variability, pupillometry and alpha amylase (Burger et al., 2020) are required to establish short-term temporal changes associated with tVNS .

Most studies used earlobe stimulation for their sham condition. The use of the earlobe is due to evidence showing the area free of vagal innervation (Burger et al., 2020) and an fMRI study showing no activation of the brain stem or cortices during stimulation (Kraus et al., 2013). Burger et al. (2020) propose that future research should include an active control condition (i.e. sham stimulation applied to the earlobe) as opposed to a sham condition where

the stimulator is turned off but attached to the same anatomical location as the active condition. While it is true that earlobe stimulation keeps the cutaneous sensations of stimulation consistent across participants, there is a change in location that cannot be kept blind for participants or researchers. If a stimulation-off control can be successfully achieving (i.e. by assessing participants beliefs about the study hypotheses and the different conditions) then this leaves research design open to double-blind procedures.

Limitations

This systematic review is not without limitations. The literature was assessed by one researcher and the results could be compromised by inevitable human error. Studies could have been omitted that would have otherwise met inclusion criteria. This could have been mitigated by two researchers both checking eligibility. Furthermore, due to administrative error, the details of excluded studies (e.g. excluded based on being an animal study) were lost. This would have added transparency to excluded and included studies and provided additional information about the range of available studies within the wider field. Extraction of data from eligible studies would have benefitted from a second researcher to ensure reliability. At the very least, a second researcher could read, extract and match a proportion of the studies to increase reliability and reduce researcher bias (e.g. subjective preference for some results over others, or limitations in understanding due to breadth of studies). The systematic review could have also benefitted from a quality assessment of the included studies. This would have provided a more objective assessment of the current strength of the evidence and guide future research with more detailed recommendations with regards to design, participants, and power.

Recommendations

In a recent paper by Burger et al. (2020) six recommendations were set forth for the field of tVNS in psychological research. They set out the need for a) adequately powered studies, b) adoption of open science to promote research transparency, c) adequately designed and controlled research, d) standardised assessments of biophysiological measures, e) clear reporting guidelines for stimulation protocols, and f) established validity for biomarkers of clinical populations. They also support greater collaboration in the field and have organised an Open Science Framework folder (<https://osf.io/sn7wt>) so that researchers can report their projects and potentially create a repository for relevant data.

Further basic, but fundamental research into the anatomy of the ABVN is recommended, as well as fMRI research into the temporal latencies of tVNS across the life-span (Badran et al., 2018). Psychophysics research could also support a profiling of stimulation protocols (Stevens, 2017). A standardised approach into the assessment of side effects would also build a safer understanding of the effects of tVNS. Further use of psychological paradigms to assess cognitive differences in psychiatric populations would also be encouraged. Notably, there is a lack of qualitative evidence concerning the phenomenological experience of stimulation. Furthermore, patient involvement in research design could support treatment completion and fidelity (Crocker et al., 2018).

Much of the research in the field suggest that the LC-NE system is the underlying mechanism of change during tVNS. This may, at first, appear contradictory given that adrenaline, the peripheral counterpart to norepinephrine, is strongly associated with sympathetic nervous system activation, while the vagus nerve is a part of the parasympathetic nervous system. However, norepinephrine release during tVNS is within the central nervous system and is involved in a variety of cognitive processes – as highlighted in the review – that

are not associated with increases in physical arousal. Nevertheless, it is important to note that two studies (Warren et al., 2019 and Ventura-Bort et al., 2018) have found increases in salivary alpha amylase (SAA), a proxy for the sympathetic-adreno activation, during tVNS compared to sham stimulation. However, SAA needs to be interpreted with caution as it cannot be exclusively used as a sympathetic marker given that the parasympathetic nervous system is also involved in its co-production (Burger et al., 2020). Furthermore, the preliminary evidence of SAA increases during tVNS is not matched by decreases in heart rate variability. These results convey a complicated picture of the interconnectedness of the para- and sympathetic nervous systems. Future research should aim to elucidate these neurological and physiological pathways and how the synergy between the two peripheral nervous systems mediate tVNS results.

Conclusions

The results of this systematic review indicate the potential breadth of use of tVNS as a neuromodulator across cognition and emotion research. They also add to the existing evidence from the invasive VNS literature showing the role of the vagus nerve in improving depression and quality of life. However, the evidence and our understanding of the underlying mechanisms of change remains inconsistent and limited. The breadth of the research within this review and the heterogeneous methodology and outcome measures mean that it is difficult to make conclusive assertions to guide future research. However, it is our hope that the review will provide future researchers with a resource to reflect on the stimulation protocols used within the field (e.g. left or right ear stimulation and custom vs homogenous stimulation amplitudes), the methodological and statistical design of experiments (e.g. within and between subjects design and randomised controlled trials), and the type of psychological paradigms used to investigate cognitive and emotion (e.g. behavioural tasks and subjective mood questionnaires).

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Chapter 2 – Empirical Study

The Compassionate Vagus: effects of transcutaneous vagal nerve stimulation on cognition, emotion and heart rate variability during compassionate mind training

Abstract

Background: Compassionate mind training (CMT) is a therapeutic intervention aimed at cultivating compassionate thoughts, emotions and behaviours that can be directed towards the self and others. CMT can positively influence affect, cognition and behaviour, and vagally mediated heart rate variability (HRV) in healthy and clinical populations. However, some individuals struggle with cultivating compassion for themselves. The aim of this study was to explore the feasibility of conducting a trial into a facilitatory CMT adjunct that involves the stimulation of the vagus nerve, a parasympathetic cranial nerve that is thought to play a key role compassion.

Methods: In a randomised, double-blind, cross-over design, 42 healthy participants received transcutaneous vagus nerve stimulation (tVNS: electrical stimulation of the vagus nerve via the outer ear) and sham stimulation over two separate sessions. The affective, cognitive and HRV effects of stimulation were assessed during a phase of stimulation/sham only (T2) and during a phase of stimulation/sham plus brief CMT (T3). Measures at T2 and T3 were adjusted for baseline measure (T1) differences across the two stimulation conditions.

Results: There was a significant positive effect of phase for safe and relaxed positive affect, emotional face processing and self-compassion from T2 to T3, indicating a positive effect of CMT. This was further seen in reductions in self-criticism and negative affect at T3. There was no significant main effect of stimulation type, indicating that tVNS did not differentially affect measures. HRV measures improved from T2 to T3 and tVNS significantly increased HRV compared to sham stimulation. There were no significant combined effects of tVNS and CMT on HRV. However, graphically, data depicted greater increases in HRV during CMT while participants received tVNS compared to sham stimulation. .

Conclusions: These results provide further evidence that CMT improves self-compassion, affect, emotional face processing and HRV. They also provide evidence of HRV increases during tVNS compared to sham stimulation, which was maintained for the duration of our experimental session. While there were no significant additive effects of combined tVNS and CMT, the direction of the results were in line with our hypothesis. The results are discussed in relation to study limitation, such as the lack of statistical power and design issues, and what would be required for any future clinical trial.

Introduction

Compassion is typically defined as the sensitivity to the suffering of the self and others that is accompanied by a desire and a commitment to alleviate and prevent that suffering (Germer & Siegel, 2012; Gilbert, 2019; Gilbert & Choden, 2013; Lama, 2013). The capacity for compassion is thought to have developed over two million years ago, alongside other cognitive competences (Gilbert, 2019; Porges, 2017) such as language, self-awareness and reflection, and theory of mind. It is these competencies that differentiate human compassion from mammalian caregiving practices (Gilbert, 2015). Most notable is our ability to be compassionate towards ourselves, but also towards complete strangers. This capacity has been described in recent years as our compassionate motivation (Gilbert, 2015, 2019), a complex cognitive, emotional and behavioural process with important real-world consequences for the self and others, including physical and mental health benefits. Given these consequences, recent advances in psychotherapy have used the evolutionary and developmental framework of compassion as the basis for Compassion Focused Therapy (CFT) (Gilbert, 2010). An integral component of CFT is compassionate mind training (CMT) where individuals begin to cultivate compassion for the self, others and from others. Despite the success of CFT for a variety of mental health problems and general wellbeing (Kirby, Tellegen, & Steindl, 2017), there are individuals who struggle to cultivate compassion for themselves. These individuals are also often those who would benefit most from self-compassion (Gilbert, McEwan, Matos, & Ravis, 2011; MacBeth & Gumley, 2012). The aim of this study was to explore a facilitatory CMT adjunct that involves the stimulation of the vagus nerve, a parasympathetic cranial nerve that is thought to play a key role in our compassionate motivation capacity.

Our compassionate motivation is thought to have evolved alongside the myelination of the vagus nerve. The vagus nerve is the 10th cranial nerve that predominantly controls the parasympathetic nervous system, the body's "rest and digest" system. Porges' polyvagal theory

(Porges, 2007, 2009, 2011) states that mammals evolved two vagal branches that perform distinct physiological processes. The evolutionarily earlier, dorsal vagal pathway regulates visceral functions and initiates immobilisation behaviour (e.g. freezing in instances of threat) via an unmyelinated part of the nerve. The more recent, ventral vagal system regulates the heart and lungs to signal and foster a state of calm, safety and soothing in response to sympathetic “fight/flight” emotions and behaviours. The ventral vagal system is thought to have evolved, in part, through mammalian care-giving motivations whereby the mother is attuned to the needs and distress of her young and can effectively meet, remedy and regulate for the benefit of infant survival (Depue & Morrone-Strupinsky, 2005; Di Bello et al., 2020; Kirby, Doty, et al., 2017; Petrocchi & Cheli, 2019; Porges, 2007). Our mammalian care-giving motivations, coupled with our evolved capacity for self-reflection and theory of mind, give rise to our compassion motivation.

Vagal activity can be monitored through heart rate variability (HRV: Billman, 2011). This is the variability in the time differences between successive heartbeats and is controlled via vagus innervation of the heart (Garfinkel & Critchley, 2016). Higher HRV reflects a parasympathetic dominance over sympathetic nervous system input. Low vagal tone (reflected in low HRV) has been associated with an increased risk of physical health problems, and it has been exhibited in individuals with depression and anxiety (Sgoifo, Carnevali, Pico Alfonso, & Amore, 2015), PTSD (Gillie & Thayer, 2014), and borderline personality disorder ((Krause-Utz, Walther, Lis, Schmahl, & Bohus, 2019). More generally, low HRV is associated with emotion regulation difficulties (Fiol-Veny, Balle, De la Torre-Luque, & Bornas, 2019; Steinfurth et al., 2018) and reduced cognitive flexibility (Thayer & Lane, 2009). Conversely, higher HRV has been associated with higher levels of positive and affiliative (e.g. feeling safe) affect, more effective emotion regulation and tolerance, and greater cognitive flexibility due to down regulated threat processing (Duarte & Pinto-Gouveia, 2017; Kogan et al., 2014; Matos

et al., 2017). Importantly, increases in HRV have also been observed following CFT and CMT (Di Bello et al., 2020; Kirby, Doty, et al., 2017).

While there is evidence that CMT can alter vagal tone, there is currently no research investigating the stimulation of the vagus nerve as a means of facilitating compassionate motivations and affect. Invasive vagus nerve stimulation has been shown to improve depression symptoms (Martin & Martín-Sánchez, 2012; Nemeroff et al., 2006), as has non-invasive transcutaneous vagus nerve stimulation (tVNS: vagus nerve stimulation through the skin at the ear, where the auricular branch of the vagus nerve innervates)(Li et al., 2019; Liu et al., 2016). The aim of the current study was to investigate the feasibility of conducting a trial assessing the potential facilitatory effects of tVNS during compassionate mind training. More specifically, we hypothesised that vagus nerve stimulation would generate increases in positive, affiliative emotions and self-compassion, and decreases in self-criticism and negative affect. We hypothesized that these effects would exhibit an incremental rise when tVNS is accompanied by CMT. Similar effects have been seen in previous studies using MDMA (ecstasy) as an adjunct to CMT (Kamboj et al., 2015; S. K. Kamboj et al., 2018). Furthermore, connections between the myelinated vagal nerve and other cranial nerves potentially influence social orienting and interactions through control of the facial nerves and throat, adjusting facial expressions, eye contact and voice tone (Petrocchi & Cheli, 2019; Porges, 2017). Previous research has shown that tVNS can positively influence emotional face processing (Koenig et al., 2019; Sellaro et al., 2018; Verkuil & Burger, 2019), which is similarly the case for CMT (S. K. Kamboj et al., 2018; McEwan et al., 2014). Considering this, we also investigated the individual and combined effects of tVNS and CMT on emotional face processing, hypothesising that there would be an additive improvement between tVNS and tVNS + CMT. In addition to the experimental results, this study will also provide us with data to inform power calculations for future trials and assess the feasibility of our study design.

Methods

Participants

Of the participants who responded to an online advertisement, 49 met eligibility criteria for the study. However, due to technical difficulties (see statistical analysis section) seven participants were excluded from the study. The remaining 42 participants attended the two testing sessions. Their average age was 24.5 (SD = 3.67) and 22 were female. Sixteen participants reported their ethnicity as White, 14 as East Asian, nine as South Asian, two as Black, one as Black African, and one as Black Caribbean.

Participants were required to be between the ages of 18 – 35 years old, have good or corrected eyesight and fluency in English. The exclusion criteria were: tragus piercings, current or recurrent ear or facial nerve problems (infections; pain), history of neurological or heart issues, current severe anxiety or depression (screening assessment using the Depression, Anxiety & Stress Scale; Lovibond & Lovibond, 1995- results not reported), receiving mental health treatment, pregnancy, and disclosed history of psychosis. Participants were also asked to refrain from alcohol and drugs for 48 hours prior to each study session.

Study Design

The study used a randomized, double-blind, sham-controlled cross-over design. Participants received both tVNS and sham stimulation over two sessions, at least one week apart. Participants were randomly allocated to their first stimulation condition using block randomisation, performed by a researcher who was not involved in any stage of data collection. In addition to the randomising researcher, each experimental session required two researchers: the blinder and the experimenter. Randomisation order was given to the blinder on the day of the experiment. The blinder set the stimulation threshold with the participants while the experimenter waited outside the lab. Once the threshold was set, the stimulator was placed in

a concealed box and could not subsequently be seen or adjusted by the experimenter. In the second session the participant received the alternative stimulation. Each session was identical except for the first session requiring participants to complete trait measures and the second session debriefing. To improve treatment concealment, participants were informed that the stimulation involved either low or high frequency (rather than active and sham) stimulation.

Procedure

Within each identical session there were three discreet experimental phases. The first phase required participants to complete baseline state affect, self-compassion and self-criticism measures and trait measures of self-compassion, self-criticism and attachment avoidance in the absence of stimulation. A 10-minute baseline recording of HRV was also taken. The measures taken during this phase will be referred to as the ‘baseline timepoint’ (T1). The next phase was a 15-minute period of stimulation only in which HRV was recorded for 15 min. The state measures then were subsequently taken again. The measures taken during and immediately after this phase will be referred to as the ‘stimulation/sham only timepoint’ (T2). The third phase was a 17-minute period of stimulation/sham combined with CMT. HRV was recorded during this period and state measures were administered for a third time. This will be referred to as the ‘stimulation/sham + CMT timepoint’ (T3). After state measures were administered at T2 and T3 participants also completed the emotional face task.

Upon arriving at session one, participants attached the ECG monitor under the guidance of the experimenter. The monitor was given a 5-minute period of stabilisation. Participants were then asked to sit quietly, in an upright position with legs uncrossed for the baseline HRV recording. Participants were then asked to clean their tragus region with an alcohol wipe. Prior to attaching the electrodes to the ear, participants were given an introduction to the stimulation procedure and were able to trial the stimulation on their finger to familiarise themselves with

the sensation of stimulation. After this, the electrode was attached to the right tragus and secured in place with surgical tape. Participants were guided through threshold setting with the blinder. They were instructed to slowly increase the amplitude to a point where they could clearly feel the stimulation. They were then asked to lower the amplitude to a level where they could just feel the stimulation. This amplitude was documented, and the blinder secured the TENS machine in an opaque box inside a locked box. The experimenter returned to administer the first set of state and trait measures (T1 assessment). Participants completed their questionnaires prior to the onset of stimulation only HRV recording. After 15 minutes of stimulation, participants completed the state measures again (T2 assessment) and the emotional face processing task. This was then followed by the compassionate mind imagery. At the end of the imagery participants completed the state measures and emotional face processing task again (T3 assessment). Finally, they were asked to rate whether they thought they had received the high or the low frequency stimulation. This was a dummy question to reduce expectancy effects associate with active stimulation. They were also asked to rate the confidence of their answer. The experimenter also completed the same questions. At the end of session two, participants were debriefed about the study's true hypotheses (participants were led to believe that the study was investigating the effects of tVNS on the vividness of mental imagery) and given a £30 participation fee.

All participants provided written informed consent. All procedures were performed in accordance with the ethical standards of the institution and were in line with the Declaration of Helsinki. The study received ethical approval by University College London Research Ethics Committee. The ethics approval letter is available in Appendix 2.

State Affect Measures

Types of Positive Affect Scale (TPAS): The TPAS measures the extent to which participants endorse 18 different positive emotion adjectives (Gilbert et al., 2008). Factor analysis of the original items revealed three potential forms of positive affect: Active Affect (e.g. energetic, excited), Relaxed Affect (e.g. relaxed, calm) and Safe Affect (e.g. content, warm). The significance of this scale is that it allows for a better approximation of affect systems associated more specifically with self-compassion (Gilbert, 2015; Gilbert et al., 2008). Participants rate on a 5-point Likert scale (1 = “not at all” to 5 = “very much so”) how strongly they are experiencing these emotions at the current moment in time. There are 4 Safe Affect items (range 4–20), 6 Relaxed Affect items (range 6–30), and 8 Active Affect items (range 8–40). The authors of the scale reported a Cronbach's alpha of .83 for Active and Relaxed Affect, and .73 for Safe Affect.

The International Positive and Negative Affect Schedule, Short Form (I-PANAS-SF): positive and negative affect were measured with the 10-item I-PANAS-SF (Thompson, 2007). Participants rated how strongly they were currently experiencing a particular emotion on a 5-point Likert scale (1 = “not at all” to 5 = “very much so”) (e.g. Positive Affect range 5–25: active, inspired; Negative Affect range 5–25: ashamed, hostile). Cronbach's alpha for the Positive Affect and Negative Affect scales were .78 and .76, respectively (Thompson, 2007).

State Self-Compassion & Self-Criticism Measures

Self-Compassion and Self-Criticism Scale (SCCS): The SCCS (Falconer, King, & Brewin, 2015) consists of five scenarios that are potentially self-threatening and can elicit varying degrees of self-criticism or self-compassion (e.g., “A third job rejection letter in a row arrives in the post”; “You arrive after walking to a meeting to find that you are late and the doors are closed”). Participants are instructed to imagine, as vividly as possible, that these scenarios are happening to them at the current moment in time and rate on 7-point Likert scales

(1= “not at all” to 7= “highly”) the extent to which they would react to themselves in a Harsh, Contemptuous, Critical, Soothing, Reassuring, and Compassionate manner in relation to each imagined scenario. The scale is separated into two orthogonal subscales. The positive items are summed across scenarios to generate the Self-Compassion Scale (range 15–105) and the negative items are summed to generate the Self-Criticism Scale (range 15–105). The scale has good internal reliability with a Cronbach's alpha of .91 and .87, respectively, and has been used in clinical and non-clinical research (Falconer et al., 2016; Falconer et al., 2014).

Trait Measures

Forms of Self-Criticizing/Attacking & Self-Reassuring Scale (FSCRS): The FSCRS (Gilbert, Clarke, Hempel, Miles, & Irons, 2004) was used to measure trait self-criticism and self-reassurance. Participants indicated on a 5-point Likert scale the extent to which various statements were true of themselves (0 = “not at all like me” to 4 = “extremely like me”). The scale comprises three subscales: inadequate self (IS, range 0–36; e.g. “There is a part of me that feels I am not good enough”), hated self (HS, range 0–20; e.g. “I stop caring about myself”), and reassured self (RS, range 0–32; e.g. “I find it easy to forgive myself”). The scale has high internal reliability, with a Cronbach's alpha of .90 for IS and .86 for HS and RS scales. The scale has been validated in both healthy and clinical populations.

Fear of Compassion Scale (FOCS): The FOCS (Gilbert et al., 2011) assess levels of fear for experiencing compassion for oneself (15 items: example, ‘I fear that if I am more self-compassionate I will become a weak person’) and from others (13 items: example, ‘Feelings of kindness from others are somehow frightening’). All items are rated on a 5-point scale (0= “don’t agree at all” to 4 = “completely agree”). High internal reliability with a Cronbach’s alpha of .85 and .87, respectively and validity data have been reported (Gilbert et al., 2011). The scale has been validated in both healthy and clinical populations.

The Experiences in Close Relationships-Revised Questionnaire (ECR): The ECR (Fraley, Waller, & Brennan, 2000) was used as a measure of avoidant attachment. The avoidant attachment scale of the ECR consists of 18 items rated on a 7-point Likert scale (1 = “strongly disagree” to 7 = “strongly agree”). The items measure the extent to which a person feels discomfort with intimacy and seek independence (e.g. “I prefer not to be too close to romantic partners”). Cronbach’s alpha was reported as 0.94 (Brennan, Clark, & Shaver, 1998).

Physiological index of vagal activity

Activity of the vagus nerve during the experiment was indirectly assessed using HRV metrics obtained via an electrocardiogram (ECG) device (Firstbeat Bodyguard 2, Jyväskylä, Finland). Cardiac activity was recorded using Ag/AgCl electrodes attached below the right clavicle and the left ribcage. Raw data (in the form of inter-beat intervals) was analysed in Kubios software (Kubios Oy, Finland). The root mean square of successive R-R interval differences (RMSSD), the percentage of consecutive inter-beat intervals differing by > 50 ms (pNN50) and the high frequency (HF) component of heart rate variability (HRV) are all widely used metrics of vagal activity. These three vagal tone measures were extracted from the raw data and are recommended for use in tVNS research (Burger et al., 2020).

Emotional Face Processing Task

Empathy Assessment Task: This was adapted from the task originally described by !! (Ali, Amorim, & Chamorro-Premuzic, 2009). The Empathy Assessment Task using the Self-Assessment Manikin (EAT-SAM) (S. K. Kamboj et al., 2018) was programmed in PsychoPy (Peirce, 2007) and involved presenting and recording subjective arousal and valence responses evoked by facial affect stimuli comprising photographic images of complex interpersonal

emotions (compassion, criticism and natural: **Figure 1**) . For details on how face stimuli were created and validated see Falconer et al. (2019).

Immediately before the task, the participants were instructed on the meaning of the Self-Assessment Manikin (SAM) pictograms in terms of rating their current feelings on dimensions of arousal and valence, based on standard instructions for the SAM (Bradley & Lang, 1994). Individual facial expression images were preceded by a central fixation cross (1s) and presented in randomised order on a 15-in. laptop monitor until the participant responded to indicate their current arousal/valence in response to the facial expression. The next trial then began. Each scale was displayed below each affect image and consisted of nine radio buttons along with manikin-form anchors (Bradley & Lang, 1994). Using a mouse, the participants selected one of the radio buttons for each scale to indicate their current emotional state in response to the images (1 = negative/low to 9 = positive/high) for each stimulus trial (each stimulus was presented once to assess valence, and once to assess arousal; 36 trials in total consisting of six different identities for each expression of compassion, criticism and neutral). The subjective arousal response to the affective displays of other people is considered an implicit measure of emotional empathy (Ali et al., 2009; Dziobek et al., 2008).



Figure 1. Composite images of neutral (left), critical (centre) and compassionate (right) expressions. These images were used for the EAT-SAM.

Vagus Nerve Stimulation

Vagus nerve stimulation was achieved using a transcutaneous electrical nerve stimulation (TENS) device (V-TENS Plus, Body Clock Health Care Ltd, UK) and custom ear clip electrodes designed by Antonino et al. (2017) (**Figure 2**). tVNS stimulated the right tragus, was set to a sensory threshold whereby participants were required to set the amplitude to a level that was just perceptible. Amplitudes ranged from .7 to 1.3mA. Stimulation frequency was set at 30Hz, with a pulse width of 200 μ s and was applied continuously in an asymmetrical biphasic rectangular wave. For sham stimulation, all procedures and parameters were kept the same, with the exception that once the amplitude level was set the blinding researcher disconnected the electrodes from the TENS machine.

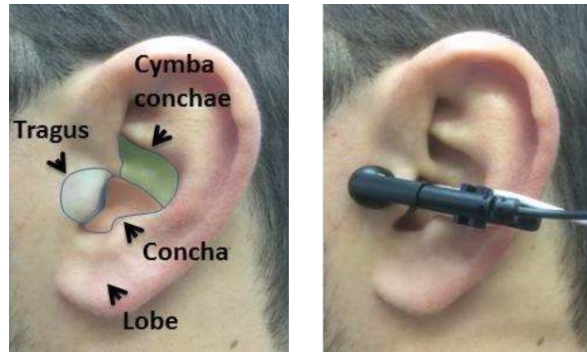


Figure 2. Anatomy of the outer ear (Left) and positioning of tVNS electrode to the Tragus (Right)

Compassionate Mind Training

CMT partly involves a common form of guided imagery with the aim of cultivating self-compassion and affiliative emotions such as safety and contentment. The task guides participants through building up compassionate qualities, expressions and behaviours that can be applied to difficult situations and towards themselves in times of need. This is also preceded by a soothing rhythm breathing exercise. The imagery is similar to that used by (Kamboj et al., 2015; S. K. Kamboj et al., 2018; Rockliff et al., 2011). Copies of the audio files are available on request.

Statistical Analysis

Statistical Package for Social Sciences (SPSS, version 26, IBM) was used to perform all statistical analysis. Data was examined graphically and statistically for normality and outliers. Shapiro-Wilk tests were non-significant (all p values > 0.05) and no studentised residuals exceeded ± 3 on the outcomes. Parametric statistical analysis was therefore applied. All reported statistics are two-tailed, analysis of variance (ANOVA) effect sizes (η^2) were calculated in SPSS, and values are presented as means \pm standard errors unless otherwise indicated (in tables).

As reflected in the reported dfs, the analyses were based on differing amounts of missing data (due to technical difficulties). This resulted in participant sample sizes ranging from 28 to 42 for state and HRV measures. Furthermore, there were only 30 complete data sets for the SAM Task due to laptop theft during testing. A total of 7 participants were excluded from the study based on stimulation failure due to battery drainage. A power calculation with a small-medium effect size (Cohen's d), 80% power and alpha level of .05 resulted in a sample size of 18 participants. Thus, analyses of all variables had adequate power to detect small-medium effect.

Pearson's correlation coefficients were used to explore association between trait variables ($n = 42$). Outcome variables of affect, self-compassion, self-criticism and HRV were analysed in separate, repeated measures ANOVA with stimulation type (tVNS and Sham) and timepoint (T2 = stimulation only; T3 = stimulation + CMT) as independent variables. Due to differences in baseline measures (T1) across several outcome measures during tVNS and sham sessions, baseline measures were subtracted from T2 and T3 to adjust for any baseline difference effects on outcome change. This creates a gain outcome measure for T2 and T3, relative to baseline scores. Planned comparisons were used to follow up the main analyses using Bonferroni corrections for significant interactions, where appropriate. Outcome variables of face processing (valence ratings and arousal ratings) were also analysed in separate, repeated measures ANOVA with stimulation type (tVNS and Sham), timepoint (T2 = stimulation only; T3 = stimulation + CMT), facial emotion (compassion, critical, neutral) as independent variables.

Due to previous literature highlighting a potential moderating effect of attachment style, ERC avoidant attachments scores were used in subsequent ANOVAs of the primary outcome variables (i.e. self-compassion and self-criticism scores and HRV measures) as a covariate.

Results

State Affect

There was a significant main effect of time for Active Affect (TPAS), $F(1, 37) = 14.68$, $p < .001$, $\eta^2_p = .28$. Post hoc analysis indicated that Active Affect was significantly lower at T3 (i.e. after sham/active stimulation + CMT) compared to the preceding stimulation/sham only period (T2: Mean Difference (MD) = -2.63 Standard Error (SE) = .069). There was no significant main effect of stimulation type (active v sham), $F(1, 37) = .02$, $p = .89$, $\eta^2_p = .00$. There was no significant interaction between time and stimulation condition, $F(1, 37) = 1.18$, $p = .28$, $\eta^2_p = .03$. Descriptive data for state affect, self-compassion and self-criticism are all displayed in **Table 1**.

There was a significant main effect of time for Relaxed Affect (TPAS), $F(1, 37) = 28.85$, $p < .001$, $\eta^2_p = .44$. Post hoc analysis indicated that Relaxed Affect was significantly higher after stimulation/sham + CMT (T3) compared to the preceding stimulation/sham only (T2: MD = 3.07 SE = .57). There was no significant main effect of stimulation, $F(1, 37) = 1.09$, $p = .30$, $\eta^2_p = .03$. There was no significant interaction between time and stimulation condition, $F(1, 37) = .30$, $p = .58$, $\eta^2_p = .01$.

There was a significant main effect of time for Safe Affect (TPAS), $F(1, 37) = 18.35$, $p < .001$, $\eta^2_p = .33$. Post hoc analysis indicated that Safe Affect was significantly higher after stimulation + CMT (T3) compared to preceding stimulation/sham only (T2: MD = 1.05 SE = .25 $p = .002$). There was a significant main effect of stimulation type, $F(1, 37) = 7.56$, $p = .01$, $\eta^2_p = .17$. Post hoc analysis indicated that Safe Affect was significantly higher during sham compared to tVNS (MD = .87 SE = .32). There was no significant interaction between time and stimulation type, $F(1, 37) = 1.55$, $p = .22$, $\eta^2_p = .04$.

There was no significant main effect of time for Positive Affect (PANAS), $F(1, 34) = 1.02$, $p = .32$, $\eta^2_p = .03$. There was no significant main effect of stimulation type for Positive Affect (PANAS), $F(1, 34) = 1.01$, $p = .32$, $\eta^2_p = .03$. There was a significant interaction between stimulation type and time, $F(1, 34) = 7.32$, $p = .01$, $\eta^2_p = .12$. Pairwise comparisons revealed a significant reduction in Positive Affect scores for participants receiving tVNS at T2 to T3 (MD = $-.97$ SE = $.44$ $p = .03$).

There was a significant main effect of time for Negative Affect (PANAS), $F(1, 37) = 4.03$, $p = .05$, $\eta^2_p = .10$. Post hoc analysis indicated that Negative Affect scores were significantly lower after stimulation/sham + CMT (T3) compared to stimulation/sham only (T2: MD = $-.45$ SE = $.22$). There was no significant main effect of stimulation type for Negative Affect (PANAS), $F(1, 37) = 1.54$, $p = .22$, $\eta^2_p = .04$. There was no significant interaction between stimulation type and time, $F(1, 37) = 1.19$, $p = .28$, $\eta^2_p = .03$.

State Self-Compassion and Self-Criticism

There was a significant main effect of time for Self-Compassion scores, $F(1, 35) = 29.6$, $p < .001$, $\eta^2_p = .46$. Post hoc analysis indicated that Self-Compassion scores significantly increased at T3 (stimulation/sham + CMT) compared to the preceding stimulation/sham only phase (T2: MD = 10.5 SE = $.193$). There was no significant main effect of stimulation, $F(1, 35) = 2.16$, $p = .15$, $\eta^2_p = .06$. There was no significant interaction between stimulation and time, $F(1, 35) = 1.31$, $p = .26$, $\eta^2_p = .04$. When avoidant attachment score was added as a covariate there was a trend for an interaction between stimulation condition and avoidant attachment scores, $F(1, 33) = 4.14$, $p = .05$, $\eta^2_p = .11$. There were no other significant effects.

There was a significant main effect of time for Self-Criticism scores, $F(1, 27) = 50.9$, $p < .001$, $\eta^2_p = .65$. Post hoc analysis indicated that Self-Criticism scores significantly

decreased after stimulation + CMT (T3) compared to the preceding stimulation/sham only phase (T2: MD = 9.32 SE =1.31). There was no significant main effect of stimulation, $F(1, 27) = .08, p = .76, \eta^2 p^2 = .003$. There was no significant interaction between stimulation and time, $F(1, 27) = .01, p = .94, \eta^2 p^2 < .001$. When avoidant attachment score was added as a covariate there were no significant interaction effects (smallest $p = .13$).

Table 1. State affect, self-compassion and self-criticism scores

Sham condition														
Sham Only (T2)							Sham + CMT (T3)							
	Active Affect	Relaxed Affect	Safe Affect	Self-Compassion	Self-Criticism	Positive Affect	Negative Affect	Active Affect	Relaxed Affect	Safe Affect	Self-Compassion	Self-Criticism	Positive Affect	Negative Affect
Average	-1.56	0.73	0.37	2.36	-4.21	-1.08	-0.02	-3.56	3.85	1.61	13.9	-13.3	-0.98	-0.61
SD	4.85	3.56	1.84	8.90	8.90	2.71	1.86	6.75	4.53	2.15	15.5	12.7	3.05	1.59
tVNS condition														
Stimulation Only (T2)							Stimulation + CMT (T3)							
	Active Affect	Relaxed Affect	Safe Affect	Self-Compassion	Self-Criticism	Positive Affect	Negative Affect	Active Affect	Relaxed Affect	Safe Affect	Self-Compassion	Self-Criticism	Positive Affect	Negative Affect
Average	-1.21	0.28	-0.26	0.00	-4.95	-1.08	-0.67	-4.44	3.18	0.59	9.50	-13.3	-2.21	-0.90
SD	6.23	3.79	1.77	8.09	9.99	2.89	2.53	5.24	3.85	1.97	14.0	12.1	3.09	3.16

NB: Scores represented are adjusted from baseline scores (T1) due to baseline differences across stimulation sessions. Baseline scores were subtracted from raw T2 and T3 scores. Scores therefore represent average gains relative to baseline.

Trait measures

Descriptive data for trait measures of compassion, self-criticism and avoidant attachment style can be found in **Table 2**. Pearson's correlations revealed the expected positive associations between Inadequate Self, Hated Self, Fear of Self-Compassion, Fear of Compassion from Others and Avoidant Attachment scores (largest $p = .04$). There was also an expected negative association between Reassured Self scores and Inadequate Self, Hated Self, Fear of Self-Compassion, Fear of Compassion from Others and Avoidant Attachment scores (largest $p = .01$).

Table 2. Averages and correlations between self-report trait measures

	Inadequate Self	Reassured Self	Hated Self	Fear of Self-Compassion	Fear of Compassion from Others	Avoidant Attachment
Inadequate Self	1	-.63**	.56**	.61**	.59**	.42**
Reassured Self		1	-.56**	-.42**	-.50**	-.40**
Hated Self			1	.59**	.49**	.32*
Fear of Self-Compassion				1	.68**	.51**
Fear of Compassion from Others					1	.31*
Avoidant Attachment						1
<i>Average</i>	13.2	21.8	1.90	10.6	11.9	2.82
<i>SD</i>	8.13	4.89	2.38	10.9	9.1	1.07

Heart Rate Variability

There was a significant main effect of time for RMSSD levels, $F(1, 41) = 28.7, p < .001, \eta_p^2 = .41$. Post hoc analysis indicated that RMSSD levels significantly increased during

stimulation/sham + CMT (T3) compared to preceding stimulation/sham only (T2: MD = 17.5 SE =3.28). There was no significant main effect of stimulation type, $F(1, 41) = 2.35, p = .13, \eta_p^2 = .05$. There was no significant interaction between time and stimulation type, $F(1, 41) = 3.16, p = .08, \eta_p^2 = .07$. However, the direction of data does appear to support our hypothesis of an additive effect of tVNS and CMT compared to CMT alone (**Figure 3**). When avoidant attachment score was added as a covariate there were no significant interaction effects (smallest $p = .41$).

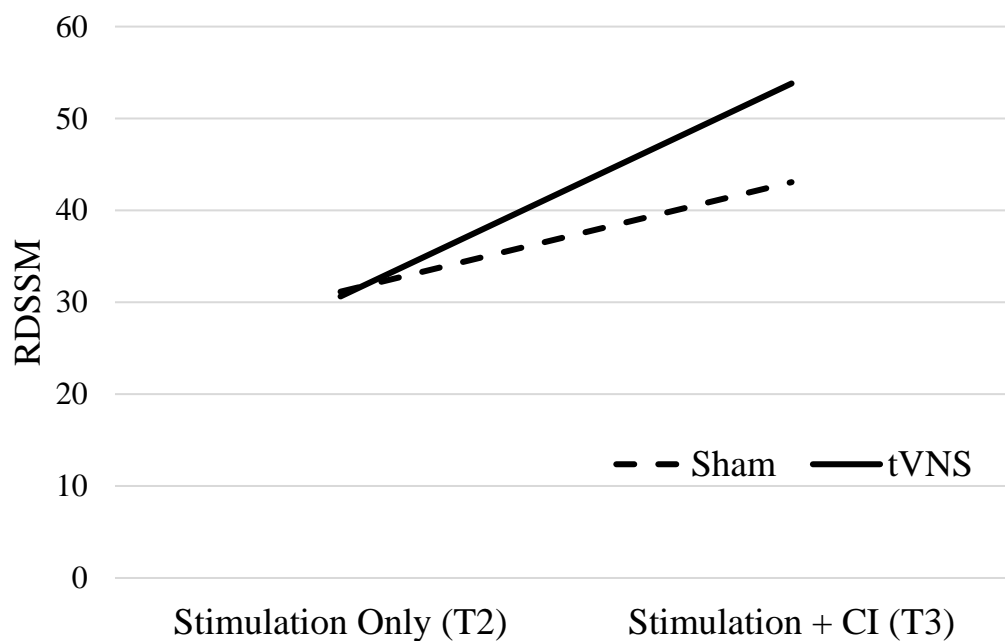


Figure 3. Baseline adjusted RDSSM levels significantly increased from T2 to T3. RDSSM appears to have increased the most at T3 during tVNS compared to sham stimulation (although not statistically significant).

There was a significant main effect of time for pNN50 levels, $F(1, 41) = 24.5, p < .001, \eta_p^2 = .37$. Post hoc analysis indicated that pNN50 levels significantly increased during stimulation + CMT (T3) compared to preceding stimulation/sham only (T2: MD = 15.7 SE = 3.16) (**Figure 4**). There was a significant main effect of stimulation type, $F(1, 41) = 9.09, p = .004, \eta_p^2 = .181$. pNN50 levels were significantly higher during tVNS (MD = 12.2 SE = 4.06) (Figure 3). There was no significant interaction between stimulation type and time, $F(1, 41) = .33, p = .57, \eta_p^2 = .01$. When avoidant attachment score was added as a covariate there were no significant interaction effects (smallest $p = .13$).



Figure 4. pNN50 represents a measure of vagal tone. pNN50 levels significantly increased over time from T2 to T3. Overall pNN50 levels were significantly higher during tVNS compared to sham stimulation.

There was a significant main effect of time for High Frequency HRV, $F(1, 41) = 12.5$, $p = .001$ $\eta_p^2 = .23$. Post hoc analysis indicated that High Frequency HRV levels significantly increased during stimulation + CMT (T3) compared to preceding stimulation/sham only (T2: MD = 12.5 SE = 3.53). There was a significant main effect of stimulation type, $F(1, 41) = 128.1$, $p < .001$ $\eta_p^2 = .76$. High Frequency scores significantly increased during tVNS compared to sham stimulation (MD = 60.2 SE = 5.32). There was no significant interaction between stimulation type and time, $F(1, 41) = .75$, $p = .39$ $\eta_p^2 = .02$. When avoidant attachment score was added as a covariate there were no significant interaction effects (smallest $p = .14$).

Emotional Face Processing - Self-Assessment Manikin (SAM) Task

There was a significant main effect of emotion expression for SAM arousal ratings, $F(2, 58) = 15.5$, $p < .001$ $\eta_p^2 = .35$. Pairwise comparisons revealed that compassionate, critical and natural faces were all significantly different from one another in arousal ratings (largest $p = .02$). Compassionate faces were rated as the most arousing (M = 4.78 SE = .30), followed by criticism (M = 4.18 SE = .26) and neutral (M = 3.43 SE = .28) expressions (**Figure 5**). There was a significant main effect time for SAM arousal ratings, $F(1, 29) = 9.84$, $p = .004$ $\eta_p^2 = .25$. Arousal ratings significantly increased during stimulation + CMT (T3) compared to stimulation only (T2: MD = .29 SE = .09) (Figure 4). There was no significant main effect of stimulation, $F(1, 29) = .83$, $p = .37$ $\eta_p^2 = .03$. There was no significant two- or three-way interactions between emotion expression, time and stimulation type (smallest $p = .28$).

There was no significant main effect of stimulation for SAM valence ratings, $F(1, 29) = .003$, $p = .96$ $\eta_p^2 = .08$. There was no significant main effect of time for SAM valence ratings, $F(1, 29) = 2.53$, $p = .12$ $\eta_p^2 < .001$. There was a significant main effect of facial emotion for

valence ratings, $F(2, 58) = 94.5$, $p < .001$, $\eta_p^2 = .78$. Pairwise comparisons revealed that compassionate, critical and neutral faces were all significantly different from one another in valence ratings (largest $p < .001$). Compassionate faces had the highest valence rating ($M = 6.45$, $SE = .16$), followed by neutral ($M = 4.69$, $SE = .13$) and critical ($M = 4.01$, $SE = .17$) expressions. There was no significant two- or three-way interactions between face emotion, time and stimulation (smallest $p = .23$).

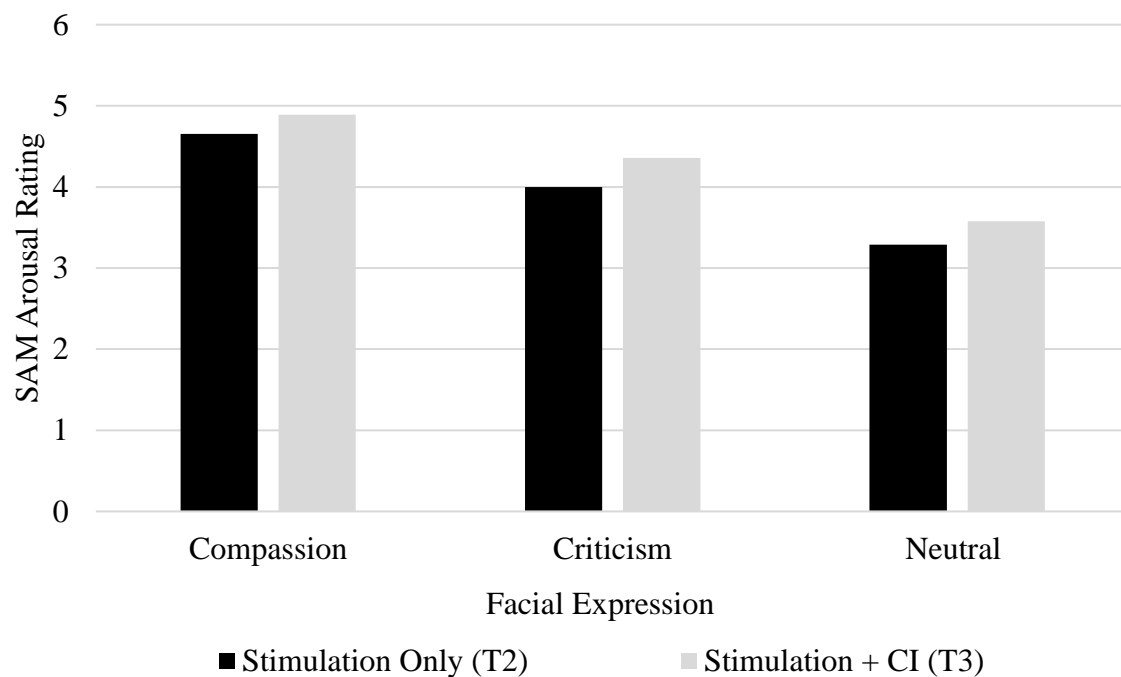


Figure 5. SAM arousal ratings for compassionate, critical and neutral faces during stimulation only (T2) and stimulation + CMT (T3). Ratings significantly increased over time and there was a significant difference in arousal ratings between all three facial expressions.

Discussion

The aim of this study was to conduct a feasibility trial into the effects of transcutaneous vagus nerve stimulation (tVNS) as a facilitatory adjunct to compassionate mind training (CMT). To that effect, participants received tVNS and sham stimulation on two separate occasions. Three discrete experimental phases were completed in each session. The first was a baseline period (T1), the second was a stimulation/sham only phase (T2) and the third phase was stimulation/sham + CMT (T3). Participants completed state measures of affect, self-criticism, and self-compassion, and had their HRV recorded during each phase. An emotional face processing task was also employed at T2 and T3 given evidence that tVNS and CMT can affect emotional face processing (Koenig et al., 2019; McEwan et al., 2014; Sellaro et al., 2018; Verkuil & Burger, 2019) .

We were interested in whether there were facilitatory and additive effects at T2 and T3 on HRV, affect, self-criticism, and self-compassion compared to baseline (T1). A similar pattern of effect has been seen in the use of MDMA as an adjunct to CMT (Kamboj et al., 2015; S. K. Kamboj et al., 2018). However, despite randomising participants, baseline measures were significantly different in each of the stimulation conditions (tVNS vs sham). As a result, we adjusted the effects at T2 and T3 by subtracting the baseline (T1) scores. The remaining T2 and T3 scores are representative of gains from T1. We were therefore unable to assess the effects of T2 from baseline and subsequent additive effects from T2 to T3. Nevertheless, we were able to assess for any change in gain scores from T2 to T3 under tVNS and sham stimulation.

Heart Rate Variability

All measures of HRV (RMSSD, pNN50 and HF) significantly increased from T2 to T3. CMT therefore increased vagally mediated HRV. This is consistent with previous CMT literature and indicates an activation of the brains soothing system and a positive change in vagal tone (Di Bello et al., 2020; Kirby, Doty, et al., 2017). Importantly, there were significant increases in both pNN50 and HF during tVNS compared to sham stimulation. These results indicate that tVNS is activating the vagus nerve and increasing HRV. In tVNS research, it is not always the case that changes in HRV are noted, notably because stimulation amplitudes can be low and there is a tendency to use the left ear, which innervates the heart less (Burger et al., 2020). While there were no significant additive effects during both tVNS and CMT, the direction of data indicted a greater increase in RMSSD levels during tVNS (compared to sham) while participants received CMT. This is in line with our hypothesis and is encouraging for any future trial. Any facilitatory effects from a tVNS adjunct could assist people who struggle with fears of self-compassion, a block to CMT and higher levels of HRV (Gilbert et al., 2011; Rockliff, Gilbert, McEwan, Lightman, & Glover, 2008; Rockliff et al., 2011). It could be the case that tVNS can regulate and overcoming some of these potentially threatening blocks to compassion.

Affect, self-compassion and self-criticism

As expected, there were significant increases in state levels of self-compassion and reductions in self-criticism from T2 to T3. These are consistent with result from CMT research (Falconer et al., 2014; Kamboj et al., 2015; S. K. Kamboj et al., 2018). However, there was no main effect of stimulation type or interaction with timepoint. If there were additive effects of tVNS + CMT from T2 then we may have expected to see this as an interaction between stimulation type and timepoint, which was not the case. Nevertheless, we cannot rule out

potential small effects at T2 due to tVNS (compared to sham) as our study was insufficiently powered to detect small effect sizes.

There were significant changes in all affect measures from T2 to T3. Active affect (TPAS), and positive and negative affect (IPANAS) scores all reduced at T3 compared to T2. While reductions in positive affect may appear contradictory as a result of CMT, it is consistent with the literature that proposes three different types of positive affect (Falconer et al., 2014; Gilbert et al., 2008). This is further reflected in the safe (TPAS) and relaxed (TPAS) positive affect *increases* from T2 to T3. Active affect, as measured by the TPAS, and positive affect measured by the IPANAS are thought to be underpinned by energising, dopaminergic systems, while safe and relaxed affect are thought to be mediated by soothing, opiate/oxytocin systems (Gilbert et al., 2008). Engaging this soothing system is a key aim for CFT (Gilbert, 2010). Interestingly, there was a significant main effect of stimulation type for safe affect. Post hoc analysis revealed that safe affect was generally higher in the sham condition. Our hypothesis was that safe affect would be increased by tVNS due to its proposed downregulation of the threat system and activation of the soothing system. The reason for this result is unclear. However, it could be that stimulation itself (an electrical current through the ear) fosters feelings of uncertainty or discomfort and therefore lower safety ratings. Nevertheless, feelings of safety did increase overtime with CMT.

Emotional Face Processing

Our results revealed a significant increase in arousal ratings for emotional face stimuli from T2 to T3. This suggests that CMT enhances the way in which participants were affected by the emotional faces. This has been considered an enhancement of emotional empathy (S. K. Kamboj et al., 2018). Compassionate faces were also significantly rated as being the most arousing of the face stimuli. S. K. Kamboj et al. (2018) also found increases in arousal ratings

after CMT, but this was for critical faces. We found no effect of stimulation type for arousal ratings and there were also no changes in valence rating over time or across stimulation type.

tVNS research has shown increased emotional empathy for easy trials on the Reading the Mind in the Eye Test (RMET) (Colzato et al., 2017), as well as improved accuracy in the categorisation of facial emotion (Sellaro et al., 2018). We hypothesised that tVNS would similarly improve valence and arousal. However, none of the tVNS studies investigated these reactions to facial emotion. Furthermore, the face stimuli used in the current study may also be categorised as more complex social expressions than the basic facial stimuli used by Sellaro et al. (2018). It may also be the case that these expressions are more akin to the harder category of stimuli in the REMT, which found no effect of tVNS (Colzato et al., 2017).

Limitations

There are several limitations to this study. First and foremost is the loss of T1 due to baseline differences in measures across stimulation conditions. To account for these differences, we computed gain scores by subtracting T1 data from T2 and T3 data. Ideally, we would have performed an analysis of covariance (ANCOVA). This takes into account the correlation between baseline scores and change scores and regression to the mean (Clifton & Clifton, 2019; Vickers & Altman, 2001). However, the repeated-measures design of the current study did not permit the use of an ANCOVA. This means that the results of the current study could be overestimated. There may be other statistical methods that would allow for a comparison of T1 and T2 while controlling for the differences, however this is not yet clear. Similarly, there were many missing values within the dataset that resulted in reduced sample sizes during statistical analysis. Further exploration into statistical methods of managing missing values may provide us with an opportunity for increased sample sizes.

The loss of baseline measures meant that we were unable to test the hypothesis that tVNS alone would alter state affect, HRV, self-criticism and self-compassion, and that there would be an additive effect of tVNS + CMT at T3. We could expect that the additive effect of tVNS + CMT at T3 would be shown in an interaction between stimulation type and timepoint, but this was generally not the pattern of results. We also cannot rule out potential small effects at T2 between the tVNS and sham as our study may have been insufficiently powered to detect small effect sizes. Furthermore, while the study may have had enough power to detect some small-medium sized main effects, the study was underpowered to detect interaction effects.

The lack of power, the number of variables under investigation and the number of comparisons within the study design also present the possibility of Type 1 error. Greater power would allow us to assess for smaller main effects at T2 between sham and tVNS (i.e. whether tVNS can increase self-compassion in the absence of CMT) and for interaction effects between stimulation type and CMT (i.e. whether there is an additive effect of tVNS and CMT for self-compassion and HRV). While the double-blind, cross-over design is a controlled and adequate design for evidentiary conclusions, future studies will require adequate power to ensure reliable results and interpretations. Recent recommendations suggest that a minimum of 110 participants would be required to establish an adequately powered (i.e. 80% power) interaction effect in a 2 x 2 repeated-measures ANOVA for one dependant variable (Brysbaert, 2019).

Randomising participants to either sham or tVNS in the first session should have mitigated baseline differences. By increasing the number of participants (as a consequence of increasing power) in future studies, the likelihood of this occurring again will be reduced. It is also possible that future trials use a stratified randomisation methodology to allocate participants to either sham or tVNS after, and based on, their baseline measurements.

While CMT exhibited a positive effect on affect, self-compassion/criticism, HRV and emotional empathy towards face stimuli there was no active control task. Part of CMT also involves the technique of soothing rhythm breathing (Gilbert, 2010) and changes in breathing can affect HRV (Billman, 2011; Shaffer & Ginsberg, 2017). However, changes to breathing are unlikely to account for all of the effects at T3. Future research should aim for an active control task to assess for specific CMT effects over and above potential effects of breathing.

The participants of this study were young and healthy university students. We cannot therefore generalise these findings to other groups of individuals. Furthermore, average scores on trait self-criticism and avoidant attachment were relatively low. We therefore cannot generalise our results to individuals with higher traits or those with mental health problems. Nevertheless, despite these low averages the results are promising. Further research should aim to replicate this study with a group of participants categorised with high self-criticism and avoidant attachment. This would allow for a better assessment of tVNS effects on measures pertinent to mental health problems (Mackintosh et al., 2018).

A further factor to consider is the duration of stimulation. Within tVNS field the temporal aspects of tVNS and its activation of neural networks, such as the pre-frontal cortex, locus coeruleus, limbic system, and cingulate cortex (Dietrich et al., 2008; Frangos et al., 2015; Kraus et al., 2007; Kraus et al., 2013), are unclear. Frangos et al. (2015) note a rise and plateau in hippocampal activation after 6 minutes of tVNS. Thus, a minimum of six minutes of stimulation has been commonly used in the field but the overall duration of stimulation varies substantially, both in one off experimental sessions and longitudinal therapeutic studies (Falconer & Kamboj, *in prep*). In the current study, stimulation was approximately 70 minutes. It could be the case that tVNS plateaued during this time or continued to ramp up effects on the vagus nerve. However, the increased effects of HRV at T3, especially during the tVNS

condition, would suggest that tVNS is continuing to affect the vagus nerve until the end of the session.

No formal assessment was made of the side effects of tVNS. This information could have been used to make sense of reduced safe affect responses during tVNS. It would also contribute to our understanding of the potential costs (i.e. pain/discomfort) associated tVNS as tool in research and therapy. Verbal reports from participants suggest that tVNS is tolerable with some sensations of tingling and throbbing. However, this was also the case for sham stimulation and could be attributed to the ear clip pressure. Burger et al. (2016) and Steenbergen et al. (2020) provide examples of more formalised assessments of side effects in tVNS research. A similar approach would be recommended for a future trial of the current study.

Similarly, a systematic approach for determining the threshold of stimulation would help guide participants in a more structured way and ensure that the subjective experience of the stimulation sensation is assessed. For example, Genheimer et al. (2017) measured their “tingling threshold” of tVNS by assessing the feeling on an 11-point Likert scale (0 = ‘no sensation’, 3 = ‘slight tingling’, 6 = ‘strong tingling’ and 10 = ‘painful’). Stimulation was titrated down in steps of 0.1mA until stimulation rated below 7. This procedure was completed twice, and the average intensity of both thresholds was used and assessed again for a rating of either 6 or 7.

Conclusion

The results of this study provide further evidence that CMT can positively influence state affect, self-compassion/criticism, HRV and emotional face processing. tVNS also increased HRV compared to sham stimulation, providing evidence that tVNS activated the vagus nerve. While there was no significant evidence that tVNS has an additive, positive effect on HRV during CMT, the data appear to be in the hypothesised direction. This is an

encouraging finding for a future trial. Future research, with increased power, an additional active control task to CMT, as well as participants higher in trait self-criticism and attachment avoidance, would be required to establish the potential therapeutic benefits of tVNS before a clinical trial.

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Chapter 3 – Critical Appraisal

Introduction

I started the clinical doctorate at UCL after completing a research PhD in cognitive neuroscience and spending five years in clinical psychology research as a post-doctoral research associate. Doctoral training was a conscious decision after years of feeling inadequately skilled and knowledgeable in the design of new or adjunct psychological interventions for mental health problems. I was also acutely aware of my own desire to be able to give more to patients who participated in my research.

To be able to straddle both clinical and academic spheres, to feed knowledge about the phenomenological experience of mental health back into research, and scientific knowledge from the research back into clinical practice, was my main motivator for clinical training. Even though this is still a key motivator, my clinical experience during training has brought to my attention the therapeutic components of the alliance, empathy and genuineness in the relationship (Flückiger, Del Re, Wampold, & Horvath, 2018; Horvath & Luborsky, 1993; Nienhuis et al., 2018). While the therapeutic relationship is one of the most investigated variables in psychotherapy research, and while the common factors debate continues (Cuijpers, Reijnders, & Huibers, 2019), this remains a neglected component of new or adjunct intervention design and evaluation in research. I also think this is a neglected component of clinical training, often side-lined for the purpose of learning formulation and intervention strategies. However, there is one psychological framework that has allowed me to cultivate aspects of myself that I value such as empathy, an understanding of the human condition, an understanding of human connection and genuineness, which I also feed into my therapeutic alliance: Compassion Focused Therapy (Gilbert, 2010).

Compassion and Compassion Focused Therapy (CFT) was an area of research and personal practice for me prior to training. While CFT training on the course was a one-day

introduction, it continues to be my most valued skillset. CFT provides me with a framework not only for formulation and intervention but for my therapeutic alliance.

It is my affinity with CFT that guided my choice in thesis topic. It is also true that clinical training took me away from fulltime research and continuing to build my publication record and research impact, something that is essential if I wish to continue my academic and research career. Considering this, I also wanted to continue my research record in the area of compassion and adjunct intervention design.

Research Design

We (I use the term “we” because research is almost always a collective effort) set about an ambitious research design of a randomised, double-blind, cross-over trial. This is something that we had experience of before, in part, when investigating the combined effects of MDMA and compassionate mind training (CMT) (Kamboj et al., 2015; Sunjeev K. Kamboj et al., 2018), a key component of CFT. Having an example experimental design is always the best place to start when embarking on new research. I have also always found it helpful to anchor my understanding of statistical analysis to examples of experimental design in the literature.

Although I am a mixed-methods researcher, quantitative research represents most of my work. I think there is a comfort and familiarity in quantitative design and analysis, partially driven by an emphasis in quantitative teaching in undergraduate (and doctoral) psychology degrees, but also in the need for a scientific approach to psychological phenomena. Since the completion of this thesis I am left wondering at the potential results of a qualitative component. In the field of tVNS there is a lack of qualitative reports on the experience of stimulation and stimulation combined with psychological tasks or interventions. I also think qualitative research and patient involvement is necessary to address design issues for the development of clinical tVNS interventions. For example, what might be some of the barriers and solutions to

using tVNS at home during a longitudinal intervention? What might be an appropriate stimulation schedule for longitudinal interventions? What are the motivations for continuing to use tVNS despite potential short-term discomfort? These are all necessary questions for the development of effective, patient informed clinical interventions (Crocker et al., 2018).

Expectations

Throughout training, the research component was never a source of stress or dread, as it was for many of my fellow trainees. My initial clinical experience at the start of training was substantially less than others on the course and therefore this was my source of stress and dread of incompetence. However, roles within the cohort naturally emerged and those with research experience supported those without and vice-versa for clinical experience or clinical specialities.

I felt an expectation for me to complete the dissertation with relative ease, which was far from my actual experience. I have found it incredibly difficult to juggle the research components with clinical and academic work. Research often took a back seat and I tried to reassure myself with the knowledge that my decade long experience in research would help me succeed in completing my thesis. However, I have often wondered at the (lack of) quality of my work and assessed my standards harshly at a level beyond that which is expected of the clinical doctorate. I have also had to grapple with feelings of shame at requiring an extension to my thesis deadline, despite knowing health problems contributed to this. Expectations of the level at which I “should” be at during various stages of training (clinical, academic, and research domains) had dogged my entire training experience. I have had to learn to tolerate this uncertainty and conscious incompetence, and embrace the idea of *training* - a position I have not been in before.

While I am proud of the research I have been able to accomplish during training, I think there is more that can be done to elevate the write-up and contribution to both the CMT and tVNS field. For example, the systematic review would benefit from a quality assessment of the publications included (e.g. Guyatt et al., 2008; Ross et al., 2011). Most of the components for this are already available in the text. This would help further the interpretation of results and provide a guide for future researcher in their attempt to produce high quality research. I would also like to take time, prior to publishing this study, to explore the evidence of cognitive domains affected by tVNS in more detail. This would provide me with an opportunity to synthesise potential cognitive mechanisms of change that may mediate improvement in depression during tVNS. For the empirical paper, I would like to seek additional statistical support to explore ways to recover T1 data and to work with missing values. There is also potential to conduct mediation analysis to investigate the mediating role of, for example, heart rate variability in the increase and decrease of self-compassion and self-criticism scores, respectively.

Research Realities

This thesis was ambitious for a DClinPsy project. It is for this reason that we recruited the assistance of two MSc students. It would not have been possible to conduct this research without them, not least because of the double-blinding required in the design but also the volume of participants and two testing sessions. It would not have been possible for me to achieve this with three days per fortnight of allocated research time. As mentioned before, I also did not expect the mental, physical and emotional difficulties of switching between research, clinical and academic components of the course, which impacted my ability to engage in aspects of the research. The sheer volume of eligible publications returned from the systematic review was also unexpected. The breadth of cognitive and emotional domains covered also made the extraction and synthesis of results more mentally challenging as almost

each publication was different. Nevertheless, I think the systematic review is an asset to the field and it would have been a useful resource for designing our empirical study. Conducting a systematic review of that magnitude alone is also uncommon. Prior to publication it will be important that a second researcher check a percentage of data extraction for reliability. Fresh researcher perspectives may also provide an opportunity to shed new light on the synthesis of results.

The recruitment of MSc students to assist in conducting the research was also an opportunity for me to take a supervisory role. This is something I have experience of from my post-doctoral roles and it was a reminder of how much I enjoy supervision and training of students. I have always appreciated the investment from others in my own training needs and this is something that I like to pass forward to students. I was also concerned for their wellbeing when our research laptop was stolen during testing. Not only was this a loss of equipment but a loss of valuable and hard-earned data that resulted in one task being unanalysable. Unfortunately, the loss of data is a common occurrence in research and I made the assumption that data back-ups were being made regularly when I was not present. I take responsibility for this as my previous experience with data loss should make this an integral part of my research training for students.

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Appendices

Appendix 1 - Systematic Review Protocol (PRISMA Checklist)

Title:	What are the cognitive and emotional effects of non-invasive vagus nerve stimulation?
Registration	No
Authors:	Caroline Falconer, Sunjeev Kamboj, Giulia Piazza (for reference checking reliability)
Contact	c.falconer@ucl.ac.uk , sunjeev.kamboj@ucl.ac.uk
Contributions	CF: conceptualisation, literature search, data extraction and synthesis, and write up SK: conceptualisation and commented on the write up
Amendments	NA
Support:	
Sources	Systematic review undertaken as part of clinical psychology doctorate at UCL.

Sponsor	NA
Role of sponsor or funder	NA
INTRODUCTION	
Rationale	<p>There has been a rise in interest into the function of the vagus nerve as a neuromodulator of cognition and emotion. Research has shown that certain psychological states (e.g. feeling safe, relaxed or frightened) can influence vagal activity. Conversely, new research is showing the potential of non-invasive, transcutaneous vagus nerve stimulation (tVNS) to alter psychological states. This is of interest to clinicians who are exploring methods to augment psychological therapy. However, a review of the current evidence-base of tVNS modulated cognition and emotion is required for clinical studies to proceed in an effective and ethical way.</p>
Objectives	<p>The objective of this review will be to address the following questions (including references to PICO)</p>

	<ol style="list-style-type: none"> 1. Which domains of cognition and emotion are affected by non-invasive vagus nerve stimulation (tVNS)? 2. What psychological paradigm/tests have been used in non-invasive vagus nerve stimulation studies. 3. What measures (e.g. subjective and objective) of cognition and emotion have been used in tVNS studies? (O) 4. What populations (e.g. clinical, healthy, young, old) have been used in these tVNS studies? (P) 5. What stimulation protocols have been used in tVNS studies (e.g. laterality, intensity, duration. Frequency, what type of stimulator)? (I) 6. What comparators (e.g. control conditions, different durations or ears) have been used in these tVNS studies? (C)
METHODS	
Eligibility criteria:	

Inclusion	Published in peer reviewed English language journal; Non-invasive VNS; use of at least one psychological paradigm (e.g. task or manipulation such as fear conditioning) or one outcome measure (e.g. mood questionnaire/rating); outcome measures are quantitative;
Exclusion	Invasive VNS; Animal studies; Unpublished data; Not Peer Reviewed; Review; Non-empirical;
Information sources	The following databased were searched for studies published prior to 3 rd February 2020: Web of Science (Thomson Reuters), PsycInfo, ProQuest and Medline.
Search strategy	<p>Key words:</p> <p>VNS -</p> <p>Vagus Nerve; Vagus Nerve Stimulation; Transcutaneous vagus Nerve Stimulation; tVNS; Transcutaneous auricular vagus nerve stimulation; Non-invasive vagus nerve stimulation</p> <p>Cognition and Emotion –</p>

	<p>Depression; Anxiety; Autism Spectrum Disorder; Psychosis; PTSD; OCD; Dementia; Eating disorder; Personality disorder; dysthymia; phobia; trauma</p> <p>Mood; affect; Memory; Fear; anger, surprise; happiness; disgust; Social cognition; Attention; Cognition; Emotion; Learning; Stress; Motivation; Judgement; Decision making; mindfulness; compassion, affiliation; Executive function; Kindness; Pro-social behaviour</p> <p>Search Strategy (altered for each journal where appropriate):</p> <p>(“Vagus Nerve Stimulation” OR “Transcutaneous Vagus Nerve Stimulation” OR tVNS OR “Transcutaneous auricular vagus nerve stimulation” OR “Non-invasive vagus nerve stimulation” OR “Vagal Nerve Stimulation”)</p> <p>AND</p>
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	<p>(Depression OR Anxiety OR “Autism Spectrum Disorder” OR Psychosis OR Schizophrenia OR PTSD OR “Post Traumatic Stress Disorder” OR OCD OR “Obsessive Compulsive Disorder” OR Dementia OR “Eating disorder” OR “Personality disorder” OR dysthymia OR phobia OR trauma OR Mood OR affect OR Memory OR Fear OR Disgust OR Sadness OR Happiness OR Surprise OR Anger OR “Social cognition” OR Attention OR Cognition OR Emotion OR Learning OR Stress OR Motivation OR Judgement OR “Decision making” OR Mindfulness OR Compassion OR Kindness OR affiliation OR “executive function OR “pro-social behaviour” OR “positive and negative affect” OR Valence OR Arousal)</p>
Study records:	
Data management	<p>Literature found in database searches will be downloaded into an Endnote file for further processing.</p>

	Data extracted from the literature will be stored in an excel file table according to PRISMA guidance.
Selection process	There will be one reviewer of the literature (CF). If no consensus is reached, then another researcher will be recruited (SK). SK to check 20% of CF's data extraction for reliability.
Data collection process	Literature found in database searches will be downloaded into an Endnote file for further processing. Once duplicates are removed the remaining titles and abstracts will be reviewed in Endnote. Literature that does not meet eligibility criteria will be siphoned off into another Endnote file. The remaining literature will be read to further establish eligibility. Remaining literature references will be checked for other, eligible studies missed from the search. This process and the number of studies at each stage will be presented in a flow diagram.

	<p>Data extraction will be in accordance with PRISMA guidance and stored in an excel file, formatted as a table for publication.</p>
<p>Data items</p>	<p><i>Participants:</i> Age, gender, ethnicity</p> <p><i>Intervention:</i> psychological interventions, manipulations or tasks; method of tVNS</p> <p><i>Comparators:</i> control conditions, different stimulation (ear, duration, intensity)</p> <p><i>Outcomes:</i> subjective measures of mood; objective behavioural measures of cognition (e.g. reaction times or error rates); heart rate variability</p>
<p>Outcomes and prioritization</p>	<p>Subjective measures of mood; objective behavioural measures of cognition (e.g. reaction times or error rates); heart rate variability</p> <p>Priority will be given to subjective measures of mood as we predict this would be the most widely collected data. If a meta-analysis were possible it would be on mood measures. Measures of cognition may be more disparate than measures of mood.</p>

<p>Risk of bias in individual studies</p>	<p>We will record which studies are pre-registered, blinded and note their own limitations. This will be done at a study level.</p> <p>Outcome measures within each study will also be discussed in terms for their validity and reliability. We will use this information to comment on the reliability of the evidence base and make recommendations to improve this.</p>
<p>Data synthesis:</p>	
	<p>No quantitative data synthesis is planned.</p> <p>This is because the studies are likely to be too disparate to conduct a meta-analysis.</p> <p>However, the results will be summarised in the following sections:</p> <ol style="list-style-type: none"> 1. Emotional effects of tVNS <ol style="list-style-type: none"> a. According to population (e.g. healthy or clinical populations) b. With commentary on quality of measures 2. Cognitive effects of tVNS

	<ul style="list-style-type: none"> a. According to population (e.g. healthy or clinical populations) b. With commentary on quality of paradigms and measures <ul style="list-style-type: none"> 3. tVNS methodology 4. tVNS study design 5. Future recommendations
Meta-bias(es)	No plan has been made to account for meta biases such as publication bias as this review is not a meta-analysis.
Confidence in cumulative evidence	GRADE or SAQOR (where appropriate) will be used to assess the quality and confidence of the evidence.

Appendix 2 – Ethical Approval

UCL RESEARCH ETHICS COMMITTEE
OFFICE FOR THE VICE PROVOST RESEARCH



18th October 2018

Dr Sunjeev Kamboj
Department of Clinical, Educational and Health Psychology
UCL

Dear Dr Kamboj

Notification of Ethics Approval with Provisos

Project ID/Title: 4277/001: The effects of vagus nerve stimulation on compassionate mind training and threat processing

I am pleased to confirm in my capacity as Joint Chair of the UCL Research Ethics Committee (REC) that your study has been ethically approved by the UCL REC until 1st March 2022 subject to a satisfactory response to the following comments together with a revised version of your application form.

1. Inclusion/Exclusion criteria: please qualify 'good' English as an inclusion criteria and 'risk of pregnancy'. Will this include all women of reproductive age? Also, the inclusion/exclusion criteria need to tally with the Participant Information Leaflet (PIL).
2. It was noted that Sections E1 and E5 were contradictory: either the participant or the researcher applies the VNS clip.
3. Section E8: Does the V-TENS device not fall under this criteria and potentially the heart rate monitor?
4. What would you do if a significant mental health condition was suspected or revealed in the course of the study? Would the participant be referred to their GP?
5. The title of the study on the PIL and consent form should be the same as the title of the application form for this study.
6. It was noted that the use of deception seemed acceptable although it was recommended that it might be prudent to have a secondary outcome measure which is around acceptability of this aspect after, say, 5 or 10 people.
7. Section B2: What is the rationale for the upper age limit?
8. Consent Form: The section on being contacted to partake in future studies seemed fine, but it was unclear how this would be stored or how the participants would be contacted. Also, could this be used to give them the results/findings from the study? List the various activities that the participant will be asked to complete so that they can agree to each. Also, please proof-read point 9 for accuracy '*fully compensated if choose to withdraw.*'
9. Section C5: Participants should be given a copy of the PIL to read ahead of the session.

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<http://ethics.grad.ucl.ac.uk/>

10. Advert: It was suggested that instead of stating that participants would be paid a £30 inconvenience payment that you indicate that they will be paid £10 per hour. And what happens if a participant withdraws part way through? Are they paid only for the time they have participated? Also, reference to the Data Protection Act 1998 needs to be removed and updated to make reference to the new regulation.

11. PIL: correct wording as follows: 'The legal basis for processing your personal data will be *'task in the public interest'* rather than 'consent'.

Ethical approval is also subject to the following conditions:

Notification of Amendments to the Research

You must seek Chair's approval for proposed amendments (to include extensions to the duration of the project) to the research for which this approval has been given. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing an 'Amendment Approval Request Form'

<http://ethics.grad.ucl.ac.uk/responsibilities.php>

Adverse Event Reporting – Serious and Non-Serious

It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator (ethics@ucl.ac.uk) immediately the incident occurs. Where the adverse incident is unexpected and serious, the Joint Chairs will decide whether the study should be terminated pending the opinion of an independent expert. For non-serious adverse events the Joint Chairs of the Ethics Committee should again be notified via the Ethics Committee Administrator within ten days of the incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Joint Chairs will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

Final Report

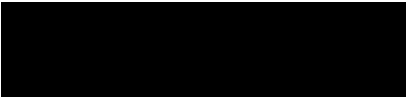
At the end of the data collection element of your research we ask that you submit a very brief report (1-2 paragraphs will suffice) which includes in particular issues relating to the ethical implications of the research i.e. issues obtaining consent, participants withdrawing from the research, confidentiality, protection of participants from physical and mental harm etc.

In addition, please:

- ensure that you follow all relevant guidance as laid out in UCL's Code of Conduct for Research: <http://www.ucl.ac.uk/srs/governance-and-committees/resgov/code-of-conduct-research>
- note that you are required to adhere to all research data/records management and storage procedures agreed as part of your application. This will be expected even after completion of the study.

With best wishes for the research.

Yours sincerely



Professor Michael Heinrich
Joint Chair, UCL Research Ethics Committee

Cc: Dr Caroline Falconer