Childhood Trauma as a Moderator in a Study of Compassionate Imagery Training with Adjunctive Non-Invasive Vagus Nerve Stimulation: An Exploratory Secondary Analysis

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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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Overview

Volume 1 of this thesis reports on an exploratory secondary analysis investigating the level of reported childhood trauma as a moderator within a study exploring the combination of transcutaneous vagus nerve stimulation (tVNS) with a compassion focused imagery task. This combination is one such example of recent investigations of the effects of combining a method of non-invasive neurostimulation with a psychotherapeutic intervention.

Part 1 examines the effect of combining methods of non-invasive brain stimulation or neuro-modulation techniques with psychotherapeutic interventions for anxiety disorders and trauma-related disorders. The evidence is synthesised using a meta-analytic approach and a narrative synthesis. The quality of the current evidence base and methodological issues are discussed.

Part 2 is an exploratory secondary analysis of an initial study by Kamboj and colleagues, that investigated the combination of transcutaneous vagus nerve stimulation (tVNS) with a compassion focused imagery task. This follow-up exploratory study investigates whether the effects were moderated by level of childhood trauma. Three-way (stimulation x imagery x level of childhood trauma) independent measures ANOVAs were conducted on the short-term and longer-term change in: Heart rate variability (HRV), state self-compassion, state mindfulness, state safe/contentment positive affect, trait mindfulness, and trait self-compassion.

Part 3, the critical review, explores critically the entire research process, the background, my theoretical orientation and its relationship with the theoretical orientation of this avenue of research, conceptual issues in the analysis approach and research design, the challenges of conducting research using at-home study requirements, and some reflections on conducting neuroscientific-focused research.

Table of Contents

Tables and Figures

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Impact Statement

The systematic review found that there was no consistent additive effect of combining non-invasive brain stimulation or neuro-modulation techniques with psychotherapeutic techniques for anxiety disorders or trauma-related disorders. The review could have a beneficial impact on the field of academia if it leads to future research with clearly proposed, theoretically sound mechanisms underlying carefully chosen and methodologically rigorous protocols. This should move the field along more quickly and enable a consensus to be reached sooner on whether there is a possible additional benefit of combining non-invasive neurostimulation and psychotherapy, and if so in what protocols. Outside of academia, it could be of beneficial impact if it can encourage caution within clinical settings using or considering using a combination of non-invasive brain-stimulation or neuro-modulation techniques with psychotherapeutic techniques for anxiety disorders or trauma-related disorders. This is particularly important considering the safety implications and the current mixed and limited state of the research evidence. At the very least, professionals working in clinical settings should be clear with service-users about the current state of the evidence to allow them to make an informed choice about the intervention. These benefits could be achieved by publication in a research journal and presentation at a research conference.

The empirical paper found that overall, there was no evidence that an individual's level of childhood trauma moderated the treatment effects and interactions from the original study by Kamboj and colleagues (in prep). Of particular importance, there was no evidence to suggest that regardless of stimulation condition individuals with higher levels of reported childhood trauma achieved poorer outcomes in the change in heart rate variability or self-reported behavioural outcome

measures targeted by compassion-focused imagery exercises. The research could be of benefit within the field of academia to encourage researchers to conduct adequately powered and tailored primary research to test the hypotheses proposed within the theories around fears, blocks, and resistances to compassion. The research could also be of benefit within the field of academia to encourage researchers to continue to investigate the nature of the pathway, if any exists, between childhood trauma, disrupted functioning of the parasympathetic nervous system, and psychopathology risk. Outside of academia, clinical services offering compassion-focused interventions should think strongly about exclusion criteria related to experiences of childhood trauma until further research exists. At the very least, careful decision-making based on individual formulation and efforts to produce practice-based evidence would be helpful and warranted, rather than blanket exclusion of any individual who has experienced significant levels of childhood trauma. These benefits could be achieved through publication in a research journal, presentation at a research conference, and dissemination through other methods to UK mental health services offering group compassion-focused therapy interventions, such as NHS Talking Therapies services (formerly known as Increasing Access to Psychological Therapies).

Part 1: Review Paper

The Effect of Combining Methods of Non-invasive Brain Stimulation or Neuro-Modulation Techniques with Psychotherapeutic Interventions for Anxiety Disorders and Trauma-Related Disorders.

Abstract

Introduction: A variety of non-invasive techniques have been developed for the modulation or influence of the activity of the human brain and nervous system. These techniques have received rapidly growing research interest in recent years, including around the effects of combining them with psychotherapy for a variety of psychological disorders, including anxiety and trauma-related disorders.

Aims: The current review aimed to build on previous reviews in what is a fast-moving area of research, to explore the effect of combining non-invasive brain stimulation or neuro-modulation techniques with psychotherapy (techniques) for anxiety and trauma-related disorders, relative to psychotherapy (techniques) alone.

Method: Studies had to meet inclusion criteria related to the population, research design including an appropriate comparison, and reporting of outcome measures. Twelve studies meeting inclusion criteria were identified from four electronic databases (Medline, PsycInfo, Embase and WebOfScience) and references from previous relevant reviews. Data was synthesised using a meta-analysis where data was available, and with a narrative synthesis to complement this.

Results: The meta-analyses revealed that there were no significant differences between groups receiving psychotherapeutic interventions with versus without an active non-invasive neurostimulation intervention. Through the narrative synthesis, the results were mixed with what were deemed broadly positive results in five studies, neutral results in six studies and negative results in one study. The proposed mechanisms of interaction between the stimulation and psychotherapy

varied in their clarity and extent to which they aligned with current theoretical understanding of psychotherapy (techniques) processes.

Conclusions: The review produced less optimistic results than previous reviews suggesting that a combination of psychotherapy and non-invasive neurostimulation does not consistently enhance the effects of psychotherapy alone for anxiety disorders and trauma-related disorders, with no clear site of stimulation, or combination of psychotherapy and non-invasive neurostimulation intervention producing consistently reproduced enhancing effects. Further research with carefully chosen, theoretically grounded protocols is needed to reach a consensus on whether there is an additional benefit of combining non-invasive neurostimulation and psychotherapy for anxiety and trauma-related disorders, and if so in what protocols.

Introduction

A variety of techniques have been developed for the modulation or influence of the activity of the human brain and nervous system. These techniques for brain stimulation or neuromodulation have been receiving rapidly growing interest in recent years, with a variety of applications now established or under investigation. Applications of invasive methods of neuromodulation for the treatment of neurological conditions include electroconvulsive therapy (ECT) which induces seizures in patients, and deep brain stimulation (DBS) which involves implanting stimulating electrodes within the brain. These invasive procedures were developed through the 19th and 20th centuries and continue to be used today (Lewis, Thomson, Rosenfeld & Fitzgerald, 2016). Non-invasive methods have been developed and investigated since the late 19th century but have received increasingly growing research interest in the past few decades (Schulz, Gerloff & Hummels, 2013; Polaína, Nitcshe & Ruff, 2018). Non-invasive techniques that can alter neuronal activity include those more established such as transcranial magnetic stimulation (TMS) and transcranial electric stimulation (TES) and more novel methods such as transcutaneous vagus nerve stimulation (tVNS). These three methods shall now be outlined in brief.

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) uses a copper wire coil placed near the head to produce short-lasting, strong electric currents to produce a rapidly changing magnetic field. By placing the coil over the surface of the head, this magnetic field induces currents within the brain that are strong enough to depolarise

neuronal elements and influence cortical excitability (Schulz et al., 2013). TMS can be delivered in single pulses, paired pulses or in trains of pulses. Repetitive TMS (rTMS) involves repetitive magnetic field perturbations to enhance or suppress cortical activity and modulate excitability. Theta burst stimulation (TBS), is a pattern of rTMS, which uses high-frequency pulses (50 Hz-100 Hz) that can induce both inhibitory (reducing synaptic transmission) or facilitatory (enhancing synaptic transmission) long-lasting effects (Huang et al., 2005). Huang et al. (2005) reported on three variety of patterns that TBS can be delivered in. This includes either using 600 total uninterrupted pulses delivered in a continuous train for a total of 40 seconds (continuous theta-burst stimulation; cTBS), 600 total pulses delivered using 2-second trains of TBS repeated every 10 seconds for a total of 190 seconds (intermittent theta-burst stimulation; iTBS), or 600 pulses of 5-second trains of TBS repeated every 15 seconds for a total of 110 seconds (intermediate theta-burst stimulation; imTBS). For a detailed review of the modalities and mechanisms of TMS please see Kim, Hong, Kim and Yoon (2019).

There is now a significant amount of evidence on the use of TMS protocols to treat a variety of mental health difficulties, including depression, obsessive-compulsive disorder, addictions and anxiety and trauma-related disorders (Brunoni et al., 2017a; Brunoni et al., 2017b; Cirillio et al. 2019; De Risio et al., 2020; Fitzsimmons et al., 2022; Nguyen et al., 2021; Song et al., 2019).

In terms of safety of the use of TMS in clinical and research applications, possible side effects include seizure induction, transient and long-lasting hearing effects, hypomania, syncope, transient headache and other pain, transient cognitive changes, burns, structural brain changes and phytotoxicity (Rossi, Hallett, Rossini and Pascaul-Leone, 2009). These safety concerns are significant and are not all

rare. Therefore they should be seriously considered when planning to use TMS clinically or in research. For a full outline of ethical and safety considerations please see Rossi et al. (2009).

Transcranial Electric Stimulation

Transcranial Electric Stimulation (TES) includes several non-invasive brain stimulation techniques involving delivery of a weak electrical current onto the scalp using two or more electrodes to alter brain function (Reed & Kadosh, 2018). Techniques within this umbrella include Transcranial Direct Current Stimulation (tDCS), Transcranial Alternating Current Stimulation (tACS) and Transcranial Random Noise Stimulation (tRNS). Whilst these techniques all involve the passing of a current through the scalp, the electrical signal patterns and therefore the effects on the brain differ between them. These differences are summarised in *Table 1.* For a detailed description of the different types of TES and their mechanisms of action, please refer to Reed & Kadosh, 2018, and Radman, Ramos, Brumberg & Bikson, 2009.

Promising results of the effects of TES on healthy individuals led to hypothesised applications as a therapeutic tool in both neurological and psychiatric populations (Yavari et al., 2018). There has been accumulating evidence that suggests a clinically relevant potential effect of TES as an intervention for individuals with depression, chronic pain, and addictions (Bruoni et al., 2016; Kuo, Paulus & Nitsche, 2014).

In terms of safety and tolerability of TES, adverse effects include skin burning, skin irritation, headaches, and fatigue. For a full outline of safety and ethical considerations as well as application guidelines, please refer to Antal et al. (2017).

Table 1. *A Comparison of Different Forms of TES in terms of Direction of Current, Frequency and Mechanism of Action*

Technique	**Direction of current**	**Frequency: Fixed or Changing**	**Mechanism of Action**
Transcranial Direct Current Stimulation (tDCS)	One-way from one or more anodes to a cathode	Fixed	Induces change in excitability or neurons below cathode, usually an increase in excitability. When increasing excitability, it brings neurons closer to their firing threshold but does not elicit depolarisation.
Transcranial Alternating Current Stimulation (tACS)	Alternating between two electrodes	Fixed	Entrains neurons in a specific brain region to fire at a specific frequency by altering the transmembrane potential of neurons
Transcranial Random Noise Stimulation (tRNS)	Alternating between two electrodes	Randomly changing within specified range	Mechanism underlying tRNS in humans is not yet fully understood but appears to induce excitability changes that are intensity dependent, with lower intensities (0.4 mA) eliciting inhibition and higher intensities excitation.

Transcutaneous Vagus Nerve Stimulation

The vagus nerve is a major component of the parasympathetic nervous system. It serves as an important bidirectional conduit between the body and the brain, with both afferent and efferent fibres, serving largely to maintain homeostasis (Butt, Albusoda, Farmer & Aziz, 2020). Techniques to stimulate the vagus nerve include both invasive (surgically implanted) and non-invasive (transcutaneous). Although invasive methods are more well-established, they are expensive (Farmer et al., 2020) and several adverse effects have been reported including cough, voice alteration, swallowing difficulties, and bradycardia (Liporace et al., 2001). As a result, there has been increasing interest in the use of transcutaneous vagus nerve stimulation (tVNS) across basic, translation and clinical research (Farmer et al. 2020). tVNS techniques use stimulation sites either at the external ear for the auricular branch of the vagus nerve (taVNS) or at the neck for the cervical branch of the vagus nerve (tcVNS). Adverse events stemming from the surgery involved in invasive VNS can be avoided with tVNS which is only accompanied by more minor side effects of slight pain, itching, burning, and tingling at the location of the electrode (Van Leusden, Sellaro & Colzato, 2015).

There is increasing research investigating the potential use of tVNS in a whole range of psychological and physiological applications, including for depression, schizophrenia, worry, extinction of fear memory, neurodevelopmental disorders, epilepsy, traumatic brain injury, and pain, as well as others (Butt et al., 2020; Farmer et al. 2020; Hilz & Bolz, 2022).

Anxiety and Trauma-Related Disorders

Anxiety and trauma-related disorders include a range of conditions related to maladaptive fear processing and resultant behavioural changes (Marin, Comprodon, Dougherty & Milad, 2014). The DSM-V (American Psychiatric Association, 2013) includes eleven anxiety disorders, with the most common being Generalised Anxiety Disorder (GAD), Social Anxiety Disorder (SAD), Panic Disorder (PD) and Agoraphobia, and Specific Phobia (SP; Bandelow & Michaelis, 2015). The unifying feature of the listed disorders is excessive fear and anxiety that differs from normal feelings of anxiousness or nervousness that causes disturbances to functioning. However, each disorder includes a range of specific features such as intense and sudden fear with somatic sensations, anticipation of future events, worry, hypervigilance, and avoidance.

Cognitive behavioural therapy (CBT) is the most supported psychological treatment, with efficacy being shown in many controlled studies (Bandelow, Michaelis & Wedekind, 2017). Whilst there are well-established psychological therapies, CBT achieves an average response rate of 49.5% across anxiety disorders, meaning around 50% of individuals fail to show an adequate response (Loerinc et al., 2015). It should be noted that in this review (Loerinc et al., 2015) a wide range of methods for determining what constituted a response rate were used (e.g., reduction from baseline alone and in combination with a clinical cut-off, or statistically reliable change alone and in combination with a clinical cut-off).

For trauma-and-stressor-related disorders, the DSM-V (American Psychiatric Association, 2013) lists seven, including Post-Traumatic Stress Disorder (PTSD), which are categorised together as being stress response disorders that result from specific triggering events.

Trauma-focused psychological therapies that have been most extensively investigated and shown to be the most effective are exposure-based interventions (Foa, 2011), cognitive therapy for PTSD (Ehlers & Clark, 2008), and Eye Movement Desensitization and Reprocessing (EMDR; Lewis, Roberts, Andrew, Starling & Bisson, 2020; Shapiro, 2014). Whilst these are well-established and supported treatments, recent research suggests that, in a similar picture to anxiety disorders, up to 50% of individuals fail to show an adequate response (Resick et al., 2017).

Combining Psychotherapy and Non-Invasive Neuromodulation Techniques

Interest in methods of augmenting the effects of psychotherapy has been an area of growing research interest in recent years. Within this, there has considerable research interest in the effect of combining non-invasive brain stimulation with psychotherapy for several difficulties.

A review by Herrmann (2019) investigated the additional benefit of non-invasive brain stimulation on fear extinction in 7 studies with healthy participants using conditioned fear paradigms. They reported that there was promising evidence that rTMS and tDCS can improve fear extinction learning, as well as some null findings. The authors highlight potentially promising stimulation sites of the mPFC and vmPFC. The authors stated that the vmPFC appeared very promising based on a study using rTMS to stimulate an area of the cortex with functional coupling with the vmPFC (Raji et al., 2018). They recommended that future research should

consider and differentiate which part of the different processes involved in extinction were being targeted, for example, the avoidance preventing extinction learning, the extinction learning, or the extinction learning consolidation.

A more recent review (Marković et al., 2021) of 30 studies, investigated the impact of rTMS and tDCS on fear memory and extinction in animals and humans, both in clinical and healthy populations. They concluded that both techniques can be effective methods to modulate fear memory and extinction, specifically highlighting excitability-enhancing stimulation applied over the vmPFC as showing the strongest potential to enhance fear extinction. In terms of when the stimulation is delivered in relation to the extinction (i.e. stimulation before, during or after extinction), for tDCS there were mixed results for both stimulation delivered during and after extinction in studies of humans (across both healthy and clinical populations), and so the authors stated that further studies were warranted to determine optimal timing of stimulation. For rTMS, the limited number of studies to draw upon suggested that both stimulation before and after extinction can be enhancing.

A previous review solely focused on individuals with anxiety disorders and trauma-related disorders, (Herrmann et al., 2019) reviewed four studies combining rTMS or dTMS (deep TMS, which stimulates deeper cortical regions than standard TMS) with exposure-based psychotherapies. Three of the studies were for PTSD and one was for specific phobia. They used a basic meta-analytic method, calculating a mean weighted effect size estimate of f = 0.32, based on the f statistic from the interaction between the treatment group (active versus sham stimulation) and time (pre versus post). This indicated a medium-to-large effect size (Cohen, 1988), but they did not use a statistical method to calculate statistical significance. They concluded that the initial work in this area was promising and demonstrated a

benefit of adding TMS to exposure-based psychotherapies for the treatment of anxiety disorders. However, they stated that it remained unclear what exact stimulation parameters were optimal.

A more recent review looked at the combination of non-invasive brain stimulation with psychotherapy, across all mental illnesses (Tatti et al., 2022). They identified twenty-four studies, with disorders including Major Depressive Disorder (MDD), anxiety disorders, Post-Traumatic Stress Disorder (PTSD), Obsessive-Compulsive Disorder (OCD), Alcohol Use Disorder (AUD), opioid addiction, and Binge Eating Disorder (BED). They concluded that overall, a combination of NIBS and psychotherapy appeared more effective compared to sham treatments, but they were tentative with their conclusions due to the limited number of studies with an appropriate control. Furthermore, five of the twenty-four studies were single case studies, which limits the confidence of conclusions that can be made.

Aims

The current systematic review and meta-analysis aimed to build on the previous reviews in what is a fast-moving area of research. It aimed to focus more sharply than the review conducted by Tatti et al. (2022) on anxiety and trauma-related disorders. It also aimed to solely focus on designs with participants randomised to groups that allowed a comparison of psychotherapy with and without active non-invasive neurostimulation of any kind. Finally, it aimed to add a more complex meta-analytic component, which neither of the reviews by Tatti et al. (2022) nor Herrmann et al. (2019) included.

The review aimed to address the following questions:

1) What is the effect of adding non-invasive brain stimulation or other non-invasive neurostimulation to psychotherapy or specific psychotherapeutic technique relative to this psychotherapy (technique) alone in anxiety and trauma/stressor-related disorders?

2) What are the biological and psychological mechanisms of interaction proposed in research studies investigating this interaction?

Method

The review was pre-registered on Prospero (registration number: CRD42023466268).

Literature Search Strategy

Literature Search Searches on EMBASE, Medline, PsycINFO and Web Of Science were conducted on November 24th 2023 using a three-component strategy. There was no restriction on the publication date. The first component comprised terms related to psychotherapy and psychotherapeutic techniques, including psychother*, psychological treatment, psychological therapy, extinction, exposure therapy, acceptance, reappraisal, bias modification, cognitive behav*, cognitive control, emotion* regulation, compassion*, meditat*, mindful*, attention*, control, habituation, inhibitory learning, and retrieval inhibition. The second component comprised terms related to non-invasive brain stimulation techniques, including noninvasive, non-invasive, neurostimulation, brain stimulation, NIBS, tvns, transcutaneous vagus nerve stimulation, tDCS, transcranial direct current stimulation, tACS, transcranial alternating current stimulation, TMS, rTMS, transcranial magnetic stimulation, and repetitive transcranial magnetic stimulation. The final component comprised terms related to anxiety and trauma-related

disorders, including posttraumatic stress disorder traum*, stress disorder, anxiety, and *phobia.

Inclusion Criteria

Papers were included in the systematic review if they met the following criteria:

1) Published in a peer-reviewed journal published in English.

2) Studies of human participants aged 18 years and older.

3) Experimental studies including a comparison of active non-invasive brain or neurostimulation plus psychotherapy versus psychotherapy alone or with sham stimulation.

4) Clinical samples used with a primary problem of an anxiety disorder, including generalised anxiety disorder, social anxiety disorder, panic disorder and phobias, or trauma-related disorder, including PTSD.

5) Assessed symptom level before and after the intervention.

6) Results reported at group level.

Exclusion Criteria

Papers were excluded if:

1. Studies of individuals with chronic pain, fibromyalgia, and other pain-related difficulties.

2. Included individuals with severe and enduring mental health difficulties, such as psychotic illnesses and schizophrenia.

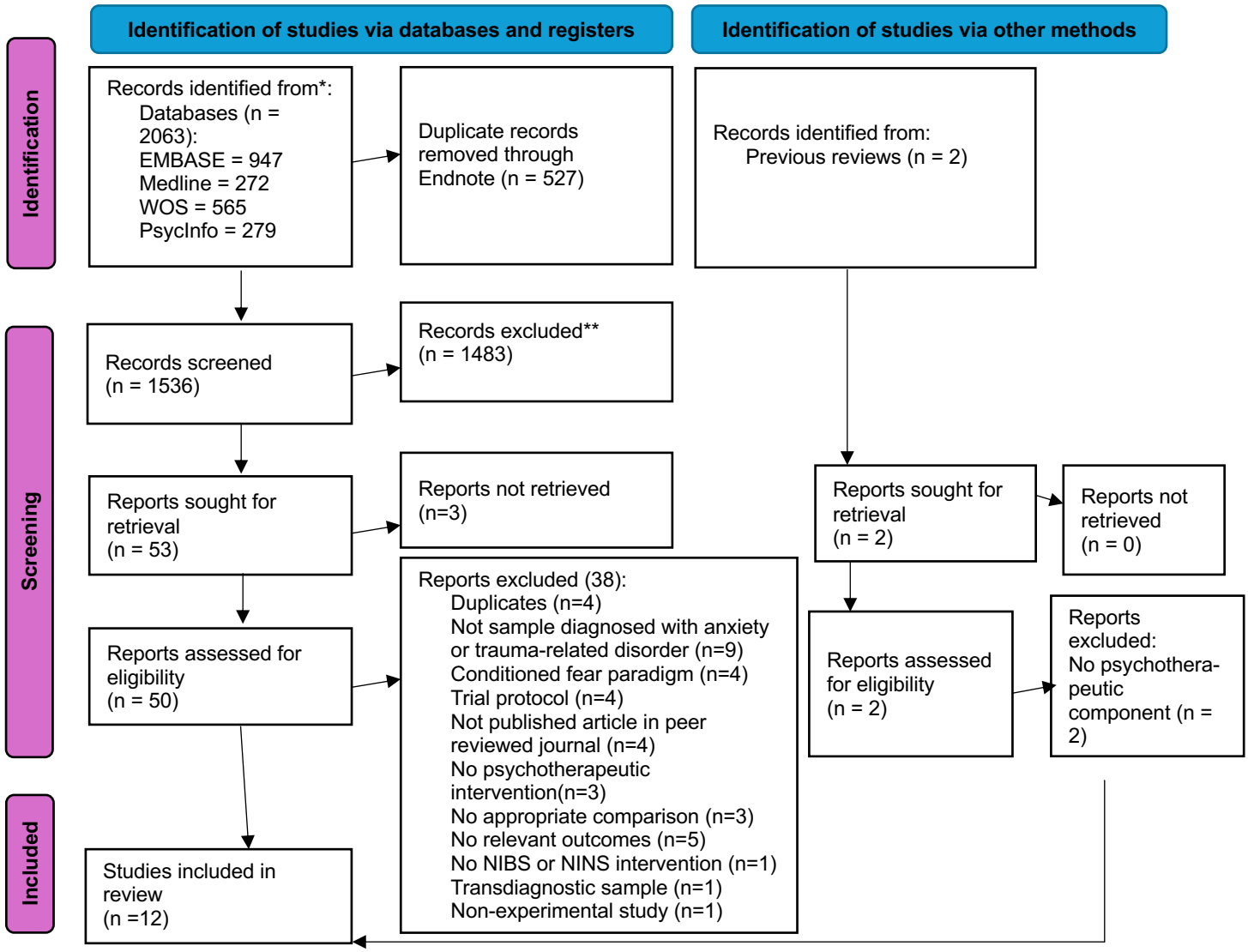
3. Studies of individuals with acquired brain injuries, stroke, and dementia.

Screening and Selection

Following removal of duplicate papers appearing in more than one of the initial searches, 1536 papers remained. All titles were screened and for those that appeared relevant, the abstract was reviewed. Any studies that referred to an anxiety or trauma-related disorder and treatment involving psychotherapy and non-invasive brain or neurostimulation were included for full-text screening. A subset of 25% of the papers were title and abstract screened by a second reviewer to check for the reliability of the application of the screening process. Any disagreements were discussed to reach a resolution and refine the screening process.

Following this, 50 papers were retrieved in full and reviewed against the inclusion and exclusion criteria. Following this full-text screening process, 38 papers were excluded, leaving 12 studies to be included in the review. The reasons for exclusion following the full-text review are summarised in Figure 1.

Figure 1: *Prisma Flow Diagram of Screening Process*



Note. From Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Quality Assessment

To assess the quality of and risk of bias in the studies, a modified version of the Cochrane Risk of Bias tool (Sterne et al., 2019) was created and completed for each study. The modified tool consisted of nine items across five domains. The domains were as follows: Randomisation Process (three items), Blinding of participants and personnel (two items), Blinding of outcome assessors (one item), Missing data (two items), Selective reporting (one item). Each item was scored as either Yes, Partially Yes, No information, No or Not Applicable. Item one, pertaining to the allocation method, could be scored as non-specific random allocation. An overall rating of low risk of bias, unclear risk of bias and high risk of bias was given for each domain and for the overall rating of the study, based on the domain ratings.

Method of Synthesis and Analytic Procedure

The studies were grouped into those of trauma-related disorders and those of anxiety disorders for meta-analyses. Within the group of studies of individuals with trauma-related disorders (all of PTSD), separate meta-analyses were performed on self-reported outcome measures of PTSD symptoms and clinician-rated outcome measures of PTSD symptoms. Where multiple symptom-based outcome measures or subscales were reported, the primary outcome measure was selected if it had been stated. Otherwise a decision was made on which seemed to be the most psychometrically robust and theoretically sensible option through discussion with the second reviewer.

Effect sizes based on the standardised mean difference (SMD) between active groups (i.e. involving a combination of psychotherapeutic intervention and non-invasive brain stimulation or neurostimulation) and control groups (those

receiving psychotherapeutic intervention with no stimulation or sham stimulation) at the end of intervention time-point were calculated using restricted maximum likelihood effects models. Larger positive effects indicated that mean scores on the selected symptom outcome measure at the end of intervention time-point were lower in the experimental group than the control group. Effect sizes in the range 0.20–0.49 were defined as small, 0.50–0.79 as moderate and ≥ 0.80 as large (Cohen, 1988).

Analyses were conducted using JASP, the open-source statistics programme (version 0.17.1; Jasp Team 2023). Heterogeneity was assessed using a point estimate of the amongst-study variance of true effects (τ^2) and the approximate proportion of total variability (I^2). An I^2 of 25% was considered small, 50% moderate and 75% large (Higgins, 2008). When moderate or high heterogeneity was observed a sensitivity analysis was conducted whereby studies were removed stepwise to assess the impact of their removal on levels of heterogeneity.

The findings of the papers were also brought together through a narrative synthesis. Studies were discussed in terms of whether the results were broadly positive (i.e. stimulation was psychotherapy-enhancing), negative (i.e. psychotherapy-interfering), or neutral (i.e. neither enhancing nor interfering).

Results

Twelve studies fulfilled the inclusion criteria for the review. Within these, seven studies were of individuals with PTSD, three of specific phobias, one of panic disorder or agoraphobia, and one of generalised anxiety disorder with comorbid depression. Table 2 summarises the characteristics of all included studies.

Table 2. *Summary of Included Studies*

Study	Disorder	Design	N	Psychotherapy (technique)	Stimulation Type	Stimulation Parameters	Stimulation Location	Timing: Priming, Simultaneous or Consolidation
Bremner et al., (2021)	PTSD	2 Arm Parallel	20	Script-driven imagery (SDI) exposure	tcVNS	Alternating voltage signal consisting of five 5kHz sine bursts (1 ms of five sine waves with pulse width 40 ms) repeating at 25 Hz envelopes. 0-30 v for active, up to threshold when still tolerated without pain	Carotid artery of neck	Simultaneous
Depperma nn et al., (2017)	Panic Disorder	2 Arm Parallel	44	Group CBT	iTBS	15x daily sessions over first 3 weeks of intervention. 80% motor threshold. The iTBS protocol consisted of a total of 600 pulses applied in intermittent biphasic bursts at a frequency of 15 pulses per second via 2 second trains, starting every 10 seconds	Left dlPFC	Consolidation
Fryml et al., (2019)	PTSD	4 Arm Parallel	8	Prolonged exposure using audio recording of verbal recall	rTMS	120% motor threshold, 10 Hz, 5-second train duration, and 10-second intertrain interval for 30 minutes (6000 pulses) once a week for 8 weeks (total 48,000 pulses)	dlPFC	Simultaneous

Herrmann et al., (2017)	Acrophobia	2 Arm Parallel	39	Virtual reality exposure	rTMS	2 sessions. 40 trains of 4 s duration (1560 pulses) with a 10 Hz stimulation frequency. Inter train intervals 26 s. 100% RMT	vmPFC	Priming
Isserles et al., (2013)	PTSD	3 Arm Parallel	30	Script-driven imagery (SDI) exposure	dTMS	120% of MT, 42 x 20 Hz trains of 2 s each, 20 s inter-train interval (total 1680 pulses)	mPFC	Consolidation
Isserles et al., (2021)	PTSD	2 Arm Parallel	125	Script-driven imagery (SDI) exposure	dTMS	12 sessions. 8 Hz, 2second trains, 20second inter train intervals, with 80 trains at 100% of leg RMT	mPFC & ACC	Consolidation
Kozel et al., (2018)	PTSD	2 Arm Parallel	103	Cognitive processing therapy	rTMS	110% of MT at 1 Hz rTMS continuously for 30 min (total 1800 pulses)	dlPFC	Priming
Leuchter et al., (2022)	Spider phobia	2 Arm Parallel	17	Repeated in-vivo exposure	iTBS	Starting from 80% MT advancing as tolerated, bursts of 3 pulses at 50 Hz every 200 ms, 5 Hz carrier wave. Pulse delivery over 2s, repeated every 10 s, 20x in succession (total 600 pulses)	vmPFC	Consolidation

Nasiri et al., (2020)	GAD and comorbid depression	3 Arm Parallel	43	Unified protocol	tDCS	10 sessions direct current of 2.0 mA for 30-minutes	Right dlPFC	Unclear
Notzon et al., (2015)	Spider phobia	2 Arm Parallel	41	Virtual reality exposure	iTBS	600 pulses in intermittent biphasic bursts at a frequency of 15 pulses per second via 2 s trains, starting every 10 s.	Left dlPFC	Priming
Osuch et al., (2009)	PTSD	2 Arm Crossover	9	Imaginal exposure	rTMS	Each session 30 min. 10% MT, 30 min of continuous 1 Hz right frontal active or sham stimulation. 1800 stimulations per session; for a total of 36,000 stimuli in each condition	dlPFC	Simultaneous
Van't Wout-Frank et al., (2019)	PTSD	2 Arm Parallel	12	Virtual reality exposure	tDCS	6 sessions of 2 mA for 25-minutes.	vmPFC	Simultaneous

Note. MT/RMT = Motor threshold/Resting motor threshold. Study by Notzon et al., (2015) included healthy participants as well as individuals with spider phobia. N listed here is just of those with spider phobia. For 'Timing', priming = stimulation delivered before the psychotherapy session, simultaneous = delivered at the same time as the psychotherapy session, and consolidation = delivered after the psychotherapy session.

Summary of Risk of Bias

Risk of bias assessment is summarised in Table 3. As can be seen there was variation in the quality of reporting for the methodological domains. Overall, there were widespread issues causing concern. Only two studies were given an overall risk of bias rating of low, five were given a rating of unclear risk of bias and five were given a rating of high risk of bias.

Table 3. *Risk of bias ratings for the included studies*

Study	Domain 1. Randomisation Process	Domain 2. Blinding of Participants and Personnel	Domain 3. Blinding of Outcome Assessors	Domain 4. Missing Outcome Data	Domain 5. Selective Reporting	Overall
Notzon et al., 2015	🟡	🟡	🟡	🟢	🔴	🟡
Deppermann et al., 2017	🟡	🟡	🟡	🔴	🔴	🔴
Herrmann et al., 2017	🟡	🟡	🟡	🟢	🟢	🟡
Nasiri et al., 2020	🟡	🟡	🟢	🟢	🔴	🟡
Leuchter et al., 2022	🟡	🟡	🟢	🔴	🔴	🔴
Osuch et al., 2009	🔴	🟡	🟢	🟢	🔴	🔴
Isserles et al., 2013	🟡	🔴	🟢	🟢	🔴	🔴
Kozel et al., 2018	🟢	🟡	🟢	🔴	🟢	🟡
Van't Wout-Frank et al., 2019	🟡	🟡	🟢	🟢	🟢	🟡
Fryml et al., 2019	🔴	🟡	🟢	🔴	🔴	🔴
Bremner et al., 2021	🟢	🟢	🟢	🟢	🔴	🟢
Isserles et al., 2021	🟢	🟢	🟢	🟢	🟢	🟢

Note. This figure depicts the risk of bias ratings for the included studies. Red corresponds to a rating of high risk of bias, yellow corresponds to unclear risk of bias and green corresponds to low risk of bias. For ratings for each individual domain item and notes on reasons for coming to some decisions please see Appendix X.

For domain 1, randomisation process, notable issues included seven studies describing using random allocation without any specific detail of method and only three studies reporting allocation concealment.

For domain 2, blinding of participants and personnel, whilst nine of the studies described participants being blinded to their allocated group for the non-invasive neuromodulation intervention (either active or sham), only two studies described personnel being blinded to this. Whilst this is a technically challenging issue to overcome, it is possible with innovative approaches. For example, Nasiri et al. (2020) used a computer chip that programmed active or sham tDCS, which enabled the tDCS therapist to be blinded.

For domain 3, blinding of outcome assessor, this was not deemed applicable to three studies that only used self-reported outcome measures, and as such they were given a rating of low risk of bias.

For domain 5, selective reporting, four studies pre-registered plans for analysis and reported data and statistical analyses in full, and as such were given a rating of low risk of bias for this domain. There were multiple instances of what could be seen as selective reporting of outcome data and statistical tests, that led to a more favourable picture of results suggesting a psychotherapy-enhancing effect of non-invasive neuromodulation techniques.

Studies of PTSD

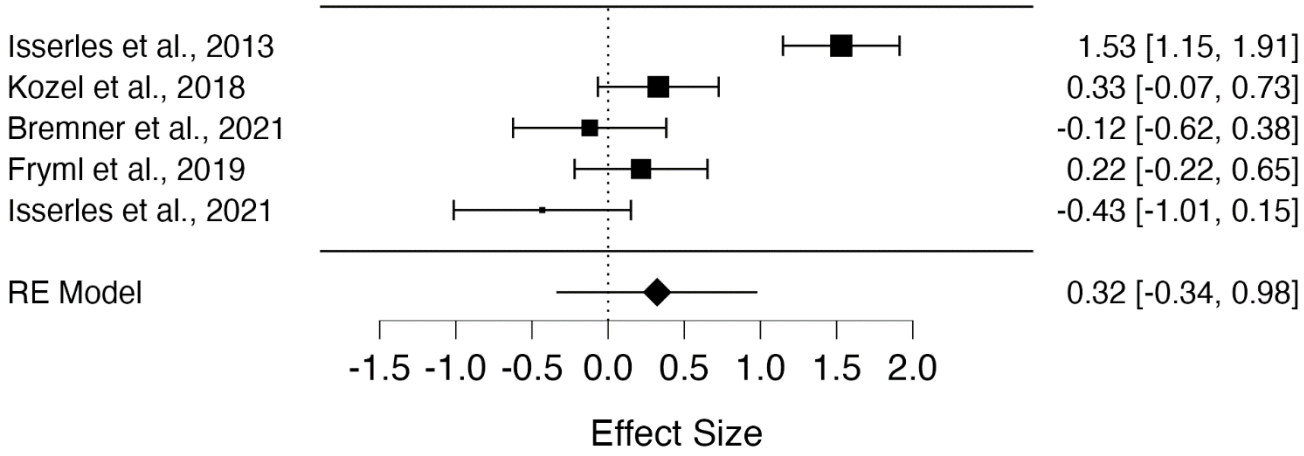
Six of the seven studies of PTSD used exposure-based psychotherapeutic procedures, using virtual reality methods (Van't Wout-Frank et al., 2019), script-driven imagery procedures (Bremner et al., 2021; Isserles et al., 2013; Isserles et al., 2021), exposure through verbal recall (Osuch et al., 2009), and prolonged exposure through an initial verbal recall with subsequent exposure to an audio recording of this

(Fryml et al., 2019). The remaining PTSD study used cognitive processing therapy (Kozel et al. 2018).

Five studies used TMS methodologies. Of these, three used rTMS (Fryml et al., 2019; Kozel et al. 2018; Osuch et al., 2009), and two dTMS (Isserles et al., 2013; Isserles et al., 2021). One study used tcVNS (Bremner et al., 2021) and one tDCS (Van't Wout-Frank et al., 2019).

Meta-analysis of Clinician-reported Effects on PTSD symptoms

Figure 2. *Forest Plot of Individual Effect Sizes for Studies of PTSD with Clinician-Rated Symptom Measures*



Note. Means, standard deviations and sample sizes used to calculate the effect sizes are included in Appendix 3. Positive effect size indicates that results favour psychotherapeutic procedures combined with non-invasive neuromodulation techniques, negative effect size indicates that results favour control groups receiving psychotherapeutic procedures without active non-invasive neuromodulation techniques.

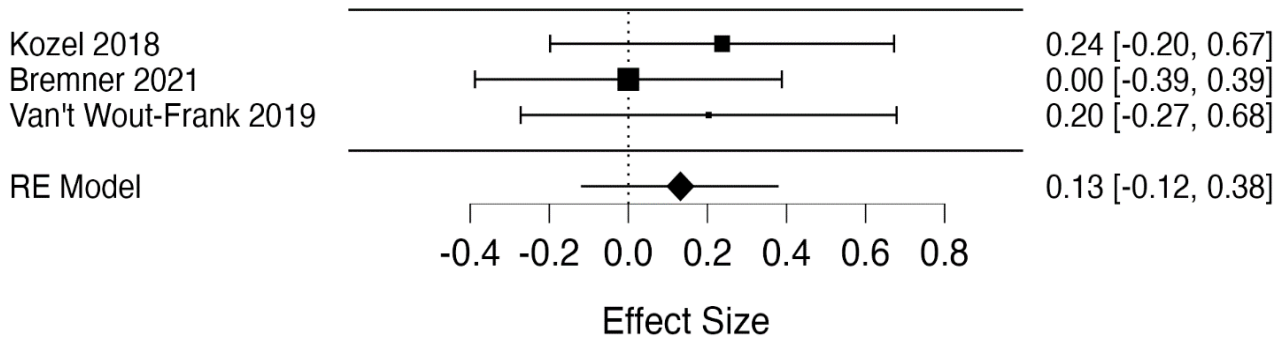
Five studies provided required data for clinician-rated symptom measures comparing individuals receiving exposure-based psychotherapeutic procedures combined with non-invasive neuromodulation techniques (total n = 117) with control groups receiving psychotherapeutic procedures without active non-invasive neuromodulation techniques (total n = 121). As indicated in Figure 2 the effect size (ES) was small and not significantly greater than 0, SMD = 0.32 (95% CI; -0.34 to

0.98). There was a large degree of heterogeneity (τ^2 = 0.511, 95% CI; 0.149 to 4.563; I^2 = 90.70%, 95% CI; 74.01% to 98.87%). Excluding Isserles et al. (2013) reduced the heterogeneity (τ^2 = 0.047, 95% CI; 0.000 to 1.585; I^2 = 44.86%, 95% CI; 0.00% to 96.49%) and also reduced the ES, SMD = 0.05 (95% CI; -0.27 to 0.36).

Meta-analysis of Self-reported Effects on PTSD symptoms

Three studies provided data for self-rated PTSD symptoms, with a total of *n* = 45 in psychotherapeutic procedure plus neuromodulation groups and a total of n = 44 in psychotherapeutic procedure-only (or plus sham) groups. As indicated in Figure 3 the ES was small and not significantly greater than 0, SMD = 0.13 (95% CI; -0.12 to 0.38). There was no estimated heterogeneity although with very large confidence intervals (τ2 = 0.000, 95% CI; 0.000 to 0.606; I2 = 0.00%, 95% CI; 0.00% to 92.60%).

Figure 3. *Forest Plot of Individual Effect Sizes for Studies of PTSD with Self-Rated Symptom Measures*



Note. Means, standard deviations and sample sizes used to calculate the effect sizes are included in Appendix 3. Positive effect size indicates that results favour psychotherapeutic procedures combined with non-invasive neuromodulation techniques, negative effect size indicates that results favour control groups receiving psychotherapeutic procedures without active non-invasive neuromodulation techniques.

Narrative synthesis of studies of PTSD

In the first published study of the effects of combining psychotherapeutic techniques with non-invasive brain stimulation for PTSD, Osuch et al. (2009) combined inhibitory rTMS of the dlPFC (some right and some left but analysed as one group) with imaginal exposure therapy in a sample nine individuals with chronic, treatment-refractory PTSD. They reported results that are deemed broadly neutral. Aside from indicating that there were no statistically significant differences on any behavioural outcome measures, the authors did not report in full descriptive and inferential statistics. They reported that planned comparisons demonstrated improvement of a moderate ES for hyperarousal symptoms on the CAPS (clinician-administered PTSD scale; Blake et al., 1995) for those receiving exposure plus active rTMS but no effect for those receiving exposure plus sham rTMS. The authors stated that hyperarousal symptoms on active treatment were lower at endpoint relative to sham. The table included by the authors showed that the CAPS intrusion subscale and Impact of events avoidance subscale were lower at endpoint in sham relative to active rTMS but the authors did not acknowledge this and did not report any related statistical test. It should be noted that due to the small sample size the study was underpowered which the authors acknowledged.

Isserles et al. (2013) compared patients receiving active excitatory dTMS of the mPFC combined with script-driven imagery exposure of a traumatic incident (Exp-Stim), sham dTMS with script-driven imagery exposure (Exp-Sham) and active dTMS with script driven imagery of a non-traumatic incident (N Ex-Stim). They did not find a significant group x time interaction to indicate a greater reduction in the active versus sham group, for the CAPS total, the PTSD Symptom Scale—Self Report version (PSS-SR; Foa, Riggs, Dancu & Rothbaum, 1993) total, or for the

hyperarousal or avoidance subscales of the CAPS, but did for the intrusion subscale of the CAPS. However, they reported that planned comparisons demonstrated a significant difference from baseline for only the Exp-Stim group on every subscale of CAPS and CAPS total, as well as PSS-SR. The results were therefore deemed broadly positive. As well as using a different type of stimulation to Osuch et al. (2009), they also used stimulation to consolidate exposure learning (i.e. delivered after exposure), as opposed to simultaneously.

Isserles et al. (2021) conducted a larger study (n=125) with a similar protocol as in Isserles et al. (2013). They again compared patients receiving active dTMS of the mPFC combined with script-driven imagery exposure of a traumatic incident (Exp-Stim), sham dTMS with script-driven imagery exposure (Exp-Sham) and active dTMS with script-driven imagery of a non-traumatic incident (N Ex-Stim). They did not find the same positive pattern of results as in Isserles et al. (2013) and instead found a negative, psychotherapy-interfering effect of dTMS. Whilst both groups showed reductions on the CAPS and MPSS (The modified PTSD scale; Falsetti, Resnick, Resick & Kilpatrick, 1993) both at end of intervention and follow-up (4 weeks later), there were greater reductions in the Exp-Sham group compared to Exp-Stim. Unexpectedly, response rates were also better in the Exp-Sham compared to Exp-Stim at both the primary efficacy endpoint of the intervention (54.9% v 42.5%) and at 9-week follow-up (68% v 53.8%).

Kozel et al. (2018) reported broadly positive findings in their study that combined rTMS of the dlPFC delivered immediately before cognitive processing therapy in combat veterans with PTSD. For the CAPS and PCL (PTSD checklist; Weathers et al., 1993) there were significantly greater reductions during the intervention phase and at follow-up in those receiving CPT plus active versus sham

rTMS. For the M-PTSD (Mississippi Scale for Combat-Related PTSD; McFall, Smith, Mackay, & Tarver, 1990) there were significant reductions in both groups at all time points but a significantly greater reduction at 6-month follow-up in those receiving active versus sham rTMS.

Van't Wout-Frank et al. (2019) reported findings that are deemed broadly neutral in their study that delivered tDCS targeting the vmPFC simultaneously with virtual reality exposure sessions in individuals with war-related PTSD. Both active and sham groups showed a clinically meaningful reduction on the PCL-5 (PTSD checklist for the DSM-V; Blevins et al., 2015), however, there was no significant tDCS group-by-time interaction. They did, however, find a tDCS group-by-time interaction favouring active over sham tDCS indicating that SCRs (Skin conductance response) to VR events diminished more quickly over sessions when combined with active tDCS.

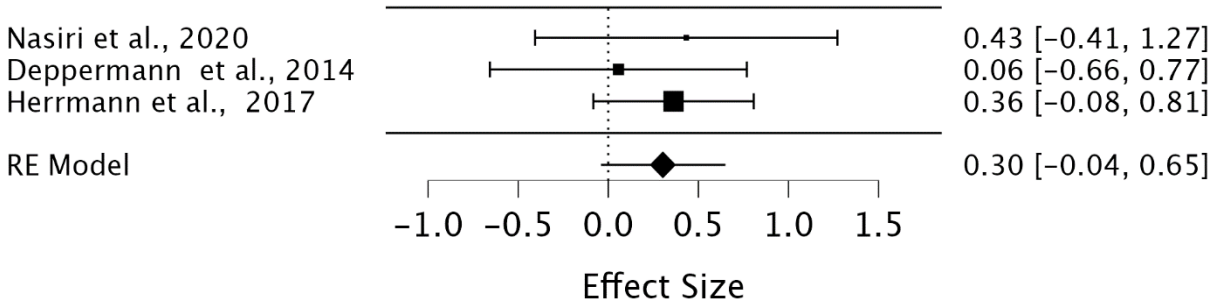
Fryml et al. (2019) conducted a pilot study for which they stated the main aim was to explore the percentage of participants who completed all sessions of their protocol comparing individuals receiving prolonged exposure therapy combined with one of four rTMS conditions (right or left PFC x active or sham). The authors stated that there was a general non-significant trend toward improvement in CAPS scores, favouring active versus sham rTMS. However, no inferential statistics were reported in the paper for any of the outcome measures, other than a significant time-by-group interaction on the HRSD24 (Hamilton Depression Rating Scale; Hamilton, 1960), favouring active versus sham rTMS at the fourth and fifth sessions. As such, the results of this study were viewed as neutral, favouring neither active nor sham rTMS.

Bremner et al. (2021), in the only example identified utilising tVNS in combination with a psychotherapeutic intervention, delivered tcVNS at the neck for

the cervical branch of the vagus nerve, immediately after exposure to personalised traumatic scripts. Results were deemed broadly positive. They reported a significant decrease in the active but not sham tcVNS group for the PTSD Checklist-Civilian Version (PCL-C; Ruggerio, Ben, Scotti & Rabalais, 2003) total with a large ES for the active tcVNS group, a significant decrease in the active but not sham tcVNS group for the hyperarousal subscale of the PCL-C with a large ES for the active group, and a significant decrease in the active but not sham tcVNS group for the somatic anxiety symptoms as measured by the HAM-A (Hamilton Anxiety Rating Scale; Hamilton, 1959) with a medium-to-large ES. There was a significant reduction in CAPS total for both active and sham tcVNS groups.

Studies of Anxiety Disorders

Figure 4. *Forest plot of Individual Effect Sizes for Studies of Anxiety Disorders*



Note: Means, standard deviations and sample sizes used to calculate the effects sizes are included in Appendix 3. Positive effect size indicates results favour psychotherapeutic procedures combined with non-invasive neuromodulation techniques, negative effect size indicates that results favour control groups receiving psychotherapeutic procedures without active non-invasive neuromodulation techniques.

Of the five studies of anxiety disorders, three were of specific phobias (Herrmann et al., 2017; Leuchter et al., 2022; Notzon et al. 2015), one was of panic disorder (Deppermann et al., 2017), and one generalised anxiety disorder (GAD)

with comorbid depression (Nasiri et al., 2023). The three specific phobia studies (Herrmann et al., 2017; Leuchter et al., 2022; Notzon et al. 2015) utilised exposure-based psychotherapeutic interventions, the study of panic disorder (Deppermann et al., 2017) CBT, and the study of GAD with comorbid depression (Nasiri et al., 2020) the unified protocol for transdiagnostic treatment of emotional disorders (UP). The study of GAD with comorbid depression utilised tDCS (Nasiri et al., 2020) whilst the remaining four studies (Deppermann et al., 2017; Herrmann et al., 2017; Leuchter et al., 2022; Notzon et al. 2015) all utilised iTBS.

Meta-analysis of Effects on Anxiety Disorder Symptoms

Three of the studies (Deppermann et al., 2017 Herrmann et al., 2017; Nasiri et al., 2020) provided usable data of anxiety disorder symptom measures comparing individuals receiving exposure-based psychotherapeutic procedures combined with non-invasive neuromodulation techniques (total *n* = 55) with control groups receiving psychotherapeutic procedures without active non-invasive neuromodulation techniques (total *n* = 56). Herrmann et al. (2017) provided the scores for the anxiety and avoidance subscales of the Acrophobia Questionnaire (AQ; Cohen, 1977) separately. It was decided to use the anxiety subscale data for the meta-analysis. As indicated in Figure 4 there was no statistically significant difference in symptom measures at the end of intervention between experimental group participants and control group participants, with an estimated ES of SMD = 0.30 (95% CI; -0.04 to 0.65). There was no estimated heterogeneity although the confidence intervals were wide ($\tau^{.2}$ = 0.00, 95% CI; 0.00 to 1.445 ; I^2 = 0.00%, 95% CI; 0.00% to 92.91%).

Narrative Synthesis of Studies of Anxiety Disorders

Notzon et al. (2015) combined iTBS of the left dlPFC with virtual reality exposure for individuals with spider phobia and found a significant decrease on the fear of spiders questionnaire (FSQ; Szymanski & O'Donohue, 1995) for both groups, with no significant differences between those receiving active versus sham iTBS on this. There was no significant change over time on the spider phobia questionnaire (SPQ) in either group and no significant difference between the groups. As such, overall, the results were deemed neutral.

A more recent study of spider phobia combined iTBS of the vmPFC with in-vivo exposure (Leuchter et al., 2022) and again produced results that were deemed neutral. They reported a significant decrease on the FSQ and SPQ in both those receiving active and sham iTBS with no significant effect of treatment group. As such the results were deemed neutral. The authors, however, stated that their findings support the potential efficacy of rTMS augmentation, highlighting that correlation analyses revealed that subjects who received more intense active stimulation experienced a greater reduction in both subjective and physiologic distress with treatment.

Herrmann et al. (2017) conducted another study of a specific phobia, this time acrophobia, delivering rTMS of the vmPFC immediately before virtual reality exposure sessions. The results produced were deemed positive. They found a significant group-by-time interaction, with a higher reduction in the active compared to the sham rTMS group on both the anxiety and avoidance subscale of the acrophobia questionnaire (AQ). At follow-up, there was further improvement without any difference by group. Interestingly, there was no similar positive result favouring

active versus sham rTMS on the behavioural avoidance test, as both groups showed an improvement without any group-by-time interaction.

Deppermann et al. (2017) reported what were deemed neutral results in their study of agoraphobia. Both individuals receiving active and sham iTBS of the left dlPFC combined with a 9-week group CBT intervention showed a decrease on the panic and agoraphobia scale (PAS; Bandelow, 1999) total score with no group-by-time interaction. There was a group-by-time interaction on the self-rated agoraphobic avoidance subscale, favouring the active group, who maintained their reductions at the final follow-up time point, whereas the sham group did not.

Finally, Nasiri et al. (2020) reported positive results in their study of individuals with generalised anxiety disorder (GAD) with comorbid depression. They investigated the effect of combining tDCS targeting the right dlPFC with the unified protocol for transdiagnostic treatment of emotional disorders (UP). Both the group receiving UP alone (there was no sham tDCS used) and the group receiving UP with tDCS (UP-tDCS) showed a significant reduction in anxiety symptoms but with a significantly greater reduction in the UP-tDCS group. They reported a higher rate of clinical remission in the UP-tDCS group versus UP group but did not report any inferential statistics.

Summary of Rationales for Different Stimulation Locations

Six studies targeted the dlPFC with some consistency in rationales proposed for this. Three studies (Deppermann et al., 2017; Kozel et al., 2018; Notzon et al., 2015) discuss pathological anxiety in terms of hyperactivity of the amygdala, and the inhibitory influence that the dlPFC (which is linked to subcortical regions including

the amygdala) can have on the amygdala. Relatedly, Nasiri (et al., 2020) discuss the dlPFC being a key region implicated in cognitive control of emotion processing, and impairments of this region being reported in GAD patients. Two studies were quite vague on the rationale for targeting this region. Fryml et al. (2019) discuss evidence of TMS delivered to the dlPFC reducing PTSD symptoms but without any further rationale. Osuch et al., (2008) discuss, in relatively vague terms, decreasing activity of this region in order to improve functional brain abnormalities associated with PTSD. Leuchter et al., (2022) and Van't Wout-Frank et al. (2019) both targeted the vmPFC and discuss a functional and structural connectivity with subcortical regions involved in fear learning and recall, such as the amygdala and hippocampus. Hermmann et al., (2017) also targeted the vmPFC but offered less detail. They simply state that animal and human research demonstrates that it is highly relevant for fear extinction learning. Isserles et al. (2013; 2021) targeted the mPFC in two studies and again discuss its connectivity with the amygdala. They argue that PTSD is caused by a reduced ability to achieve and preserve extinction of the acquired fear response, due to functional impairment in the medial prefrontal cortex (mPFC) control over the amygdala. Finally, Bremner et al., (2021) discuss evidence of PTSD being associated with an increase in the blood concentrations of the inflammatory markers at baseline and when exposed to traumatic scripts. They then point to evidence of tcVNS reducing such inflammatory markers.

Summary of Proposed Mechanisms of Interaction

Ten of the included studies were exposure-based. These were seven of the PTSD studies (Van't Wout-Frank et al., 2019; Bremner et al., 2021; Fryml et al.,

2019; Isserles et al., 2013; Isserles et al., 2021; Kozel et al., 2018; Osuch et al., 2009) and the three specific phobia studies (Herrmann et al., 2017; Leuchter et al., 2022; Notzon et al., 2015). Within these, a commonly proposed mechanism was stimulation of the PFC facilitating extinction, although with some variation.

Isserles et al. (2013) hypothesised that tDCS targeting the mPFC delivered immediately after exposure during the consolidation window after recall of the traumatic memory would convert the fear memory to a safety memory and thus improve PTSD symptoms. Isserles et al. (2021) again used stimulation of the mPFC in the consolidation window and expanded on their previously stated hypothesised mechanism. They hypothesised that stimulation of the mPFC would facilitate inhibitory control of amygdala-mediated threat and fear responses and so help to facilitate the extinction process targeted by the exposure procedure. To support this, they pointed to literature where hypoactivity of the mPFC was inversely correlated with amygdala hyperactivity (Francati, Vermetten & Bremner, 2007; Millad, Rauch, Pitman & Quirk, 2006).

Van't Wout-Frank et al. (2019) also used tDCS, this time targeting the vmPFC, and instead delivered it simultaneously to VRE sessions. They suggested that the weak constant current used may facilitate extinction learning and memory formation by modulating resting membrane potentials. They argued that as PTSD is a disorder of learning and memory, simultaneous stimulation during attempted habituation would be particularly effective.

Three PTSD studies used rTMS of the dlPFC with variation in the mechanisms of interaction, or lack thereof, that they proposed. Osuch et al. (2009) delivered rTMS at the dlPFC simultaneously with exposure, proposing that rTMS

would bring the neural circuits and autonomic arousal involved in the conditioned fear “on-line” when attempting to extinguish the fear response. Fryml et al. (2019) also used simultaneous delivery of rTMS of the dlPFC although did not state any theoretical rationale for the combination, other than discussing their individual effects on PTSD symptoms and so that they were combining the two interventions to acutely target symptoms. Kozel et al. (2018) used rTMS of the dlPFC immediately before cognitive processing therapy sessions. They pointed to findings that rTMS of the dlPFC reduces hyperarousal to threatening stimuli in PTSD and so hypothesised that it would work synergistically with CPT to reduce symptoms. However, again they did not go into any clear theorised mechanisms of synergy, with a possible implicit interpretation on reading that they were suggesting both interventions reduce symptoms and so can be combined for a greater effect, similar to Fryml et al. (2019).

Nozton et al. (2015) delivered iTBS targeting the left dlPFC immediately before VRE, like the PTSD studies, although in this case with individuals with spider phobia. They hypothesised that the iTBS would attenuate anxiety and disgust during VRE. Presumably, this could enable better treatment results by allowing the completion of more challenging VRE tasks, although the authors did not explicitly state a detailed and clear mechanism of interaction. Leuchter et al. (2022) also studied individuals with spider phobia utilising iTBS, this time however they targeted the vmPFC, and after in vivo exposure. Their proposed mechanism however, strangely (considering the delivery of stimulation in the consolidation window) discussed priming effects. They proposed stimulation before a behavioural avoidance test would lead to a greater willingness to approach a novel spider and result in greater reductions in psychophysiological measures. To support this they referenced the vmPFC’s functional and structural connectivity with subcortical

regions involved in fear learning and recall, such as the amygdala and hippocampus. Herrmann et al. (2017) also studying specific phobia, utilised rTMS of the vmPFC delivered before VRE. They proposed a different mechanism to the preceding two studies that was clear and specific. They hypothesised that the stimulation would augment the memory trace formed during the VRE, and thus accelerate fear extinction learning leading to better treatment results.

Deppermann et al. (2017) focused solely on a proposed biological mechanism of iTBS normalising hypoactivity of the prefrontal cortex, which they state is characteristic in panic disorder, both generally and during fear-relevant situations. There was no specified psychological component to their hypothesised rationale for combining tDCS with CBT.

Bremner et al. (2021) differed in terms of method of non-invasive neuromodulation with their use of tcVNS, and resultingly differed in their proposed mechanism. They argued that the PSTD symptom of hyperarousal is underpinned by noradrenergic and peripheral sympathetic nervous system function, which is targeted by tcVNS. Whilst they discuss convincingly the theoretical rationale for using tcVNS to target the neurobiology of PTSD symptoms, they do not go beyond this neurobiological explanation and as far as to explicitly state how tcVNS would work synergistically with the exposure procedure used. Interestingly there is no mention of the psychotherapeutic component in their title and very little in their abstract, suggesting, like many of the studies discussed here, a more neuroscientific focus.

Finally, Nasiri et al. (2020) proposed a specific, theoretically plausible mechanism focused on increasing capacity for cognitive control. They argued that

tDCS of the dlPFC may enhance the ability to engage adaptive emotion regulation skills that are the focus of the UP psychotherapeutic intervention they utilised.

Discussion

This study examined the effects of adding a non-invasive neurostimulation technique to psychotherapeutic interventions for anxiety and trauma-related disorders, using a meta-analytic approach (where possible) and a narrative synthesis. These found no clear and consistent benefit of adding non-invasive neurostimulation technique to psychotherapeutic interventions for anxiety and trauma-related disorders (see Table 4 below). The following section breaks down results by area, timing and type of stimulation to determine if this can produce any patterns in the results.

Table 4. *Summary of Findings from Different Methods of Synthesis*

Method of Synthesis	Summary of Findings
Meta-analysis PTSD studies clinician-rated symptoms	No significant difference favouring experimental groups
Meta-analysis PTSD studies self-reported symptoms	No significant difference favouring experimental groups
Narrative synthesis PTSD studies	No clear and consistent benefit favouring experimental groups; results broadly positive in 3 studies, neutral in 3 studies, negative in 1 study
Narrative synthesis anxiety disorder studies	No clear and consistent benefit favouring experimental groups; results broadly positive in 2 studies, neutral in 3 studies

Note: Experimental group = non-invasive neurostimulation technique combined with psychotherapeutic intervention, control group = psychotherapeutic intervention alone

Area, Timing and Type of Stimulation

Six studies targeted the dlPFC although with some variation in type and timing of stimulation. There was mixed evidence of the use of inhibitory stimulation of the dlPFC. Osuch et al. (2009) delivered inhibitory rTMS simultaneous to exposure producing neutral results, whilst Kozel et al. (2018) delivered inhibitory rTMS before exposure producing positive results. Excitatory stimulation of the dlPFC using rTMS was used in three studies, producing neutral results in all. Notzon et al. (2015) delivered iTBS to the left dlPFC prior to exposure, Fryml et al. (2019) delivered rTMS to the left or right dlPFC simultaneous to prolonged exposure, whilst Deppermann et al. (2017) delivered daily iTBS to the left dlPFC for 15 days. Nasiri et al. (2020) delivered excitatory stimulation of the dlPFC using tDCS with individuals with GAD and comorbid depression receiving the unified protocol and reported positive results. The timing of tDCS in relation to the psychotherapy (UP) sessions was not clearly stated in the text.

Three studies targeted the vmPFC with excitatory stimulation. Leuchter et al. (2022) delivered iTBS after in-vivo exposure sessions for spider phobia and produced neutral results whilst Herrmann et al. (2017) delivered excitatory rTMS to the left vmPFC before virtual reality exposure sessions for acrophobia and produced positive results. In the third, Van't Wout-Frank et al. (2019) delivered excitatory tDCS to the vmPFC during VRET sessions for PTSD and produced what were deemed as broadly neutral results, with an effect on the psychophysiological measure but not in terms of clinical symptoms of PTSD.

In two studies Isserles and colleagues (2013; 2021) delivered dTMS to the mPFC following SDI exposure sessions. They first produced positive results in their

feasibility study and then in the larger follow-up RCT produced negative results. It should be noted that in the second study, they reduced to 8Hz trains at 100% MT from 20Hz at 120% MT and also utilised a novel coil design but otherwise the two studies are similar. The authors stated that novel coil design may have led to differential relative stimulation of dACC/DLPFC/mPFC which combined with the SDI psychotherapy may have led to different outcomes between the two studies.

Taken together there has been a variety of approaches taken within the literature, with little replication of protocols that would allow more confident conclusions to be drawn about what is optimal. Where there has been replication, the results are not consistent, without an obvious convincing explanation. Excitatory vmPFC stimulation delivered before exposure (Herrmann et al. (2017) and tcVNS delivered simultaneous to exposure (Bremner et al., 2021) have produced positive results and warrant further investigation.

The great variety that is possible with non-invasive neurostimulation is both exciting and offers great opportunity whilst also presenting a problem. This problem of near-infinite number of protocols that could be used has been discussed in relation to rTMS (Caulfield & Brown, 2022). Add to this other forms of non-invasive neurostimulation and multiple psychotherapies to potentially explore, in its own evolving field, and with different options of timing of stimulation in relation to the psychotherapy, and there is a great deal of potential variation in approaches yet to be explored. Together this suggests that the task of determining the optimal parameters for combination with psychotherapies, if any exist, is a complex one. Therefore the point at which an initial consensus can be reached may be far off.

Relation to Previous Literature

The conclusions from the current review are less optimistic and not completely in line with the results of Herrmann et al. (2019). They concluded following their systematic review of four studies that the initial work in this area had shown a benefit of adding rTMS to exposure-based therapy for the treatment of anxiety disorders. They stated that the initial results were promising but that further research was required to show the best-suited stimulation parameters. The present review's conclusions may differ due to it being an update on this previous review that draws upon a larger body of evidence, as it included twelve studies, including the four included in Herrmann et al. (2019). Additionally, there were some methodological differences between the two reviews which may account for the differing conclusions. Herrmann et al. (2019) calculated a mean weighted effect size estimate of f = 0.32, indicating a medium-to-large effect size (Cohen, 1988), based on the f statistic from the interaction between the treatment group (active versus sham stimulation) and time (pre versus post). However, they did not use a statistical method to calculate statistical significance. The present review used a meta-analytic procedure to synthesise effect sizes based on the standardised mean difference (SMD) between active groups (i.e. involving combination of psychotherapeutic intervention and non-invasive brain stimulation or neurostimulation) and control groups (those receiving psychotherapeutic intervention with no stimulation or a sham stimulation) at the end of intervention time-point only. The estimated effect size estimates from the current review meta-analyses were 0.32, 0.12, 0.30 or the clinician-reported PTSD symptoms, self-reported PTSD symptoms, and studies of anxiety disorders respectively, all in the small effect size range or lower (Cohen, 1988), and thus differed to the review by Herrmann et al. (2019). Furthermore, none

of the ES estimates were statistically different from zero. Had Herrmann et al. (2019) utilised a statistical method to calculate the statistical significance of their mean weighted effect size estimate, they may not have had such optimistic conclusions. Finally, the effect size estimate for clinician-rated symptom measures for PTSD studies was reduced substantially (0.32 to 0.05) following the exclusion of a single outlier (Isserles et al. (2013). This was one of the included studies in the review by Herrmann et al. (2019).

Previous reviews of combining non-invasive brain stimulation with extinction in studies of healthy participants and animal studies had identified the vmPFC and mPFC as both being potentially promising (Herrmann 2019; Marković, et al., 2021). The vmPFC was highlighted as a very promising stimulation site (Herrmann 2019). In terms of timing, the previous reviews had concluded that work had shown that stimulation both prior to and following extinction could be effective (Herrmann 2019; Herrmann et al., 2019; Marković, et al., 2021). The present results temper the highlighted promise of the mPFC and vmPFC as potential stimulation sites. In terms of timing the current study was somewhat in line with these previous reviews, finding that delivering non-invasive neurostimulation both, before, during and after psychotherapies can be effective as an add-on, but it can also be ineffective. More work is needed to fully understand the factors contributing to these variable effects. Again, the present review can be seen as an update on these previous reviews as it included additional studies. It also highlights the challenges of translating findings from animal and non-clinical human studies into clinical studies.

Theoretical Grounds for Combinations

There was variability in the quality of theoretical grounds for combination of non-invasive neurostimulation with psychotherapeutic techniques within the identified studies. Occasionally, the rationale was clearly stated, plausible based on theoretical understanding of psychological processes, and linked to the chosen protocol for the study. For example, Herrmann et al. (2017) proposed that stimulation would augment the memory trace formed during the VRE, thus accelerating fear extinction learning. This is coherent with current understanding of extinction learning involving the creation of a new safety memory that inhibits the fear memory at later retrieval, leading to clinical benefit (see Craske et al., 2008; Craske, Liao, Brown & Vervliet, 2012). Other proposed mechanisms were not coherent with this current understanding of extinction learning. For example, Isserles et al. (2013; 2021) hypothesised that tDCS targeting the mPFC delivered immediately after exposure during the consolidation window after recall of the traumatic memory would convert the fear memory to a safety memory and thus improve PTSD symptoms.

Often proposed mechanisms were somewhat vague about how the non-invasive neurostimulation would work synergistically with the psychotherapeutic component (Osuch et al., 2009; Kozel et al. 2018). Also, they were sometimes much more neurobiological without linking to a psychotherapeutic change mechanism (Bremner et al., 2021; Deppermann et al., 2017). One study did not provide a theoretical basis, except that the individual elements were shown to be effective in their own right (Fryml et al., 2019).

As stated, there is a great variety of possible protocols and combination parameters. It would be helpful to have clear, theoretically sound mechanisms

underlying carefully chosen protocols. This should enable fine-tuning of approaches, faster progress within the field and a consensus to be reached sooner on whether there is a possible additional benefit of combining non-invasive neurostimulation and psychotherapy, and if so in what protocols.

Methodological Issues and Risk of Bias

Several frequently occurring methodological issues were identified in the included studies, which was reflected in the risk of bias appraisal ratings. For example, only one study described blinding of participants and all personnel involved in the studies. Whilst this is a technically challenging problem to overcome when using non-invasive neurostimulation techniques, it is possible with effort and ingenuity (e.g. Nasiri et al., 2020). There were also issues with how data was presented and reported, with incomplete reporting of descriptive and inferential statistics (e.g. Fryml et al., 2019; Osuch et al., 2009).

Of course, it should be acknowledged that many of the included studies were pilot, feasibility or proof-of-concept studies (e.g. Fryml et al., 2019; Leuchter et al., 2022; Osuch et al., 2009). As such they, understandably, do not meet all of the standards expected in larger randomised controlled trials. Nonetheless, it would be helpful to have more rigorous, pre-registered randomised controlled trials that are reported in better detail to enable more confident interpretation and conclusions.

Limitations

There are some limitations in the current review. First, there was a small number of studies within each of the meta-analyses, which may have affected the

precision of the ES estimates. Secondly, and related to this first point, there was a moderate-to-high level of heterogeneity for one of the meta-analyses conducted, which limits the confidence of conclusions that can be drawn about the true ES.

Thirdly, there was variability in the studies' protocols of combining psychotherapy with non-invasive neurostimulation. It is potential limitation to conduct a meta-analysis when there is variety in the protocols and a vast number of factors that could account for differences in outcomes. These factors include dose, type and location of stimulation, clinical diagnosis, type and dose of psychotherapy, therapeutic relationship, and other population factors such as age. Due to the small number of studies, it was not possible to fully account for this variability in the meta-analyses. A larger number of studies would have enabled sub-group analyses to be conducted. This could have potentially helped to make more confident conclusions and to reduce heterogeneity in the ES estimates. A meta-analysis would be more strongly indicated where there is greater consistency in methodology between studies.

Pre-existing reviews had either not included a meta-analytic component or had included a simple method of synthesising effect size estimates without a test of statistical significance. Therefore, the present review adds to the pre-existing literature and attempts to conduct a more rigorous and objective review of this area of research. Of course, it is only a starting point. Once there is a greater number of published studies it will beneficial to conduct further meta-analyses with sub-group analyses. This will enable better accounting for and consideration of variety of factors that may account for differences in outcomes.

Finally, the review utilised a second reviewer for title and abstract screening but lacked a second reviewer for full-text screening, data extraction and judging the broad nature of the results of each included study (i.e. broadly negative, neutral or positive). The inclusion of a second reviewer at every stage would have reduced the likelihood of any errors, ensured the inclusion of all relevant studies, and reduced the risk of bias in data extraction and judgements made.

Conclusions

The review produced less optimistic results than previous reviews. It suggests that the combination of psychotherapy and non-invasive neurostimulation does not consistently enhance the effects of psychotherapy alone, for anxiety and trauma-related disorders. There was no clear site of stimulation or combination of psychotherapy and non-invasive neurostimulation intervention with consistently reproduced enhancing effects. Further research with carefully chosen, theoretically grounded protocols is needed to reach a consensus on whether there is a possible additional benefit of combining non-invasive neurostimulation and psychotherapy for anxiety and trauma-related disorders, and if so in what protocols.

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Part 2: Empirical Paper

Childhood Trauma as a Moderator in a Study of Compassionate Imagery Training with Adjunctive Non-Invasive Vagus Nerve Stimulation: An Exploratory Secondary Analysis

Abstract

Introduction: The vagus nerve is part of the parasympathetic nervous system. It has been proposed that vagus nerve activation is necessary but not sufficient for compassionate behaviour. Kamboj and colleagues conducted a sham-controlled study combining transcutaneous vagus nerve stimulation with a compassionate imagery task to determine whether a causal relationship exists and produced some positive findings. Experiences of childhood trauma are thought to lead to disrupted functioning of the parasympathetic nervous system and are separately argued to lead to difficulties engaging in compassion-based interventions. The current study sought to investigate whether level of childhood trauma interacted with the treatment effects found in the main (currently unpublished) study by Kamboj and colleagues.

Method: An exploratory secondary analysis was conducted, in which healthy adult participants were allocated to one of four conditions (Stimulation: active vs sham x imagery: compassion vs control). A new variable was created to allow comparison of individuals with lower and higher levels of childhood trauma. Three-way (stimulation x imagery x level of childhood trauma) univariate measures ANOVAs were conducted on the change within a single lab session and over a week on the following outcomes: heart rate variability (HRV), state self-compassion, state mindfulness, state safe/contentment positive affect, trait mindfulness, and trait self-compassion.

Results: Although stimulation condition did not interact with the other explanatory variables, a significant two-way imagery-by-level of childhood trauma interaction was

found for change from start to end of the trial in HRV. Specifically, those with higher levels of childhood trauma showed a significantly greater increase in HRV following the compassionate imagery task compared to a control imagery task, whereas those with lower levels of childhood trauma showed a significantly greater increase following the control imagery task compared to the compassionate imagery task.

Conclusions: There was no evidence to suggest that individuals with higher levels of childhood trauma achieved a less desirable change in any of the outcome measures following practice of a compassionate imagery task, and the pattern of results was not suggestive of disrupted parasympathetic nervous system functioning in those with higher levels of childhood trauma. Further research is required to determine whether a pathway exists between experiences of childhood trauma, altered parasympathetic nervous system functioning, and response to compassion-based psychological interventions.

Introduction

The autonomic nervous system (ANS) consists of two reciprocal branches, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The SNS coordinates the “fight or flight” response, which mobilises an individual’s resources to respond to environmental *demands* and facilitates active avoidance of perceived threats (Porges, 2004; Porges, 2007). The PNS (often referred to as the “rest and digest” system, e.g. Murray-close et al., 2016) inhibits sympathetic arousal and functions to reduce physiological arousal and to promote homeostasis. It supports self-regulation, sustained attention, and social engagement (Del Giudice et al., 2011; Porges, 2004; Porges, 2007).

The vagus nerve is part of the parasympathetic nervous system. Its fibres are spread throughout the upper body, face, and neck, including branches that innervate parts of the external ear, close to the skin. Recent research has suggested that the vagus nerve is involved in several psychological processes including memory, threat/fear processing, positive affect, and emotion regulation (Kirby et al, 2017; Burger et al. 2016; Thayer et al., 2012). The activity of the vagus nerve can be assessed non-invasively using an ECG device that measures changes in heart rate (heart rate variability; HRV) and is a commonly used index of parasympathetic nervous system functioning. However, the extent to which HRV is a reliable and valid indicator of general vagal tone, rather than a more circumscribed index of the cardioinhibitory effects of VN activity is questioned (Grossman, 2023a, 2023b). Respiratory sinus arrhythmia (RSA) is the modulation of heart rate (HR) in response to inhalation and exhalation, where typically there is an increase of HR with inhalation and a decrease with exhalation. RSA under non-stress-inducing conditions

(or “baseline RSA”) is an index of vagal tone. “Vagal tone” indicates the degree to which the vagus nerve can enable the body to be in a relaxed state. “Vagal responsivity” reflects a change from baseline RSA to RSA under conditions of challenge, with a decrease of RSA from baseline to challenge reflecting a withdrawal of vagal activity.

Autonomic Nervous System Responsivity and Childhood Trauma

Polyvagal Theory (Porges, 2007; 2009) emphasizes the neurophysiological and neuroanatomical distinction between two branches of the vagus. These are the ventral vagal complex (VVC) and the dorsal ventral complex (DVC). The VVC, the newest circuit in evolutionary terms, includes the myelinated vagus nerve, whilst the DVC includes the unmyelinated vagus nerve. Polyvagal theory proposes that each branch supports different adaptive behavioural strategies and that circuits from these two branches of the PNS are organised hierarchically, along with the circuitry of the SNS.

It is proposed that when the environment is perceived as safe there is an increased influence of the VVC, which actively inhibits the SNS’ influence on the heart and dampens hypothalamic-pituitary-adrenal (HPA) axis activity (Porges, 2007; 2009). This enables the individual to engage in social communication, to promote self-soothing behaviours and calm states. When the environment is perceived as dangerous and life-threatening, the human nervous system recruits two more primitive neural circuits to regulate defensive strategies, the SNS circuitry and the DVC. The SNS circuitry, as previously mentioned, facilitates active avoidance of perceived threats (i.e. a fight-flight response). The DVC is linked to immobilization and enables death feigning, behavioural shutdown, and passive avoidance. Porges

(2009) proposes that there is a hierarchy of adaptive responses, whereby the VVC circuit is used first, if that circuit fails to provide safety, the older circuits are recruited for either an active avoidance/fight-flight response or a passive avoidance/shutdown response.

Ventral vagal complex (VVC) activity as putatively measured by RSA was found to be dampened in female college students with childhood maltreatment history but who did not meet criteria for PTSD (Dale et al., 2018), in a non-clinical community sample of young adults who had experienced physical abuse in childhood (Beilharz et al., 2020), and in a sample of adolescent females with exposure to childhood maltreatment (Miskovic et al., 2009). Taken together this would suggest an association between experiences of childhood trauma (CT) and disrupted PNS functioning. However, a large population-based cohort study of adults found no association between self-reported childhood adverse life events and HRV (van Ockenburg et al., 2015). Meanwhile, other research raises questions about the relative importance of PNS dysfunction in the pathway between experiences of childhood maltreatment and later psychological functioning, including psychopathology risk. A longitudinal study comparing adolescent females with and without a history of maltreatment found no evidence to suggest that the relationship between childhood maltreatment and PTSD symptoms was mediated by RSA reactivity (Shenk et al., 2014). Secondly, a study of healthy young women found an association between experience of adverse childhood experiences (ACEs) and HR reactivity, but that was only shown to be mediated by systolic blood pressure and not by RSA, suggesting a mediating effect of SNS functioning but not PNS functioning (Winzeler et al., 2017).

Interestingly, there is some evidence that type of traumatic experience may be an important factor in predicting later effects on ANS responsivity. In a cross-sectional study of healthy adult women (Stevens et al., 2023), greater levels of childhood abuse were significantly predictive of lower HRV whereas greater neglect was significantly predictive of higher HRV. In addition, greater levels of abuse, but not neglect, were predictive of greater adult symptoms found to be related to adult mood-related pathology. The authors therefore conclude that differentiation between abuse and neglect may be important when investigating the impact of maltreatment in childhood on adult outcomes.

Beyond this evidence from adult and adolescent samples, Young-Southward et al. (2020), conducted a review of 22 studies of maltreated children, with ages across the studies ranging from 2 years to 19 years. It aimed to evaluate the evidence for disruptions in ANS functioning in maltreated children and to explore the role of ANS responsivity in the pathway from maltreatment to psychopathology. They found that most included studies reported a similar pattern of blunted SNS responsivity but more mixed findings for PNS activity. Evidence for ANS functioning as a mediator or moderator of child maltreatment effects on psychopathology risk was mixed and limited. On balance, it seems that the evidence suggested that SNS responsivity may mediate the relationship between childhood maltreatment and psychopathology, but that PNS responsivity does not. Additionally, it appears that PNS functioning may moderate the relationship between childhood maltreatment and psychopathology, although with only one study to base this latter judgement on.

In their review, Young-Southward et al. (2019) discuss two theoretical models relevant to understanding the relationship between history of childhood maltreatment, ANS functioning, and later psychopathology risk; the differential

susceptibility theory (DST; Belsky et al., 2007) and the adaptive calibration model (ACM; Del Giudice et al., 2011). The DST proposes that children vary in their susceptibility to both positive and negative environmental influences and that those most susceptible suffer the worst outcomes when exposed to poor/harmful parenting behaviour, such as childhood maltreatment. DST argues that these differences in susceptibility may be the result of genetic or other biologically based factors including differences in the responsivity of stress systems. As such, Young-Southward et al. (2019) propose that ANS functioning may moderate the risk of psychopathology from maltreatment exposure. The ACM (Del Giudice et al., 2011) argues that individual differences in responsivity of the stress systems are the result of an individual's adaptation to their environment, including highly stressful conditions during early life experiences. Young-Southward et al. (2019) propose that it follows from the model that experiences of childhood maltreatment could result in an adaptation of a very reactive ANS to allow the child to detect threats and take appropriate action. Conversely it could result in an adaptation of low reactivity of the ANS to threat to allow insensitivity to their context of persistent and severely stressful experiences.

A full discussion of these two theories is beyond the scope of this study. For a thorough discussion of the models and their supporting evidence please refer to Young-Southward et al. (2019). They conclude from their review that there was some support found for both the DST and ACM theories, but that the strength of conclusions is limited by inconsistencies in the findings. They argued that the role of ANS responsivity in the pathway from experiences of childhood maltreatment to psychopathology could not yet be determined and required further exploration.

Evidently the association between experiences of childhood trauma or maltreatment and disruption of ANS, and specifically PNS, functioning appears to be variable. Whether a pathway exists between CT, PNS functioning, and later psychological functioning, including psychopathology risk, is equally unclear and warrants further investigation.

The Vagus Nerve and Compassionate Behaviour

Porges (2017) has proposed that vagus nerve activation is necessary, but not sufficient, for compassionate behaviour. To substantiate this proposition, one can look to previous research that has examined the effects of inducing compassionate feelings and then measuring vagus nerve activity as measured by HRV, in which HRV has been shown to increase (Kirby et al., 2017). In addition, a meta-analysis (di Bello et al., 2020) found a significant medium-strength association between compassion and vagus nerve activity, looking at studies with a variety of methodologies. This included studies comparing high self-compassion individuals to low-self compassion individuals, as well as methodologies such as those discussed in Kirby et al. (2017). However, no published study has yet demonstrated the association between vagal activity and compassion by modulating the vagus nerve itself to determine whether a causal relationship exists. Such studies not only have theoretical implications but are also potentially valuable in the future development of interventions that employ transcutaneous vagus nerve stimulation (tVNS) or similar technology to augment psychological treatments incorporating compassion-focused techniques (e.g. compassionate mind training; compassion-focused therapy).

An unpublished feasibility study (Title: The effects of vagus nerve stimulation on compassionate mind training and threat processing; Falconer 2020) compared the effects of active tVNS versus 'sham' tVNS combined with a compassionate imagery exercise, using a repeated measures design. Participants completed three discreet experimental phases in each session. Firstly, a baseline period (t1), second an active or sham tVNS-only phase (t2), and third active or sham tVNS + a compassionate imagery task (t3). They found significant increases in measures of HRV from t2 to t3 and significant increases in state levels of self-compassion and reductions in self-criticism from t2 to t3. There were, however, no interactions between timepoint and tVNS condition suggestive of an additive effect of combining active tVNS with the compassionate imagery task. The author commented that whilst there were no significant additive effects during both tVNS and CMT on HRV, the data was in the direction of favouring active tVNS versus sham for one measure of HRV (RMSSD), which was suggestive of a possible additive effect. The author concluded that the results were encouraging for a larger future trial, considering their study was underpowered.

The protocol of this feasibility study (Falconer, 2020) only used one relatively brief tVNS session and evidence of vagal nerve modulation was weak. According to recent research (Yap et al., 2020), the stimulation protocol used may have been insufficient to generate behavioural (including subjective) changes. In addition, the design of Falconer's study (2020) included a compassionate imagery exercise in both the active and sham tVNS conditions, without a control imagery task. The author proposed that future research should include an active control imagery task to assess for specific effects of the compassionate imagery task.

Kamboj and colleagues recently conducted a follow-up proof-of-concept experimental study (ClinicalTrials.gov Identifier: NCT05441774; in prep) that aimed to directly test the relationship between vagus nerve activity and compassionate responding using non-invasive stimulation of the vagus nerve in healthy volunteers aged 18-35 years. They employed a tVNS protocol of eight stimulation sessions, instead of one as used in the previous study (Falconer, 2020). Additionally, Kamboj and colleagues employed a four-group factorial (stimulation condition x imagery condition) design in which participants were randomly assigned to (i) tVNS + control imagery, (ii) tVNS + compassionate imagery (iii) sham-stimulation + control imagery and (iv) sham-stimulation + compassionate imagery. The inclusion of an active control imagery task enabled examination of the effects of the compassionate imagery task in isolation. Participants undertook eight daily sessions of their assigned combination of stimulation and imagery. On days 1 and 8, the participants attended in-person lab sessions.

The lab sessions allowed for a more fine-grained assessment of changes in outcomes, Participants completed self-repot outcome measures (t1) of state self-compassion, state self-criticism, state mindfulness, and state positive affect, then completed their allocated tVNS stimulation for 30 minutes, then completed the self-reported outcomes once more (t2), followed by their allocated imagery task, followed by completing the self-reported outcomes one final time (t3). They looked at interactions between *Stimulation* (sham, active tVNS) *Imagery* (control imagery task, compassionate imagery task), and time, either *short-term* within-session time effects on day 1, or longer-term between-sessions (days 1-8) time effects.

In line with one of their hypotheses, they found support for the notion that activation of the vagus (using tVNS) and compassionate imagery interacted additively when looking at state self-compassion and state mindfulness during the first lab session. However, this additivity was not sustained at the end of the trial, on day 8. Although participants randomised to the compassion imagery condition continued to show higher state self-compassion (and lower self-criticism) relative to control training. It was noteworthy, however, that Kamboj et al *did not* show an effect of stimulation or training on HRV suggesting either that neither manipulation affects this outcome, or, more controversially perhaps, that HRV is not a reliable or valid index of parasympathetic (vagal) control of psychological outcomes (Grossman 2023a; 2023b).

For the trait measures, trait mindfulness scores showed no significant changes from day 1 to day 8, with no significant main effect of day and no two-way or three-way interactions involving stimulation and imagery condition. For trait self-compassion, there was an interaction between day and stimulation condition of a modest effect size, showing that those in the active but not sham tVNS groups showed an increase in state self-compassion. There were no other main effects or significant two-or-three-way interactions.

Childhood Trauma and Fears, Blocks and Resistances to Compassion

Gilbert et al., (2011) describe clinical observations suggesting that some individuals can find self-compassion and receiving compassion difficult, can be fearful of compassion, and may have difficulty with their motivations to be self-compassionate or receive compassion. Gilbert (2005; 2010) proposed that

individuals' capacities for compassion are rooted in and developed by the attachment system. It is further proposed that when attachment system development is influenced by experiences of emotional conflict, neglect, and abuse, reactivation of the attachment system will reactivate these emotional memories and bring with it difficult feelings.

It is argued that re-emergent feelings can result in kindness and compassion being perceived as a potential threat, leading to fight, flight or shutdown (Gilbert, 2009; Kirby et al., 2019). These perceptions and reactivation of emotional memories are argued to partially underpin fears, blocks, and resistances to compassion. It has been argued that fears, blocks, and resistances to compassion could pose a barrier to psychological therapy, including compassion-based interventions, but also could be targeted through compassion-based interventions (Gilbert, 2005; 2010; Gilbert & Mascaro, 2017; Kirby et al., 2019).

There is a small amount of evidence to support this theoretical perspective (Gilbert, 2009; Kirby et al., 2019) that CT may result in adverse responses to compassion-focused interventions. HRV response to a compassion-focused imagery (CFI) task was negatively correlated with anxious attachment in two studies conducted with healthy adults recruited from university settings (Rockliff et al., 2008; Baldwin et al., 2019). Whilst experiences of CT were not directly measured in either of these studies, there are well-established links between experiences of childhood trauma and fearful attachment style in adulthood (e.g. Erozkan, 2016; Bifulco et al., 2006; Lo et al., 2019). It is possible that attachment style was a mediating factor between childhood adversity and adverse responses to CFI tasks within these two studies.

Additionally, a study of individuals diagnosed with a personality disorder (Mwale, 2017) found that experience of adverse childhood experiences (ACEs) was associated with difficulties generating a compassionate image, although the associations found did not remain after correction for multiple comparisons. The author included a qualitative element to investigate all participants' experiences of the CFI task. Several participants' responses were grouped into a theme of *Anxiety and Tension and Feelings of loss related to lack of compassionate experiences in one's life*, which seems linked to emotional neglect. In addition, some participants reported that engaging with the compassionate imagery was hindered by emotional distress triggered by memories of adverse experiences. Interestingly, some participants expressed feelings of mistrust in response to the compassionate 'other' and reported imagining a malevolent perpetrator with harmful intentions, rather than a caring nurturer. Seemingly, experiences of childhood adversity influenced some participants' experiences with CFI.

Aims

The current study reports on an exploratory secondary analysis of the data from Kamboj and colleagues (in prep). It aimed to investigate whether there was an interaction between the level of childhood trauma (CT) experienced and the other explanatory variables (i.e. stimulation condition and imagery condition). This is an interesting avenue of investigation, given that there is some evidence linking, or suggestive of a link between, experiences of CT and disruption of the PNS, and theoretical arguments with some supportive evidence that experiences of CT may be related to or underpin fears, blocks, and resistances to compassion. Considering Porges (2017) argues that vagus nerve activation is necessary, but not sufficient, for

compassionate behaviour. Given the literature above on the possible link between CT and altered PNS functioning, it was of special interest to explore whether those with higher levels of CT showed reduced changes in self-compassion and other related outcome measures which may be the result of altered PNS functioning. Secondly, given the literature and theoretical propositions related to (fears, blocks and resistances) compassion and the importance of childhood experiences including those of abuse, it could be anticipated that individuals with higher levels of CT would have difficulties with a CFI task (Gilbert, 2009; Kirby et al., 2019). This could result in differences in change in HRV and self-report outcome measures over the course of the study between those with higher versus lower levels of CT. Were this the case, it would be of interest whether the addition of tVNS changed any effects.

Methods

The original study by Kamboj and colleagues (in prep) was approved by the University College London Research Ethics Committee; study reference number 0760/006 (approval date: 11th May 2021; please refer to Kamboj et al., 2023 for the rationale and study protocol of the original study).

Participants

Participants were (total n = 120) healthy volunteers, recruited from University College London and surrounding areas using online adverts. Participants received £80 compensation for taking part in the study. Written consent was obtained and recorded electronically before any experimental procedure was performed.

The justification for the sample size in the initial study is provided in Kamboj et al. (2023). They determined that group sizes of n=30 was adequate in order to detect a difference of a relatively large effect size between the double-sham and double-active conditions on either subscale of the Self-Criticism and Self-Compassion Scale using independent samples t-tests with 80% power (two-sided; $\alpha = 0.05$). The current exploratory study was not necessarily adequately powered to detect other effects, including those reported here, which were not expected to be of a similarly relatively large effect size.

Participants were eligible for the study if they were aged 18-35 years, fluent in English, and had good (including corrected) vision and hearing. The 18-35 years inclusion criterion was included in the primary study to allow more direct comparison with other related pre-existing literature. Participants were excluded for any of the following reasons: currently using any medication for a psychiatric condition, regularly using any medication used to treat a cardiovascular or inflammatory condition, using any illicit recreational drug more than twice a week, iregularly consuming more than 14 standard UK 'units' of alcohol, currently receiving treatment for any mental health condition, their scores on screening measures of depression (Patient Health Questionnaire, 2-item version; PHQ-2; Kroenke et al., 2003) or anxiety (Generalized Anxiety Disorder rating scale, 2-item version; GAD-2; Kroenke et al., 2007) indicating significant levels of anxiety or depression (scores on either >4), history of serious mental health problems, past or current cardiovascular disease or neurological problems, past or current chronic/recurrent facial or ear pain, experienced skin irritation or broken skin at the stimulation site, they were pregnant or there was a likelihood of them being pregnant during the study, previous adverse response to meditation. Participants self-declared that they met these criteria during

screening.

Design

The study employed a 2x2 between-subjects factorial experimental design, with repeated assessment of outcomes. The between-subjects factors were *tVNS stimulation condition* (active versus sham) and *imagery condition* (compassionate imagery task versus control imagery task). Participants were therefore randomly assigned to one of four conditions with a total of 30 participants assigned to each condition: active tVNS-compassionate imagery; active tVNS-control imagery; sham tVNS-compassionate imagery; and sham tVNS-control imagery.

Participants attended two in-person lab sessions one week apart during which psychophysiological (eye-tracking and HRV) measures were taken, as well as self-report state measures (see below for full detail). Participants were randomly assigned to a tVNS stimulation condition and an imagery task condition at the beginning of the first in-person lab session (session 1). Participants were instructed to use the tVNS device and complete the imagery task once between the two in-person lab sessions (i.e. days 2–7), during which they repeated the subjective state measures used in the lab sessions.

The original study by Kamboj and colleagues (in prep) included time point as a within-subjects factor. For this exploratory secondary analysis, this within subjects' factor was removed and instead, change scores were used based on measures collected at the first and the third time points of day 1, and the first and third time points on day 8 (see below).

For this exploratory secondary analysis, a third between-subjects variable was created for the *level of reported childhood trauma* (moderate to severe or higher, referred to as '≥ moderate', versus low to moderate or lower, referred to as '≤ lower'), based on self-reported outcome measures.

Randomisation

Participants were randomly and evenly assigned to the four experimental conditions. An allocation sequence was created by computer-generated code, in a way that balanced gender across the four groups in the original 2x2 design. The allocation sequence was created by a member of the research team not involved in recruitment or conducting of in-person lab sessions. Members of the research team conducting the in-person lab sessions determined which condition participants were allocated to upon arrival, by referring to the sequence which detailed which condition the next male or female participant should be allocated to. Members of the research team did not refer to the allocation sequence when recruiting participants. A full description of the method of randomisation is provided in Kamboj et al. (2023).

Blinding

The aims and hypotheses of the original study were concealed from participants to avoid expectancy effects around the allocated active versus sham tVNS stimulation. Study information provided to participants before Session 1 described tVNS, but concealed the nature of active versus sham stimulation, and a 'mental imagery task' but did not state the exact form such a task might take. The nature of participants' imagery condition (compassion versus draw-a-face/control)

was only disclosed prior to consent on Session 1. Participants were fully debriefed at the end of the study.

Interventions

Transcutaneous vagus nerve stimulation

Sham stimulation of the earlobe and active stimulation of the tragus was delivered using a Parasym tVNS device (Parasym Ltd, United Kingdom). The stimulation parameters are described in *Table 1* (copied from Kamboj et al., 2023). For each stimulation session, participants were instructed to increase the current level from 0 mA in one-unit increments on the tVNS device (corresponding to steps of 0.8 mA per increment, based on a fixed resistance of 500 Ohms) until they reached their sensory threshold (the point at which they felt a clear tingling or pulsing sensation but that was not painful). The stimulation level used for each participant was set separately for each of the eight lab or at-home sessions. Stimulation intensity on the device (range 0–40) was recorded during each session.

Table 1. *Stimulation parameters of the tVNS used within the study.*

Stimulation parameter	Details
Device manufacturer	Parasym Ltd
Control	Variable current (constant voltage in tissue)
Individualisation	Individualised intensity, above sensory threshold
Direction	Preferentially afferent[l]
Location	Active: left tragus (anterior and posterior surface); Sham: left earlobe
Electrode:	
• Number	Two
• Composition	Gold-plated
• Attachment method	Ear-clip

Duty cycle	Constant (no on/off cycling)
Frequency	20 Hz
Pulse shape	Rectangular
Pulse width	200 uS
Amplitude	0.8mA/increment (based on fixed resistance of 500 Ω)
Stimulation period	
Day 1	~70 minutes*
• Days 2-7	~30 minutes/day
• Day 8	~65 minutes¶
• Total (intended)	~315 minutes§

Note: ǀ Information provided by manufacturer. * 45 minutes pre-stimulation plus during imagery, plus ~25 minutes until end of eye-tracking. ¶ 40 minutes pre-stimulation plus during imagery, plus ~25 minutes until end of eye tracking. § 315 minutes represents the maximum total stimulation for the 8 days if 100% compliance with the two in-person lab sessions and 100% compliance with the 6 at-home sessions.

An initial pre-imagery, 'offline' period of 30 minutes active/sham stimulation began immediately after the completion of pre-stimulation state measures (see procedure below). After 30 minutes, the imagery instructions were presented (see below) and stimulation continued throughout the imagery task. Approximate total stimulation periods for the lab and at-home sessions are outlined in *Table 1*.

Mental Imagery Tasks

The imagery instructions for the compassion-focused imagery task (the active condition) and the 'draw-a-face-in-imagination' task (the sham or control condition; referred to below as control imagery task) were carefully matched as described in Kamboj et al. (2023).

Across the study for all participants, all audio instructions used the same male voice. The instructions were presented after the initial period of stimulation, while stimulation continued. For both imagery conditions, the instructions were presented sequentially, in three sections during Session 1. The first, introductory audio described the aims of the specific imagery task to which the participant was randomly assigned (compassion versus control) and the rationale for combining mental imagery with tVNS. The second section provided a more specific description of the respective imagery tasks, and the third section guided the participant through the actual imagery task.

For the compassion-focused imagery condition, the first introductory audio instructions stated that tVNS might be "…an effective non-invasive way of activating brain processes involved in producing feelings of safeness and comfort, which are a prerequisite for self-compassion". For the draw-a-face/control condition, they stated that tVNS could be "…an effective non-invasive way of activating brain processes involved in forming and manipulating mental images". These instructions informed participants that stimulating the vagus nerve with tVNS "might make it easier to form…mental images". Additionally, they stated that the researchers hoped the findings would enable new treatment techniques to be developed either "for people with depression and other psychological disorders, in which self-compassion is often lacking" (compassion-focused imagery) or "for improving memory for faces that would otherwise be difficult to remember… [for] application in forensic cases, for example" (control imagery).

The third audio section for the compassionate imagery condition was derived from Paul Gilbert's 'compassionate mind training' (Gilbert, 2014) and adapted from

previous studies by Kamboj and colleagues (2015; 2018). This section instructed participants to direct compassionate feelings inwards, towards the self (i.e. self-compassion) using mental imagery. To avoid additional respiration-mediated effects on vagal activity, and to ensure that it was closely matched with the control imagery condition, the compassion imagery instructions used in the present study did not contain a breathing component or an instruction to focus on posture and mindfulness.

The third audio section for the control imagery task consisted of instructions to imagine using a drawing/painting implement of the participant's choice to recreate in their imagination a standardised unfamiliar face, provided during a 'face rating task' at the start of day 1. For the face rating task, participants were presented with this unfamiliar face in the form of a computer-generated photograph, which they rated on several characteristics. The third section's instructions of the control task asked participants to recall the face of the individual from the face rating task and then to "add details to your imaginary canvas" as different parts of the face were mentioned in the audio instructions. Participants were asked to memorise the photograph so that they were able to repeat the control imagery task during the at-home sessions, during which they were not presented with the photograph.

An abbreviated version of the third recorded section was used in the at-home sessions on Days 2–7, the audio for which was presented via Qualtrics. On their second in-person session on day 8 participants only listened to the third recording (the guided imagery task). Verbatim scripts for the two imagery conditions can be found in *Appendix 8.*

Measures

For this exploratory secondary study, a coherent group of related outcomes was selected from the full range of outcome measures collected in the study by Kamboj and colleagues (in prep). For brevity, only outcome measures included in this exploratory secondary study will be described. For a full description of the outcome measures collected in the original study, please refer to the published rationale and study protocol (Kamboj et al., 2023).

Self-report outcome measures

The self-report outcome measures included in this exploratory secondary analysis were as follows:

The Self-Compassion-Self-Criticism (SCCS) Scale (Falconer et al., 2015), specifically the self-compassion subscale. The SCCS is a self-report measure that produces scores on two scales: self-compassion and self-criticism. It consists of eight imaginary scenarios that one is asked to rate on a seven-point scale how likely they would be to behave towards themselves in different self-compassionate and self-critical ways. The scale has good internal consistency (Cronbach's alphas) of 0.91 and 0.87, for the self-compassion and self-criticism subscales respectively. The scale has been used in previous research with clinical and non-clinical populations (Falconer et al., 2016; Falconer et al., 2014; Falconer 2020).

Types of Positive Affect Scale (TPAS; Gilbert et al., 2009), specifically the Safe-Content Positive Affect subscale. The TPAS is an 18-item self-report measure where participants are asked to rate the degree to which they felt a certain affect word (e.g. ‘secure’, ‘calm’, ‘active’… etc). The TPAS consists of three subscales:

Activating Positive Affect, Relaxed Positive Affect, and Safe-Content Positive Affect. For this study, participants were asked to rate the extent to which they were experiencing these feelings at that moment in time using a 5-point scale ranging from '0=Not characteristic of me', to '4=Very characteristic of me'. The TPAS has been found to have internal consistencies (Cronbach's alphas) of .88 for Activating Positive Affect, .93 for Relaxed Positive Affect, and .83 for Safe/Contentment Positive Affect (Duarte & Pinto-Gouveia, 2017).

The Sussex Oxford Compassion for the Self Scale (SOCS-S; Gu et al., 2020). The SOCS-S is a measure of trait self-compassion that consists of five subscales. It has been produced based on a theoretical and empirically supported definition of compassion. The measure was validated in a population of students and a population of healthcare staff. The internal consistency (Cronbach's alpha) of the SOCS-S total and subscales across the two populations ranged from .75 to .93. The measure has been found to have adequate interpretability, floor and ceiling effects, and discriminant and convergent validity (Gu et al., 2020).

The Five Facet Mindfulness Questionnaire 15-item version (FFMQ; Gu et al., 2016). This is a frequently used and comprehensive measure of trait mindfulness, measured across five facets that are theorised to comprise mindfulness (Danielson and Jones, 2017). In a study investigating a mindfulness-based cognitive therapy intervention, the internal consistency (Cronbach's alpha) of the FFMQ subscales ranged from .78 to .90 (Gu et al., 2018).

The State Mindfulness Scale (SMS) Short-Form as used in Shobham et al. (2017). This is a 5-item version of the original, 21-item self-report measure (Tanay & Bernstein, 2013) designed to assess state mindfulness. It asks participants to rate

the extent to which they agree with a series of statements, on a 5-point scale (e.g. ‘In the last 5 min, I paid attention to what I was doing in the present moment’).

Predictor Self-Report Measure: Childhood Trauma Questionnaire Short-Form

The Childhood Trauma Questionnaire Short-Form (CTQ-SF; Bernstein et al, 2003) is a 28-item screening measure for histories of maltreatment validated for use in both clinical and non-clinical groups. It has five subscales: physical abuse, sexual abuse, emotional abuse, emotional neglect, and physical neglect. In a community sample, the internal consistency for these subscales was found to be 0.83, 0.92, 0.86, 0.91, and 0.61 respectively.

Individuals were first categorised on each of the CTQ-SF subscales using the cut-offs from Bernstein et al. (1998). Then to create a categorical variable from the CTQ-SF participants were categorised as to whether they reported moderate-severe levels of abuse on any of the five subscales of the CTQ-SF (those who did referred to as ‘≥ moderate’, those who did not referred to as ‘≤ lower’). This categorical split was chosen, as opposed to a lower cut-off for splitting such as whether they reported any trauma at all in any category, as there is evidence of dose-response relationships between CT and adult mental health outcomes (Edwards et al., 2003; England-Mason et al., 2018), which led to thoughts that differences may be most pronounced when grouping individuals who have experienced more severe levels of CT. This method of splitting also created more equal groups, than splitting as to whether participants reported any trauma at all in any category.

Psychophysiological Measures

A heart-rate monitoring device (Bodyguard 2, Firstbeat) was used during the in-person lab sessions to record inter-beat interval data. The device has been validated against gold-standard laboratory-based ECG recording procedures and produced highly similar indices of HRV across resting and active conditions (Palmer et al., 2021). The analysis of the current study focused solely on one time-domain measure of 'vagal tone', RMSSD, which is the root mean square of successive differences between normal heartbeats (Di Bello et al, 2020). The study by Kamboj and colleagues (in prep) included a second measure, a frequency domain measure, as well as RMSSD. These two measures were selected a priori as reported in the original study rationale and protocol (Kamboj et al., 2023). Extreme RMSSD data points (more than 3 z-scores from the mean) were removed from the dataset before analysis.

The study by Kamboj and colleagues also assessed participants' attentional bias towards compassionate faces, using an eye-tracking computer task. This was beyond the scope of the current study.

Procedure

Screening

Participants were recruited to the study between June 2022 and March 2023. Interested participants responding to the study adverts first completed an online screening process to ensure that they met the inclusion and exclusion criteria. Those who did so were contacted for a follow-up telephone screening to verify that the responses to the online screening were correct, and to ensure that participants had received and read the study information sheet (*Appendix 5*) and were aware of the study requirements.

Day 1

Participants confirmed that they had read the study information sheet and then were provided with additional standardised information on the imagery task that they had been randomly allocated (*Appendix 8*). Participants were allowed to ask questions following which formal consent was sought to continue with the study.

After consenting to continue, participants connected the first-beat device and attached the Parasym tVNS device electrode on either their tragus or earlobe but did not turn it on. The participants then completed the following baseline measures: CTQ, SOCS-S, FFMQ, SCCS, SMS and TPAS. The participants then completed the tVNS thresholding procedure described above. This delay in attaching the electrode and completing this thresholding procedure was to allow adjustment to the sensation of the clip being attached and therefore avoid interference with the thresholding procedure. They then began 30 minutes of continuous stimulation. During this, participants were asked to relax and watch a nature documentary on a computer screen (Blue Planet II; BBC Studios Natural History Unit, 2017). This was selected to be emotionally neutral. Participants then repeated the SCCS, SMS and TPAS. Following this, participants completed their allocated imagery task, whilst stimulation continued and then repeated once more the SCCS, SMS and TPAS. The eye-tracking task was then completed, after which participants removed the first-beat device and turned off and removed the tVNS device.

At the end of the session, participants were given detailed instructions on use of the tVNS device and attachment of the electrode to the tragus or earlobe for daily stimulation, along with instructions on accessing the online meditation audio at home.

Days 2-7

Participants received an email at the same time each morning, with a link to log on to the at-home study site. They were instructed to access and complete the at-home imagery and stimulation tasks at the same time each day as far as possible.

Before starting, participants verified the tVNS stimulation settings and recorded these on the study survey site. Participants completed the sensory-thresholding procedure on each at-home study day. They completed 30 minutes of stimulation and then completed the SCCS, SMS and TPAS. Following this they listened to their allocated meditation instructions (15 min; the same audio as Day 1), while stimulation continued. As described above, an abbreviated version of the third recorded imagery audio section was used in the at-home sessions. Participants then completed the SCCS, SMS and TPAS once more.

Participants' access and completion of the at-home study survey were automatically registered and monitored by members of the research team each day. Where participants had failed to log on to or complete the at-home study survey or had not spent the required time on either the stimulation or imagery section, a member of the research team contacted the participants by phone the following day to ensure that they understood the requirements of the study and request that they log on and complete in full the at-home study requirements each day.

Day 8

The second lab session was mostly identical to Day 1. Participants connected the first-beat device and attached the Parasym tVNS device electrode on either their tragus or earlobe but did not turn it on. The participants then completed the SOCS-S,

FFMQ, SCCS, SMS and TPAS. After which, they completed the tVNS thresholding procedure and began 30 minutes of continuous stimulation. During this, participants were asked to relax and watch a different episode of the same nature documentary as day 1 (Blue Planet II; BBC Studios Natural History Unit, 2017). Participants then repeated the SCCS, SMS and TPAS.

Participants then completed their allocated imagery task whilst stimulation continued. A shortened form of the imagery task was used, where participants only listened to the third recording (the guided imagery task). Participants then repeated once more the SCCS, SMS and TPAS. The eye-tracking task was then completed, after which participants removed the first-beat device and turned off and removed the tVNS device.

Analysis

To investigate the short-term interaction effects, change scores between time-point 1 (t1) on day and time-point 3 (t2) on day 1 were calculated for the SMS total, the SCCS self-compassion subscale, the TPAS Safe-Content subscale, and RMSSD. To investigate the longer-term effects, change scores between time-point 1 on day and time-point 3 on day 8 were calculated the SMS total, the SCCS self-compassion subscale, the TPAS Safe-Content subscale, and RMSSD. Change scores between time-point 1 on day 1 and time-point 1 on day 8 were calculated the SOCS-S total and for the FFMQ total.

Because the two categories of level of reported CT were not formed through randomization, an independent samples t-test was conducted to compare the mean age in years of the two CT categories. A chi-square test of independence was conducted to compare gender.

Baseline mean state and trait self-compassion were calculated for the whole sample as well as when split into sub-categories of level of childhood trauma ('≥ moderate' and ≤ lower'), as this may be of interest.

Three-way (2x2x2) independent measures ANOVAs were conducted on these change scores with factors of stimulation (active versus sham), imagery (compassion versus control), and level of CT (≥ moderate versus ≤ lower). Where three-way interactions were present, the data was split into two parts by level of CT and simple two-way ANOVAs were conducted to investigate whether effects and interactions related to imagery and stimulation conditions differed by level of CT. It was decided to use Fisher's LSD (equivalent to unadjusted) for post-hoc simple main effects analysis in the case of significant two-way interactions. This approach was taken as the current study was an exploratory follow-up analysis of the original study by Kamboj and colleagues (in prep), intended to generate hypotheses for future testing. It was deemed acceptable to use this liberal approach to follow-up tests to avoid the risk of type 2 errors of any interactions between level of CT and stimulation condition and/or imagery condition, which may have been of a relatively small effect size.

Results

Participants Demographic Data and Baseline Trait and State Self-compassion

A total of 120 individuals completed the study. Table 2 summarises the demographic data of participants as an overall sample and by groups broken down by treatment arm and level of trauma. Gender was balanced across the four conditions of the original experiment. Across the whole study sample, 71 (59.2%)

reported moderate-severe levels of abuse on one or more of the five subscales of the CTQ-SF (referred to as '≥ moderate'), and 49 (40.8%) did not report moderate-severe levels of abuse on any of the five subscales of the (referred to as '≤ lower'). An independent samples t-test found no significant difference between the age in years of those categorised as '≥ moderate' (*M* = 23.08, SD = 4.44) versus those categorised as '≤ lower' (*M* = 22.76, *SD* = 3.81), t (118, N = 120), = -.4.24, p=.142. A chi-square test of independence showed that there was no significant association between gender and level of reported childhood trauma (CT) ('≤ lower' = 70.4% female, '≥ moderate' = 77.6% female), X^2 (1, *N* = 120) = .753, *p* = .385.

The sample as a whole had a mean of 41.72 (*SD* = 20.01) for state self-compassion. Those categorised as '≤ lower' had a mean of 43.76 (*SD* = 20.96) whilst those categorised as '≥ moderate' had a mean of 38.76 (*SD* = 18.34). The sample as a whole had a mean of 13.06 (*SD* = 20.01) for trait self-compassion. Those categorised as '≤ lower' had a mean of 13.49 (*SD* = 3.08) whilst those categorised as '≥ moderate' had a mean of 12.43 (*SD* = 3.34).

Table 2. *Demographic information of the participants*

		Overall Sample	**tVNS & Imagery:**	**Sham - Control**		**Sham - Compassion**		**Active - Control**		**Active - Compassion**	
			CTQ-SF:	**≤ lower**	**≥ moderate**	**≤ lower**	**≥ moderate**	**≤ lower**	**≥ moderate**	**≤ lower**	**≥ moderate**
Variable	Sub-Variable	N (%)		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of Participants		120 (100%)		15 (12.50%)	16 (13.33%)	20 (16.67%)	9 (7.50%)	18 (15%)	12 (10%)	18 (15%)	12 (10%)
Age in Years	Mean (S.D)	22.89 (4.07)		21.60 (3.74)	23.69 (5.06)	22.70 (3.73)	24.22 (5.29)	23.56 (3.28)	21.50 (2.75)	23.00 (4.49)	23.00 (4.37)
	Range	18-34		18-29	18-33	18-32	18-34	19-34	19-27	18-32	18-33
Gender	Male	32 (26.7%)		6 (5.00%)	3 (2.50%)	5 (4.17%)	2 (1.67%)	5 (4.17%)	3 (2.50%)	5 (4.17%)	3 (2.50%)
	Female	88 (73.3%)		9 (7.50%)	13 (10.8%)	15 (12.5%)	7 (5.83%)	13 (10.83%)	9 (7.50%)	13 (10.83%)	9 (7.50%)
Ethnicity	Chinese	44 (36.67%)		8 (6.67%)	6 (5.00%)	7 (5.83%)	3 (2.50%)	6 (5.00%)	2 (1.67%)	8 (6.67%)	4 (3.33%)
	Any Other Asian	21 (17.50%)		1 (0.83%)	3 (2.50%)	3 (2.50%)	2 (1.67%)	3 (2.50%)	2 (1.67%)	2 (1.67%)	5 (4.17%)
	White British	18 (15.00%)		3 (2.50%)	1 (0.83%)	2 (1.67%)	0 (0%)	3 (2.50%)	4 (3.33%)	3 (2.50%)	2 (1.67%)
	White Other	21 (17.50%)		2 (1.67%)	3 (2.50%)	4 (3.33%)	1 (0.83%)	4 (3.33%)	2 (1.67%)	4 (3.33%)	1 (0.83%)
	Black Caribbean & Black African	4 (3.33%)		0 (0%)	1 (0.83%)	1 (0.83%)	1 (0.83%)	0 (0%)	0 (0%)	1 (0.83%)	0 (0%)
	Multiple Ethnic Background	7 (3.33%)		0 (0%)	1 (0.83%)	2 (0.83%)	2 (1.67%)	1 (0.83%)	1 (0.83%)	0 (0%)	0 (0%)
	Any Other Ethnic Background	5 (3.33%)		1 (0.83%)	0 (0%)	1 (0.83%)	1 (0.83%)	1 (0.83%)	1 (0.83%)	0 (0%)	0 (0%)

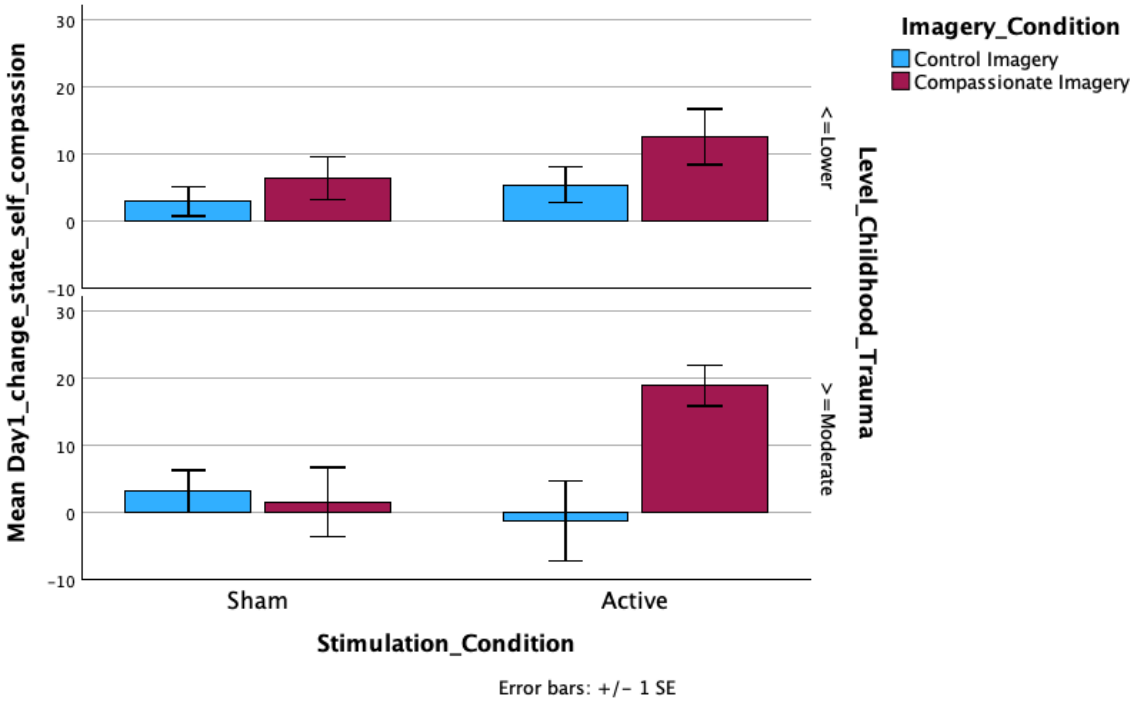
Note. Percentages represent those of the entire study sample, as opposed to within each sub-group. S.D = standard deviation

Short-Term Effects of Stimulation, Imagery and Level of Childhood Trauma

Self-report Outcome Measures

State Self-Compassion

Figure 1. *State Self-Compassion: Mean Change in Self-Compassion and Self-Criticism Scale, Self-Compassion Subscale on Session 1 between Pre-Stimulation and Post-Imagery*



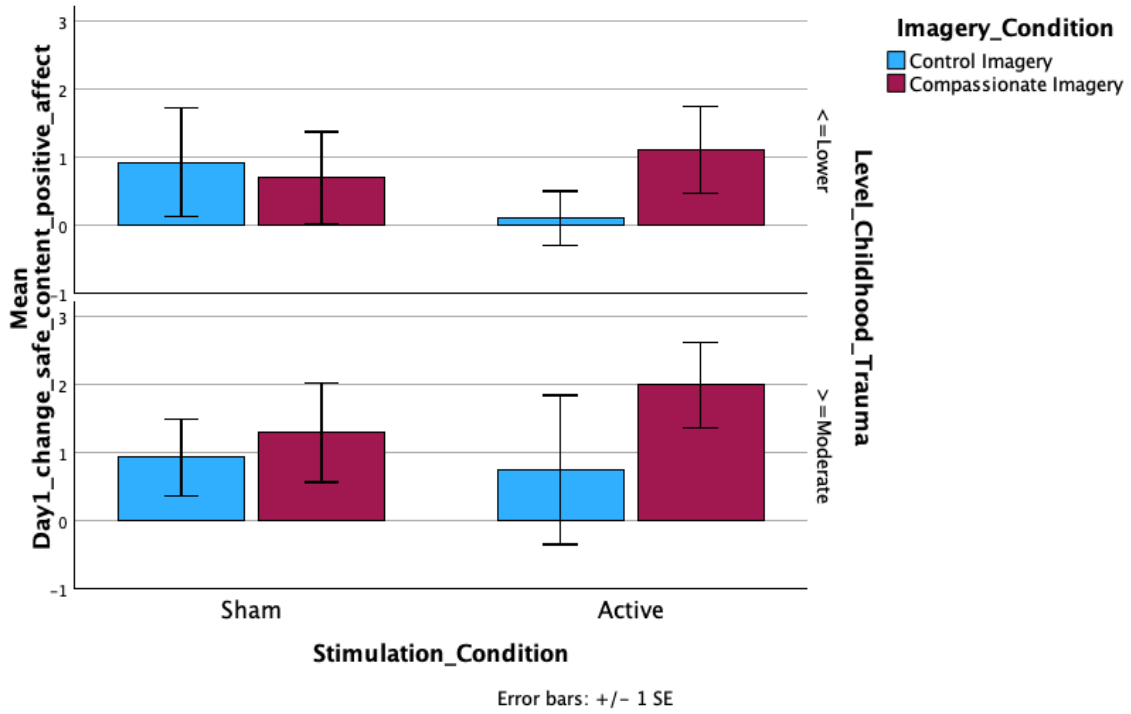
Note. The error bars represent +/- 1 standard error of the mean. Change scores were calculated by subtracting t1 Day 1 mean from t3 Day 1 mean. An increase is desirable for this outcome, representing an increase in levels of state self-compassion.

Figure 1 shows the effects of stimulation and imagery on short-term change in state self-compassion in the two CT severity categories. Three-way factorial ANOVA indicated that there was there was no significant three-way interaction between CT, stimulation condition and imagery condition, F (1, 112) = 2.86, p =.094. There were no significant two-way interactions between CT and stimulation condition, F (1, 112) = .159, p =.691, or between CT and imagery condition, F (1, 112) = .547, p =.461. There was also no significant main effect of CT, F (1, 112) = .227, p =.635.

There was, however, a significant two-way interaction between stimulation and imagery conditions, F (1, 112) = 5.706, p =.019. Simple main effects analysis revealed that there was a significant effect of imagery condition for those receiving active stimulation, F (1, 54) = 13.267, (P<.001), whereby those who completed the compassionate imagery task showed a significantly greater increase in state self-compassion on day 1 (*M* = 15.79, *SE* = 2.65, 95 CI [10.55, 21.03]) than those who completed the control imagery task (*M* = 2.17, *SE* = 2.65, 95% CI [-3.07, 7.41]). There was no significant simple main effect of imagery for those receiving sham stimulation, F (1, 54) = .060, (p=.807), whereby there was no significant difference between those completing the compassionate imagery task (*M* = 4.03, *SE* = 2.75, 95% CI [-1.42, 98.47]) and those completing the control imagery task (*M* = 3.10, *SE* = 2.59, 95% CI [-2.04, 8.24]). There was a significant simple main effect of stimulation for those completing the compassionate imagery task, F (1, 54) = 9.514, (p=.003), whereby those receiving active stimulation showed a significantly greater increase (*M* = 15.79, *SE* = 2.65, 95% CI [10.55, 21.03]), compared to those receiving sham stimulation (*M* = 4.03, *SE* = 2.75, 95% CI [-1.42, 98.47]). There was no significant simple main effect of stimulation for those completing the control imagery task, F (1, 54) = .064, (p=.801), whereby there was no significant difference between those receiving active stimulation (*M* = 2.17, *SE* = 2.65, 95% CI [-3.07, 7.41]) and those receiving sham stimulation (*M* = 3.10, *SE* = 2.59, 95% CI [-2.04, 8.24]).

State Safe-Content Positive Affect

Figure 2. *State Safe and Content Positive Affect: Mean Change in Types of Positive Affect Scale, Safe-Content Subscale on Session 1 between Pre-Stimulation and Post-Imagery*



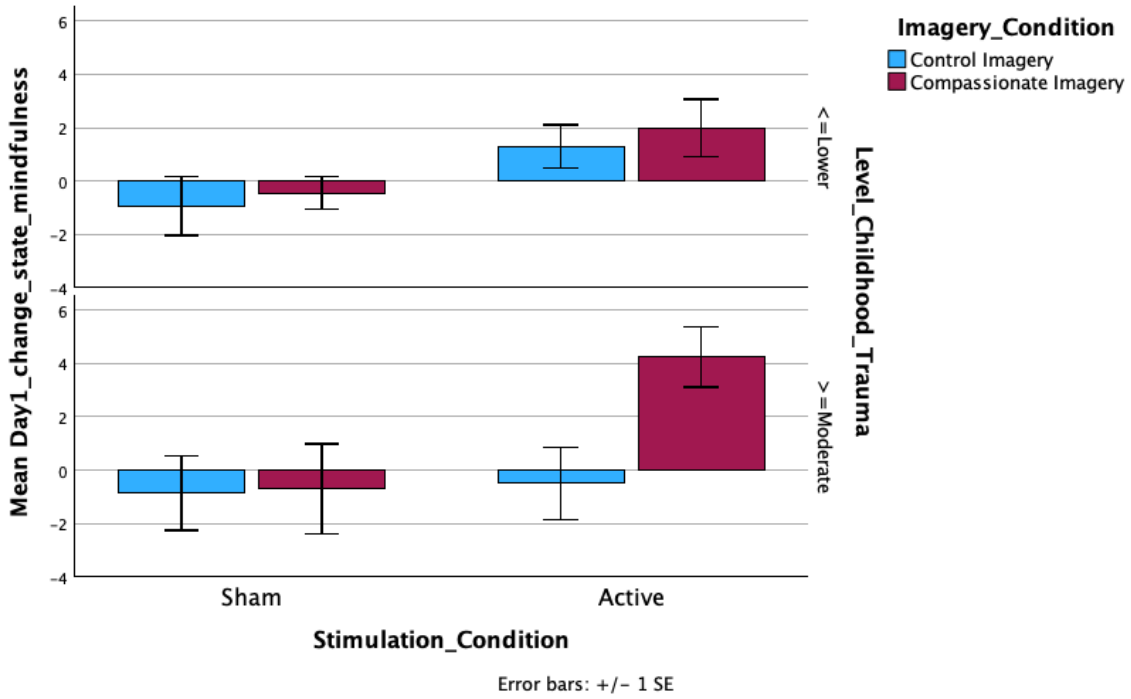
Note. The error bars represent +/- 1 standard error of the mean. Change scores were calculated by subtracting t1 Day 1 mean from t3 Day 1 mean. An increase is desirable for this outcome, representing an increase in levels of state levels of safe and content positive affect.

Figure 2 shows the effects of stimulation and imagery on short-term change in state safe and content positive affect in the two CT severity categories. Three-way independent measures ANOVA indicated that there was no significant three-way interaction between level of CT, stimulation condition, and imagery condition, F (1, 112) = .030, p =.862. There were no significant two-way interactions between CT and stimulation condition, F (1, 112) = .213, p =.645, between CT and imagery condition, F (1, 112) = 1.288, p =.673, or between imagery and stimulation conditions, F (1, 112) = 1.110, p =.294. There were no significant main effects of stimulation, F (1,

112) = .003, p =.958, imagery, F (1, 112) = 1.407, p =.238, or CT, F (1, 112) = 1.21, p =.292.

State Mindfulness

Figure 3. *State Mindfulness: Mean Change in State Mindfulness Scale Short-Form Total on Session 1 between Pre-Stimulation and Post-Imagery.*



Note. The error bars represent +/- 1 standard error of the mean. Change scores were calculated by subtracting t1 Day 1 mean from t3 Day 1 mean. An increase is desirable for this outcome, representing an increase in levels of state mindfulness.

Figure 3 shows the effects of stimulation and imagery on short-term change in state mindfulness in the two CT severity categories. Three-way independent measures ANOVA indicated that there was no significant three-way interaction between level of CT, stimulation condition, and imagery condition, F (1, 110) = 1.872, p =.174. There were also no significant two-way interactions between CT and stimulation condition, F (1, 110) = .040, p =.841, CT and imagery condition, F (1, 110) = 1.368, p =.245 or imagery and stimulation conditions, F (1, 110) = 2.274, p =.134.

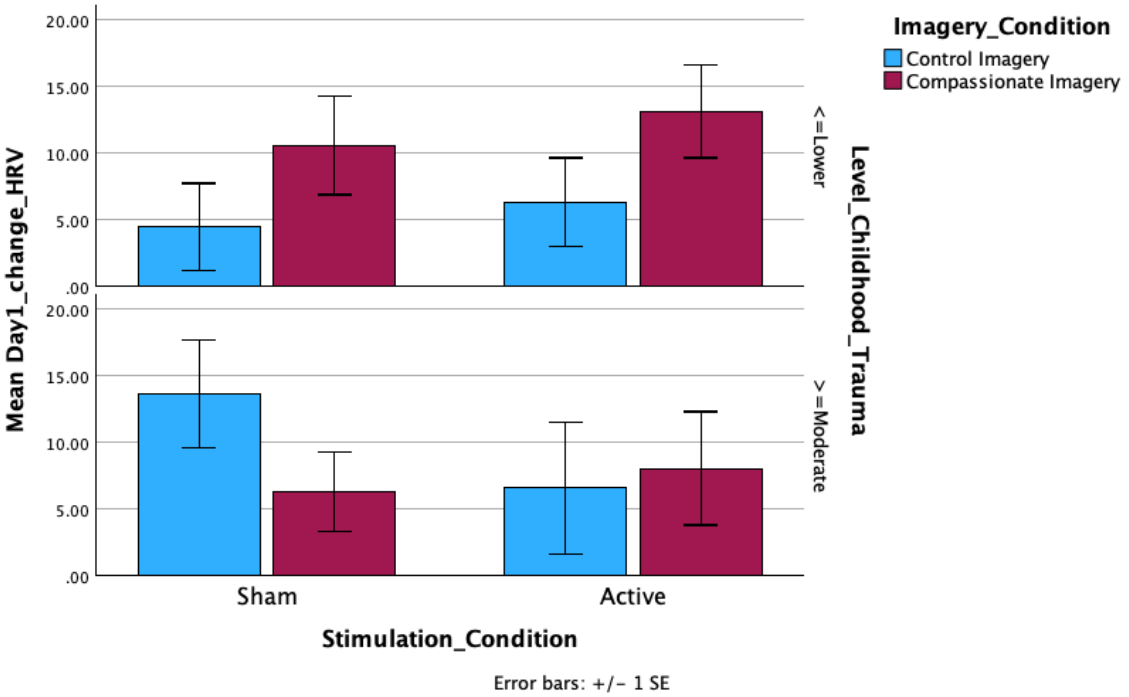
There was, however, a significant main effect of stimulation condition, F (1, 110) = 9.833, p =.002. Participants receiving active stimulation showed an increase in SMS scores on day 1 (*M* = 1.761, *SE* = .564, 95% CI [.64, 2.88]) whereas those receiving sham stimulation showed a small decrease (*M* = -.738, *SE* = -.563, 95% CI [-1.85, .38]), and the difference between these two groups was statistically significant. There were no significant main effects of imagery condition, F (1, 110) = 3.670, p =.058, or level of CT, F (1, 110) = .007, p =.932.

Heart Rate Variability: Root Mean Square of the Successive Differences

Figure 4 shows the effects of stimulation and imagery on short-term change in HRV in the two CT severity categories. After the removal of extreme data points, there was usable HRV data from t1 and t3 on day 1 for 114 participants.

Three-way independent measures ANOVA indicated that there was no significant three-way interaction between level of CT, stimulation condition, and imagery condition, F (1, 106) = .545, p =.462. There were also no significant two-way interactions between CT and stimulation condition, F (1, 106) = .767, p =.383, CT and imagery condition, F (1, 106) = 12.887, p =.092, or imagery and stimulation conditions, F (1, 106) = .730, p =.395. There were no significant main effects of stimulation condition, F (1, 106) = .006, p =.937, imagery condition, F (1, 106) = .406, p =.525, or CT, F (1, 106) = .000, p =.999.

Figure 4. *Heart Rate Variability: Mean Change in RMSSD on Session 1 between Pre-Stimulation and Post-Imagery*



Note. The error bars represent +/- 1 standard error of the mean. Change scores were calculated by subtracting t1 Day 1 mean from t3 Day 1 mean. An increase is desirable for this outcome, representing an increase in vagal tone.

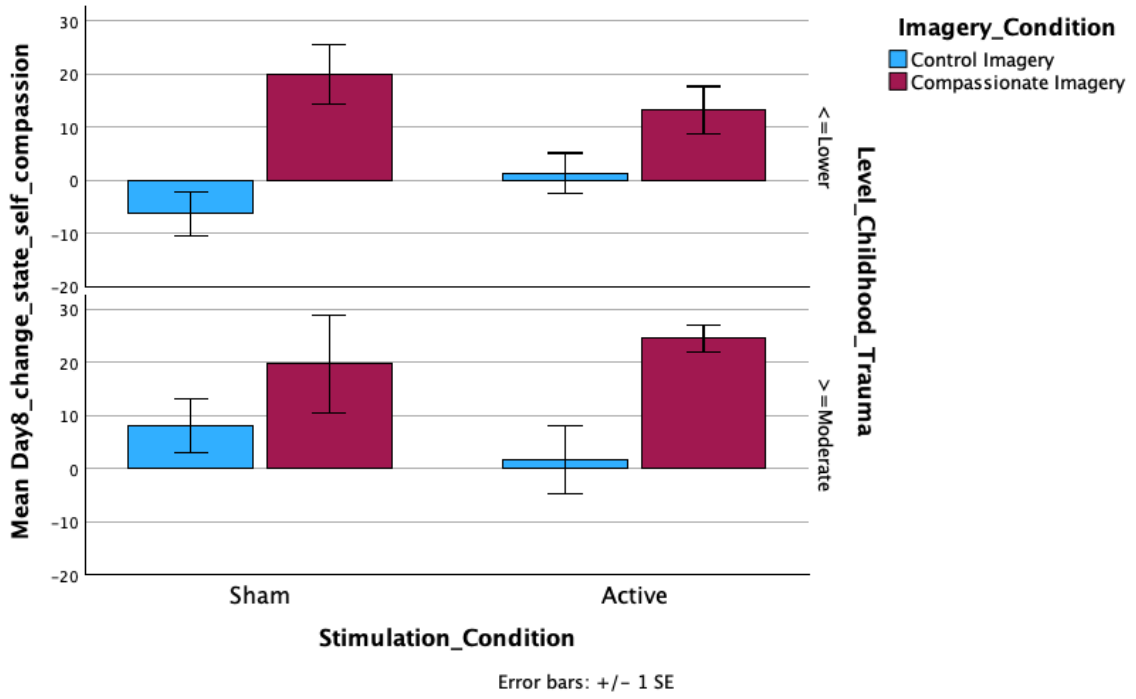
Longer-Term Effects of Stimulation, Imagery and Level of Childhood Trauma

Self-report Outcome Measures

State Self-Compassion

Figure 5 shows the effects of stimulation and imagery on longer-term change in state self-compassion in the two CT severity categories. Three-way independent measures ANOVA indicated that there was no significant three-way interaction between level of CT, stimulation condition, and imagery condition, F (1, 112) = 2.883, p =.092.

Figure 5. *State Self-Compassion: Mean Change in Self-Compassion and Self-Criticism Scale, Self-Compassion Subscale between Pre-Stimulation on Day 1 and Post-Imagery on Day 8*



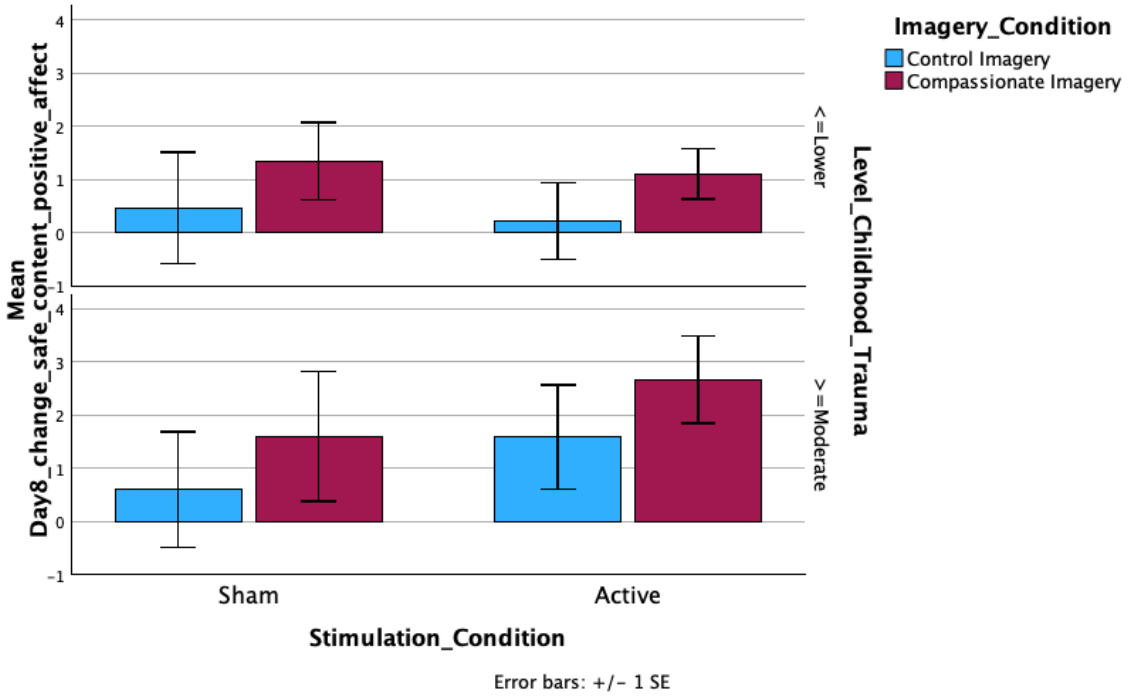
Note. The error bars represent +/- 1 standard error of the mean. Change scores were calculated by subtracting t1 Day 1 mean from t3 Day 8 mean. An increase is desirable for this outcome, representing an increase in state self-compassion.

There were also no significant two-way interactions between CT and stimulation condition, F (1, 112) = .027, p =.870, CT and imagery condition, F (1, 112) = .058, p =.810, or imagery and stimulation conditions, F (1, 112) = .046, p =.831.

There was a significant main effect of imagery condition, F (1, 112) = 23.108, p <.001. Participants completing the compassionate imagery task showed an increase (*M* = 19.36, *SE* = 2.71, 95% CI [13.99, 24.72]) whereas those completing the control imagery task showed a small increase (*M* = 1.21, *SE* = 2.63, 95% CI [-3.99, 6.42]), with the difference between the two significant. There were no significant main effects of stimulation condition, F (1, 112) = .002, p =.962, or CT, F (1, 112) = 2.873, p =.093.

Safe-Content Positive Affect

Figure 6. *State Safe and Content Positive Affect: Mean Change in Types of Positive Affect Scale, Safe-Content Subscale between Pre-Stimulation on Day 1 and Post-Imagery on Day 8*



Note. The error bars represent +/- 1 standard error of the mean. Change scores were calculated by subtracting t1 Day 1 mean from t3 Day 8 mean. An increase is desirable for this outcome, representing an increase in state levels of safe and content positive affect.

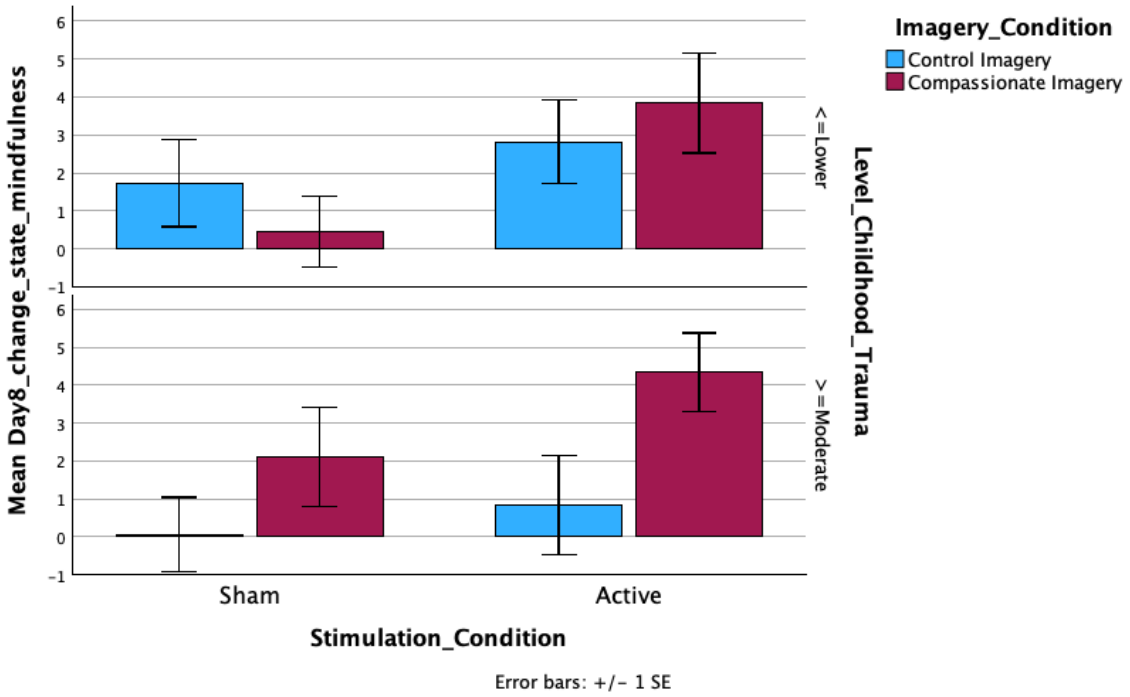
Figure 6 shows the effects of stimulation and imagery on longer-term change in safe and content positive affect in the two CT severity categories. Three-way independent measures ANOVA indicated that there was no significant three-way interaction between level of CT, stimulation condition, and imagery condition, $F(1, 112) = .001$, $p = .975$.

There were also no significant two-way interactions between CT and stimulation condition, $F(1, 112) = 1.014$, $p = .316$, CT and imagery condition, $F(1, 112) = .015$, $p = .902$, or imagery and stimulation conditions, $F(1, 112) = 1.110$, p

=.294. There were no significant main effects of stimulation, F (1, 112) = .388, p =.535, imagery, F (1, 112) = 2.350, p =.128, or level of CT, F (1, 112) = 1.721, p =.192.

State Mindfulness

Figure 7. *State Mindfulness: mean change in State Mindfulness Scale Short-Form Total between Pre-Stimulation on Day 1 and Post-Imagery on Day 8.*



Note. The error bars represent +/- 1 standard error of the mean. Change scores were calculated by subtracting t1 Day 1 mean from t3 Day 8 mean. An increase is desirable for this outcome, representing an increase in state mindfulness.

Figure 7 shows the effects of stimulation and imagery on longer-term change in state mindfulness in the two CT severity categories. Three-way independent measures ANOVA indicated that there was no significant three-way interaction between level of CT, stimulation condition, and imagery condition, F (1, 110) = 4.995, p =.802.

There were no significant two-way interactions between level of CT and stimulation condition, F (1, 110) = 1.275, p =.261, CT and imagery condition, F (1,

110) = 3.013, p =.085, or imagery and stimulation conditions, F (1, 110) = 1.275, p =.261.

There was a significant main effect of stimulation condition, F (1, 110) = 4.995, p =.027. Participants receiving active stimulation showed a greater increase in SMS score (*M* = 2.953, *SE* = .591, 95% CI [1.78, 4.12]) compared to those receiving sham stimulation (*M* = 1.087, *SE* = .590, 95% CI [-.81, 2.26]). There were no significant main effects of imagery condition, F (1, 110) = 2.492, p =.117, or CT, F (1, 110) = .201, p =.655.

Trait Self-Compassion

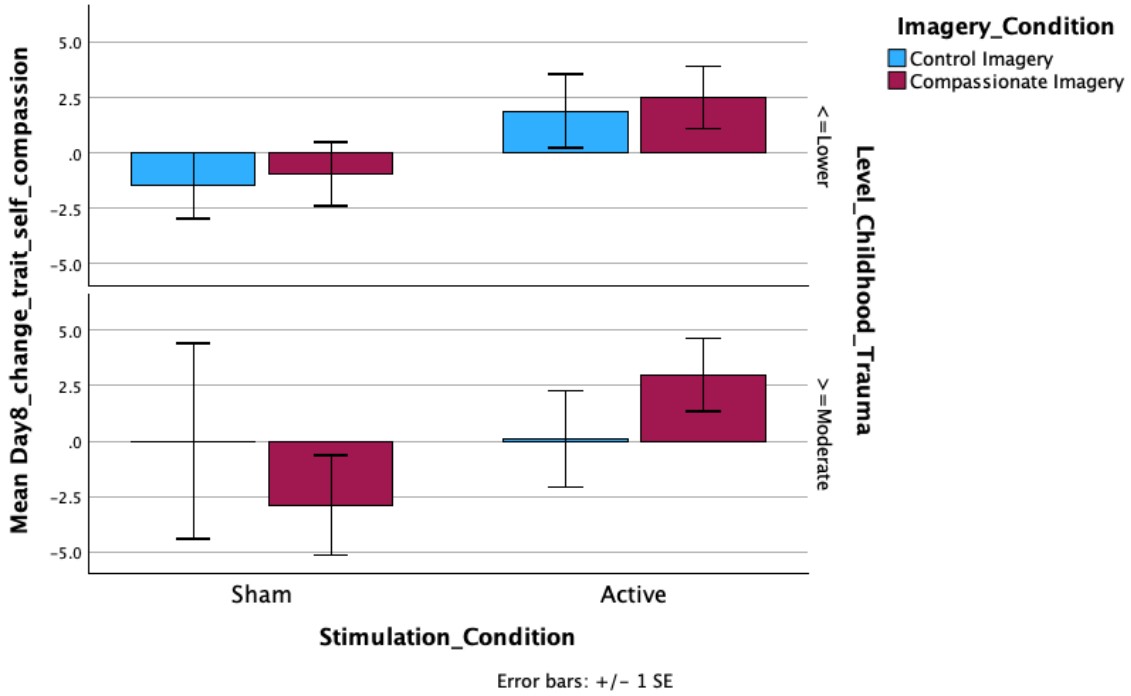
Figure 8 shows the effects of stimulation and imagery on change in trait self-compassion in the two CT severity categories. Three-way independent measures ANOVA that there was no significant three-way interaction between level of CT, stimulation condition, and imagery condition, F (1, 112) = .792, p =.375.

There were also no significant two-way interactions between level of CT and stimulation condition, F (1, 112) = .016, p =.898, CT and imagery condition, F (1, 112) = .030, p =.863, or imagery and stimulation conditions, F (1, 112) = .845, p =.360.

There was a significant main effect of stimulation condition, F (1, 112) = 3.955, p =.049. Participants receiving active stimulation showed an increase in trait self-compassion (*M* = 1.868, *SE* = 1.131, 95% CI [-.37, 4.11]) whereas those receiving sham stimulation a decrease (*M* = -1.329, *SE* = .590, 95% CI [-3.59, .93]), and the difference between these two groups was statistically significant. There were no

significant main effects of imagery condition, F (1, 112) = .032, p =.859, or CT, F (1, 112) = .077, p =.781.

Figure 8. *Trait Self-Compassion: Mean Change in The Sussex Oxford Compassion for the Self Scale between Pre-Stimulation on Day 1 and Pre-Stimulation on Day 8*



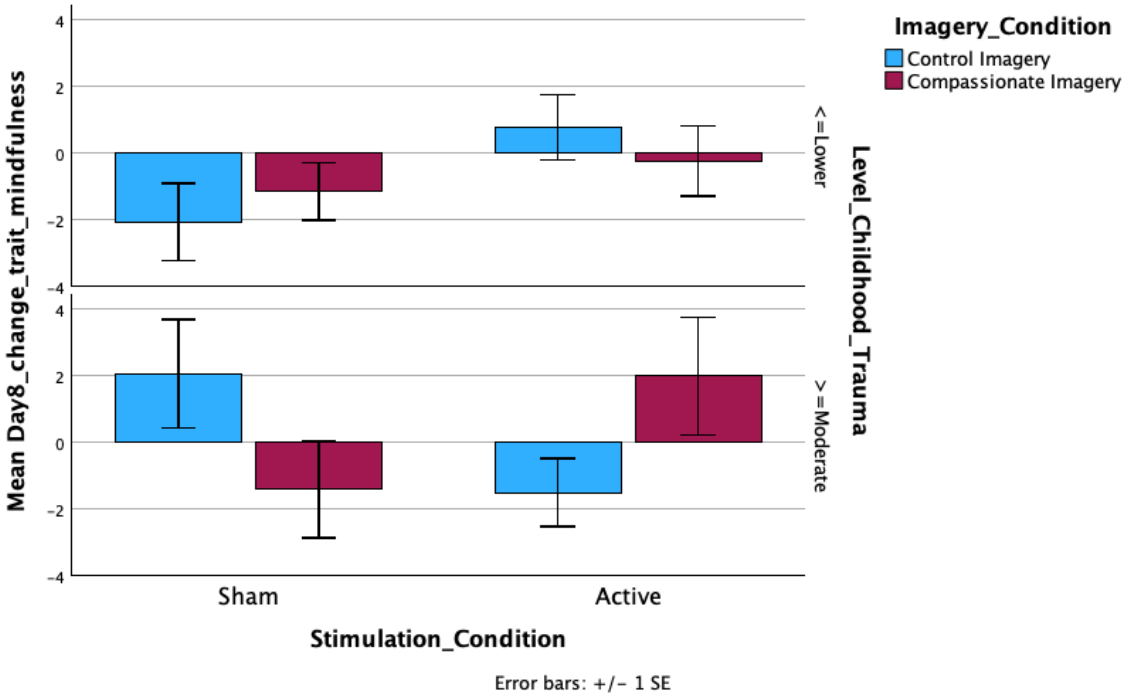
Note. The error bars represent +/- 1 standard error of the mean. Change scores were calculated by subtracting t1 Day 1 mean from t3 Day 8 mean. An increase is desirable for this outcome, representing an increase in trait self-compassion.

Trait Mindfulness

Figure 9 shows the effects of stimulation and imagery on change in trait mindfulness in the two CT severity categories. Three-way independent measures ANOVA indicated that there was a three-way interaction between level of CT, stimulation condition, and imagery, F (1, 112) = 6.295, p =.014. To investigate the three-way interaction, simple two-way (stimulation x imagery) ANOVAs were conducted at each level of CT. For those in the '≤ lower' category of CT, there were no significant main effects of stimulation, F (1, 67) = 3.477, p =.067 or imagery, F (1, 67) = .002, p =.967, and there was no significant interaction between stimulation and

imagery, F (1, 67) = .898, p =.347. For the '≥ moderate' category of CT, there were no significant main effects of stimulation, F (1, 45) = .003, p =.957 or imagery, F (1, 45) = .0001, p =.991. There was a significant interaction between stimulation and imagery condition, F (1, 45) = 5.047, p =.030, which seemed to reflect opposing effects of stimulation in the two imagery conditions. However, post-hoc simple main effects analysis revealed that there was no significant simple main effect of imagery for those receiving active stimulation, F (1, 45) = 2.547, p = .117, or for those receiving sham stimulation, F (1, 45) = 2.499, p=.121, and no significant simple main effect of stimulation for those completing the compassionate imagery task, F (1, 45) = .003, p =.146, or for those completing the control imagery task, F (1, 45) = .003, p=.093.

Figure 9. *Trait Mindfulness: Mean Change in Five-Facet Mindfulness Questionnaire Total between Pre-Stimulation on Day 1 and Pre-Stimulation on Day 8*



Note. The error bars represent +/- 1 standard error of the mean. Change scores were calculated by subtracting t1 Day 1 mean from t3 Day 8 mean. An increase is desirable for this outcome, representing an increase in trait mindfulness.

There were no significant two-way interactions between level of CT and stimulation condition, F (1, 112) = 1.238, p =.268, CT and imagery condition, F (1, 112) = .001, p =.974, or imagery and stimulation conditions F (1, 112) = 2.035, p =.157. There were also no significant main effects of stimulation, F (1, 112) = 1.037, p =.311, imagery, F (1, 112) = .000, p =.989, or level of CT, F (1, 112) = 1.169, p =.282.

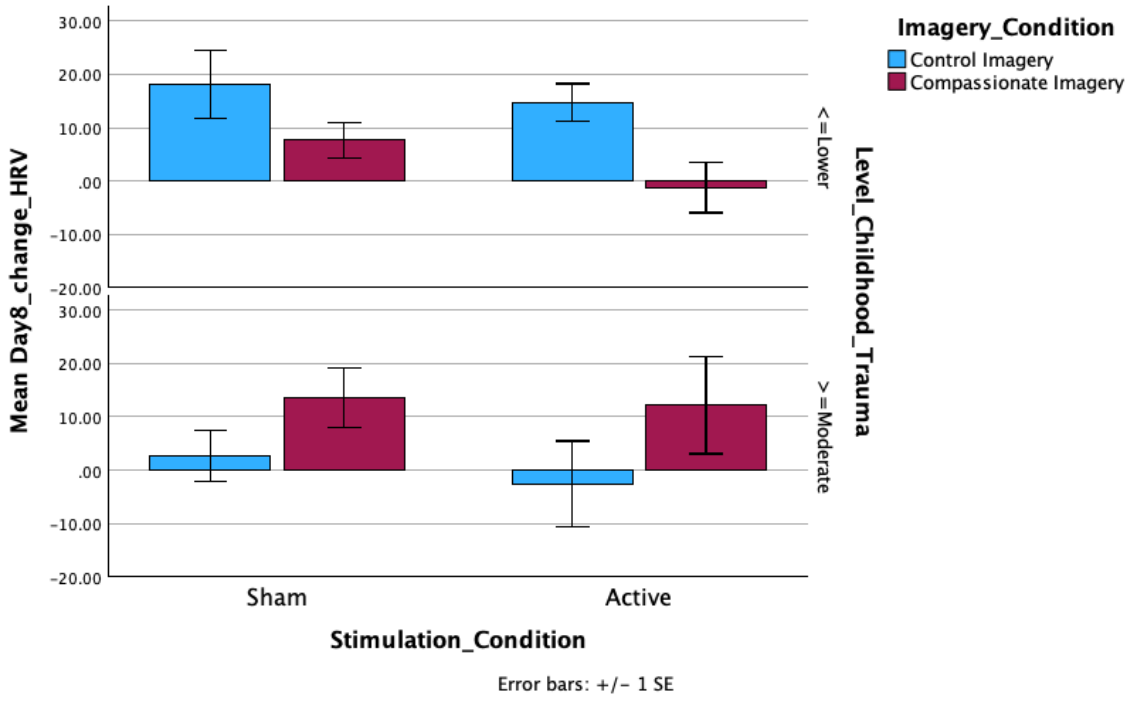
Heart Rate Variability: Root Mean Square of the Successive Differences

Figure 10 shows the effects of stimulation and imagery on longer-term change in HRV in the two CT severity categories. After the removal of extreme scores, there was usable HRV data for both t1 on day 1 and t3 on day 8 for 115 participants to enable calculation of longer-term change scores. Three-way independent measures ANOVA indicated that there was no significant three-way interaction between level of CT, stimulation condition, and imagery condition, F (1, 107) = .343, p =.559.

There was, however, a significant two-way interaction between level of CT and imagery condition, F (1, 107) = 12.887, p =.002. Simple main effects analysis revealed that there was a significant effect of CT for those completing the control imagery task, F (1, 107) = 8.539, (P=.004), whereby those in the '≤ lower' category of level of CT showed a significantly greater increase (*M* = 16.391, *SE* = 3.64, 95% CI [9.18, 23.60]) than those in the '≥ moderate' category of level of CT showed a much smaller increase, (*M* = .050, *SE* = 4.247, 95% CI [-8.37, 8.47]). There was no significant simple main effect of level of CT for those completing the compassionate imagery task, F (1, 107) = 2.823, (p=.096). There was a significant simple main effect of imagery for those in the '≤ lower' category of level of CT, F (1, 107) = 6.859, (p=.010), whereby those completing the control imagery task showed a significantly

greater increase in HRV, (*M* = 16.391, *SE* = 2.65, 95% CI [10.55, 21.03]), than those completing the compassionate imagery task showed a smaller increase (*M* = 3.2193, *SE* = 3.47, 95% CI [-3.67, 10.12]). The pattern of results was the opposite for those in the '≥ moderate' category of CT. There was a significant simple main effect of imagery, F (1, 107) = 4.216, (p=.042), whereby those completing the compassionate imagery task showed a significantly greater increase (*M* = 12.887, *SE* = 4.59, 95% CI [3.79, 21.98]) than those completing the control imagery task (*M* = .050, *SE* = 4.247, 95% CI [-8.37, 8.47]).

Figure 10. *Heart Rate Variability: Mean Change in RMSSD between Pre-Stimulation on Day 1 and Post-Imagery on Day 8*



Note. The error bars represent +/- 1 standard error of the mean. Change scores were calculated by subtracting t1 Day 1 mean from t3 Day 8 mean. An increase is desirable for this outcome, representing an increase in vagal tone.

There were no significant two-way interactions between CT and stimulation condition, F (1, 107) = .119, p =.731, or imagery and stimulation conditions, F (1, 107) = .010, p =.919. There were also no significant main effects of stimulation, F (1,

107) = 1.365, p =.245, imagery, F (1, 107) = .002, p =.967, or level of CT, F (1, 107)

= .692, p =.407.

Summary of Results

Table 3. *Summary of Findings for Each Outcome of Interest in Terms of Main Effects and Interactions Involving Level of Childhood Trauma*

Outcome		Any Significant Main Effect or Interactions Involving Level of Childhood Trauma
Short-Term Changes:	State Self-Compassion	None
	State Safe-Content Positive Affect	None
	State Mindfulness	None
	Heart Rate Variability (HRV)	Significant Imagery-by-Level of Childhood Trauma Interaction. Opposing effects of imagery practice depending on level of childhood trauma. Higher levels of childhood trauma achieved more desirable change (increase) in HRV.
Longer-Term Changes:	State Self-Compassion	None
	State Safe-Content Positive Affect	None
	State Mindfulness	None
	Heart Rate Variability	None
	Trait Self-Compassion	None
	Trait Mindfulness	None* (Apparent 3-way Imagery-Stimulation-Level of Childhood Trauma but did not remain when conducting post-hoc tests)

Discussion

The current study was an exploratory secondary analysis of a study by Kamboj and colleagues (in prep). The original study investigated the effects of combining tVNS stimulation with compassionate imagery training, with sham controls for both the tVNS and imagery components. The current study aimed to investigate whether there were interactions between level of reported childhood trauma (CT) and the effects of tVNS stimulation and the compassionate imagery task.

No main effects or interactions involving level of CT (either two-way or three-way interactions with stimulation condition and/or imagery condition) were found for short-term change in HRV, state self-compassion, state mindfulness, or state levels of safe and content positive affect. Similarly, no interactions involving level of CT were found for longer-term change in state self-compassion, state mindfulness, or state levels of safe/contentment positive affect, or trait self-compassion. As such, the exploratory analysis here added no further insight to the initial findings reported by Kamboj and colleagues (in prep) for these outcomes. There was an apparent three-way interaction for trait mindfulness, however, simple two-way ANOVAs at different levels of CT revealed no significant interactions or main effects involving stimulation or imagery condition.

There was however an apparent two-way interaction between level of CT and imagery condition on longer-term change in HRV that remained when conducting post-hoc simple main effects analyses. The study by Kamboj and colleagues (in prep) found no effects of stimulation or imagery condition on the longer-term effects on HRV (as measured by RMSSD) between day 1 and day 8, with all groups showing a generalised increase. The exploratory analysis here has added some

further insight to the initial analysis. Individuals' cardio-vagal response to the imagery tasks was dependent on their level of CT. Participants in the '≤ lower' category of level of CT responded with a greater increase in HRV between day 1 and day 8 when completing the control imagery task. Participants in the '≥ moderate' category of level of CT responded with a more desirable change in HRV to the compassionate imagery task compared to the control imagery task. They showed an increase in RMSSD score between t1 on day 1 and t3 on day 8, but a much smaller change when completing the control imagery task, with the difference between these two change scores significant.

The HRV change score results were surprising given the background literature and theories. Gilbert (2005; 2010) proposed that individuals' capacities for compassion were rooted in, and developed by, the attachment system. It is argued that when the attachment system development is influenced by experiences of emotional conflict, neglect and abuse, reactivation of the system will reactivate these emotional memories and bring with it difficult feelings. It is proposed that these re-emergent feelings can result in kindness and compassion being perceived as a potential threat, thus leading to a fight, flight or shut-down response (Gilbert, 2009; Kirby et al., 2019). These perceptions and reactivation of emotional memories are argued to partially underpin fears, blocks, and resistances to compassion that could pose a barrier to psychological therapy, including compassion-based interventions (Gilbert, 2005; 2010; Gilbert & Mascaro, 2017; Kirby et al., 2019). As mentioned in the introduction, there has been evidence showing that anxious attachment style was associated with adverse responses to compassion-focused interventions, specifically a decrease, as opposed to the desired increase, in HRV (Rockliff et al., 2008; Baldwin et al., 2019). Given the links between childhood and trauma and anxious

attachment style in adulthood, it was anticipated that individuals with higher levels of CT may experience difficulty with and show an adverse response when completing the compassionate imagery task, leading to a smaller increase, or even a decrease, in HRV, compared to those with lower levels of CT. This did not appear to be the case for either the short-term effects (day 1 change scores) or longer-term effects (day 8 change scores). In fact, it appears that individuals with higher levels of CT can achieve a beneficial effect on HRV change, in the longer-term following practice of a compassionate imagery task, compared to a control imagery task.

Those with lower levels of CT showed a greater longer-term HRV increase following the control imagery task compared to the compassionate imagery task and compared to the change scores following the control imagery task for those with higher levels of CT. The original study by Kamboj and colleagues expected a greater increase in HRV following the compassionate imagery task, rather than the control imagery task, but did not observe any effects of the imagery task (or stimulation). The lack of observed effect within the original study may have been due to unaccounted-for variance related to the level of CT.

There appeared to be no moderating effect of active tVNS stimulation on this pattern of results on HRV change between day 1 and day 8. This may be due to several reasons. Despite observing the hypothesised effect on state self-compassion, Kamboj and colleagues (in prep) highlight that the stimulation of the vagus nerve by tVNS achieved in their study was likely weak and imprecise (relative to invasive techniques, although invasive techniques are also somewhat imprecise). However, in their original study, Kamboj and colleagues found effects (some stronger and clearer than others) providing evidence that stimulation of the vagus nerve was

likely achieved. It may be that the interaction between level of CT and practice of imagery tasks is influenceable by tVNS, but given the relatively weak and imprecise nature of the tVNS used an effect was not visible. It me be that the differential effects of type of imagery practice depending on level of CT were not due to generalised differences in PNS functioning, and therefore not strongly influenceable by the addition of tVNS. As a result, this somewhat limits the strength of conclusions that can be drawn. Further research is needed to understand the neurobiological basis for the differential effects of imagery practice on HRV, depending on level of CT.

Overall, the pattern of results in this study do not provide strong evidence to suggest that participants with higher levels of CT may have disrupted PNS functioning resulting in smaller increases in HRV and self-report state or trait compassion following practice of a compassion-focused imagery task. There is mixed evidence of whether an association exists between experiences of CT and disrupted parasympathetic nervous system (PNS) functioning in adulthood, with some evidence suggesting dampened or disrupted functioning (Beilharz et al., 2020; Dale et al., 2018; Miskovic et al., 2009), and some evidence to the contrary (Shenk et al.,2014; van Ockenburg et al., 2015; Winzeler et al., 2015). A review (Young-Southward et al., 2019) of 22 studies of children (ages ranging from 2-19 years) who have experienced maltreatment found that most included studies reported a similar pattern of blunted SNS responsivity but more mixed findings for PNS responsivity.

The current study included only those who were not receiving treatment for any mental health condition, those who were not significantly depressed or anxious, and those with no history of serious mental health conditions. This may mean that those in the current study who had experienced moderate levels of childhood trauma

had some resilience which meant they had not experienced mental health difficulties in the past or currently. It is important to hold this in mind when comparing to previous literature. The studies by Rockliff et al. (2008) and Baldwin et al. (2019) also used a sample of healthy adults (university students) and are therefore comparable to the current study. Two of the studies providing evidence suggestive of dampened or disrupted functioning were also comparable, non-clinical samples, (Beilharz et al., 2020; Dale et al., 2018). It therefore does not appear that the nature of the current study's sample excluding those with past or current history of mental health difficulties explains the disparity in findings when compared to this previous literature.

In their review Young-Southward et al. (2019), discussed two theoretical models that may be relevant for understanding the variable relationship between history of childhood maltreatment, ANS functioning and later psychopathology risk, the differential susceptibility theory (DST; Belsky et al., 2007) and the adaptive calibration model (ACM; Del Giudice et al., 2011). The DST proposes that children vary in their susceptibility to both positive and negative environmental influences, and that those most susceptible suffer the worst outcomes when exposed to poor/harmful parenting behaviour, such as childhood maltreatment. DST argues that these differences in susceptibility may be the result of genetic or other biologically based factors including differences in the responsivity of stress systems. The ACM (Del Giudice et al., 2011) argues that individual differences in responsivity of the stress systems are the result of an individual's adaptation to their environment, including highly stressful conditions during early life experiences. Young-Southward et al. (2019) propose that it follows from the ACM model that experiences of childhood maltreatment could result in an adaptation of a very reactive autonomic

nervous system to allow the child to detect threats and take appropriate action, or conversely could result in an adaptation of low reactivity of the ANS to threat to allow insensitivity to their context of persistent and severely stressful experiences. In the current study, those with higher levels of CT appeared to have neither a generalised more reactive or less reactive PNS. As such the results presented here do not appear to offer support for either the DST or the ACM. Whether, and if so of what kind, a clear pathway exists between experiences of CT, altered PNS functioning, and response to psychological treatments incorporating compassion-focused techniques remains unclear and requires further investigation.

Limitations

The method of creating binary categories of level of CT was deemed the most appropriate method due to sample size constraints which would not allow for more fine-grained categories, and so to allow for a parsimonious statistical approach. However, this approach did not permit examination of the specific effects, for example of different types of abuse/neglect or different levels of severity of CT. In addition, there is evidence of dose-response relationships with CT (i.e. poorer outcomes in those who have experienced more instances of CT; Edwards et al., 2003; England-Mason et al., 2018). A more fine-grained approach with more than two levels may have revealed additional effects.

Although the original study by Kamboj and colleagues aimed to directly test the role of vagal activation in compassionate behaviour, stimulation of the vagus nerve by tVNS is relatively weak and imprecise compared to invasive vagus nerve stimulation. Within the current study, this somewhat limits the confidence of conclusions that can be drawn about whether the effects on HRV in relation to the

combination of imagery task and CT category were in part due to differences in PNS function that is influenceable by tVNS. However, the results from the original study by Kamboj and colleagues (in prep) did find some effects of tVNS (some clearer than others), to suggest at least some stimulation of the vagus nerve had been achieved.

As noted in the methods section, the sample size of the study was determined by a power calculation for the purposes of the original study by Kamboj and colleagues (in prep). This power calculation related to a specific hypothesis they had for which they expected to detect a difference equating to a relatively large effect size. The current study was exploratory and did not expect to detect similarly large effect sizes. It is highly likely that the current study was therefore underpowered. This raises the possibility of both type 1 and type 2 errors. It is possible that true effects for some of the state and trait outcome measures were missed due to the relatively small group sizes and the impact of variance and measurement error. Furthermore, there is a possibility that the significant interaction detected for longer-term change in HRV was a type 1 error, again due to the relatively small group sizes and the impact of variance and measurement error. In relation to the finding for longer-term change in HRV, whilst a high quality, validated heart rate monitor was chosen, there was likely still some measurement error in the HRV measurement. Therefore, the results of the current study should be interpreted with some caution.

The lack of an apriori power analysis is a further related limitation of the current study. It would have been helpful to determine in advance the approximate extent to which the study would be underpowered. One option was to conduct a post-hoc power analysis, but it has been documented that these are not helpful and potentially meaningless (Althouse, 2020; Levine & Ensom, 2001).

The original study by Kamboj and colleagues (in prep) had an inclusion criterion for participants to be aged 18-35 years, so that the study was more comparable to other related literature. This does however have some implications for the current study reported here. In particular, it may limit the generalisability of the results to older participants. The pathway between experiences of childhood trauma, altered parasympathetic nervous system functioning, and response to compassion-based psychological interventions would be longer in years for an older person. A pathway over a longer number of years may also be more complex. The pattern of results in the current study may relate to resilience, potentially of a biological or genetic basis (see differential susceptibility theory). An older person may have had more of an opportunity to build resilience of another (non-bioliogical/genetic basis), or for other factors or events to be included in a pathway between experiences of childhood trauma, altered parasympathetic nervous system functioning, and response to compassion-based psychological interventions. As a result, this may limit the generalisability of results to older participants than those included in the study here. Future research could extend the current study to explore whether a similar pattern of results is found for older participants.

The current study excluded who were currently experiencing or had a history of mental health difficulties. This may mean that the group of individuals who had experienced moderate levels of childhood trauma and neglect may have some resilience that meant they had not experienced mental health difficulties in the past or currently. This may limit how generalisable the results are to individuals typically seen within clinical services, where greater levels of childhood abuse and neglect are associated with greater levels of, and more complex, mental health difficulties.

The current study required completion of at-home stimulation and imagery practice on days 2-7. This had benefits of enabling a larger number of practice sessions within the procedure without vastly increasing the time and resource demands of the study team, and without requiring participants to attend in person on many occasions. There was however some uncertainty about the extent to which participants followed the imagery task instructions at home. Unfortunately, this is an inevitable consequence of using at-home study requirements and does affect the confidence around treatment fidelity of the interventions within the current study. Members of the research team contacted participants when they had not logged on to the study site the previous day, to encourage completion of the at-home study requirements. This however prevented a more valid assessment of the acceptability of the intervention (i.e. it prevented observation of engagement with at-home study requirements without any intervention following missed sessions).

To conclude, there were notable limitations in the study in terms of method of categorisation of CT, a likely lack of statistical power, uncertainty about the strength and precision of vagal nerve stimulation achieved by tVNS, potentially poor generalisability to older individuals and individuals with current or past mental-health difficulties, and uncertainty about fidelity of at-home study requirements. Despite these limitations, the current study provides useful and relatively good evidence to add to this body of literature to help further the understanding of the relationship between CT, disrupted functioning of the parasympathetic nervous system, experiences of compassion-based interventions, and psychopathology risk. Future research that overcomes some of these limitations would be valuable.

Future Research

Future research should seek to further understand the effect of experiences of CT on outcomes with compassionate imagery practices/compassion-focused interventions. Although there is not a compelling rationale at this stage to perform larger studies that permit a more complex approach to CT (e.g. by type of trauma and/or exploring more levels than the two used here), accumulation of data from related studies might allow this idea to be examined in the future with larger sample sizes. Future research without the tVNS component would allow use of a similar statistical approach as used in Kamboj et al. (in prep) with the inclusion of time-related factors, to allow investigation of more nuanced patterns of change over time using raw scores, as opposed to change scores as in the current study. This was deemed not appropriate in the current study as it would have required exploration of four-way interactions with factors of time, imagery, stimulation, and level of CT in a study with a relatively small sample. Aside from being challenging to interpret such analysis would likely be very underpowered to detect four-way interactions. Future research investigating the effect of experiences of CT on compassion focused interventions with both non-clinical samples and clinical samples who are not seeking treatment directly in relation to the traumatic experiences (i.e. not seeking treatment for PTSD resulting from their experiences of CT) would be valuable.

Conclusions

This research aimed to further explore the findings from an initial study by Kamboj and colleagues (in prep) that investigated the effects of combining tVNS with a compassionate imagery task. Specifically, it aimed to investigate whether the effects found within the initial study interacted with participants' level of childhood

trauma (CT). Findings from this study suggested that this was largely not the case. The initial study by Kamboj and colleagues (in prep) found no interaction between imagery condition and time on HRV. The current study suggested that there was an interaction between imagery condition and level of CT on longer-term HRV change. However, this was not in ways that fit with existing theories and research around fears, blocks and resistances to compassion, and research suggesting a possible pathway between CT, disrupted functioning of the parasympathetic nervous system, and psychopathology risk.

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Part 3: Critical Appraisal

Introduction

This critical appraisal will begin with an introduction of my personal and professional contexts that informed my choice of joining a research project investigating the neuroscience of compassionate behaviour and compassion-focused psychotherapeutic interventions, including compassionate mind training (Gilbert, & Procter, 2006). I will discuss the impact of conducting both the empirical paper and systematic review, considering my interests and theoretical orientation within the field of clinical psychology. Lastly, I will reflect on the impact of the research process on my professional and personal learning.

Locating myself in the Research

I come from an Indian background and as such was exposed to contemplative traditions and spirituality from a young age. I grew up learning about Hinduism, Buddhism, Yoga, breathwork and meditation practices through my family and cultural environment. Separate from this, an interest in science and psychology grew throughout my childhood and teenage years, university studies and early career, but these two areas of interest did not meet until later on.

Initially, in my psychology career, I was trained in low-intensity second-wave cognitive behavioural therapy and employed this with children, young people, and families, first within a child and adolescent mental health service and later in a paediatric psychology service. Often this approach was useful, but it did not always feel best suited to meet the needs of individuals experiencing objective, realistic challenges, such as young people living in challenging family environments or with long-term physical health difficulties. At this point, my supervisor encouraged my exploration of third-wave cognitive behavioural therapies, including acceptance and

commitment therapy (Hayes et al., 1999) and compassion-focused therapy (Gilbert, 2009). I was intrigued by the strong emphasis on some of the elements from the contemplative traditions, religion and spirituality I had been exposed to from a young age. I found these models extremely helpful for many individuals, but again not everyone. In particular, some individuals found engaging in some of the mindfulness and imagery elements of these models challenging or found it challenging to respond to difficulties they were experiencing in self-compassionate ways despite engaging consistently with in-session and between-session practices.

Throughout this time, I had found the focus on an evolutionary-based neuroscientific model of compassion-focused therapy convincing and interesting but was somewhat frustrated by individuals discussing the model as if it was proven beyond any doubt and presenting the *theory* as *fact* (although this is by no means an issue limited to compassion focused therapy). Upon starting the doctorate in clinical psychology, the opportunity to join a research project investigating the neuroscience of compassionate behaviour and compassion focused psychotherapeutic interventions was therefore highly appealing.

After assisting with the data collection for the project, I explored possible exploratory research questions I could take up for my doctoral thesis. One such option was investigating whether there was a moderating influence of the experience of childhood trauma within the study. In the preceding year, I had completed a placement at an increasing access to psychological therapies (IAPT) service. The service had been running a compassion focused therapy group intervention, for which they had included an exclusion criterion of anyone who had experienced significant levels of interpersonal trauma. This turned out to be a significant number

of people referred to the group. The exclusion criteria was justified with reference to theory around fears, blocks and resistances to compassion.

Gilbert (2005; 2010) has proposed that individuals' capacities for compassion are rooted in and developed by the attachment system and that when the attachment system development is influenced by experiences of emotional conflict, neglect, and abuse, reactivation of the attachment system will reactivate these emotional memories and bring with it difficult feelings. It's argued that these re-emergent feelings can result in kindness and compassion being perceived as a potential threat, leading to fight, flight or shutdown (Gilbert, 2009; Kirby et al., 2019). This was argued to partially underpin fears, blocks, and resistances to compassion, that could pose a barrier to psychological therapy, including compassion-based interventions, but also could be targeted through compassion-based interventions (Gilbert, 2005; 2010; Gilbert & Mascaro, 2017; Kirby et al., 2019).

Whilst this to me seemed a well-argued theory, there did not appear to be a significant amount of research evidence investigating the relationship between experiences of childhood trauma and outcomes and experiences within compassion focused interventions. My supervisor was supportive of my interest in exploring the question of '*what is the impact of childhood trauma?',* within the primary study that was underway.

Conducting Research with At-Home Study Requirements

As mentioned in the limitations section of part 2, related to the empirical study, the participants were required to complete at-home stimulation and imagery practice on days 2-7. This had the benefit of enabling a larger number of practice sessions within the procedure without vastly increasing the time and resource demands of the

study team, and without requiring participants to attend in person on many occasions. There was however some uncertainty about the extent to which participants followed the imagery task instructions at home. Unfortunately, this is an inevitable consequence of using at-home study requirements and does affect the confidence in treatment fidelity of the interventions within the current study. In order to address this, we discussed as a research team how best to intervene if we noticed participants did not log in to the study site or did not appear to be completing the full length of stimulation.

On the one hand, if we did not intervene, this would offer good insight into the acceptability of the at-home imagery and stimulation tasks, or the motivation of participants to complete the tasks. On the other hand, if we chose to intervene when it appeared participants were not engaging with the at-home study tasks, we would reduce missing data and increase intervention fidelity and potentially give us the best chance of observing any true effects. Ensuring there was little missing data and giving us the best chance of observing true effects felt like the priority. We agreed to contact participants the following day if it did appear they had not completed the at-home tasks correctly or at all, to gently enquire how they were getting on and to make sure they understood the study requirements. We then agreed to add a question to ask people to report honestly how much they were engaging in the imagery practice. In fact, there appeared to be good fidelity for the at-home study requirements, and only occasionally were the research team required to contact participants. It only required a few minutes each day for one of the research team to check at-home study task completion, and saved many hours of work compared to if the sessions were to be completed in the research laboratory instead. I would encourage future researchers to be open to conducting research with at-home study

requirements, even in studies with complex procedures, as a way to manage resources but also to assess the acceptability of an intervention.

Conceptualising and Operationalising the Variable of Childhood Trauma

Once the decision had been made to explore the interaction of the level of childhood trauma with the effects of stimulation condition and imagery condition in the original study by Kamboj and colleagues (in prep), it was necessary to decide how to operationalise the variable of childhood trauma. This was not an entirely simple decision to make as it was possible to use the childhood trauma questionnaire short-form (CTQ-SF; Bernstein et al, 2003) in a number of ways. For example, it was possible to use the total score on the CTQ-SF as a continuous predictor variable, total scores on each subscale of the CTQ-SF as continuous predictor variables, categorisation on each of the subscales as individual categorical predictors, or in some other categorical way.

My supervisor advised me to look at existing research and consider whether it made more theoretical sense to think about childhood trauma as a categorical or continuous variable. It seemed to me as if it could be conceptualised as both, as trauma is something you have either experienced or not (i.e. it is categorical) but I was also aware of dose-response relationships with CT (i.e. poorer outcomes in those who have experienced more instances of CT; Edwards et al., 2003; England-Mason et al., 2018). I looked at other research to see how it was operationalised and discovered it was treated in different ways in different pieces of research. Beilharz et al. (2016) conducted a study of the impact of childhood trauma on psychosocial functioning and physical health in a non-clinical community sample of young adults and defined a participant as a case of childhood trauma if their total score was

greater than 36 and each subtype of trauma was categorized as a case if it was scored in the ‘slight’ to ‘extreme’ range (with a different cut-off for each subscale, as advised by the scoring guide). In another example, Cakir et al. (2016) conducted a study of the relationship between experience of childhood trauma and treatment outcome in bipolar disorder and utilised the total score on the CTQ-SF and scores on each of the subscales as continuous predictor variables. Evidently, there were different approaches I could feasibly take. It occurred to me that taking a continuous approach using the CTQ-SF total score would treat a single-point increase due to experience of sexual abuse as equal to a single-point increase due to experience of emotional neglect. This felt problematic and in fact, the cut-offs in the published scoring guide (Bernstein et al., 1998) for each subscale are different to reflect the nuance needed to interpret experiences of childhood trauma. Taking this into account and after some deliberation and discussion with my supervisor, the decision was made to create a two-level categorical dummy variable from the CTQ-SF, using the published scoring guide. This was deemed most appropriate on the balance of options and with the sample size available, and also allowed for a parsimonious statistical approach using univariate ANOVAs.

The process of operationalising the level of childhood trauma highlighted to me one of the challenges of conducting secondary exploratory research, where the study design and sample size has been created for the primary research study and can result in methodological challenges and can limit the options available one can take. I was left with a sense of wondering if interactions could have been discovered with a different, tailor-made research design. For example, seeing as compassion focused approaches have a strong focus on affiliative emotions, I wondered whether there may be strongest effects for emotional abuse for example. In addition, there is

some evidence that type of traumatic experience may be an important factor in predicting later effects on ANS responsivity (Stevens et al., 2023), with greater levels of childhood abuse predictive of lower HRV whereas greater neglect was predictive of higher HRV. Nonetheless, it was a good starting point for exploring the research question. I do not wish to discourage future clinical psychology doctorate trainees from conducting exploratory secondary research, but I have learned the reality that you may need to compromise on the theoretically most appropriate approach with an approach that is workable with the sample size available in secondary research.

Completing a Research Project with a Neuroscientific Focus

As previously stated, I had found the evolutionary-based neuroscientific model of compassion-focused therapy convincing and interesting. More generally, I had found neuroscientific models for other psychotherapeutic processes interesting, but I had not spent much time exploring them. When completing the systematic review (part 1) of this volume, I was interested by the research I came across but was at times bothered by the sole focus on neurobiological processes with very little discussion of the psychological processes. As someone undertaking their training in clinical psychology, this was striking. I had anticipated the area of research I was exploring in my systematic review to be balanced at the intersection of the fields of neuroscience and psychotherapy, but at times it lent much more toward the former.

What was more bothersome as time went on was the sense of an individualistic focus in this avenue of research – essentially it was trying to answer the questions of '*how can we understand what is going on in the brain during psychotherapeutic processes'* and '*how can we use technology to optimise individual psychotherapeutic outcomes?'.* Whilst this is interesting to me, and in an ideal world

could translate into improved practice in the near future, it did not align with my growing sense that it is essential to take a more systemic approach to psychological difficulties, for example, thinking about the individual in context and thinking about how the context can be shaped to better prevent and support individuals' mental ill-health. This felt particularly pertinent as the cost-of-living crisis unfolded in the UK during the course of my studies. With regards to the cost-of-living crisis, it feels paramount to take a more preventative and population-based approach, when the largest crises unfolding currently in the UK are in relation to housing and the increasing rates of people living in poverty. This certainly created some tension at times throughout the research process as I questioned the value of conducting research in an area that is inherently individualistic. In addition, it was becoming increasingly clear how stretched the NHS resources and budgets were. The possibility of NHS psychology services being able to regularly make use of non-invasive brain stimulation technology any time in the near future seemed highly unlikely.

Nonetheless I am content with choice of research and have found it very interesting. I still think and hope the avenue of research could be useful to the clinical practice in the future. I have learned that one of the most interesting things about being a trainee clinical psychologist, and I assume too about being a qualified clinical psychologist, is this opportunity to explore multiple different avenues all in the same topic – whether that be neuroscientific, psychodynamic, systemic, cognitive, spiritual or any combination of these. It was enjoyable and interesting to conduct research in a topic that integrated different strands.

Conducting a Technically Challenging Study

I assisted with the data collection of the primary study by Kamboj and colleagues (in prep). This was a complex and technically challenging study that involved the use of a computer, a heart-rate monitor, a transcutaneous vagus nerve stimulation device, and eye-tracking equipment. At the start of the research process, I spent time running through the experiment procedure with a member of the research team once, and then observed another member of the research team conducting the procedure with a participant, before commencing data collection on my own. Whilst this familiarisation process was helpful, I certainly was not totally familiar and comfortable with the technology during early experimental sessions. In particular, the eye tracking equipment was somewhat temperamental, particularly with participants who wore corrective glasses. In addition I struggled with the downloading the data from the heart rate monitor device quickly in between back-to-back experimental sessions. During moments when things went slightly wrong with the eye-tracking equipment, I tried to stay calm and adjust the settings. Most participants were very patient when this did occur, but I noticed some became a little unsettled and seemed to react as if they had done something wrong. I found it helpful to reassure them that I did not think they had done anything wrong, and that the system can be a bit temperamental.

Fortunately, a member of the research team had created a crib sheet to help problem solve difficulties with the eye-tracking equipment. I would strongly encourage future researchers conducting research with eye-tracking equipment to do something similar. In addition, I could have benefited from more repeated dry runs of the experimental procedure before commencing data collection on my own. I would encourage future researchers to heed this advice and ensure they are very familiar with their experiment equipment. This would enable the procedure to run as

smoothly as possible and prevent participants from becoming a little unsettled when things do go wrong, and so that difficulties can be addressed more calmly and confidently. Finally, it may have been helpful in the early stages of data collection to have ensured larger gaps between back-to-back participants to allow for time taken up by technological challenges.

Determining the Scope of the Systematic Review

Initially, when discussing with my supervisor a topic and question for part 1 of my thesis, the systematic review, we settled on a much broader question than the final question I settled on. To start with, I planned to conduct a meta-analysis investigating the effect of combining any kind of non-invasive brain or neurostimulation with any kind of psychotherapeutic technique for any kind of psychological disorder. I was reassured by my supervisor that whilst this may result in a large number of included studies, it was manageable to conduct a review with sixty to seventy studies plus. I was somewhat daunted by this, but I heeded their advice. However, I soon discovered when conducting the title and abstract searching that there was a much larger than anticipated number of studies that met the inclusion criteria. As such I adjusted the plan and settled on just including studies of anxiety disorders and trauma-related disorders. Later on, I discovered that it was not possible to include many studies in a meta-analysis due to the data that was available or made available after contacting the corresponding author and as such I complemented the meta-analysis with a narrative synthesis. Knowing this now, it may have been possible to continue with the original much broader research question, as it is likely that many studies, although meeting the inclusion criteria on face value would not be included in a meta-analysis due to the available data. I

would encourage future researchers conducting a meta-analysis as part of the doctorate in clinical psychology to hold this in mind when determining the scope of their research question.

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Appendix 1: Search strategy for systematic review

Stimulation search terms:
“"noninvasive" AND “neurostimulation"” OR “"non-invasive" AND “neurostimulation"” OR “"noninvasive" AND “brain stimulation"” OR “"non-invasive” AND “brain stimulation"” OR "NIBS" OR “tvns" OR "transcutaneous vagus nerve stimulation" OR "TDCS"
OR "Transcranial direct current stimulation" OR "TACS" OR "Transcranial alternating current stimulation" OR "TMS" OR "rTMS" OR "Transcranial magnetic stimulation" OR “repetitive transcranial magnetic stimulation”

Psychotherapeutic technique search terms:
“psychother*” OR “psychological treatment” OR “psychological therapy”OR “extinction” OR “exposure therapy” OR “acceptance” OR “reappraisal” OR “bias modificationOR cognitive behav*OR “cognitive control” OR “emotion* regulation” OR “compassion*” OR “meditat*” OR “mindful*” OR attention*” OR “ control” OR “habituation” OR “inhibitory learning” OR “retrieval inhibition”

Anxiety and trauma disorder search terms:
“posttraumatic stress disorder” OR “Traum*” OR “*stress disorder” “anxiety” OR “*phobia”

N.B: Anxiety and trauma disorder search terms, Psychotherapeutic technique search terms, and Stimulation search terms were combined with Boolean operator “AND” for all four databases searched (EMBASE, MEDLINE, PSYCINFO, and Web of Science).

Appendix 2: Full risk of bias ratings and notes related to decisions made for certain items

	Domain 1. Randomisation process				Domain 2. Blinding of Participants and Personnel			Domain 3. Blinding of outcome assessors		Domain 4. Missing outcome data			Domain 5. Selective reporting		Overall Rating
Study	**1.1**	**1.2**	**1.3**	**Overall**	**2.1**	**2.2**	**Overall**	**3.1**	**Overall**	**4.1**	**4.2**	**Overall**	**5.1**	**Overall**	
Nasiri et al. 2020	Y	NI	Y	U	Y	PY	M	N/A	L	Y	**N/A**	L	N	H	U
Isserles 2013	NSR	NI	Y	U	Y	N	H	Y	L	Y	N/A	L	N	H	H
Kozel 2018	Y	Y	Y	L	Y	PY	U	Y	L	N	N	H	Y	L	U
Leuchter 2022	NSR	NI	N	U	Y	PY	U	Y	L	N	N	H	N	H	H
Notzon 2015	NSR	NI	Y	U	Y	NI	U	NI	U	Y	N/A	L	N	H	U
Bremner 2021	Y	Y	Y	L	Y	Y	L	Y	L	Y	N/A	L	N	H	L
Deppermann 2017	NSR	NI	Y	U	Y	PY	U	NI	U	N	N	H	N	H	H
Osuch 2009	N	NI	NI	H	Y	PY	U	Y	L	Y	N/A	L	N	H	H
Fryml 2019	NSR	NI	N	H	NI	NI	U	N/A	L	N	N	H	N	H	H
Isserles 2021	Y	Y	Y	L	Y	Y	L	Y	L	N	Y	L	Y	L	L
Herrmann 2017	NSR	NI	PY	U	Y	PY	U	NI	U	Y	N/A	L	Y	L	U
Van't Wout-Frank 2019	NSR	NI	Y	U	NI	NI	U	N/A	L	Y	N/A	L	Y	L	U

Note: “y” = yes, “N” = no, “NSR” = non-specific random, i.e. said it was random but not specified a method, “PY” = partially yes, “NI” = no information, “N/A” = not applicable, “L” = low risk of bias, “U” = unclear risk of bias, “H” = high risk of bias.

Extra notes relevant to decision making process for each study

Nasiri et al. 2021: For selective reporting of outcomes, the analysis plan was not pre-registered. Whilst the authors did report all primary outcomes there did appear to be some selective reporting of post-hoc comparisons whereby the authors only state in text comparisons that are in line with hypothesised outcomes and do not acknowledge or speak to post hoc comparisons that one would assume were not significant and therefore not in line with the hypotheses. As a result, this item was rated N and the overall rating for this domain was rated as H.

Isserles et al . 2013: For selective reporting, whislt the authors speak to all outcomes, the full data was not discernible from the paper due to some data only being shared in graph format which was near-impossible to read due to formatting. Furthermore, the article describes the results for preplanned contrasts but there is no way of knowing whether these were in fact pre planned, as they were not recorded or published anyway before the study began. As a result this item was rated N and the overall rating for this domain was rated as H.

Kozel et al. 2018: Nothing of note to add.

Leuchter et al. 2022: For selective reporting, the analysis plan was not pre-registered.

Notzon et al. 2015: This study involved a VR challenge as one of the outcomes. It is not clear whether this involved experiment personnel, and thus it was unclear whether there would have been a necessity to ensure that these personnel were blind to the allocated condition of each participant. Therefore, for the domain of Blinding of outcome assessors, a rating for the item of NI and an overall rating for this domain of M was given.

Douglas Bremner et al. 2021. For selective reporting, the analysis plan was not pre-registered.

Deppermann et al. 2017: For selective reporting of outcomes, the analysis was not pre-registered. In the supplementary material the authors report outcomes in subscale form rather than in total, without any explanation and in a way that is inconsistent with the outcomes reported in the paper for the other timepoints. As a result the item for this domain was rated N and the overall domain rated H.

Osuch et al. 2009: Randomisation process described only as consecutive assignment. For selective reporting of outcomes, the analysis was not pre-registered.

Fryml et al. 2019: For randomisation, no statistical test was reported that allowed assessment of whether groups were equal at baseline for the outcome measures. The HRSD in particular appeared unequal between groups. After conducting a t-test using the reported sample size, means and standard deviations, there was found to be a significant difference between the two groups baseline means for the HRSD ($p<.05$). This should have been reported in the paper and addressed. As a result, this item was rated as N and the overall domain was rated as H. For selective reporting, the analysis plan was not pre-specified or recorded. Furthermore, means for all time points and all outcomes were not reported and not all statistical tests were reported. As a result, the item was rated as N and the overall domain was rated as H.

Isserles et al. 2020: Nothing of note to add.

Herrman et al. 2017: For selective reporting of outcomes some means and standard deviations were not reported for the follow-up time point. As a result, the item for this domain was rated PY and the overall domain rated M.

Van't Wout-Frank et al. 2019: For Blinding of participants and personnel, the report simply states

that there was single blinding, with no further information. Therefore, for this item, the items were rated as NI and the domain given an overall rating of M.

Appendix 3: Means and standard deviations used for meta-analysis

3a: Means and standard deviations used for meta-analysis for self-report PTSD symptoms

PTSD Studies self-report	Author	Problem	Stimulation type	Exp Mean	Exp S.D	Exp N	Control Mean	Control S.D	Control N
1	Kozel et al., 18	PTSD	rTMS	39.25	12.25	31	42.35	13.86	30
2	Bremner et al., 21	PTSD	tcVNS	51	18	8	51	20	8
3	Van't Wout-Frank et al., 19	PTSD	tDCS	32.5	16.3	6	35.8	16.2	6

Note: Exp = experimental group, i.e. stimulation plus psychotherapy, control = psychotherapy alone

3b: Means and standard deviations used for meta-analysis for clinician-reported PTSD symptoms

PTSD studies clinician-reported	Author	Problem	Stimulation type	Exp Mean	Exp S.D	Exp N	Control Mean	Control S.D	Control N
1	Isserles et al. 13	PTSD	dTMS	61	8.8	9	76	10.7	9
2	Kozel et al. 18	PTSD	rTMS	45.94	22.49	31	53.86	25.52	30
3	Bremner et al., 21	PTSD	tcVNS	32	17	8	29	11	8
4	Fryml et al., 19	PTSD	rTMS	37.8	23.79	9	43.8	31.27	9
5	Isserles et al., 21	PTSD	dTMS	26.48	14.23	60	20.68	12.62	65

Note: Exp = experimental group, i.e. stimulation plus psychotherapy, control = psychotherapy alone

3c: Means and standard deviations used for meta-analysis for anxiety disorder symptoms

Study	Author	Problem	Stimulation type	Exp Mean	Exp S.D	Exp N	Control Mean	Control S.D	Control N
1	Nasiri et al., 2020	GAD & Dep	tDCS	10.54	2.44	13	11.87	3.52	15
2	Deppermann et al., 2017	Agoraphobia/PD	rTMS	14.91	6.9	22	15.34	8.3	22
3	Herrmann et al., 2017	Acrophobia	rTMS	36.3	18.7	20	43.2	19.4	19

Note: Exp = experimental group, i.e. stimulation plus psychotherapy, control = psychotherapy alone

Appendix 4. UCL ethics approval

UCL RESEARCH ETHICS COMMITTEE
OFFICE FOR THE VICE PROVOST RESEARCH

11th May 2021

Professor Sunjeev Kamboj
Research Department of Clinical, Educational and Health Psychology
UCL

Dear Professor Kamboj

Notification of Ethics Approval with Provisos
Project ID/Title: 0760/006: Transcutaneous vagus nerve stimulation (tVNS) and mental imagery

Further to your satisfactory responses to the Committee's comments, I am pleased to confirm in my capacity as Chair of the UCL Research Ethics Committee (REC) that your study has been ethically approved by the UCL REC until **31st December 2023**. Ethical approval is granted on condition that you:

1. provide the name and contact details of the researcher when appointed;
2. correct the following in your application and provide an updated version:
   (a): B2 still states that the DASS-21 is included in the online screening questionnaire, rather than the PHQ2 and GAD2.
   (b): B2 does not mention that the DASS-21 will be administered in session 1.
   (c): Appendix V still states that the DASS-21 scores will be used for screening and does not include the PHQ2 and GAD2 in the list of questionnaires.
   (d): Advert: GDPR 2018, not 2016.

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

Office of the Vice Provost Research, 2 Taviton Street
University College London
Tel: +44 (0)20 7679 8717
Email: ethics@ucl.ac.uk
http://ethics.grad.ucl.ac.uk/

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: https://www.ucl.ac.uk/srs/file/579
- 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 Lynn Ang
Joint Chair, UCL Research Ethics Committee

Appendix 5. Consent form for experiment

RESEARCH DEPARTMENT OF CLINICAL, EDUCATIONAL AND HEALTH PSYCHOLOGY

CONSENT FORM FOR HEALTHY ADULTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and have received satisfactory responses to any questions you have asked,

Title of Study: Transcutaneous vagus nerve stimulation (tVNS) and mental imagery
Department: Clinical Educational and Health Psychology
Name and Contact Details of the Researcher(s): Mr Matt Peniket; email: matthew.peniket.19@ucl.ac.uk
Name and Contact Details of the Principal Researcher: Prof Sunjeev Kamboj,sunjeev.kamboj@ucl.ac.uk
Name and Contact Details of the UCL Data Protection Officer: Alexandra Potts, data-protection@ucl.ac.uk
This study has been approved by the UCL Research Ethics Committee: Project ID number: 4277/001

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

I confirm that I understand that by ticking/initialling each box below I am consenting to this element of the study. I understand that it will be assumed that unticked/initialled boxes mean that I DO NOT consent to that part of the study. I understand that by not giving consent for any one element that I may be deemed ineligible for the study.

		Tick Box
1.	*I confirm that I have read and understood the Information Sheet for the above study. I have had an opportunity to consider the information and what will be expected of me. I have also had the opportunity to ask questions which have been answered to my satisfaction	
2.	*I understand that I will be able to withdraw my data up to *3 months after the submission of this informed consent form*.	
3.	*I consent to the processing of my personal information *including my age, assigned sex at birth, current identified gender, ethnicity, relevant health details and data collected for the purposes of this study* explained to me. I understand that according to data protection legislation, 'public task' will be the lawful basis for processing and 'research purposes' will be the lawful basis for processing special category data.	
4.	**Use of the information for this project only**	

	*I understand that all personal information will remain confidential and that all efforts will be made to ensure I cannot be identified. I understand that my data gathered in this study will be pseudonymised prior to secure storage. It will not be possible to identify me in any publications.	
5.	*I understand that my information may be subject to review by responsible individuals from the University or monitoring and audit purposes.	
6.	*I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without penalty, or my legal rights being affected. I understand that if I decide to withdraw during the study, any personal data I have provided up to that point will be deleted unless I agree otherwise. I understand that after completing all study procedures, my data will be used for the study and can no longer withdraw my data.	
7.	I have read the mental health information leaflet that accompanied the information sheet and understand how to access mental health support should I need it.	
8.	I understand the direct/indirect benefits of participating.	
9.	I understand that the data will not be made available to any commercial organisations but is solely the responsibility of the researcher(s) undertaking this study.	
10.	I understand that I will not benefit financially from this study or from any possible outcome it may result in in the future beyond.	
11.	I understand that I will be compensated for the time spent in the study (if applicable).	
12.	I understand that I will receive course credit or payment, which will be processed via bank transfer, after I complete the second lab session and return the tVNS device.	
13.	I understand that I will be loaned the tVNS device for at home stimulation and that I must look after it and return it to the lab on the second session	
14.	I understand that the tVNS device is only for use by me and only as instructed by the researcher.	
15.	I agree that I will not make any adjustments to the device or ear-clip.	
16.	I agree that my pseudonymised research data may be used by others for future research. No one will be able to identify you when this data is shared.	
17.	I understand that the information I have submitted will be published as a report and I can request a copy of it.	
18.	I hereby confirm that I understand the inclusion criteria as detailed in the Information Sheet and explained to me by the researcher.	
19.	I hereby confirm that: (a) I understand the exclusion criteria as detailed in the Information Sheet and explained to me by the researcher; and (b) I do not fall under any exclusion criterion.	
20.	I have informed the researcher of any other research in which I am currently involved or have been involved in during the past 12 months.	
21.	I am aware of who I should contact if I wish to lodge a complaint.	
22.	I voluntarily agree to take part in this study.	
23.	**Use of Data:** Your name email, phone numbers and bank details will be stored for contact and reimbursement purposes for the duration of the study. These data will be stored separately to any other data on you. It is collected so that we can contact you to arrange sessions and organise your payment upon study completion. Your identifying data will be linked to anonymous study data via an alphanumeric code that contains no individually identifying information, but allows matching of your data across study sessions and measures. In order to ensure the same	

	participant number is used for the two lab sessions and the 'at home' sessions, we will need to keep a list of participant numbers and participants names. This pseudonymisation code we be stored on an encrypted, password protected file on UCL storage. This, and any other document with identifiable information, will never be sent by email. I would be happy for the anonymous data I provide to be archived at UCL. I understand that other researchers will have access to my pseudonymised data.	

If you would like your contact details to be retained so that you can be contacted in the future by UCL researchers who would like to invite you to participate in follow up studies to this project, or in future studies of a similar nature, please tick the appropriate box below.

	Yes, I would be happy to be contacted in this way	
	No, I would not like to be contacted	

_____	_____	_____
Name of participant	Date	Signature

_____	_____	_____
Researcher	Date	Signature

Appendix 6. Information sheet given to participants.

RESEARCH DEPARTMENT OF CLINICAL, EDUCATIONAL AND HEALTH PSYCHOLOGY

Participant information sheet for participants involved in research studies investigating transcutaneous vagus nerve stimulation

UCL Research Ethics Committee Approval ID Number: 0760/006

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

Title of Study: Transcutaneous vagus nerve stimulation (tVNS) and mental imagery.
Department: Clinical Psychopharmacology Unit, Clinical Educational and Health Psychology, UCL
Name and Contact Details of the Researcher(s):
Mr Matt Peniket; email: matthew.peniket.19@ucl.ac.uk

Name and Contact Details of the Principal Researchers:
Prof Sunjeev Kamboj; email: sunjeev.kamboj@ucl.ac.uk

The purpose of this information sheet:

We would like to invite you to participate in a research project at UCL. There is no obligation to take part. You should only participate if you want to; choosing not to take part will not disadvantage you. Before you decide it is important for you to understand why the research is being done, and what participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this and considering participation in the study.

What is the project's purpose?
This study involves a **non-invasive** method for stimulating the 'vagus nerve' with a *transcutaneous vagus nerve stimulation (tVNS)* device, which is attached to your ear. The vagus nerve is part of the peripheral nervous system (formed of nerves outside of the brain and spinal cord). In this study we are interested to know whether activating this nerve by stimulating the ear can affect different types of mental imagery capabilities (our ability to visualise things in our 'mind's eye').

Because the vagus nerve passes close to the skin of the ear, we will stimulate it to varying extents by applying small electrical pulses to different parts of the outer ear through an ear clip attached to a tVNS device. This is totally non-invasive and should not cause significant discomfort or pain. We hope our results will lead to methods of enhancing mental imagery capabilities, which could be useful for improving academic or physical (sports) performance, or for improving psychological treatments that involve mental imagery techniques.

Who are we recruiting?
We are asking men and women who are aged between 18 and 35 years old to take part. Participants must be fluent in spoken English and have good literacy skills, as well as good (including corrected) vision. To take part, you should not currently be experiencing or receiving treatment for any mental health, heart or neurological problems. You should also not have any inflammatory diseases or have experienced any chronic facial or ear pain. In addition, participants must not be regular heavy drinkers (i.e. regularly drinking more than 14 units per week) or regular users of recreational drugs (more than twice a week, excluding alcohol, tobacco and caffeine). You must be willing to abstain from any recreational drug use and heavy drinking for the week of the study. Women participants must not be pregnant nor likely to become pregnant during the study.

There are also some additional things we will need to ask you about to check whether you are eligible to take part.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You can withdraw at any time without giving a reason. If you decide to withdraw you will be asked what you wish to happen to the data you have provided up that point.

What is involved?
After you have completed the basic eligibility questions online, we will arrange a telephone call to ask a few more questions to make sure you are eligible. As part of the screening process, we will ask you about your physical and mental health. In addition, we will ask for some personal details, such as your name and contact details. If you are eligible, we will also ask you about your sex at birth, current ` and ethnicity. Women will also be asked about whether they use a contraceptive (and if so, which type), and the last time they had a period. If you are eligible, the study will involve coming to the lab at UCL in Central London on two occasions. We will lend you a tVNS device for 6 days because the study also requires you to do the stimulation at home before returning the device on the second session.

Sessions 1 and 2: You will come to the lab for two sessions, one week apart. Each sessions lasts approximately 2 hours. You will be asked to fill out questionnaires about your mood and personality and complete some computerised tasks that measure your response to various stimuli while we record your eye movements.

In order for us to understand the physiological effects of the stimulation, we will measure your heart-rate using some sticky probes applied to your chest and abdomen, as well as your breathing rate, using a belt that is tied around your chest. There is also a small device (like an oxygen saturation monitor) that we attach to one of your fingers. We will then attach the tVNS device to your ear. This is not painful, and most people report a tingling or pulsing sensation on their ear. After a period of stimulation you will complete some questionnaires and computer tasks. You will then listen to an audio recording that provides instructions on a mental imagery task. This lasts about 15 min and during this, we will ask you to imagine doing some simple arithmetic or to imagine relaxing and being kind to yourself. You will then complete some final questionnaires and tasks. The two lab sessions are very similar, although at the end of Session 1 you will receive some extra instructions at the end on how to use the tVNS device at home, and how to remotely access the imagery instructions that you listened to in Session 1. We will lend you the tVNS device which we will ask you to return on Session 2. You should be aware that as part of the protocol, we ask participants about troubling childhood experiences (including experiences of abuse and neglect). If you are likely to find this very upsetting, please do not participate. *We also ask you to complete a questionnaire that asks about your levels of stress, anxiety and depression. If you are likely to find this distressing, please do not participate***.**

At home stimulation (days 2-7): After Session 1 (on day 1), we will ask you to repeat the stimulation and imagery procures at home. This involves logging on to the experiment website and completing some questions, starting on the day after Session 1 (i.e. on day 2). You will then attach the ear-clip of the tVNS device as instructed, and switching the device on for about 45 min in total. For the first 30 min we will ask you to simply relax during the stimulation. You can listen to relaxing music or read during this period. After the 30 min, you will be alerted by the study webpage to play the audio of the imagery instructions, which last for ~15 min. After this you will complete some more brief questions. This procedure is then repeated on days 3,4,5, 6 and 7, before returning to the lab for Session 2 on day 8.

What are the risks of taking part in this study?
For most research it is not possible to guarantee absolutely no risk to you. However, for this study, we believe the risks of taking part are very low. Vagus nerve stimulation uses a small electrical current applied to the outer ear using a plastic clip which can be removed easily. This should not be painful. When we set up the stimulation we will ensure that the settings are not uncomfortable. If at any point you feel any discomfort it is very easy to remove the clip.

What are the benefits to me?
While there are no direct benefits to you for taking part, you will leave with the knowledge that you have contributed to our understanding of the effects vagus nerve stimulation on mental imagery, which could inform future research in clinical, health and sports psychology.

Will I receive compensation for giving my time?
When you complete both sessions you will be receive £80 to compensate you for your time and travel. If you are a UCL student, you can alternatively do the study for course credit. Please note, we cannot provide any further compensation for travel.

What if something goes wrong?
Should you wish to raise a complaint please contact the principal researcher (Prof Sunjeev Kamboj: sunjeev.kamboj@ucl.ac.uk). We will do our very best to resolve any issues. If you feel your complaint cannot be handled to satisfaction through these routes you can contact the Chair of the UCL Research Ethics Committee – ethics@ucl.ac.uk.

Will my taking part in this project be kept confidential?
All the information that we collect about you during the research will be kept strictly confidential. The only limit to this confidentiality is if we become concerned for your wellbeing or the wellbeing of someone else. Your data will be pseudonymised. This means that it can only be connected to you via a random code that only the researchers have access to. Once we have finished data collection, your personal details will be securely deleted and the data will become fully anonymous. At that point it will be impossible to link any personal details to your data (not even with a code). You will not be identifiable in any reports or publications. When the data is fully anonymised it may be shared with other researchers for the purpose of scientific research and publications only.

Use of Deception
Research designs often require that the full intent of the study not be explained prior to participation. Although we have described the general nature of the tasks that you will be asked to perform, the full intent of the study will not be explained to you until after the completion of the study.

What will happen to the results of the research project?

The results of the study will be published in scientific peer-reviewed journals and dissertations. Anonymous numerical data is made available to other researchers. If you would like to receive an overview of the study's results once it has been completed, please contact the investigator who will arrange for the findings to be shared with you once they are available.

Local Data Protection Privacy Notice:

The controller for this project will be University College London (UCL). The UCL Data Protection Officer provides oversight of UCL activities involving the processing of personal data, and can be contacted at data-protection@ucl.ac.uk

This 'local' privacy notice sets out the information that applies to this particular study. Further information on how UCL uses participant information can be found in our 'general' privacy notice:

For participants in research studies, click here

The information that is required to be provided to participants under data protection legislation (GDPR and DPA 2018) is provided across both the 'local' and 'general' privacy notices.

The categories of personal data used will be as follows:

- Name
- Phone number
- Email address
- Bank account number/sort code
- Ethnicity
- Mental health status
- Gender/sex

The lawful basis that will be used to process your personal data are: 'Public task' for personal data and' Research purposes' for special category data.

Your personal data will be processed so long as it is required for the research project. If we are able to anonymise or pseudonymise the personal data you provide we will undertake this, and will endeavour to minimise the processing of personal data wherever possible.

If you are concerned about how your personal data is being processed, or if you would like to contact us about your rights, please contact UCL in the first instance at data-protection@ucl.ac.uk.

Contact for further information
Name and Contact Details of the Researcher:
Mr Matt Peniket; email: matthew.peniket.19@ucl.ac.uk

Name and Contact Details of the Principal Researchers:
Prof Sunjeev Kamboj, Email: sunjeev.kamboj@ucl.ac.uk

Thank you for reading this information sheet and for considering taking part in this research study.

COVID-19 Information

Before your appointment:

We may contact you 24 hours before your appointment to go over the details of your visit and to confirm your current state of health using the NHS COVID-19 symptom questionnaire (https://www.nhs.uk/conditions/coronavirus-covid-19/symptoms/). All face-to-face interaction involves a risk of Covid-19 infection. The researcher you will be interacting with will have tested negative for Covid-19 via a Lateral Flow Test within 24 hours of the appointment, if appropriate. If you fall within an at-risk group, as defined by the NHS, or are sharing a household with an at-risk individual, we encourage you to carefully consider participating.

Arrival at the research facility:

Please make sure to arrive on time.

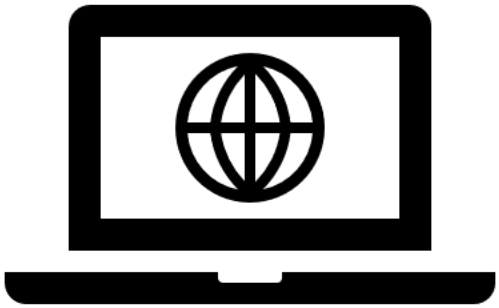
On arrival:

You may wear a face mask during the testing session: please tell the experimenter if you would prefer them to wear a mask

Appendix 7. Mental health information sheet given to participants

Mental Health Awareness &
How to Access Mental Health Services

Mental health services are free on the NHS.
In some cases you'll need a referral from your GP to access them.
There are some mental health services that allow people to refer themselves.



NHS Online
For local support and information services near you, you can search for:
Mental health support services
Mental health support services for young people

If you have concerns about your mental wellbeing, you'll find lots of tips and advice on dealing with stress, anxiety and depression in the MoodZone at https://www.nhs.uk/conditions/stress-anxiety-depression/
You can also try the mood assessment quiz, which is designed to recommend resources to help you better understand how you feel at https://www.nhs.uk/conditions/stress-anxiety-depression/mood-self-assessment/
This quiz uses questions that GPs often use to assess whether someone is anxious or depressed. It also includes links to useful information and advice on mental wellbeing.
You can compare mental health service providers using the services near you search tool. Enter the name of the mental health service or the service provider and your postcode at https://www.nhs.uk/service-search
This includes therapies like cognitive behavioural therapy (CBT) for common problems like stress, anxiety, depression, OCD and phobias. You can refer yourself directly to a psychological therapies service without seeing your GP at https://www.nhs.uk/service-search/Psychological-therapies-(IAPT)/LocationSearch/

Face-to-face
You can also make an appointment with your GP. You may like to take a printout of your quiz results along, but bear in mind that your GP won't be able to use them to make a diagnosis.
A GP will assess your circumstances and offer appropriate advice or treatment. They can also refer you to a psychological therapy service or a specialist mental health service for further advice or treatment.

If you have had thoughts of self-harming or are feeling suicidal, contact someone you can trust immediately, such as a GP or a friend or relative.
A mental health emergency should be taken as seriously as a medical emergency.

In an emergency

Examples of mental health emergencies include thinking you're at risk of taking your own life or seriously harming yourself and needing immediate medical attention.
Call 999 if you or someone you know experiences an acute life-threatening medical or mental health emergency.
You can go to A&E directly if you need immediate help and are worried about your safety.

On the phone

You can call NHS 111 if you or someone you know needs urgent care, but it's not life threatening.
For example:

- if you have an existing mental health problem and your symptoms get worse
- if you experience a mental health problem for the first time
- if someone has self-harmed but it does not appear to be life threatening, or they're talking about wanting to self-harm

If you want to talk to someone, the NHS mental health helpline webpage has a list of organisations you can call for immediate assistance at https://www.nhs.uk/conditions/stress-anxiety-depression/mental-health-helplines/
These are helplines with specially trained volunteers who'll listen to you, understand what you're going through, and help you through the immediate crisis.
Whether you're concerned about yourself or a loved one, these helplines and support groups can offer expert advice.
The Samaritans helpline is available 24 hours a day, 365 days a year, for people who want to talk in confidence. Call 116 123 (free).

Appendix 8. Imagery instructions

Imagery task (Lab Session 1)

CFI Script	Control Script
Introduction (Recording 1) Welcome to the mental imagery part of this study, which will explore your reactions to compassionate mental imagery – and in particular, mental images that are intended to produce compassionate feelings in *you* towards *yourself*. We're interested to know about your thoughts and feelings when you're trying to imagine being cared for and having compassionate feelings directed towards you. You might not be used to this…..to directing kind feelings towards yourself, and people respond in many different ways. There are no right or wrong ways to feel when you try it. Just flow with the instructions the best you can. As previously explained, one of the main things we're looking at in this study is the effect of stimulating a nerve that passes near the surface of the ear before going to the brain. This nerve is called the vagus nerve and we'll be stimulating it using a transcutaneous vagus nerve stimulator or tVNS device. TVNS might be an effective non-invasive way of activating brain processes involved in producing feelings of safeness and comfort, which are a prerequisite for self-compassion. As a result, stimulating the vagus nerve using tVNS might make it easier to form compassionate mental images. In this study we will examine your response to the mental imagery and stimulation procedures using questionnaires and measures of positive and negative feelings. We hope our findings will eventually help us to develop new treatment techniques for people with depression and other psychological disorders, in which self-compassion is often lacking. Before the mental imagery exercise, let me briefly explain what we mean by mental imagery. Mental imagery consists of our ability to form visual, auditory, and other sensory experiences in our minds. We use our ability to imagine in many different ways, for example, imagining what someone looks like when we've only heard their voice. Or we could imagine what they sound like when we've only seen their face. So, although visual imagery is common,	**Introduction (Recording 1)** Welcome to the mental imagery part of this study, which will explore your reactions to forming mental images of a person. We want to know how easily participants are able to form mental images of relatively unfamiliar people. We'll assess this by asking you to form mental images of the person whose picture you saw at the beginning of the experiment. This is the picture of the person that you rated for friendliness, approachability and trustworthiness. In particular, we'll be asking you to imagine drawing a picture of this person. You might not be used to this kind of mental imagery and people respond in many different ways. There are no right or wrong ways to feel when you try it, sojust flow with the instructions the best you can. As previously explained, one of the main things we're looking at in this study is the effect of stimulating a nerve that passes near the surface of the ear before going to the brain. This nerve is called the vagus nerve and we'll be stimulating it using a transcutaneous vagus nerve stimulator or tVNS device. TVNS might be an effective non-invasive way of activating brain processes involved in forming and manipulating mental images. As a result, stimulating the vagus nerve using tVNS might make it easier to form mental images. In this study, we will examine your response to the mental imagery and stimulation procedures using questionnaires and measures of positive and negative feelings. We hope our findings will eventually help us to develop new techniques for improving memory for faces that would otherwise be difficult to remember. This could have application in forensic cases, for example. Before the mental imagery exercise, let me briefly explain what we mean by mental imagery. Mental imagery consists of our ability to form visual, auditory, and other sensory experiences in our minds. We use our ability to imagine in many different ways, for example, imagining what someone looks like when we've only heard their voice. Or we could imagine what they sound like when we've only seen their face. So, although visual imagery is common, we can imagine scenarios using all of our senses.

we can imagine scenarios using all of our senses. Sometimes this happens easily, yet at other times we struggle to form clear images even when we try. Don't worry if this happens to you when you try the imagery exercise here. It's your efforts that are important rather than being able to form very clear images in your mind. After all, our mental images are often hazy and impressionistic rather than perfectly formed pictures in the mind. This is especially true when we're asked to imagine something unusual or something we don't imagine very often. But this ability can improve with practice. As mentioned previously, we'll be asking you to form compassionate mental images in today's task. We're testing the idea that stimulating the vagus nerve might be a way to improve a person's mental imagery ability. **~3 min 30 Secs** **Flesch-Kincaid Grade Level:** 10.9 *454 words*	Sometimes this happens easily, yet at other times we struggle to form clear images even when we try. Don't worry if this happens to you when you try the imagery exercise here. It's your efforts that are important rather than being able to form very clear images in your mind. After all, our mental images are often hazy and impressionistic rather than perfectly formed pictures in the mind. This is especially true when we're asked to imagine something unusual or something we don't imagine very often. But this ability can improve with practice. As mentioned previously, we'll be asking you to imagine drawing a picture of someone you've only seen once in a photograph. We're testing the idea that stimulating the vagus nerve might be a way to improve a person's mental imagery ability. **~4 min** **Flesch-Kincaid Grade Level:** 10.4 *490 words*
Expectancy/Credibility Assessment	
Record time before Recording 2:	Record time before Recording 2:
CFI (Recording 2) Now we'll start the section on self-compassionate mental imagery which involves imagining yourself receiving compassion. This task might test the limits of your imagination, so if while listening to the instructions you start to feel a little sceptical about this exercise or your ability to form compassionate imagery or to feel self-compassion, please try and suspend these judgements and stick with the instructions the best you can. Treat it like an experiment to see whether you can form these types of mental images. In a few minutes, we'll ask you to create a mental image in which you imagine yourself to be the focus of a compassionate being that cares deeply for, and about you.	**Control imagery (Recording 2)** Now we'll start the section on mental imagery……which involves imagining yourself drawing a picture of the person you saw at the beginning of the experiment. It really doesn't matter whether you're a good artist. The main point of this exercise is to develop a mental picture of the person that you're drawing in imagination. This task might test the limits of your imagination abilities, so if while listening to the instructions you start to feel a little sceptical about this exercise or your ability to form mental images or to draw a person purely in imagination, please try and suspend these judgements and stick with the instructions the best you can. Treat it like an experiment to see whether you can form these types of mental images. In a few minutes, we'll ask you to create a mental image in which you imagine yourself drawing a person. We'd like you to imagine, that you have a

Just like you might imagine an ideal friend or companion, who has all of the qualities you would want of them, you can also create images of an ideal compassionate being who has the qualities you would want from someone who cares very deeply about you. For example, you might want them to always be kind, patient, understanding, never judgmental, and so on. This compassionate being can be beyond human failings or inconsistencies. They can be exactly as you need them to be. They can be superhuman in their capacity for kindness.

When doing this exercise, some people have images of a compassionate person; others imagine an animal. Your compassionate being can take whatever form you need it to take. It can be any gender….it can be older or younger than you. For some people, a compassionate being is represented by the sea or sun, or as an energy, while others don't initially get clear images but just a hazy sense of something or someone that is being compassionate towards them.

Remember any images of a compassionate source might be fragmentary and hazy to begin with, rather than a clear picture. The goal is for you to try to get a sense of this compassionate being's presence, even if you can't see it clearly.

You might have feelings in your body or hear a voice in your head that makes you feel that you are experiencing the presence of a compassionate being that wishes you well and would want to relieve you of distress and pain.

Whatever form your imagery takes we would like you to imagine that the mind of this ideal compassionate being has certain qualities. Again, these are superhuman qualities – complete and perfect compassionate qualities that you can actually experience.

427 words
Flesch-Kincaid Grade Level: 11.4

CFI (Recording 3)

If you're comfortable doing so, please close your eyes or have them partially closed for this task.

pencil, a pen or a paintbrush and a canvas in front of you.

And we'd like you to draw in imagination, the person that you saw a picture of at the start of the experiment. We want you to recreate a picture of this person by drawing them in your mind's eye as well as you can.

Even if you only have a very hazy sense of what that person looked like, and can only picture a generic face to begin with, please use that hazy, generic mental picture as your starting point and follow the instructions the best you can. If you're able to form a detailed mental picture of this person quickly, please still follow the instructions in the order they're given. The goal is for you to try to build up the picture gradually, adding detail *on* your imaginary canvas as you go.

To help you draw this person in your mind's eye, you can use any artistic tools you like in your imagination. Pencils, brushes….any material you like. And your pallet of colours can be infinite. Because you're using your imagination, you won't be limited by the usual speed at which you might ordinarily draw– you'll be able to work much more quickly.

377 words
Flesch-Kincaid Grade Level: 10.0

Control (Recording 3)

If you're comfortable doing so, please close your eyes or have them partially closed for this task.

Now, draw attention to the muscles in your face. Let these muscles relax. And now, gently make a friendly expression, as if you are greeting someone you really like, and feel safe with. This might just be a gentle, welcoming, smiling expression. Now with a welcoming attitude we can start to develop your mental image of a compassionate being. Ask yourself these questions: What would I want my ideal compassionate image to look and sound like? Focus for a moment on what a compassionate, kind voice would sound like if spoken to you right now. What might it say? Next consider what colours, sounds and physical sensations you associate with qualities of wisdom, strength, warmth and non-judgement. Please now try to start developing a sense of this compassionate presence as I mention its qualities. They include; -Firstly, a *deep Commitment* to you – to help you cope with, and re*l*ieve your suffering, and take joy in your happiness - Secondly, *wisdom* gained through experience and maturity. An understanding of the struggles of life - and especially an understanding of *your* struggles. -Third, *strength of mind* – this being cannot become overwhelmed by your pain or distress, but remains present, enduring it with you. -Fourth *warmth*- shown by kindness, gentleness, care and openness -And lastly, *acceptance* – your compassionate being is never judgemental or critical, it understands your struggles and accepts you as you are. With this image of your ideal compassionate being beginning to form in your mind continue to develop a sense of its qualities. Think about how deeply committed this being is to your happiness and wellbeing…. Imagine yourself experiencing a feeling of safeness with the strength and dependability of this compassionate being; this wise and caring mind. (10 Sec)	Now we can start to develop your mental image of the person. Ask yourself these questions: First : what is their gender? Second, what might their ethnicity be? And third, approximately how old are they? In the following sections, I will mention different parts of the person's face and then give you some time to imagine drawing this feature. You can use the periods of silence that follow to really develop a sense of what this person looks like. Try to do this this even if you d*id*n't register the details of a particular facial feature when you looked at their image. Now, start to develop a picture of this person in your mind's eye, adding details to your imaginary canvas as I mention different parts of their face. Consider first the *shape* of their face and start by drawing its outline. Is it a long or a more round face? (10 sec) To this basic outline, start to add the first detail – the person's eyes. Consider the shape and size of their eyes, whether they're close together or further apart…..their colour…. The shape of the person's eyebrows. Draw in these details on your imaginary canvas the best you can, and feel free to use your imagination to fill in any details you can't recall. There will be a period of silence to allow you to imagine drawing these details. (30 Sec) Now consider the person's nose, again asking yourself about its shape, whether it is long or wide, pointy or flat, straight or crooked. Draw the person's nose the best you can. (30 Sec)

Take your time and use the periods of silence that follow, to really develop a sense of this compassionate being (15 Sec) Focus on the wisdom and understanding that is expressed towards you. (30 Sec) Imagine feeling completely understood and accepted. (30 Sec) Focus on the great warmth and kindness that permeates the whole image and is directed at you. (30 Sec) Focus on the feelings of loving-kindness that are directed towards you. (30 Sec) Imagine feeling a sense of care and concern directed towards you. (30 Sec) Imagine the gentle warmth of this compassion flowing toward you. (30 Sec) Imagine the emotions that are being expressed towards you. Kindness, care, acceptance and understanding. (30 Sec) Allow yourself to hear a compassionate voice that expresses a desire for your well-being, and sense the friendliness and safeness, even	Now think about the person's ears. Don't worry if you can't initially picture these……just think about the shape and size of ears that would fit this person's face. Draw the person's ears on your imaginary canvas now. And in your drawing, the tops of the ears should be at the same level as the person's eyes as you're drawing them facing you. (30 Sec) Next consider the shape of the person's mouth….their lips….the distance from their upper lip to their nose. Ask yourself, are the lips thin or full? Is their mouth open or closedAdd the person's mouth on your canvas now. (30 Sec) Consider the colour of the person's skin….is it light or darker….use your imaginary palette to add colour to the face….. (30 Sec) Add in the details of the person's hair now. Do they have long or short hair. Is it dark or light in colour? Add in their hair and include any colour while you are drawing. (30 Sec) Now think about any detail that might be missing….piercings, make-up, blemishes, or anything else you remember about the person's face…..drawing in these additional details as well. (30 Sec) Now bring to mind the complete face, bringing together all of the details you drew. Keep as many of the details in mind as possible. (30 Sec) Now, in your own time open your eyes, letting the image begin to fade away.

joyfulness as you experience this compassionate being relating to you in this way (30 Sec) Now, let the image begin to fade away and in your own time, open your eyes.	
Flesch-Kincaid Grade Level: 10.6 393 words	**Flesch-Kincaid Grade Level:** 5.7 490 words

Post imagery assessment scales:

AT HOME SESSIONS

CFI Script	**Control Script**
Thank you for continuing with the imagery section of this session. As before, you'll be asked to imagine yourself to be the focus of a perfectly compassionate being. Regardless of how you found this exercise previously, please see today's exercise as a new beginning and simply 'go with' the imagery instructions the best you can, without judging your experience too much. You might find it helpful to close your eyes for this task. As before, your ideal compassionate being can take any form - human, animal or any other natural or supernatural form. It might be a sensation in your body or a voice in your head that makes you feel that you're experiencing the presence and soothing influence of a compassionate being that wishes you well and would want to relieve you from suffering or distress. Whatever form your mental imagery takes we would like you to imagine that this compassionate being has certain superhuman qualities. Please try to develop a sense of this compassionate presence as I mention its qualities. -Firstly, this ideal compassionate being has a *deep commitment* to you – to help you cope with, and relieve your suffering, and take joy in your happiness - Second, *wisdom* gained through experience and maturity. An understanding of *your* struggles.	Thank you for continuing with the imagery section of this session. As before, you'll be asked to imagine drawing a person's face. Regardless of how you found this exercise previously, please see today's exercise as a new beginning and simply 'go with' the imagery instructions the best you can, without judging your experience too much. You might find it helpful to close your eyes for this task. As before, you'll be drawing in your imagination the person whose face you rated for friendliness, approachability and trustworthiness in the lab session. I will again guide you as you draw in various facial features. Please now try to start developing a picture of this person, adding details to your imaginary canvas as I mention different parts of their face. There will be periods of silence to allow you to imagine drawing in the various facial features. Start by recalling basic details about what the person looked like …their approximate age, their gender, their ethnicity; and draw an outline of their face based on how you recall the overall shape of their face. To this basic outline, draw the first detail on your imaginary canvas – the person's eyes. Consider the shape, size and colour of their eyes. Use your imagination to fill in any details you can't recall.

-Third, *strength of mind* – this being cannot be overwhelmed. It will remain by your side, enduring your difficulties with you. -Fourth, w*armth*- conveyed though kindness, gentleness and care And -Lastly, *acceptance* – it will never judge or criticise you, it accepts you as you are. Pause (in the audio recording) Keeping these qualities in mind, take a moment to really try to develop a sense of this compassionate presence.....Think about how deeply committed it is to your happiness and welfare…. Pause (in the audio recording) Consider the voice of this ideal compassionate presence – what would it sound like……what would it say to you right now to give you a sense of ease and comfort? Take your time and use the periods of silence that follow, to continue to develop a sense of this compassionate being, allowing yourself to feel the deep commitment, wisdom, warmth and acceptance that it directs towards you (20 sec) Imagine yourself experiencing a feeling of safeness with the strength and dependability of this compassionate being; this wise and caring mind… (20 sec) Focus on the wisdom and understanding that is expressed towards you… (20 Sec) Imagine feeling completely understood and accepted …. (20 Sec) Focus on the great warmth and kindness that permeates the whole image and is directed at you… (20 Sec) Focus on the feelings of loving-kindness that are directed towards you. (20 Sec) Experience a sense of care and concern directed towards you …. (20 Sec)	(20 Sec) Now draw in the person's nose, adding any detail you can recall. (20 Sec) Now think about the person's ears and add this feature to the drawing in your mind. (20 Sec) Next consider the shape of the person's mouth….their lips….the distance from their upper lip to their nose….whether they are smiling. Draw in the person's mouth now. (20 Sec) Use your imaginary palette to add colour to the face….. (20 Sec) Now add in the details of the person's hair, including colour while you draw. (20 Sec) Now think about any details that might be missing and draw in those details as well. (20 Sec) Now bring to mind the complete face, bringing together all of the details you drew. (20 Sec) Please keep an impression of this person you drew in your memory…..…..perhaps this will help you to bring it to mind more easily next time. (10 Sec) Now, let the image begin to fade away and in your own time, open your eyes.

Sense the gentle warmth of this compassion flowing into you….. (20 Sec) Think about the emotions that are being expressed towards you: kindness, care, acceptance, understanding…… (20 Sec) Allow yourself to hear a compassionate voice that expresses a desire for your well-being, and sense the friendliness and safeness, even joyfulness as you experience this compassionate being relating to you in this way. (20 Sec) Please keep an impression of the compassionate being in your memory…..perhaps this will help you to bring it to mind more easily next time. (10 sec) Now, let the image begin to fade away and in your own time, open your eyes.	

Imagery task (Session 2- Day 8)

Record time at start of imagery instructions

CFI Script	**Control Script**
Record time before Recording 3:	Record time before Recording 3:
CFI (Repeat Recording 3 from Session 1)	**Control imagery (Recording 2)**

Appendix 9a. At home tVNS instructions - Earlobe version

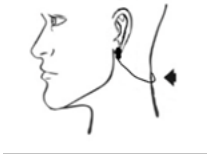
UCL tVNS-imagery study
Instructions for Device Use

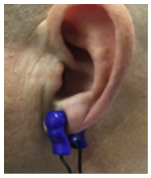
Please read before using the tVNS device.

Earlobe version:

I. Insert lead into plug port marked Ch 1

II. Ensure the clip has a firm connection to the earlobe of the **left** ear, running the cable behind the neck over the right shoulder.





II. Ensure the clip has a firm connection to the earlobe of the **left** ear, running the cable behind the neck over the right shoulder.

III. Push the power button (labelled 2 in the image above)

IV. Settings are pre-set (as above, the top line should read 20Hz and 200μs)

V. Slowly increase stimulation intensity using the ‘up’ triangle button (labelled 3 in the above picture) until you feel a light tingling
VI. Adjust from here aiming to feel a comfortable pulsing. If you experience any pain, lower the Intensity right away. If the sensation is sharp, you made need to adjust the placement of your earpiece.
VII. Once you find a comfortable level you can begin your session. You may want to adjust the level again during your session, this is normal and can be done at any time.
VIII. Press the clock button (4 in the image) so that the time display (6 in the image) reads “C min”
IX. Stimulate for 20-25 min, then listen to the online audio *while continuing to stimulate*
X. One you have completed the audio task and online questionnaires, please switch off the device (2 in image above) before removing the ear-clip.
XI. Please do this at about the same time every day, preferably at the same time as the first lab session.

Common Questions

My stimulation intensity changes frequently throughout my treatment session, is this ok?

It is common for sensory thresholds to change throughout sessions as well as between sessions. This is because the variables that affect conductivity, which causes perception of the stimulation, can vary depending on time of day, skin conductivity and stress levels etc.

Should I be able to feel the stimulation during my session?

You should be able to feel a mild tingling or pulsing sensation at your earlobe although it is common to become used to this sensation.

Note: The earlobe is a sensitive area and it is important not to over-stimulate with too high an Intensity level or for too long a period of time.

- Do not use the study device if:
  - The skin on the ear is broken or cracked.
  - The device casing is cracked, dented, or appears to be damaged.

- Discontinue use if you experience:

- Light-headedness, dizziness, or chest pain.
- Excessive skin irritation.

- *Reactions such as irritation at the stimulation site are rare. If this does occur, and becomes unpleasant, stop the stimulation. The irritation or discomfort should cease shortly after stopping stimulation. If skin irritation persists and makes treatment difficult, discontinue use and consult your study coordinator.*

- **Warnings**

- Read these instructions carefully to ensure proper use of the Study device.
- Do not inhale or swallow small parts.
- Do not wrap the lead wire around the neck.
- Do not apply stimulation in the bath or shower or while sleeping.
- Do not get the Study device wet.
- Do not apply stimulation while driving, operating machinery, or during any activity in which electrical stimulation can put the patient at risk of injury.
- Do not apply stimulation over open wounds or rashes, or over swollen, red, infected, or inflamed areas or skin eruptions (e.g., phlebitis, thrombophlebitis, varicose veins).
- Do not apply stimulation over, or in proximity to, cancerous lesions.
- Do not apply stimulation over the neck or mouth because this could cause severe muscle spasms resulting in closure of the airway, difficulty in breathing, or adverse effects on heart rhythm or blood pressure.
- Do not apply stimulation across the chest, because the introduction of electrical current into the chest may cause rhythm disturbances to the heart, which could be lethal.
- Do not apply electrodes near the thorax because the introduction of electrical current may increase the risk of cardiac fibrillation.
- Stimulation should not be applied across or through the head, directly on the eyes, covering the mouth, on the front of the neck, (especially the carotid sinus), or from electrodes placed on the chest and the upper back or crossing over the heart.
- Use this device only with the electrodes, and accessories provided to you, as using others may be unsafe.
- Potential hazard from simultaneous connection to high frequency surgical equipment and the device that may result in burns and possible damage to the device.
- Operation in close proximity (e.g. 1 m) to shortwave or microwave therapy equipment may produce instability in the stimulator output.
- The long-term effects of the chronic use of the device have not been evaluated.
- Electronic monitoring equipment such as EKG alarms may not operate properly when the Study device is in close proximity while being used.

- **Precautions**

Before Use:

- You must read the Study Device Instructions for Use before using Device. However, reading the Instructions for Use may not be enough to fully explain the safe and effective use of the device. Ask your study coordinator if you have any questions about how to use the device or require any further clarification of these Instructions.
- Only use the Study Device as described in these Instructions for Use or as otherwise directed by your study coordinator.
- Remove jewellery that may interfere with the electrode location (earrings etc.) before using the device.
- Always carefully examine the device for any signs of damage or defects before use.
- Do not strip the batteries' outer seal when inserting (for risk of short-circuiting), this can be avoided by taking care when inserting.
- Do not share your device with another person.

Caring for Your Device:

- Do not pull lead wires to remove electrode.
- Keep the device away from water or other liquids.
- Keep the device away from steam as moisture may damage the device.
- Store device in a safe location out of reach of children.
- Do not place the unit close to excessive heat.
- Do not open or take apart the case, or attempt to repair or modify the device. There are no user serviceable parts. If the device is not working, contact support.
- Use only the specified batteries: 2x 1.5 volt AA Alkaline. Use of any other battery could damage the unit.
- Remove the batteries from the unit, when it is not used for a long time.
- Keep the unit away from sources of high magnetic fields such as TV'S, microwave ovens and hi-fi speakers, as these may affect the LCD screen.

If the device seems to malfunction, when possible, contact your study coordinator for assistance.

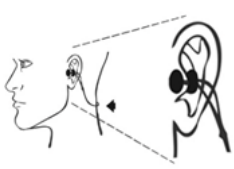
Appendix 9b. At home tVNS instructions - Tragus version

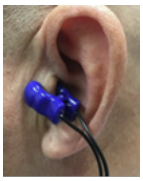
UCL tVNS-imagery study
Instructions for Device Use

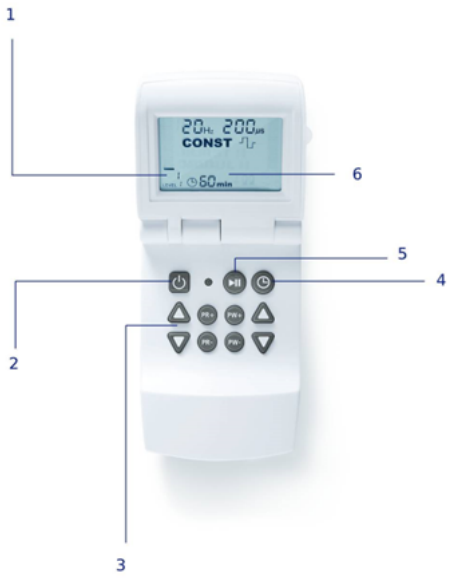
Please read before using the tVNS device.

I. Insert lead into plug port marked Ch 1

II. Ensure the clip has a firm connection to the tragus of the **left** ear, running the cable behind the neck over the right shoulder.







III. Push the power button (labelled 2 in the image above)

IV. Settings are pre-set (as above, the top line should read 20Hz and 200μs)
V. Slowly increase stimulation intensity using the 'up' triangle button (labelled 3 in the above picture) until you feel a light tingling
VI. Adjust from here aiming to feel a comfortable pulsing. If you experience any pain, lower the Intensity right away.
VII. Once you find a comfortable level you can begin your session. You may want to adjust the level again during your session, this is normal and can be done at any time.
VIII. Press the clock button (4 in the image) so that the time display (6 in the image) reads "C min"
IX. Stimulate for 20-25 min, then listen to the online audio *while continuing to stimulate*
X. Once you have completed the audio task and online questionnaires, please switch off the device (2 in image above) before removing the ear-clip.
XI. Please do this at about the same time every day, preferably at the same time as the first lab session.

Common Questions

My stimulation intensity changes frequently throughout my treatment session, is this ok?

It is common for sensory thresholds to change throughout sessions as well as between sessions. This is because the variables that affect conductivity, which causes perception of the stimulation, can vary depending on time of day, skin conductivity and stress levels etc.

Should I be able to feel the stimulation during my session?

You should be able to feel a mild tingling or pulsing sensation at your tragus although it is common to become used to this sensation.

Note: The tragus is a sensitive area and it is important not to over-stimulate with too high an Intensity level or for too long a period of time.

- Do not use the study device if:
  - The skin on the ear is broken or cracked.
  - The device casing is cracked, dented, or appears to be damaged.

- Discontinue use if you experience:
  - Light-headedness, dizziness, or chest pain.
  - Excessive skin irritation.

- *Reactions such as irritation at the stimulation site are rare. If this does occur, and becomes unpleasant, stop the stimulation. The irritation or discomfort should cease shortly after stopping stimulation. If skin irritation persists and makes treatment difficult, discontinue use and consult your study coordinator.*

Warnings

- Read these instructions carefully to ensure proper use of the Study device.
- Do not inhale or swallow small parts.
- Do not wrap the lead wire around the neck.
- Do not apply stimulation in the bath or shower or while sleeping.
- Do not get the Study device wet.
- Do not apply stimulation while driving, operating machinery, or during any activity in which electrical stimulation can put the patient at risk of injury.
- Do not apply stimulation over open wounds or rashes, or over swollen, red, infected, or inflamed areas or skin eruptions (e.g., phlebitis, thrombophlebitis, varicose veins).
- Do not apply stimulation over, or in proximity to, cancerous lesions.
- Do not apply stimulation over the neck or mouth because this could cause severe muscle spasms resulting in closure of the airway, difficulty in breathing, or adverse effects on heart rhythm or blood pressure.
- Do not apply stimulation across the chest, because the introduction of electrical current into the chest may cause rhythm disturbances to the heart, which could be lethal.
- Do not apply electrodes near the thorax because the introduction of electrical current may increase the risk of cardiac fibrillation.
- Stimulation should not be applied across or through the head, directly on the eyes, covering the mouth, on the front of the neck, (especially the carotid sinus), or from electrodes placed on the chest and the upper back or crossing over the heart.
- Use this device only with the electrodes, and accessories provided to you, as using others may be unsafe.
- Potential hazard from simultaneous connection to high frequency surgical equipment and the device that may result in burns and possible damage to the device.
- Operation in close proximity (e.g. 1 m) to shortwave or microwave therapy equipment may produce instability in the stimulator output.
- The long-term effects of the chronic use of the device have not been evaluated.
- Electronic monitoring equipment such as EKG alarms may not operate properly when the Study device is in close proximity while being used.

Precautions

Before Use:

- You must read the Study Device Instructions for Use before using Device. However, reading the Instructions for Use may not be enough to

fully explain the safe and effective use of the device. Ask your study coordinator if you have any questions about how to use the device or require any further clarification of these Instructions.

- Only use the Study Device as described in these Instructions for Use or as otherwise directed by your study coordinator.
- Remove jewellery that may interfere with the electrode location (earrings etc.) before using the device.
- Always carefully examine the device for any signs of damage or defects before use.
- Do not strip the batteries' outer seal when inserting (for risk of short-circuiting), this can be avoided by taking care when inserting.
- Do not share your device with another person.

Caring for Your Device:

- Do not pull lead wires to remove electrode.
- Keep the device away from water or other liquids.
- Keep the device away from steam as moisture may damage the device.
- Store device in a safe location out of reach of children.
- Do not place the unit close to excessive heat.
- Do not open or take apart the case, or attempt to repair or modify the device. There are no user serviceable parts. If the device is not working, contact support.
- Use only the specified batteries: 2x 1.5 volt AA Alkaline. Use of any other battery could damage the unit.
- Remove the batteries from the unit, when it is not used for a long time.
- Keep the unit away from sources of high magnetic fields such as TV'S, microwave ovens and hi-fi speakers, as these may affect the LCD screen.

If the device seems to malfunction, when possible, contact your study coordinator for assistance.