

**Integrating Neuroimaging and Neuromodulation to Understand the Mechanisms
of Cognitive Behavioural Interventions**

By

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Abstract

Mental health disorders, including depression, anxiety, and posttraumatic stress disorder (PTSD), are highly prevalent in Canada and are associated with disability and reduced quality of life. Cognitive behavioural therapies are the most evidence-based treatments for these conditions, yet the neurobiological mechanisms underlying their effectiveness remain poorly understood. This thesis comprises two studies that investigate how cognitive therapies—Cognitive Processing Therapy (CPT) for PTSD and Cognitive Behavioural Therapy with mindfulness (CBTm) for depression and anxiety—affect brain structure and behavioural outcomes.

The first study explores structural brain changes associated with CPT in individuals with PTSD. Sixty-seven participants (40 with PTSD, 27 healthy controls) underwent MRI scanning at baseline and 12 weeks later. The PTSD group received 12 weeks of CPT, while controls received no intervention. Structural neuroimaging data were analyzed using voxel-based morphometry (VBM), cortical thickness (CT), and diffusion tensor imaging (DTI). Our results show that clinician-rated PTSD symptom severity (CAPS-5) significantly decreased following treatment. Neuroimaging results showed decreased grey matter volume in the thalamus, increased white matter volume in the cerebellum, and enhanced fractional anisotropy in the cerebellar region among the PTSD group post-treatment. These findings suggest CPT may modulate thalamic and cerebellar structures involved in emotional regulation and trauma-related processing.

The second study investigated whether combining Cognitive Behavioural Therapy with mindfulness (CBTm) and high-definition transcranial direct current stimulation (HD-tDCS) could improve outcomes in individuals experiencing symptoms of depression and anxiety. Twenty participants were randomized to receive either active or sham HD-tDCS while participating in a five-week CBTm program. Both groups demonstrated improvements in

depression and anxiety symptoms following treatment. Improvements in psychological resilience were observed in the active stimulation group, and changes in resilience were associated with reductions in anxiety symptoms. However, no significant differences between groups were observed, suggesting that these findings should be interpreted cautiously and require replication in larger samples

Together, these two studies offer insights into the neural mechanisms underlying effective cognitive therapies for distinct psychiatric disorders. The CPT study provides evidence of structural brain adaptations following therapy in PTSD, while the CBTm study introduces a non-invasive neuromodulation approach to enhance psychological treatment in depression and anxiety. Findings from this thesis contribute to a growing body of research aimed at improving the accessibility of mental health interventions.

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List of Abbreviations

BOLD	Blood Oxygen Level Dependent
CAPS-5	Clinician-Administered PTSD Scale DSM-5
CBF	Cerebral Blood Flow
CBT	Cognitive Behavioural Therapy
CBTm	Cognitive Behavioural Therapy with mindfulness
CD-RISC	Connor-Davidson Resilience Scale
CPT	Cognitive Processing Therapy
CSF	Cerebral Spinal Fluid
CT	Cortical Thickness
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5 th edition
DTI	Diffusor Tensor Imaging
EDMR	Eye Movement Desensitization and Reprocessing
EEG	Electroencephalography
FA	Fractional Anisotropy
FC	Functional Connectivity
FWE	Family Wise Error
GAD	Generalized Anxiety Disorder
GAD-7	Generalized Anxiety Disorder-7
GLM	General Linear Model
GM	Gray Matter
HC	Healthy Controls
HD-tDCS	High Definition Transcranial Direct Current Stimulation

MRI	Magnetic Resonance Imaging
PCC	Posterior Cingulate Cortex/Precuneus
PCL-5	PTSD Checklist for DSM-5
PHQ-9	Patient Health Questionnaire-9
PTSD	Posttraumatic Stress Disorder
ROI	Region of Interest
TR	Repetition Time
SPM	Statistical Parameter Mapping
VBM	Voxel-Based Morphometry
VLPFC	Ventrolateral Prefrontal Cortex
WM	White Matter
VBM	Voxel-Based Morphometry
WM	White Matter

Author Contributions

Study 1: Examining Structural Brain Changes in Patients with PTSD following Cognitive Processing Therapy

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CHAPTER 1: Introduction

Despite increased awareness and education, the rates of mental disorders in Canada are continuing to climb (Stephenson & Statistics Canada, 2023). A 2022 survey indicated that over 5 million Canadians have met the diagnostic criteria for a mental illness, and that the prevalence of mood and anxiety disorders have almost doubled since 2012 (Stephenson & Statistics Canada, 2023). These disorders include anxiety, depression and post-traumatic stress disorder; all of which are investigated by the present thesis. Importantly, these disorders frequently co-occur, complicating both diagnosis and treatment. Major depressive disorder is a mood disorder that causes persistent feelings of sadness, decreased interest and a range of cognitive and physical symptoms that can impair daily functioning (American Psychiatric, 2022), whereas generalized anxiety disorder is defined by the persistent anticipation of future concern causing avoidant behaviour (American Psychiatric, 2022). Anxiety disorders such as GAD are also common, affecting around 30% of individuals at some point in their lifetime (American Psychiatric, 2022). The comorbidity between anxiety and depression is especially high, with up to 90% of individuals with anxiety also experiencing depressive symptoms (Bui & Fava, 2017; Tiller, 2013). This overlap suggests shared neurobiological mechanisms and contributes to greater symptom burden and functional impairment. PTSD, similarly, is a psychiatric condition that occurs in individuals following exposure to a traumatic event, with symptoms including intrusive thoughts, debilitating flashbacks and avoidant behaviours (American Psychiatric, 2022). These conditions often present chronically as well, and many individuals experience recurrent episodes throughout their lives, with symptoms persisting despite treatment efforts (American Psychiatric, 2022). These manifestations cause a large burden on individuals living with mental health disorders, underscoring the need for a thorough understanding of their causes and treatment.

PTSD symptoms are classified using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and the PTSD Checklist for DSM-5 (PCL-5).

Cognitive-Behavioural Therapy (CBT) remains the gold standard treatment option for mood and anxiety disorders (Driessen & Hollon, 2010). CBT works to reframe the maladaptive thoughts, believed to contribute to the person's emotional distress, thereby reducing symptom manifestation (Naeem et al., 2015). This includes specific, more targeted branches of CBT such as Cognitive Processing Therapy (CPT), primarily used to treat PTSD, and Cognitive Behavioural Therapy with Mindfulness (CBTm), a brief, group-based program used to treat those experiencing anxiety and depression. These therapies target underlying thought patterns and behavioral habits that contribute to psychological distress, helping individuals reframe negative thinking and develop healthier coping strategies (Naeem et al., 2015). Despite the well-established effectiveness of CBT, the neurobiological factors that influence this success are not well understood. Developing a more thorough understanding of these mechanisms will allow for the further optimization of these therapies.

Structural and functional changes in the brain can be examined using various neuroimaging techniques to further understand the success of these therapies (Zhang et al., 2021). In the present thesis, magnetic resonance imaging (MRI) was used before and after CBTm to investigate the potential neuroanatomical drivers of change. Structural MRI analyses can shed light on grey matter volume (GMV) and white matter volume (WMV) changes, using techniques such as voxel-based morphometry (VBM), cortical thickness (CT) and diffusor-tensor imaging (DTI; Symms et al., 2004). Functional MRI works differently, by quantifying regional changes in brain metabolism (Glover, 2011). This is done by tracking cerebral blood flow and changes in oxygenation concentration (BOLD signals; Glover, 2011). Using this technique, the functional

connectivity between various regions in the brain can be mapped (Glover, 2011). Temporal correlation between spatially distinct brain regions is indicative of functional connectivity (FC) (Glover, 2011). Collectively, these MRI techniques allow a framework for examining the anatomical changes that occur in response to treatment.

While neuroimaging techniques provide correlational insights, they cannot infer causality when examining clinical improvement. To establish this causality, our CBTm study also included an experimental manipulation component known as high-definition transcranial direct current stimulation (HD-tDCS). Previous analyses demonstrated that decreased symptom burden following CBTm treatment was accompanied by an increase in FC between the posterior cingulate cortex (PCC) and ventrolateral prefrontal cortex (VLPFC) at the 12-week follow up (Khanam, 2022). These regions are involved in emotional regulation and decision making and therefore have known clinical significance relating to anxiety and depression (Bluhm et al., 2009; Sakagami & Pan, 2007; Zhou et al., 2010). By pairing CBTm with HD-tDCS, we can examine whether enhancing functional connectivity using HD-tDCS increases clinical outcomes when compared to CBTm alone.

The present thesis investigates the neural modulators of CBT based therapies using MRI imaging and neuromodulation techniques. This was done through two independent but contextually aligned studies. Study 1 examined structural brain changes in individuals with PTSD following 12-weeks of CPT. An MRI was completed in 32 PTSD patients and 23 healthy controls prior to CPT and at the end of the 12-week treatment period. These images were then analyzed using VBM, CT and DTI to assess structural changes in both grey and white matter. Clinical symptom severity of PTSD was assessed using the CAPS-5 and PCL-5 assessments. Study 2 included 24 participants undergoing CBTm for a 5-week period. Twelve participants

were subject to real HD-tDCS stimulation, and 12 were subject to sham HD-tDCS stimulation. The CBTm was delivered weekly for 90 minutes over zoom, and the HD-tDCS was delivered 3x/week, both for the same 5-week period.

Overall, this work aims to shed light on the structural and functional neurobiological drivers of CBT, using neuroimaging and neuromodulation techniques. This is investigated using two distinct but related studies, that together provide insight into the success of CBT. Both studies offer novel contributions to the field, as to our knowledge, no prior investigations have examined the structural brain changes following CPT in PTSD patients or have combined neuromodulation with CBTm in individuals with anxiety and depression. By investigating the neural mechanisms associated with therapeutic outcomes, this thesis aims to contribute to a more thorough understanding of how CBT interventions contribute to measurable changes within the brain. This understanding will further our ability to optimize therapies, increasing clinical improvements in mood and anxiety disorders.

CHAPTER 2: Background

To understand the present thesis, it is crucial to explore the basics of mental health disorders such as anxiety, depression and PTSD, as well as the possible treatment options and modalities used to investigate these disorders. These disorders are common and often co-occurring conditions which create a large burden on quality of life. Further understanding the neural mechanisms that drive the success of CBT will enhance our ability to effectively treat mental health disorders. The following background will outline the clinical features of these disorders, current treatment approaches and the neuroimaging methods that inform this research.

2.1 Mental Health

An estimated 3.5 million Canadians seek healthcare services for a mood or anxiety disorder each year (Thakur et al., 2019). This makes understanding and managing these conditions especially important, as they have a widespread effect on the individuals and society at large (Thakur et al., 2019). Mental health disorders are most commonly defined using the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Many mental illnesses present with a comorbid and chronic nature (Launders et al., 2022). This, along with the high prevalence of mental illness makes it incredibly important that we have a thorough understanding on the possible treatment options and their driving forces. Despite this high prevalence, treatment options remain limited and inaccessible for many.

2.1.1 PTSD

Anxiety, depression and PTSD are often concurrent disorders, which is explained by the overlapping symptoms and similar risk factors (Flory & Yehuda, 2015). According to the DSM-5, a person is considered to have PTSD if they are more than 6 years old and meet the criteria A-H (Weathers et al., 2013). Meeting *criterion A* requires direct or indirect exposure to actual or

threatened death, injury or sexual violence. Meeting *criterion B* requires the presence of one or more intrusion symptoms that are associated with and began after a traumatic event(s). Meeting *criterion C* requires that the individual is persistently avoiding the stimuli associated with the traumatic event(s). *Criterion D* requires that there are negative cognitions and mood associated with the event(s). Meeting *criterion E* requires marked alterations in arousal and reactivity associated with the traumatic event. *Criterion F* states that the duration of disturbances (criterion B,C,D and E) is more than 1 month. *Criterion G* states that the disturbance causes clinically significant distress or impairment in daily functioning. Lastly *criterion H* states that the disturbances are not attributable to the physiological effects of another medical condition or a substance (American Psychiatric, 2022; Weathers et al., 2013)

By definition, PTSD is a psychiatric condition that occurs in people with symptoms lasting more than one month who have experienced a traumatic event as emotionally or physically harmful (American Psychiatric, 2022). These events may include physical or sexual abuse, natural disaster, death, injury or medical illness (American Psychiatric, 2022; Nemeroff & Marmar, 2018). PTSD symptoms are grouped into four categories; intrusion, avoidance, changes in mood and cognition, changes in arousal and reactivity and may include re-experiencing of trauma, resistance towards triggers, low mood and irritability (American Psychiatric, 2022). Symptoms of PTSD can manifest differently among individuals. Primary dissociation involves intense flashbacks coupled with autonomic reactions like heightened heart rate and hyperarousal (Lanius et al., 2006). On the other hand, secondary dissociation entails zoning out, depersonalization, or derealization (Lanius et al., 2006). To meet the definition of PTSD, these symptoms must cause significant impairment of daily functioning and last a minimum duration of one month (Van Ameringen et al., 2008). This impairment translates into various aspects of

life, and a high symptom burden is associated with poor outcomes in social and occupational performance (Taylor et al., 2006).

PTSD symptom severity can be measured using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and PTSD Checklist for DSM-5 (PCL-5) scores. The CAPS-5 score is the gold-standard assessment for PTSD (Weathers et al., 2018). It is a 30-item structured interview that is built to assess 20 DSM-5 PTSD symptoms (Weathers et al., 2018). This score is used throughout the present study to assess symptom severity. Alongside CAPS-5, PCL-5 was also administered. PCL-5 is a self-report questionnaire that uses a 0-4 scale to assess the severity of 20 PTSD symptoms (Weathers et al., 2013). For both scales, a score of 33 or above is suggestive of PTSD.

2.1.2 Anxiety and Depression

Anxiety and depression are amongst the most diagnosed mental health disorders (Aquin et al., 2017; Brenes, 2007). According to the DSM-5, a person is diagnosed with generalized anxiety disorder if they experience excessive anxiety and worry more than 50% of the time for at least 6 months during various events or activities that is accompanied by three (or more) of the following symptoms: (a) restlessness, (b) easily fatigued, (c) lack of concentrating or mind going blank, (d) being irritable, (e) tensed muscle, (f) sleep disturbances (Aquin et al., 2017; Williams, 2014b). Similarly, major depressive disorder is diagnosed in an individual presenting with five or more of the following symptoms (present daily, for a minimum 2-week period, with at least one symptom being depressed mood or decreased pleasure associated with significant hindering of psychosocial functioning): depressed mood, loss of interest or pleasure, weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, excessive guilt, decreased concentration and/or thoughts of death or suicide (Tolentino & Schmidt, 2018). The

episode must not be explainable by another medical condition, substance or psychotic disorder (Tolentino & Schmidt, 2018). It is well-established that individuals living with these disorders face significant impairment in their quality-of-life (Rapaport et al., 2005). Early diagnosis and access to evidence-based treatment are especially important for improving long-term outcomes given the chronic nature and functional impairments associated with these conditions (Tolentino & Schmidt, 2018).

The PHQ-9 is a criterion based tool to measure symptom severity within depression (Williams, 2014a). This tool involves nine self-administered questions which are aligned with the DSM criteria for major depressive disorder (Kroenke et al., 2001). Each item on the scale – including mood, fatigue, anhedonia, appetite changes, concentration difficulties and psychomotor changes – are all scored on a 0-3 Likert scale (Kroenke et al., 2001). This scale reflects symptom severity over the past two weeks, yielding a score from 0-27 points (Kroenke et al., 2001). The score is then interpreted along a severity continuum from minimal depressive symptoms to severe depressive symptoms, which allows for effective measurement of treatment response (Kroenke et al., 2001; Williams, 2014a). Likewise, anxiety is measured using the Generalized Anxiety Disorder-7 (GAD-7) (Williams, 2014b). This is a seven item self-report questionnaire which measures the intensity and prevalence of anxiety symptoms (Williams, 2014b). Each item is rated on a 0-3 Likert scale, producing a total score ranging from 0-21, with higher scores indicating greater anxiety severity. (Williams, 2014b).

2.1.3. Resilience

Resilience is defined as the personal tools an individual possesses that provide positive personality characteristics and enhance adaptability (Kunzler et al., 2020). An individual's ability to exhibit resilience is often an outcome of various elements, including genetic, psychological,

social and environmental influences (Kunzler et al., 2020). The Connor-Davidson Resilience Scale (CD-RISC) is the gold-standard measure of resilience (Campbell-Sills & Stein, 2007). It is a self-report scale including 25 items attempting to quantify resilience, capturing multiple dimensions of resilience including adaptability, stress control, tolerance of negative events and ability to recover following hardship (Campbell-Sills & Stein, 2007). CD-RISC scores have been shown to increase following treatment aiming to enhance resilience (Campbell-Sills & Stein, 2007).

2.2 Treatment

The treatment of mental health disorders is a large and important area of exploration, as current pharmacological and therapeutic approaches are not accessible to all peoples.

Pharmacological therapy uses prescription medications to manage mental health conditions which can be very limiting as it is often accompanied by a wide range of side effects, including loss of appetite, weight loss or gain, nausea or vomiting, sexual dysfunction, drowsiness, increased suicidal thoughts, fatigue and increased risk of cardiovascular events (Braund et al., 2021; Moret et al., 2009; Wang et al., 2018). Additionally, long-term dependence on pharmacotherapy is also a concern for many patients (Amir et al., 2022). An alternative is therapeutic treatments, which commonly involve talk therapy, allowing individuals to further understand and reframe thought processes. While therapeutic approaches mitigate these concerns, they are often accompanied by a large burden on time and financial resources. Social determinants create distinct inequities in the accessibility of these treatments, making it important that a wide variety of treatment options are available. To mitigate these challenges, various symptom-specific and group-based branches of CBT have been created. PTSD is typically treated using Cognitive Processing Therapy (CPT) or Eye Movement Desensitization

and Reprocessing Therapy (EMDR), delivered for a 12-week period (American Psychiatric, 2022; Kar, 2011). Depression and anxiety, similarly, can be treated using programs such as CBTm delivered for a 5-week period, which can also be used to increase resilience in those without mental health disorders (Thakur et al., 2019).

2.2.1 CBT

Cognitive behavioural therapy is a form of psychotherapy that has been shown to increase quality of life dramatically (American Psychiatric, 2022). It has been shown to be as equally or more effective when compared to psychiatric medications, creating a good alternative for those who do not want to explore pharmacotherapy (American Psychiatric, 2022). The core principles of CBT are as follows; psychological problems are based in unhelpful ways of thinking, psychological problems are based on learned patterns of unhelpful behaviour and people suffering from psychological problems can learn better ways of coping with them (American Psychiatric, 2022; Nakao et al., 2021). CBT instructs individuals how to change thinking patterns by reframing thoughts considering reality, better understanding the motivation of others, improving confidence and using problem-solving (American Psychiatric, 2022; Nakao et al., 2021). Despite the widespread effectiveness of this intervention, individuals face variety of barriers, including large wait times and financial constraints when seeking care (J. A. López-López et al., 2019). This highlights the need for more accessible programs, such as CBTm, which is delivered via zoom at no cost.

2.2.2 CBTm

In 2014, large-group CBT was designed and implemented in Winnipeg, MB to mitigate the long wait times associated with psychotherapy (Thakur et al., 2019). This reduced wait times for CBT from one year to three months (Thakur et al., 2019). This reduction, along with

promising client feedback, allowed for the development of CBTm by the Manitoba Mental Health Research Group (Thakur et al., 2019). CBTm is delivered in five group-based sessions, where individuals are provided self-help resources and basic mindfulness techniques (Thakur et al., 2019). Mindfulness is defined as using a non-judgmental approach to assess experiences in the present moment (Segal et al., 2002). This practice has been thought to reduce negative thoughts by promoting a detached perspective of one's consciousness (Segal et al., 2002). CBTm combines traditional CBT with mindfulness techniques, and despite its short duration has been shown to be widely effective in treating mental health conditions and improving resilience overall (Davidson et al., 2022).

2.2.3 CPT and EMDR

Cognitive processing therapy is a branch of cognitive behavioural therapy, that focuses more specifically on trauma-related symptoms (American Psychiatric, 2022). It is delivered over a 12-week period, with one session per week. The treatment begins with education regarding PTSD (American Psychiatric, 2022; Kar, 2011). It then involves the identification of “stuck points”, related to the trauma, being challenged (Moring et al., 2020). This allows the patient to progress using cognitive strategies to process larger trauma-related issues (Moring et al., 2020). A similar therapy is Eye Movement Desensitization and Reprocessing (EMDR), which consists of 8-sessions that focus on the role of information processing and memory formation (Shapiro, 2014). EMDR pairs eye movements with the cognitive processing of traumatic memories (Landin-Romero et al., 2018). This is thought to influence the processing of traumatic memories, as PTSD symptoms are thought to result from improper processing of the image, beliefs and emotion linked to the trauma (Landin-Romero et al., 2018).

2.3 Magnetic Resonance Imaging

The development of MRI has been instrumental in the progression of modern medicine. It is a non-invasive technique that minimizes the use of ionizing radiation and creates detailed images of soft-tissues, such as the brain (Grover et al., 2015). The human body has a high water content, meaning it contains an abundance of hydrogen nuclei (Grover et al., 2015). These nuclei have a spin momentum and when placed under a uniform magnetic field, they may align parallel in a low-energy state or antiparallel to the field in a high energy state (Grover et al., 2015). A radiofrequency (RF) pulse is applied perpendicular to the uniform magnetic field, creating transverse magnetization. This RF pulse is then turned off and relaxation occurs through T1 (spin-lattice) or T2 (spin-spin) relaxation (Grover et al., 2015). Measurement of this relaxation allows for the visualization of white and grey matter within the brain, as different tissues have different densities and magnetic compositions. Structural MRI is the typical modality used to visualize the density of brain tissues, including grey matter, white matter and cerebral spinal fluid (CSF) (Grover et al., 2015).

2.3.1 Structural MRI

Structural MRI allows for the visualization of brain anatomy to define size, volume and thickness of the cortex (Symms et al., 2004). This allows for the quantification of changes that may occur due to injury, aging, or disorders such as PTSD. These structural MRI techniques are quite robust when compared to functional MRI, as they can quantify changes in brain anatomy independent of fluctuating neural activity. The two types of structural MRI that exist are T1-weighted and T2-weighted sequences (Symms et al., 2004). These sequences allow for the distinct contrast between different tissue types, including grey matter, white matter and cerebrospinal fluid (CSF) (Kawahara & Nagata, 2021). T1-weighted imaging is particularly

useful for looking at anatomy, as it provides clear images of fatty tissue (Kawahara & Nagata, 2021). This allows for the visualization of white matter as its myelination causes a bright appearance, while the CSF appears dark (Zimny et al., 2013). In contrast, in T2-weighted images fluid is more easily identifiable as it appears bright, making these images useful in detecting inflammation and edema within the brain (Kawahara & Nagata, 2021). Structural MRI has been used to examine brain volume in PTSD patients when compared to healthy controls and the literature commonly notes reduced volume in the insula, anterior cingulate cortex and hippocampus in patients with PTSD (Bromis et al., 2018).

The present study uses voxel-based morphometry (VBM), cortical thickness (CT) and Diffusor-Tensor Imaging (DTI) to assess structural changes in PTSD patients, following CPT. In order to prepare the images for analysis, preprocessing must be completed. In the present study this was done in SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/>), using the CAT12 toolbox (<http://www.neuro.uni.jena.de/cat/>) in MATLAB (Version R2023a). The images are longitudinally segmented, meaning the pre-treatment and post-treatment scans for each subject are aligned to analyze changes over time. VBM allows for a statistics-based voxel-by-voxel comparison of the whole brain structure, using T1-weighted MRI images (Matsuda, 2013). This allows for the observation of atrophy on a whole brain level, without having to pre-define regions of interest (ROI). Once images are segmented, VBM analyses can be completed on grey and white matter to assess for any neurodegeneration or neurogenesis. CT is another technique used in structural imaging that allows for a whole brain-analysis, specifically examining the width of the cerebral cortex. Cortical thinning is a process that has been associated with psychological and neurological conditions, making it a good biomarker for the prognosis of disease (Tahedl, 2020). DTI uses water diffusion characteristics to evaluate the microstructure of

white matter integrity in the brain (Jang et al., 2013). This allows for the characterization of integrity and connectivity of white matter tracts, as healthy white matter facilitates unidirectional water movement while damaged or disorganized tracts allows unorganized movement (Chanraud et al., 2010). There are many measures that can be calculated using DTI, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). Fractional anisotropy is a widely used measure that quantifies the directionality of diffusivity and is highly sensitive to changes in the microstructure (Hulkower et al., 2013). Mean diffusivity is a reflection of cellular and membrane density, which is particularly helpful in conditions of edema or necrosis (Alexander et al., 2007; Le Bihan et al., 2001). Axial diffusivity is often used for brain maturation, often indicating the presence of axonal development and radial diffusivity is a measure of myelin integrity and demyelination (Alexander et al., 2007; Le Bihan et al., 2001). Changes in one modality do not always pair with changes in other modalities, and therefore they may be viewed as independent measures.

2.3.2 Functional MRI

Functional MRI (fMRI) is used as an estimate of neural activity and relies on cerebral blood flow. The specific signal fMRI measures is called the blood oxygen level dependant (BOLD) signal (Glover, 2011). These measurements rely on the neurovascular coupling hypothesis, which states that increased blood flow is equated to increased neural activity (Drew, 2022). When fully deoxygenated, hemoglobin is paramagnetic, causing a distortion in the magnetic field (Thulborn et al., 1982). This distortion may be referred to as a local gradient, and can be detected as a disruption in a uniform magnetic field (Thulborn et al., 1982). Regions with increased oxygen demand contain more deoxygenated hemoglobin which allows increased

metabolic activity to be visualized (Hillman & Hyman, 2014). This can be used to quantify changes in brain metabolism following a treatment, activity or stimuli.

Functional connectivity (FC) can be measured using fMRI and depicts the statistical relationship between the activity within two isolated brain regions (Mohanty et al., 2020). This represents a temporal correlation, as anatomically distinct brain regions that show similar patterns of activity over time may reflect underlying communication or coordination between those regions. (Mohanty et al., 2020). A pilot study completed previously within our lab demonstrated that reduction in PTSD and depressive symptoms following 12-weeks of CBTm was accompanied by an increase in FC between the posterior cingulate cortex/precuneus (PCC) and the left ventrolateral prefrontal cortex (VLPFC) of the brain (Kanhm et al, in progress). This increased FC is hypothesized to be representative of increased neural communication between these two regions. Functional connectivity was found to be a significant predictor of individuals CD-RISC score at 12-weeks post treatment, linking FC to psychiatric symptom reduction.

In addition to MRI, electroencephalogram (EEG) is able to measure and quantify changes in synchronized neural activity through the assessment of voltages (Warbrick, 2022). Electrodes are placed all over the surface of the scalp, and electrical potential differences are measured between electrodes (Abreu et al., 2022). These voltages must pass through the skull and reach a scalp electrode in order to be recorded, making EEG an indirect measure of neural activity (Warbrick, 2022). EEG is especially strong in its temporal resolution, but lacks spatial resolution, therefore it is most useful when collected in addition to another technique such as fMRI (Abreu et al., 2022). In the present study, both fMRI and EEG will be collected to investigate changes in

neural activity by optimizing both spatial and temporal resolution. EEG will shed light on the real time high-frequency neural connectivity.

2.3.3 Pseudo-continuous arterial spin labeling

Another functional measure, cerebral blood flow (CBF), quantifies the amount of blood flow per unit mass within the brain and is estimated by arterial spin labeling (ASL). ASL is achieved through the delivery of RF pulses to the base of the brain or neck, which “labels” the protons in the arterial blood (Clement et al., 2022). This is followed by a delay where blood flows into brain tissue, allowing for a control image to be acquired alongside the label image (Clement et al., 2022). The difference between these two images is then representative of the amount of labeled blood that has perfused the tissue, and deemed the cerebral blood flow (Clement et al., 2022). One of the most clinically relevant forms of ASL is pseudocontinuous ASL (pCASL) (Clement et al., 2022). This technique involves delivering a pulsed RF and has been shown to provide a superior labeling efficiency in comparison to other ASL techniques (Alsop et al., 2015; Borogovac et al., 2012). In same pilot study mentioned previously, CBF was reduced in the VLPFC but remained unchanged in the PCC.

Using both BOLD and ASL in conjugation is optimal to further understand resting brain networks (Jann et al., 2015). When these modalities are not used concurrently, it is important to consider their limitations (Jann et al., 2015). While BOLD imaging yields superior temporal resolution, ASL provides direct, quantitative measurements of activity within specific networks (Jann et al., 2015). More specifically, FC can be differentiated from CBF as FC represents the correlates in synaptic signalling between two distinct regions, while CBF is representative of all synaptic inputs received by a region of the brain.

2.4 Neuroanatomical Basis of Diagnosis and Treatment

2.4.1 Diagnosis

The neuroanatomical basis for the diagnosis of PTSD, anxiety and depression involves overlapping regions that control high order executive function, memory, stress and emotional regulation. These regions include the amygdala, hippocampus and prefrontal cortex.

2.4.1.1 Neurobiology of PTSD

Traditionally, PTSD has been characterized by structural and functional changes in regions responsible for the learning and memory of fear; including the amygdala, prefrontal cortex and hippocampus (Harnett et al., 2020). However, increasing evidence highlights the involvement of additional regions, particularly the thalamus and cerebellum, in the manifestation and regulation of PTSD symptoms.

The thalamus has a longstanding reputation of being a sensory hub used to relay information to the cortex (Hwang et al., 2022; Yoshii, 2021). More recently, it has been recognized that the thalamus may play a role in fear mediated stimulation (Burra et al., 2019). This may be explained by its role in relaying sensory information and fear-related learning networks through its connections with the amygdala (Yoshii, 2021).

Similarly, the cerebellum has been viewed primarily for its role in gait-control and motor coordination. (Rudolph et al., 2023). In addition to this role, the cerebellum also contributes heavily to emotional regulation and cognition (Baumann et al., 2022; Huggins et al., 2024). The cerebellums extensive connections with the stress network and amygdala make it particularly susceptible to the effects of stress including threat detection and processing (Huggins et al., 2024).

2.4.1.2 Neurobiology of Anxiety and Depression

Neuroanatomical abnormalities are commonly seen across various brain regions in anxiety and depression, including the prefrontal cortex, the thalamus, the amygdala, and the hippocampus (Pandya et al., 2012). Particularly, dysfunction is common within corticolimbic circuits, which govern emotional processing and regulation (Pandya et al., 2012).

2.4.2 Neurobiology of treatment

A preliminary study in our lab identified changes in FC between the VLPF and PCC following CBTm (Khanam, 2022). These results were reinforced by the CD-RISC scores of participants posttreatment, suggesting that increased FC between the PCC and VLPFC are a driving factor in the psychiatric symptom reduction observed following CBTm intervention. These findings suggest that the VLPFC strengthens cognitive control over episodic memory retrieval, leading to improved outcomes following CBTm.

2.4.2.1 Ventrolateral Prefrontal Cortex (VLPFC)

The VLPFC is an anatomical region within the prefrontal cortex of the brain (Levy & Wagner, 2011). Its superior margin is the inferior frontal sulcus and its inferior margin is the lateral sulcus (Levy & Wagner, 2011). The prefrontal brain network functions in high-order personality and goal-directed behaviour (Friedman & Robbins, 2022). Dysregulation within the prefrontal cortex is strongly linked to psychiatric disorders, including PTSD, anxiety and depression (Friedman & Robbins, 2022). The VLPFC is a node within the prefrontal cortex that specializes in cognitive control, response inhibition and resilience (Fischer et al., 2018; Sakagami & Pan, 2007). Heightened activity in the VLPFC has been found to be associated with depression (Drevets et al., 2002). This may explain the decreased CBF in the left VLPFC observed following CBTm in the pilot study (Khanam, 2022).

2.4.2.2 Posterior Cingulate Cortex (PCC)

The PCC is located within the medial part of the inferior parietal lobe of the brain (Leech & Sharp, 2014). Specifically, it is contained within the posteromedial cortex, alongside the retrosplenial cortex and precuneus (Leech & Sharp, 2014). Functionally, it is a highly metabolically active and deeply interconnected brain region believed to play a key role in cognitive processing (Leech & Sharp, 2014). The activity of the PCC is highly variable with arousal and is hypothesized to be important in mediating consciousness (Leech & Sharp, 2014). More specifically, activity in the PCC is heightened when individuals use their episodic memory to retrieve autobiographical memories (Leech & Sharp, 2014). It is a core part of the default mode network (DMN), a brain network that is active during internally directed thought processes and at rest (Leech & Sharp, 2014). Prior to the discovery of the DMN, it was thought that the brain was largely inactive during periods of rest (Azarias et al., 2025). The DMN is essential for emotional processing, self-reflection and mental narratives, making it widely influential in the maintenance of mental health (Azarias et al., 2025). Imaging studies have found that DMN activity, particularly in the PCC, is decreased in patients with PTSD when compared to healthy controls (Lanius et al., 2010). Similarly, one of the most commonly altered brain regions affected by CBT is the PCC, further speaking to its role in mental health and resilience (Yuan et al., 2022). This has been replicated in various other studies, where symptom improvement has been matched by increased CBF and metabolic activity in the PCC (Goldapple et al., 2004; Martin et al., 2001). Therefore, the PCC has a well-established role in resilience, and functional abnormalities in this region have been observed in various psychiatric disorders including depression, schizophrenia, PTSD and attention-deficit disorder (Kelley et al., 2022; Leech & Sharp, 2014).

2.4.2.3 Interaction between the VLPFC and PCC

Study 2 was designed to expand upon various parent clinical trials conducted in our lab (Bolton et al. in progress, (Khanam, 2022)). The first clinical trial demonstrated that CBTm reduced subthreshold PTSD symptoms in participants (Bolton et al. in progress), while the second clinical trial expanded on these findings further to understand the neurobiological drivers of this effectiveness (Khanam, 2022). Khanam et al. chose the PCC as their main seed-region due to its well-established role in symptom improvement and its core function in the DMN (Khanam, 2022). Using a seed-based connectivity analysis, this study found that FC increased significantly between the PCC and the VLPFC following CBTm (Khanam, 2022). Additionally, PCL-5 scores decreased significantly throughout the treatment period (Khanam, 2022). This increased FC and decreased PCL-5 score remained at the 12-week follow up, indicating treatment effectiveness persisted (Khanam, 2022). The present study will build on this further by combining this treatment with High-Definition Transcranial Direct Current Stimulation.

2.5 High-Definition Transcranial Direct Current Stimulation

Despite the findings within our pilot study, the results are purely correlational in nature due to the lack of direct modulation. Alongside therapeutic treatment, a second treatment option for psychiatric conditions is non-invasive brain stimulation (NIBS), which has gained increasing popularity over recent years (Parlikar et al., 2021). Transcranial direct current stimulation (tDCS) is one form of NIBS that involves the delivery of a weak electrical current through the placement of two electrodes on the scalp (Parlikar et al., 2021; Thair et al., 2017; Zhang et al., 2024). Despite the success of this therapy, the lack of specificity in the spatial current delivery makes its effects quite inconsistent (Zhang et al., 2024). To combat this issue, high definition tDCS (HD-tDCS) was developed to optimize precision (Dmochowski et al., 2011; Zhang et al., 2024). HD-

tDCS allows for localized electrode montages to be used, which allows particular brain regions to be targeted resulting in longer-lasting clinical effects (Kuo et al., 2013). HD-tDCS is similar to conventional tDCS in that an anode and cathode are placed over the scalp, however the electrodes are smaller in size and typically arranged in a 4x1 montage configuration (Parlikar et al., 2021). This 4x1 montage consists of 1 central electrode placed over the region of interest, which is then surrounded by 4 electrodes of opposite polarity in a ring formation (Kuo et al., 2013; Parlikar et al., 2021).

This leads us to believe the simultaneous stimulation of the VLPFC and PCC may increase the FC between these two regions. This is investigated in the present study, where 9 electrodes (8 channels + 1 ground) were used to deliver a peak current of 2 mA to patients. The electrodes were positioned to target the VLPFC with inward field orientation and current intensity was determined using computer stimulation using the HDTargets software (Soterix Inc.).

2.6 Background Summary

In summary, mental health disorders such as PTSD, anxiety, and depression represent a significant burden with complex symptom profiles, frequent comorbidity, and limited access to effective treatment. Cognitive behavioural therapies—including CPT and CBTm—have demonstrated promising efficacy in reducing psychiatric symptoms and improving resilience, though accessibility remains a challenge. Similarly, advances in neuroimaging techniques, including structural and functional MRI have acted as powerful tools to investigate the underlying neural mechanisms of these disorders and their treatment responses. For overall mental health, the VLPFC and PCC have been found to behave as key regions in symptom regulation and resilience, with alterations in functional connectivity between these areas

reflecting treatment outcomes. Novel neuromodulatory approaches such as HD-tDCS offer additional opportunities to directly influence functional connectivity and enhance clinical outcomes. The present thesis aims to use neuroimaging techniques to advance our understanding of therapeutic interventions and their efficacy in the treatment of psychiatric disorders.

**CHAPTER 3: Study 1: Examining Structural Brain Changes in Patients with PTSD
following Cognitive Processing Therapy**

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3.1 Preface

This manuscript is the first study within the present thesis and works directly to investigate the neural mechanisms that drive success within evidence-based cognitive behavioural therapies. This paper investigates how gold-standard PTSD treatment influences brain structure, which is a current gap that exists within the literature. The findings of this manuscript contribute to the broader objective of this thesis by linking structural neuroimaging changes to improvement within PTSD patients.

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3.2 Abstract

Posttraumatic stress disorder (PTSD) is a psychiatric condition occurring following exposure to psychological trauma. Neuroimaging studies have highlighted neuroanatomical differences in individuals with PTSD. Cognitive Processing Therapy (CPT) is an evidence-based frontline treatment for PTSD. Although CPT has shown success in decreasing clinical symptom severity, its underlying neural mechanisms remain unclear. We hypothesize that structural changes occur following CPT within key brain regions that have previously been linked to PTSD. Fifty-six participants, including patients with PTSD ($n = 32$) and healthy controls ($n = 24$), underwent T₁-weighted structural magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) scans at baseline and follow-up. The PTSD group completed a twelve-week CPT treatment, while the controls did not undergo any treatment. To investigate the effects of successful CPT treatment, four participants who did not respond to treatment were excluded from analyses. T₁-weighted images were analyzed using voxel-based morphometry and cortical thickness was estimated within pre-defined regions-of-interests. Fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity were estimated using DTI. Significant interactions between group and time were observed in both grey matter (GM) and white matter (WM) volume analyses—decreased left thalamic GM volume and increased left cerebellar WM volume were observed in patients with PTSD, following CPT treatment. Furthermore, a significant interaction between group and time showed increased fractional anisotropy in the left cerebellum following treatment in the PTSD group. Cortical thickness and other DTI-related measures did not differ. Our findings suggest that CPT leads to neuroanatomical changes in the thalamus and the cerebellum, and these may be associated with lasting effects of CPT-related benefits in PTSD.

Keywords

Posttraumatic Stress Disorder

Cognitive Processing Therapy

Magnetic Resonance Imaging

Voxel based morphometry

Diffusion Tensor Imaging

3.3 Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disorder which occurs after direct or indirect exposure to a psychologically traumatizing event (Van Ameringen et al., 2008). The stress response to trauma can have diverse impacts on the brain (Ely et al., 2023). Globally, 70.4% of individuals report having experienced a form of trauma in their lifetime (Kessler et al., 2017). The lifetime prevalence of PTSD is 5.6% amongst trauma-exposed people (Koenen et al., 2017). The first-line treatment for PTSD, mood, and anxiety disorders is cognitive behavioural therapy (CBT), which aims to establish links between thoughts, behaviours and emotions (Naeem et al., 2015). Cognitive processing therapy (CPT) is a specialized form of CBT which focuses on reframing intrusive thoughts that have occurred following a traumatic experience (Resick et al., 2017). Specifically, this evidence-based, “gold standard” therapy (Schrader & Ross, 2021) uses written exposures to reduce distress, which helps patients modify their maladaptive appraisals (Asmundson et al., 2019; Moring et al., 2020). These maladaptive cognitions are often overaccommodated or assimilated within PTSD patients (Holliday et al., 2018) and are typically referred to as “stuck points,” which are rigid, maladaptive beliefs about oneself, others or the environment that arise from trauma (Held et al., 2025). CPT is typically delivered over a twelve-week period, once a week for 90 minutes, in either individual or group settings (Tran, 2016). Various meta-analytic reviews have shown that CPT is effective in reducing trauma-related distress (Asmundson et al., 2019; Holliday et al., 2018; Lenz et al., 2014). This reduction has been shown to persist at 5-10 year follow-ups (Resick et al., 2012), suggesting that neurobiological changes—potentially including structural plasticity—may contribute to sustained symptom improvement (Korem et al., 2024)

Historically, the prefrontal cortex, amygdala, and hippocampus are the brain regions most implicated in PTSD (Bremner, 2007; Sherin & Nemeroff, 2011; Yakemow et al., 2024). Alterations in regional activity have been investigated using neuroimaging modalities such as MRI (Patel et al., 2012). A meta-analysis by Patel et al. reported consistent findings of reduced activation in medial prefrontal regions alongside heightened amygdala reactivity (Patel et al., 2012). Functional MRI (fMRI) data further revealed potential hyperactivation of the salience network, as well as altered patterns of engagement within the central executive and default mode networks (Patel et al., 2012). More recently, other regions of the brain such as the thalamus (Guo et al., 2025; Wright et al., 2022; Yoshii, 2021) and cerebellum (See et al., 2025; Turner et al., 2007; Wright et al., 2022) have been recognized for their functions related to PTSD. Alterations to these structures may alter the regulatory behaviours of an individual, including both cognitive function and emotional regulation (McEwen & Morrison, 2013). In the present study, structural MRI is used to further understand these changes. While functional alterations reflect dynamic neural responses, structural measures may index longer-term neuroplastic changes that could underlie sustained therapeutic effects (Korem et al., 2024).

Although CPT has been associated with clinically meaningful reduction in PTSD symptoms (Walter et al., 2023), the neurobiological mechanisms underlying these therapeutic effects remain incompletely understood. fMRI has been used previously to investigate CPT and revealed altered connectivity in PTSD patients (Vuper et al., 2021); however, functional measures capture dynamic brain states and may not fully explain the durability of treatment response (Korem et al., 2024). To date, most neuroimaging studies evaluating structural brain changes in PTSD are basic science in nature (i.e., does brain structure in PTSD differ from HC); clinical trials (i.e., evaluating the effects of treatment on brain structure) are critically needed (Hinojosa et al., 2024).

In a study conducted by Yakemow et al. (2024) brain volume differences in PTSD ($n = 40$) vs. HC ($n = 27$) participants were assessed only prior to receiving CPT therapy. The authors found that there was reduced grey matter volume (GMV) in the mid-temporal lobe region of PTSD patients, a finding which parallels related research (Stevens et al., 2018). Kroes et al. found a link between increased flashbacks and decreased volume in the medial temporal gyrus of PTSD patients (Kroes et al., 2011). Alongside the hippocampus, the mid-temporal region of the cortex functions in memory, particularly within the re-experiencing of traumatic events (Stevens et al., 2018). This suggests that alterations in temporal lobe structure may be involved in flashbacks that occur due to PTSD (Kroes et al., 2011).

Structural neuroimaging may provide complementary insight into longer-term neuroplastic changes that could support sustained symptom improvement. Previous studies have identified gray and white matter abnormalities associated with PTSD symptom severity, yet the extent to which these structural features are modifiable following evidence-based psychotherapy remains unclear (Cardenas et al., 2011; Stephen et al., 2024). In the current study, T₁-weighted MRI and diffusion tensor imaging (DTI) were used to examine gray and white matter structural changes, respectively, in PTSD patients following CPT, in comparison to healthy controls (HC). T₁-weighted MRI was used for voxel-based morphometry (VBM) and cortical thickness (CT) analyses, which represent the level of atrophy and deformation. DTI was used to assess fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD), which represent the microstructural integrity of white matter (Figley et al., 2022). To our knowledge, this is the first study in adults to evaluate the neural anatomical changes associated with CPT in a community sample of individuals with PTSD.

We hypothesize that CPT will be associated with measurable structural changes in brain regions implicated in PTSD, reflecting neuroplastic processes related to improved cognitive and emotional regulation. Specifically, we expect patterns consistent with partial normalization or compensatory adaptation within corticolimbic and regulatory networks (e.g., prefrontal cortex, amygdala, hippocampus, thalamus, and cerebellum), when compared with HCs. By integrating multiple structural neuroimaging modalities, this study aims to advance understanding of the neural mechanisms that may support the therapeutic effectiveness and durability of CPT in PTSD.

3.4 Materials and Methods

Participants

A total of 67 participants were recruited for our parent clinical trial investigating overall neural changes associated with a twelve-week CPT treatment intervention (Wright et al., under review). However, not all participants completed the study due to the onset of the COVID-19 pandemic, resulting in 56 participants with baseline and follow-up MRI data. Participants were sorted into PTSD ($n = 32$) and HC ($n = 24$) groups. The PTSD group consisted of treatment-seeking participants from the community and operational stress injury clinic (Winnipeg, MB, Canada) who had experienced a Criterion A traumatic event—trauma types were highly variable and were not amenable to grouping. Scores from the CAPS-5 (Weathers et al., 2018) and PTSD Checklist-5 (PCL-5) (Bovin et al., 2016) were used to characterize PTSD symptoms and severity, in accordance with the DSM-5. Exclusion criteria for PTSD participants included the presence of a neurological illness, as well as substance dependence and/or uncontrolled bipolar or psychotic disorder, as defined by the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). To investigate the effects of successful CPT treatment, participants from the PTSD group

were excluded ($n = 4$) if they showed no change in CAPS-5 scores following treatment, or if symptoms worsened (i.e., CAPS-5 scores increased); these participants made up the non-responder (NR) group. The HC group consisted of trauma-exposed controls (TEC; $n = 10$) who had experienced a criterion A traumatic event but subthreshold symptoms (i.e., CAPS-5 total severity scores ≤ 5), along with trauma-naïve controls (TNC; $n = 13$). All control participants were pooled to make up the HC group due to low sample size, and none had any diagnosed psychiatric disorders. The HC group did not undergo any CPT intervention, while the PTSD group received twelve weeks of CPT (one 90-minute session/week), which was co-facilitated by a registered psychologist and psychology trainee/mental health clinician, who have been trained in the administration of CPT. (Tran, 2016). Only PTSD participants who finished all CPT sessions were included in our study.

Data acquisition

MRI data were obtained with a 3 Tesla Siemens MAGNETOM Verio IMRIS scanner (Erlangen, Germany) equipped with a 12-channel head coil. These images were collected at the Kleysen Institute for Advanced Medicine at the University of Manitoba, Bannatyne campus (Winnipeg, Manitoba). An MPRAGE sequence was used to acquire T_1 -weighted structural data with the following parameters: TR/TE/TI = 2300/3.02/900 ms; flip angle = 9° ; field of view (FOV) = 256 mm x 256 mm with 1.00 mm x 1.00 mm x 1.00 mm resolution; 240 slices; interleaved acquisition. DTI data were acquired using a diffusion-weighted single-shot spin echo EPI sequence with the following parameters: TR/TE = 10,400/79 ms; flip angle = 90° ; FOV = 240 mm x 240 mm with 2.5 mm x 2.5 mm x 2.5 mm resolution; 65 slices; slice thickness = 2.5 mm (no inter-slice gap); interleaved acquisition; 30 diffusion weighted images ($b = 700 \text{ s/mm}^2$); 5 reference images ($b = 0 \text{ s/mm}^2$). MRI data was obtained from two time points; baseline (2-4 weeks prior to treatment

starting), and follow-up (within 2 weeks following the final CPT session; one participant was scanned 3 weeks after treatment ended).

Voxel-Based Morphometry Preprocessing and Analysis

T₁-weighted images were preprocessed in SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/>), using the CAT12 toolbox (<http://www.neuro.uni.jena.de/cat/>) in MATLAB (Version R2023a). Longitudinal segmentation (optimized for plasticity/learning effects) was performed through the pairing of baseline and follow up scans. The high-dimensional shooting template was used for registration; forward and inverse deformation maps were saved and modulation was applied. Images were then smoothed (FWHM = 4mm x 4mm x 4mm), estimated, and visualized using SPM12 and XJView (<https://www.alivelearn.net/xjview>) software. Factorial analyses were used to examine the effects of successful CPT treatment on GMV and WMV separately; interaction effects (group × time) were examined for both volume measures. Age, sex, years of education, and total intracranial volume (TIV) were used as covariates. A cluster forming threshold was defined at $p < 0.001$ (peak-level), with extent threshold corrected using a false discovery rate (FDR) at $q < 0.05$. GMV and WMV were extracted from any significant clusters for further post-hoc analyses (contrasting pre- vs. post- for each group) using the Statistical Package for the Social Sciences (SPSS, IBM Corp., version 27.0, Armonk, NY) software.

Cortical Thickness Analysis

CT measurements were obtained through SPM12, using the CAT12 toolbox. The Desikan-Killiany-Tourville (DKT) atlas (Klein & Tourville, 2012) was used and is made up of thirty-four pre-defined regions-of-interest (ROI) in each of the left and right cerebral hemispheres. These 68 ROIs were used to analyze CT changes across groups in pre- and post-CPT scans. Differences

between groups were compared using general linear model (GLM) with age, sex, and years of education used as covariates.

DTI analysis

In our subset of 52 HCs and PTSD responders, one was excluded from DTI analysis as no DTI data were available, resulting in 28 PTSD responders and 23 HCs. Probabilistic tractography was performed using SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/>), ACID (<http://www.diffusio.tools.org/>), and DTI&Fiber (<https://www.uniklinik-freiburg.de/mren/research-groups/diffperf/fibertools.html>) toolboxes in MATLAB (Version R2023a). Segmented structural T₁-weighted images from the CAT12 analyses described above were used for spatially normalizing the DTI data. DTI data were converted from 4D images to 3D images and preprocessed using the ACID toolbox. Motion and eddy current correction were performed to ensure spatial alignment and reduce geometric distortions, followed by fitting of the diffusion tensor (robust tensor fitting algorithm; default values: normalization factor = 4, confidence interval = 0.3, residual smoothing = 16, regularization = 0.0001, smoothing kernel = 3 x 3 x 3). FA, MD, AD and RD were all examined—an average white matter mask created from all of the participants was applied during analysis. The same statistical approach was used in the VBM analysis

Statistical analysis

Statistical analyses were performed using SPSS software. Demographic data was statistically analyzed using independent and paired t-tests or chi-square tests in SPSS. Repeated-measures GLMs were used to examine the changes in CAPS-5 and PCL-5 scores from visit one to visit two, controlling for age, sex, and years of education.

3.5 Results

Demographics

Education significantly differed among HC and PTSD groups whereas sex and age did not (see Table 1). However, all three variables were used as covariates within our neuroimaging analyses. Details of clinical benefits will be published elsewhere (Patel et al., in preparation).

Table 1: Demographic data and mean ($\pm$ SD) questionnaire scores for baseline (pre-treatment) and twelve-week follow-up (post-treatment, values in bold). Data are presented for chi-squared analysis (i.e., sex) or independent t-tests contrasting PTSD vs. HC.

Questionnaire	PTSD	HC	t or χ^2	df	p
N	32	24			
Age	40.2 ($\pm$ 11.6)	33.7 ($\pm$ 13.8)	1.884	54	0.065
Sex (M:F)	12:20	10:14	0.015	1	0.902
Education	13.9 ($\pm$ 2.8)	16.4 ($\pm$ 3.4)	3.027	54	0.003*
CAPS-5 pre-CPT treatment	32.2 ($\pm$ 9.2)	0.8 ($\pm$ 1.5)	16.475	54	<0.001*
CAPS-5 post-CPT treatment	18.0 ($\pm$ 11.4)^a	0.3 ($\pm$ 0.6)	7.570	54	<0.001*
PCL-5 pre-CPT treatment	43.7 ($\pm$ 13.3)	2.3 ($\pm$ 2.9)	14.893	54	<0.001*
PCL-5 post-CPT treatment	27.3 ($\pm$ 17.3)^a	2.0 ($\pm$ 2.8)	7.075	54	<0.001*
Medication (N)	23	0			
Anxiolytics	8	0			
Antidepressants	14	0			
Antipsychotics	3	0			
Mood stabilizers	3	0			
Stimulants	0	0			
Cannabis	5	0			

*significant after Bonferroni correction for multiple comparisons. CAPS-5: Clinician-Administered PTSD Scale for DSM-5; PCL-5: PTSD Checklist. ^a paired t-test from baseline, $p < 0.001$.

CAPS-5 and PCL-5 Scores

The CAPS-5 and PCL-5 scores were significant for the main effect of time (CAPS-5: $F(1,52) = 8.996, p = 0.004$; PCL-5: $F(1,52) = 9.613, p = 0.003$), group (CAPS-5: $F(2,52) = 95.036, p < 0.001$; PCL-5: $F(2,52) = 8.950, p < 0.001$), and group $\times$ time interaction effects (CAPS-5: $F(2,52) = 33.456, p < 0.001$; PCL-5: $F(2,52) = 82.085, p < 0.001$). Post hoc analyses indicate that the CAPS-5 and PCL-5 scores were significantly different pre-and-post intervention in the PTSD group (Table 2). These were corrected for multiple comparisons using a Bonferroni $p < 0.05$ threshold.

Table 2. Post-hoc analysis evaluating differences in CAPS-5 and PCL-5 score from each group at visit 1 and visit 2. The mean difference (standard error) was calculated using visit 1 minus visit 2.

Questionnaire	Mean Difference	<i>p</i>
<i>CAPS-5 score</i>		
HC group	0.522 (1.621)	0.749
PTSD group	16.857 (1.469)	<0.001*
NR group	-4.000 (3.887)	0.308
<i>PCL-5 score</i>		
HC group	0.304 (3.041)	0.921
PTSD group	17.643 (2.757)	<0.001*
NR group	8.000 (7.293)	0.278

* = significant at the $p < 0.001$ level

CAPS-5 = clinician-administered posttraumatic stress disorder scale for DSM-5

PCL-5 = posttraumatic stress disorder checklist-5

NR = Non-responder

VBM Analysis—Grey Matter

Using VBM, a significant group $\times$ time interaction was observed for GMV using the HC and PTSD responder groups. Age, sex, years of education and TIV were all controlled for as covariates. A significant cluster ($F(1,96) = 21.81$; $p = 0.012$, FDR corrected; 176 voxels; $x = -9$, $y = -26$, $z = -4$) was identified in the thalamus (see Figure 1); post hoc analyses revealed that GMV decreased over time within the thalamus cluster in PTSD patients (mean difference = -0.028 , CI = 0.010 – 0.046 , $p = 0.003$) while it was increased in HC (mean difference = 0.025 , CI = 0.006 – 0.045 , $p = 0.013$).

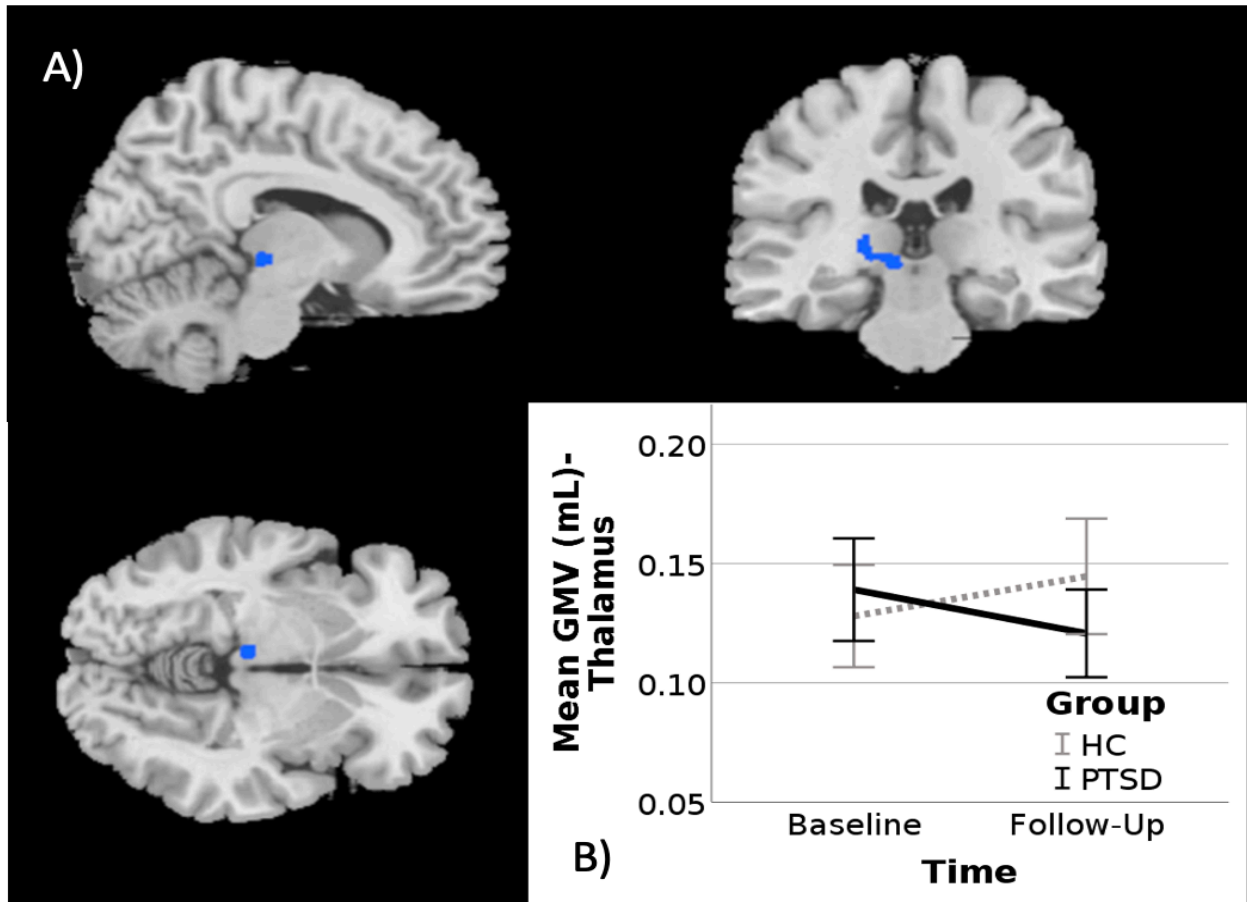


Figure 1. A) Grey matter volume significantly differed in the thalamus (blue). B) The interaction of group $\times$ time was significant (cluster-defining threshold $p < 0.001$, corrected for multiple comparisons at FDR $q < 0.05$, with post hoc analyses revealing grey matter volume decreased over time in the PTSD group.

VBM Analysis—White Matter

Using VBM, a significant group $\times$ time interaction was also observed for WMV using the HC and PTSD responder groups. Age, sex, years of education and TIV were all controlled for as covariates. A significant cluster ($F(1,96) = 21.81$; $p = 0.040$, FDR corrected; 253 voxels; $x = -27$, $y = -78$, $z = -34$) was identified in the posterior lobe of the left cerebellum (crus I/II; see green cluster in Figure 2); post hoc analyses revealed that WMV increased over time within the cerebellum cluster in PTSD patients (mean difference = 0.022, CI = 0.000–0.045, $p = 0.048$) while it was decreased in HC (mean difference = -0.031, CI = 0.007–0.055, $p = 0.011$).

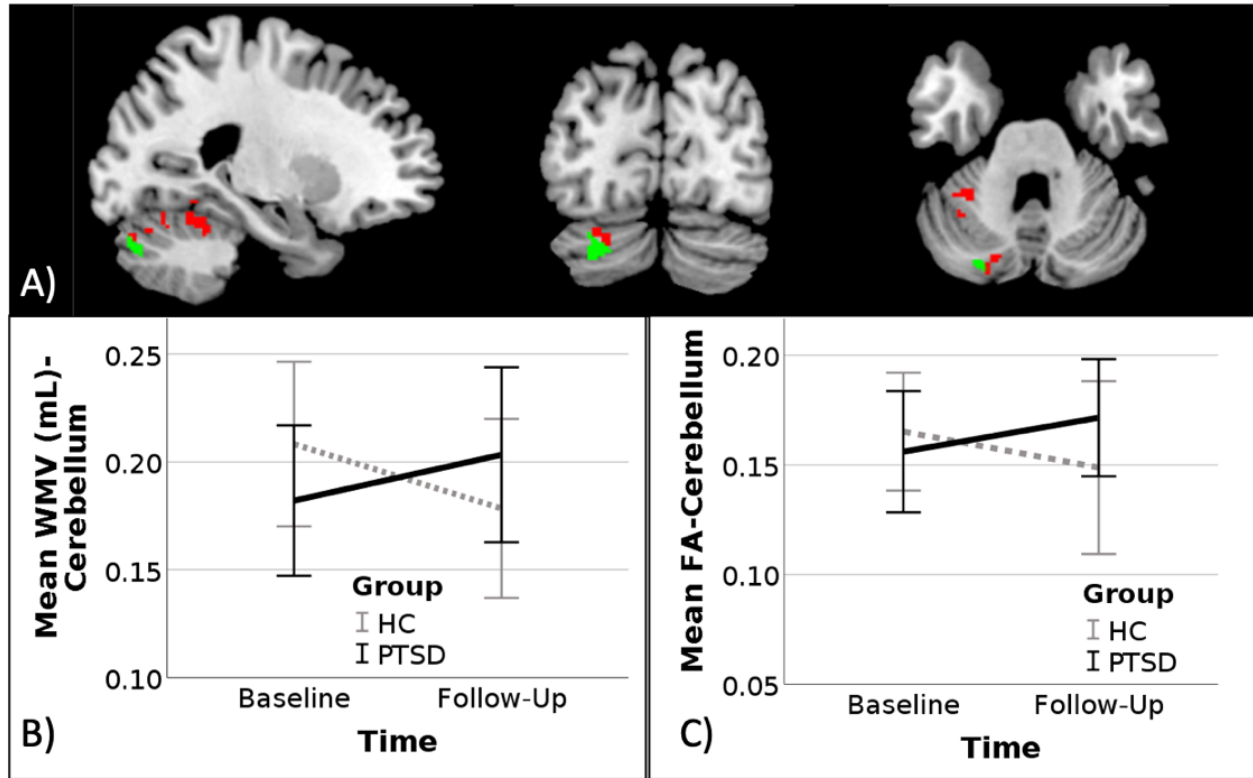


Figure 2. A) Significant white matter changes in the cerebellum (white matter volume shown in green [crus I/II]; fractional anisotropy shown in red). B) White matter volume significantly differed in the cerebellum for the interaction of group $\times$ time (cluster-defining threshold [CDT] $p < 0.001$, corrected for multiple comparisons at FDR $q < 0.05$). Post hoc analyses revealed white matter volume increased over time in the PTSD group. C) Fractional anisotropy significantly differed in the cerebellum for the interaction of group $\times$ time (CDT $p < 0.05$, corrected for multiple comparisons at FDR $q < 0.05$). Post hoc analyses revealed fractional anisotropy increased over time in the PTSD group.

DTI Analysis

DTI data were used to examine FA, MD, AD and RD. FA results showed a significant group (PTSD responder vs. HC) $\times$ time (pre vs. post) interaction (cluster defining threshold $p < 0.05$), while controlling for age, sex and years of education in the cerebellum ($F(1,95) = 10.88$; $p = 0.013$, FDR corrected; 920 voxels; $x = -18$, $y = -46$, $z = -16$; see red cluster in Figure 2). Post hoc analyses revealed that FA increased over time within the identified cluster in PTSD patients (mean

difference = 0.015, CI = 0.007–0.023, $p < 0.001$) while it was decreased in HC (mean difference = -0.016, CI = 0.007–0.025, $p = 0.001$).

Cortical Thickness

No significant CT differences were observed between the HC and PTSD groups, following CPT treatment.

3.6 Discussion

This novel study provides a deeper understanding of the neuroanatomical changes which occur in PTSD patients following successful CPT treatment: we observed reduced thalamic GMV and increased left cerebellar FA and WMV (crus II) following successful treatment (Figures 1 and 2). Basic science research has shown decreased cerebellar WMV in patients with PTSD compared to HC, with significant effects in the left crus II and left lobule VIIB (Blithikioti et al., 2022; Huggins et al., 2024; See et al., 2025). Furthermore, in a recent large scale ($N = 4,215$) VBM study, researchers identified reduced GMV and WMV in the cerebellum, including in crus II for patients with PTSD, compared to HC (Huggins et al., 2024). These cerebellar GMV and WMV findings were also found in a large-scale meta-analysis, with emphasis in the left cerebellar hemisphere for GMV (See et al., 2025). Interestingly, these results were still observed when PTSD was compared to TEC, suggesting the differences were due to PTSD itself, rather than trauma-exposure. Coupled with the current clinical trial, these data suggest that successful twelve-week CPT intervention may work to reverse WM atrophy within these regions and begin to normalize brain structure. Importantly, this further suggests that white matter within this region can undergo neuroplastic adaptations following relatively brief behavioral interventions (Blithikioti et al., 2022). Indeed, structural changes in GMV and WMV following short interventions have previously been documented (Driemeyer et al., 2008) (Taubert et al., 2012). For example, Taubert et al. (2012)

reviewed multiple studies showing both GMV and WMV changes in response to skill acquisition, and that these structural adaptations correlate with behavioral improvements (Taubert et al., 2012). The present study highlights the potential for CPT to induce meaningful neuroplasticity and contribute to long-term improvements in mental health.

The role of the cerebellum in mental health research has been significantly underappreciated in the past, primarily because it has historically been regarded as the hub for neuromotor regulation (Kolesar et al., 2019; Olson et al., 2023). Cerebellar contributions were believed to be limited to coordinating and fine-tuning movements, overshadowing its potential involvement in broader aspects of mental health and cognitive functions (Olson et al., 2023). This narrow focus has resulted in a lack of comprehensive exploration into the influence of the cerebellum on emotional regulation, cognitive processes, and overall mental well-being (Olson et al., 2023). To understand the full extent of the role of the cerebellum, it is crucial to recognize that the cerebellum is extensively interconnected with other regions throughout the brain including stress-related regions including the hippocampus and amygdala (Huggins et al., 2024). These connections may influence PTSD symptoms by interfering with normal brain-mediated stress responses through cerebro-cerebellar circuits (Huggins et al., 2024). CPT allows individuals to alter fear conditioning and processing, potentially through the increase of WMV in the cerebellum (Resick et al., 2017). This finding was reinforced through our DTI analysis, as FA values increased following successful treatment in the neighboring regions of the left cerebellum (see Figure 2). This may indicate increasing white matter integrity within the left cerebellum and strengthened structural connections with the cortex (Kozel et al., 2011).

Cortical projection from the cerebellum to the cortex is mediated through the thalamus, another structure implicated in the present study. The thalamus has been recognized for its

functions beyond acting as a sensory hub, including the regulation of awareness and cognition (Yoshii, 2021). Due to reciprocal pathways between the thalamus and amygdala, visual and auditory stimuli are relayed from the thalamus to the amygdala, allowing for the initiation of a fear response (Asami et al., 2018; Leppla et al., 2023). PTSD can cause increases in thalamic activation, including connectivity with the amygdala, which may be responsible for flashbacks and triggers (Yoshii, 2021). Although the thalamic changes induced by PTSD are not uniformly agreed on, emotional dysregulation within PTSD patients may be caused by hyperactivation of the thalamus, causing the person to relive traumatic experiences (Bossini et al., 2017). In our study, we observed a decrease in GMV in the left thalamus following successful treatment in PTSD. Indeed, a prior study examining eye movement desensitization and reprocessing (EMDR) therapy also found decreased GMV in the left thalamus of patients with PTSD after treatment (Bossini et al., 2017). These patients also showed decreased re-experiencing symptoms after EMDR therapy. Taken together with our findings, alterations in left thalamic gray matter volume may act as a critical neural substrate or marker for symptom improvement or normalization following psychological interventions in PTSD. One hypothesis is that the observed decrease in GMV reflects pruning of maladaptive neuroplasticity, which may have developed in response to chronic trauma (Bremner et al., 2007). This structural refinement could reduce unnecessary or hyperactive synaptic connections, potentially lowering metabolic demand within the thalamus. In other words, the thalamus after therapy may become more functionally efficient, with decreased overactivation, which could contribute to improved regulation of sensory processing and fear responses (Kotkowski et al., 2022). However, it should be noted that investigations of whole-thalamus volume in PTSD have been inconsistent—meta-analysis tends to show smaller thalamic volume in PTSD, with the exception that high comorbidity with major depressive disorder is correlated

with higher thalamic volume (Steele et al., 2025). Additionally, severity of symptom clusters (e.g., re-experiencing vs. hyperarousal) may be more relevant to thalamus size than overall symptom severity (Steele et al., 2025)—the present parent clinical trial observed improvements in both re-experiencing and hyperarousal [Wright et al., under review]. Further investigations should be conducted to clarify the causal mechanisms underlying these structural changes and their ability to predict treatment outcomes. This may be possible through the identification of biomarkers that allow clinicians to stratify patients based on their likelihood of benefiting from CPT and support the development of more targeted interventions. CPT may potentially help to normalize thalamic responses, thereby contributing to improved emotional regulation and overall mental health (Asmundson et al., 2019).

These neuroanatomical findings in the cerebellum and thalamus can be understood within the broader clinical framework of trauma-related psychology. PTSD is characterized by disruptions in emotion regulation, increased threat sensitivity, maladaptive cognitive processing, cognitive distortions, and affective symptoms such as sensory hyperactivity, even in the absence of threat (Clancy et al., 2017; Ouhmad et al., 2023). CPT directly targets these dysfunctional beliefs and responses, reducing the psychological stress response to them. Some evidence shows that by altering maladaptive thoughts and beliefs through CPT, activation of the hypothalamic-pituitary-adrenal axis (the body's primary driver of stress) reduces, as evidenced by improvements in heart rate variability (Watkins et al., 2023). This modification is rooted in the cognitive processing theory which suggests that when new, inconsistent information is processed, either assimilation or accommodation occurs (Sobel et al., 2009). The central aim of CPT is to help patients replace inappropriately assimilated or overaccommodated beliefs (Sobel et al., 2009). The observed structural changes in the cerebellum may reflect improvements to a bottom-up control over an

overactive thalamus, caused by the cognitive restructuring learned via CPT. These cerebellar WM changes may result in better control over the thalamus, reducing the sensory flooding and hyperarousal often experienced in PTSD.

Extending this further, acute psychiatric responses following traumatic exposure highlight the extensive interaction between psychological trauma and neurobiological stress systems (Morris & Rao, 2013). These responses often involve heightened stress reactivity, which may contribute to long term changes in structure and function of the brain (Liberzon & Abelson, 2016). High adversity populations such as veterans and war-exposed individuals/refugees typically have higher rates of PTSD than other traumas (Khalil et al., 2024), and are often less amenable to treatment (ter Heide & Smid, 2015). Prompt intervention is necessary—perhaps successful early treatment in this group prior to the development of PTSD could help mitigate the neurological changes and symptomology associated with PTSD. Analyzing PTSD within the context of a broader trauma spectrum provides context for the interpretation of trauma-focused interventions in facilitating adaptation.

Interestingly, in our interaction analysis between time (pre- vs. post-) and group (PTSD vs. HC), we did not observe altered volume in the medial temporal region, which has often been observed to be relevant to PTSD symptoms (Kroes et al., 2011; Stevens et al., 2018). Indeed, we have previously reported brain volume differences in the temporal regions in this sample of PTSD participants ($n = 40$) vs. HC ($n = 27$) at baseline (prior to intervention) (Yakemow et al., 2024). This discrepancy may be because while this PTSD cohort does have reduced volume in this region for the PTSD group (Yakemow et al., 2024), successful treatment was not dependent on regaining volume in this region, which was in line with a previous study that found a lack of change within this region following CBT (Garrett et al., 2021). Instead, it is likely the case that improvement in

PTSD symptom severity resulted from an alternate, compensatory pathway in more flexible brain regions that were able to structurally re-organize, via psychosocial intervention.

Our CT analysis did not reveal any significant differences when examining the group x time interaction. These outcomes may suggest there is a parallel trend in cortical thinning across both groups, or may simply be explained by the fact that because CT investigates changes in cerebral cortex, it is unlikely to see any change when structural differences are within the thalamus or cerebellar volume (Tahedl, 2020). It is equally important to consider that the variability in CT might be influenced by the choice of atlas utilized. Specifically, the DKT atlas employed in our study has been fine-tuned for the cerebral cortex but lacks rigorous validation and uses large parcellations, which may have been unable to detect small changes in thickness.

A puzzling observation was that all changes in PTSD were accompanied with changes in the opposite direction in HC. These participants were recruited from the community at large, and no intervention was provided. The scan interval was twelve weeks, and thus the observed structural changes in HC are likely be within the unspecific fluctuation of measurement error, rather than to other factors such as age. A recent computer simulation study suggested a nuanced approach is necessary when interpreting post hoc results in control groups following a significant voxel-wise interaction effect due to Berkson's paradox (Ko, 2025). Berkson's paradox occurs when independent data appear to be negatively correlated, due to the way data is selected. In low-powered neuroimaging studies, "selection" occurs when a significant cluster (observed during a voxel-wise interaction) is chosen for post hoc testing, which can result in spurious, opposite findings in the control group, compared to the treatment group (Ko, 2025). The interaction effect identifies regions of maximal difference, thus, only voxels with highly different values will be identified in the interaction. When treatment effects are weak, random noise within the significant

region in the HC group have already been “selected” based on their maximally different signals, introducing a spurious negative correlation. In fact, in the simulation study (Ko, 2025), and the present data, a voxel-wise paired t-test within the HC group examining pre and post data did not reveal any significant changes ($p < 0.05$, FDR-corrected), indicating the opposite findings to the PTSD group are likely due to noise. This simulation study highlights that this paradox should not hinder the overall validity of the findings, rather, significant effects in the control condition may suggest that the overall statistical analysis was underpowered, i.e., there may be more false negatives while positive intervention effects are still valid (Ko, 2025).

Limitations of the present study include the small sample size which may have increased the likelihood of detecting false positive changes in HC, as well as limited the generalizability of these results. However, this “likely” false positivity in HC should not deter the interpretation of significant changes occurring in PTSD patients. Additionally, the HC group included individuals both with and without Criterion A trauma exposure. This introduces heterogeneity within the control group that may contribute to attenuated differences between the PTSD and HC groups. However, a recent large-scale VBM meta-analysis ($N = 3507$) observed that differences in GMV and WMV were highly similar whether the PTSD group was compared to trauma-exposed or trauma-naïve control groups (See et al., 2025). In any case, future research should be done with large sample sizes and multi-site datasets in order to improve statistical power and allow for stratification of variables (i.e., trauma-exposure in controls, trauma-type in PTSD groups, responders vs. non-responders, etc.). Second, although longitudinal changes were interpreted as reflecting therapy-related neuroplasticity, structural MRI measures are subject to short-term neurobiological fluctuations which are possible even in the absence of intervention (Kalc et al., 2026). While the inclusion of a control group helps to mitigate this concern, it is complicated by

the fact that opposing directions of change are observed in HCs, although as discussed, this may be due to Berkson's Paradox. It is worthwhile to reiterate that the increase of cerebellar WMV in the PTSD group is in line with the literature—reduced cerebellar volume is often observed in PTSD while our results show that CPT shifts volume towards normalization. Our results are further strengthened by the use of a more conservative 'whole-white matter' analysis, rather than a region-of-interest analysis targeting the cerebellum. Another limitation is that the FA results are exploratory in nature (i.e., cluster-defining threshold $p < 0.05$); however, they align well with the more robust WMV changes observed in the cerebellum (see Figure 2), lending credibility to their likelihood of being true effects. Finally, the exclusion of treatment non-responders may limit the generalizability of these findings to all individuals with PTSD; future work should investigate neural differences between these groups to identify differences that may underlie the success of CPT treatment.

Overall, through VBM analysis we observed a reduction in GMV in the left thalamus in our PTSD group following treatment, possibly reflecting changes in thalamic function associated with trauma processing and recovery. Additionally, our results indicated an increase in WMV and FA in the cerebellum of PTSD patients following successful treatment, suggesting alterations in white matter structure and integrity are associated with improving resilience and reducing PTSD symptom severity. These results highlight the potential for CPT to effect rapid and significant improvements in symptom severity, but also pave the way for further research into the neuroanatomical mechanisms underlying these changes and their implications for long-term recovery in PTSD patients.

Patient consent

All participants provided written, informed consent. The study was approved by the University of Manitoba Biomedical Research Ethics Board.

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Competing Interests

None.

CHAPTER 4: Study 2: Behavioural Outcomes Following Simultaneous High Definition Transcranial Direct Current Stimulation Targeting the Left Ventrolateral Prefrontal Cortex and Posterior Cingulate Cortex During Cognitive Behavioral Therapy with Mindfulness: Preliminary Findings From a Randomized Sham-Controlled Study

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4.1 Preface

This manuscript is the second study within the present thesis and directly investigates whether augmenting a mindfulness-based cognitive behavioural therapy (CBTm) program with high-definition transcranial direct current stimulation (HD-tDCS) can enhance psychological outcomes beyond those achieved through psychotherapy alone. While CBTm has demonstrated effectiveness in reducing symptoms of anxiety and depression, the capacity to potentiate its therapeutic benefits through targeted neuromodulation remains a critically underexplored area in the literature. This paper examines how the concurrent stimulation of the posterior cingulate cortex (PCC) and ventrolateral prefrontal cortex (VLPFC) influences behavioural outcomes in a clinical population. The findings of this manuscript contribute to the broader objective of this thesis by demonstrating that resilience, rather than conventional symptom measures alone, may be the most sensitive indicator therapeutic change.

This manuscript is in the final stages of peer-review for publication.

4.2 Abstract

Background: Anxiety and depression are among the most prevalent mental health disorders and are associated with significant impairments to quality of life. Cognitive behavioural therapy with mindfulness (CBTm) is an accessible, group-based intervention that has demonstrated effectiveness in reducing psychiatric symptoms and improving resilience. Our previous neuroimaging study showed that the posterior cingulate cortex (PCC) and ventrolateral prefrontal cortex (VLPFC) are related to resilience and play key roles in CBTm benefit. High-definition transcranial direct current stimulation (HD-tDCS) is a non-invasive neuromodulation technique that can directly manipulate neuronal activities, in turn influencing behavioural outcomes.

Objective: This feasibility study aimed to evaluate whether simultaneously stimulating the PCC and VLPFC using HD-tDCS is associated with changes in behavioural outcomes during CBTm.

Methods: Twenty participants were randomized to receive active or sham HD-tDCS alongside a 5-week CBTm program, dividing participants into 2 groups (each $n = 10$); CBTm+sham and CBTm+stim. Stimulation was delivered three times weekly for 20 minutes at 2 mA. Behavioural outcomes were assessed using the Patient Health Questionnaire-9 (PHQ-9; depression score), Generalized Anxiety Disorder-7 (GAD-7; anxiety score), and Conner-Davidson Resilience Scale (CD-RISC; resilience score) at baseline and post-treatment. Repeated measures analyses were conducted to examine group and time effects.

Results: Both groups demonstrated significant decreases in PHQ-9 (CBTm+stim: -6.9 ± 5.5 ; CBTm+sham: -7.0 ± 3.2) and GAD-7 (CBTm+stim: -5.6 ± 6.3 ; CBTm+sham: -5.8 ± 2.5) scores over time ($ps < 0.002$). CD-RISC scores increased significantly in the CBTm+stim group (6.3 ± 6.6 , $p = 0.002$) but not in CBTm+sham group (3.1 ± 4.3 , $p = 0.095$). No significant interaction effects (stim condition $\times$ time) were noted ($ps > 0.2$). In CBTm+stim, the changes in GAD-7 were

associated with changes in CD-RISC ($\rho = -0.669$, $p = 0.035$). This was not observed in the CBTm+sham group ($\rho = -0.121$, $p = 0.740$). The improvement in PHQ-9 was associated with lower baseline CD-RISC only in the CBTm+stim group ($p = 0.011$) which was significantly different from the CBTm+sham group ($p = 0.021$).

Conclusions: Clinical symptoms (depression and anxiety) were similarly improved in both the CBTm+stim and the CBTm+sham groups. In the CBTm+stim group, reduction in anxiety symptoms were associated with improved resilience and participants with lower baseline resilience demonstrated greater improvements in symptom measures. These findings suggest a relationship between resilience and symptom changes in the CBTm+stim group, however, the absence of significant Group x Time interaction effects indicates that these observations should be replicated in larger sample sizes as they are exploratory rather than confirmatory.

Keywords

Mental Health

High-Definition Transcranial Direct Current Stimulation

Cognitive Behavioural Therapy with Mindfulness

Functional Connectivity

Resilience

4.3 Introduction

Mental disorders are a leading cause of global health-related burden (Fan et al., 2025), with anxiety and depression being the most frequently diagnosed (Aquin et al., 2017; Brenes, 2007). Both depression and anxiety disorders cause impairments affecting an individual's quality of life, including the ability to work and participate in social situations ("Researchers from University of Connecticut Describe Findings in Anxiety Disorders," 2019). Cognitive behavioural therapy (CBT) is a gold-standard psychological intervention for the treatment of anxiety and depression (Cuijpers et al., 2019; Ghahari et al., 2020; José A. López-López et al., 2019). CBT aims to identify and change maladaptive thought patterns and behaviours in order to alleviate psychological distress and improve mood (Naeem et al., 2015). To improve the accessibility of CBT skills, a multi-disciplinary team of researchers and clinicians developed a 5-session group-based program that introduces participants to introductory CBT skills with a mindfulness component (CBTm) (Thakur et al., 2019). CBTm classes have shown great promise in their effectiveness of reducing psychiatric symptoms in individuals with mental disorders (Ghahari et al., 2020). Specifically, CBTm has been shown to be effective in cases of comorbid depression and anxiety (Davidson et al., 2022; Thakur et al., 2019; Zemestani & Fazeli Nikoo, 2020). Our recent studies also showed some level of improvement in psychological resilience after CBTm intervention in physicians and medical students (Garg, Submitted.). Resilience is defined as an individual's ability to adapt to stress and adversity, making it a protective factor in the development of psychiatric conditions (Shrivastava & Desousa, 2016).

Our recent functional magnetic resonance imaging (fMRI) pilot study of public safety personnel without clinically diagnosed mental health disorders showed that the 5-week CBTm intervention increased the functional connectivity (FC) between the posterior cingulate

cortex/precuneus (PCC) and the left ventrolateral prefrontal cortex (VLPFC) (Khanam, 2022). The PCC functions in self-regulation and decision-making (Sakagami & Pan, 2007; Zhou et al., 2010) and similarly, the VLPFC functions in goal-directed behaviour (Sakagami & Pan, 2007; Zhou et al., 2010). This effect persisted at the 12-week follow-up and VLPFC-PCC connectivity significantly predicted the participant's level of psychological resilience (measured by the Connor–Davidson Resilience Scale (CD-RISC)) (measured by the Connor-Davidson Resilience Scale [CD-RISC]; Campbell-Sills & Stein, 2007) at 12-weeks post-treatment (Khanam, 2022). Neuroimaging studies have previously shown that both the PCC and VLPFC have clinical significance relating to anxiety and depression (Sakagami & Pan, 2007; Zhou et al., 2010).

Transcranial direct current stimulation (tDCS) is a neuromodulatory technique that has become increasingly popular in the field of clinical neuroscience (Parlikar et al., 2021). tDCS directly modulates membrane potential and increases or decreases neuronal excitability depending on its polarity (Parlikar et al., 2021). Previous fMRI studies have demonstrated that anodal tDCS increases FC in the targeted area (Carther-Krone et al., 2025; Keeser et al., 2011; Sankarasubramanian et al., 2017). The caveat of conventional tDCS is that the stimulation site is not focal (causing diffuse stimulation effects), and the receiving electrode (e.g., cathodal end for anodal stimulation) can induce opposite effects (Müller et al., 2022). Therefore, multi-region targeting is not readily feasible. This has been resolved by the recent development of high-definition tDCS (HD-tDCS) (Müller et al., 2022). This technique allows two brain areas to be focally targeted simultaneously with the same polarity by placing multiple small receiving electrodes around the stimulating electrode (Müller et al., 2022). These surrounding electrodes distribute the return current across several pathways, which reduces current spread and

constraints in the electric field (Parlikar et al., 2021). This allows for more targeted treatment and is longer lasting in its effects when compared to tDCS (Parlikar et al., 2021).

This study examined whether simultaneous stimulation of the left VLPFC and PCC using HD-tDCS would strengthen improvements in behavioural measures, as seen in CBTm alone. Our previous study suggested that the PCC-VLPFC connectivity is associated with increasing resilience and clinical benefits of CBTm, and thus directly promoting this FC using HD-tDCS may enhance resilience. Therefore, we have hypothesized that increasing the neural activities in these two brain regions would enhance resilience, which could indirectly improve symptoms of depression and anxiety. It is important to note that the neuroimaging pilot study used to generate this hypothesis [14] examined CBTm alone in a non-clinical sample and did not involve HD-tDCS. The extrapolation of its findings to a stimulation-based mechanism is therefore a working hypothesis rather than an established model linking neural and behavioural change.

4.4 Materials and Methods

Participants

Twenty-four individuals were recruited from an ongoing open-label clinical trial, referred to as the “parent trial”. The parent trial includes patients that are enrolled in CBTm classes and may or may not meet the criteria for a diagnosable mental health disorder at the onset of their involvement in the study. Individuals must have met the following criteria to participate in the parent trial: be enrolled in a CBTm program, be located within Manitoba, be over the age of 12 years old, have access to the internet, and speak English. The study uses a parallel design with a 1:1 allocation ratio for treatment and sham groups.

Exclusion criteria for the present sub study included a history of seizures, pregnancy, and age <18 years old. Any potential harms of HD-tDCS were included in the consent form. All HD-tDCS participants provided written, informed consent and were randomly assigned to one of two groups using a computerized random number generator: CBTm+sham ($n = 10$) or CBTm+stim ($n = 10$; stim = HD-tDCS). We ended up recruiting 24 individuals due to logistical constraints. Twenty participants completed and were included in this study. The personnel operating the stimulator were aware of patient's allocation to either treatment or sham, but the assessors were blinded. Participants were not formally asked to guess their treatment allocation, and the credibility of the sham condition was not directly assessed; the ramp-up/ramp-down sensation was maintained in both the sham and control arms to preserve participant blinding. The study was approved by the University of Manitoba Biomedical Research Ethics Board. All methods were performed in accordance with the relevant guidelines and regulations. Patient reports on age, sex and demographics were obtained using self-report questionnaires.

HD-tDCS treatment was administered three times a week for five weeks (weekdays only; 15 sessions in total) at Health Sciences Centre in Winnipeg. Prior to the first CBTm session, participants completed all self-report questionnaires and were scanned with MRI at baseline. The assessments were repeated within a week after the completion of the last HD-tDCS session for follow up of treatment benefits. Participants who dropped out of the study or had missing data were excluded from analyses for completeness. As this is a preliminary study, the MRI data is not included in this report but will be published at a later date.

Of the 24 individuals recruited, 3 discontinued participation before completing the study and 1 was excluded due to an artifact in their MRI scan, yielding the final sample of 20 (10 per group); intention-to-treat or imputation-based sensitivity analyses were not conducted.

Clinical Assessments

Validated self-report symptom questionnaires were administered at baseline (prior to the first CBTm session), as well as 1-week post-treatment, through our parent clinical trial. The questionnaires included the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), Patient Health Questionnaire 9 (PHQ-9; measuring depression symptoms) (Williams, 2014a), Generalized Anxiety Disorder 7 (GAD-7) (Williams, 2014b) and CD-RISC. The MoCA is a cognitive screening tool used to detect mild cognitive impairment and was administered here as a cognitive screening covariate, to characterize the sample and confirm that participants did not present with clinically significant cognitive impairment, rather than as a primary outcome of interest. The PHQ-9 scale consists of nine standardized questions to measure the severity of depressive symptoms in the past two weeks. It has shown strong internal reliability and test-retest reliability (Kroenke et al., 2001). Each of the nine items are graded on a Likert scale, producing a total score between 0 and 27, with a higher score indicating a higher amount of depressive symptoms (Kroenke et al., 2001). The GAD-7 is a seven item screening tool used to examine symptoms of anxiety, scored from 0 to 21, with 21 being the highest score for anxiety symptoms (Spitzer et al., 2006). The GAD-7 has been shown to have high concordance with anxiety disorder diagnoses, making it reliable for the evaluation of anxiety (Spitzer et al., 2006). Lastly, the CD-RISC is a self-report measure that assesses resilience, or, an individual's ability to 'bounce back' following adversity, with a higher score indicating higher levels of resilience (Campbell-Sills & Stein, 2007). This is defined as an individual's ability to cope with stress and adapt to adversity (Campbell-Sills & Stein, 2007).

Cognitive Behavioural Therapy with Mindfulness

Both CBTm+sham and CBTm+stim groups received weekly virtual (i.e., Zoom) CBTm classes. For a 5-week period, one weekly 90-minute, group class was delivered in PowerPoint format. The sessions are interactive, with a range of 5-40 participants in size and were led by one or two trained clinicians and one research assistant. Homework was assigned during each session relating to the material that was covered, allowing participants to practice the skills learned during each session. The 5-week schedule was as follows: **Class 1.** Introduction and outline of the course, rules and expectations, self-help resources, mindfulness exercises, basics of cognitive therapy and thought records. **Class 2.** Mindfulness exercise, review homework, basics of behaviour therapy, introduction to exposure therapy, behavioural activation, and goal setting. **Class 3.** Mindfulness exercise, review homework, and tips for healthy living focused on sleep, nutrition, physical activity, and substance use. **Class 4.** Mindfulness exercise, review homework, anger management strategies, goal setting, assertiveness training, self-compassion and problem-solving. **Class 5.** Mindfulness, dealing with stress and stressful experiences, and wellness planning.

High-Definition Transcranial Direct Current Stimulation

The CBTm+stim group received HD-tDCS (throughout 5-week CBTm period) over the course of 5 weeks, while the CBTm+sham group received a sham HD-tDCS (throughout 5-week CBTm period). The MxN-GO EEG stimulator (Soterix Medical Inc., New York, NY, USA) was used to deliver direct current to the target brain areas via electrodes and conductive gels. In both groups, 9 electrodes are placed on the scalp through 8 channels + 1 ground position.

CBTm+stim group: Current intensity was determined based on computer simulation using HDTargets software (Soterix Medical Inc., New York, NY, USA)) that results in maximum focal

current on the left VLPFC ($x=-50$, $y=+26$, $z=+8$) and the PCC ($x=1$, $y=-61$, $z=38$) with inward field orientation (Figure 1). During HD-tDCS, a constant current was applied for 20 minutes with a peak current of 2 mA. **CBTm+sham group:** Electrodes were configured in the same manner as the stimulation group and using the sham-option of the machine, stimulation current was applied to the left VLPFC and the PCC for a 30 second ramp-up followed by a 30 second ramp-down, with no active stimulation being administered, except for the ramping-up and ramping-down periods to match the CBTm+stim group.

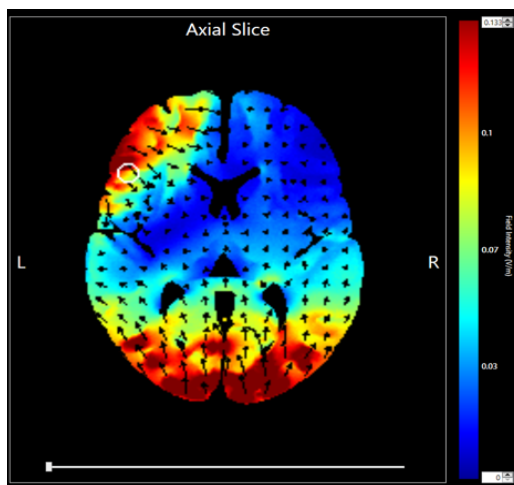


Figure 1. Simulated electrical current map used to deliver optimal current using HD-tDCS. The map was generated using HDTargets software (Soterix Medical Inc., New York, NY, USA) with red indicating the strongest amount of current and blue indicating the weakest amount of current.

Adverse Events and Tolerability

Some participants did report slight scalp tingling and itching, but this did not cause discomfort or interfere with study continuation. Participants did not report erythema, headache, or other discomfort at the electrode sites and no participants discontinued due to stimulation-related discomfort or other safety concern.

Statistical Analysis

PHQ-9, GAD-7, and CD-RISC are the primary behavioural outcomes of this study, as per the parent trial. MoCA was included as a cognitive screening covariate rather than an outcome of interest. Correlational analyses relating baseline and change scores across these measures were not pre-specified and are reported as exploratory analyses.

All statistical analyses were completed using the Statistical Package for the Social Sciences (SPSS, IBM Corp., version 27.0, Armonk, NY) software using standard parametric and non-parametric approaches, as appropriate, for sample size and data distribution. Baseline demographic and clinical characteristics (age, sex, education, MoCA, PHQ-9, GAD-7, and CD-RISC) were compared between the CBTm+sham and CBTm+stim groups using independent samples t-tests or chi-squared tests, as appropriate. Baseline correlations between clinical measures (MoCA, PHQ-9, GAD-7, and CD-RISC) were assessed using Pearson's correlation coefficients. This was done separately for both pre- and post timepoints.

To complement the baseline correlation analyses described above, change of scores (Δ ; post-pre) were calculated for all outcome measures to examine associations between treatment-related changes. Pearson's correlation analyses were used to assess associations between changes in PHQ-9, GAD-7, and CD-RISC across the full sample. Spearman's rank correlation coefficients were used within each group ($n = 10$ per group) to assess associations between baseline CD-RISC and changes in symptom measures, as well as between Δ CD-RISC vs. Δ PHQ-9 and Δ GAD-7. Differences between the group-specific correlation coefficients were tested using Fisher's r-to-z transformation.

To evaluate treatment effects over time, repeated measures general linear models (GLM) were used with Group (CBTm+sham vs. CBTm+stim) as the between-subjects factor and Time

(pre- vs. post-intervention) as the within-subjects factor. Group $\times$ Time interaction effects were assessed for all outcome variables. Planned within-group comparisons (pre- vs. post-intervention) were conducted using Bonferroni-adjusted post hoc tests to assess changes over time within each group.

4.5 Results

For all examined variables (age, sex, education, MoCA, PHQ-9, GAD-7, and CD-RISC), there were no significant differences between CBTm+sham and CBTm+stim groups ($ps > 0.18$; Table 1) at baseline and following treatment. Correlation analyses at baseline (Table 2) revealed that PHQ-9 (depression) and GAD-7 (anxiety) scores were highly correlated with each other ($r = 0.780, p < 0.001$) while CD-RISC scores were marginally but significantly correlated with both measures (GAD-7: $r = -0.480, p = 0.032$; PHQ-9: $r = -0.466, p = 0.038$). MoCA (cognition) was also correlated with PHQ-9 ($r = -0.448, p = 0.048$) with a trend-level correlation with GAD7 ($r = -0.438, p = 0.053$). CD-RISC did not correlate with MoCA ($r = 0.095, p = 0.690$).

While no significant interaction (Group $\times$ Time) effects were observed for any variables ($ps > 0.2$; Table 1), planned contrasts of time (before vs. after 5-week intervention) within each group (Table 3) showed that both PHQ-9 (depression) and GAD-7 (anxiety) were significantly reduced in both groups ($ps < 0.001$, Figure 2), the changes of which were also highly correlated with each other ($r = 0.819, p < 0.001$; Table 4; Figure 3). CD-RISC (resilience) scores were significantly enhanced only in the CBTm+stim group ($p = 0.002$), while a trend-level improvement was also observed after sham stimulation in the CBTm+sham group ($p = 0.095$; Table 3). The improved CD-RISC scores were significantly correlated with lowered GAD-7 scores ($r = -0.451, p = 0.046$; Table 4; Figure 3), which was more pronounced within CBTm+stim group ($\rho = -0.669, p = 0.035$) while no significant correlation was observed in

CBTm+sham group ($\rho = -0.121, p = 0.740$; Table 5). Δ CD-RISC was not associated with Δ PHQ-9 ($r = -0.216, p = 0.361$). MoCA (cognition) was not significantly changed in either group ($p > 0.5$), therefore, no correlational analyses were conducted with Δ MoCA. Baseline CD-RISC scores correlated with Δ PHQ-9 ($\rho = 0.758, p = 0.011$) and Δ GAD-7 ($\rho = 0.70, p = 0.034$) only in the CBTm+stim group while no significant correlation was observed in the CBTm+sham group ($\rho = -0.280, p = 0.432$; Table 5). Direct comparison of the group-specific coefficients showed that the association between baseline CD-RISC and Δ PHQ-9 differed significantly between groups ($z = 2.30, p = 0.021$), whereas the corresponding comparisons involving Δ GAD-7 did not (baseline CD-RISC: $z = 1.28, p = 0.199$; Δ CD-RISC: $z = -1.25, p = 0.212$). These comparisons were not pre-specified and are uncorrected.

Table 1. Demographic data and mean ($\pm$ SD) questionnaire scores for baseline (pre-treatment) and five-week follow-up (post-treatment, values in bold). Data are presented for chi-squared analysis (i.e., sex) or independent t-tests contrasting CBTm+sham and CBTm+stim groups.

Questionnaire		CBTm+stim	CBTm+sham	<i>T</i> , <i>F</i> or χ^2	<i>df</i>	<i>p</i>
<i>N</i>		10	10			
Age (years)		46.6 $\pm$ 13.0	40.4 $\pm$ 10.1	1.760	1,18	0.205
Sex (M:F)		4:6	3:7	1.800	1,1	0.180
MoCA	Pre	27.8 $\pm$ 3.0	27.2 $\pm$ 2.6	0.014	1,18	0.638
	Post	27.6 $\pm$ 4.2	27.2 $\pm$ 1.9	0.806	1,18	0.787
	Interaction			0.067	1,18	0.789
PHQ-9	Pre	11.0 $\pm$ 6.1	12.5 $\pm$ 3.5	2.006	1,18	0.509
	Post	4.1 $\pm$ 3.4	5.5 $\pm$ 3.0	0.252	1,18	0.347
	Interaction			0.002	1,18	0.961
GAD-7	Pre	8.1 $\pm$ 6.7	9.7 $\pm$ 4.4	1.364	1,18	0.535
	Post	2.5 $\pm$ 2.5	3.9 $\pm$ 2.8	0.000	1,18	0.255
	Interaction			0.009	1,18	0.926
CD-RISC	Pre	22.2 $\pm$ 5.3	21.8 $\pm$ 7.4	0.887	1,18	0.891
	Post	28.5 $\pm$ 8.1	24.9 $\pm$ 8.8	0.011	1,18	0.351
	Interaction			1.655	1,18	0.215

MoCA = Montreal Cognitive Assessment

PHQ-9 = Patient Health Questionnaire-9

GAD-7 = Generalized Anxiety Disorder 7-Item Scale

CD-RISC = Connor-Davidson Resilience Scale 10-Item Scale

Table 2. Correlations across measured variables at baseline. Pearson's correlation coefficient, r (p -value presented in parentheses).

	MoCA	PHQ-9	GAD-7	CD-RISC
MoCA		-0.448 (0.048)*	-0.438 (0.053)	0.095 (0.690)
PHQ-9	-0.448 (0.048)*		0.780 (<0.001)*	-0.480 (0.032)*
GAD-7	-0.438 (0.053)	0.780 (<0.001)*		-0.466 (0.038)*
CD-RISC	0.095 (0.690)	-0.480 (0.032)*	-0.466 (0.038)*	

* = *significant at the $p < 0.05$ level, uncorrected*

MoCA = Montreal Cognitive Assessment

PHQ-9 = Patient Health Questionnaire-9

GAD-7 = Generalized Anxiety Disorder 7-Item Scale

CD-RISC = Connor-Davidson Resilience Scale 10-Item Scale

Table 3. Effect of time within group on behavioural outcomes in CBTm+sham and CBTm+stim groups. Data is presented as mean change (post-pre; $\pm$ SD); p -values are estimated using repeated measures GLM. d_{rm} is effect size.

Questionnaire		Change	p	d_{rm}
MoCA	CBTm+stim	-0.2 $\pm$ 2.1	0.546	-0.046
	CBTm+sham	0.0 $\pm$ 1.3	0.546	0.000
PHQ-9	CBTm+stim	-6.9 $\pm$ 5.5	<0.001*	-1.310
	CBTm+sham	-7.0 $\pm$ 3.2	<0.001*	-2.138
GAD-7	CBTm+stim	-5.6 $\pm$ 6.3	0.002*	-1.024
	CBTm+sham	-5.8 $\pm$ 2.5	0.001*	-1.269
CD-RISC	CBTm+stim	6.3 $\pm$ 6.6	0.002*	0.878
	CBTm+sham	3.1 $\pm$ 4.3	0.095	0.365

* = significant at the $p < 0.05$ level, uncorrected

MoCA = Montreal Cognitive Assessment

PHQ-9 = Patient Health Questionnaire-9

GAD-7 = Generalized Anxiety Disorder 7-Item Scale

CD-RISC = Connor-Davidson Resilience Scale 10-Item Scale

Table 4. Correlation across changes in variables. Pearson's correlation coefficient, r (p -value).

	Δ PHQ-9	Δ GAD-7	Δ CD-RISC
Δ PHQ-9		0.819 (<0.001)*	-0.216 (0.361)
Δ GAD-7	0.819 (<0.001)*		-0.451 (0.046)*
Δ CD-RISC	-0.216 (0.361)	-0.451 (0.046)*	

* = significant at the $p < 0.05$ level, uncorrected

PHQ-9 = Patient Health Questionnaire-9

GAD-7 = Generalized Anxiety Disorder 7-Item Scale

CD-RISC = Connor-Davidson Resilience Scale 10-Item Scale

Table 5. Association between CD-RISC and its changes with changes in PHQ-9 and GAD-7. Spearman's ρ (p -value).

		Δ PHQ-9	Δ GAD-7
CBTm+sham	CD-RISC (pre)	-0.268 (0.454)	0.104 (0.774)
	Δ CD-RISC	0.034 (0.926)	-0.121 (0.740)
CBTm+stim	CD-RISC (pre)	0.758 (0.011)*	0.670 (0.034)*
	Δ CD-RISC	-0.280 (0.432)	-0.669 (0.035)*

* = significant at the $p < 0.05$ level, uncorrected

PHQ-9 = Patient Health Questionnaire-9

GAD-7 = Generalized Anxiety Disorder 7-Item Scale

CD-RISC = Connor-Davidson Resilience Scale 10-Item Scale

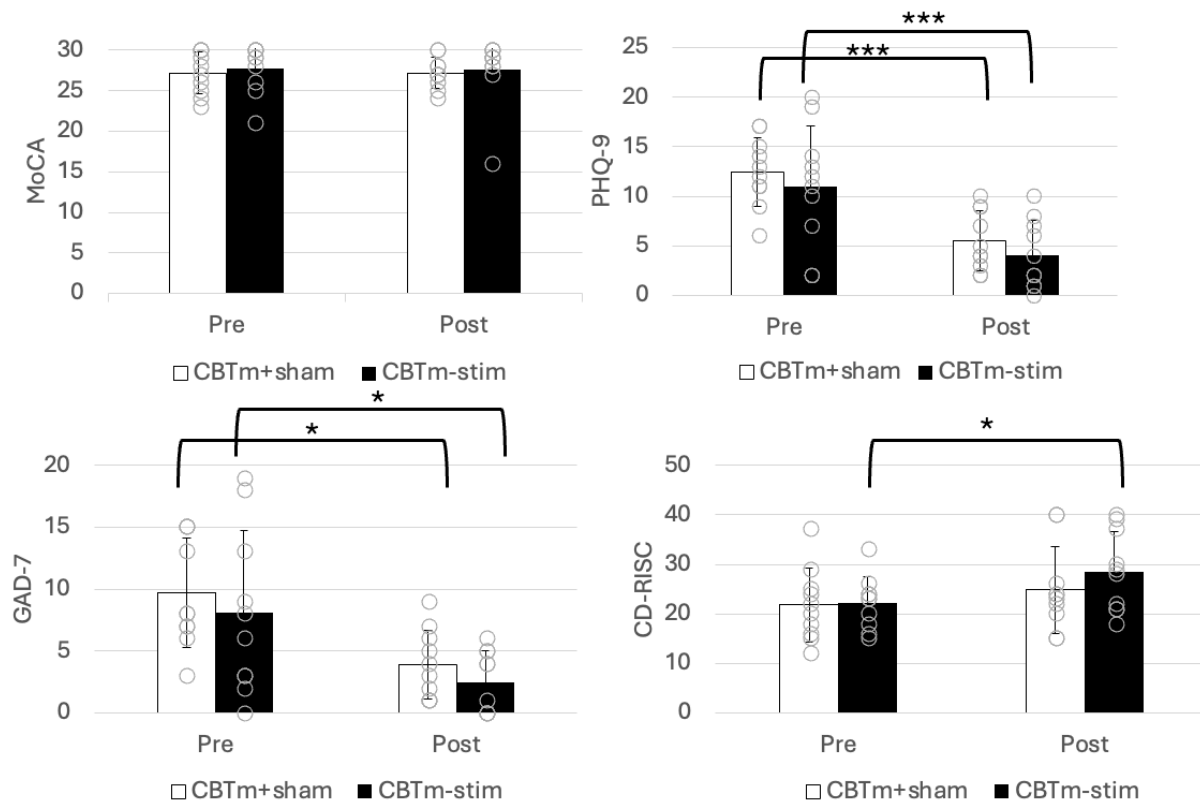


Figure 2. Changes in behavioural outcome measures following intervention. Bar graphs illustrating pre- to post-intervention scores for CBTm+sham and CBTm+stim groups. A. MoCA scores did not differ significantly in either group. B. PHQ-9 scores significantly decreased in both groups, indicating reduced depressive symptoms. C. GAD-7 scores significantly decreased in both groups, indicating reduced anxiety symptoms. D. CD-RISC scores significantly increased in the CBTm+stim group, reflecting improved psychological resilience, while only a trend-level increase was observed in the CBTm+sham group. Error bars represent standard deviation. *** $p < 0.001$, * $p < 0.05$.

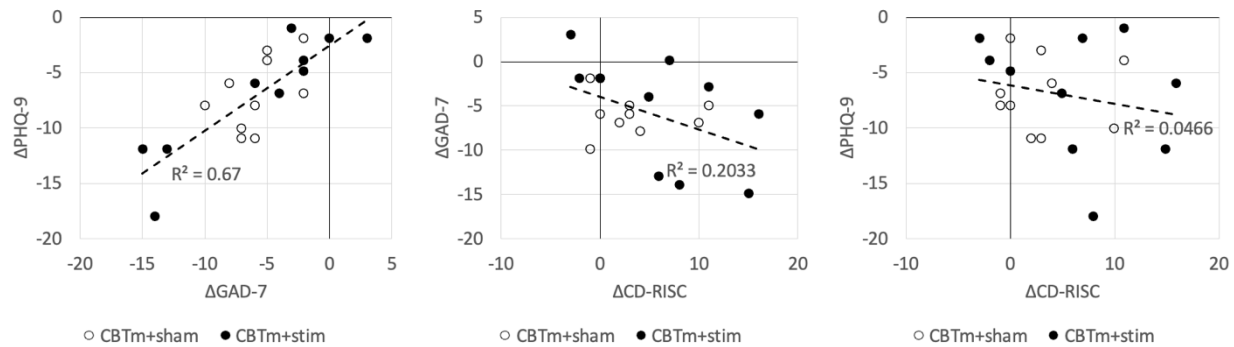


Figure 3. Correlational Analysis of Changes in GAD-7, PHQ-9, and CD-RISC. Scatterplots illustrating relationships between change scores (Δ ; post–pre) in clinical outcomes following the intervention. A. Δ PHQ-9 and Δ GAD-7 were positively correlated ($r = 0.819, p < 0.001$), indicating that reductions in depressive symptoms were closely associated with reductions in anxiety symptoms. B. Δ CD-RISC were negatively correlated with Δ GAD-7 ($r = -0.451, p = 0.046$), indicating that improvement in psychological resilience were associated with reductions in anxiety symptoms. C. Δ CD-RISC and Δ PHQ-9 were not significantly correlated ($r = -0.216, p = 0.361$).

4.6 Discussion

The present study examined whether CBTm combined with HD-tDCS targeting the PCC and VLPFC was associated with changes in mental health outcomes and psychological resilience. This hypothesis was driven by prior work from our lab showing that increased FC between these regions is associated with sustained psychiatric symptom reduction and improved resilience following CBTm (Khanam, 2022). Both groups (CBTm+stim and CBTm+sham) improved in PHQ-9 and GAD-7, and they did not differ significantly in the interaction effect, suggesting CBTm alone can produce meaningful reductions in depression and anxiety symptom severity. This finding is consistent with prior research validating CBTm, as it has been shown to decrease symptoms of both depression and anxiety (Thakur et al., 2019).

Participants receiving active HD-tDCS demonstrated significant improvements in psychological resilience, while those receiving CBTm alone only showed a trending increase (Davidson et al., 2022; Thakur et al., 2019). The noteworthy increase in resilience, as measured by the CD-RISC, reflects an increase in individuals' ability to adapt to stress and maintain psychological wellbeing during adverse circumstances (Shrivastava & Desousa, 2016). These findings should be interpreted in the context of our prior neuroimaging work, which identified the PCC-VLPFC FC to be associated with improved resilience rather than primary symptom severity (Khanam, 2022). Importantly, these stimulation targets (left VLPFC–PCC) were derived from an fMRI study in which CBTm was specifically used to enhance resilience in public safety personnel without clinically significant mental health symptoms, with the goal of strengthening resilience as a preventative factor for PTSD (Khanam, 2022). While PHQ-9 and GAD-7 measure symptom severity, resilience through the CD-RISC measures a broader capacity for adaptive coping and flexibility (Yao & Hsieh, 2019). As such, the results of this work are consistent with our hypothesis that the left VLPFC and PCC connectivity is associated with psychological resilience (Khanam, 2022)—the HD-tDCS tailored to target the resilience-related regions (left VLPFC and PCC) may be associated with CD-RISC score changes in this preliminary sample. However, because no significant Group $\times$ Time interaction was observed, these findings do not demonstrate a differential treatment effect of HD-tDCS and should be interpreted as preliminary observations.

Our correlational findings suggest that changes in resilience and anxiety symptoms were related within the CBTm+stim group. More specifically, increases in CD-RISC were significantly associated with reductions on the GAD-7, only in the CBTm+stim group, whereas this relationship was less apparent in the CBTm+sham group. However, despite this association,

anxiety symptoms (GAD-7) did not show a significantly greater reduction in the CBTm+stim group compared to CBTm+sham, which may reflect limited statistical power due to the small sample size ($n = 10$ per group) and relatively low baseline symptom severity. It is also possible that HD-tDCS preferentially enhances cognitive processes involved in cognitive control and stress adaptation as opposed to acute symptom expression, however this possibility was not directly tested in the present study. In this context, resilience represents an upstream foundational process which supports long-term mental health, whereas specific symptom measures may capture immediate symptom change. Overall, this may indicate that CD-RISC scores are associated with anxiety symptoms in the active stimulation group, although the underlying mechanism remains unclear (Yao & Hsieh, 2019).

The Group x Time interactions for the depression and anxiety scales were not significant. However, it is important to note that participants were not required to meet a threshold for depression or anxiety symptoms prior to study participation. This allowed for more modest symptom severity to exist within the participant group. Resilience, alternatively, can be improved in all individuals regardless of baseline mental health, and has been identified as a key protective factor against the onset and reoccurrence of psychiatric symptoms (Shrivastava & Desousa, 2016). Resilience may be a marker of long-term mental health benefits, even in the absence of specific mental health-related symptom change (Chmitorz et al., 2018). Another potential explanation for the lack of interaction includes the short 5-week follow up period in the current analyses which may limit the ability to detect differential changes in symptom severity over time and instead, reflect limitations of the measures themselves. Future studies with longer follow-up intervals may help determine the clinical significance of the observed changes in resilience.

Our correlational findings provide additional insight into the relationships between the measured variables. As expected, PHQ-9 and GAD-7 scores were strongly correlated, reflecting the well-established comorbidity between depression and anxiety. Within the CBTm+stim group, participants with lower baseline resilience showed the greatest reduction in depressive symptoms, and this relationship differed significantly from that in the CBTm+sham group. This is consistent with the possibility that stimulation is of most benefit to those with the least pre-existing capacity to adapt to stress.

Limitations to this study should be acknowledged. Primarily, the small sample size ($n = 20$) may have limited the statistical power to detect small or moderate effects. We originally targeted to recruit 24 individuals, but the study had to be prematurely concluded due to logistic and personnel constraints. Small sample sizes also increase the likelihood that variability exists within the symptom severity of participants, potentially affecting treatment response. Second, the leniency of the inclusion criteria allowed for heterogeneity within the sample as the participants varied in baseline symptom severity. Despite this heterogeneity, this approach increases real-world clinical applications as it is reflective of potential patient populations. Lastly, the 5-week study duration is relatively short and limits the ability to detect more long-term changes in symptom expression. Longer follow-ups would have allowed us to better characterize the persistence and clinical relevance of the observed behavioural changes. In addition, adequate within-subject statistical power does not guarantee generalizable between-group effects. Given the considerable inter-individual variability typically observed in the response to psychotherapy and neuromodulation, a sample of $n = 10$ per group limits the generalizability of the comparisons reported here. The correlation and sub-group analyses (Tables 2, 4, and 5) are based on small samples ($n = 10$ per group for the group-specific analyses) and are therefore sensitive to

individual data points, therefore these associations should be interpreted as hypothesis-generating rather than confirmatory. Finally, because functional connectivity between the PCC and VLPFC was not assessed in this report, the present findings cannot establish whether any behavioural changes were mediated by the hypothesized neural mechanism, which will be tested in future work that reports behavioural and connectivity outcomes together.

Importantly, these effects were observed in a sample that was not required to meet clinical thresholds for depression or anxiety, highlighting the potential for HD-tDCS to enhance resilience even in a largely sub-clinical population. This is important due to the increased interest in non-pharmacological approaches to treat mental health, making HD-tDCS a promising area of research. This suggests that such interventions may have both therapeutic and preventative applications by strengthening resilience prior to the onset of more severe psychiatric symptoms. Future studies should aim to replicate these findings in larger sample sizes to understand these benefits more thoroughly and investigate functional brain changes using neuroimaging. This future work would allow for a deeper understanding of the neural mechanisms that underly mental health treatment. Additionally, examining participants who have been formally diagnosed with anxiety or depression may allow for the detection of potential additive effects of HD-tDCS on symptom reduction.

Overall, while HD-tDCS did not significantly reduce depression or anxiety symptoms beyond the changes from CBTm alone, the CBTm+stim group showed a significant group increase in psychological resilience, whereas the CBTm+sham group showed only a non-significant trend. Because the Group $\times$ Time interaction was not significant, this pattern should not be interpreted as evidence that active stimulation improved resilience beyond CBTm alone.

Despite this, these results warrant further investigation, as they suggest a relationship may exist between active stimulation and resilience-related outcomes.

This study investigated the behavioural effects of combination therapy, using CBTm and HD-tDCS targeting the PCC and VLPFC. Within-group analyses showed a significant increase in psychological resilience in the CBTm+stim group, with only a non-significant trend in the CBTm+sham group. However, because the Group $\times$ Time interaction was not significant, these findings cannot conclude that HD-tDCS improved resilience beyond CBTm alone. The correlation observed between baseline resilience and decreased depressive symptoms in the CBTm+stim group is an exploratory finding based on a small sample ($n = 10$ per group). These findings suggest neural drivers of change but cannot be taken as evidence of a neuromodulatory mechanism since functional connectivity between the PCC and VLPFC was not assessed in this report. Continuing to examine these therapies through further studies with larger sample sizes and more extended follow-up periods are warranted to determine the clinical significance of these findings.

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Competing Interests

None.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Clinical Trial Information

Clinical Trial Government ID: NCT05555056

Date submitted: 2022-09-20

Chapter 5: Discussion

This thesis aims to investigate the neurobiological changes associated with psychological interventions in mental health disorders, using neuroplasticity and resilience as treatment measures. The influence of neuroscience on psychiatric illness is a growing field and recent perspectives argue that mental illnesses are disorders of neural circuitry rather than clinical symptoms alone (Gordon et al., 2024). The present thesis contributes to this understanding by demonstrating that evidence-based psychotherapies are associated with neural processes through two independent studies. These studies were conducted to assess how therapeutic interventions and neuromodulation impact mental health symptoms and associated neural processes. The first study examines neuroanatomical changes following CPT in patients with PTSD using voxel-based morphometry and diffusor-tensor imaging. The second study investigated whether HD-tDCS targeting the PCC and VLPFC could enhance behavioural outcomes when combined with CBTm. Together, these studies support the idea that psychological interventions are associated with measurable neurobiological adaptation. Importantly, both studies support the idea that treatment-related improvements extend beyond immediate symptom reduction and may involve more broad neural processes associated with psychological resilience. Although the studies differed in methodology and patient population, they are related by a central question: how do targeted psychotherapies and neuromodulation techniques alter the brain to support mental health?

5.1 Overview of the Studies

The first study examines the neuroanatomical changes in individuals with PTSD following 12-week CPT, compared to healthy controls. Using VBM and DTI, the study identified two regions where structural change occurred—the left thalamus and the left cerebellum (crus

I/II). More specifically, patients with PTSD showed a decrease in GMV in the left thalamus and an increase in WMV in the left cerebellum following treatment, a pattern not observed in the HC group. This was supported further by the DTI analysis, which found increased FA in the left cerebellum. Together, these findings suggest that CPT leads to structural neuroplastic reorganization in regions implicated in fear processing and emotional regulation. The second study examined whether the delivery of CBTm alongside HD-tDCS augmented the therapeutic outcomes. Both the active stimulation (CBTm+stim) and sham (CBTm+sham) groups demonstrated significant reductions in depression (PHQ-9) and anxiety (GAD-7) symptoms over the five-week program. Interestingly, however, only the CBTm+stim group showed a statistically significant improvement in psychological resilience as measured by the Connor-Davidson Resilience Scale (CD-RISC), with the CBTm+sham group showing only a trend-level improvement. Furthermore, CD-RISC scores were significantly negatively correlated with GAD-7 scores in the active stimulation group, but not the sham group, suggesting that HD-tDCS-enhanced resilience may contribute to the improvement of anxiety symptoms. Combined, these studies demonstrate that the changes in neuroplasticity produced following these interventions is a viable and clinically meaningful mechanism of therapeutic benefit.

5.2 Integrating Neuroimaging and Neuromodulation

Neuroimaging has transformed our understanding of the brain, in part through its ability to identify regions associated with therapeutic benefit (Langguth et al., 2012; Yen et al., 2023). Techniques such as MRI allow researchers to observe which brain regions change following a psychological intervention, providing an idea of the neural processes that accompany therapeutic benefit (Langguth et al., 2012; Yen et al., 2023). Although neuroimaging is a powerful tool, its

main limitation is that it is observational in nature. When a brain region changes alongside symptom improvement, that association is correlational meaning it cannot imply causality.

Neuromodulation addresses this limitation by moving from observation to intervention (Hartwigsen & Volz, 2021; Parpura et al., 2013). Rather than passively recording what the brain does during treatment, neuromodulation actively perturbs neural activity in a targeted region and then measures the behavioural consequences (Hartwigsen & Volz, 2021). This approach, known as "perturb-and-measure" in neuroimaging, evolved from the logic that if you manipulate a variable and the outcome changes, you have evidence of a causal relationship that correlation alone cannot establish (Paus, 2005). In neuroscience, non-invasive techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) make it possible to briefly enhance or suppress activity in specific brain circuits in healthy and clinical populations (Hartwigsen & Volz, 2021; Paus, 2005).

The present thesis integrates both approaches across its two studies. Chapter 3 uses neuroimaging to characterize structural brain changes following CPT in individuals with PTSD. Like all neuroimaging work, these findings are correlational in that they revealed regions that change alongside symptom improvement but cannot confirm that the neural changes drove symptom improvement. Chapter 4 in the present work addresses this limitation by using HD-tDCS to facilitate activity in the VLPFC-PCC network during CBTm. This allows for a causal relationship to be established between the VLPFC-PCC network and behavioural outcomes, particularly resilience. This translates into important clinical value, as it indicates that pairing stimulation with therapeutic intervention can maximize symptom improvement.

Taken together, the two studies demonstrate the added benefit of using neuromodulation in neuroimaging studies, as it allows for the inference of causality. This framework is

generalizable across psychiatric conditions and therapeutic approaches and represents a path toward understanding not just whether treatments work, but why they work.

5.3 The Common Theme of Resilience

One theme that unifies both manuscripts is psychological resilience—defined as an individual’s ability to adapt to adverse situations—as both a target and marker of treatment success (Wu et al., 2013). Resilience has emerged as a potentially distinct therapeutic process with its own measurable behavioural and neurobiological correlates (Srivastava et al., 2024). Additionally, resilience at baseline has been shown to act as a protective factor against the development of anxiety and depression (Srivastava et al., 2024), making it a good marker for the development of mental illness. In the first study examining CPT, resilience was not directly measured, but structural changes observed within the thalamus and cerebellum have been implicated within the neurobiology of stress regulation and adaptive coping, processes that are foundational to resilience (Wu et al., 2013; Yoshii, 2021). In the second study examining CBTm+HD-tDCS, resilience was the primary outcome measure that differentiated the active stimulation group from the sham group, while similar levels of improvement were measured in depression and anxiety. Unlike symptom-specific measures, resilience reflects an individual’s broader ability to cope and adapt to wellbeing in the face of ongoing stressors (Nutritional Epidemiology Research et al., 2021). This finding may suggest that measures of resilience capture dimensions of recovery that extend beyond conventional symptom scales such as the PHQ-9 and GAD-7.

The overlap between these two suggests that psychological interventions operate through a resilience-mediated pathway that is distinct from symptom suppression alone. The CBTm+HD-tDCS study demonstrates that targeted neuromodulation selectively enhances CD-RISC scores

without causing changes in PHQ-9 or GAD-7 outcomes beyond those attributed to CBTm alone. This pattern raises the possibility that resilience may represent a more sensitive or earlier marker of therapeutic response than symptom change itself. In other words, interventions may first strengthen the cognitive and emotional capacities required to manage distress before this translates into measurable reductions in depressive or anxiety symptom burden. Longer term studies with follow up are required to determine the long-term effects of increased resilience on PHQ-9 and GAD-7 symptoms, but current literature suggests increased resilience leads to symptom improvement in both anxiety and depression (Nutritional Epidemiology Research et al., 2021; Wang et al., 2025).

The CPT structural neuroimaging study further complements this interpretation by demonstrating that successful CPT is associated with structural alterations in regions implicated in resilience. The cerebellum, increasingly recognized for its role in affective processing in addition to motor coordination, has been linked to emotional prediction and stress response (Turner et al., 2007). Similarly, the thalamus serves as a critical relay centre involved in filtering emotional information and coordinating communication between brain regions involved in fear processing and executive control (Yoshii, 2021). (Shrivastava & Desousa, 2016). Effective integration of these processes may facilitate emotional regulation and cognitive flexibility, both of which are considered important components of resilience (Wu et al., 2013). Structural changes within these regions following CPT may therefore reflect enhanced activity within neural systems that support adaptive coping and recovery after trauma.

Overall, these findings support the idea that resilience is closely intertwined with, rather than secondary to, symptom improvement. This indicates resilience may be a foundational mechanism through which the long-term benefit of therapeutic intervention exerts its effects.

This coincides with other research suggesting that strengthening resilience-related neural circuits may enhance an individual's ability to tolerate distress and lead to improved emotional well-being (Srivastava et al., 2024). This interpretation also helps explain why symptom-based measures alone may fail to fully capture meaningful therapeutic change, particularly in interventions aimed at modifying underlying neurocognitive processes. The findings of this thesis suggest resilience may represent an important intermediate treatment target in psychiatric care.

5.4 The Role of the Implicated Brain Regions

The present thesis examines the regions involved in emotional regulation, trauma processing and cognition, extending beyond the limbic system into the cerebellum, posterior cingulate cortex and ventrolateral prefrontal cortex. Growing evidence has suggested that regions beyond the corticolimbic circuit play a role in the regulation of mental health, supported further by this work.

In the CPT study, decreased GMV in the thalamus was observed in patients with PTSD. The thalamus has been described as a major relay centre involved in sensory integration and fear-processing (Yoshii, 2021). Altered thalamic structure within PTSD has been related to hypervigilance and maladaptive threat processing (Yoshii, 2021). This suggests changes in GMV of the thalamus post-CPT may reflect the normalization of trauma-related sensory processing (Yoshii, 2021). Similarly, the cerebellar involvement in emotional regulation may be responsible WMV structural changes following CPT (Strata et al., 2011). Increased WMV and FA integrity supports improved cognitive flexibility following treatment for PTSD in treatment responders.

The targets for the CBTm+HD-tDCS study were predetermined based on prior lab work which demonstrated increased FC in the VLPFC-PCC region following 5-week treatment with

CBTm (Khanam, 2022). The PCC is a highly connected brain region that has an important role in cognition, importantly through processes such as self-reflection and attention regulation (Leech & Sharp, 2014). It is a major region within the brain's default mode network which becomes active during introspective thinking (Leech & Sharp, 2014). Abnormal activation of the PCC has been reported in conditions including depression and PTSD (Leech & Sharp, 2014). Similarly, the VLPFC plays a role in integrating cognitive control with emotional regulation. (Weintraub-Brevda & Chua, 2018). The executive functions of the VLPFC include decision making and inhibition and emotional regulation, which help to organize behaviour and interpret emotional stimuli (Weintraub-Brevda & Chua, 2018). Together the VLPFC-PCC plays a large role in emotional regulation by integrating higher order cognitive control with self-processing. Strengthening this network appears to increase resilience, which is thought to enhance an individual's ability to regulate emotions and respond effectively to challenging experiences (Khanam et al, in progress).

5.5 Neuroplasticity as a Driver of Change

Both studies investigated whether brief psychological interventions could produce measurable change within the brain. In the CPT study, neuroplasticity manifested as changes in the architecture of GMV, WMV, and FA following treatment. The increase of cerebellar WMV and FA is consistent with the idea that psychotherapy allows for increased WMV in regions that support the integration of cognition and emotion (Bang et al., 2023). The decrease in left thalamic GMV is a more nuanced finding, but may be explained by pruning of maladaptive connections within a region that had become hyperactive in PTSD patients (Yoshii, 2021). In the CBTm+HD-tDCS study, we investigated whether applying external neuromodulation would catalyze functional changes in the PCC-VLPFC network that CBTm is thought to engage. This

hypothesis was formulated based on prior functional MRI work from our laboratory showing that functional connectivity increases in CBTm patients at the 5- and 12-week follow ups. Despite the lack of neuroimaging findings within our pilot study, the current behavioural findings support the idea that HD-tDCS deepens the cognitive effects of CBTm, most visibly in the domain of resilience. In future studies, increasing the sample size will be crucial to furthering our understanding of these results. Together, these findings align with a growing literature demonstrating that therapeutic interventions can produce neuroplastic changes in the adult brain (Samodien et al., 2026).

5.6 Methodological limitations

Both studies share methodological limitations including small sample sizes, brief follow-up periods, and broad inclusion criteria. These limitations should be acknowledged within our work and will guide our future directions. Importantly, both studies were designed as pilot clinical trials intended to explore preliminary neurobiological and clinical trends, and therefore smaller sample sizes were expected at this stage of investigation. For sample size, the CPT study had a $n = 56$ (reduced further in specific analyses) and the CBTm+HD-tDCS study had a $n = 20$. Both samples are considered underpowered for neuroimaging and clinical trials in research. Despite this, many neuroimaging studies report small sample sizes, limiting statistical power and contributing to concerns regarding reproducibility and inflated effect estimates within the field (Szucs & Ioannidis, 2020). A large methodological review of neuroimaging research demonstrated that although sample sizes have gradually increased over time, many studies remain underpowered which increases the likelihood of false positive findings and reducing the reliability of reported associations (Szucs & Ioannidis, 2020). These limitations may partly explain the inconsistent neuroimaging findings observed across psychiatric and neuromodulation

research (Szucs & Ioannidis, 2020). In the structural MRI study specifically, the small sample may have contributed to the paradoxical findings in the HC group, as explained by Berkson's Paradox (Ko, 2025). Berkson's paradox explains that control-group effects can emerge as statistical artifact in underpowered interactions (Ko, 2025). Larger scale analyses would be valuable for both studies. A second limitation is the short follow up time present within both studies. The study outcomes were obtained one-week post treatment in the CBTm+HD-tDCS study and within two-weeks post treatment in the CPT study. Neither study design allows for the investigation of long-term changes following treatment, including both behavioural measures and neuroimaging investigations. A previous study within our lab has demonstrated increased VLPFC-PCC FC at the 12-week follow up, which is promising in terms of treatment durability, but should be further investigated for sustained clinical benefit (Khanam, 2022). Lastly, the inclusion criteria were heterogenous in each study. In the CBTm+HD-tDCS study, the eligibility criteria included self-referral to the CBTm program, allowing for a diverse range of symptom presentation. In the CPT study, the HC group included both trauma-exposed patients and trauma-naïve patients due to small sample size. This heterogeneity introduces potential variability in the brain structures of the participants and can attenuate group differences. Future work should stratify these groups further to strengthen the potential results.

Chapter 6: Clinical implications and Future Directions

The findings of this thesis will contribute to further our understanding of treatments for mental health intervention. The CBTm+HD-tDCS study supports the feasibility of adding non-invasive neuromodulation to the treatment regimen in psychiatric conditions such as depression and anxiety. The preferential enhancement of resilience within the active stimulation group suggests that HD-tDCS may be a good adjuvant therapy alongside psychotherapy. Similarly, the CPT study provides insight into the neural processes responsible for success with therapeutic treatment. The cerebellum and thalamus may be regions that are partially responsible for symptom relief in patients with PTSD, allowing for the development of PTSD specific neuroimaging biomarkers. These allow for the prediction of treatment response and the planning of clinical treatment.

Future directions for this work include further investigation with larger, more homogenous samples, which will hopefully reinforce the findings within this thesis. This will increase the reliability and generalizability of these findings, while allowing for the robust identification of treatment-related neural changes and biomarkers.

Chapter 7: Conclusion

The present thesis includes two studies that complement each other in their overlap investigating the neural and behavioural mechanisms through which psychological interventions improve mental health. The CBTm+HD-tDCS study demonstrated that targeting the VLPFC-PCC network can increase resilience beyond the ability of CBTm alone, while the CPT study showed that PTSD patients undergo structural changes within the thalamus and cerebellum following treatment. Together, these studies emphasize that the brain is adaptive in its dynamic responses to treatment.

Beyond their individual findings, these studies showcase the value of integrating neuroimaging and neuromodulation approaches. Neuroimaging allows for the identification of changes within neural circuits alongside clinical improvement, providing a tangible explanation for treatment response. However, because these findings are correlational, they cannot explain whether the observed neural changes are causal in symptom recovery. Neuromodulation is a complementary approach that allows for the direct modulation of candidate neural networks. In this way, neuromodulation enhances the field of neuroimaging beyond observation alone.

Together, this thesis demonstrates the effectiveness of combining neuroimaging with neuromodulation to investigate treatment-related brain changes. Understanding these changes and learning to enhance them is the key to optimizing and diversifying the treatment options for mental health conditions. More broadly, these findings support a growing model of psychiatric treatment in which psychological interventions promote measurable neuroplastic adaptation, laying the groundwork for future therapies that integrate various forms of therapy to improve outcomes in depression, anxiety, and PTSD.

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