Neural Correlates of an Introductory Cognitive Behavioral Intervention with Mindfulness in Strengthening Resilience to Post-Traumatic Stress Injuries Among Public Safety Personnel

By

Manzuma Khanam

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Department of Human Anatomy and Cell Science

University of Manitoba

Winnipeg, Manitoba

ABSTRACT:

The term “post-traumatic stress injuries (PTSI)” means highly prevalent mental disorders among public safety personnel (PSP) which can be developed as a result of repeated exposure to different traumatic events as a part of their job. PTSI is associated with a range of negative outcomes and its underlying neurophysiological mechanisms are still not well understood. Cognitive behavioral therapies (CBT) are the ‘gold standard’ interventions for the treatment of PTSD. Cognitive Behavioral Therapy with Mindfulness (CBTm) is a brief intervention that introduces introductory cognitive behavioral strategies and mindfulness meditation. Preliminary evidence suggests that CBTm may be effective in mitigating subthreshold PTSD symptoms in PSP who do not meet diagnostic criteria for the condition. There is little research on the neurological mechanisms of PTSI resiliency. Previous studies showed that the posterior cingulate cortex (PCC; including the precuneus) of the Default Mode Network (DMN) is associated with preventing and treating PTSI. We have conducted a functional magnetic resonance imaging (fMRI) study to investigate the neural mechanisms of the resilience in PSP who underwent CBTm with a particular interest on PCC connectivity. Twenty-five PSP individuals with no or low symptoms of common mental disorders completed the current randomized neuroimaging study. 11 participants underwent the 5-week CBTm intervention, and 14 participants were waitlisted as control group. All participants were assessed by self-report measures, resting-state fMRI (measuring functional connectivity (FC)), and pseudo-continuous arterial spin labeling (pCASL; measuring cerebral blood flow) at baseline, 5-week and 12-week follow-up. The benefits of CBTm observed with self-report measures were accompanied with increased FC between the PCC and the left vlPFC at 5-week and 12-week follow-up, and decreased CBF in the left vlPFC at 12 weeks. At baseline, the CBF of PCC and vlPFC were correlated with self-reported psychological resilience as assessed by the Connor-Davidson Resilience Scale (CD-RISC), while FC between the two regions was a dominant predictor for the CD-RISC at 12-weeks. This finding suggests that the PCC and the left vlPFC play an important role in resilience against PTSI, and the benefit of CBTm may be associated with FC changes between the two regions.

Keywords: post-traumatic stress injuries, post-traumatic stress disorder, cognitive behavioral therapy, mindfulness, functional magnetic resonance imaging, resting state network, functional connectivity, cerebral blood flow.

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ACC	Anterior Cingulate Cortex
ASL	Arterial Spin Labelling
BOLD	Blood Oxygen Level Dependent
CAPS	Clinician Administered PTSD Scale
CASL	Continuous Arterial Spin Labelling
CBF	Cerebral Blood Flow
CBT	Cognitive Behavioral Therapy
CBTm	Cognitive behavioral therapy with a mindfulness component
CD-RISC	Connor Davidson Resilience Scale
CEN	Central Executive Network
CNS	Cerebral Nervous System
CPT	Cognitive Processing Therapy
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual
DTI	Diffusion Tensor Imaging
EMDR	Eye Movement Desensitization and Reprocessing
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
FWHM	Full width at half maximum
GAD	Generalized Anxiety Disorder
IC	Intrinsic Connectivity
ICA	Independent Component Analysis
MBCT	Mindfulness Based Cognitive Therapy
MINI	Mini International Neuropsychiatric Interview
MRI	Magnetic Resonance Imaging
MTL	Medial temporal lobe
OFC	Occipitofrontal Cortex
PASL	Pulsed Arterial Spin Labelling
PCC	Posterior Cingulate Cortex

PCL	PTSD Checklist
PCT	Present-centered therapy
PD	Psychological debriefing
PE	Prolonged Exposure
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PHQ	Patient Heath Questionnaire
PSP	Public Safety Personnel
PTSD	Post-traumatic stress disorder
rACC	rostral Anterior Cingulate Cortex
SN	Salience Network
SPSS	Statistical Package for the Social Science
VLPFC	Ventrolateral Prefrontal Cortex

1 INTRODUCTION:

The term “post-traumatic stress injuries (PTSI)” refers to a wide range of mental disorders that can develop following exposure to a traumatic event, including clinically diagnosed post-traumatic stress disorder (PTSD), major depressive disorder (MDD), and generalized anxiety disorder (GAD) (1). The term PTSI has become more frequently used criteria to cover wider mental health problems developing following trauma exposure. Tri-services (police – including the Royal Canadian Mounted Police, firefighters and paramedics), correctional employees, border services personnel, operational and intelligence personnel, search and rescue personnel, Indigenous emergency managers, dispatch personnel are public safety personnel (PSP) (1), and they are more prone to develop PTSI due to more frequent exposure to potentially psychologically traumatic events (PPTE) . While systemic workplace adaptation to technological advancement (e.g., using drones or robots for higher risk situations) may reduce the number of trauma exposures that PSP are facing in order to reduce the incidence of PTSI, another equally important strategy is to foster resilience among PSP as a preventive measure (2-4).

Resilience is an ability to adapt to trauma, adversity or significant threat (5). Emotion regulation, positive emotions, cognitive flexibility, and reappraisal are some of those factors which can increase resilience (6). Resilience enhancing interventions have been shown to be effective for the management, recovery and relapse prevention of PTSI (7). High levels of resilience have shown protective effects against suicidal ideation associated with depression or anxiety (8). Different studies showed that resiliency is inversely correlated with PTSI symptoms (9-11). Accordingly, it has been suggested that promoting resilience can be used as a key factor in the treatment of anxiety and depression (9).

The two most commonly used approaches to promote resilience are cognitive behavioral therapy and mindfulness-based interventions (12). CBT is the first-line treatment for PTSI. It is a goal-oriented, systematic psychotherapy to resolve symptoms of PTSI through challenging unhelpful or overly negative cognitions and changing maladaptive behaviors (13). CBT can be offered in a group format with group numbers ranging from 5 to 20 people (14, 15), or delivered in individual format. Mindfulness-based interventions are another widely used treatment for anxiety and mood disorders and are characterized by attending to ongoing events and

experiences in the present moment in a receptive and non-judgmental way (16). There is evidence that both CBT and mindfulness-based interventions are effective at reducing the severity of different mental disorders (15, 17-20).

In recent years, more resources have been invested to increase access to these evidence-based interventions for individuals living with mental health problems. Yet, one of the limiting factors for timely delivery of these interventions has been the shortage of mental healthcare resources and increased wait times for individuals who need more rapid access to psychological interventions. To address this problem, a team of clinician-scientists led by Dr. Jitender Sareen developed an introductory Cognitive Behavioral Therapy with Mindfulness (CBTm) skills class consisting of four 90-minute weekly sessions that can be delivered to large groups (21). These strategies are designed to promote resilience by improving anxiety and depressive symptoms. To date, these classes have been delivered to hundreds of individuals in Manitoba in a range of mental health settings. More recently, the team hypothesized that offering CBTm to PSP who have not developed PTSI (e.g., new PSP recruits) could potentially prevent future development of PTSI via increased resilience. The clinical trial to test this hypothesis was recently completed (NCT4002050) and the findings based on self-report measures of symptoms of mental disorders will be published elsewhere (Bolton et al., in preparation). The preliminary data showed significant clinical benefits of CBTm, yet the neurophysiological evidence for the effectiveness of the intervention is still lacking (i.e., that CBTm in fact re-organizes brain functions). This limitation is also common in most psychological intervention studies for PTSI.

Recent advances of neuroimaging analytic techniques have proven to be useful for providing this evidence (22-25). Synchronous fMRI signals between remote brain regions over time indicates that the two regions are functionally "connected," (26) and a collection of different functionally connected brain regions comprise resting state networks (27). One of the ways to investigate the functional connections of a specific brain region is seed-based connectivity analysis. This method investigates the specific brain network organizations by examining the resting-state time series of this 'seed' region and its correlations with the time series of the rest of the brain (28). The results of these investigations yield functional connectivity maps (fcMap) which show the functional connections of the predefined brain region (29-31). For example, the amygdala is the brain structure that is the most extensively

investigated in the context of fear conditioning and PTSD (32). The functional connectivity of the amygdala, anterior cingulate, parahippocampus, and insula has consistently shown to be abnormal in PTSD patients (33).

Multivariate pattern recognition methods such as independent component analysis (ICA) combined with fMRI have dramatically improved our capacity to understand brain connectivity and shed light on the neurophysiological underpinnings of many mental disorders (34, 35). The default mode network (DMN) is one of the most extensively studied ICA-derived resting state networks, the disturbance of which has been associated with many neurological and psychiatric disorders including PTSD, anxiety, depression (36-39). The DMN is situated in the posterior cingulate cortex/precuneus (PCC) and medial prefrontal cortex (mPFC), with prominent nodes in the medial temporal lobe (MTL) and the angular gyrus (26). The DMN has a role in episodic memory, autobiographical processes, and social cognitive processes (40). Among all the regions of DMN, the PCC is often regarded as a significant node for the DMN for different reasons. The PCC shows the highest brain metabolism at resting state (41), and it correlates reliably with the other regions of the DMN. Thus, PCC-based connectivity maps can replicate DMN topology (42, 43). Abnormal PCC activity has been identified in patients with PTSD (44, 45), anxiety disorders (46), and depression (47, 48).

Recent brain imaging studies suggest that CBT rectifies the abnormal DMN, limbic, and prefronto-parietal connectivity associated with PTSD, which partly explains the neurophysiological foundation of CBT-related benefits (22-25). The underlying neuropsychological mechanisms of CBT have been associated with improved positive reappraisal, which is a component? of resilience, and with increased activity in the dorsolateral, ventrolateral and medial prefrontal cortical regions (49). Higher resilience has also been associated with the hyperactivation of the prefrontal cortex (50). One year post-CBT results showed increased activation of the prefrontal cortex-parietal region of the brain which was associated with cognitive reappraisal which reduced the symptoms related anxiety (51).

Mindfulness-based exposure therapy (MBET), which is a combination of the traditional in vivo exposure therapy and mindfulness training such as breathing exercise and self-compassion training, has shown to reduce PTSD symptoms, and it increases PCC-dorsolateral prefrontal cortex (dlPFC) functional connectivity (24). This finding suggests that along with

PCC, the PFC may play an important role for symptom improvement, which is in line with the neurocircuitry model of PTSD - the loss of top down control from the areas such as medial prefrontal cortex (mPFC), ventromedial prefrontal cortex (vmPFC), subcallosal cortex and orbitofrontal cortex (OFC) over the limbic areas (52).

As summarized above, resting-state functional connectivity studies have shed light on the level of neural communication among distant brain regions. However, it does not address how much neural information is processed at the regional level, which in fact can be estimated using older technologies such as positron emission tomography with specific radiotracers, e.g., fluorodeoxyglucose (measuring glucose metabolism) and $H_2{}^{15}O$ (measuring cerebral blood flow (CBF)). Both CBF and glucose metabolism are indicators of the synaptic transmission (53), and their abnormality in the same key regions (PFC, PCC, etc.) have been associated with PTSD, depression (54-56) and lower resilience (57). The CBF can also non-invasively be estimated by MRI using pseudo-continuous arterial spin labeling (pCASL) (58). The pCASL estimates CBF of each region by subtracting tagged-control image pairs with and without radiofrequency labelling of arterial blood water (59). While moderately coupled, pCASL and resting-state fMRI provide complimentary information about regional activity and connectivity, respectively (60).

Building on our parallel randomized clinical trial that tested the clinical effects of CBTm on subthreshold symptoms of PTSI in PSP (Bolton et al., in preparation), I investigated the neural underpinnings of CBTm using resting-state fMRI and pCASL in relation to one's resilience. This is the first brain imaging study to investigate the neural effects of a preventive intervention for PTSI. I hypothesized that both regional neural activity (measured by pCASL) and connectivity (measured by resting-state fMRI) of the PCC would be related to resilience to PTSI, and CBTm would affect PCC connectivity as well as the activity of its connected regions, during strengthening resilience to PTSI among PSP.

2 BACKGROUND

2.1 Post-Traumatic Stress Injuries

PTSI is a non-clinical term which includes PTSD, MDD and GAD (1). PTSD is a psychiatric disorder that can be developed following direct or indirect exposure to traumatic events like physical or sexual assault, injury, combat-related trauma, natural disaster, or death (61). PTSD symptoms include avoidance, flashbacks of the traumatic events, hyperarousal, hypervigilance, insomnia, and anhedonia (62). A higher risk of suicidal ideation and incidence of suicide have also been associated with PTSD (63, 64). The incidence of PTSD is particularly high among PSP due to their increased risk of trauma exposure on the job (14, 65-67).

In addition to PTSD, PSP also have high prevalence estimates of other mental health problems including depression (68, 69) and anxiety (70, 71). Depressive disorders involve low mood, loss of pleasure in activity engagement, feelings of emptiness, and irritability along with somatic and cognitive changes that can impact functioning in multiple domains(61). Anxiety disorders are accompanied by excessive fear and anxiety, avoidance of the feared situations, and associated behavioral disturbances like restlessness, irritable, being fatigue easily (61). Generalized anxiety disorder (GAD) is the most common anxiety disorder, and is characterized by fear or worry about different areas (e.g., health, finances, interpersonal relationships, etc.) for more than 6 months and the worrying is more than is expected for that situation (72).

The term PSP indicates the tri-services (police – including the Royal Canadian Mounted Police, firefighters and paramedics), correctional employees, border services personnel, operational and intelligence personnel, search and rescue personnel, Indigenous emergency managers, and dispatch personnel provide the safety and security to Canadians across all jurisdictions (1). As PSP are frequently exposed to different traumatic events (e.g., suicides, accidents and disasters) as a part of their daily job responsibilities that are often not possible to avoid, they are prone to developing PTSI (73). The government of Canada specifically targets PTSI in their action plan (Supporting Canada's Public Safety Personnel: An Action Plan on Post-Traumatic Stress Injuries) to support the overall mental health and well-being of all PSP.

2.1.1 Epidemiology

PTSD and related conditions including major depressive disorder, generalized anxiety disorder, and panic disorder are highly prevalent among PSP worldwide, typically ranging between

10% and 44% (74-78). Meanwhile, the lifetime prevalence among the adult general population ranges between 6.1 to 9.2% percent in United States and Canada (79-82). In the US, the past year prevalence of PTSD was 3.6% in adults aged 18–54 years (83). Previous studies showed that women are more prone to developing PTSD than men and the prevalence in women is twice than that in men (84). Research suggests that women have a higher tendency to blame themselves for the trauma, disengage mentally, experience intense event-related fear, suppress emotions and thoughts, or avoid the trauma and trauma triggers (85-88).

PSP often face other psychiatric disorders. The rate of depression, for example, is estimated at 26.4% among PSP (69) which is significantly higher than in the general population at 11.3% (68). Women are 1.6 to 3.1 times more likely to have depression than men (89). The prevalence of anxiety is up to 10% in the general population (70) while it is 15% among PSP (71). It is twice as prevalent in women than men (90, 91). Patient with anxiety may be associated with other mental illnesses like the depression (90). One study revealed that 22% paramedics showed both the symptoms of depression and anxiety (78).

2.1.2 Symptoms

Symptoms of PTSD usually appear within 3 months of experiencing traumatic events (83). However, up to 25 percent of individuals with PTSD show delayed onset of symptoms after 6 months or more (92). A person can be diagnosed with PTSD if they are more than six years old and meet the threshold of each criteria (A through H) given by American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (61): A person will meet *criterion A* of PTSD if he or she has the experience of exposure to actual or threatened death, serious injury, or sexual violence directly or indirectly. A person will meet *criterion B* if he or she experiences one (or more) of the intrusion symptoms like recurrent, unwanted distressing memories associated with the traumatic event(s) which begins after the traumatic event(s) occurred. *Criterion C* is related to the persistent avoidance of stimuli related to the traumatic event(s) like trauma-related thoughts or feelings, or other external trauma reminders which appears after the traumatic event(s) occurred. *Criterion D* can be described as the negative alterations in cognitions and mood related to the traumatic event(s) which appears or worsens after the traumatic event(s) occurred. Marked changes in arousal and reactivity related to the traumatic event(s) which appears or worsens after the traumatic event(s) occurred can be

treated as *criterion E*. *Criterion F* is met when the duration of the above-mentioned disturbances (criteria B, C, D, and E) is more than one month. If the disturbance causes any clinically significant distress or any impairment in social, occupational, or other important areas of functioning it will be treated as *criterion G*. A person will meet *criterion H* if the disturbance is not attributable to the physiological effects of a substance like medication, alcohol or another medical condition.

People with PTSD show more occupational problems, have poorer supports from family and friends and more disability than healthy controls (96). A previous systematic review revealed that the quality of life is poor among patients with PTSD (97). PTSD symptoms like re-experiencing trauma and hyperarousal are particularly associated with the impairment of work performance (98). Additionally, suicidal ideation and dying by suicide are more common among patients with PTSD (63, 64, 99, 100). Thus, there is an immediate need to establish a preventive measure to protect against PTSD, particularly among those at an increased risk, such as PSP.

PTSD has high comorbidity with other mental disorders like depression and anxiety and different studies suggested different causes behind this co-occurrence. Some suggested mechanisms are (a) PTSD may be act as a risk factor of developing depression and anxiety; (b) the comorbidity may be an artifact of symptom overlap; (c) depression and anxiety increase the risk of PTSD development, or (d) depression and anxiety are different mental disorders which just share common risk factors (101-103).

According to DSM-5, a person can be diagnosed as a patient with major depressive disorder (MDD) if he or she has five or more of the following symptoms present almost daily for at least 2 weeks, with at least one symptom which includes either depressed mood or loss of interest or pleasure, and associated with significant hampering of psychosocial functioning: (a) depressed mood, (b) fatigue or reduced energy levels, (c) prominent and/or repeated thoughts of death or suicide, (d) difficulties with concentration, memory, or decision-making, (e) sleep disturbances, (f) significant lack of interest in usual activities, or loss of pleasure/enjoyment (anhedonia), (g) marked feelings of guilt or self-blame (which may be delusional), (h) loss of appetite or weight, or increased appetite or weight, (i) observable psychomotor agitation or retardation. In spite of being a common mental disorder, depression is often yet misunderstood, under-reported and largely untreated (104). A meta-analysis revealed that approximately 52% individuals have

depression as a comorbid condition of PTSD (105). Another longitudinal study showed that the rate of comorbidity of depression among patients with PTSD is between 21% to 94% (106). In case of PTSD with depression there are more symptoms and poor quality of life (107). Individuals with both PTSD and depression also have more neurocognitive memory dysfunction and a higher likelihood of engaging in suicidal behavior (108-110). Even the symptoms severity of PTSD are poorer in patients with MDD in comparison to the patients without MDD (108). Some symptoms like lack of interest, restricted range of affect and sleep disturbances overlap between PTSD and MDD (111).

According to DSM-5, a person can be diagnosed as a patient of GAD if he or she has excess anxiety and worry in more days than not for at least 6 months during many events or activities ; faces difficulties to control the worry; the anxiety and worry are accompanied by three (or more) of the following symptoms (with at least some symptoms having been present for more days than not for the past 6 months): (a) restlessness, (b) easily fatigued, (c) lack of concentrating or mind going blank, (d) being irritable, (e) tensed muscle, (f) insomnia or not having sound sleep. In GAD, there may be clinically significant impairment in social, occupational, or other important sites by the anxiety, worry, or physical symptoms and this impairment is not for any other medical or psychiatric condition. GAD increases the mortality rate (as it increases risk of cardiovascular diseases), physical illnesses, smoking and alcohol consumption (112, 113). The comorbidity rate of anxiety in the patients with PTSD is 39% - 97% (106). There are some symptoms overlapping between PTSD and GAD like irritability, hypervigilance and increased startle reflex (111). However, the association between PTSD and GAD is not related to any specific type of trauma (114). GAD increases the symptoms severity of PTSD (115).

2.1.3 Treatment

There are two primary lines of treatment for PTSD. One is psychotherapy and another one is pharmacological therapy (119, 120). CBT, Cognitive Processing Therapy (CPT), Narrative Exposure Therapy (NET), Prolonged Exposure (PE) Therapy, Brief Eclectic Psychotherapy (BEP), Eye Movement Desensitization and Reprocessing (EMDR) therapy, Mindfulness Training are commonly used psychotherapies for PTSD, however, CPT and PE have been the most widely studied to date (CITE). Pharmacological therapies are not discussed for the purpose of this thesis.

In different clinical trials, it has been found that these psychotherapies are more effective for PTSD? in comparison to pharmacological treatments and have fewer side effects (119, 121, 122). CBT is a systematic, goal-oriented psychotherapy to solve problems related to maladaptive emotions, behaviors, and cognitions (13). CBT is considered the first-line treatment for PTSD patients and can be offered as group sessions with numbers ranging from 5 to 20 people (14, 15). This therapy can also be delivered in individual format. The main focus of CBT is to reduce patients' symptoms by the identification and alteration of unhelpful cognitions and behaviors (123). Cognitive Processing Therapy (CPT) is a type of CBT with more emphasis on trauma-related symptoms, which aims to directly change maladaptive beliefs and assumptions related to traumatic events (124). Prolonged Exposure (PE) therapy is another type of CBT which has been established on the basis of two components (125). One is imaginal exposure of the traumatic event and another one is in vivo gradual exposure to trauma-related situations. A meta-analysis showed that following PE, treated PTSD patients performed 86% better than PTSD patients in the control group (120). Narrative Exposure Therapy (NET) aims on experiences with the strongest arousal responses which stimulates fear and helplessness leading to dissociative responses where the participants are asked to remember prominent, positive experiences (125). Brief Eclectic Psychotherapy (BEP) is an effective trauma-focused exposure treatment where the main focus of the exposure to the trauma is to feel relieved rather than habituation (126). Eye Movement Desensitization and Reprocessing (EMDR) therapy is a comprehensive eight-phase approach which works on the roles of memory and information processing (127). The unprocessed memories of adverse life events are stored in episodic memory inappropriately and causes dysfunctional responses. EMDR therapy processes those unpleasant memories by short exposures of paired with sequential sets of bilateral eye movements which ultimately decreases arousal, negative affect, and imagery vividness (128).

Mindfulness-based interventions are used to treat anxiety and mood disorders and this therapy is conducted by focusing on present events and experiences in a receptive and non-judgmental way (16). Mindfulness-based interventions have been shown to improve cognitive flexibility, working memory capacity, goal-directed behavior, and emotional regulation because one's attention and cognitive resources are shifted away from dysfunctional thoughts and emotions (129).

In depression, antidepressant medications, psychotherapies or a combination of antidepressant medications and psychotherapies can be used (130). The balance between various neurotransmitters in the central nervous system is restored by antidepressants to stabilize the depressed mood. On the other hand, psychotherapies work to improve self-esteem and promote flexible thinking. Psychotherapies like CBT, interpersonal psychotherapy, problem-solving therapy and behavioral activation are used for the treatment of depression (131). CBT has been discussed above; interpersonal psychotherapy focuses on unresolved grief, relationship conflict, role transition like loss of job, retirement, social isolation; problem-solving therapy identifies problems and implements problem-solving techniques; behavioral activation works by increasing positive reinforcing activities (89). Likewise, anxiety disorders also have two types of treatment options - medications (e.g., antidepressants, anxiolytics) and psychotherapy (e.g., CBT) (132).
Resilience and Prevention

Reviews of the literature on the prevention of PTSD have been conducted and show that there are very few studies in this area (133-135). Most studies have focused on post-traumatic event measures, e.g., CBT has shown to be effective in preventing PTSD when administered after the exposure of traumatic events (136-139). A randomized control trial showed that a three-session modified prolonged exposure intervention is capable of preventing PTSD during follow-up (140). A collaborative care approach is another intervention to prevent PTSD where trauma exposed participants are referred to CBT, pharmacological management, or a combination depending on symptoms and patient preferences. A randomized controlled trial among 207 acutely traumatized patients showed reduced PTSD symptoms among those who received collaborative care after the trauma (141). According to Howlett et al., 2016, psychotherapies like CBT are more effective than pharmacological therapies for PTSD prevention albeit the number of clinical studies on pharmacological therapies to prevent PTSD is limited (133).

There has been no evidence-based guideline for a pre-trauma prevention strategy against PTSI (135), while it has been postulated that strengthening one's resilience may prevent PTSD among PSP (2). Resilience has been described differently among researchers. According to Horn et al (2018), it encompasses the ability to adapt to any adversity or trauma (5). According to Hobfoll et. al (2015) it is the capability of a person or a human system to return back to normal state when the stressor is lifted without causing any long term harm or damage (142). Another

study stated resilience as the ability to accept failure, humiliation or depression and not only to bounce back to previous normal state but also to achieve greater height of success, happiness, and inner strength (143). In sum, resilience is the development of that ability which is necessary to adapt any kind of adversity and return to normal state and/or improvement of the current state. Of note, a resilient person may still have PTSI symptoms as resilience is not simply the absence of disorder (144). Depression, anxiety, and OSIs are inversely associated with resilience, however (3, 4, 116). Previous research suggests that a resilience enhancing intervention may promote management, recovery, and relapse prevention of these mental disorders (7). A study found that moderate to severe suicidal ideation among those with higher levels of depression or anxiety can be protected by a higher level of resilience (8).

Psychological resilience is related to emotion regulation, positive emotion, and cognitive flexibility and reappraisal (6). Emotion regulation is a mental process to monitor, evaluate and modify emotional reactions (145). It is modulated by the top-down cortical regulation of fear processing structures (146). Positive cognitive style of emotion regulation is a target for CBT to improve resilience (147). Cognitive reappraisal is an explicit emotion regulatory procedure to change an emotion by altering one's thinking (148). More balanced and helpful cognitive reappraisal is one of the components of CBT therapies for PTSD (49). Positive reappraisal is not only beneficial to patients with PTSD but also helpful in developing resilience among patients with anxiety and depression. A study suggested positive reappraisal as a potential target for psychotherapeutic intervention to improve resilience in the patients with anxiety or depression (149).

The effect of mindfulness-based training has also been associated with positive reappraisal (150) and it is effective for the treatment of anxiety and depression (151). Over the last decade there have been different studies on the effects of mindfulness on resilience development as well as symptom reduction of different psychological illnesses (152, 153). Previous work investigated preventative effect of the mindfulness-based programs for trauma exposed adults. Mindfulness Based Resilience Training (MBRT) is an integrating program where the participants are trained in standardized mindfulness practicing of those factors that is related to resilience (155). One study on MBRT suggested that this training can improve sleep quality and reduce burnout levels, perceived stress, and fatigue (156). Another study showed that

mindfulness training can help to decrease burnout by increasing resilience (157). The mindful awareness and resilience skills training (MARST) program is an eight-week mindfulness-based intervention that can be delivered either in person or online (158). MARST can increase resilience by improving mindfulness skills, positive cognitive-reappraisal skills, and greater awareness of positive emotions (159, 160).

Though CBT and mindfulness training both have been using for the development and strengthening of resilience, they have some differences. CBT focuses on negative thoughts and aims to replace those thoughts with positive thoughts. On the other hand, mindfulness focuses on present moment and aims to accept everything without any judgement. CBT needs qualified CBT therapist to identify the thoughts and situations which can create a problem and working together with the therapist may improve or change a particular way of thinking. This may involve evaluating thinking patterns and using behavioral experiments to help consider alternative ways of thinking and behaving. Mindfulness, however, can be learned and practiced by own with the help of books or online information or as part of a workshop, course or practice group.

There are very few studies that have examined the neural mechanisms of developing resilience. According to Richard Davidson in his book, “The Emotional Life of Your Brain”, resilience is associated with the hyperactivation of the prefrontal cortex of the brain (50). Resilience is associated with decreased gray matter in the frontal and occipital lobe of the brain (161). A previous study showed that CBT increased activity in the dorsolateral, ventrolateral and medial prefrontal cortical regions and increased positive reappraisal which is a psychological factor of resilience (49). In another study, one year post-CBT results showed that brain activity increased in the prefrontal cortex-parietal region which was associated with reappraisal during social anxiety reduction (51). Resilient individuals showed higher activation in the prefrontal cortex during voluntary upregulation of emotional responses (162). During top-down attentional control in the presence of emotional distracters, an increased activation of frontal regions in resilient subjects was also found (163). However, the neural mechanisms of resilience development associated with CBTm (and of CBT more broadly) are yet unclear.

2.2 Development of CBTm

While there is clear evidence that psychological interventions that include cognitive behavioral strategies and/or mindfulness can help in increasing resilience and alleviating PTSD symptoms, one of the most significant limiting factors is the shortage of mental healthcare resources which can lead to significantly increased wait times for individuals who need immediate access to psychological interventions such as CBT. To solve this problem, a new CBT program was developed which can be delivered to a large group of individuals with varying diagnoses (164). After further improvement of this concept and to enhance the acceptability and accessibility of CBT, a team of clinician-scientists led by Dr. Jitender Sareen at the University of Manitoba developed a 4-session class called CBTm that provides introductory exposure to cognitive behavioral and mindfulness strategies and can be delivered to large groups (90-minute weekly session) (21). After completion of 4 classes, if clients required more intensive treatment, booster sessions or conventional CBT group therapy had been delivered.

The use of CBTm as a preventive measure for PSP was recently investigated in our parent study which was funded by the Workers Compensation Board of Manitoba (NCT4002050: PI: Dr. Sareen). As part of their initial pilot work, they created a Project Advisory Committee (PAC), consisting of members and leadership from the Winnipeg Fire and Paramedic Service and the Winnipeg Police Service. This group reviewed the CBTm content and recommended that a fifth class be added specifically focused on responding to traumatic events and stress using a CBT approach along with safety and well-being planning for managing crisis situations. As such, the program was adapted to a 5-session model for use in PSP. The duration of each session is 90 minutes.

2.2.1. Preliminary Results of the Parent Trial

In this randomized clinical trial, a total of one hundred and two (n = 102) PSP were recruited. Among them forty-two (n = 42) were excluded. Exclusion criteria included: (1) being less than 18 years old, (2) scoring above the clinical cut off on the following self-report symptom measures: (a) Posttraumatic Checklist-5 (PCL-5) score >37 (to exclude PTSD symptoms) (165), (b) Patient Health Questionnaire-9 (PHQ-9) score >10 (to exclude depression) (166), (c) Generalized Anxiety Disorder-7 (GAD-7) score >7 (to exclude anxiety) (167), (3) a history of receiving treatment (e.g., medication or psychological interventions) for a mental disorder in the

past 6 months, (4) having any psychiatric disorder including PTSD or suicidal ideation in the past six months.

From the remaining sixty participants (n = 60), CBTm was administered among twenty-eight (n = 28) participants and thirty-two (n = 32) participants were waitlisted. To avoid any kind of selection bias, participants enrolled in the study were randomly assigned to either the CBTm intervention or the waitlisted control group. Nine self-report mental health scales were used to assess mental health and related constructs of the PSP at baseline, 5-week follow-up (within 1-week of completion of the CBTm classes) and at 12-week follow up (165-173) (Table 1). These scores were analyzed to examine the effectiveness of CBTm in increasing resilience and decreasing PTSI symptoms.

The researchers found significant reductions in PCL-5 and PHQ-9 scores after the CBTm (Bolton et al., in preparation). This was in line with previous studies showing that CBTm may improve symptoms of depression and anxiety in civilian cohorts (21, 164). Interestingly, Connor-Davidson Resilience Scale (CD-RISC) scores which was used to assess the level of resilience were not significantly changed after the CBTm.

CBTm is easily accessible, acceptable, cost effective and even it can be delivered through online (174). This therapy is designed to improve resilience (5). The purpose of my thesis is to investigate the neural mechanisms of CBTm effects as a preventative measure among PSP using neuroimaging techniques.

2.3 Neuroimaging and PTSI

There are different neuroimaging techniques to analyze functions of the brain. Magnetic resonance imaging (MRI) utilizes the facts that each different molecules have specific resonance frequencies, e.g., different brain tissues have different compositions of hydrogen atoms which allows differentiation between grey matter and white matter, which is useful for assessing structural damages. By quantitating the magnetic signal changes in response to certain intervention or spontaneous changes, fMRI can monitor blood oxygen level dependency (BOLD) which is tightly coupled with regional cerebral blood flow (rCBF) (175). rCBF or regional cerebral metabolic rate of glucose (rCMTG), using radioactively labelled molecules (tracer molecules) can be measured by PET (176-178). SPECT measures change in rCBF and identifies neural activities to form tomographic three-dimensional images like PET (176, 178). EEG measures electrical

potentials generated by synchronously activated neurons (179). Similarly, the external magnetic field generated by the synchronous neural activity of the brain can be measured by MEG (180). There are some differences among these functional imaging methods (e.g., X, Y) which are described briefly in Table 2 (180).

2.3.1 Structural Imaging

T1-weighted structural MRI is one kind of imaging measure for the visualization and analysis of the anatomical properties of the brain as well as to detect brain damage and abnormalities. It can also be used to quantify geometric structural properties, including not only the size and volume of a given structure, but also thickness of the cortical area like grey matter (181, 182). Previous T1-weighted imaging studies showed mixed results in the context of PTSD. For example, Li et al., (183) showed increased cortical thickness in the right superior temporal gyrus, inferior parietal lobule, left precuneus while the white matter volume was reduced in the posterior portion of the corpus callosum in the patients with PTSD. They also revealed that the cortical thickness of the left precuneus is positively correlated with PTSD. Other studies showed reduction of cortical thickness in the bilateral superior and middle frontal gyri, the left inferior frontal gyrus, and the left superior temporal gyrus (184), and reduced hippocampal volume in PTSD (185). Interestingly, PTSD patients who benefited from EMDR therapy showed decreased gray matter density in the bilateral posterior cingulate after the treatment, as well as anterior insula, anterior parahippocampal gyrus and amygdala in the right hemisphere (186). Previous studies showed gray matter volumes alteration in anxiety in different areas of the brain (187-190). Patients with anxiety showed significantly decreased white matter volumes in the DLPFC, anterior limb of the internal capsule (ALIC) and midbrain (191). Patients with higher depressive symptoms showed significant associations with decreased hippocampal gray matter volume, decreased cortical thickness in vmPFC/medial orbitofrontal cortex and increased pallidal gray matter volume (192).

DTI is an imaging procedure to visualize the microstructures by characterization of the anisotropy, white matter tractography and the direction of the diffusion (193). Previous DTI studies demonstrated that PTSD patients have decreased fractional anisotropy (FA means less coherent organization of WM tracts) in the ACC, prefrontal cortex, posterior central gyrus, angular gyrus, posterior internal capsule (194), and PCC (195). Others showed that the increased FA in the right cingulum is associated with greater severity or persistence of PTSD symptoms (196). White matter

imaging showed that cingulum can predict EMDR treatment response to PTSD as PTSD participants with increased baseline FA showed poorer treatment response later (197). In an earlier study, decreased FA values in the left uncinate fasciculus (UF) (the UF connects the amygdala and the orbitofrontal cortex (OFC)) and in the right inferior longitudinal fasciculus had been seen in the patients with anxiety (198). A study showed an inverse relation between FA and depression severity and showed that FA reduced both in the frontal and temporal lobes of depressed patients (199). Another study on major depressive disorder showed that the FA reduced in the left sagittal stratum, the right cingulate cortex and the posterior body of the corpus callosum, areas of the brain believed to play an important role in emotional regulation (200).

2.3.2 Resting-State Functional Activity Imaging

According to the neurovascular coupling hypothesis, increased regional CBF measured by $H_2{}^{15}O$ PET reflects increased synaptic transmission which accompanies increased glucose metabolism (201). The increased metabolic demand can be measured by FDG-PET. A previous FDG-PET study revealed hypometabolism in the PCC and in the parietal and frontal lobes in patients with PTSD (185). A PET study with a specific radiotracer showed increased level of metabotropic glutamate receptor-5 (mGluR5) in patients with PTSD (202). There are some studies on single photon emission computed tomography (SPECT) scan which showed increased activity in the limbic and paralimbic regions in PTSD, especially in the posterior cingulate gyrus, amygdaloid complex, and right basal ganglia (203-205).

A study revealed that participants with higher anxiety symptoms had lower levels of cortical CBF and lower anxious subjects have higher levels of cortical CBF (206). Patients with anxiety showed lower absolute metabolic rates in basal ganglia and white matter and increased relative metabolism in the left inferior area 17 in the occipital lobe, right posterior temporal lobe, and the right precentral frontal gyrus (207). In the same study, the patient group showed decreases in absolute metabolic rates for cortical surface, limbic system, and basal ganglia after taking Benzodiazepines, a medication used for anxiety reduction.

In fact, studies on depression showed similar results. Previous studies suggested that increased activity in the VLPFC is related to unpleasant emotional processing (208-210) and unmedicated depressive states (211). In one PET study depressed patients showed global dysfunction by demonstrating decreased regional CBF in left anterior medial prefrontal cortex and

increases in the cerebellar vermis (212) where another PET study showed increased activity in the prefrontal and parietal cortex is related to clinical symptoms improvement (213). Depressed patients with poor treatment response showed decreased CBF in the bilateral frontal lobes, right hippocampus, left precuneus, and cerebellar vermis in SPECT study (214).

Arterial spin labeled (ASL) perfusion MRI is a non-invasive measure to quantify blood flow and can be used as a measure of brain activity (58). The overall idea is similar to $H_2{}^{15}O$ PET, where radiolabeled water is traced in the brain which can be modeled to estimate cerebral blood flow (CBF). In ASL, MRI magnetizes the blood in the neck level, then CBF is estimated by subtracting tagged-control image pairs with and without radiofrequency labelling of arterial blood water (59). Pulsed ASL (PASL) uses a single short radiofrequency (RF) pulse or a limited number of pulses to invert a thick slab of arterial water spins which usually takes 10–20 ms (215, 216). Continuous ASL (CASL) uses a single, long label (typically 1-3 s) to tag the blood (217). The most advanced form is pseudo-CASL (pCASL) where 1000 or more shaped RF pulses are applied at a rate of around one per millisecond (218), which produces a high signal-to-noise ratio (58).

There are also some studies on EEG and MEG which focused on neural mechanisms of PTSD, depression and anxiety (219, 220), which is not discussed in this thesis.

2.3.3 Task-based Functional Activity Imaging

Functional MRI (fMRI) is another type of imaging technique which can be used to detect brain activity by assessing changes in the oxygenation level of blood (i.e., Blood Oxygen Leven Dependency or BOLD), which is correlated with CBF (221). The advantage of BOLD fMRI over ASL is higher spatio-temporal resolution which enables more accurate modeling of state-dependent signal changes (e.g., task-based fMRI) and functional connectivity between remote regions, while the caveat is that it uses arbitrary scales.

There are various ways to obtain functional brain imaging data where most commonly used fMRI mechanism is measuring BOLD signal which arises from the hemodynamic response (68, 69). Oxygen which is required by the neurons for metabolism is provided in excess by the local vasculature after neurons are active (70). Oxygenated hemoglobin (HbO) is diamagnetic and deoxygenated hemoglobin (HbR) is paramagnetic (71). HbR distorts the magnetic field by causing transverse magnetization from longitudinal magnetization and changes the field strength of the surrounding protons causing alteration of the precession frequency. This precession frequency

change translates to a quicker dephasing of the local protons and causes a shorter transverse relaxation time, T2* (the time by which period the protons cause dephasing and reduction of transverse magnetization) (222) with higher concentrations of HbO compared to tissues (70). Active tissues require increased HbO for their metabolism. However, the HbO supply to these tissues is overabundant and the T2*-relaxation time increases and T2*-weighted MR signals in those regions (and the downstream venules and veins) are increased compared to baseline conditions (70). By measuring changes in blood oxygenation following either intrinsic (i.e., resting state) or task related neural activity, the BOLD signal reflects changes in metabolic demand of neural tissues.

Changes in brain activity in different states (e.g., performing different tasks or responding to different events) can be investigated using fMRI by quantitating the changes of magnetic field disturbance induced by deoxygenated hemoglobin and neural activity as well as cerebral blood flow regulate its concentration (223). Different brain areas are affected in PTSD, such as the hippocampus, amygdala, prefrontal cortex, insula, anterior cingulate cortex (224-226). Previous task-based fMRI studies showed increased amygdala and insula activation in response to viewing emotional processing such as viewing fearful faces and retrieving negative word in participants with PTSD compared with healthy controls (227). In comparison to controls, another study showed significantly greater BOLD responses in left amygdala and right insular cortex in participants with PTSD (228). Others found less emotional task-related activities in the rostral ACC (rACC) and medial frontal gyrus in PTSD patients (226). In aggregate, limbic regions like the amygdala, hippocampus, cingulate gyrus is hypersensitive to emotionally negative stimuli while lesser activities were observed in top-down cognitive control areas like the prefrontal areas in PTSD. Sustained hypersensitivity in the amygdala and ventral anterior cingulate was associated with lesser clinical benefits of CBT in PTSD patients (229).

In response to negative vs. neutral words in an emotional Stroop task, it had been found that patients with anxiety showed increased activity in the amygdala in comparison to healthy controls (230). Another study showed similar results in response to negative emotional image (231). GAD patients, compared to healthy controls, showed diminished ACC reactivity when they see fearful faces comparing with neutral faces (232, 233). During listing or imagining items after a narrative instruction, GAD patients showed reduced vmPFC responses to worry or disorder-

related stimuli in comparison to neutral stimuli (234, 235) and showed greater vlPFC (Ventrolateral Prefrontal Cortex) and dmPFC (Dorsomedial Prefrontal Cortex) responses (235) in comparison to healthy controls. Another study found evidence of decreased BOLD signal in prefrontal cortex during emotion regulation of the patients with anxiety (236). A study also revealed that patients with anxiety show increased BOLD signal in response to angry faces in right vlPFC (237).

Studies showed increased BOLD signal in the limbic regions, especially in the amygdala, in depressed patients when viewing faces with negative emotions, compared to controls (238, 239). Relative to healthy participants, the MDD patients showed decreased dorsolateral PFC activity on a digit-sorting task (240). A study showed that there is increased limbic activity in response to emotional information processing decreased activity in the dorsolateral prefrontal cortex during cognitive digit-sorting task in depressed participants in relation to healthy participants (241).

2.3.4 Hypothesis-driven Seed-based Functional Connectivity

While largely ignored earlier as physiological noise, it has repeatedly been demonstrated that there exists highly re-producible low-frequency (0.008-0.09 Hz) synchronous fluctuation of fMRI signals that are simultaneously detectable in multiple brain regions during rest, in the absence of any explicit task (242). The coupled regions are now regarded as "functionally connected" (26, 243). One way to investigate the functional connections of a specific brain region is seed-based connectivity analysis. This method looks at the resting-state time series of a particular region-of-interest and its correlations with the times series of the rest of the brain to investigate the pattern of functional connectivity (28, 244). For example, if one takes the fMRI signal from the left primary motor cortex and search brain regions that are synchronously fluctuating with the left primary motor cortex (i.e., a seed-based connectivity analysis), a highly reproducible map of brain regions, so called the sensorimotor network which is comprised of bilateral primary sensorimotor cortices, premotor cortices, and supplementary motor areas, can be identified. For details about different intrinsic connectivity networks, please see *2.3.5. Data-driven Multivariate Pattern Analysis*. This hypothesis-driven region-of-interest (ROI)-based connectivity analysis is often used delineate functional brain network re-organization in response to disease and treatment. The noise due to head motion or scanner induced artefacts is the main disadvantage of this method, but this

problem can be reduced by pre-processing techniques such as motion correction and temporal filtering (244).

The results of the seed-based connectivity analysis show functional connectivity maps (fcMap) which demonstrated the functional connections of the predefined brain region (29-31). The resting-state time-series of the seed voxel is correlated with the resting-state time-series of the region to be examined to measure the level of functional connectivity between the selected seed voxel and a second brain region (for example a region in the contralateral motor cortex). A high level of functional connectivity between these regions is expressed as a strong correlation between the time-series of those voxels. The time-series of the selected seed voxel can be correlated with the time-series of all other voxels in the brain to get the functional connectivity map which will show those regions that have high functional connectivity with the selected seed region (28).

2.3.4.1 The Role of PCC in PTSI

The PCC is regarded as one of the key nodes that is associated with PTSI. The PCC is the one of the areas that shows the highest brain metabolism at resting state (41). The rate of normalized glucose metabolism is about 20% higher in PCC along the midline than the rest of the brain (245). And PCC-based connectivity maps can replicate default mode network (DMN) topology, which is one of the key connectivity-based brain networks that is implicated in many neurological and psychiatric disorders (42, 43). Finally, prior imaging studies worked with this region and have identified that the DMN activity decreased, especially in PCC of the PTSD patients which means PCC can be affected by the PTSD (44, 45).

The PCC is associated with episodic memory retrieval and encoding (246-248). The term “episodic memory” refers to the group of cognitive processes that are consciously involved in the recollection of unique events and the circumstances in which they occurred (249). The “encoding processes” are the formation of a new memory after experiencing an event and the “retrieval processes” are the recollection of that event at a later time (249). For example, when a child gets a gift from his/her grandparents for a birthday, he/she makes the association among the gift, grandparents and birthday event. This association is called encoding. After a while, when he/she sees the gift, it will remind him/her the grandparents and the birthday party. This recollection is called retrieval. It has been hypothesized that PCC is especially implicated in processing the memory that involves self (self-referential memory) (250-252).

In PTSD, decreased PCC activity and connectivity has been observed in earlier works (40, 45, 253). A previous fMRI study showed that within the DMN, functional connectivity decreased between PCC and occipital cortex in PTSD patients compared to controls (40). This study also showed that connectivity between PCC and the hippocampus is associated with elevated anxiety and trauma severity. Another study demonstrated that the connectivity of PCC with the right amygdala and hippocampus/parahippocampal gyrus is greater in healthy controls than in PTSD patients (45). An fMRI study showed that the functional connectivity decreased between posterior hippocampus with some regions of DMN like PCC, vmPFC, and precuneus in the PTSD group (254).

The PCC plays a significant role not only in PTSD but also in other psychological disorders. Cortisol response which was hypothesized to be related with neurobiological coping mechanisms against psychosocial stress was related with regulation of PCC-amygdala connectivity in response to psychosocial stress and the increased connectivity was associated with the development of resilience against psychological stressors (255). PET scans showed increasing metabolism in the PCC, while patients with panic disorder had decreased symptoms after CBT treatment (256). A previous study on major depressive disorder showed that following interpersonal psychotherapy, the CBF in PCC increased along with symptom improvement (257). There is also evidence of increased metabolic activity in PCC following administration of CBT in patients with major depressive disorder (258). In these studies, the changes in the PCC described as the clinical influence of psychotherapy on PCC. So, changes in the PCC activity are expected after CBTm treatment.

2.3.5 Data-driven Multivariate Pattern Analysis

The caveat of seed-based connectivity analysis is that the result is highly dependent on how the ROI is defined. The most common solution is to use independent component analysis (ICA). ICA is a data-driven multivariate pattern recognition method to differentiate a combined signal into independent components (IC) (259). Though ICA has some advantages such as avoiding prior spatial assumptions and noise, having the ability to compare the activity of multiple voxels simultaneously, this technique has some disadvantages (260). There may be run-to-run variability which means if ICA runs more than a single time on the same data collected at different time point (even minutes apart), the results may significantly vary. The dimensionality reduction and model

order selection procedures are done randomly in ICA, and one has to decide how many components need to be estimated. ICA result can be divided into different sub networks and by this analysis a large number of components can be estimated, but this fact may make the identification and classification procedure difficult (261).

ICA typically produces a handful of known ICs, and the abnormality of three key networks have repeatedly been reported in many different psychiatric and neurological disorders including PTSD. Those networks are default mode network (DMN), salience network (SN) and central executive network (CEN) (26).

Default Mode Network (DMN):

The DMN is comprised of the PCC and medial prefrontal cortex (mPFC) with prominent nodes in the medial temporal lobe (MTL) and the angular gyrus (26). The DMN has a role in episodic memory, social cognitive process and autobiographical process (40). The brain regions of DMN are activated during rest and deactivated during different cognitive tasks (262). Mixed results have been reported in DMN connectivity in PTSD (263, 264), while majority of studies have pointed out reduced DMN activity (40, 45, 253). There are several evidence of DMN disturbances in depression and anxiety. The subgenual cingulate and thalamic functional connectivity of the DMN were significantly greater in the patients with depression (38). The subgenual cingulate and the adjoining ventromedial PFC (vmPFC) showed increased functional connectivity with other nodes of the DMN in depressed subjects and in Alzheimer's Disease the PCC and medial temporal lobe showed significantly decreased connectivity (39). The cardinal features or most common presenting symptoms of Alzheimer's Disease are episodic and autobiographical memory loss (265), and depression is associated with rumination and the recurrent reflective focus on the self (266) which indicates two separate types of disruption. For this reason, depression differentially impacts the PFC nodes of the DMN (26). Reduced deactivation of mPFC and increased deactivation of the PCC of DMN had been found in the patients with anxiety (267). Recent brain imaging studies suggest that CBT rectifies the abnormal brain functional connectivity patterns associated with DMN observed in PTSD (22-25). However, it is as yet unknown how preventive CBTm administered to healthy individuals changes the brain functional connectivity and the resilience to PTSD.

Central Executive Network (CEN):

The CEN is distributed in the dorsolateral, mid-dorsolateral, and dorsomedial prefrontal cortex (Brodmann Areas (BA) 45/46, 9, and 8), the orbitofrontal cortex (BA 47), the superior parietal cortex (BA 7), and the angular gyrus (BA 39) (268). The role of the CEN is related to working memory and attentional control (26). Decreased connectivity with CEN regions has been reported in the cerebellum (269, 270), precuneus (271), and medial prefrontal cortex (270) in PTSD patients, while increased connectivity with CEN was observed after CPT (272). The functional connectivity of CEN specially the connectivity of the dorsolateral prefrontal cortex of CEN with other nodes in the network decreases more in MDD patients than the control group (273). In anxiety, the connectivity of CEN increases (274).

Salience Network (SN):

The SN is situated in the anterior insula (BA 47/12) and dorsal ACC (BA 24/32), as well as the dorsolateral prefrontal cortex (BA 46), amygdala, hypothalamus, the thalamus, and red nucleus (268, 275). The SN is associated with the detection, integration and filtration of different information like interoceptive, autonomic and emotional information (276). In PTSD, increased connectivity has been reported within SN (25) as well as with hippocampus and amygdala (277). The abnormally increased SN connectivity was normalized after present-centered therapy (PCT) in PTSD patients (272). Hyperactivity had been noticed in the anterior insula of SN in the patients with anxiety (278). Greater activation of the amygdala node had also been found in anxiety (279). In depression the salience network functional connectivity increases (280) which normalizes following taking antidepressant (281).

3 OBJECTIVES AND HYPOTHESIS:

As the incidence of PTSI is higher among PSP than in the general population, it is important to establish interventions that are effective in preventing the development of mental disorders in this population. In this thesis, the overall objective is to obtain neurophysiological evidence for the demonstration of successful preventive effects of CBTm classes for PTSI by using fMRI. This is the first brain imaging study to investigate the effects of CBTm as a preventive intervention for PTSI. There is a wide range of evidence supporting the altered function in the PCC to be relevant to PTSI symptoms as well as treatment-related benefits. Therefore, I hypothesize that the functional connectivity as well as regional activity of the PCC of DMN will be altered in response to strengthening resilience to PTSI by CBTm among PSP.

4 METHODS:

4.1 Participants

PSP from Winnipeg Fire Paramedic Service (WFPS) without any mental health disorders were recruited from our larger clinical trial ("parent clinical trial"; Bolton et al., in preparation). One hundred and two participants were initially assessed for eligibility, and 60 participants underwent either 5-week CBTm (n = 28) sessions or waitlist (n = 32). Among these, 30 individuals were recruited for the current neuroimaging study (14 in CBTm group and 16 in waitlist). Participants were scanned with MRI three times: at baseline, within 1 week of the last CBTm session, and 12 weeks after the first CBTm session. Five participants did not complete the study and were thus excluded from the analyses.

The details of inclusion and exclusion criteria are described elsewhere (Bolton et al., in preparation). For those participants enrolled in the neuroimaging study, additional exclusion criteria included i.e., having any psychiatric disorder, including PTSD, in the past 12 months, as diagnosed by Clinician-Administered PTSD Scale (CAPS-5) and Mini International Neuropsychiatric Interview (MINI; version 7.0.2), and contraindications to MRI like claustrophobia, history of brain injury, fainting, panic attack, heart disease, or respiratory distress. Demographic information is summarized in Table 3. An outline of the overall study design is shown in Figure 1. All participants provided written informed consent. The study was approved by the University of Manitoba Biomedical Research Ethics Board.

Additionally, we included a separate set of cohorts who participated in a separate clinical trial that involves CPT and fMRI (referred as CPT study cohort) (Wright et al., in preparation). Thirty-two patients with PTSD were scanned with fMRI before and after the 12-week CPT, and twenty-four healthy individuals were scanned 12-week apart without any intervention applied. The purpose of including this separate cohort was to examine if the same neural mechanisms of CBTm in PSP without clinically diagnosable mental disorders is also present in PTSD patients who are undergoing a gold-standard psychotherapy (i.e., CPT). For this cohort, different clinical assessment was utilized from the current study while the same fMRI protocol was used with the same MRI scanner.

4.2 Clinical Assessments

The primary objective of the parent clinical trial (Bolton et al., in preparation) was to promote resilience and to address sub-threshold mental health problems. In this study, the CD-RISC, PCL-5, PHQ-9 and GAD-7 self-report measures had been used at the baseline, 5-week follow-up and 12-week. In our neuroimaging study CAPS and MINI scoring had been done to assess presence of mental illnesses including PTSD at the baseline and at the 12-week follow-up.

4.2.1 10-item Connor-Davidson Resilience Scale (CD-RISC)

Participants' resilience was assessed by the CD-RISC, a measure of an individual's ability to manage stress, problem solve, and use adaptive coping skills (170). Higher CD-RISC scores at baseline have previously been associated with less PTSD symptom development at 6 months follow-up (282). The CD-RISC scale first developed by Connor and Davidson in 2003 (283). It consists of 25 items. Later different studies worked on this scales and documented that this scale has better psychometric properties compared to others and it is one of the more widely used resilience measures (284).

Later, Campbell-Sills & Stein (2007) extracted and validated the CD-RISC 10, a 10 item scale that has higher level of consistency than the original 25 item of Connor and Davidson (2003)(170). CD-RISC has very good test-retest reliability of $r = 0.90$ (Pearson's correlation) (285).

4.2.2 Posttraumatic Stress Disorder Checklist-5 (PCL-5)

The PCL-5 is a 20-item self-report measure which measures the degree of DSM–5 PTSD symptoms related to the person's most distressing event, and how much it has been bothered a person in the past month (286). Each item is rated from 0 (not at all) to 4 (extremely). There are four subscale scores on the basis of DSM-5 PTSD symptom clusters: intrusions (Items 1–5), avoidance (Items 6–7), negative alterations in cognitions and mood (Items 8–14), and alterations in arousal and reactivity (Items 15–20). It has a very good test-retest reliability (0.84), sensitivity (88%) and specificity (69%) (287).

4.2.3 Patient Health Questionnaire 9-item (PHQ-9) Scale

The presence of depressive symptoms was evaluated using the PHQ-9, which asks the participants to indicate how often they have been bothered by common symptoms of depression over the past two weeks. Total symptom scores indicate level of depression severity: minimal

(0–4); mild (5–9); moderate (10–14); moderately severe (15–19); and severe (20–27) (166, 288). A 4-point item was also included to assess the level of difficulty in terms of domestic, occupational, and social functioning caused by depressive symptoms. The PHQ-9 has demonstrated good test–retest reliability and validity as a general measure of depressive symptoms. The test–retest reliability of PHQ-9 is 0.873 and the validity is 0.73 (289).

4.2.4 Generalized Anxiety Disorder 7-item (GAD-7) Scale

The presence of anxiety symptoms was assessed using the GAD-7, which asks respondents to indicate how often they have been bothered by common symptoms of anxiety over the past two weeks, and total scores indicate level of anxiety symptom severity: minimal (0-4); mild (5-9); moderate (10-14); and severe (15-21) (167). This measure also included a 4-point item to assess the level of difficulty these symptoms have caused in terms of domestic, occupational, and social functioning. The GAD-7 has demonstrated good test–retest reliability and validity. The test-retest reliability is 0.83 and a cut off score 10 or higher provides sensitivity of 89% and a specificity of 82% (167).

4.2.5 Clinician-Administered PTSD Scale (CAPS-5)

The CAPS-5 is a thorough, fully structured interview administered by a clinician to diagnose lifetime and current PTSD by assessing the frequency and severity of different PTSD symptoms. It is the ‘gold standard’ assessment for PTSD and has shown strong validity and reliability (Interrater reliability = .78 to 1.00 and test–retest reliability = .83) (290).

4.2.6 Mini International Neuropsychiatric Interview (MINI ; version 7.0.2)

The MINI-5 is a widely used DSM-5 structured diagnostic interview that determines the presence or absence of a number of mental disorders, including mood, anxiety, and substance use disorders (Interrater reliability = 0.88 to 1.00 and test–retest reliability = 0.76 – 0.93) (291).

4.3 Conducting CBTm

The details of the 5-session CBTm program that participants underwent is described elsewhere (Bolton et al., in preparation). In the first class, participants learn about CBT, mindfulness and the importance of CBTm classes. They practice a mindfulness exercise for 5 minutes using a mindfulness app like “Mindshift”, “Stop, Breathe, Think”, or “Mindfulness Coach” in the class. They also learn other strategies like realistic thinking, solving different thought traps and recording and challenging their thoughts. At last, they are explained about a

homework assignment. In the second class, participants practice a mindfulness exercise. Their homework as well as realistic thoughts are reviewed in the class too. In the same class they learn about behavioral therapy. The facilitator teaches about goal setting to increase motivation and confidence. Goal setting can take many forms, like reconnecting with friends from the past, starting a new hobby, spending more quality time with a partner or children, or saving money for a vacation. Again, homework is explained. Participants in the third session practice mindfulness exercise as before. They learn about the principles of healthy living to improve the quality of life by knowing about exercise, nutrition, proper sleep. They also learn about the importance of adequate sleep and different sleeping tips as well as they set goals. The trainer reviews the homework and outcomes of behavioral therapy of the previous class. Finally, the trainer explains the homework assignment. Participants practice a mindfulness exercise and different problem-solving strategies in the fourth session. In the same class they also learn about anger, assertiveness, and self-compassion. The trainer reviews the previous homework and then explain the next day homework assignment. Like the previous classes, on the fifth class the participants practice a mindfulness exercise. Participants review their homework in practicing the skills. Participants learn about stress. They also learn how to cope with stressful experiences by applying some of the previous strategies to stressful or traumatic situations. They develop a wellness plan and how to monitor their mental health and stress levels.

The classes were facilitated by a mental health professional on a weekly basis and the duration of each class was 90 minutes. These classes spanned 5 weeks for a total of 5 sessions. Participants were also given some suggested weekly homework following each class, for example, reviewing materials given in the class, doing any mindfulness exercise for 5 min twice a day, recording thoughts, spending 15 min on anxiety-related self-help program websites, i.e., anxietybc.com or heretohelp.bc.ca.

4.4 Image Acquisition

MR images were acquired using a 3 Tesla Siemens MAGNETOM Verio IMRIS scanner (Erlangen, Germany) equipped with a 12-channel head coil located at the Kleysen Institute for Advanced Medicine at the University of Manitoba, Bannatyne campus. Structural (T_1-weighted) data were acquired with an MPRAGE sequence with the following parameters: TR/TE/TI = 1900/2.47/900 ms, 176 slices, flip angle = 9°, field of view (FOV) = 250 mm x 250 mm with

1.00 mm x 1.00 mm x 1.00 mm resolution. Resting state functional data (T_2^*-weighted) acquisition parameters were as follows: TR/TE = 2000/28 ms; flip angle = 77°; FOV = 220 mm x 220 mm with 3.4 mm x 3.4 mm x 4.0 mm resolution; scan duration = 11 minutes. The perfusion data (pCASL) acquisition parameters were TR/TE = 4000/12 ms, FOV = 240 mm × 240 mm, matrix = 64 mm × 64 mm × 20 mm, slice thickness = 5 mm, inter-slice space = 1 mm, labeling time = 2 s, post label delay time = 1.2 s, bandwidth = 3 kHz/pixel, flip angle = 90°. M0 images were also acquired (TR/TE = 8000/12 ms) to calibrate pCASL images. During scanning, subjects were instructed to keep their eyes open, not to fall asleep and not to move.

4.5 Image Preprocessing and Analysis

4.5.1 Seed-based Functional Connectivity Analysis

Standard preprocessing was applied to the fMRI data using the default preprocessing pipeline in CONN software, version 18a (http://nitrc.org/projects/conn). First, the functional data were co-registered to participants' structural T_1-MRI scans, slice scanning correction was done, data were segmented and spatially normalized to MNI space, then smoothed (FWHM = 8 mm × 8 mm × 8 mm). To denoise the data, a linear regression was performed using the white matter and cerebrospinal fluid masks produced from segmentation, realignment parameters, and outlier scans. Band-pass filtering was applied (0.008-0.09 Hz) and linear detrending was performed. Individual grey matter probability maps were constructed during the segmentation stage and the default regions-of-interest (ROI) provided by CONN were masked (inclusive) with grey matter probability maps.

Seed-based connectivity analysis was conducted using CONN, with PCC as a seed region. The PCC was taken from networks.nii image file pre-packaged in CONN software. The PCC is a part of DMN delineated by performing independent component analysis on human connectome project dataset (n= 497). The PCC of DMN delineated in network.nii, in fact, comprises of both PCC and precuneus (peak coordinate: x=1, y=-61, z=38). The seed-based connectivity analysis computes the level of synchronous fMRI signal fluctuation between the seed (i.e., PCC) and the rest of the brain within each subject in voxel-wise manner, the alteration of which has been associated with the PTSD, depression and anxiety (44, 45, 292, 293). The interaction effect on PCC-connectivity was investigated between group (CBTm vs. waitlist) and time (baseline vs. after 5 weeks of intervention). A statistical significance was set at a threshold

of $p < 0.001$ (peak level, uncorrected) and $q < 0.05$ (cluster level, FDR corrected). A significant cluster was identified, and the functional connectivity values (z-score) between the seed (i.e., PCC) and the resulting cluster (i.e., the left VLPFC) had been extracted for all three time points.

The functional connectivity between the same ROIs, i.e., PCC and the left VLPFC, was extracted from the separate cohort of PTSD patients who were scanned the same fMRI protocol before and after the 12-week CPT and healthy controls who were scanned twice with fMRI 12-week apart (Wright et al., in preparation).

4.5.2 Cerebral Blood Flow Analysis

For the cerebral blood flow analysis, pCASL images were pre-processed (realigned, coregistered, spatially normalized, segmented, and smoothed) using the default parameters of the ASLtbx toolbox (294). Perfusion differences were estimated for each label/control pair (simple subtraction), then voxel-wise CBF images were estimated (labeling efficiency = 0.9) with unique M0 images and white matter M0 values. The mean CBF values were extracted from the same ROIs that were used in the seed-based functional connectivity analysis (i.e., PCC and the resulting cluster - left VLPFC) at each time point.

4.6 Statistical Analysis

Statistical analyses were completed using the Statistical Package for the Social Sciences (SPSS, IBM Corp., version 27.0, Armonk, NY) software. Baseline group differences on demographic data were tested with independent t-tests or chi-square tests, as appropriate. The time-dependent changes (5-week and 12-week vs. baseline) of functional connectivity, CBF, CD-RISC, PCL-5, PHQ-9 and GAD-7 were analyzed between groups (CBTm vs. waitlist) by general linear model with repeated measures design, followed by post-hoc Bonferroni tests. The functional connectivity changes in the separate cohort of PTSD and healthy controls were also analyzed using general linear model with repeated measures (2×2 design). The relevance of imaging-based variables (dependent variables: functional connectivity and CBF) in participants' resilience (independent variable: CD-RISC scores) were investigated using multiple linear regression at each time point. Sex and group were included as covariates. In all cases, $p < 0.05$ was considered as significant.

5 RESULTS:

5.1 Demographic and Behavioral Data Analysis

Age, sex, occupation, years of service, marital status, CD-RISC, and CAPS-5 scores did not significantly differ between groups who underwent 5-week CBTm classes vs. waitlisted at the baseline (Table 3). The results of self-report measures of mental health associated with CBTm are discussed elsewhere (Bolton et al., in preparation). In the parent study that involved all 60 participants, the CBTm intervention significantly reduced scores depression (PHQ-9) and PTSD symptoms (PCL-5) compared to the waitlist, and the effects lasted throughout the 12-week follow-up period (effect size 0.31 – 0.41). In the subset of 30 of 60 participants who also underwent neuroimaging component of the study, the interaction effects between group (CBTm vs. waitlist) and time (baseline vs. 5-week vs. 12-week) did not reach statistical significance for any of the behavioral variables (i.e., CD-RISC (F (2,46) = 1.193, p = 0.318), PCL-5 (F (2,46) = 0.396, p = 0.676), PHQ-9 (F (2,46) = 0.727, p = 0.491), and GAD-7 (F (2,46) = 0.209, p = 0.812) (Figure 2).

The demographic information of the CPT study cohort and the main effects of CPT in the PTSD patients vs. healthy controls have been discussed elsewhere (Wright et al., in preparation). Briefly, sex was not significantly different between the groups (χ^2 = 0.100, p = 0.752) while PTSD patients were relatively older than the healthy controls (t (54) = 1.884, p = 0.065), and thus age was included as a covariate in the following general linear model analyses.

5.2 Seed Based Functional Connectivity Analysis

A seed-based connectivity analysis was performed to investigate if functional connectivity of the brain changed in relation to the PCC, a DMN hub after CBTm. A cluster with significant interaction effect between group (CBTm vs. waitlist) and time (baseline vs. 5-week) was identified only in the left VLPFC (Brodmann Area 44; x = -50, y = +26, z = +8, k = 149; Peak level: $p < 0.001$, uncorrected; Cluster level: q = 0.018, FDR corrected; Figure 3A). The post-hoc analysis of the seed-based functional connectivity results between the PCC and the left VLPFC confirmed that the significantly increased functional connectivity in the CBTm group compared to the waitlist group persisted over 5-week ($p < 0.001$) and 12-week periods (p = 0.009; post-hoc Bonferroni test, Figure 3B).

The functional connectivity between the same ROIs (PCC and left VLPFC) was extracted from the separate cohort of PTSD patients who were scanned before and after 12-week CPT and healthy controls who were scanned twice 12-week apart. Notably, a significant interaction effect was replicated between group and time (F (1,53) = 5.216, p = 0.026) (Figure 4).

5.3 Cerebral Blood Flow Analysis

To examine the effects of CBTm on the overall neural activity changes in the ROIs identified in the functional connectivity analysis, CBF values were estimated within each ROI for all three time points. Significant interaction effects for group and time were observed only in the left VLPFC (F (2,46) = 4.310, p = 0.019; Figure 1D) but not in the PCC (F (2,46) = 0.305, p = 0.739; Figure 1C). The post-hoc analysis showed that in the left VLPFC, the CBTm group had significantly lower CBF changes compared to the waitlist group at 12-week follow-up (p = 0.006, post-hoc Bonferroni test).

5.4 Clinical Relevance of Functional Connectivity and CBF

To examine the clinical relevance of the neuroimaging findings described above, univariate linear regression analysis was performed to predict CD-RISC scores (dependent variable) with covariates being the functional connectivity (between PCC and left VLPFC) and CBF values of the PCC and the left VLPFC at each time point. Sex and groups were also included as covariates. The results are summarized in Table 4. At baseline, CD-RISC scores were significantly predicted by the model (F (5,18) = 7.118, $p < 0.001$). Significant coefficients include sex ($p < 0.001$) and both CBF values from the PCC (p = 0.004) and left VLPFC (p = 0.021). At the 5-week follow-up, the model did not significantly predict the CD-RISC scores (F (5,13) = 0.739, p = 0.608). However, at the 12-week follow-up, the model fit was again significant (F (5,12) = 3.377, p = 0.039), and the CD-RISC score was significantly predicted by the functional connectivity values between PCC and left VLPFC (p = 0.014), but not by CBFs of either brain regions ($p > 0.139$).

6 DISCUSSION:

The mental health benefits of CBTm are beginning to be documented (21, 174). In our recent parent clinical trial, we demonstrated that CBTm reduced symptoms related with PTSI in PSP, suggesting its potential preventive effects via building resilience (Bolton et al., in preparation). In the current study, we sought to investigate the neural underpinnings of the clinical benefits of CBTm treatment in the subgroup of PSP (30 of 60) who participated in our parent clinical trial. The PCC was chosen as our main region of interests because of its well-established role as the core of the DMN (40, 42, 43, 45, 295) and its relevance to symptom improvement as well as resilience building (24, 296-298). The seed-based connectivity and post-hoc analysis identified that the functional connectivity of the left VLPFC with the PCC was significantly increased following CBTm treatment and stayed elevated up to 12-weeks follow-up (Figure 1A, 1B). This is in line with our clinical findings (Bolton et al., in preparation) where we reported that the PCL-5 scores decreased significantly after the intervention in CBTm group and stayed reduced at 12-week follow-up. The role of the VLPFC has been associated with cognitive control of memory (299) while the PCC has been implicated with recollection of prior experiences (300), and thus this finding suggests that CBTm strengthened the cognitive control (via VLPFC) over episodic memory retrieval (via PCC).

Our finding of increased functional connectivity between PCC and the prefrontal cortex after CBTm treatment is in line with previous studies in PTSD (24, 301). The abnormality of PCC/precuneus, the core of DMN, has been hypothesized to be involved with many neurological and psychiatric disorders (26). Decreased PCC activity and connectivity has been reported in PTSI patients (40, 45, 47, 253, 267). Particularly interesting was that cortisol response (which was hypothesized to be related with neurobiological coping mechanisms against psychosocial stress) was related with regulation of PCC-amygdala connectivity in response to psychosocial stress, implicating the importance of PCC connectivity in resilience (255). A meta-analysis demonstrated that increased activity in the prefrontal regions were observed in trauma-exposed individuals who did not develop PTSD compared to the subjects without exposure to severe trauma, suggesting the increased prefrontal activity as a neural marker of resilience (302). The role of VLPFC has been associated not only with the cognitive control of the memory but also with generation and regulation of emotions (209, 303), and its connectivity changes has been implicated in resilience against depression (304) and generalized anxiety disorder (305).

Interestingly, the CBF level (measured by pCASL analysis), which reflects overall neuronal input that a brain region receives (306), was not changed in the PCC (Figure 3C) while it was reduced in the left VLPFC (Figure 3D) after the CBTm especially in the 12-week follow-up. Increased activity in the VLPFC has been associated with unpleasant emotional processing (208-210) and unmedicated depressive states (211). And thus, the decreased CBF in the left VLPFC after CBTm may partly explain the improved depressive symptoms in PSP.

While causality cannot be concluded, the timing of the events (i.e., functional connectivity was increased first, then followed by CBF decrease in the left VLPFC) may suggest that CBTm-induced increased prefrontal control over PCC (or DMN network), leading to a decreased overall neuronal input to the left VLPFC. A decreased afferent activity (measured by CBF) has been associated with improved efficiency of neural processing after repeated practice (307). In other words, as participants take classes and practice mindfulness training over the follow-up period, it may have become "easier" for the left VLPFC to exert control over the PCC.

Interestingly in PCC, no significant group × time interaction effects were observed in the CBF, although previous positron emission tomography (PET) studies with fluorodeoxyglucose (a radioactive glucose analog, the update of which represents metabolic demand which is associated with synaptic activity) and $H_2{}^{15}O$ (measuring CBF) showed increased metabolism and CBF in the PCC after CBT in patients with panic disorder (256) and major depressive disorder (257, 258). While lower signal-to-noise ratio of pCASL MRI vs. PET and limited sample size of the current study may be factors for non-significance (albeit significant effect was observed in the left VLPFC), another difference from the previous studies is that our participants were not diagnosed with any mental disorders. In other words, if decreased PCC CBF indicates pathological DMN abnormality and that it was restored after CBT in patient populations (256-258), it is possible that the PCC CBF level in healthy individuals is already at ceiling and thus resulting in non-significant changes after CBTm intervention.

Indeed, the behavioral relevance of the CBFs of the PCC as well as the left VLPFC have been demonstrated by linear regression analysis at baseline, where CBFs from both structures significantly and separately predicted resilience scores (CD-RISC; Table 4). As expected, CD-RISC score was also significantly predicted by sex (higher in females vs. males). Interestingly, the CD-RISC score was oppositely predicted by CBFs between PCC (negative) and left VLPFC

(positive). While the higher prefrontal activity in more resilient individuals may be interpreted as having healthier top-down cognitive control (308), the negative correlation between CD-RISC and PCC CBF should be interpreted with caution. Traditionally, the lower PCC activity has been associated with different mental health problems (256-258).

At the 5-week follow-up, CD-RISC was not predicted by any of the covariates, and the model was not significant. However, at the 12-week follow-up, the linear regression model fit was significant again, and the functional connectivity between the PCC and left VLPFC significantly predicted the CD-RISC score (negative correlation). Other covariates did not significantly predict the CD-RISC score. This finding suggests, after the CBTm treatment, that the functional connectivity between the two regions (the PCC and left VLPFC) became a dominant factor that explains one's resilience over their individual regional activities (CBFs), which were significant predictors at baseline. Interestingly, the direction of the correlation was negative between CD-RISC and the functional connectivity. Here, it should be noted again that resilience is not simply an inverse of psychiatric symptoms and thus it does not contrast our findings that functional connectivity was increased after CBTm treatment (Figure 3B). For example, a negative correlation between DMN connectivity and resilience scores was previously reported in healthy participants (310). Rather, this finding weighs in on the complexity of how one's resilience contribute to the expression of psychiatric symptoms, and how it may be influenced by interventions targeting resilience.

One of the unexpected, yet interesting findings was that the functional connectivity between the PCC and the left VLPFC was decreased in waitlisted PSP, as much as it was increased in those who received CBTm (Figure 3B). While it is challenging to definitively conclude on the cause of this decreased functional connectivity, we replicated significant interaction effect between group and time in separate cohorts where patients with PTSD (n=32) were scanned before and after CPT while control subjects (n=24) were scanned twice, 12-weeks apart without any intervention (Figure 4). Interestingly, we observed a similar decrease of functional connectivity in the 2nd visit of healthy controls ($p=0.013$, post-hoc Bonferroni test). This result suggests that the decreased functional connectivity that we observed in the waitlist group was not noise, but a systemic phenomenon associated with having repeated MRI sessions, which may be related with exposure to a novel environment, such as the MRI unit, and

subsequent habituation (e.g., change in VLPFC activity has previously been implicated in novel object identification task) (311). It is possible that the increase of functional connectivity associated with CBTm may have masked this habituation-related connectivity reduction.

7 LIMITATIONS AND FUTURE DIRECTIONS:

The original target recruitment for this study was 40 participants; however, the parent clinical trial was concluded prematurely due to the COVID-19-related restrictions imposed on early 2020 on clinical trials involving human participants. Therefore, the imaging study recruitment ended early, resulting in a smaller sample size (n=30) than originally planned. The limited sample size may have contributed to the failed replication of behavioral effects of the parent clinical trial (n=60) where significant reduction of PTSI symptoms were observed (Bolton et al., in preparation). They found that the symptoms of PTSD (measured by PCL-5) and depression (measured by PHQ-9) were significantly decreased in CBTm class group in comparison to waitlist group following CBTm. Nevertheless, we observed significant effects of CBTm on neuroimaging-based variables, which were correlated with participants' level of psychological resilience (measured by CD-RISC), confirming the behavioral relevance of the current neurophysiological findings.

The CBTm intervention did not significantly improve resilience per se (measured by CD-RSIC) compared to the waitlist, the details of which has been discussed elsewhere (Bolton et al., in preparation). Considering that the majority of the PSP have already experienced trauma and that we only recruited PSP without any mental health disorders, it is possible our samples were biased such that we only included individuals with high level of resilience. To test the generalizability of our finding, a follow-up study to include PSP with broader range of mental health problems is currently being sought.

It should be noted that majority (93.75%) of our PSP participants previously experienced criterion A trauma (determined by CAPS-5), the repeated exposure of which could promote resilience (305). Because of the small sample size of non-trauma exposed individuals (6.25%), we did not investigate the effects of previous trauma exposure. A potential future study includes a clinical trial targeting only trauma-naïve newly recruited PSP and/or trainees.

Due to the limited sample size, no subgroup analyses were performed. For example, resilience and the rate of development of PTSI can be different based on age and sex. Different cultural background has also been associated with different resilience level (11). It is currently unknown if CBTm benefits are different across individuals with different sex, age, and cultural background. A larger sample size study is warranted.

The follow-up duration was limited to 12-week due to the logistical challenges. It is currently unknown if the CBTm-related clinical and/or neurophysiological changes would persist beyond 12-week period. A longer follow-up study is warranted to determine if it would be beneficial to receive refresher CBTm classes. And if so, how often it should be provided.

8 CONCLUSION:

In this study, we demonstrated that the CBTm increased functional connectivity between the PCC and the left VLPFC, and decreased CBF in the left VLPFC, but not in the PCC. In addition, CBF of these structures predicted one's level of resilience at the baseline while the functional connectivity between the structures become more prominent in the 12-week follow-up when the effect of CBTm might have been more consolidated. This finding potentially suggests that CBTm may have strengthened cognitive control (via VLPFC) over self-referential memory (via PCC) which is reflected by increased connectivity, thereby strengthening resilience in the healthy PSP without significant mental health problems.

Table 1: Self report Mental health scales and their purposes.

Mental Health Scales	Purpose
Life Events Checklist for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (LEC-5)	To measure lifetime trauma exposure, type of trauma whether it happened directly to the individual or whether they witnessed or heard about it
Posttraumatic Stress Disorder Checklist-5 (PCL-5)	To assess the presence of DSM-5 PTSD symptoms in the past month
Generalized Anxiety Disorder-7 (GAD-7)	To know about anxiety symptoms in the past two weeks
Patient Health Questionnaire-9 (PHQ-9)	To assess depression symptoms in the past two weeks
Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)	To measure of general distress in the past month in multiple mental health domains
10-item Connor-Davidson Resilience Scale (CD-RISC 10)	To assess the perceived ability to manage stress, problem solve, and use adaptive coping skills
Medical Outcomes Short-Form (SF)	To know the mental and physical quality of life
Maslach Burnout Inventory	To assess occupational stress and burnout
Education Session Usefulness Scale	To identify the usefulness of the classes

Table 2: Differences among functional neuroimaging methods.

	fMRI	PET	SPECT	EEG	MEG
Measured biological process	Hemodynamic response	Hemodynamic response	Hemodynamic response	Neuroelectric potentials	Neuromagnetic field
Way of neuronal activity measurement	Indirect	Indirect	Indirect	Direct	Direct
Invasiveness	Non-invasive	Invasive	Invasive	Non-invasive	Non-invasive
Radiation	No	Yes (0.5–2.0 mSv)	Yes (3.5–12.0 mSv)	No	No
Spaces	Confined	Confined	Confined	Not confined	Confined
Spatial Resolution	Excellent (2 mm)	Good/excellent (4 mm)	Good (6 mm)	Reasonable/good (10 mm)	Good/excellent (5 mm)
Temporal Resolution	Reasonable (4–5 s)	Poor (1–2 min)	Poor (5–9 min)	Excellent (<1 ms)	Excellent (<1 ms)

Table 3: Demographic measures. Data indicate mean ± standard deviation, or percentage of sample. Statistical difference between groups was analyzed using either one-way ANOVA or chi square test.

	Waitlist	CBTm	*p*-value
Age	37.7 ± 9.6	40.6 ± 10.6	0.478
Sex (Male: Female)	6:8	2:9	0.099
Occupation	Dispatcher: 21.4% Firefighter: 28.6% Paramedic: 50.0%	Dispatcher: 9.1% Firefighter: 45.5% Paramedic: 45.5%	0.577
Years of Service	16.6 ± 7.2	13.3 ± 9.3	0.538
Marital Status	Married: 50.0% Common-Law: 21.4% Divorced: 7.1% Single: 21.4% Separated: 0%	Married: 81.8% Common-Law: 9.1% Divorced: 9.1% Single: 0% Separated: 0%	0.267
CD-RISC at Baseline	30.8 ± 5.1	33.4 ± 4.4	0.206
CD-RISC at 5-week	27.8 ± 11.0	30.9 ± 5.4	0.435
CD-RISC at 12-week	30.9 ± 4.0	32.5 ± 4.6	0.143
CAPS-5 at Baseline	0.29 ± 0.8	0.64 ± 1.8	0.523

CD-RISC: the Connor-Davidson Resilience Scale; CAPS-5: Clinician-Administered PTSD Scale for DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition: DSM-5)

Table 4: Linear regression analysis to predict CD-RISC with the sex, group (CBTm vs waitlist), functional connectivity values between PCC and left VLPFC and CBF values of PCC and left VLPFC.

Timepoint	Variables	Unstandardized coefficient		Standardized Coefficient Beta	t	*p*
		B	Standard Error			
Baseline	Sex	-7.136	1.499	-0.731	-4.762	<0.001*
	Group	3.630	2.120	0.372	1.712	0.104
	CBF (PCC)	-0.240	0.074	-0.769	-3.258	0.004*
	CBF (VLPFC)	0.218	0.086	0.628	2.528	0.021*
	FC (VLPFC-PCC)	-9.755	5.406	-0.333	-1.805	0.088
5-week	Sex	-0.989	4.058	-0.096	-0.244	0.811
	Group	-1.519	3.813	-0.148	-0.398	0.697
	CBF (PCC)	-0.035	0.195	-0.054	-0.182	0.859
	CBF (VLPFC)	-0.060	0.223	-0.104	-0.268	0.793
	FC (VLPFC-PCC)	-14.996	8.896	-0.457	-1.686	0.116
12-week	Sex	-4.177	2.226	-0.463	-1.887	0.085
	Group	-2.914	1.913	-0.325	-1.523	0.154
	CBF (PCC)	0.022	0.092	0.062	0.236	0.818
	CBF (VLPFC)	-0.160	0.101	-0.379	-1.583	0.139
	FC (VLPFC-PCC)	-19.131	6.658	-0.662	-2.874	0.014*

CD-RISC: the Connor-Davidson Resilience Scale (CD-RISC); PCC_CBF: CBF values of the left posterior cingulate cortex; VLPFC_CBF: CBF values of the left ventrolateral prefrontal cortex; FC : Functional Connectivity values between left PCC and left VLPFC.

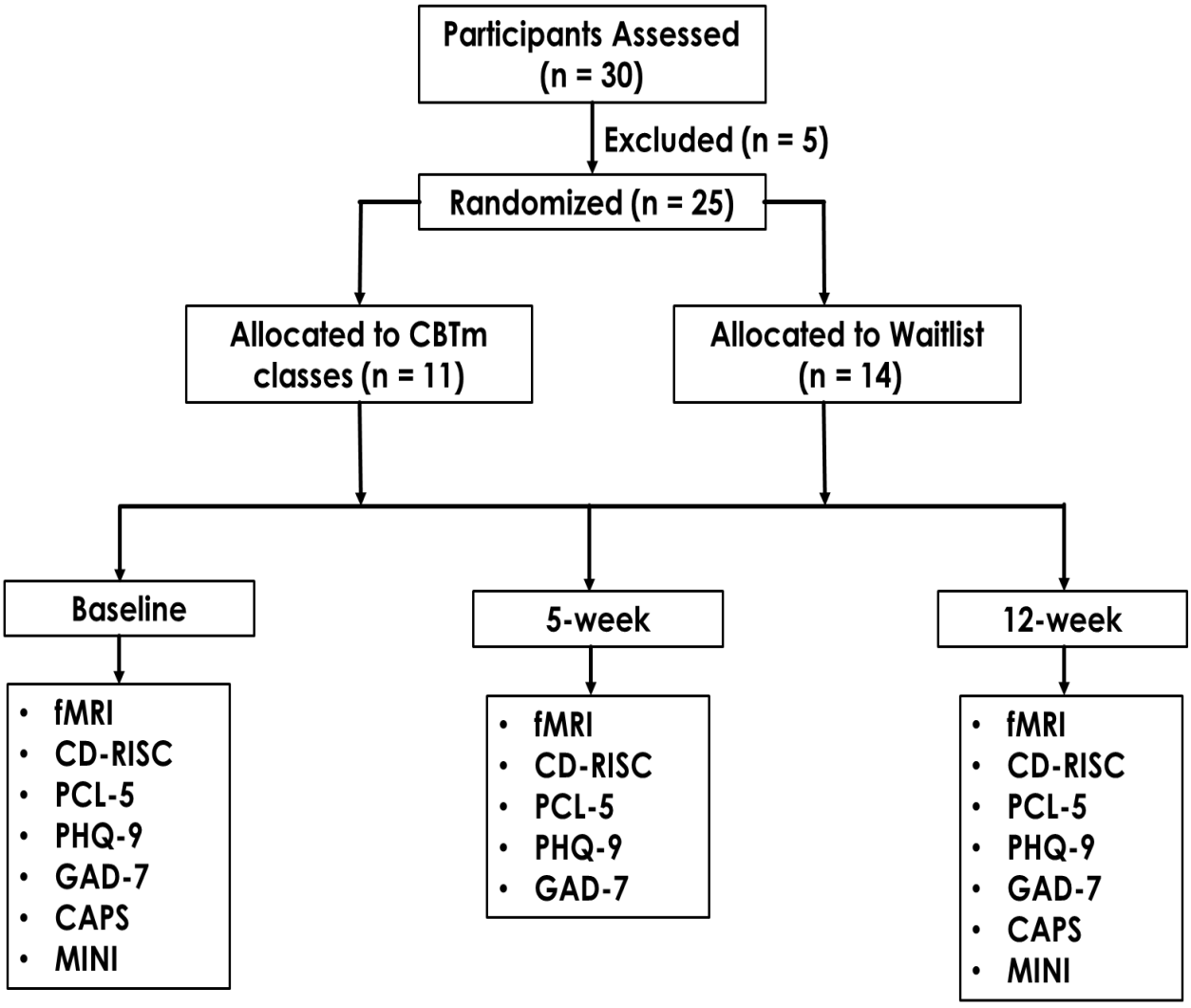

Figure 1: Overall study design. 30 participants were recruited in this study. 5 participants did not complete the study and thus excluded. Among 25 ramaining participants 11 participates were randomly allocated to the CBTm classes and 14 participants were waitlisted. All participants underwent functional Magnetic Resonance Imaging at the baseline, at the 5-week and 12-week follow-up. In the same time points, clinical assessments had been done to all participants by the Connor Davidson Resilience Score (CD-RISC), Posttraumatic Stress Disorder Checklist (PCL-5), Patient Health Questionnaire (PHQ), Generalized Anxiety Disorder (GAD-7). Additionally, at the baseline and 12-week follow-up participants had been assessed by the Clinician-Administered PTSD Scale (CAPS-5) and Mini International Neuropsychiatric Interview (MINI; version 7.0.2).

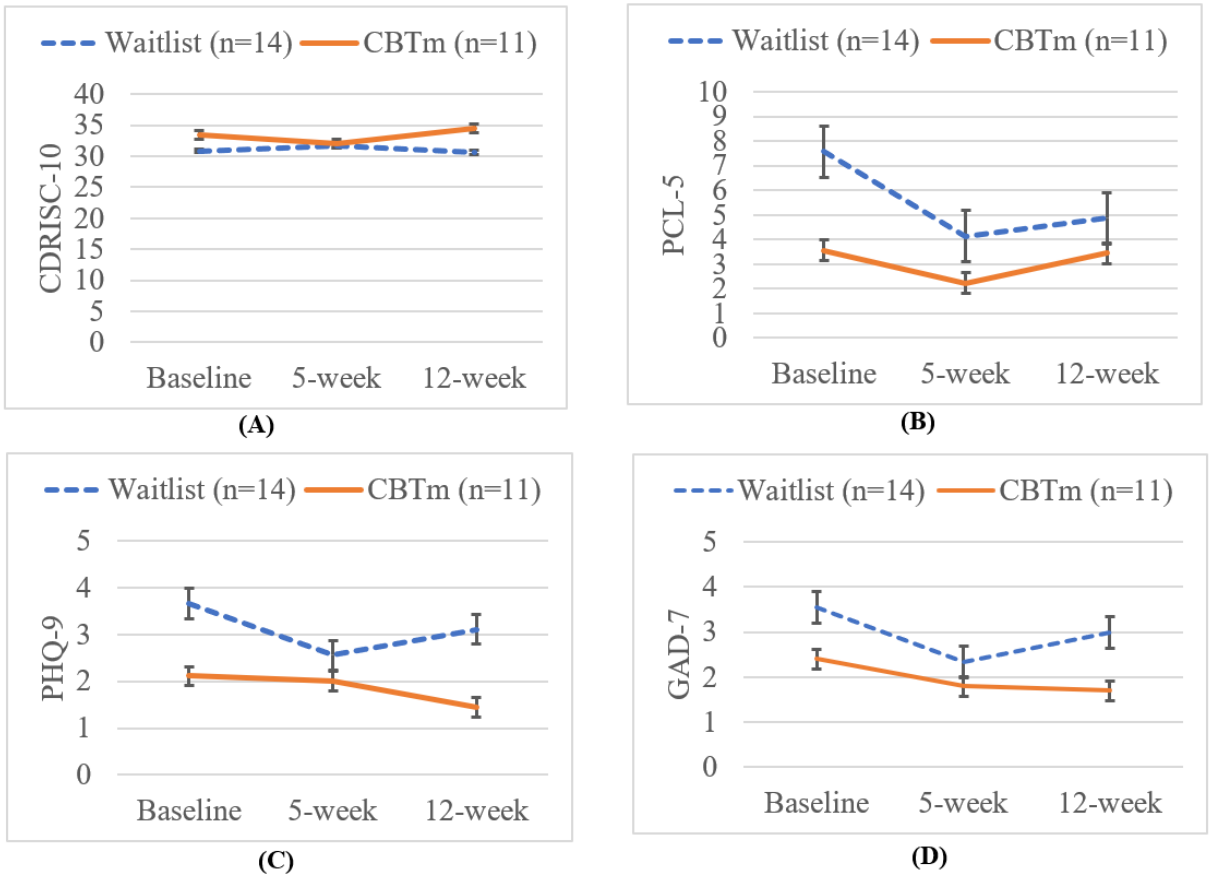

Figure 2: Changes in the behavioral data. (A) Connor Davidson Resilience Score (CD-RISC), (B) Posttraumatic Stress Disorder Checklist (PCL-5), (C) Patient Health Questionnaire (PHQ), (D) Generalized Anxiety Disorder (GAD-7). The orange line represents the CBTm group, and the blue line represents the waitlist group. No significant interaction effects between group and time were observed in any of the test scores ($p > 0.3$). Error bars represent standard error.

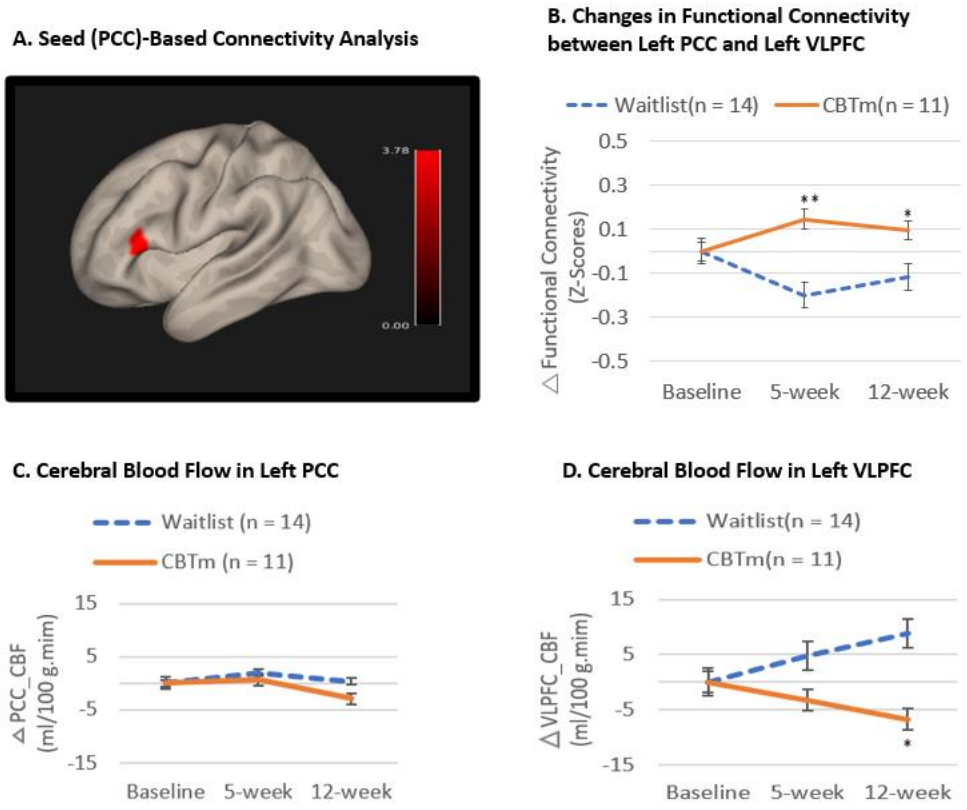

Figure 3: The effects of CBTm on the PCC connectivity. 11 subjects underwent 5-week CBTm treatment, and 14 subjects were waitlisted. Imaging data was acquired before and after. **A.** There was a significant interaction effect of group (CBTm vs. Waitlist) and time (5-week later vs. baseline) of PCC seed-based connectivity in the left VLPFC (Brodmann Area 44; x = -50, y = +26, z = +8, k = 149; Peak level: $p < 0.001$, uncorrected; Cluster level: $q = 0.018$, FDR corrected). **B.** The PCC-VLPFC connectivity values (z-score) are visualized. The orange line depicts CBTm group, and the blue line depicts waitlist group. The increased connectivity in CBTm group stayed elevated at 12-week follow-up period compared to the waitlisted Individuals ($p = 0.009$, post-hoc Bonferroni test). **C.** The changes in the cerebral blood flow (CBF) estimated by pseudo-continuous arterial spin labeling (pCASL) in the seed region (i.e., PCC) was not significantly different between CBTm vs. waitlisted ($F(2,46) = 0.305$, $p = 0.739$). **D.** However, the changes in CBF in the left VLPFC was significantly different between CBTm vs. waitlisted ($F(2,46) = 4.310$, $p = 0.019$). And the group differences (CBTm vs. waitlist) were greatest at 12-month follow-up period ($p = 0.006$, post-hoc Bonferroni test). $P < 0.05$; $^{**}p < 0.001$. Error bars represent standard error.

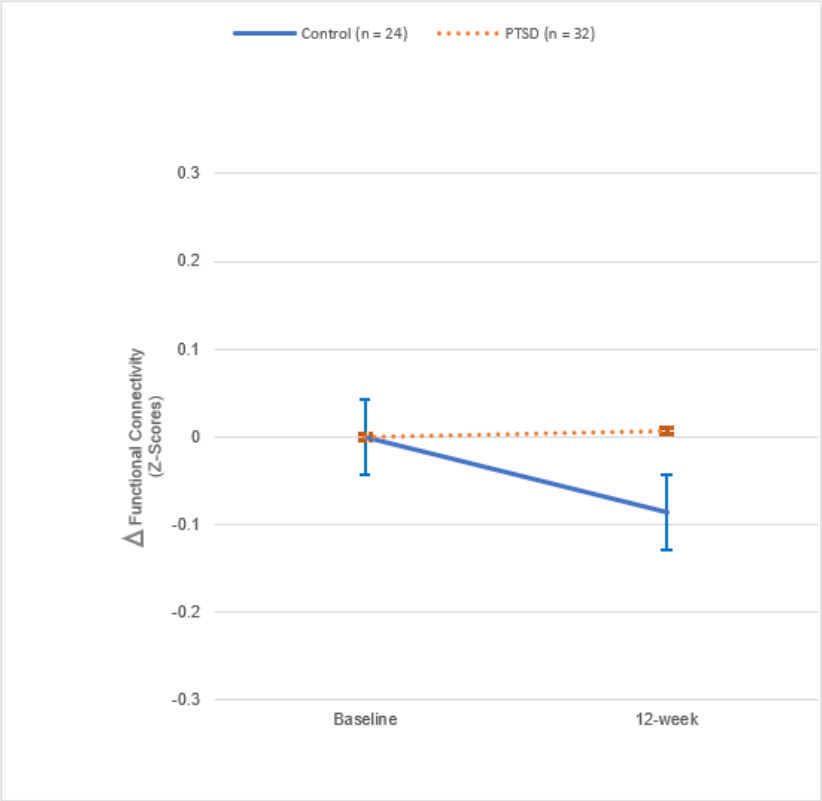

Figure 4: Functional connectivity changes following cognitive processing therapy (CPT).

The functional connectivities between VLPFC and PCC (z-score) are visualized for the separate cohorts. PTSD patients were scanned with fMRI after 12-week CPT. Healthy controls were scanned without any intervention. Significant interaction effect was observed between group and time ($F(1,53) = 5.216$, $p = 0.026$). Error bars represent standard error

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