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Neurobiological Mechanisms of Cognitive Processing Therapy for Post-traumatic Stress Disorder: A Brain Network Approach

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Abstract

Psychotherapy research is increasingly targeting both psychological and neurobiological mechanisms of therapeutic change. This trend is evident in and applicable to post-traumatic stress disorder (PTSD) treatment research given the high nonresponse rate of individuals with PTSD who undergo cognitive-behavioral therapy (CBT). A review of the literature investigating neurobiological mechanisms of CBT in PTSD reveals inconsistent results that fail to fully support dual process or learning models of CBT effects in the brain. However, network-based models of psychopathology provide a new framework from which to understand both mental disorder symptoms and therapeutic mechanisms. The current study investigated a) whether brain networks commonly implicated in psychopathology (e.g., default mode network [DMN], central executive network [CEN], and salience network [SN]) changed following Cognitive Processing Therapy (CPT) for PTSD and b) whether change in these networks was associated with PTSD and/or transdiagnostic symptom change. Independent components analysis was implemented to investigate resting-state functional connectivity in DMN, CEN, and SN in 42 women with PTSD and 18 trauma-exposed controls (TEC). Results indicated no significant differences in DMN, CEN, or SN functional connectivity in participants with PTSD versus TEC before or after CPT. Further, participants who completed CPT did not evince significant change in these networks pre- or post-CPT. Several methodological reasons for null results and future directions for research are discussed.

Keywords: PTSD, CPT, functional connectivity, DMN, CEN, SN

Neurobiological Mechanisms of Cognitive Processing Therapy for Post-Traumatic Stress Disorder: A Brain Network Approach

Psychotherapy research has established that cognitive behavioral therapy (CBT) is effective for anxiety and stress disorders, although prevalence rates of mental disorders remain relatively stable (Kessler et al., 2005). In some disorders, such as post-traumatic stress disorder (PTSD), this problem is amplified by high rates of nonresponse in individuals who undergo CBT (Schottenbauer et al., 2008). This dilemma has prompted a wealth of research on mechanisms of therapeutic change, which are defined as the precise processes or events that caused the change (Kazdin, 2007). Research on therapy mechanisms enables scientist-practitioners to understand why therapy is effective and thus ultimately deliver more efficient treatments (Kazdin, 2007). Neuroscience approaches have increasingly been used to study neural substrates of cognitive, affective, and behavioral variables. Investigating the neural correlates of psychotherapy mechanisms is an attempt to understand how psychotherapy affects those neurobiological systems.

Two related methods to study the relation between psychotherapy and brain change exist. Lueken and Hahn (2016) and Fournier and Price (2014) contrast mechanistic and predictive approaches to studying psychotherapy effects in the brain. These authors note that mechanistic approaches seek a model of the psychotherapeutic process and predictive approaches seek to understand neurological markers of individual treatment response. As such, though mechanistic and predictive methods are complementary, they answer different theoretical questions about the relation between psychotherapy and neurobiology. This paper will focus solely on mechanistic studies of

CBT in PTSD, necessarily with pre- and post-treatment designs. CBT was selected given its extensive evidence base, its status as either a ‘well-established’ or ‘probably efficacious’ treatment for PTSD (Chambless et al., 1998), and its frequent use in the literature. Studies were only included if CBT produced clinically significant improvement in symptom measures.

PTSD & Cognitive Behavioral Models of PTSD

Post-traumatic stress disorder has received significant clinical and research attention given its lifetime prevalence rate of 6.1 %, its detrimental impact on social and occupational functioning, and its high comorbidity with other mental disorders (Goldstein et al., 2016). The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) denotes three symptom clusters that characterize PTSD (American Psychiatric Association, 2000). The first cluster includes re-experiencing symptoms, such as recurrent memories, thoughts, or dreams of the event, flashbacks, and physiological reactivity to trauma reminders. The second cluster involves persistent avoidance of trauma-related cognitions (e.g., thoughts, memories), emotions, and environmental stimuli, as well as emotional numbing (e.g., restricted affect range, decreased interest in activities, and detachment from others). The third cluster captures heightened physiological arousal, as demonstrated by sleep difficulty, hypervigilance, irritability, difficulty concentrating, and an exaggerated startle response (APA, 2000). To meet criteria for PTSD, an individual must exhibit symptoms from each cluster following exposure to a traumatic event.

CBT theory assumes that cognitions, affect, behavior, and physiology interact to contribute to mental disorders (Westbrook et al., 2011). CBT most frequently targets

change in behaviors and cognitions that are presumed to underlie the specific mental disorder (Zayfert & Becker, 2007). As such, cognition and behavior are the indices used to assess change during and after treatment; importantly, behavior change is often implemented through cognitive change and vice versa (Dobson & Dozois, 2010).

Common CBT techniques include cognitive restructuring and exposure; these are also applicable to CBT for PTSD (Zayfert & Becker, 2007). Cognitive restructuring assumes that emotional distress is the result of maladaptive thoughts and has the goal of modifying these thoughts to reduce distress (Dobson & Dozois, 2010). Similarly, exposure, which can involve in-vivo, imaginal, or interoceptive methods, is thought to facilitate extinction learning, or new associations between the feared stimulus and a more neutral meaning (Vorstenbosch et al., 2014). Although CBT occasionally involves other techniques (e.g., relaxation, mindfulness), they have not been widely investigated in neuroimaging studies of PTSD treatment outcomes and will thus not be reviewed in this paper.

Cognitive behavioral conceptualizations of PTSD stemmed from Mowrer's two-factor theory of anxiety, which posited that a learned fear response arises due to classical conditioning and is maintained due to operant conditioning (Zayfert & Becker, 2007; Cahill & Foa, 2004). In PTSD, the traumatic event, and contextual variables from the event (e.g., sights, sounds, smells, etc.) become associated with a physiological fight, flight or freeze response and with intense emotions. Subsequently, individuals with PTSD behaviorally and cognitively avoid trauma reminders, thus both failing to extinguish the association between the reminders and their response *and* perpetuating avoidance behavior via negative reinforcement. As such, PTSD theorists emphasize behavioral and

cognitive avoidance of trauma reminders as a critical factor in the disorder (Zayfert & Becker, 2007; Cahill & Foa, 2004).

Later CBT conceptualizations of PTSD elaborate on this conditioning principle. Emotional processing theory posits that a traumatic event is stored in a 'fear structure' in the client's memory, which includes representations of trauma stimuli, emotional and physiological responses, and thoughts or meanings about the trauma. Subsequent contact with one part of the fear structure (e.g., an environmental trauma reminder) then activates the other components of the fear structure (Cahill & Foa, 2004). Treatment of this pathological fear structure thus requires activating the fear structure to enable the learning of corrective information- e.g., that trauma reminders do not always signify imminent danger, and/or that one can confront a trauma reminder without experiencing feared outcomes. Prolonged exposure is designed to achieve this and to prevent the negative reinforcement that avoiding trauma stimuli provides (Cahill & Foa, 2004).

Other conceptualizations of PTSD focus on belief systems that are either disrupted or reinforced by a traumatic event. Schema theories of PTSD note that processing a trauma requires resolving the conflict between beliefs the individual had before the trauma and what the occurrence of the trauma means about themselves or the world (Zayfert & Becker, 2007; Cahill & Foa, 2004). Interestingly, schema theorists suggest that re-experiencing symptoms result from cognitive attempts to resolve this conflict (Cahill & Foa, 2004). Often, this discrepancy can result in non-anxious emotions also common in PTSD, such as shame, anger, or guilt (Zayfert & Becker, 2007). An appropriate intervention to address maladaptive schemas is cognitive restructuring. Notably, both emotional processing and schema theories require the individual to

confront stimuli he/she has been avoiding (e.g., thoughts or emotions about the trauma, environmental trauma stimuli) in order to achieve PTSD remission. This confrontation may occur via exposure or cognitive restructuring techniques (and often require both) (Zayfert & Becker, 2007).

In addition to the above CBT conceptualization of PTSD, some researchers have observed that emotion dysregulation plays a “key role” in PTSD (Liberzon & Sripada, 2008; Sheynin & Liberzon, 2017). Emotion regulation is defined as “how we try to influence which emotions we have, when we have them, and how we experience and express these emotions” (Gross, 2008, p. 497). Gross (2008) has outlined five processes through which humans regulate emotions. Cognitive control of emotion refers to two such processes comprising attentional deployment (e.g., distraction, rumination) and cognitive change (e.g., reappraisal of the meaning of the situation) (Gross, 2008; Ochsner & Gross, 2005; Hartley & Phelps, 2010). These are contrasted with other emotion regulation processes, including behavioral response modulation (e.g., avoidance, relaxation) and the selection and modification of specific types of situations leading to emotions (Gross, 2008; Ochsner & Gross, 2005). The cognitive change strategy of the cognitive control of emotion is analogous to cognitive restructuring, whereas behavioral response modulation and selection/modification of specific situations are addressed by exposure techniques.

Biological Correlates of PTSD

As previously reviewed, a prominent conceptualization of PTSD is that it results from impaired fear learning and extinction. An extensive literature on fear conditioning and extinction across animals and humans has established distinct neural regions

associated with these learning processes. The basolateral amygdala is the structure most associated with fear conditioning or acquisition. During fear conditioning, the basolateral nuclei of the amygdala process sensory input from the cortex and thalamus while the central nucleus modulates physiological fear responses originating in the brain stem (Casey et al., 2015; Shin & Liberzon, 2010). The ventromedial prefrontal cortex (VMPFC), and particularly the dorsal and rostral divisions of the anterior cingulate cortex (ACC), either promotes or inhibits fear expressions via projections to the amygdala, and is routinely activated during fear conditioning and extinction trials, respectively (Casey et al., 2015; Shin & Liberzon, 2010). Similarly, the hippocampus, which projects to both the amygdala and VMPFC, can promote an amygdala fear response or facilitate contextual fear extinction depending on the presence of threat or safety in the environment (Casey et al., 2015; Shin & Liberzon, 2010). As such, the amygdala, hippocampus, and dorsal and rostral divisions of the ACC are commonly activated during fear conditioning and extinction trials (Shin & Liberzon, 2010).

These regions are similarly extensively cited in neurobiological models of PTSD. The most commonly cited neuroanatomical model of PTSD posits that a hypo-responsive medial prefrontal cortex (MPFC) fails to inhibit a hyper-responsive amygdala when encountering threat stimuli. A hyper-responsive amygdala leads to hyperarousal symptoms, whereas the hypo-responsive MPFC prevents both fear extinction and the individual from being able to shift attention away from trauma reminders. Further, dysfunctional hippocampi contribute to problems with identifying safe contexts (Rauch et al., 2006; Shin & Liberzon, 2010). Finally, PTSD also involves a hyperactive insula (Shin & Liberzon, 2010; Shvil et al., 2013). This model has been supported by a wealth of

research documenting greater amygdala responses when PTSD participants are exposed to trauma stimuli, masked and unmasked fearful faces, and fear conditioning trials in addition to reduced MPFC activation when PTSD participants are exposed to trauma stimuli, negative emotional stimuli, and fear extinction trials (Rauch et al., 2006; Shin & Liberzon, 2010; Shvil et al., 2013). Importantly, numerous researchers distinguish the rostral ACC and VMPFC functions in emotion regulation from the dorsal ACC and dorsomedial prefrontal cortex (DMPFC) functions in emotion awareness (Duval et al., 2015; Clark & Beck, 2010; Lipka et al., 2014). PTSD participants have normal or exaggerated dorsal ACC activation during fear conditioning and a hypo-responsive rostral ACC (Shin & Liberzon, 2010). Additionally, there is evidence that the hippocampus shows decreased activation when PTSD participants undergo learning paradigms (Rauch et al., 2006), although other researchers observe that the direction of hippocampal activation (e.g., increased or decreased) differs based on the task used (Shin & Liberzon, 2010). Finally, the insula is increasingly implicated in PTSD pathology, with hyperresponsivity noted during presentation of trauma stimuli, negative emotional stimuli, and fear conditioning/extinction tasks (Shin & Liberzon, 2010; Shvil et al., 2013).

Notably, regions involved in extinction and conditioning are also recruited during processing of negative emotions. In a quantitative meta-analysis, Patel et al. (2012) found that across cognitive, emotional, and symptom provocation paradigms, PTSD participants showed a) greater activation in amygdala, hippocampus, insula, and putamen and b) decreased activation in the posterior cingulate, MPFC, and left middle frontal gyrus compared to healthy controls. However, PTSD participants showed a) greater activation

in dorsal ACC, precuneus, and medial temporal lobe and b) decreased activation in MPFC, parahippocampal gyrus, lateral PFC, dorsal ACC, and orbitofrontal cortex compared to trauma-exposed controls. The authors note that the amygdala only exhibits increased activation in PTSD compared to healthy controls; however, the MPFC appears to evince hypoactivation across comparison groups.

Another meta-analysis compared regions recruited during emotional processing in PTSD, social anxiety, and specific phobia. Results indicated that the only commonality in all three disorders was hyperactivity of the amygdala and insula while processing negative stimuli (e.g., emotional facial expressions, trauma scripts, or phobic objects) (Etkin & Wager, 2007). Although amygdala hyperactivation was more common in social anxiety and specific phobia than PTSD, it was also present during fear conditioning in healthy controls and was thus proposed to represent a general “engagement of fear circuitry” (Etkin & Wager, 2007, p. 1482). Additionally, PTSD was the only disorder that exhibited hypoactivations, with hypoactivation of VMPCF during emotional processing associated with greater symptomology. Importantly, hypoactive frontal regions were associated with hyperactive limbic regions in PTSD, with no hyper- or hypoactivity of frontal regions found in social anxiety or specific phobia (Etkin & Wager, 2007). The authors conceptualize these results as indicative of PTSD being a “more complex” disorder than social anxiety and specific phobia, as it involves both intense fear and more widespread emotional dysregulation (Etkin & Wager, 2007, p. 1483).

However, some argue that altered fear conditioning and extinction processes do not account for all symptoms of PTSD, including re-experiencing and avoidance (Liberzon & Martis, 2006). Indeed, later researchers specifically highlight the MPFC and

its role in contextualization processes in order to more fully explain PTSD symptomology (Patel et al., 2012; Liberzon & Garfinkel, 2009; Liberzon & Sripada, 2008). The contextualization hypothesis notes that the MPFC, in addition to its role in inhibiting the amygdala, assists in contextualizing stimuli across numerous domains (e.g., cognitive, social, and internal), which enables the individual to appropriately respond to the environment. In PTSD, failure to interpret trauma reminders within the current spatial and temporal context could lead to re-experiencing symptoms. Further, emotional numbing could result from a failure to experience emotions consistent with the context (Liberzon & Garfinkel, 2009; Liberzon & Sripada, 2008).

In sum, PTSD is posited to be a result of a hyperresponsive amygdala, insula, and dorsal ACC to threat stimuli. PTSD also appears to show a hypo-responsive rostral ACC when viewing negative emotional stimuli, suggesting the VMPFC inadequately inhibits the amygdala in this disorder (Shin & Liberzon, 2010). Additionally, PTSD patients show an inability, or resistance to, extinction and extinction recall (Graham & Milad, 2011). Finally, altered hippocampal activity, in combination with MPFC hypo-responsivity, leads to problems with contextualization processes. Though initial biological models of PTSD focused on altered threat detection and fear learning systems, others observe that these processes are not specific to PTSD pathology (Liberzon & Martis, 2006) and point instead to dysfunctional MPFC contextualization as the “core process” of the disorder (Liberzon & Garfinkel, 2009).

General Models of Psychotherapy Action in the Brain

Models of psychotherapy action in the PTSD brain are not specific to PTSD and are largely based on theories of altered pathology in anxiety disorders. Authors

hypothesizing extinction as the underlying mechanism of anxiety disorders conceptualize exposure therapy as invoking extinction of learned responses (Roffman et al., 2005; Graham & Milad, 2011). Indeed, Etkin et al. (2005) describe “the biology of psychotherapy” as a “biology of learning” (p. 146). As such, changes following psychotherapy may necessarily appear in regions engaged in fear conditioning and extinction, and may involve either reduced activation of limbic areas (e.g., amygdala), increased activation of VMPFC, or both (Roffman et al., 2005; Porto et al., 2009; Sheynin & Liberzon, 2017).

In contrast, dual process models of brain changes after psychotherapy suggest that psychotherapy promotes explicit emotion regulation via prefrontal cortical structures (e.g., dorsolateral prefrontal cortex, ACC, ventrolateral prefrontal cortex) strengthening their activity in relation to subcortical limbic structures in the presence of emotional stimuli (Messina et al., 2013; Messina et al., 2016; Kumari, 2006; Frewen et al., 2008; Fournier & Price, 2014; Brooks & Stein, 2015; Sheynin & Liberzon, 2017). This is also the theory proposed by cognitive therapy developers, who report that cognitive therapy corrects “biased information processing and dysfunctional schema activation” (Clark & Beck, 2010, p. 419) by reducing activation in subcortical structures like the amygdala and hippocampus (“bottom-up”) and increasing activation in prefrontal cortex (PFC) regions responsible for the cognitive control of emotion (“top-down” or inhibitory) (Clark & Beck, 2010; Etkin et al., 2005; Hartley & Phelps, 2010). Others describe the change as exaggerated fear circuits in limbic and hippocampal regions becoming inhibited by PFC regions affected by cognitive restructuring learned in therapy (Brooks & Stein, 2015; Straube, 2016; Porto et al., 2009; Lueken & Hahn, 2016). Additionally, Etkin et al.

(2005) note that neuroimaging studies of psychotherapy have both demonstrated normalization effects, in which resting-state brain activity in treated groups resembles that of healthy controls after treatment (as also described in Barsaglini et al., 2014), and stimulus-specific effects, in which brain activity during symptom provocation is altered after treatment. It has also been suggested that psychotherapy aids the activation of “compensatory” brain regions, or regions that did not show altered activity before treatment (Barsaglini et al., 2014; Etkin, 2014; Weingarten & Strauman, 2015; Straube, 2016). This might be indicated by activation changes in PFC regions in patients after treatment that were not significantly different from healthy controls before treatment. As such, therapy effects would manifest in regions that did not indicate pathology prior to therapy.

An important caveat in the literature is the significant overlap between the brain regions implicated in emotion regulation and learning models, as both are thought to involve prefrontal inhibition of emotionally reactive brain regions (Messina et al., 2013). As such, both extinction and emotion regulation proponents suggest psychotherapy decreases amygdala activation and increases VMPFC activation, but their theories differ on precise mechanism of this change. This results in a thorny theoretical impasse, as hypotheses for both models are the same and results implicating amygdala and VMPFC activity do not falsify either theory. However, this may also be a false distinction between these concepts. For example, though some researchers argue that extinction models do not account for the cognitive features of anxiety disorders, particularly catastrophic interpretations of feared stimuli (Graham & Milad, 2011), others report that exposure therapy involves focusing attention on emotional stimuli (De Raedt, 2006) and thus

cannot proceed without the involvement of cognitive processes (Hofmann, 2008; Bishop, 2007). Specifically, exposure therapy involves altering the participant's perception of controllability, predictability and the expected harm from the relationship between the conditioned and unconditioned stimulus, which is also the target of cognitive restructuring techniques (Hofmann, 2008). Conversely, DeRaedt (2006) notes that behavioral experiments designed to test emotionally arousing cognitive errors should also recruit the hippocampus to inhibit the amygdala, as the patient learns the arousing situation can also be safe. Importantly, altered amygdala-prefrontal circuitry is associated with both associative learning processes (e.g., exposure) and with the negative interpretation of ambiguous stimuli (e.g., cognitive restructuring), suggesting that both a conditioned stimulus and an ambiguous stimulus signal potential danger to the anxious person (Bishop, 2007). Hartley and Phelps (2010) cite research that directly addresses the overlap in brain regions in extinction and cognitive control of emotion, which found that when undergoing both processes, amygdala activation decreases and VMPFC activation increases. However, lateral PFC regions are only activated when participants use cognitive control strategies (Hartley & Phelps, 2010). Importantly, lateral PFC has no direct projections to the amygdala, but does project to the amygdala via VMPFC (Hartley & Phelps, 2010).

Brain Changes after CBT in PTSD

In a brief report, Felmingham et al. (2007) found that following eight sessions of exposure and cognitive restructuring, eight PTSD patients showed greater activation in the bilateral rostral ACC, left middle temporal gyrus, right inferior frontal gyrus, and hippocampus in response to fearful faces compared to neutral faces- e.g., while

processing fear. Further, increased activation in ACC was associated with change in symptom severity, such that patients with the greatest symptom reduction evinced the greatest increase in ACC activation after treatment (Felmingham et al., 2007). Notably, though amygdala activation did not differ between pre- and post-treatment scans, bilateral amygdala activation was negatively correlated with change in symptom severity, such that patients with the greatest symptom reduction showed decreased amygdala activation during fear processing (Felmingham et al., 2007). The authors interpreted these results as an indication of fear extinction learning.

Similar results were found by Peres et al. (2007), who utilized single photon emission computed tomography (SPECT) imaging in patients with subthreshold PTSD symptoms who read a personalized trauma script after exposure and cognitive restructuring. Like Felmingham et al. (2007), they found a positive correlation between change in blood flow to the PFC and scores on the Clinician-Administered PTSD Scale (CAPS), as well as a negative correlation between change in blood flow to amygdala and CAPS scores (Peres et al., 2007). Further, compared to a wait-list control group of other subthreshold PTSD patients, the treated patients showed increased blood flow to the parietal lobes, ACC, hippocampus, thalamus, and PFC after exposure and cognitive restructuring therapy (Peres et al., 2007). In contrast, they exhibited decreased blood flow to left amygdala. The authors also interpreted this as PFC inhibition of the amygdala after treatment, with increased thalamic and hippocampal activity interpreted as reflecting integration of sensory details into the traumatic memory (Peres et al., 2007).

Importantly, one study examined psychotherapy effects on policemen who had experienced the same traumatic event (Peres et al., 2011). The authors administered

exposure and cognitive restructuring therapy to 24 policemen who exhibited subthreshold PTSD symptoms- specifically, hyperarousal and re-experiencing, but not avoidance/numbing, symptoms. Prior to treatment, both the treatment group and a wait-list control group which also exhibited subthreshold symptoms showed increased amygdala and decreased medial PFC activation when exposed to a trauma-related sound sequence (e.g., gunfire; Peres et al., 2011). After therapy, the treatment group had significantly decreased amygdala activation compared to before therapy. Additionally, the treatment group showed significantly greater medial PFC activation than the wait-list control group when hearing the trauma-related sound sequence (Peres et al., 2011). Notably, the treated group showed similar activation patterns to the healthy control group (who had also experienced the same trauma), suggesting that therapy normalized the treated group's amygdala and MPFC activation to levels in the asymptomatic group. As in the previous PTSD studies, Peres et al. (2011) found a positive correlation between change in symptom severity and MPFC activation, and a negative correlation between symptom severity change and amygdala activation change after therapy. However, a major limitation to this study is that the sample underwent other therapies in conjunction with exposure and cognitive restructuring as mandated by the police force's own guidelines. Additional therapies included art therapy and ecological walks over a 28-day rehabilitation program, calling into question the specificity of the treatment effects to CBT.

Fonzo et al. (2017) examined the neurobiological changes associated with emotional processing and reappraisal tasks after participants completed 9-12 prolonged exposure sessions. In line with dual process models of psychotherapy and neurocircuitry

theories of PTSD, they hypothesized that prolonged exposure would decrease insula and amygdala activation and increase PFC activation during these tasks. The tasks required participants to identify the color of emotional faces, identify the emotion expressed by a face when superimposed with a conflicting emotion word, and engage in reappraisal when presented with a negative image (Fonzo et al., 2017). Compared to a wait-list control group ($n = 30$), the treated group ($n = 36$) exhibited increased activation in the left lateral frontopolar cortex specifically during the reappraisal task following prolonged exposure. Further, change in activation of this region was positively correlated with hyperarousal symptoms and psychological well-being in the treated group, but not in the wait-list control group. The authors observe this result fails to support the dual process model, and instead suggests that prolonged exposure prompts brain changes during cognitive reappraisal in the frontopolar cortex, without affecting limbic regions (Fonzo et al., 2017).

Aupperle et al. (2013) investigated whether a 12-week cognitive trauma therapy designed for women who had experienced interpersonal violence affected neural activity during a) cued anticipation and b) presentation of negative and positive affective images. Eleven women who met full PTSD criteria and three women with subclinical PTSD symptoms completed functional magnetic resonance imaging (fMRI) scans before and after Cognitive Trauma Therapy for Battered Women (CTT-BW). Results indicated that after treatment, activation in the left ACC and left posterior cingulate increased during the anticipation phase and activation in the right anterior insula decreased (Aupperle et al., 2013). Further, treatment response was correlated with decreased activation in the left anterior insula, posterior cingulate, and precuneus and increased activation in the right

posterior insula. In contrast, during the presentation phase, bilateral posterior cingulate and right inferior parietal cortex activation increased after treatment, whereas DLPFC and right amygdala activation decreased. Treatment response was correlated with increased activation in the precuneus, posterior cingulate, left posterior insula, medial frontal, precentral, lingual, and inferior temporal gyri, and cerebellum. Response was also correlated with decreased activation in the right superior temporal gyrus, cerebellum, and caudate (Aupperle et al., 2013). Like other reviewed studies, the authors interpret increased ACC activation during the anticipation phase after treatment as a sign of enhanced emotion regulation. They hypothesized that this enhanced emotion regulation may have in turn attenuated the DLPFC response during the presentation phase, when the participant was confronted with the affective stimulus (Aupperle et al., 2013). Finally, Aupperle et al. (2013) suggest that the reduced insula and amygdala activation following treatment indicate normalization of these regions; however, this hypothesis could not be tested in this study given the lack of a control group.

Summary

Most studies indicated therapy resulted in greater activation in inhibitory regions of PFC and that change in activation was positively correlated with symptom improvement (Felmingham et al., 2007; Peres et al., 2007, 2011; Fonzo et al., 2017; also reviewed in Brooks & Stein, 2015). These changes were noted in general emotion processing (Felmingham et al., 2007), emotion regulation (Fonzo et al., 2017) and trauma-specific symptom-provocation tasks (Peres et al., 2007, 2011). Though Aupperle et al. (2013) also found increased rostral ACC activation during anticipation of an affective picture following CBT, this activation was not correlated with symptom

improvement. Interestingly, the authors also found evidence of *reduced* DLPFC activation during the presentation of an affective picture following CBT. Further, though the amygdala evinced no change after treatment in two studies (Felmingham et al., 2007; Fonzo et al., 2017), it exhibited decreased activation after treatment in three others (Peres et al., 2007, 2011; Aupperle et al., 2013). However, amygdala activation negatively correlated with symptom measures in three studies (Felmingham et al., 2007; Peres et al., 2007, 2011). Aupperle et al. (2013) additionally found evidence of reduced anterior insula activation during anticipation of an affective picture following CBT, with change in insula activation correlated with treatment response.

Critical Summary

In three of the five reviewed studies, the amygdala exhibited decreased activation during task scans following CBT, providing some support for the role of CBT in altering subcortical fear systems. However, decreased amygdala activation was not consistent, and limited evidence of a) reduced insula or dorsal ACC activation b) changes in hippocampal activation was found. Further, PFC changes after CBT were not localized to one region, although support for change in the rostral ACC, lateral frontopolar cortex, and DLPFC was found.

Mixed findings on the precise location and direction of change in prefrontal regions after therapy, in conjunction with limited or no change in other brain regions associated with PTSD (e.g., insula, hippocampus) suggests that the CBT effect on brain regions is more complex than that accounted for in dual process and extinction models (as also noted by Messina et al., 2013; Barsaglini et al., 2014; Fournier & Price, 2014). Prochaska et al. (2008) compiled a list of criteria to evaluate theories, which include

clarity, consistency, parsimony, testability, and empirical adequacy, among others.

Although dual process and extinction models of psychotherapy are clear and consistent (e.g., they are operationalized, explicit, and non-contradictory), parsimonious (implying that psychotherapy affects one set of processes), and testable, mixed results of changes in brain regions denoted in both theories calls their empirical adequacy into question (Prochaska et al. 2008). As noted by numerous authors, these inconsistencies in results are likely an effect of methodology, with unclear conclusions about CBT effects likely an effect of incomprehensive theories.

Methodological Critique. Across the reviewed literature, methodological differences complicate comparisons between studies and thus, conclusions about CBT mechanisms in the brain. For example, studies employed a range of scanning techniques (fMRI versus SPECT), paradigms (emotional processing, symptom provocation, and emotion regulation) and CBT modalities (individual versus group; Roffman et al., 2005; Straube, 2016). As such, CBT appears to affect brain activity during symptom provocation and processing of negative emotional stimuli in PTSD. It is important to note the task used influences the interpretation of CBT effects. For example, symptom provocation tasks may not capture all implicated symptoms of the disorder: a trauma script may engage the re-experiencing, but not the avoidance or numbing, symptoms of PTSD (Frewen et al., 2008). This is a major limitation to the current research, and future studies should attempt to investigate brain changes across paradigms (MacNamara et al., 2016).

In addition to the above differences, researcher decisions on sample size, appropriate comparison groups, and appropriate assessments affect study results. Small

sample sizes were recruited in most studies, thus potentially making them under-powered to detect more changes (Frewen et al., 2008). Importantly, the use of a healthy and psychiatric control group at baseline confirms that brain functioning in clinical populations is ‘abnormal’ to begin with (e.g., compared to healthy controls) and not different between the treated and wait list clinical groups (Frewen et al., 2008; Fournier & Price, 2014). Appropriate comparison groups would also reduce the likelihood that observed changes were due to passage of time, and not treatment effects (Roffman et al., 2005). Additionally, Frewen et al. (2008) recommend future psychotherapy studies collect and correlate measures of psychological mechanisms of change with imaging findings. This would allow conclusions as to whether the purported psychotherapeutic mechanism was responsible for clinical change, or whether symptom reduction occurred independent of this mechanism (Frewen et al., 2008). Linden (2006) importantly states that current designs do not allow conclusions about whether brain changes after therapy (e.g., decreased amygdala activation) are the *cause* or *effect* of symptom reduction via therapy. As such, he notes that neuroimaging studies of CBT effects are not immune to the third (or confounding) variable problem, as it is plausible that changes in other brain areas led to altered stimulus processing in limbic regions (Linden, 2006). This highlights a critical distinction between brain regions associated with symptom expression/remission and those that serve as mechanisms of CBT, which have frequently been conflated (Etkin et al., 2005).

Conceptual Critique. One reason the amygdala might be demonstrating equivocal change after CBT for PTSD is explained by the following theory. A recent “two-systems” view of fear and anxiety posits that regions responsible for generating

behavioral responses to threat are separate from those responsible for generating conscious feelings of fear and anxiety (LeDoux & Pine, 2016). In this model, subcortical structures like the amygdala produce behavioral responses to threat, whereas lateral and medial PFC and insula produce conscious states of fear and anxiety. This is supported by research showing that 1) amygdala activation is not always correlated with subjective fear ratings, and 2) amygdala activation also occurs in response to subliminally processed threat (e.g., without conscious fear) (LeDoux & Pine, 2016). Crucially, the authors propose that the amygdala is not the center of a “fear circuit” that leads to conscious feeling states, but rather serves to detect threat and modulate circuits that are responsible for consciousness and thus, fearful feelings (LeDoux & Pine, 2016). The crux of this argument is that researchers cannot conflate the subcortical regions producing behavioral and physiological responses to threat detection with cortical regions causing subjective anxiety or fear states. Thus, the previously reviewed studies which solely employ threat detection tasks to measure CBT effects may not be adequately investigating regions that contribute to anxious states when individuals are *not* processing threat, e.g., in a resting state. As such, treatments might target *either* a hyperactive subcortical or cortical circuit, and cognitive therapies may be more appropriate for individuals with ‘normal’ subcortical circuits and ‘abnormal’ cortical circuits (LeDoux & Pine, 2016). This might explain why CBT effects across brain regions are inconsistent (as individuals in the same study might have differently activated circuits) and why symptom measures do not always correlate with brain changes in subcortical circuits (as symptom measures assess conscious feelings generated in cortical circuits).

This problem is highlighted in two recent reviews of brain changes after therapy (Messina et al., 2013, 2016). In the first review, a meta-analysis including both depressive and anxiety disorders and a variety of therapy approaches (including CBT and Interpersonal Therapy), found activation changes in both resting-state and task scans in the fronto-parietal attentional system, which includes a region of the left superior and medial frontal gyrus. Additionally, the DMPFC, posterior cingulate, and a region of the temporal lobe evinced activation changes following treatment, which the authors interpret as change in self-related thought processes mediated by therapy (Messina et al., 2013). Importantly, when analyzing studies on specific phobia separately, Messina et al. (2013) found decreased activation in the parahippocampal gyrus after treatment, which supports a therapy effect on limbic regions in this disorder (although the absence of the amygdala and insula in this analysis is notable). However, the remaining results indicating treatment effects in brain regions not predicted by emotion regulation or extinction theories suggest a more comprehensive model of therapy effects is needed (Messina et al., 2013).

Based on results from their meta-analysis, Messina et al. (2016) argued that psychotherapy may additionally affect implicit (as opposed to explicit) emotion regulation via changes in regions associated with semantic processing. Implicit or spontaneous emotion regulation may not involve executive processes, but semantic processes that encode and interpret external stimuli (Messina et al., 2016). Semantic processing occurs in the inferior parietal lobe, temporo-parietal junction (TPJ), anterior-medial temporal lobes, VMPFC, and posterior cingulate. Whereas the VMPFC and inferior parietal lobe encode emotional semantic representations, the TPJ and temporal

lobes encode social cognitive representations (Messina et al., 2016). Another meta-analysis of cognitive reappraisal studies supports the notion that reappraisal modulates semantic representations of stimuli which uniquely affect the amygdala (Buhle et al., 2014). It is possible that the cortical regions involved in semantic processing are those leading to conscious feeling states in the “two-systems” view of fear and anxiety, and thus the regions evincing change after CBT (LeDoux & Pine, 2016).

New Directions: Network-Based Models of Psychopathology

Conceptual Importance

As suggested by the critique of the literature, the investigation of CBT mechanisms in the brain is hindered by two overarching problems- one concerning theory comprehensiveness and the other concerning methodology. First, the overlap between emotion regulation and extinction-based models of therapy effects mean that neither model can be falsified, as results can be found to fit either theory (Bishop, 2007). Furthermore, current results are inconsistent and do not fully support either theory, questioning the empirical adequacy of both (Prochaska et al., 2008). With regard to methodology, dual process models hinge on the idea that cortical structures are “strengthening control” over limbic structures. However, traditional fMRI analyses cannot directly test this hypothesis. Similarly, in the LeDoux and Pine (2016) “two systems” model, the insula and MPFC are cortical regions thought to modulate fearful feelings, but also overlap with those implicated in fear extinction. As such, fMRI activation studies that simply note change in these disparate regions cannot determine to which circuit the insula and MPFC belong. Clearly, a new type of methodology is needed to clarify the hypotheses generated by different theories. Functional connectivity

analyses, which investigate the functional correlations between brain regions, are more appropriate for both testing the dual process model (e.g., investigating relations between brain regions) *and* elaborating on treatment effects in the brain after CBT (as also noted in Barsaglini et al., 2014). Further, connectivity analyses allow the investigation of brain networks. As argued by the National Institute of Health Research Domain Criteria, psychological disorders often represent deficits in multiple domains (attention, emotion regulation, cognition, etc.) which are more accurately encapsulated by network models (Cuthbert & Insel, 2013). Numerous network-based models of psychopathology have been posited, which could also be used to test psychotherapy effects. As such, utilizing functional connectivity analyses to investigate neurobiological mechanisms of CBT both addresses a critical methodological issue in the literature and enables the generation of new theories.

Network-Based Models of Psychopathology

Network-based models of psychopathology refer to “cognition-specific brain circuits” that are implicated in transdiagnostic clinical symptoms. Network-based models of psychopathology suggest that abnormal connectivity within and between functional networks observed across neurodegenerative and psychological disorders results in transdiagnostic symptom clusters and is a key factor in pathology (Buckholtz & Meyer-Lindenberg, 2012; Menon, 2011). This finding has led some to refer to them as “disorders of brain connectivity” (Fornito & Bullmore, 2012). Transdiagnostic symptom clusters refer to deficits in executive, affective, motivational, and social functioning domains of cognition (Buckholtz & Meyer-Lindenberg, 2012). Indeed, disrupted functional connectivity within networks can essentially serve as an intermediate

phenotype between genotype and clinical presentation (Fornito & Bullmore, 2012).

Network models argue for a systems, as opposed to regional, level of analysis (Fornito & Bullmore, 2012; Buckholtz & Meyer-Lindenberg, 2012).

A tri-partite model of psychopathology and aberrant cognitive and affective networks was first proposed by Menon (2011). The first aberrant network implicated is the central executive network (CEN), which is activated during decision-making and working memory tasks (Menon, 2011), as well as being critical for attention allocation (Buckholtz & Meyer-Lindenberg; 2012). The CEN is a frontoparietal system which includes the lateral PFC, dorsal ACC, and posterior parietal cortices (Menon, 2011; Buckholtz & Meyer-Lindenberg, 2012). The second aberrant network implicated is the salience network (SN), which is a corticolimbic system including lateral and medial PFC, ACC, amygdala, substantia nigra, and insula. The SN is responsible for processing salient environmental and internal information (including emotion) and is thus prone to influencing negative affective states (Menon, 2011; Buckholtz & Meyer-Lindenberg, 2012). Fornito & Bullmore (2012) directly implicate this network in emotion regulation. The third aberrant network is the default mode network (DMN), which is commonly activated during resting states (as opposed to during cognitive tasks) or self-referential processes. The DMN comprises the lateral parietal lobes, posterior cingulate, and medial PFC (Menon, 2011; Buckholtz & Meyer-Lindenberg, 2012; Fornito and Bullmore, 2012).

Notably, though various disorders may exhibit aberrant connectivity in any of these core neurocognitive networks, Menon (2011) emphasizes that different disorders show different patterns of abnormal connectivity. For example, whereas depression and Alzheimer's disease both have altered DMN connectivity, he notes that depressed

patients show increased medial PFC connectivity, and those with Alzheimer's disease show reduced posterior cingulate cortex connectivity (Menon, 2011). Further, the specific "dysfunction" in any one network differentiates clinical disorders by causing varied symptomology: in autism, social stimuli are improperly detected, whereas in social anxiety, social stimuli are over-detected. The disorder-specific symptom then leads to "cascading effects" with regard to attention allocation and other executive processes (Menon, 2011). The model further suggests that the SN, once it detects salient stimuli, facilitates the recruitment of the CEN and the disengagement of the DMN to produce a behavioral response to the stimulus (Menon, 2011). An abnormally functioning SN may either fail to adaptively detect salient stimuli (either enhancing or prohibiting detection), or fail to recruit other networks (e.g., CEN) to process stimuli (Menon, 2011). Thus, the *interaction* of these networks, particularly the SN and CEN, affect how information is processed and attention is allocated- and dysfunction in any one network can lead to dysfunction in the others (Menon, 2011).

Proposed Dysfunctional Networks in PTSD

Although initial dysconnectivity hypotheses centered on research findings in schizophrenia and autism (Menon, 2011), researchers are increasingly acknowledging the ways in which networks are specifically altered in PTSD. Currently, many researchers conceptualize PTSD network dysfunction in emotion-generating and modulating networks, similar to the dual process model previously reviewed. Disrupted amygdala-frontal networks have been demonstrated in PTSD (between the amygdala and medial PFC) in both task and resting states (Duval et al., 2015; MacNamara et al., 2016). These authors conceptualize these patterns as reflecting impaired emotion regulation and threat

processing (MacNamara et al., 2016) or as an interaction of threat processing and emotion regulation circuits (Duval et al., 2015).

A more recent review notes that functional connectivity studies in PTSD largely implicate altered connectivity within the networks of Menon's tripartite model (2011). Akiki et al. (2017) hypothesize that re-experiencing, dissociation, and avoidance symptoms result from dysfunctional DMN connectivity, with altered CEN connectivity implicated in reduced prefrontal inhibition and attention/memory problems. Finally, they suggest disrupted SN connectivity translates to hyperarousal symptoms via increased sensitivity to threat detection. Taken together, the authors conceptualize PTSD as consisting of a hyperactive SN and hypoactive CEN and DMN. Further, the CEN is impaired in top-down regulation of the SN (Akiki et al., 2017). This aligns with other researchers who observed reduced DMN connectivity, altered SN connectivity, and increased connectivity between the DMN and SN in PTSD (MacNamara et al., 2016). These authors argue that rather than involving regional hypo- or hyper-activations, anxiety disorders may better be characterized as disorders of "widespread distributed disturbances in functional brain organization" (MacNamara et al., 2016, p. 282).

However, increasing evidence for disruptions both within and between broader cognitive and emotional networks is mounting. Williams (2017) proposes that specific disruptions in DMN, SN, affective (e.g., "threat"), and attention networks might serve as "biotypes" for depressive and anxiety symptoms. Specifically, an anxiety or stress disorder "biotype" might involve hypoconnectivity within both the SN and the affective network, leading to feelings of apprehensiveness and threat dysregulation/arousal, respectively (Williams, 2017). Notably, Williams (2017) notes the overlap in nodes of the

SN and affective networks, which both include different regions of the ACC, amygdala, and insula. The affective network additionally includes the VMPFC and hippocampus.

Though these models speak to the etiology of PTSD, CBT's effects on networks are less clearly defined. If one hypothesizes that CBT normalizes the etiological processes of PTSD, the SN and CEN, which comprise oft-cited prefrontal-limbic regions, might be implicated first (Weingarten & Strauman; 2015). However, CBT may also modulate networks responsible for transdiagnostic symptoms inherent to anxiety and stress, such as impaired concentration (Frewen et al., 2008). In this case, the intermediate phenotypes (as described by Fornito & Bullmore, 2012) or transdiagnostic symptoms (Buckholtz & Meyer-Lindenberg, 2012; Williams, 2017) of anxiety and stress disorders are affected by CBT (MacNamara et al., 2016). At any rate, researchers are beginning to propose that changes in functional connectivity networks will serve as "key neurobiological outcomes" of psychotherapy treatment research (Weingarten & Strauman, 2015, p. 201). In PTSD specifically, investigating disrupted networks may serve as a better representation of the heterogeneous clinical profiles of those with PTSD than studies examining activity in isolated brain regions (Patel et al., 2012).

Research on Mechanisms of CBT in PTSD Using Functional Connectivity Analyses

Few studies have examined pre-post CBT brain changes in PTSD using functional connectivity analyses. As part of the larger previously reviewed study, Fonzo et al. (2017) found that the frontopolar cortex, which exhibited activation changes after prolonged exposure, also showed increased connectivity with VMPFC during a reappraisal task after treatment. The authors suggest this demonstrates that CBT enhances attention toward emotion regulation processes (Fonzo et al., 2017). A second study found

that PTSD participants exhibited increased connectivity between rostral ACC and VMPFC during an extinction recall task after prolonged exposure treatment compared to a scan at baseline (Helpman et al., 2016). A third study examining resting-state functional connectivity changes after prolonged exposure demonstrated increased connectivity between specific amygdala nuclei and orbitofrontal cortex as well as between hippocampus and MPFC in PTSD participants (Zhu et al., 2018). Notably, the connectivity between these regions was significantly reduced in PTSD participants compared to TEC before prolonged exposure but had normalized to TEC levels after treatment (Zhu et al., 2018). The authors concluded that this pattern indicated that PTSD participants had better ability to evaluate threat and process emotional information following prolonged exposure treatment (Zhu et al., 2018).

Another study found that after 16 weeks of group mindfulness-based exposure therapy, combat veterans with PTSD exhibited increased connectivity between the posterior cingulate in the DMN and prefrontal regions (DLPFC, ACC) compared to scans before treatment. Importantly, veterans who underwent an active control treatment did not show this pattern (King et al., 2016). Furthermore, posterior cingulate-DLPFC connectivity was associated with avoidance and hyperarousal symptom improvement (King et al., 2016). Notably, all connectivity analyses in these studies were restricted to specific regions, and future research should include data-driven approaches to uncover potential new mechanisms in other networks. No other studies investigating functional connectivity changes pre-post CBT in PTSD were found.

Aims and Hypotheses

Though CBT for PTSD causes brain changes that are often associated with symptom reduction, extant studies do not unilaterally support traditional dual process or learning models which posit that CBT has therapeutic effects via an emotion regulation or extinction mechanism, respectively. The current research on neurobiological mechanisms of CBT for PTSD is plagued by a small literature with inconsistent results that likely stems from inconsistent methodology. For example, behavioral paradigms, imaging modalities, and comparison groups differ across studies. Beyond these methodological considerations, future research should utilize functional connectivity analyses, as opposed to traditional fMRI activation analyses, in order to test hypotheses about the relation among brain regions that are posited in dual process and extinction models. Additionally, brain network approaches may generate new hypotheses about a) disrupted neurobiological processes in PTSD and b) the reason therapeutic processes may engender their effects. Though this knowledge would be greatly beneficial to both psychotherapy and PTSD literatures, there is a dearth of research analyzing brain changes after CBT in PTSD using functional connectivity methods. Further, there is no research examining functional connectivity changes after Cognitive Processing Therapy (CPT) in a PTSD sample. The current study will address these gaps in the literature by utilizing functional connectivity analyses to examine changes in the DMN, CEN, and SN following CPT. These networks were selected based on their empirical support in healthy and psychiatric samples (Menon, 2011), as well as in PTSD (Akiki et al., 2017; MacNamara et al., 2016).

Aim 1

Investigate whether resting-state functional connectivity in DMN, CEN, and SN is significantly different between PTSD participants before and after CPT compared to trauma-exposed controls (TEC).

Hypothesis 1. At Time 1, PTSD participants ($n = 42$) in the intent-to-treat sample will exhibit reduced DMN and CEN functional connectivity compared to TEC participants ($n = 18$). PTSD participants will also exhibit increased SN functional connectivity compared to TEC participants.

Hypothesis 2A. At Time 1, PTSD participants ($n = 26$) who completed CPT will exhibit reduced DMN and CEN functional connectivity compared to TEC participants ($n = 18$). PTSD participants will also exhibit increased SN functional connectivity compared to TEC participants.

Hypothesis 2B. At Time 2 (following CPT), PTSD participants ($n = 26$) will not exhibit significantly different DMN, CEN, or SN functional connectivity compared to TEC participants.

Aim 2

Investigate whether resting-state functional connectivity in DMN, CEN, and SN changes following CPT in PTSD participants.

Hypothesis 3. PTSD participants ($n = 26$) will exhibit increased DMN and CEN functional connectivity and reduced SN functional connectivity after CPT compared to before CPT.

Aim 3

Investigate whether change in resting-state functional connectivity in DMN, CEN, and SN following CPT is related to change in PTSD and/or transdiagnostic symptoms.

Hypothesis 4. Change in resting-state functional connectivity in DMN, CEN, and SN after CPT in PTSD participants will be correlated with change in PTSD symptoms as measured by the Clinician-Administered PTSD Scale (CAPS).

Hypothesis 5. Change in resting-state functional connectivity in DMN, CEN and SN after CPT in PTSD participants will be correlated with change in rumination, positive affectivity, and negative affectivity (i.e., transdiagnostic symptoms of mental disorders).

Exploratory Aim

Investigate whether change in resting-state functional connectivity in other networks identified by the current study's analysis is related to change in PTSD and/or transdiagnostic symptoms following CPT.

Method**Participants**

All participants were already recruited from a larger study. The intent-to-treat sample included 42 women aged 18-55 with a DSM-IV-TR diagnosis of PTSD (American Psychiatric Association, 2000) resulting from interpersonal violence and 18 TEC. In the larger study, 16 women in the treatment group discontinued treatment, leaving 26 women with pre- and post-CPT data. Exclusion criteria from the larger study

included: diagnosed neurological disorders, current substance abuse disorders, schizophrenia/psychotic disorder, bipolar, or obsessive-compulsive disorder. Additionally, participants were excluded if they displayed active suicidality as determined by the investigator, were taking psychotropic drugs (e.g., beta blockers, antipsychotics, antidepressants), or had ever experienced a loss of consciousness greater than five minutes. All participants provided written informed consent in accordance with criteria established by the University's Human Subjects Committee.

Measures Establishing PTSD Diagnostic Criteria

Life Events Checklist

This checklist is administered as part of the CAPS and is used to determine whether Criterion A for a PTSD diagnosis has been met. It contains items such as “physical assault,” “sexual assault,” and “other unwanted or uncomfortable sexual experience.” Participants endorsed events that have happened to them personally, that they have witnessed happening to someone else, or that they have learned happened to a close other.

Clinician-Administered PTSD Scale (CAPS)

The CAPS is a 30-item structured interview that corresponds to the DSM-IV criteria for PTSD (Blake et al., 1995). The scoring criteria proposed by the authors consider a PTSD symptom present if the frequency of the CAPS item is rated as 1 or higher and the intensity is rated at a 2 or higher. Previous studies have reported high test-retest reliability ($r = .90-.98$) and internal consistency ($\alpha = .94$) of the overall severity score (Weathers & Litz, 1994). Additionally, severity scores for each symptom cluster displayed test-retest coefficients between .77-.96 and alpha coefficients between .85-.87

(Weathers & Litz, 1994). For the current analysis, PTSD diagnosis will be based on cutoff scores > 45 on the CAPS.

Measures for Hypothesis Testing

Clinician-Administered PTSD Scale (CAPS)

See above description.

Ruminative Thought Style Questionnaire (RTS)

This is a 20-item assessment measuring an individual's tendency to ruminate (Brinker & Dozois, 2009). Participants rate how well each statement describes them on a Likert scale from 1 to 7. Examples of items include "I find my mind often goes over things again and again," "If I have an important event coming up, I can't stop thinking about it," and "I tend to replay past events as I would have liked them to happen" (Brinker & Dozois, 2009). The measure exhibits high internal consistency ($\alpha = .87$) and test-retest reliability ($r = .80$) (Brinker & Dozois, 2009).

Positive and Negative Affect Schedule-Expanded (PANAS-X)

This 60-item assessment measures positive and negative affect, which are factors that contribute largely to mood states (Watson & Clark, 1999). Participants are provided a list of 60 words or phrases that describe emotional states and asked to rate on a Likert scale of 1 ("not at all") to 5 ("extremely") how much they have felt that way in the last few weeks (Watson & Clark, 1999). Sample items include cheerful, lonely, nervous, ashamed, frightened, irritable, and distressed (Watson & Clark, 1999). Both the Positive Affect and Negative Affect scales of the PANAS-X display high internal consistency (ranging from .83 - .90) across student, nonclinical adult, and psychiatric samples

(Watson & Clark, 1999). Further, the Positive Affect and Negative Affect scales are not highly correlated with each other, suggesting they are measuring independent constructs. Finally, both scales exhibit moderate test-retest reliability (.39 and .43 for Positive and Negative Affect, respectively) (Watson & Clark, 1999).

Procedure

In the larger study, all participants completed a baseline assessment in which they were administered the CAPS, Life Events Checklist, RTS, and PANAS. On a second day, all participants underwent structural and resting-state fMRI scans, which lasted approximately 1.5 hours. Subsequently, participants diagnosed with PTSD received a standard course of CPT, a “strongly recommended” therapy for PTSD according to the American Psychological Association Clinical Practice Guideline for PTSD (American Psychological Association, 2017). After completing treatment, PTSD participants completed a follow-up assessment of the measures collected at baseline and underwent a second resting-state fMRI scan which lasted approximately 1.5 hours. In sum, PTSD participants who completed CPT underwent two fMRI scans. TEC completed one fMRI scan.

fMRI Data Acquisition

fMRI images were collected on a Siemens 3T TrioTim MRI scanner (Erlangen, Germany) as part of a larger study. The protocol included localizer images, a high-resolution, magnetization prepared rapid gradient echo (MPRAGE) structural image, and a series of functional images. The structural images were acquired with $1 \times 1 \times 1 \text{ mm}^3$ resolution using a sagittal 3-D T1-weighted sequence with repetition time (TR) of 2.4 s,

time-to-echo (TE) of 3.13 ms, flip angle=8°, and inversion time (TI) of 1000 ms.

Functional resting-state images were collected using an asymmetric spin-echo echo-planar sequence TR=2.2 s, TE=27 ms, flip angle=90° and field of view (FOV) of 384 cm. One acquisition consisted of 36 transverse slices, 4 mm thick (no gap), and with an in-plane resolution of 4×4 mm.

Functional Connectivity Analysis

Functional magnetic resonance imaging scans measure changes in the blood oxygen level dependent (BOLD) signal within brain tissue. Changes in the BOLD signal are considered an indirect measure of neuronal activity; thus, comparing the BOLD signal across different brain regions, groups, and paradigms (e.g., resting-state, emotional processing task, etc.) allows researchers to infer which regions are activated and how brain activation changes across these conditions (Rogers et al., 2007). Functional connectivity analyses measure BOLD signal *correlations* throughout the brain, indicating which anatomically separated regions may be functionally related during specific tasks or in specific groups (Biswal et al., 1995; Rogers et al., 2007; Sheline et al., 2010). Brain regions with correlated BOLD signal over time or during performance of specific tasks are considered ‘functionally connected’ and part of the same brain network.

Functional connectivity can be measured with numerous types of analyses. The most common approach is seed-based connectivity, a univariate test which calculates the correlation between activity in a chosen “seed” region with activity in the rest of the brain (Margulies et al., 2010). However, this approach requires researchers to determine *a priori* regions of interest to examine. In contrast, independent components analysis (ICA) in fMRI uncovers spatial signals which are maximally independent over time (Calhoun et

al., 2001). It is a multivariate, data-driven approach which is ideal for examining brain activity when no models exist to inform seed region selection (Calhoun et al., 2003). Given the lack of research on pre-post CBT brain changes in PTSD using data-driven methods, the current study investigated functional connectivity networks using ICA.

As the current study conducted analyses on archival data, power analyses were not utilized. There are numerous arguments against the use of post-hoc power analyses in clinical trials (Levine & Ensom, 2001), in fMRI data (Mumford, 2012), and in scientific research generally (Hoenig & Heisey, 2001). These authors emphasize that post-hoc power analyses are redundant, as nonsignificant results inherently imply low observed power (Mumford, 2012; Levine & Ensom, 2001). Additionally, of the previously reviewed studies, samples ranged from 8-36 participants. Only one study (Fonzo et al., 2017) analyzed more participants than our proposed analyses, suggesting that our sample size is adequate.

Functional connectivity analyses were conducted using the group-ICA approach within the CONN toolbox (release 18.a; Whitfield-Gabrieli & Nieto-Castanon, 2012). Imaging data underwent spatial preprocessing using standard methods in the Statistical Parametric Mapping software package (SPM12) (Friston et al., 2007), which included realignment, slice-timing correction, coregistration, segmentation, normalization, and smoothing (using a 6-mm FWHM Gaussian kernel) (Whitfield-Gabrieli & Nieto-Castanon, 2012; Vergara et al., 2017). Data then underwent denoising, which included regression of subject motion (e.g., realignment parameters) from the voxel-level time series, followed by linear detrending, despiking, and band-pass filtering at .008-.09 Hz.

CONN implements spatial group-ICA analyses using methods previously described by Calhoun (Calhoun et al., 2001; 2009). As such, CONN conducted variance normalization pre-conditioning and concatenated the BOLD signal along the temporal dimension (Whitfield-Gabrieli & Nieto-Castanon, 2017). After the fMRI data was pre-processed (as described above), the number of independent components (e.g., functional connectivity networks) to be estimated was determined by the minimum description length technique as implemented in the GIFT toolbox (GIFT Documentation Team, 2017). This technique resulted in an estimated 194 components in the data. However, review of other papers using ICA in PTSD samples indicated no other study had analyzed more than 44 components; therefore, 100 components were determined to be sufficient for this analysis (St. Jacques et al., 2013; Shang et al., 2014; Rabellino et al., 2015; Tursich et al., 2015; Zhang et al., 2015; Reuveni et al., 2016). Subsequently, CONN utilized the G1 fastICA algorithm to identify 100 independent spatial components (e.g., functional connectivity networks) in the fMRI data. Finally, GICA3 back-projection was used to recreate individual subject spatial maps to be used in the second-level analyses (Whitfield-Gabrieli & Nieto-Castanon, 2017). All neuroimaging data (e.g., from both time points and all groups) was entered simultaneously into the group-ICA to ensure comparisons between the same components (networks) could be made.

After these steps, CONN produced numerous spatial maps of brain regions whose z-scores were correlated in their time course. In this analysis, z-scores indicate the correlation between activation in each voxel (e.g., the BOLD signal) and the time course of the entire network. The produced spatial maps were then correlated with template maps within CONN. Template maps are commonly identified functional connectivity

networks in the literature, such as the DMN, SN, and visual networks (Whitfield-Gabrieli & Nieto-Castanon, 2017). A high correlation between a spatial map identified in the current dataset and a template map within CONN indicated the presence of that network within the dataset. In this dataset, the components with the strongest correlation with the networks in the template map were selected for further analysis. In other words, the component with the highest correlation with the DMN, SN, and CEN template maps were selected as the DMN, SN, and CEN components, respectively. Spatial maps that were composed of regions within white matter or cerebrospinal fluid were identified as noise and discarded from second-level analyses. White matter and cerebrospinal fluid are identified as noise because fMRI is only applied to gray matter in the brain. This method for selecting functional networks for second-level analysis has been utilized in Zhang et al. (2015), Liao et al. (2010), and Hoekzema et al. (2014).

Second-Level Analyses

All second-level analyses were conducted within the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) or in SPSS (IBM SPSS Statistics for Windows, Version 24.0). Of note, the CONN toolbox utilized voxel-level thresholds of $p < .001$ and cluster-level FDR-corrected thresholds of $p < .05$ to detect significant differences in brain activation between groups (Hypotheses 1-3). Additionally, data analyses only consisted of the planned comparisons outlined in the hypotheses and p -values, effect sizes, and confidence intervals are reported for each test (Althouse, 2016). Given the lack of research investigating brain network change after CPT for PTSD and the exploratory nature of the current study, these results will require future replication.

Results

Demographic Characteristics

Please see Table 1 for a summary of the demographic characteristics of the whole sample and each experimental group. Independent samples t-tests indicated that the ITT group did not significantly differ from TEC on age ($t(58) = -0.26, p = .79$) or education level ($t(58) = 0.80, p = .43$). Similarly, the PTSD treatment completer group did not significantly differ from TEC on age ($t(42) = 0.53, p = .60$) or education level ($t(42) = 1.05, p = .31$). An independent samples t-test indicated that CAPS scores at Time 1 were not significantly different between participants who completed treatment and those that dropped out of treatment ($t(40) = -0.34, p = .74$).

Preliminary Analyses

Pearson's correlation coefficient was used to determine the relation between length of time in treatment (in weeks) and change in PTSD and transdiagnostic symptoms (e.g., rumination, positive affectivity, negative affectivity) in the treatment completer sample. Symptom change was calculated by subtracting CAPS scores at Time 2 from CAPS scores at Time 1. Change in rumination, positive affectivity, and negative affectivity was calculated by subtracting participant's scores at Time 2 from these same scores at Time 1. Time in treatment was not significantly correlated with change in CAPS ($r(22) = .11, p = .62$), rumination ($r(22) = -.15, p = .50$), positive affectivity ($r(22) = -.36, p = .09$), or negative affectivity ($r(22) = .05, p = .81$) scores. This indicates that change in PTSD and transdiagnostic symptoms was not simply due to passage of time. Notably, a paired-samples t-test found that CAPS scores at Time 1 were significantly different from

CAPS scores at Time 2 ($t(23) = 12.18, p = .00$), indicating that CPT resulted in a reduction of PTSD symptoms. Finally, age was considered as a possible covariate given evidence for the relation between age and network connectivity (Vértes & Bullmore, 2015). To determine whether age should be included as a covariate in our analyses, we calculated Pearson's correlation coefficient between age and connectivity in DMN, CEN, and SN at Time 1 and Time 2. Participant age was not significantly correlated with connectivity in any network at Time 1 or Time 2 (see Table 2). As such, age was not included as a covariate in our analyses.

Data Cleaning

Z-scores for the DMN, CEN, and SN representing average connectivity within these networks at Time 1 and Time 2 were inspected for univariate outliers and normality. Univariate outliers were defined as those subjects whose z-scores were three standard deviations from the mean. At Time 1, inspection of histograms for DMN and SN appeared normal and there were no univariate outliers. Examination of the CEN histogram revealed a non-normal distribution, and there was one z-score outlier in the TEC group. Upon removal of this outlier, the histogram appeared normal and there were no univariate outliers. At Time 2, histograms for the DMN, CEN, and SN appeared normal and there were no univariate outliers.

Aim 1

Three two-tailed independent-samples t-tests were used to compare the 1) DMN, 2) CEN, and 3) SN network z-scores between experimental groups in each hypothesis. For Hypothesis 1, DMN, CEN, and SN z-scores in the intent-to-treat sample of PTSD

participants were not significantly different from the DMN, CEN, and SN z-scores of TEC at Time 1 (see Table 3). For Hypothesis 2A, DMN, CEN, and SN z-scores from the Time 1 scan in the treatment completer sample of PTSD participants were not significantly different from the DMN, CEN, and SN z-scores of TEC (see Table 4). For Hypothesis 2B, DMN, CEN, and SN z-scores from the Time 2 scan in the treatment completer sample of PTSD participants were not significantly different from the DMN, CEN, and SN z-scores of TEC at Time 1 (see Table 5).

Tests of Equivalence

Fundamentally, a rejection of the null hypothesis when implementing null hypothesis significance testing (NHST) only indicates there was insufficient evidence to reject the null hypothesis. Rejection of the null hypothesis does not indicate whether the alternative hypothesis is true or false (deGraaf & Sack, 2018), nor suggest that the null hypothesis should be accepted (Hupe, 2015). In other words, obtaining null results does not reflect evidence for the absence of an effect (deGraaf & Sack, 2018; Kazdin, 2003). One potential method of further evaluating null results is in using equivalence tests, which determine whether “effects that are large enough to be considered meaningful can be rejected” (Lakens et al., 2018). In one method of equivalence testing, the two-one sided tests procedure, upper and lower bounds are set based on the smallest effect size of interest the researcher deems meaningful, and two null hypotheses are tested: that the effect is less than the lower bound or greater than the upper bound (Lakens, 2017). If these tests are rejected, the researcher may conclude that the effect lies within the bounds, and is thus “practically equivalent” (Lakens, 2017). To determine whether the means between experimental groups in the above hypotheses were practically equivalent to each

other, two one-sided tests of equivalence (TOST) were conducted for each of the above hypotheses using a spreadsheet provided in Lakens (2017). For each TOST, the smallest effect size of interest was determined by calculating the smallest effect size we would be able to observe based on our sample size, as demonstrated in Lakens et al. (2018).

Hypothesis 1. For Hypothesis 1, a sensitivity analysis in G*Power indicated that with sample sizes of 42 (ITT) and 18 (TEC) and an alpha of 5% (two-sided), we would have 80% power to detect an effect of $d = 0.80$. Subsequently, the upper and lower equivalence bounds were set at -0.80 and 0.80 , following the guidelines by Lakens (2017). The TOST procedure indicated that the observed effect sizes in the DMN ($t(58) = 1.86, p = .03$) and CEN ($t(57) = 1.84, p = .04$) were significantly within the equivalent bounds of $d = -0.80$ and $d = 0.80$, indicating that the functional connectivity within these networks in the ITT and TEC groups was statistically equivalent at Time 1 (Lakens et al., 2018). However, the observed effect size of the SN ($t(58) = 1.43, p = .08$) was not significantly within the equivalent bounds, indicating we cannot reject an effect larger than $d = 0.80$ and SN connectivity in ITT and TEC groups is not statistically equivalent at Time 1 (Lakens et al., 2018).

Hypothesis 2A and 2B. For Hypothesis 2A and 2B, a sensitivity analysis in G*Power indicated that with sample sizes of 26 (PTSD treatment completers) and 18 (TEC) and an alpha of 5% (two-sided), we would have 80% power to detect an effect of $d = 0.88$. Subsequently, the upper and lower equivalence bounds were set at -0.88 and 0.88 .

Hypothesis 2A. The TOST procedure indicated that the observed effect sizes in the DMN ($t(42) = -2.78, p = .00$), CEN ($t(41) = -2.85, p = .00$), and SN ($t(42) = 1.92, p = .03$) were significantly within the equivalent bounds of $d = -0.88$ and $d = 0.88$, indicating

that the functional connectivity within these networks in the TEC group were statistically equivalent to the functional connectivity in the PTSD treatment completers at Time 1 (Lakens et al., 2018).

Hypothesis 2B. The TOST procedure indicated that the observed effect sizes in the DMN ($t(42) = -2.57, p = .01$), CEN ($t(41) = -2.73, p = .01$), and SN ($t(42) = 2.43, p = .01$) were significantly within the equivalent bounds of $d = -0.88$ and $d = 0.88$, indicating that the functional connectivity within these networks in the TEC group were statistically equivalent to the functional connectivity in the PTSD treatment completers at Time 2 (Lakens et al., 2018).

Aim 2

Three paired-samples t-tests were used to compare the 1) DMN, 2) CEN, and 3) SN z-scores in the treatment completer sample of PTSD participants at Time 1 versus Time 2. DMN, CEN, and SN z-scores at Time 1 were not significantly different from the z-scores at Time 2 (see Table 6).

Tests of Equivalence

TOSTs were also conducted for this aim. A sensitivity analysis in G*Power indicated that with a sample size of 26 PTSD treatment completers and an alpha of 5% (two-sided), we would have 80% power to detect an effect of $d = 0.57$. Subsequently, the upper and lower equivalence bounds were set at -0.57 and 0.57 . The TOST procedure indicated that the observed effect sizes for the DMN ($t(25) = -2.51, p = .01$), CEN ($t(25) = -2.77, p = .01$), and SN ($t(25) = -2.33, p = .01$) were significantly within the equivalent

bounds of $d = -0.57$ and $d = 0.57$, indicating that the z-scores of the PTSD treatment completers at Time 1 and Time 2 were statistically equivalent (Lakens et al., 2018).

Aim 3

Given the lack of statistically significant change in functional connectivity in DMN, CEN, or SN of the treatment completer sample from Time 1 to Time 2, Hypotheses 4 and 5 were not tested.

Exploratory Aim

For the exploratory aim, none of the remaining networks identified by the ICA exhibited statistically significant change in within-network functional connectivity from Time 1 to Time 2. Thus, this aim was not tested.

Discussion

Results of our null hypothesis significance tests indicated that there were no differences in DMN, CEN or SN functional connectivity between participants with PTSD compared to TEC either pre- or post-CPT. Additionally, we did not find evidence of differences in DMN, CEN, or SN connectivity within PTSD participants from pre- to post- CPT. Equivalence tests largely found statistically equivalent connectivity in these networks between experimental groups and within the PTSD sample from Time 1 to Time 2; an exception was that SN connectivity did not appear equivalent between the ITT sample and TEC at Time 1. One possible interpretation of these results is that resting-state functional connectivity in those with PTSD does not differ from TEC, and thus CPT could not lead to ‘normalization’ of resting-state functional connectivity in PTSD. Another possible interpretation is that CPT also does not generate ‘compensatory’

changes in resting-state functional connectivity in PTSD participants. However, the context of the null results, as well as several possible reasons for their production, merit further consideration prior to accepting these conclusions.

First, there is little research investigating brain changes related to CPT specifically. Only one other study examining pre-post CPT brain changes has been published. This study demonstrated that participants who completed a present-centered (or control) treatment exhibited reduced SN connectivity during a symptom provocation task compared to pre-treatment (i.e., a normalization effect), but this effect was not exhibited in those who completed CPT (Abdallah et al., 2019). However, CPT participants did evidence increased executive network connectivity during symptom provocation after CPT. Notably, Abdallah et al. (2019) did not find any evidence of change in network functional connectivity during their resting-state scans. As such, the only other published study examining functional connectivity in CPT found increased executive network connectivity and stable SN connectivity during a symptom provocation task after CPT but no change in network connectivity after CPT in resting-state scans. Our own null results are in alignment with this finding. Further, when examining all studies investigating change in functional connectivity pre- and post-CBT for PTSD ($n = 5$), three studies showed changes following Prolonged Exposure (one during a reappraisal task [Fonzo et al., 2017], one during an extinction recall task [Helpman et al., 2016], and one in a resting-state scan [Zhu et al., 2018]); one study showed resting-state changes following a mindfulness-based exposure intervention (King et al., 2016); and one showed changes after both CPT and a control treatment during symptom provocation (Abdallah et al., 2019). As such, there is some evidence for

resting-state change after exposure-based interventions and some evidence for change after CPT in a symptom provocation scan, but no published evidence for resting-state change after CPT, suggesting that our null results may be unsurprising.

Second, there are several differences between our study and previous research that may have precluded us from demonstrating any functional connectivity changes after a CBT intervention for PTSD. One difference was our selection of a resting-state scan, whereas others implemented a variety of behavioral paradigms examining functional connectivity in PTSD while symptoms were provoked, while CBT techniques were employed, and while the PTSD fear structure was activated. As previously noted in the literature review, this complicates comparison of results between studies, and more research would be needed to determine whether brain changes after CBT are more robust in particular paradigms. Another difference was our utilization of ICA, as opposed to a seed-based connectivity analysis. Though we believe this to be a strength, as it is a data-driven method of network selection, it may not be directly comparable to studies that selected *a priori* networks of interest. Further, our sample was comprised of females, in contrast with other studies that used mixed sex samples. Sex differences in resting-state functional connectivity have been observed in several regions overlapping with DMN, SN, and CEN, including the cingulate, medial frontal cortex, insula, precuneus (Weis et al., 2019), and amygdala (Kilpatrick et al., 2006; Engman et al., 2016). Finally, this study focused exclusively on within-network functional connectivity. There is evidence that PTSD is also characterized by alterations in connectivity between networks (Akiki et al., 2017; MacNamara et al., 2016), and it is possible that this between-network resting-state connectivity is affected by CPT.

Third, beyond the previously discussed difficulties in comparing studies that use different tasks and types of connectivity analyses, there are also numerous methodological decisions within neuroimaging research that may lead to differing results even between studies that use the same tasks and connectivity analyses. These decisions are present at each stage of a neuroimaging analysis, from the ways in which the data are pre-processed (e.g., choice of how much data should be spatially smoothed, which impacts spatial precision; Lohmann et al., 2018; Vergara et al., 2017), to the ways in which second-level results are deemed significant. For example, researchers may apply liberal or conservative thresholds for defining significant results (Lohmann et al., 2018), potentially obtaining drastically different connectivity maps depending on the selected threshold (Klein, 2010). As such, several methodological decisions related to our neuroimaging analysis procedure may have influenced our results. We utilized a template-matching approach to identify networks of interest within our data. Though this was a procedure used by several other groups (Zhang et al., 2015; Liao et al., 2010; Hoekzema et al., 2014) and the correlations between our networks and the templates were similar to those obtained in other studies, our network-template correlations were moderate in size (versus large), indicating that our identified DMN, SN, and CEN did not overlap entirely with the template networks. Lack of precision in matching networks or regions of interest that were used in other studies is not a problem unique to our study but is instead common throughout neuroimaging research (Hong et al., 2019). Nonetheless, it could lead to problems replicating effects. We also utilized the default voxel- and cluster-level thresholds within the CONN toolbox in order to define components. Notably, there is no standard threshold level in the literature, and the threshold levels selected across the

pre-post CBT studies reviewed, as well as others using ICA analyses, differ accordingly. Taken together, it is possible our null results in comparison to other pre-post CBT for PTSD studies are due to some combination of these methodological factors.

Fourth, we implemented NHST as our statistical framework. Limitations of NHST have been widely documented both within psychology (e.g., Cohen, 1994; Wagenmakers, 2007) and within neuroimaging research (Klein, 2010; Hupe, 2015; Friston, 2012). Briefly, limitations of NHST include the arbitrary definition of a significance level (at $p < .05$) and the fact that “statistically significant” results may be found with a large enough sample size (as summarized in Hupe, 2015). Many researchers have emphasized that this pattern makes the reporting of effect sizes crucial to determining whether a) a “statistically significant” effect is trivial or meaningful and b) the lack of a “statistically significant” effect was due to an under-powered study versus a trivial effect size. Within neuroimaging research, others argue that NHST is inappropriate in “causally dense systems” where the null hypothesis must be false due to small and unimportant correlations between variables (Klein, 2010). Within our study, we demonstrated small, but statistically nonsignificant, differences in DMN, CEN, and SN connectivity at Time 1 between our ITT sample and TEC, with TEC exhibiting greater connectivity in these networks compared to the ITT sample. Similarly, we found a statistically nonsignificant but small difference when comparing SN connectivity at Time 1 between PTSD treatment completers and TEC, with TEC again exhibiting greater SN connectivity than PTSD treatment completers. Further, SN connectivity between the ITT sample and TEC at Time 1 was not statistically equivalent according to our test of equivalence, indicating that we could not reject the presence of large effects. These

results are broadly in alignment with other studies finding diminished connectivity in PTSD versus TEC, and suggest the presence of some group differences in resting state connectivity at baseline, whose effect sizes may be better defined with a larger sample. Thus, the lack of statistically significant differences between groups in our study should not automatically dismiss the presence of these effects, which would require more research to delineate.

Indeed, deGraaf and Sack (2018) posit that null results can be more or less meaningful and interpretable based on the context in which they occur. For example, if null results are obtained when replicating a study that has already found an effect or is attempting to bolster evidence for a well-established theory, these results may be more meaningful than null results found within the context of exploratory analyses in an area with little research. Similarly, if null results are obtained in studies that are low-powered or less methodologically stringent, they may be less interpretable than if null results were obtained in high-powered and carefully designed studies (deGraaf & Sack, 2018). When considering the exploratory nature of our research question, the lack of consistent results within the literature, and the presence of some small effect sizes in our data, our null results should not be considered to reflect the absence of CPT effects on resting-state functional connectivity networks within PTSD participants. Rather, they may be considered the outcome of several methodological decision points (potentially including sample size, method of network selection, and/or use of NHST). In other words, our null results may be less meaningful and interpretable than if we had used different methodologies or were attempting to replicate strong effects from the literature.

Future research could address several of the above methodological limitations. First, sample size could be increased to maximize our power to determine whether an effect is small, moderate, or large (Hupe, 2015), giving us the ability to better quantify CPT effects in PTSD brain (Friston, 2012). (Of note, our sample size was similar to other studies reviewed that did obtain effects; as such, increasing the sample size in our study would be in an effort to better quantify the effect size and identify equivalence bounds for equivalence testing, as opposed to being an effort solely to obtain significant results.) Second, our voxel and cluster thresholds that defined our components could be modified. Third, future analyses may examine whether there are changes between networks pre- to post-CPT. Finally, analysis methods that do not rely on NHST (such as machine learning) may be considered.

Conclusion

This study implemented a data-driven functional connectivity analysis method to examine large-scale brain networks implicated in PTSD pathology in an effort to obtain evidence for either dual process or extinction models of CBT effects in the PTSD brain. In sum, the interpretation of our results is largely inconclusive. Though there may be no ‘true’ effect of CPT on resting-state functional connectivity networks in PTSD, it is also possible that several methodological decisions may have prevented us from being able to adequately measure that effect in this study. This unfortunately precludes us from being able to provide evidence in support of either the dual process or extinction models of CBT effects on the brain. Nonetheless, this is the first study that implemented an ICA method in pursuit of this research question, and is only the second study to examine neurobiological changes after a course of CPT. As such, it is a unique contribution to

growing literatures concerning discoveries in both PTSD neurobiology and psychotherapy process.

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Table 1*Demographic Characteristics*

Variable	Total Sample	PTSD Treatment Completers	ITT	TEC
<i>n</i>	60	26	42	18
Age (<i>SD</i>)	31.38 (9.67)	33.62 (11.09)	31.17 (9.71)	31.89 (9.84)
Education (<i>SD</i>)	15.16 (2.57)	15.62 (1.63)	15.38 (1.89)	14.64 (3.73)
CAPS T1		66.92 (17.71)	67.64 (17.35)	
CAPS T2		23.75 (20.89)		
Ethnicity (%)				
Caucasian	37 (61.70)	16 (61.50)	25 (59.50)	12 (66.70)
African American	14 (23.30)	6 (23.10)	11 (26.20)	3 (16.70)
Hispanic	2 (3.30)	1 (3.80)	2 (4.80)	0
Other	5 (8.30)	2 (7.70)	2 (4.80)	3 (16.70)
Not reported	2 (3.30)	1 (3.80)	2 (4.80)	0

Note. ITT= Intent-to-treat sample of participants with PTSD. TEC= Trauma-exposed

controls. CAPS= Clinician-Administered PTSD scale.

Table 2*Correlation of Age with Network Connectivity*

Statistic	Time 1			Time 2		
	DMN	SN	CEN	DMN	SN	CEN
Correlation (r)	.01	.08	-.13	-.29	.17	-.20
Significance (p)	.92	.53	.34	.15	.41	.33

Note. DMN = default mode network. SN = salience network. CEN = central executive network.

Table 3*Functional Connectivity at Time 1 in ITT vs TEC Participants*

Network	ITT			TEC			<i>t</i>	df	<i>p</i>	95% CI		Effect size
	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>				<i>LL</i>	<i>UL</i>	
DMN	42	5.89	3.11	18	6.71	2.56	-1.00	58	.32	-2.49	0.84	-0.28
CEN	42	6.09	2.98	17	6.95	3.64	-0.95	57	.35	-2.71	0.97	-0.27
SN	42	6.13	3.98	18	7.61	3.02	-1.41	58	.17	-3.58	0.62	-0.40

Note. ITT= intent-to-treat sample of participants with PTSD. TEC= trauma-exposed controls. CI= confidence interval. LL =

lower limit. UL = upper limit. DMN= default mode network. CEN= central executive network. SN= salience network.

Table 4*Functional Connectivity at Time 1 in PTSD Treatment Completers vs TEC Participants*

Network	PTSD			TEC			<i>t</i>	df	<i>p</i>	95% CI		Effect size
	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>				<i>LL</i>	<i>UL</i>	
DMN	26	6.78	2.70	18	6.71	2.57	0.08	42	.94	-1.57	1.70	0.03
CEN	26	6.97	3.49	17	6.95	3.64	0.01	41	.99	-2.22	2.24	0.01
SN	26	6.52	4.18	18	7.61	3.02	-0.94	42	.35	-3.41	1.24	-0.29

Note. PTSD = Post-traumatic stress disorder. TEC= trauma-exposed controls. CI= confidence interval. LL = lower limit. UL =

upper limit. DMN= default mode network. CEN= central executive network. SN= salience network.

Table 5*Functional Connectivity at Time 2 in PTSD Treatment Completers vs TEC Participants at Time 1*

Network	PTSD			TEC			<i>t</i>	df	<i>p</i>	95% CI		Effect size
	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>				<i>LL</i>	<i>UL</i>	
DMN	26	6.96	2.87	18	6.71	2.57	0.29	42	.77	-1.45	1.95	0.09
CEN	26	7.05	3.33	17	6.95	3.64	0.09	41	.93	-2.08	2.27	0.03
SN	26	7.08	4.43	18	7.61	3.02	-0.44	42	.66	-2.96	1.90	-0.14

Note. PTSD = Post-traumatic stress disorder. TEC= trauma-exposed controls. CI= confidence interval. LL = lower limit. UL =

upper limit. DMN= default mode network. CEN= central executive network. SN= salience network.

Table 6*Functional Connectivity at Time 1 vs Time 2 in PTSD Treatment Completers*

Network	T1			T2			<i>t</i>	df	<i>p</i>	95% CI		Effect size
	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>				<i>LL</i>	<i>UL</i>	
DMN	26	6.78	2.7	26	6.96	2.87	-0.41	25	.69	-1.12	0.75	0.06
CEN	26	6.97	3.49	26	7.05	3.34	-0.14	25	.89	-1.27	1.11	0.02
SN	26	6.52	4.18	26	7.08	4.43	-0.57	25	.57	-2.56	1.45	0.13

Note. T1= Time 1. T2 = Time 2. CI= confidence interval. LL = lower limit. UL = upper limit. DMN= default mode network.

CEN= central executive network. SN= salience network.