

FUNCTIONAL CONNECTIVITY, SYMPTOM SEVERITY AND TREATMENT
OUTCOMES IN WOMEN WITH BORDERLINE PERSONALITY DISORDER

by

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Abstract

Dissociation is characterized by either heightened sensitivity to emotions (under-modulation) or dampened experience of emotions (over-modulation) (Krause-Utz & Elzinga, 2018; Lanius et al., 2010). Within fMRI studies, over- and under-modulation have been associated with differing functional connectivity when patients are exposed to memories of traumatic events (Krause-Utz et al., 2018; Ludäscher et al., 2010; Winter et al., 2016). This study included female patients with Borderline Personality Disorder taking part in a 6-week treatment program to examine the interactions between changes in symptoms (n=13) and connectivity (n=12) pre- and post-treatment. Results suggest all symptom measures had significant changes from pre- to post-treatment. Changes in symptoms did not relate to changes of functional connectivity from pre- to post-treatment, but differing neurobiology was observed between under- and over-modulation. Furthermore, the amygdala appears to be co-activated with the nucleus accumbens, hippocampus, postcentral gyrus, dorsolateral middle temporal gyrus and precentral gyrus during mood induction tasks.

List of Abbreviations Used

BOLD	Blood-Oxygenation Level Dependency
BPD	Borderline Personality Disorder
df	Degrees of Freedom
dIPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
e.g.	<i>exempli gratia</i>
et al.	<i>et alia</i>
fMRI	Functional Magnetic Resonance Imaging
i.e.	<i>id est</i>
M	Mean
MHDTP	Mental Health Day Treatment Program
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
<i>n</i>	Sample Size
NMR	Nuclear Magnetic Resonance
<i>p</i>	Significance Value
PFC	Prefrontal Cortex
PTSD	Post-Traumatic Stress Disorder
<i>r</i>	Spearman's ρ Correlation Coefficient
RSFC	Resting State Functional Connectivity
SD	Standard Deviation
<i>t</i>	Independent Samples t-test

vmPFC Ventromedial Prefrontal Cortex

z Z-Score

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CHAPTER 1 – INTRODUCTION

1.1 Borderline Personality Disorder

1.1.1 Childhood Adversity

Exposure in childhood to physical, emotional or sexual abuse or neglect can lead to complex relational trauma. Complex relational trauma generally involves interpersonal trauma between caregivers or important attachment figures. Evidence suggests that the experience of said childhood adversity can lead to the development of psychiatric symptoms and mental health impairments such as novelty seeking, harm avoidance and reward dependence (de Carvalho et al., 2015). These symptoms can persist into adulthood and develop into mental illnesses, including Borderline Personality Disorder (BPD; Glaser, 2003; Afifi et al., 2011; Hengartner, Ajdacic-Gross, Rodgers, Muller & Rossler, 2013).

It is thought that childhood adversity can interfere with the formation of secure attachment bonds with caregivers; the main source of safety and stability for the child. These attachment styles then persist throughout life and can impact the formation of future bonds and relationships (Vrtička & Vuilleumier, 2012). Childhood maltreatment has been reported to be positively associated with fearful, preoccupied and dismissing attachment styles and negatively associated with a secure attachment style (Erozkan, 2016). This maltreatment may also impair the development of emotional awareness (i.e., the capacity to be aware of and to describe emotions both in oneself and within others) (Lanius et al., 2011). When an individual experiences unavailable attachment figures from a young age, there may be confusion as the child's source of distress may also be the source of comfort (Vrtička & Vuilleumier, 2012). As a result, children recognize that their attachment figures are unresponsive or inconsistent in times of need (Lanius et al., 2011; Vrtička & Vuilleumier, 2012). Over time, an individual may either

become emotionally dysregulated, or disconnect from their emotional life as a way to distance themselves from emotions out of their control (Lanius et al., 2011).

1.1.2 Epidemiology, Clinical Manifestations and Prevalence

BPD is the most prevalent personality disorder in clinical settings (Grant et al., 2008), with rates around 10% for all psychiatric outpatients and between 15% to 25% for all psychiatric inpatients (Torgersen, 2005; Gunderson, 2009). Experiences of physical, emotional or sexual abuse, and physical or emotional neglect have been shown to be associated with the development of BPD (Afifi et al., 2011; Hengartner, Ajdacic-Gross, Rodgers, Muller & Rossler, 2013) and individuals with BPD report more adverse childhood events than any other personality disorder (Yen et al., 2002). A review of the literature between 1995 and 2007 has gone so far as to suggest a causal relationship between childhood trauma and BPD given the strength of evidence for BPD development (Ball & Links, 2009).

BPD can be diagnosed using the American Psychiatric Association's (2013) Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5) criteria. In order to be diagnosed in this way a patient must exhibit five or more of the following nine symptoms: frantic efforts to avoid real or imagined abandonment (not including suicidal or self-mutilating behaviors), a pattern of unstable and intense interpersonal relationships characterized by alternating between extreme idealization and devaluation, markedly and persistent unstable self-image or sense of self, impulsivity in two areas that are potentially self-damaging, recurrent suicidal behavior, gestures, threats or self-mutilating behavior, affect instability due to a marked reactivity of mood, chronic feelings of emptiness, inappropriate intense anger or difficulty controlling anger, or

transient, stress-related paranoid ideation or severe dissociation (American Psychiatric Association, 2013).

BPD is characterized by preoccupied attachment styles (Scott et al., 2013) and limited capacities to process and regulate emotions. Specifically, individuals with BPD display emotional sensitivity, heightened negative affect, inflexible response to emotions, and inadequate emotional regulation capacities (Carpenet & Trull, 2013). As a result, these individuals are less able to manage stress and are more likely to engage in maladaptive coping strategies (Carpenter & Trull, 2013). This in turn contributes to a variety of problematic behaviors and symptoms including impairments in self-functioning, interpersonal functioning (including intimacy and, or empathy), anxiety, separation insecurity, depression, impulsivity, risk taking behavior, self-harm, and hostility (American Psychiatric Association, 2012).

1.1.3 Borderline Personality Disorder and Post-Traumatic Stress Disorder

Post-Traumatic Stress Disorder (PTSD) is similar to BPD in many ways, as such, there has been much debate and controversy to whether the two are overlapping constructs which should be integrated (Hodges, 2003; Lewis & Grenyer, 2009). When examining the clinical features of both disorders, there are many overlaps such as disturbances in interpersonal relationships, impulse control, and emotional and affect regulation difficulties (Resick et al., 2012). Additionally, both disorders have high prevalence rates of traumatic events, including childhood maltreatment, and they are both associated with high mortality and morbidity rates, frequent hospitalizations, interpersonal difficulties and a high economic burden (Pompili, Girardi, Roberto & Tatarelli, 2009; Skodol et al., 2002; Bisson, Cosgrove, Lewis & Roberts, 2015).

From a neurobiological perspective, the similarities between BPD and PTSD continue. One technique used to study neurobiology is fMRI (see detailed description below). A recent meta-analysis comparing similarities between disorders during resting state fMRI noted decreased activation in the left and right precuneus across both diagnosis and increased activation within BPD and decreased activation in PTSD of the anterior cingulate, paracingulate gyri and the left superior frontal gyrus (Amad et al., 2019). Areas of activation commonly associated with both disorders also include the insula, left inferior frontal gyrus and portions of the cingulate gyrus (Wang et al., 2016; Ludäscher et al., 2010; Amad & Radua, 2017). These regions may be associated with networks involved in dissociative states, a common symptom to both disorders (Ludäscher et al., 2010; Lyssenko et al., 2018). Additionally, disturbances within the frontal regions include areas associated with memory, attention and response inhibition (Amad et al., 2019).

1.1.4 Dissociation as a Symptom of BPD

A severe symptom seen in BPD as well as many other trauma-related disorders is that of dissociation. Dissociation is characterized by a discontinuity in memory, identity, consciousness, perception and, or motor control (Spiegel et al., 2011; APA, 2013; van Dijke, Van der Hart et al., 2010). It has been suggested that there is a strong link between dissociation and trauma, specifically with regards to childhood trauma and BPD (Ball & Links, 2009; Scalabrini, 2017). The rates of dissociation within populations with BPD are high, ranging from 75-80% (Krause-Utz & Elzinga, 2018; Korzekwa, Dell & Pain, 2009; Scalabrini, Cavicchioli, Fossati & Maffei, 2017; Bichescu-Burian, 2012).

Although dissociation is commonly referred to as one symptom, there is emerging evidence to suggest it is comprised of symptoms which may be broken down to two general profiles. These two profiles characterize either an excessive emotional control resulting in emotional numbing (i.e., over modulation) or an inability to regulate emotional experiences resulting in increased responsivity to emotions (i.e., under modulation) (Lanius, Frewen, Tursich, Jetly & McKinnon, 2015; Maaranen, 2005; van Dijke et. al., 2010a; van Dijke et. al., 2010b; van Dijke et. al., 2011; van Dijke et. al., 2012). As such, there has been recent direction in differentiating between patients who experience under or over modulation within samples of patients with PTSD and BPD, as differing symptom profiles and neurobiological profiles have been identified which could lead to the development of different treatment approaches (Lanius et al., 2011; Nicholson et al., 2017).

1.1.4.1 Etiology of Emotional Over-Modulation

Over-modulation of emotions is most commonly seen in individuals with more severe early childhood trauma histories (Stein et al., 2013). This form of regulation however is less common than emotional under-modulation, as it has been suggested to affect approximately 25% of individuals with BPD (van Dijke, et al., 2010b). While research examining the different forms of dissociation in BPD is scarce, it has been suggested that over modulation may be similar to the dissociative subtype of PTSD (Brand & Lanius, 2014; Vermetten & Spiegel, 2014). When individuals experience over-modulation of emotions in response to traumatic stimuli, they attempt to avoid emotional experiences, and thus do not experience an elevation in heart rate in comparison to neutral stimuli (Lanius et al., 2005; Lanius et al., 2011; Sack, Cillien, & Hopper,

2012). Emotion over-modulation prevents emotional learning, leading to deficits in the development of emotion identification and regulation skills (e.g., re-appraisal), ultimately increasing symptom severity (Steidl et al. 2006; Ebner-Priemer et al. 2009). Dissociation may lead to an emotionally constricted or frozen presentation potentially limiting the capacity to maintain close relationships (van Dijke, et al., 2010b).

1.1.4.2 Over-Modulation within PTSD

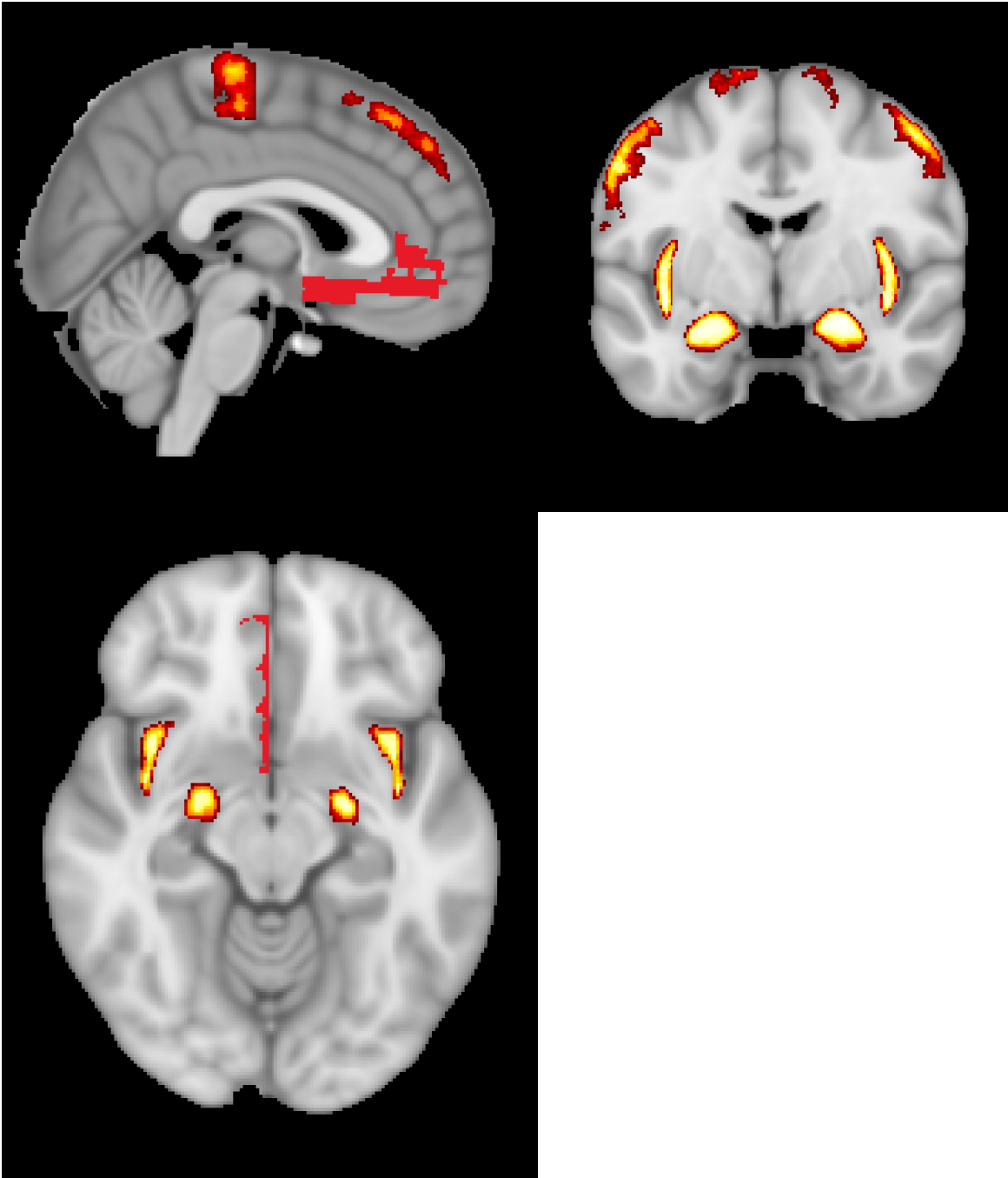
When patients with PTSD experience emotion over-modulation, there is evidence of hyper-inhibition of the limbic system (Lanius et al., 2012). Patients with dissociative PTSD reading a traumatic script exhibit increased activation within prefrontal areas and decreased activation in limbic structures (Lanius et al., 2002). This may reflect a coping strategy used by those with a history of trauma as a way to mitigate extreme arousal (Lanius et al., 2012). With over-modulation there is also evidence of increased functional connectivity between brain areas involved in emotion regulation (i.e., ventrolateral, dorsomedial and anterior cingulate) and areas involved in salience detection (i.e., the amygdala) (Lanius, Bluhm & Frewen, 2011; Nicholson et al., 2016), along with reduced connectivity between the amygdala and insula (Krause-Utz et al., 2018). Consistent with this theory, Hopper and colleagues (2017) found self-reported dissociation (as assessed by the Response to Script-Driven Imagery scale measuring depersonalization or derealization) positively correlated with activation of the left mPFC and right superior temporal cortex (areas previously involved in regulation of attention, emotion and arousal) and negatively correlated with the right anterior insula and left superior temporal cortex (areas involved in the awareness of bodily states).

Overall, over-modulation within PTSD has been suggested to be associated with decreased activation of regions involved in the awareness of bodily states (i.e., the amygdala and right anterior insula), and increased activation in areas involved in the regulation of emotional arousal (i.e., the rostral anterior cingulate and medial prefrontal cortex). This may prevent patients from experiencing the bodily sensations involved with emotions (Lanius et al., 2010). Additionally, one study suggests those with over-modulation symptoms have had changes in activation within the posterior cingulate and precuneus regions, the medial temporal and inferior frontal gyri, changes in activation not seen in under-modulation populations (Lanius et al., 2005).

1.1.4.3 Over Modulation within Borderline Personality Disorder

While the majority of research concerning the neurobiological mechanisms of dissociation have been within populations with PTSD, there has been increasing amounts of research to suggest that these differences are mirrored within BPD (see Figure 1 for a depiction of the areas of activation within BPD studies; Herman, Perry & van der Kolk, 1989; Zanarini et al., 1997; Mosquera & Steele, 2017). A review examining the neurobiological implications of dissociation in BPD identified areas associated with dissociative symptoms of over-modulation. These regions revolve primarily around the amygdala and the default mode network (DMN), (Krause-Utz, Frost, Winter, & Elzinga, 2017), a network involved in self-related activity such as autobiographical thought, self-monitoring and emotion regulation (Menon, 2011; Bressler & Menon, 2010; Menon, 2015).

Figure 1. *Depiction of areas of activation within BPD literature examining over-modulation*



A positive relationship has been observed between self-reported over-modulation dissociation and amygdala activity during the presentation of adverse pictures, as well as increased connectivity between the amygdala and the vmPFC (Paret et al., 2016). Increased amygdala activity in response to emotional pictures has also been found (Hazlett et al., 2012), as well as a positive correlation between trait dissociation and increased connectivity between the amygdala and dlPFC during a RSFC scan (Krause-Utz et al., 2014). Higher levels of over-modulation were also associated with increased bilateral amygdala connectivity with the left insula, the left precentral gyrus, right thalamus and the right anterior cingulate during an emotional distraction task (Krause-Utz et al., 2014). When looking to amygdala activation in response to negative stimuli, results suggest a negative correlation between over-modulation and bilateral amygdala activation (Krause-Utz et al., 2012).

Within other areas of the brain, increased over-modulation has been associated with diminished activation in the DMN in response to painful stimuli (i.e., heat stimulation) (Kluetsch et al., 2012), as well as increased activation within the left superior frontal gyrus and the left inferior frontal gyrus and increased connectivity between the insula and precuneus during a resting state functional connectivity paradigm (Ludascher et al., 2010). When over-modulation of emotions was induced in patients with BPD, there was increased activity in the inferior frontal gyrus and dlPFC during negative words (Winter et al., 2015). However, two other studies noted no significant relationships with over-modulation (Krause-Utz et al., 2015; Wingenfeld et al., 2009).

1.1.4.4 Etiology of Emotional Under-Modulation

Under-modulation of emotions against intolerable, trauma-associated memories and feelings is characterized by episodes of re-experiencing, flashbacks and nightmares (Lanius et

al., 2010). Under-modulation could be conceptualized as a ‘failure’ to dissociate, as it involves an inability to control emotional states and an increase in hyperarousal and re-experiencing when exposed to traumatic events (van Dijke, 2010b). As such, under modulation has been shown to be associated with an increase in heart rate when exposed to traumatic stimuli in comparison to the over-modulation group (Lanius et al., 2006; Lanius et al., 2005). This form of dissociation is more common than over-modulation, as it is present in approximately 70% of individuals with BPD (van Dijke et al., 2010b; Lanius et al., 2006).

1.1.4.5 Under-Modulation within PTSD

While there is less literature with a focus on emotion under-modulation, despite it being more common, this aspect of dissociation is thought to arise from a failure of prefrontal inhibition (Lanius et al., 2010). When examining this symptom using neuroimaging, amygdala reactivity was shown to moderate the relationship between the amygdala and the mPFC, suggesting a top-down approach to emotion regulation in PTSD (Sadeh et al., 2014). This means that when exposed to unpleasant stimuli, individuals demonstrated an impaired response from the mPFC and an increased response from the amygdala, leading to increased symptoms of re-experiencing and hyperarousal (Sadeh et al., 2014).

When examining under-modulation on a symptom level, Hopper and colleagues (2007) reported a positive correlation between the activation of the right anterior insula and symptoms of re-experiencing, as well as a negative correlation between severity of re-experiencing and activation in both the right rostral anterior cingulate cortex and the inferior frontal gyrus within a sample of patients with PTSD. Within this study, increases in the severity of self-reported re-experiencing were associated with decreases in activation within frontal regions; areas

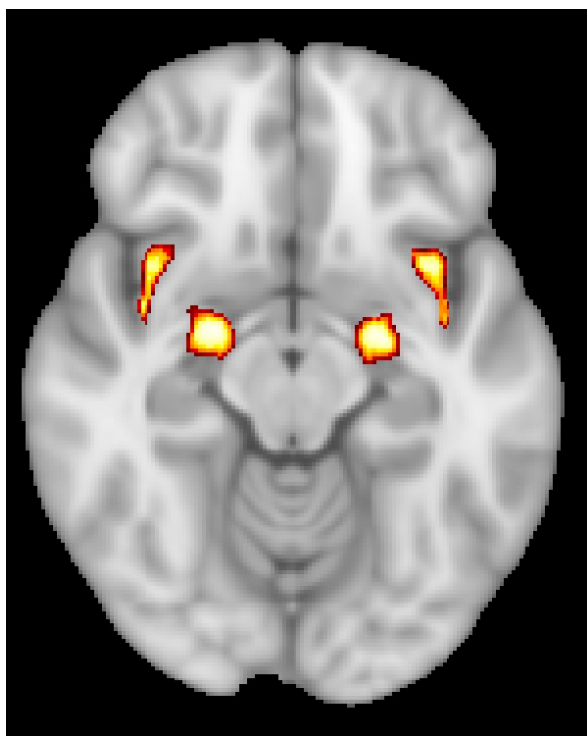
previously identified as being active during emotional over-modulation (Hopper et al., 2007; Lanius, Bluhm & Frewen, 2011; Nicholson et. al., 2016).

Additionally, re-experiencing was shown to moderate the relationship between the right hippocampus and the left inferior insula such that increases in reported re-experiencing were associated with increased co-activation of the regions during positive words, and a negative coactivation during negative words (Sadeh et al., 2014). Hyperarousal (as defined by an exaggerated startle, difficulty concentrating and hypervigilance) has been suggested to moderate the relationship between the amygdala and the mPFC such that there was stronger negative coupling between these structures in response to negative stimuli, and a similar relationship presented between the right hippocampus and the mPFC with hyperarousal moderating the relationship (Sadeh et al., 2014). Additionally, there is evidence of diminished connectivity between the anterior cingulate cortex and medial prefrontal cortex, and increased connectivity between the insula and amygdala (Krause-Utz & Elzinga, 2018; Lanius, Bluhm & Frewen, 2011; Nicholson et. al., 2016).

1.1.4.6 Under Modulation within Borderline Personality Disorder

While there have been few studies to date which have examined emotion over modulation within BPD, less have examined emotion under modulation (see Figure 2 for a depiction of areas of activation within BPD studies examining under-modulation). One review article suggested that under modulation in BPD is associated with increased activation in areas associated with recognition or awareness of bodily states, particularly the amygdala and right anterior insula, along with decreased activation of regions of the prefrontal cortex involved in emotion regulation (i.e., ventrolateral, dorsomedial and anterior cingulate) (Krause-Utz & Elzinga, 2018).

Figure 2. *Depiction of areas of activation within under-modulation in BPD literature*



1.1.5 Neurobiology of Childhood Adversity

Complex trauma involves repeated exposure to physical, emotional or sexual abuse or neglect and can impact not only behavior and psychology, but also neurobiology. Complex trauma is typically interpersonal in nature, is more severe or persistent and involves being or feeling trapped within a situation. There is a large body of research suggesting the experience of complex trauma produces alterations in brain activation and connectivity patterns (Glaser, 2000; Insana et al., 2016; Teicher & Samson, 2013; van der Werff et al., 2012). A study using healthy controls varied the probability of receiving an electric shock to elicit response to threat of danger and the danger itself to examine the fear response (Mobbs et al., 2009). When an initial threat of

fear was detected, participants demonstrated increased forebrain activation; areas associated with the assignment and control of fear and involved in emotional systems (i.e., within the amygdala, subgenual anterior cingulate cortex and hippocampus; Mobbs et al., 2009). However, once there is a direct effect of the threat (i.e., the electric shock is given), the brain patterns reverse. This study by Mobbs and colleagues (2009) observed increased coupling between the mid-brain and the mid-dorsal anterior cingulate cortex and decreased activation within the amygdala, subgenual anterior cingulate cortex and hippocampus (Mobbs et al., 2009). In another study, Mobbs and colleagues (2010) tested the fear response of healthy controls using a tarantula. When there was closer proximity of the tarantula to the participant's foot, the participants exhibited increased activation within the amygdala, the midbrain periaqueductal grey, the ventral striatum, anterior insula and dorsal anterior cingulate cortex (Mobbs et al., 2010). However, as the proximity decreased, the activation in the orbitofrontal prefrontal cortex increased. Interestingly, as escalation of the threat increased (i.e., the tarantula was brought closer) the activation of the amygdala increased and when the escalation of threat decreased, the activation in the amygdala decreased. This would suggest the amygdala may be involved in coordinating the response to threat and mediating danger (Mobbs et al., 2010).

With regards to the impact of childhood maltreatment on neurobiology, research has consistently found a decrease in activation within the neocortex (i.e., the anterior cingulate, orbitofrontal and dorsolateral prefrontal cortex; areas associated with arousal modulation, emotion processing, inhibitory control and regulation of impulses and emotions), and an increase in activation within the amygdala (an area associated with emotion processing, initiation of stress and fear responses as well as salience detection) (reviewed in Teicher & Samson, 2013). These findings indicate that the processing of fear stimuli and the regulation of emotion within

individuals who have experienced complex trauma may be impaired, contributing to the development and maintenance of mental illnesses including depression, anxiety, and personality disorders (Teicher & Samson, 2013). These areas commonly noted within research on fear in participants with histories of childhood trauma are also similar to what is seen in studies of neuroimaging examining over- and under-modulation within BPD. Suggesting the learned fear response from childhood traumas may persist in the form of coping mechanisms such as over- or under-modulation within other disorders.

1.2 Treatment Outcomes

1.2.1 Treatment of Borderline Personality Disorder

Historically, BPD has been considered one of the more challenging conditions to treat. Several psychosocial factors and pre-treatment characteristics of individuals with BPD might contribute to poorer treatment outcomes and treatment discontinuation including: impulsivity, depression, high trait anxiety, childhood emotional neglect, low levels of general functioning, and higher avoidance (McMurren, 2010). These factors may lead to the persistent use of maladaptive coping strategies, impairing emotional learning, and ultimately increasing symptom severity (Carpenter & Trull, 2013; Steidl, Mohi-Uddin & Anderson, 2006; Ebner-Priemer et al. 2009). Some of these factors have also been associated with higher dropout rates including higher levels of impulsivity, higher avoidance, high trait anxiety and higher anger levels (Barnicot, Katsakou, Marougka and Priebe, 2010).

Research has suggested the type of treatment may also have an impact on the outcomes of individuals with BPD. Mentalization-based treatments (i.e., treatments focused on understanding mental states) have been shown to be effective in treating attachment-related

traumas (Korzekwa et al., 2009). Similarly, cognitive analytic therapy, inpatient dialectical behavior therapy, psychodynamic and trauma-focused therapy have all been shown to improve dissociation within the treatment of patients with BPD (Korzekwa et al., 2009). Other research has suggested day treatment or forms of partial hospitalizations, have unique advantages in the therapeutic gains of patients with personality disorders by addressing chronic emotional and behavioural difficulties in offering an intensive and confined level of treatment (Ogrodniczuk et al., 2011). However, there has been little research to the effect this treatment has on neurobiology and additionally these studies did not separate dissociation based on differing dissociative symptoms but rather included all symptoms together.

To date, there has been limited research looking at treatment outcomes when differentiating between patterns of over- or under-modulation.

1.2.2 Dissociation as a Predictor of Treatment Outcomes

Other studies have identified over-modulation as a predictor of poorer treatment outcomes, as conscious or unconscious avoidance of emotions in psychotherapy limits therapeutic gains (Brand & Stadnik, 2013; Burum, 2007; Warwar, Links, Greenberg & Bergamn, 2008). A study by Arntz and colleagues (2015), found that baseline levels of over-modulation, and in session over-modulation predicted worse outcomes and treatment discontinuation. These findings are consistent with those of Kleindienst and colleagues (2011). In contrast, a study examining the impact of dissociation on the treatment of women with PTSD concluded that pre-treatment levels of over-modulation did not impact treatment outcomes (Resick et al., 2012). Two other (albeit smaller) studies also did not find associations with over-modulation and poorer treatment outcomes in women with BPD (Braakmann et al., 2007; Kröger, 2002).

1.2.3 Treatment of Dissociation

To date, there has been limited research looking at treatment outcomes differentiating between patterns of over- or under-modulation. Previous research has suggested patients who exhibit depersonalization (a component of emotion over-modulation) may benefit from treatments which restructure responses to past traumatic events through writing traumatic histories, while also receiving cognitive based therapy (Resick et al., 2012).

In addition to having treatment focused on treating over- and under-modulation, patients may also benefit from having treatments which are suited to their levels of dissociation. There is limited research examining the effects of over- and under-modulation separately on treatment outcomes, and the research presented below included both forms as dissociation without differentiating. Research has suggested that patients with high levels of dissociation (especially depersonalization) benefitted most from treatments which included a combination of writing the traumatic event and experiencing cognitive therapy while patients with low levels of dissociation benefitted most by therapies focused on discussing the traumatic event rather than restructuring the sensory experience of said event (Resick et al., 2012). Additionally, research has found that it was not necessary to treat dissociation before treating other symptoms, as both groups (those being treated sequentially and simultaneously) benefitted equally (Resick et al., 2012). Other research has supported these findings, suggesting patients with low to moderate levels of dissociation respond well to treatment as their dissociation diminished, while patients with high levels of dissociation continued to dissociate during treatment (Zanarini et al., 2008). Suggesting patients with higher levels of dissociation may need treatment with more focus on dissociative symptoms while patients with low and moderate levels of dissociation may be able to benefit from a generalized treatment.

It has been suggested that patients with higher levels of dissociation should undergo a phasic or stage-based treatment model (Cloitre, Petkova, Wang & Lu, 2012). This suggested model would include a stabilization phase (including skill building and psychoeducation), a trauma-processing phase and an integration phase (International Society for the Study of Dissociation, 2005). These phases initially focus on reducing symptom severity and dissociative symptoms before focusing on more advanced, strengthening skills (Cloitre et al., 2012). Further suggestions include using a psychodynamic approach, whereby the current impacts of past-traumatic events are discussed (Turkus & Kahler, 2006). This approach should include psychoeducation, to help normalize aspects of emotion as education and the use of coping skills can improve function and resilience. Furthermore, research suggests the use of skill-building groups can increase interpersonal connection, as such psychoeducation in groups is recommended (Turkus & Kahler, 2006).

However, as this research did not fully examine treatments based on symptom profiles, they did not take into account the possibility of differing treatment needs for each group. It would be beneficial to examine whether these patients respond to treatments differently, as research within neuroimaging has suggested there are significant neural differences between the two groups.

1.2.4 Mental Health Day Treatment Program

The Mental Health Day Treatment Program (MHDTP) is a clinic that offers a unique, holistic and patient-centered program that delivers intensive advanced care to patients with a history of complex trauma, often long-standing refractory anxio-depressive symptoms,

personality disorders (often Borderline Pathology), and difficulties in relational and psychosocial functioning within the QEII Hospital in Halifax, Nova Scotia. This program receives patients who are largely referred from in-patient programs, short-stay programs or community programs. Patients are prioritized based on need, as in-patients and short-stay patients are mandated to be included before out-patient referrals, as such the program has a large proportion which come from the higher-need services. This six-week program uses an integrated approach that combines multiple psychotherapy modalities (behavioural, cognitive, interpersonal, dynamic, etc.) with the goal of teaching patients to live a healthy, emotionally balanced and fulfilling life. The program uses a Dynamic Relational approach to organize therapy tasks in a hierarchical fashion to address underlying biological imperatives. This reflects an underlying reorganization of neuronal circuitry that occurs as patients progress through treatment, with critical tasks at each phase and parallel changes in the integration and homeostatic balancing of affected neural networks (Kinley & Reyno, 2016). More specifically, the primary goals of the program are to strengthen personality functioning, reduce mental disability, and prevent relapse or deterioration of mental states. Participants work through emotional pain, past trauma and set goals to develop a healthier way of coping in the future. Research conducted in this program highlights the beneficial outcomes for patients (Kinley & Reyno, 2013; Maxan, Kinley, Williams & Reyno, 2013).

1.3 fMRI Measures

There are two commonly used fMRI paradigms within the literature of affective neuroscience. Resting state functional connectivity (RSFC) MRI paradigms typically involve participants resting quietly with either eyes open or eyes closed and may be used as a way to

identify and map various resting state networks (such as the default mode network or salience network), or areas which are activated in synchrony (Lee, Smyser & Shimony, 2013).

Similarly, mood induction paradigms are commonly used within the field of affective neuroscience and clinical psychology as a way to evoke emotional responses within a controlled environment (Ellard, Farchione & Barlow, 2011). While there are a number of validated methods of mood induction, scripts (i.e. trauma/negative, neutral and positive scripts) are commonly used within the field of PTSD and BPD (Hayes, Hayes & Mikedis, 2013). Mood induction paradigms allow for participants to use personal, autobiographical experiences as a way to recall their past traumatic events while undergoing neuroimaging procedures in order to capture neurobiological changes while experiencing emotions.

1.4 Study Objectives

1.4.1 Purpose

Studies using neuroimaging techniques are extremely valuable in identifying functional connectivity during specific tasks, such as a stressful situation. This information in combination with treatment outcomes and symptomatology may be able to predict the success of treatments. Additionally, the differentiation between over- and under-modulation within BPD may be an important construct for treatment change and neurobiological changes. This study aimed to identify how patterns of functional connectivity in stressful situations could predict symptom severity and treatment outcomes across a 6-week group therapy. I hoped the findings would lead to a better understanding of how neurological connections vary with treatment outcomes and potentially inform the development of group therapy techniques to help match patients to the interventions that would most suit their treatment needs.

1.4.2 Study Hypotheses

1. In comparison to the waitlist control period, participation in the Mental Health Day Treatment Program (MHDTP) would result in a greater decrease in:
 - a. Depression as assessed by the DASS-21
 - b. Anxiety as assessed by the DASS-21
 - c. Stress as assessed by the DASS-21
 - d. Difficulties in emotion regulation as assessed by the DERS
 - e. Depersonalization as assessed by the MID
 - f. Derealization as assessed by the MID
 - g. Flashbacks as assessed by the MID
 - h. Functional Resilience as assessed by the FRQ
 - i. Over-modulation as assessed by the dissociation subscale within the RSDI
 - j. Under-modulation as assessed by the re-experiencing subscale within the RSDI
2. There would be differences in patterns of functional connectivity between the amygdala and the rest of the brain at each time point and during each script.
3. Levels of functional connectivity would be associated with levels of dissociation.
 - a. With over-modulation (as assessed by dissociation scores on the RSDI) during a negative mood induction task, there would be greater connectivity between the amygdala and prefrontal structures.

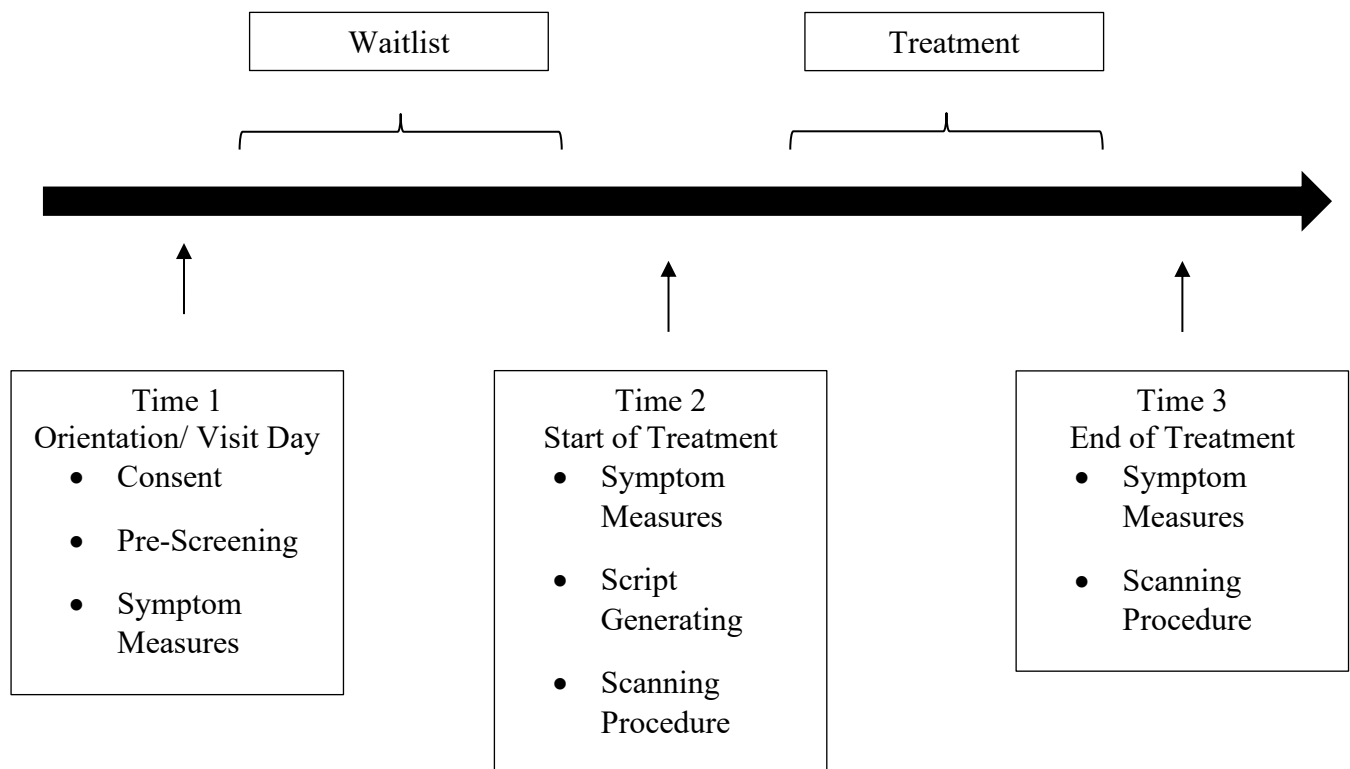
- b. With under-modulation (as assessed by re-experiencing scores on the RSDI) during a negative mood induction task, there would be greater connectivity between the amygdala and insula.
- 4. The magnitude of changes in functional connectivity between the amygdala and prefrontal structures from pre to post treatment would correlate with the magnitude of changes in symptoms of:
 - a. Depression as assessed by the DASS-21
 - b. Anxiety as assessed by the DASS-21
 - c. Stress as assessed by the DASS-21
 - d. Difficulties in emotion regulation as assessed by the DERS
 - e. Depersonalization as assessed by the MID
 - f. Derealization as assessed by the MID
 - g. Flashbacks as assessed by the MID

CHAPTER 2 – METHODS

2.1 Study Design

Participants were contacted at their orientation prior to the start of treatment in the MHDTP to determine interest in being a part of a research program. All those who were interested were invited back to determine interest and eligibility for the current study by completing the informed consent and inclusion/exclusion measures. If they were deemed ineligible for this study, participants were told there may be an opportunity for another research program and did not complete any further research questions at that time. If eligible, participants completed a series of symptom measures and were told they would be contacted again when they completed their visit days at the MHDTP. Participants had no contact with the researchers between their baseline time point and the start of treatment. When patients start at the MHDTP, they must attend at minimum 2 visit days where they go through all programming and are fully immersed in the program. Researchers contacted the participants on one of the visit days to determine if participants were still interested in being in the study and then completed the pre-treatment symptom measures. Within the first week of treatment, participants were asked to meet the researchers and complete two scripts and their MRI brain scan. Following all steps in the first week, participants were able to continue treatment as usual until the last week of treatment. Within one week of completing treatment, participants were asked to complete the same symptom measures as prior to treatment and to complete the same MRI brain scan (see Figure 3 for timeline of measures).

Figure 3. *Timeline of Measures*



2.2 Participants

Participants were recruited from patients referred to a group-based, intensive psychotherapy intervention at the MHDTP. Participants consisted of female patients between the ages of 20 and 48 with BPD and a history of complex trauma. 22 participants completed the orientation time point, 16 completed the pre-treatment questionnaires, 13 completed the post-treatment questionnaires and 12 completed the post-treatment questionnaires and post-treatment MRI scan. This study consisted of female participants as the majority of research within this area has solely examined females and while it would be an important consideration for future research, the effect of gender on emotion modulation is largely unknown. However, within the population considered, the majority of patients within the MHDTP are female, which could lead to a confound of gender when analyzing the group if we were to gather only a few males.

2.3 Exclusion Criteria

Exclusion criteria were centered on MRI safety and acquiring reliable fMRI data. Participants were excluded if they had metal implants or metal objects inside their body, heart and circulatory problems, seizure disorders, claustrophobia, or other neurologic conditions that would affect brain fMRI data. Those who were pregnant or think they might be pregnant and anyone weighing over 300lbs were also excluded from the study.

2.4 Inclusion Criteria

Study participants were referred to the MHDTP. Participants were eligible to participate if they were female, and met criteria based on formal assessment measures such as: had experienced childhood complex trauma (as assessed by the Complex Trauma Questionnaire;

ComplexTQ; Vergano, Lauriola & Speranza, 2015), were diagnosed with BPD (as assessed by the Structured Clinical Interview for the DSM-V: Personality Disorders Section; SCID), and if deemed safe to undergo an MRI scan.

2.5 Study Eligibility

Participants were deemed eligible if they completed the informed consent and met all inclusion criteria, without fulfilling the exclusion criteria. Inclusion and exclusion criteria was assessed following the orientation to the MHDTP, when participants returned to visit with the researchers prior to the start of treatment.

2.6 Clinical Procedures

2.6.1 Waitlist Procedures

Within the structure of the MHDTP, referred patients must complete an orientation which explains all aspects of the treatment program, inclusion and exclusion criteria for the program itself, and ends with a tour of the facility. Participants were recruited during this orientation by one of the researchers and were later contacted to complete the initial steps of research. At this time, participants completed the informed consent, were assessed for eligibility for the study and completed a series of measures (detailed below), 22 participants were deemed eligible and completed all orientation procedures.

BPD was assessed by Maria Simmons using the Structured Clinic Interview for the DSM-5, Personality Disorders Section (SCID-PD; Lobbestael, Leurgans, & Arntz, 2011). Maria Simmons had previously been trained to administer the SCID and was observed and assessed in

her evaluations for the first participants within this setting. The SCID is a semi-structured interview designed to evaluate whether participants meet the criteria for various mental disorders. Overall the SCID has been suggested to have between moderate and excellent reliability, while the use of the SCID for personality disorders has been shown to have excellent reliability (Lobbestael, Leurgans, & Arntz, 2011).

Complex trauma was assessed using the self-report measure the ComplexTQ (Vergano et al., 2015). Participants were considered to have a history of complex trauma if they reported physical, psychological or sexual abuse or, physical or emotional neglect during childhood above the pre-determined cut-off scores set within Vergano and colleagues (2015). The ComplexTQ is a 70-item scale used to assess neglect of care and abuse prior to the age of 15. Each item consists of a statement of a form of trauma followed by four scales; whether it was experienced, the frequency, the figure involved, and the impact for this experience (all scaled from 1 to 4). This scale has been validated and has been found to have good internal consistency and reliability (Vergano, Lauriola & Speranza, 2015).

Participants completed a number of questionnaires to assess symptom severity which included; symptoms of depersonalization, derealization and flashbacks, (using the Multidimensional Inventory of Dissociation; MID; Dell, 2006), difficulties in emotion regulation (using the Difficulties in Emotion Regulation Scale; DERS; Gratz & Roemer, 2003), depression, anxiety, and stress (using the Depression, Anxiety and Stress Scale; DASS-21; Lovibond & Lovibond, 1995), and functional resilience (using the Functional Resilience Question-Air; Air Institutes, 2017).

The MID (Dell, 2006) is used to assess pathological dissociation (both over- and under-modulation), as well as aid in diagnosis of dissociative disorders. This measure is to be used with patients who have a mixture of borderline, posttraumatic and dissociative symptoms (Dell, 2006). The assessment used within the MID (Dell, 2006) is a 218 item, self-administered questionnaire with a scale from 0 to 10, where '0 = never' and '10 = always'. This scale has been shown to have high internal reliability and high validity (Dell, 2006).

The DERS (Gratz & Roemer, 2003) is used to assess difficulties in recognizing and regulating affect. This scale consists of 36 questions rated on a scale of 1 to 5 where '1 = almost never' and '5 = almost always'. This scale has five subscales which assess non-acceptance of emotional responses, difficulties engaging in goal directed behavior, impulse control difficulties, lack of emotion awareness, limited access to emotion regulation strategies and lack of emotion clarity. This scale has been shown to be reliable and valid across multiple races and genders in a diverse sample of adults (Ritschel, Tone, Schoemann & Lim, 2015).

The DASS-21 (Lovibond & Lovibond, 1995) is a 21 item self-report scale used to measure levels of depression, anxiety and stress. This scale consists of a series of questions based on feelings in the past week with a scale from did not apply to me at all (0) to applied to me very much or most of the time (3). Results of the scale are transferred to a rating within the categories ranging from 'normal' to 'extremely severe'. Overall the DASS-21 (Lovibond & Lovibond, 1995) has been shown to be a reliable measure, and has been suggested to have high reliability, fair construct validity and good internal consistency (Henry & Crawford, 2005).

The FRQ (Air Institutes, 2017) is comprised of 16 subdomains within its four domains; Personal Effectiveness, Emotional Intelligence, Interpersonal Competence and Perspective

Taking. The FRQ (Air Institute, 2017) is a 63-item self-report measure consisting of statements of self which are rated on a scale of 1 through 6, with 1 being ‘Strongly Disagree’ and 6 being ‘Strongly Agree’. This measure has reported high validity between itself and other measures of resilience within all domains and the total score (Air Institute, 2017). Within this study only the overall resilience score was used as a measure of functional resilience.

2.6.2 Pre-Treatment Procedures

Of the 22 participants eligible to be enrolled in the study, 16 began treatment and completed the pre-treatment procedures. Within the first week of treatment, participants completed the same questionnaires noted above as a control for changes due to time rather than treatment. Participants met with a researcher, Dr. Sandra Reyno to complete the trauma scripts. Dr. Reyno is a clinical psychologist who has used traumatic narratives within her treatments and who has been trained on the implementation of various psychological measures. Participants were then asked to recall and draft a description of one of their most traumatic events using the standardized protocol included in the Traumatic Scene Form (Hopper, Frewen, van der Kolk & Lanius, 2007). This protocol includes a script of how researchers are to gather information from participants and includes a series of emotional prompts to include within the script. The participant was then asked to draft a second script depicting a neutral event (i.e., an event that did not elicit emotions) in the same manner. The Traumatic Scene Form has directions for writing about contextual information, sensations, bodily experiences, emotions and cognition, as well as a ‘menu’ of subjective visceral and muscular reactions associated with physiological arousal (Hopper, Bessel, & van der Kolk, 2017). The researcher later revised these scripts for clarity, and so experiences were portrayed in the first person, present tense.

2.6.2.1 Mood Induction Procedures

During the first week of treatment participants took part in the functional Magnetic Resonance Imaging (fMRI) mood induction procedure using the above scripts. An MRI was used to examine areas of connectivity within the brain and map changes across conditions (i.e., between the neutral versus negative mood inducing task). Participants completed the Positive and Negative Affect Schedule (PANAS X; Watson & Clark, 1994) to assess level of negative affect immediately prior to completing the induction procedure. The PANAS-X (Watson & Clark, 1994) was used as a baseline measure of affect. Participants then underwent standard calibration scans followed by the mood induction procedure. The mood induction consisted of a protocol that included three matched conditions. The conditions included: a) common neutral condition where participants read a neutral script generated by the researchers, common to all participants (see Appendix A), b) a neutral condition where the participant read their pre-generated autobiographical neutral script and c) a negative mood induction condition in which the participant read their pre-generated autobiographical negative mood inducing script. Scripts were displayed through a projector on a screen directly in front of participants while they were in the MRI scanner. During the scan, participants were cued to ‘remember the feelings and sensations as vividly as possible’. Participants read their scripts silently while no scanning took place, then underwent an approximately 6-minute event-related design where 12 cues were presented every 30 seconds on the screen before them as a RSFC scan took place (see Appendix B). These cues were designed to prompt the participant to relive the experience through various modalities (e.g., visual, auditory) in a time-locked manner and were consistent across all participants and all conditions. The entire procedure took approximately 45 minutes to complete.

Immediately following the scans, participants completed the PANAS X (Watson & Clark, 1994) a second time to assess post mood induction affect and the RSDI (Hopper et al., 2007) to assess symptoms of dissociation (used as a measure of over-modulation) and re-experiencing (used as a measure of under-modulation).

The PANAS-X (Watson & Clark, 1994) is comprised of two mood scales, one measuring positive affect and another measuring negative affect (Watson & Clark & Tellegen, 1988). The PANAS-X (Watson & Clark, 1994) consists of 60-items requiring participants to respond using a 5-point scale ranging from very slightly or not at all (1) to extremely (5). The PANAS-X (Watson & Clark, 1994) measures affect within 11 specific dimensions including; fear, sadness, guilt, hostility, shyness, fatigue, surprise, joviality, self- assurance, attentiveness, and serenity (Watson and Clark, 1999). This measure has reported high internal consistency, generally ranging from .83 to .90 for Positive Affect and .85 to .90 for Negative Affect (Watson and Clark, 1999).

The Response to Script-Driven Imagery Scale (RSDI; Hopper, Frewen, Sack, Lanius & van der Kolk, 2007) is an 11-item instrument for assessing severities of state re-experiencing, avoidance and dissociative symptoms provoked by script-driven trauma imagery, with items rated from 0 (not at all) to 6 (a great deal). It has demonstrated excellent psychometric characteristics in PTSD samples. Subscale coefficients ranged from .76 to .92, and a factor analysis supported the hypothesized three factor structure. Evidence for convergent and discriminate validity was demonstrated in relation to psychological scale and trauma-script driven induced heart rate change (Hopper, Frewen, van der Kolk & Lanius, 2007). This measure

was used to assess modulation, as the dissociation subscale is comprised of measures of over-modulation, while the re-experiencing subscale is comprised of measures of under-modulation.

2.6.3 Post-Treatment Procedures

Of the 16 participants who completed the pre-treatment measures, 13 completed all post-treatment symptom measures and 12 completed all post-treatment MRI measures. Within one week of completing the 6-week intervention, all the pre-treatment measures were re-administered (i.e., self-report measures of depression, anxiety and stress symptoms, depersonalization, derealization, flashbacks, and emotion regulation) to compare changes in symptoms over the course of treatment. In addition to these questionnaires, participants were asked to undergo the same fMRI mood induction procedure completed at pre-treatment, using the same autobiographical scripts generated prior to treatment.

2.7 fMRI Procedures

Imaging was conducted at Biotic (QEII Halifax Infirmary) using a GE MR750 3T MRI scanner operating in research mode, with data collection using an MR Instruments 32 channel RF Head Coil. Anatomical scans consisted of 3D T1 weighted scans collected to facilitate analysis using the human connectome project (HCP) processing pipelines [PMC3720813]. T1 imaging was collected using 3D IR-FSPGR with FOV 25.6 cm, 256x256, 1 mm slice, 1 signal average, flip angle 9, 450ms TI, 62.5 kHz RBW, scan time 7m3s. Additional reference scans using phase-encode blip direction reversal (to facilitate field distortion correction using FSL Topup package) and enhanced T1 weight EPI scans (MUX factor 1, 3000 ms TR) to facilitate registration to T1w anatomic scans, were also acquired and processed using HCP processing

pipelines. The stimulus paradigm was delivered using the PsychoPy presentation software package (Pierce & MacAskill, 2018) with stimulus presentation synchronized to data acquisition on the GE MRI system.

For BOLD fMRI, images were acquired using a two-shot spiral out sequence on a 3T MRI scanner located at the QEII hospital using a 32-Channel head coil and with parameters as follows: TR = 2 s, TE = 25 ms, flip angle = 90 degrees, voxel size = 3.75 X 3.75 X 3.5 mm, matrix = 64 X 64 voxels, interslice interval = 0.5 mm, number slices = 23. Low resolution T1 images will be obtained co-planar with the functional images (i.e., the same dimensions and slice locations) and high resolution T1-weighted images was obtained with voxel size = 0.93 X 0.93 X 1 mm.

2.8 Statistical Analysis of Clinical Data

Clinical data was analyzed using IBM SPSS Statistics, by performing 7 repeated-measures ANOVAs (Analysis of Variance) to examine differences between waitlist, pre-treatment, and post-treatment symptom severity (i.e., depression, anxiety, stress, difficulties with emotion regulation, dissociation, depersonalization and flashbacks). As a follow-up for results of significance, paired-samples t-tests were employed to assess group differences in symptom severity and emotion regulation capacities between waitlist, pre-treatment, and post-treatment time points. To control for multiple comparisons, a Bonferroni procedure was employed.

This study employed a completer-only analysis for pre- to post-treatment differences in symptoms rather than an Intention-To-Treat (ITT) analysis. The completer-only analysis was chosen for a number of reasons, first ITT is designed based on the initial treatment assigned not the treatment received however only one treatment was used and strict ITT requires post-

treatment measures even if participants did not strictly adhere to the protocols. While this approach may be beneficial to studies comparing treatments, this study followed only one treatment and therefore any participants who did not follow the protocol, did not complete the treatment. Additionally, with the ITT analysis missing data can be problematic as there is no consensus with how to handle missing data or participants lost to follow-up, meaning this approach can only be used when there are complete sets of outcome data on all randomized participants. In employing this analysis, we would need to make many assumptions of outcomes for lost participants or participants who did not complete the treatment would need to return following an equal time to complete post-treatment measures. This would not provide sufficient information on the effect of the treatment as a number of participants would not have completed the treatment program. This study examined solely participants who completed all stages and completed the treatment program within the analysis from pre- to post-treatment, and compared the initial measures of participants who completed treatment and those who withdrew.

2.9 fMRI Analysis

The fMRI data processing and analysis was completed as described by Newman et al. (2013), and following standard procedures established by Fox et al. (2005). Briefly, it was carried out using fMRI Expert Analysis Tool (FEAT), part of FSL (www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing were applied; motion correction using MCFLIRT; non-brain removal using BET (Smith 2002); spatial smoothing using a Gaussian kernel of FWHM 8.0mm; grand-mean intensity normalization of the entire 4D data set by a single multiplicative factor; and bandpass filtering between 0.01 and 0.1 Hz. Functional connectivity analysis followed the methods of Fox et al. (2005), deriving time courses from ROIs, and determining the

correlation of these “seed” time courses with every other voxel in the brain, while including as covariates the time courses of areas of noninterest including white matter, cerebral spinal fluid, and the average of the whole brain. This method involves normalizing the data of the time courses as the normality of the distribution of brain connectivity data is unknown and often does not satisfy the normality condition in order to employ a Pearson’s correlation. Group analysis involved spatial normalization to a standard template (MNI152) and linear mixed effects modelling of the regression coefficients from the individual subject analyses, treating subjects as a random effect, and using the multiple comparison correction based on Gaussian Random Field Theory to control for Type I error (Worsely, 2001).

Two analyses were performed using an amygdala seed region. This region was selected based on its connection to the emotional responses, interoception and how commonly it is activated within the research in this area (Fan et al., 2016). The first consisted of an amygdala to whole brain exploratory analysis to examine which areas were co-activated with the amygdala during the tasks. Given the small sample size, a second amygdala to masked region analysis was employed to examine a priori areas of interests and to be more sensitive to effects by limiting the corrections for multiple comparisons. Within this analysis, a masked region was created comprising of the insula and prefrontal areas defined within the literature (i.e., Krause-Utz & Elzinga, 2018; Lanius, Bluhm & Frewen, 2011; Nicholson et. al., 2016; Paret et al., 2016; Krause-Utz et al., 2014; Winter et al., 2015).

CHAPTER 3 – RESULTS

3.1 Clinical and Demographic Variables

This study included 22 female patients who completed waitlist symptom scales prior to the start of treatment. Of these 22, 16 came to treatment and completed the pre-treatment symptom measures and the first fMRI brain scan, and 13 participants completed the final post-treatment measures and 12 completed the fMRI protocol. Participants who completed all symptom time points were between the ages of 20 and 48 ($M = 35.54$, $SD = 9.60$) (see Table 1 for full demographic details).

An independent samples t-test was performed to assess for differences in demographic variables and symptom scale findings between participants who completed only the first time point measures, or did not come to the treatment program (i.e., control; $n = 9$) and those who completed all symptom measures (i.e., treatment group; $n = 13$).

In terms of demographics, there were no significant difference between participant's ages in the control group ($M = 32.89$, $SD = 10.89$) and the treatment group ($M = 35.54$, $SD = 9.61$); $t(20) = 0.60$, $p = 0.596$. When looking at symptom scales, there were no significant differences between treatment and control groups in terms of depression, anxiety, stress, difficulties in emotion regulation, depersonalization, derealization or flashbacks at the orientation time point (see Table 2).

3.2 Hypothesis 1

Hypothesis 1 examined the completer only data of participants who completed all three time points: the baseline, pre-treatment and post-treatment measures. 13 participants were included within the symptom measures analysis of depression, anxiety, stress, difficulties in

emotion regulation, depersonalization, derealization and flashbacks. Within the measures of under-modulation and over-modulation which was measured immediately after the MRI scan, 12 participants were included as only 12 participants completed the MRI scan.

3.2.1 Depression

A one-way repeated measures ANOVA was conducted to compare the effect of time (i.e., waitlist, pre-treatment and post-treatment) on depression scores (as assessed by the DASS; Lovibond & Lovibond, 1995) whereby higher scores indicated more severe depression symptoms. There was a significant effect of time on depression scores, Wilks Lambda = .434, $F(2, 11) = 7.16, p = .01$. Three pairwise t tests were used to make post hoc comparisons between the conditions. A first paired sample t -test indicated there was a significant difference between waitlist ($M = 25.85, SD = 7.05$) and pre-treatment depression scores ($M = 20.92, SD = 7.33$); $t = 2.61(12), p = .023$. A second paired sample t -test indicated there was a significant difference between pre-treatment ($M = 20.92, SD = 7.33$) and post-treatment depression scores ($M = 12.15, SD = 11.82$); $t = 2.99(12), p = .011$. A third paired sample t -test indicated there was a significant difference between waitlist ($M = 25.85, SD = 7.05$) and post-treatment depression scores ($M = 12.15, SD = 11.82$); $t = 3.91(12), p = .002$.

3.2.2 Anxiety

A one-way repeated measures ANOVA was conducted to compare the effect of time (i.e., waitlist, pre-treatment and post-treatment) on anxiety scores (as assessed by the DASS; Lovibond & Lovibond, 1995) whereby higher scores indicate more severe symptoms. There was a significant effect of time on anxiety, Wilks Lambda = .363, $F(2, 11) = 9.64, p = .004$. Three

pairwise t tests were used to make post hoc comparisons between the conditions. A first paired sample t -test indicated there was no significant difference between waitlist ($M = 21.69, SD = 9.89$) and pre-treatment anxiety scores ($M = 21.69, SD = 8.43$); $t = 0.00$ (12), $p = 1$. A second paired sample t -test indicated there was a significant difference between pre-treatment ($M = 21.69, SD = 8.43$) and post-treatment anxiety scores ($M = 11.38, SD = 9.78$); $t = 4.58$ (12), $p = .001$. A third paired sample t -test indicated there was a significant difference between waitlist ($M = 21.69, SD = 9.89$) and post-treatment anxiety scores ($M = 11.38, SD = 9.78$); $t = 3.76$ (12), $p = .003$.

3.2.3 Stress

A one-way repeated measures ANOVA was conducted to compare the effect of time (i.e., waitlist, pre-treatment and post-treatment) on stress scores (as assessed by the DASS; Lovibond & Lovibond, 1995) whereby higher scores indicate more severe symptoms. There was a significant effect of time on stress, Wilks Lambda = .433, $F(2, 11) = 7.22$, $p = .010$. Three pairwise t tests were used to make post hoc comparisons between the conditions. A first paired sample t -test indicated there was no significant difference between waitlist ($M = 26.92, SD = 7.15$) and pre-treatment stress scores ($M = 26.15, SD = 8.42$); $t = 0.60$ (12), $p = .563$. A second paired sample t -test indicated there was a significant difference between pre-treatment ($M = 26.15, SD = 8.42$) and post-treatment stress scores ($M = 14.54, SD = 9.65$); $t = 3.75$ (12), $p = .003$. A third paired sample t -test indicated there was a significant difference between waitlist ($M = 26.92, SD = 7.15$) and post-treatment stress ($M = 14.54, SD = 9.65$); $t = 3.95$ (12), $p = .002$.

3.2.4 Difficulties in Emotion Regulation

A one-way repeated measures ANOVA was conducted to compare the effect of time (i.e., waitlist, pre-treatment and post-treatment) on difficulties in emotion regulation (as assessed by the DERS; Gratz & Roemer, 2003) whereby higher scores indicate more severe symptoms. There was a significant effect of time on emotion regulation, Wilks Lambda = .277, $F(2, 11) = 14.34$, $p = .001$. Three pairwise t tests were used to make post hoc comparisons between the conditions. A first paired sample t -test indicated there was no significant difference between waitlist ($M = 127.92$, $SD = 21.30$) and pre-treatment emotion regulation scores ($M = 130.85$, $SD = 17.32$); $t = -0.73(12)$, $p = .481$. A second paired sample t -test indicated there was a significant difference between pre-treatment ($M = 130.85$, $SD = 17.32$) and post-treatment emotion regulation ($M = 81.38$, $SD = 30.51$); $t = 5.39(12)$, $p < .001$. A third paired sample t -test indicated there was a significant difference between waitlist ($M = 127.92$, $SD = 21.30$) and post-treatment emotion regulation ($M = 81.38$, $SD = 30.51$); $t = 4.42(12)$, $p = .001$.

3.2.5 Depersonalization

A one-way repeated measures ANOVA was conducted to compare the effect of time (i.e., waitlist, pre-treatment and post-treatment) on depersonalization (as assessed by the MID; Dell, 2006) whereby higher scores indicate more severe symptoms. There was a significant effect of time on depersonalization, Wilks Lambda = .245, $F(2, 11) = 16.91$, $p < .001$. Three pairwise t tests were used to make post hoc comparisons between the conditions. A first paired sample t -test indicated there was no significant difference between waitlist ($M = 33.13$, $SD = 17.35$) and pre-treatment depersonalization scores ($M = 33.78$, $SD = 15.78$); $t = -0.73(12)$, $p = .866$. A second paired sample t -test indicated there was a significant difference between pre-treatment ($M = 33.78$, $SD = 15.78$) and post-treatment depersonalization score ($M = 12.93$, $SD = 10.24$); $t =$

4.99 (12), $p < .001$. A third paired sample t -test indicated there was a significant difference between waitlist ($M = 33.13$, $SD = 17.35$) and post-treatment depersonalization ($M = 12.93$, $SD = 10.24$); $t = 5.59$ (12), $p < .001$.

3.2.6 Derealization

A one-way repeated measures ANOVA was conducted to compare the effect of time (i.e., waitlist, pre-treatment and post-treatment) on derealization (as assessed by the MID; Dell, 2006) whereby higher scores indicate more severe symptoms. There was no significant effect of time on derealization, Wilks Lambda = .596, $F(2, 11) = 3.72$, $p = .058$. Three pairwise t tests were used to make post hoc comparisons between the conditions. A first paired sample t -test indicated there was no significant difference between waitlist ($M = 29.11$, $SD = 20.87$) and pre-treatment derealization scores ($M = 28.60$, $SD = 16.22$); $t = 0.14$ (12), $p = .891$. A second paired sample t -test indicated there was a significant difference between pre-treatment ($M = 28.60$, $SD = 16.22$) and post-treatment derealization ($M = 14.68$, $SD = 18.07$); $t = 2.53$ (12), $p = .026$. A third paired sample t -test indicated there was a significant difference between waitlist ($M = 28.11$, $SD = 20.87$) and post-treatment derealization ($M = 14.68$, $SD = 18.07$); $t = 2.78$ (12), $p = .017$.

3.2.7 Flashbacks

A one-way repeated measures ANOVA was conducted to compare the effect of time (i.e., waitlist, pre-treatment and post-treatment) on flashbacks (as assessed by the MID; Dell, 2006) whereby higher scores indicate more severe symptoms. There was a significant effect of time on flashbacks, Wilks Lambda = .252, $F(2, 11) = 16.286$, $p = .001$. Three pairwise t tests were used to make post hoc comparisons between the conditions. A first paired sample t -test indicated there

was no significant difference between waitlist ($M = 36.82, SD = 22.77$) and pre-treatment flashback scores ($M = 32.68, SD = 18.19$); $t = 0.93 (12), p = .369$. A second paired sample t -test indicated there was a significant difference between pre-treatment ($M = 32.68, SD = 18.19$) and post-treatment flashbacks ($M = 14.93, SD = 16.39$); $t = 4.95 (12), p < .001$. A third paired sample t -test indicated there was a significant difference between waitlist ($M = 36.82, SD = 22.77$) and post-treatment flashbacks ($M = 14.93, SD = 16.39$); $t = 5.00 (12), p < .001$.

3.2.8 Functional Resilience

A one-way repeated measures ANOVA was conducted to compare the effect of time (i.e., waitlist, pre-treatment and post-treatment) on functional resilience (as assessed by the FRQ; Air Institutes, 2017) whereby higher scores indicate more positive resilience. There was a significant effect of time on functional resilience, Wilks Lambda = .351, $F (2, 11) = 7.391, p = .015$. Three pairwise t tests were used to make post hoc comparisons between the conditions. A first paired sample t -test indicated there was no significant difference between waitlist ($M = 202.20, SD = 31.72$) and pre-treatment flashback scores ($M = 199.40, SD = 33.26$); $t = 0.93 (12), p = .375$. A second paired sample t -test indicated there was a significant difference between pre-treatment ($M = 199.40, SD = 33.26$) and post-treatment flashbacks ($M = 259.40, SD = 36.91$); $t = -4.31 (12), p = 0.001$ whereby participants were more resilient at post-treatment. A third paired sample t -test indicated there was a significant difference between waitlist ($M = 202.20, SD = 31.72$) and post-treatment flashbacks ($M = 259.40, SD = 36.91$); $t = -3.99 (12), p = 0.003$ whereby participants were more resilient at post-treatment.

3.2.9 Scan Over-Modulation

Although the subscale is named ‘dissociation’ this measure assessed over-modulation. A paired samples t-test was conducted to compare the effect of time (i.e., pre-treatment and post-treatment) on levels of over-modulation (as assessed by the dissociation subscale of the RSDI; Hopper et al., 2007) during the mood induction procedure whereby higher scores indicate more severe symptoms. This test indicated there was no significant difference between pre-treatment ($M = 2.10, SD = 1.64$) and post-treatment over-modulation ($M = 2.13, SD = 1.63$); $t = -0.113$ (12), $p = .912$.

3.2.10 Scan Under-Modulation

A paired samples t-test was conducted to compare the effects of time (i.e., pre-treatment or post-treatment) on under-modulation (as assessed by the re-experiencing subscale within the RSDI; Hopper et al., 2007) whereby higher scores indicate more severe symptoms during the mood induction procedure. Results of this test indicated there was a significant difference in pre-treatment ($M = 4.00, SD = 1.68$) and post-treatment under-modulation ($M = 2.19, SD = 1.34$); $t = 2.70$ (12), $p = .019$.

3.2.11 Scan Avoidance

A paired samples t-test was conducted to compare the effects of time (i.e., pre-treatment or post-treatment) on avoidance (as assessed by the RSDI; Hopper et al., 2007) whereby higher scores indicate more severe symptoms during the mood induction procedure. Results of this test indicated there was a significant difference between pre-treatment avoidance ($M = 1.67, SD = 1.32$) and post-treatment avoidance ($M = 1.05, SD = 1.12$); $t = 2.19$ (12), $p = .049$.

3.3 Hypothesis 2

3.3.1 Amygdala to Whole Brain Results by Task and Time

The following analyses examined the functional connectivity from the amygdala seed regions to the whole brain at each time point and each condition (see Table 3). This analysis included differing numbers of participants as not all participants were able to be included in both time points. As such, 16 participants completed the first time point and were included in all pre-treatment analyses. For post-treatment analyses, two participants did not complete treatment, one completed treatment following the completions of this analysis and was unable to be included, and one participant was removed due to movement artifacts. As a result, 12 participants were included in post-treatment analyses and any analyses across groups.

3.3.1.1 Pre-Treatment

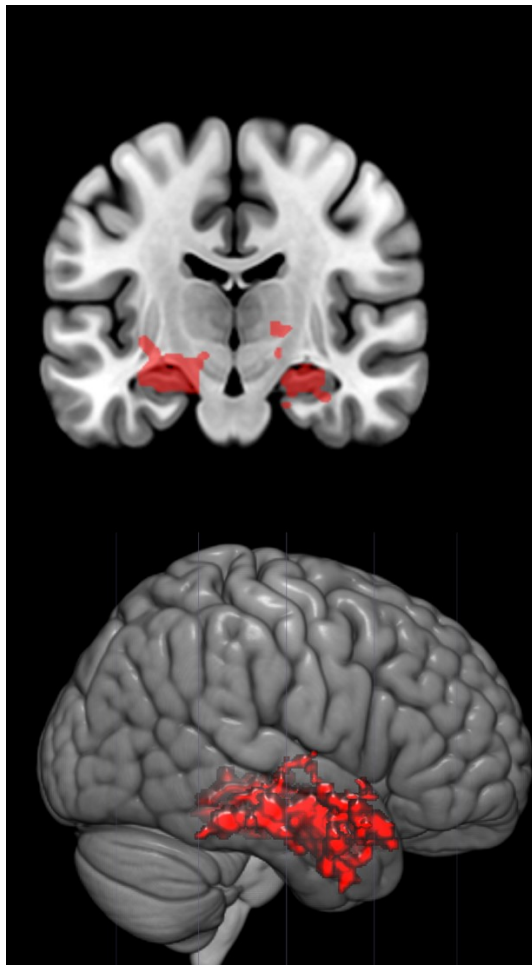
Results of the bilateral amygdala to whole-brain correlation during the autobiographical neutral script indicated two clusters of statistical significance as determined by a threshold of $Z > 3.1$, $p = 0.05$ (see Figure 4). The larger cluster ($n = 2456$ voxels) was found at the left amygdala, while a slightly smaller cluster ($n = 2239$ voxels) was found within the opposite hemisphere at the right amygdala.

Figure 4. *Amygdala to Whole Brain Pre-Treatment Autobiographical Neutral Script*



When looking at the autobiographical trauma scripts, results indicated two clusters of statistical significance, when thresholded to $Z > 3.1$, $p = 0.05$ (see Figure 5). The larger cluster ($n = 1958$ voxels) was found within the left nucleus accumbens and a smaller cluster ($n = 1789$ voxels) was found within the right hippocampus.

Figure 5. *Amygdala to Whole Brain Pre-Treatment Autobiographical Trauma Script*



3.3.1.2 Post Treatment

Within the post-treatment autobiographical neutral condition, two clusters were identified as being statistically significant when thresholded to $Z > 3.1$, $p = 0.05$ (see Figure 6). The larger

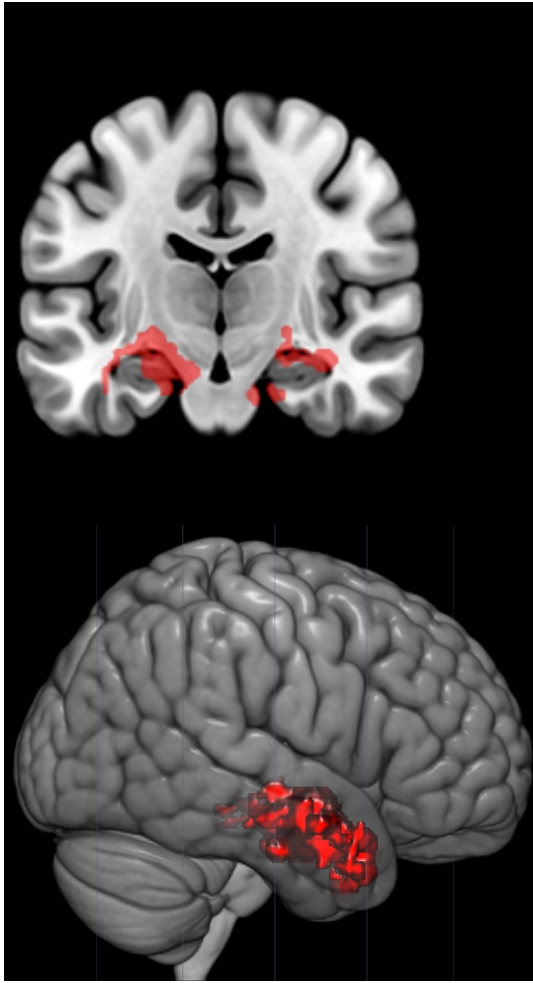
cluster (n=1807 voxels) was within the left amygdala and a slightly smaller (n=1790 voxels) within the right amygdala.

Figure 6. *Amygdala to Whole Brain Post-Treatment Autobiographical Neutral Script*



Within the post-treatment autobiographical trauma script, two clusters were identified as statistically significant when thresholded to $Z > 3.1$, $p = 0.05$ (see Figure 7). The larger (n=1863 voxels) was found within the right amygdala and another smaller cluster (n=1709) was found in the left amygdala.

Figure 7. *Amygdala to Whole-Brain Post-Treatment Autobiographical Trauma Script*



3.3.2 Whole Brain Interactions

3.3.2.1 Pre-Treatment versus Post-Treatment

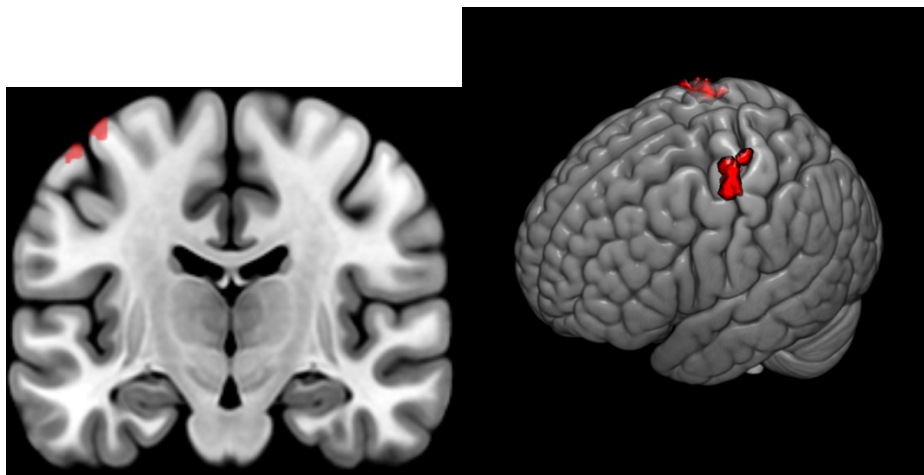
Within the bilateral amygdala to whole brain analysis at pre-treatment to post-treatment for the autobiographical neutral script, there were no statistically significant clusters identified when thresholded at $Z > 3.1$, $p = 0.05$.

Within the bilateral amygdala to whole brain analysis at pre-treatment to post-treatment for the autobiographical trauma script, there were no statistically significant clusters identified when thresholded at $Z > 3.1$, $p = 0.05$.

3.3.2.2 *Autobiographical Neutral versus Trauma Script*

Within the bilateral amygdala to whole brain analysis at pre-treatment, looking to differences between the neutral and trauma scripts two clusters were identified when thresholded at $Z > 3.1$, $p = 0.05$ (see Figure 8/ Table 4). The first cluster contained $n = 175$ voxels and was located within the postcentral gyrus while the second cluster contained $n = 167$ voxels and was also located within the postcentral gyrus.

Figure 8. *Amygdala to Whole Brain Interactions Pre-Treatment Autobiographical Neutral-Trauma Script*



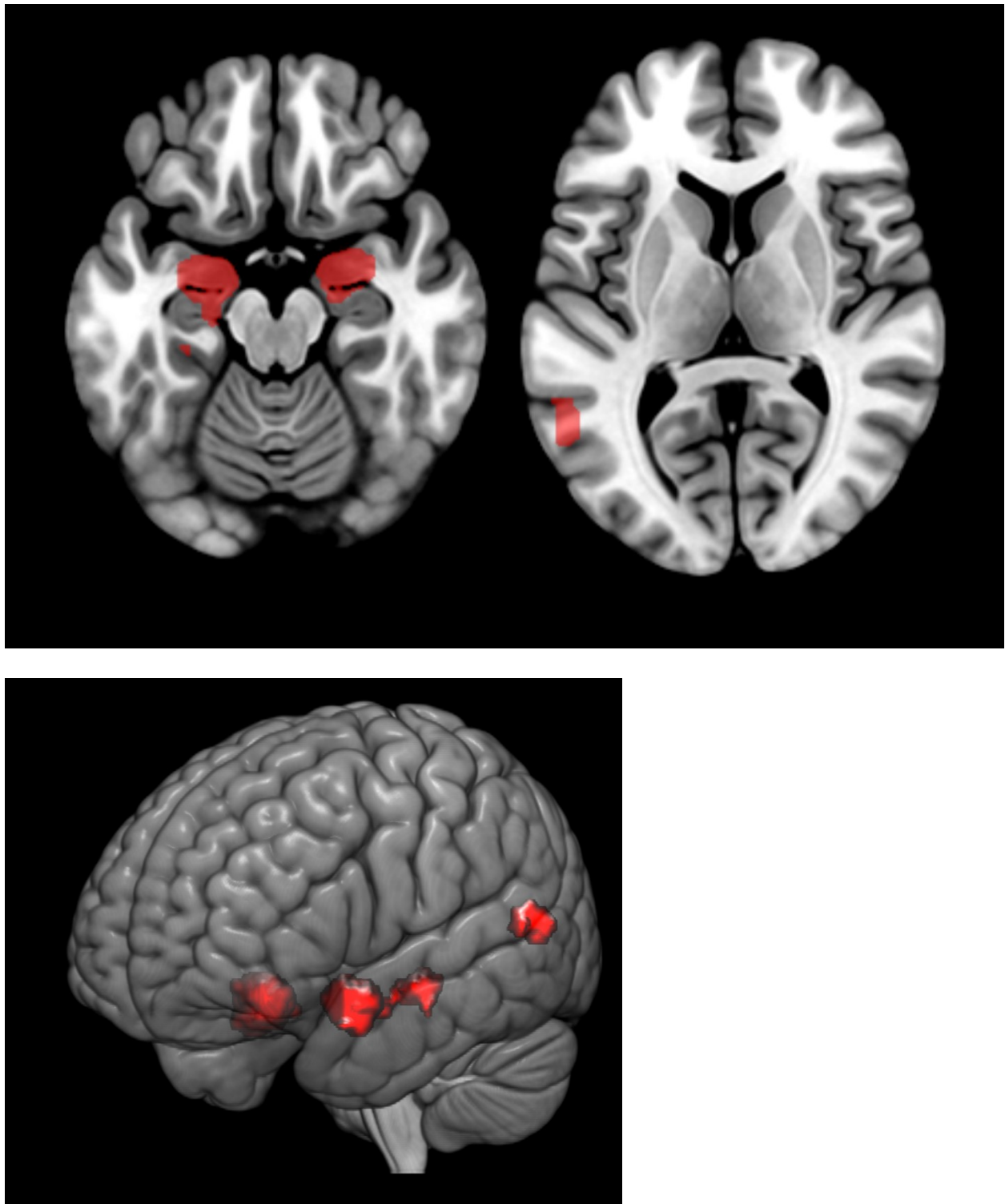
Within the bilateral amygdala to whole brain analysis at post-treatment there were no statistically significant differences between the neutral and trauma script when thresholded to $Z > 3.1$, $p = 0.05$.

3.4 Hypothesis 3

3.4.1 Emotion Over-Modulation

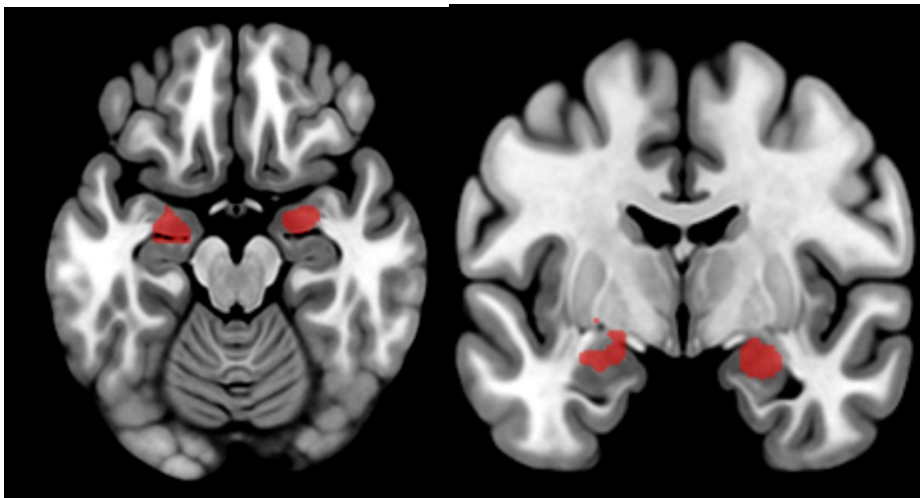
Four separate findings emerged when using self-reported ‘dissociation’ scores to measure over-modulation from the Response to Script Driven Imagery Scale as a covariate within the whole brain analysis (see Table 5). When looking to the relationship between over-modulation and the pre-treatment autobiographical neutral script three statistically significant clusters were identified at the $Z > 3.1$, $p = 0.05$ threshold (see Figure 9). The first cluster ($n = 576$ voxels) was identified within the left amygdala, the second cluster identified ($n = 530$ voxels) was identified within the right amygdala, and the third cluster identified ($n = 123$ voxels) was within the middle temporal gyrus, the temporooccipital part.

Figure 9. *Amygdala to Whole Brain Pre-Treatment Neutral Script Controlling for Over-Modulation*



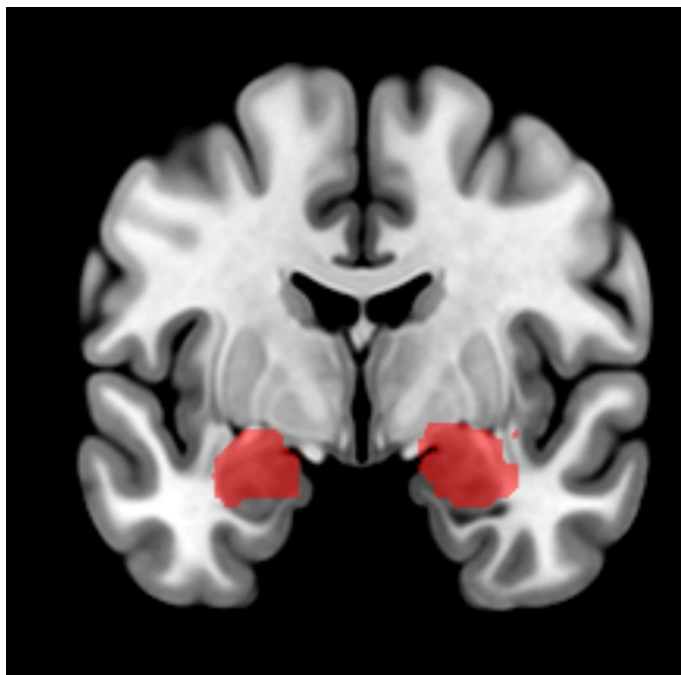
When looking to the relationship between over-modulation and the pre-treatment autobiographical trauma script two statistically significant clusters were identified at the $Z > 3.1$, $p = 0.05$ (see Figure 10). The first significant cluster ($n = 156$ voxels) was identified within the left nucleus accumbens and the second cluster ($n = 143$ voxels) was identified within the right amygdala.

Figure 10. *Amygdala to Whole Brain Pre-Treatment Trauma Script Controlling for Over-Modulation*



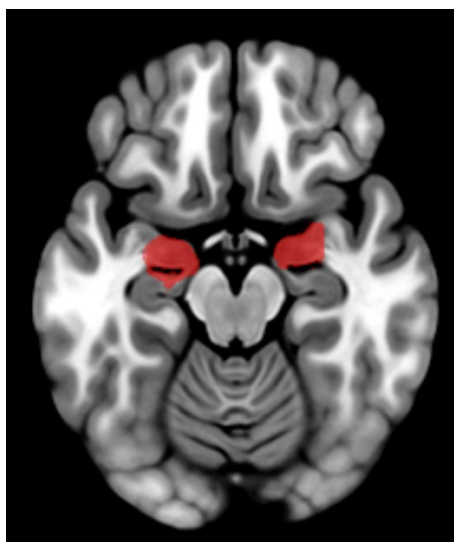
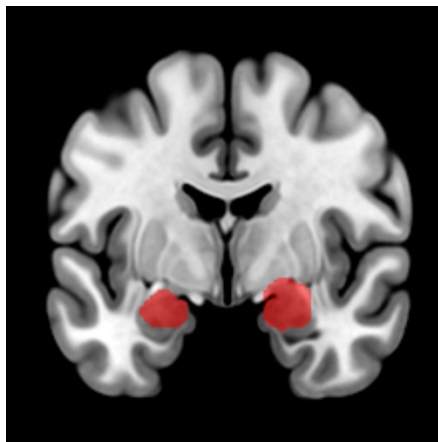
When looking to the relationship between over-modulation and the post-treatment autobiographical neutral script, two statistically significant clusters were identified within the $Z > 3.1$, $p = 0.05$ threshold (see Figure 11). A larger cluster ($n = 611$ voxels) within the right amygdala and a second cluster was identified within the left amygdala with $n = 491$ voxels.

Figure 11. *Amygdala to Whole Brain Post-Treatment Neutral Script Controlling for Over-Modulation*



When looking to the relationship between over-modulation and the post-treatment trauma script again two clusters were identified as statistically significant within the $Z > 3.1$, $p = 0.05$ threshold (see Figure 12). The first ($n = 429$ voxels) was within the right amygdala and the second ($n = 367$) was within the left amygdala.

Figure 12. *Amygdala to Whole Brain Post-Treatment Trauma Script Controlling for Over-Modulation*

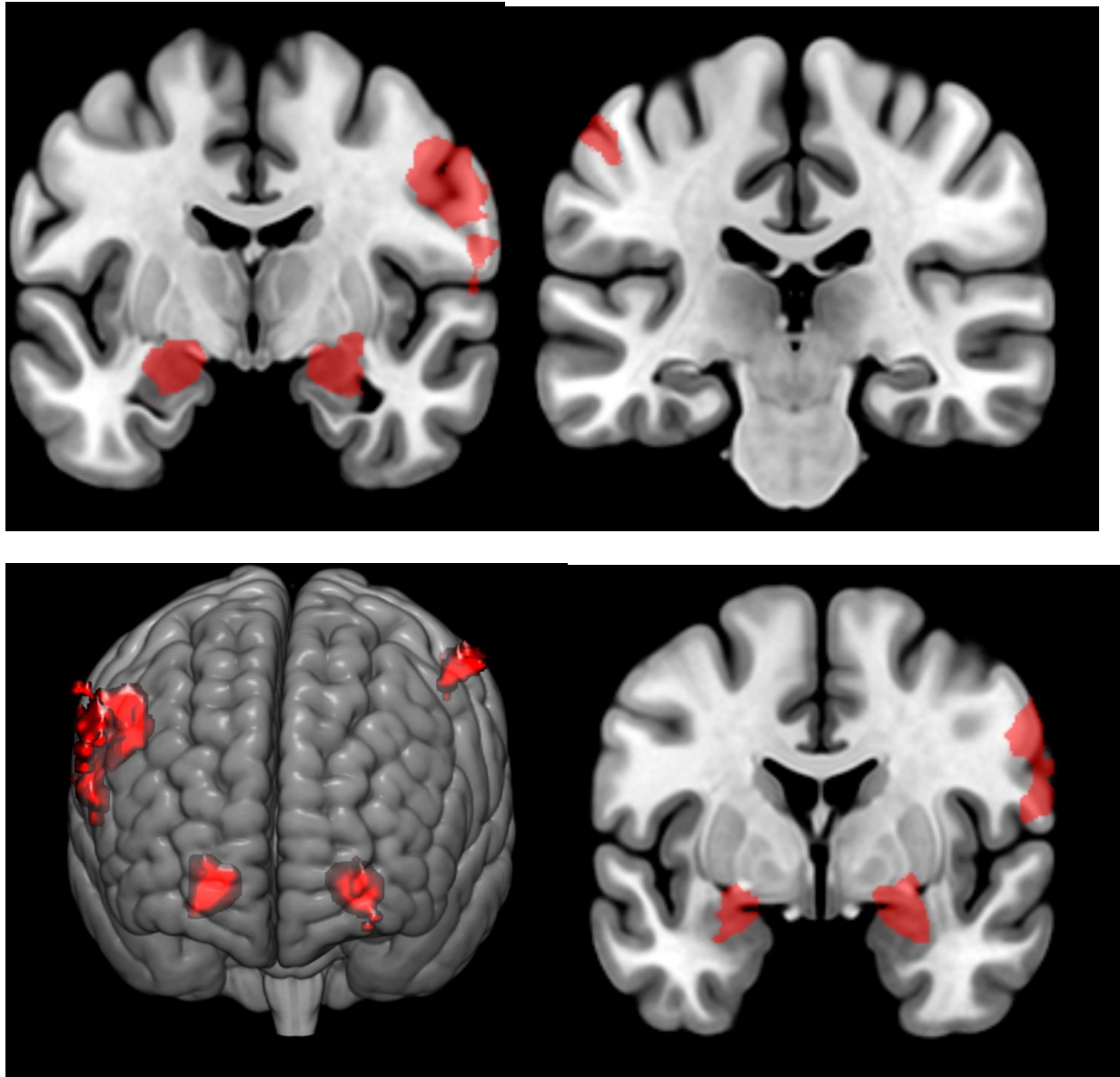


When looking to the relationship between over-modulation and interactions between time points and conditions, no clusters were identified as statistically significant with a threshold of $Z > 3.1$, $p = 0.05$.

3.4.2 Emotion Under-Modulation

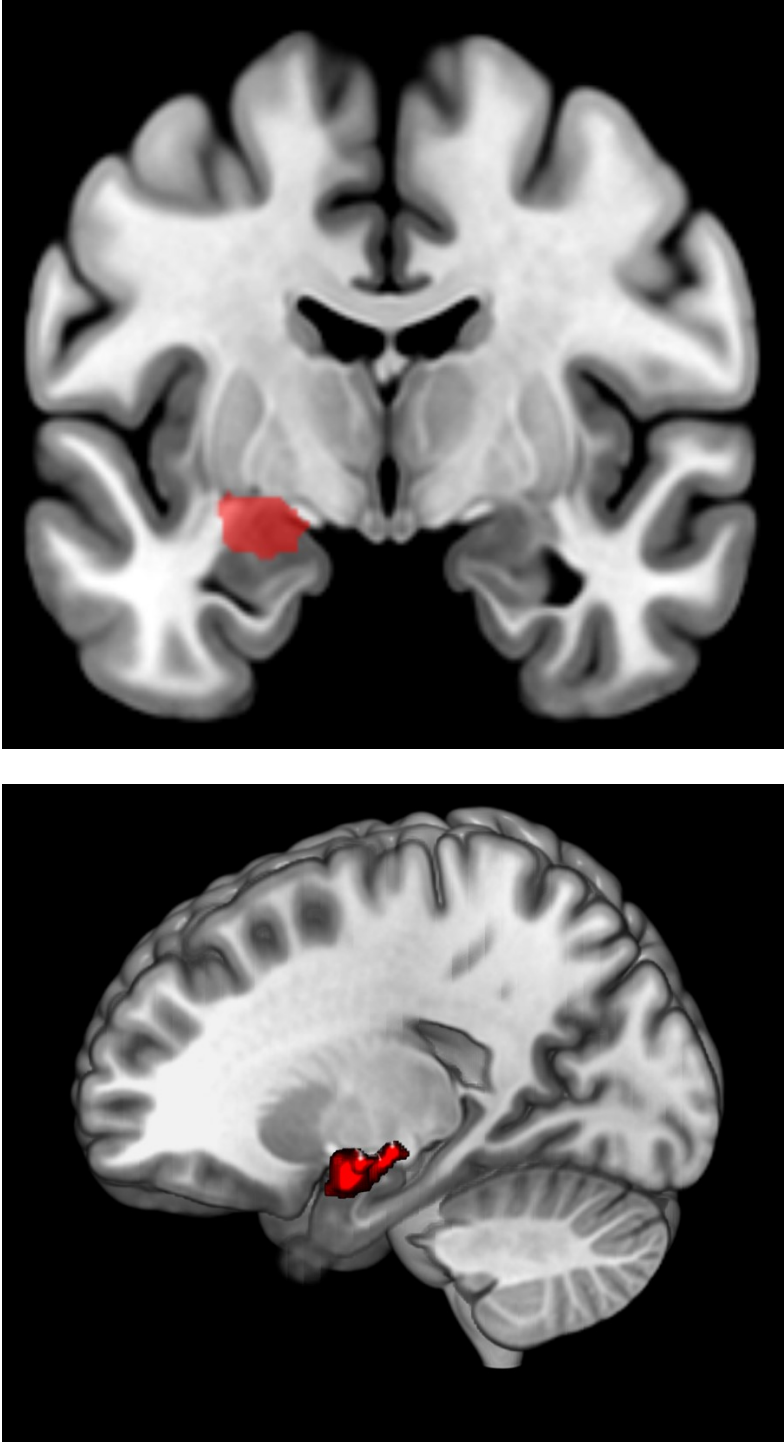
Self-reported 're-experiencing' scores from the Response to Script Driven Imagery Scale were used as a measure of under-modulation and included as a covariate within the whole brain analysis (see Table 6 for full results). When looking to the relationship between under-modulation and the pre-treatment autobiographical neutral script, four statistically significant clusters were identified when thresholded at $Z > 3.1$, $p = 0.05$ (see Figure 13). The largest cluster ($n = 763$ voxels) was identified within the right postcentral gyrus, another cluster ($n = 305$ voxels) was identified within the right amygdala, the third cluster ($n = 293$ voxels) was identified within the left amygdala and the last cluster ($n = 137$ voxels) was identified within the left postcentral gyrus.

Figure 13. *Amygdala to Whole Brain Pre-Treatment Neutral Script Controlling for Under-Modulation*



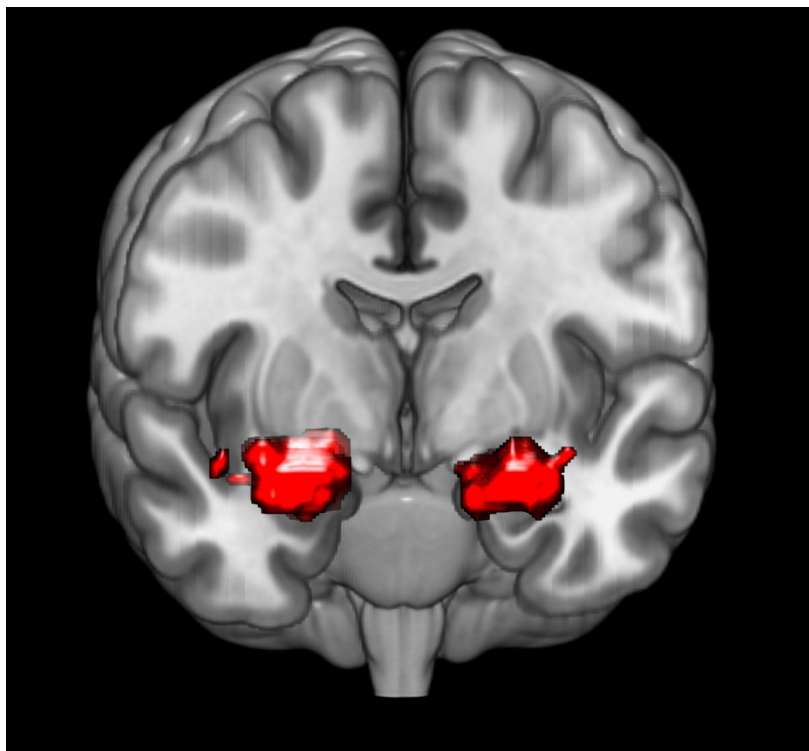
The relationship between under-modulation and the pre-treatment autobiographical trauma script yielded one statistically significant cluster at a threshold of $Z > 3.1$, $p = 0.05$. This cluster ($n = 197$ voxels) was identified within the left amygdala (see Figure 14).

Figure 14. *Amygdala to Whole Brain Pre-Treatment Trauma Script Controlling for Under-Modulation*



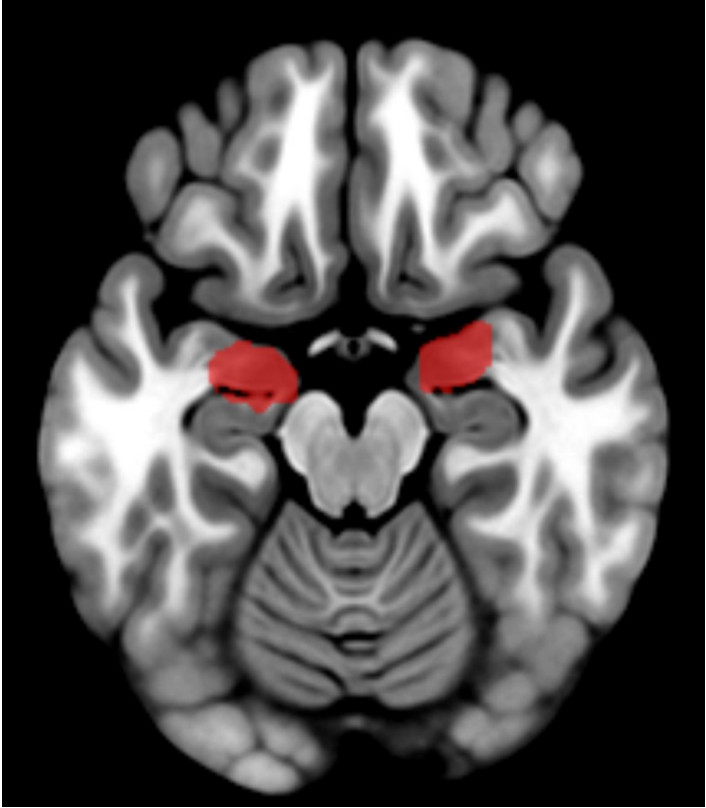
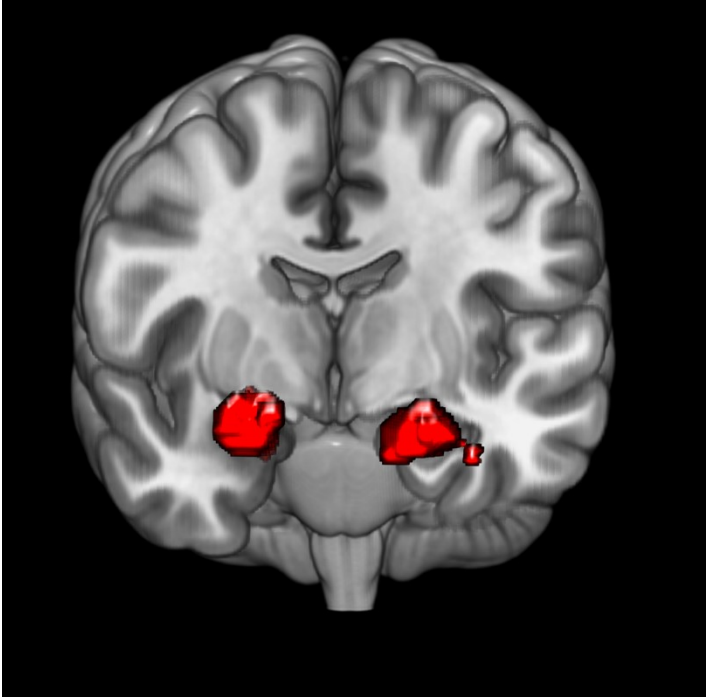
The relationship between under-modulation and the post-treatment autobiographical neutral script yielded two statistically significant clusters when thresholded at $Z > 3.1$, $p = 0.05$ (see Figure 15). The larger cluster ($n = 555$ voxels) was identified within the right amygdala and a relatively smaller cluster ($n = 426$) was identified within the left amygdala.

Figure 15. *Amygdala to Whole Brain Post-Treatment Neutral Script Controlling for Under-Modulation*



The relationship between under-modulation and the post-treatment autobiographical trauma script yielded two statistically significant voxels when thresholded at $Z > 3.1$, $p = 0.05$ (see Figure 16). The first ($n = 319$ voxels) cluster was identified within the right amygdala and the second cluster identified was within the left hippocampus.

Figure 16. *Amygdala to Whole Brain Post-Treatment Trauma Script Controlling for Under-Modulation*



When looking to the relationship between under-modulation and the interactions between time points and conditions, no clusters were identified as statistically significant with a threshold of $Z > 3.1$, $p = 0.05$.

3.5 Hypothesis 4

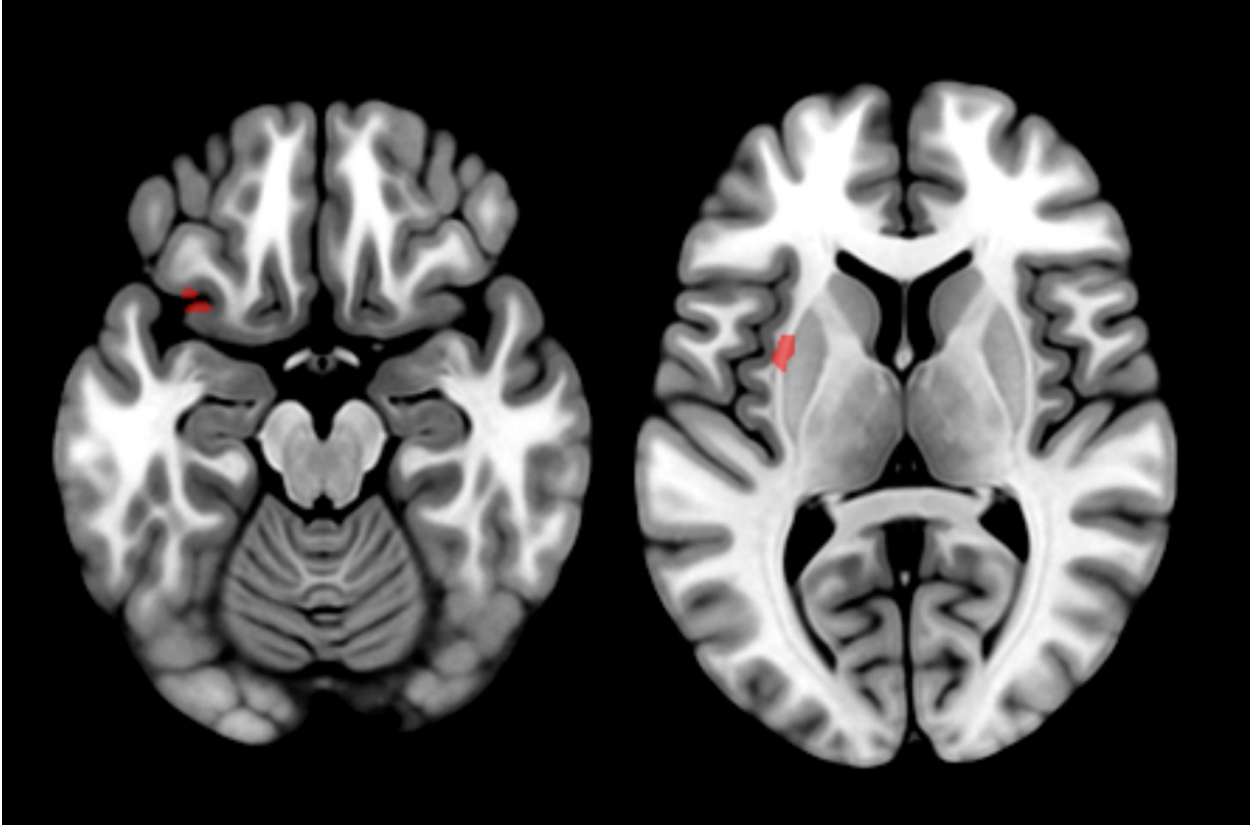
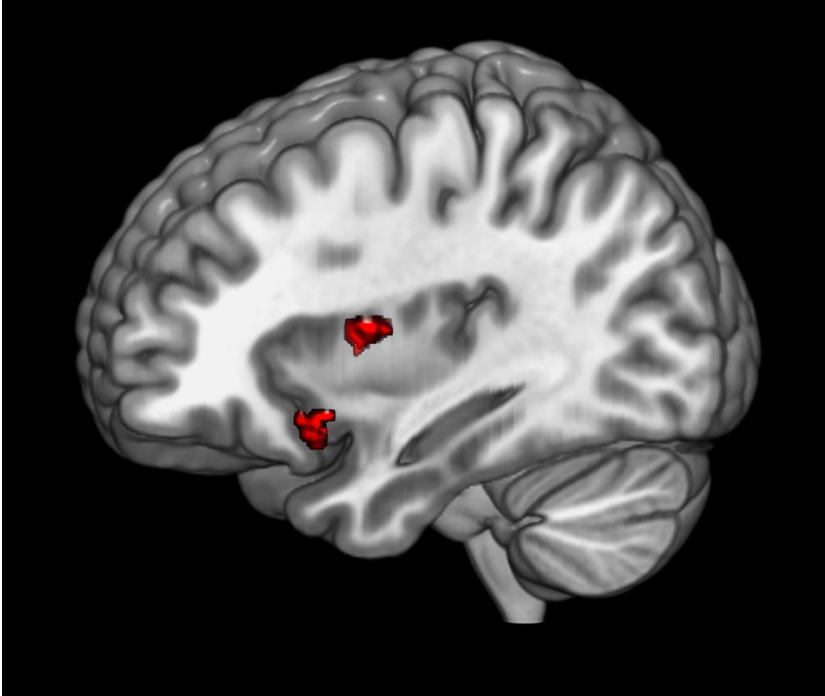
When looking to the magnitude of changes of symptoms in comparison to the magnitude of changes in functional connectivity, no significant findings emerged. All symptom measures (including depression, anxiety, stress, difficulties in emotion regulation, depersonalization, derealization and flashbacks) were examined with each individual condition and time as well as interactions and no significant findings emerged at the $Z > 3.1$, $p = 0.05$ threshold.

3.6 ROI Analysis

Given the small sample size, an analysis was completed to further examine the relationship between the amygdala, insula and prefrontal structures. This was completed by creating a mask of the insula and prefrontal structures then running the same functional connectivity analysis noted above, from amygdala to this mask, across time points and conditions. This limited the number of required corrections for multiple comparisons, as the regions denoted were much smaller than the whole brain analysis and allowed any relationships which may have been just under the level of significance to emerge.

Within this analysis, results identified two clusters during the post-treatment autobiographical neutral script, one in the left dorsal dysgranular insula and one in the left ventral agranular insula (see Figure 17).

Figure 17. *Masked Analysis Post-Treatment Neutral Script*



Another cluster was identified in the post-treatment autobiographical trauma script in the right amygdala (see Figure 18). With regard to interactions, there was one significant cluster within the right dorsal agranular insula when looking within the autobiographical trauma script subtracting post-treatment connectivity from pre-treatment connectivity (see Figure 19; see Table 7 for full results of this analysis).

Figure 18. *Masked Analysis Post-Treatment Trauma Script*

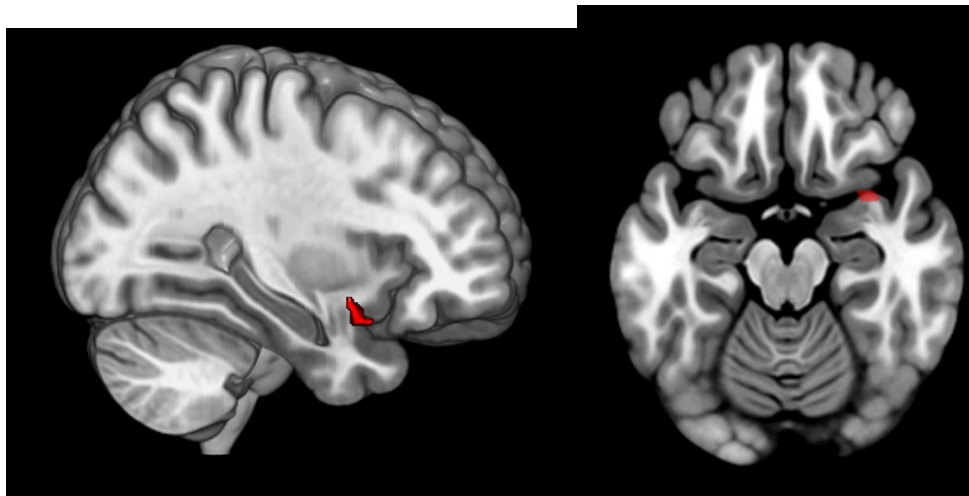
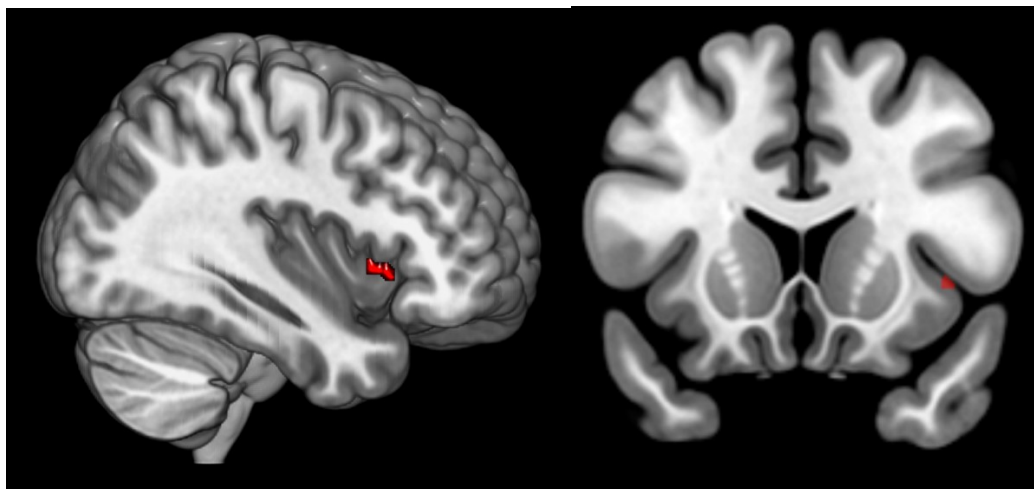


Figure 19. *Masked Analysis Pre-Treatment Trauma Script – Post-Treatment Trauma Script*



When looking to other analyses including; at each time point and condition (i.e., pre-treatment autobiographical neutral script, pre-treatment autobiographical trauma script, etc.), interactions between conditions (i.e., pre-treatment autobiographical neutral script versus post-treatment autobiographical neutral script, etc.), and the effect of over- and under-modulation on all individual factors and interactions, no significant clusters were identified.

3.7 Manipulation Check

The PANAS-X (Watson & Clark, 1994) was implemented prior to and immediately following the MRI scanning procedure as a manipulation check for the traumatic script. Within the pre-treatment time point there was a significant difference between pre-scan general positive affect ($M = 23.92$, $SD = 6.09$) and post-scan general positive affect ($M = 14.85$, $SD = 3.56$); $t = 5.57$ (12), $p < 0.001$ in that participants were less positive following the scanning procedure. Within the pre-treatment scan, there was a significant difference between pre-scan general negative affect ($M = 21.00$, $SD = 9.67$) and post-scan general negative affect ($M = 27.15$, $SD = 3.25$); $t = -3.45$, $p = 0.005$ in that participants were more negative following the scanning procedure.

When looking to the post-treatment scan, there was no significant difference between pre-scan positive affect ($M = 27.31$, $SD = 3.26$) and post-scan positive affect ($M = 27.15$, $SD = 2.43$); $t = 0.089$, $p = 0.931$. There was also no significant difference between pre-scan negative affect ($M = 17.69$, $SD = 2.32$) and post-scan negative affect ($M = 15.15$, $SD = 1.72$); $t = 1.70$, $p = 0.115$.

CHAPTER 4 - DISCUSSION

4.1 Outcome Measures

Results suggest there were no significant differences between participants who completed all stages of the study and those who did not come to the treatment program. This would suggest there was no significant sampling bias within the self-selection of participants who came to treatment, meaning that participants who came to treatment would not have been fundamentally different from the participants who decided not to come to treatment in respect to the demographic and symptom variables examined.

Overall, there were significant changes in all symptom levels from pre-treatment to the end of treatment, in that the severity of symptoms decreased following the participation in the MHDTP. On a symptom level, depression scores showed a significant change from orientation to pre-treatment, pre-treatment to post-treatment and orientation to post-treatment. This was the only symptom scale with significant changes from the waitlist timepoint to pre-treatment, indicating there were symptom changes before the start of treatment. There are numerous possible reasons for this change. It is possible participants were taking part in other treatments prior to the start of the MHDTP, which may have lowered their symptoms of depression, or that the first time point was not representative of their general symptoms. However, while the change between these scores was significant, there may not be a meaningful difference between the two time points. Based on the scoring scale, orientation scores were classified as ‘severe’, while pre-treatment levels fell in the ‘moderate to severe’ range, indicating the level of symptom severity was still elevated to a point well above normal prior to the start of treatment, while post-treatment scores dropped to a ‘mild’ classification.

Both orientation and pre-treatment anxiety scores were classified as ‘extremely severe’, which reduced to ‘moderate’ (a two-category decrease) at post-treatment. Although still elevated from ‘normal’ (by two-categories), this change in classification would suggest a meaningful decrease in anxious symptoms. From these results, we can infer that anxiety scores are unlikely to have dramatic changes in classification based on time alone and may be considered a stable symptom. If this were to be true, it would suggest the treatment had a large impact on these scores as there was a significant change in symptom levels post-treatment. Similarly, stress changed from an orientation and pre-treatment classification of ‘severe’ to a post-treatment classification of between ‘normal’ and ‘mild’. This may also be a consistent phenomenon which is stable over time and decreased quite significantly following intervention.

In regard to difficulties in emotion regulation, the DERS scale (Gratz & Roemer, 2003) used assesses symptoms of non-acceptance of emotional responses, lack of emotional clarity, difficulties with goal directed behaviors, lack of impulse control, lack of emotional awareness and emotional regulation. For this thesis only the total score was used, a measure compiling the scores of the aforementioned symptoms. Results suggest there was a significant improvement in emotion regulation following the treatment program. This would imply that the MHDTP allows for the development of emotion regulation capabilities and lessens these symptoms in comparison to time alone as there were no significant changes from orientation to pre-treatment.

Symptoms derived from the MID (Dell, 2006) include depersonalization, derealization and flashbacks. Depersonalization and derealization would commonly be classified as symptoms of over-modulation, while flashbacks are a symptom of under-modulation of emotions. Results of this thesis suggest no significant differences between orientation and pre-treatment, but there were significant decreases in these symptoms at post-treatment. This would imply that these

changes are not regressions towards the mean but are due to the treatment itself suggesting the treatment program may be effective for patients who experience either emotion over-modulation or under-modulation.

When looking to the results of symptom measures directly following the scanning procedure, results would suggest there were significant changes in under-modulation and avoidance during the mood induction, but there were no significant changes in levels of over-modulation. This may be consistent with previous literature which has suggested dissociation in the form of over-modulation is resistance to change. This is also consistent with research suggesting levels of over-modulation did not impact general treatment outcomes (i.e., Resick et al., 2012; Braakmann et al., 2007; Kröger, 2002), as the over-modulation scores remained elevated following treatment and the remainder of the scales showed improvement.

This is interesting to note over-modulation did not change between pre-and post-treatment scans when measured by the RSDI (Hopper et al., 2007), but measures of depersonalization and derealization (two concepts integrated within over-modulation) did change from pre-to post-treatment. There are numerous reasons this may have taken place, the most notable being the timing of the questionnaires. The RSDI (Hopper et al., 2007) was only measured immediately following the scanning procedure and was interested in what took place during the question cues, while the depersonalization and derealization measure asked about general instances of symptoms. It is possible that overall participants felt they were less likely to depersonalize or derealize following treatment, but when confronted with the scenario presented in this manner, they still experienced these symptoms. It is also possible that given the number of questions within the depersonalization and derealization scores, these concepts are more robust than that of over-modulation used as this consisted of only 4 questions. Therefore, it is possible

that depersonalization and derealization scores are gaining insight into an area which has not been addressed within the over-modulation score.

Additionally, when examining the manipulation check as measured by the PANAS-X (Watson & Clark, 1994), at the pre-treatment scan there were significant differences between the pre- and post-scan positive and negative affect in that positive affect was decreased while negative affect was increased. This would suggest there was a significant manipulation from the traumatic scripts and would suggest the scripts induced negative emotions. However, when looking to the changes in affect within the post-treatment scan, there were no significant changes from pre- to post-scan within either positive or negative affect. This would suggest that these the traumatic event did not have a significant effect on affect following treatment. This is important to consider as it is possible the post-treatment scan did not induce the same feelings as the pre-treatment scan. While it is possible that these changes in affect may be the result of better coping mechanism while in the scanner (i.e., less over- or under-modulation and more presence of working through emotions), it is also possible that participants were not as attuned to the trauma and may be been de-sensitized following the treatment.

Overall, the results would suggest participants experienced significant changes in their symptomatology between the start and end of treatment, suggesting the treatment improved symptom levels. Although an aim of the current study was to address the possibility of treatment matching in the future, the small sample size limits this ability. Future research should aim to gather more participants and examine the components of the treatment program separately to parse out which components are specifically related to the treatment outcomes. In using differing treatment approaches it helps to address as many areas as possible but does not allow for easy separation of treatment aspects to identify the key mechanisms of change. Previous research

within the MHDTP has examined changes in symptoms, such as improvements in attachment style and interpersonal functioning (Kinley & Reyno, 2013), there has been limited research examining the phasic model of treatment. A review of the treatment program described the possible areas of change which may contribute to the differing symptomatology including the initial down-regulation of hyperarousal, and the stabilization phase which targets the core emotional pathology and focuses on reintegrating dysregulated circuitry with the consolidation of regulation mechanisms (Kinley & Reyno, 2016). Future research should seek to examine the phases of treatment independently and should employ symptoms measures regularly to examine the phases of change within populations who over- and under-modulate.

Previous research examining the changes in treatment outcomes within populations of participants with BPD have suggested this may be a difficult population to treat given its resistance to change and has suggested there may be high drop-out rates within populations with BPD (McMurren, 2010; Barnicot et al., 2010). The current study had a relatively small drop-out rate and found changes within all symptoms scores from pre- to post-treatment and from baseline to post-treatment. This would suggest this treatment is effective for this population and given the difficulty in identifying effective treatments in the past (Korzekwa et al., 2009), it may be beneficial to examine the effects of specific components of this treatment program in the future.

4.2 Functional Imaging Outcomes

Although the results of the fMRI component of this study are limited due to small sample sizes, overall results suggest differing patterns for each condition and time point. Broadly, clusters were identified within the amygdala to whole brain analysis within each condition at each time point, as well as an interaction at pre-treatment in comparing the neutral to trauma

script, and at each condition at each time point when examining the effect of under- and over-modulation, as well as two clusters identified within the analysis using a masked region.

The results identify the left and right amygdala within the majority of the analyses, although this is more consistent with an analysis check. Because this analysis used a combined left and right amygdala seed region as a starting point to the whole brain analysis, this is not surprising and indicates that voxels around the ROI were strongly correlated with it. Research suggests the amygdala is strongly tied to emotion, a central aspect of this thesis and the main reason it was chosen as the seed region. Other roles of the amygdala include perception, interoception and it is commonly activated during tasks involving subjective emotional pictures (Fan et al., 2016). Other regions of interest identified through this analysis include the nucleus accumbens, the left and right hippocampus, the postcentral gyrus, dorsolateral middle temporal gyrus, the left and right precentral gyrus, the left dorsal dysgranular insula, the left ventral agranular insula, the right dorsal agranular insula and right cerebral cortex.

The nucleus accumbens is generally associated with the addiction/ reward pathway and it is thought the nucleus accumbens is involved in integrating sensory and emotional information to guide motor outputs (Roitman, Wheeler, Wightman & Carelli, 2008). The Human Brainnetome Atlas (Fan et al., 2016) suggests this area has also been associated with emotions (including happiness, fear and sadness), perception and cognition. Within the amygdala to whole brain analysis, the nucleus accumbens was identified as an area functionally connected with the amygdala during the pre-treatment trauma script, and also showed significant functional connectivity with the amygdala within the pre-treatment trauma script when controlling for emotion over-modulation.

The nucleus accumbens has also been suggested to be involved in emotional learning. With its role during the pre-treatment trauma scripts as well as when examining over-modulation, the nucleus accumbens may provide evidence for the learned function of emotion over-modulation. This response may be learned to aid in the avoidance of overwhelming emotions or traumatic events and therefore might be more commonly present when used as a way to regulate emotions when learned early in life.

The hippocampus is associated with a number of behavioral domains including cued explicit recognition, emotions, perception, cognition, explicit memory, paired recall, episodic recall and imagined objects or scenes (Fan et al., 2016). Within the present study, the activation time course of the hippocampus was correlated with the activation time course of the left and right amygdalae during the pre-treatment trauma script, as well as during the post-treatment trauma script when controlling for under-modulation. This finding is consistent with the domains noted above, as participants who were re-experiencing their event were likely imagining the scene and were experiencing episodic recall.

The hippocampus also plays a role in the regulation of the stress response. This would be important for our current research as this area was found to be co-activated during the trauma scripts at both pre- and post-treatment, with post-treatment only when examining under-modulation. During these scripts it's likely the participants were under more stress than during the neutral script and were likely trying to modulate that stress either through over- or under-modulation by attempting to control their stress response. The activation of the hippocampus therefore helps to provide more information for the under-modulation symptoms, it's possible that although their stress response may be attempting to regulate emotions, participants are unable to

exert this control appropriately when experiencing under-modulation which would therefore result in an overwhelming amount of emotions (presenting as re-experiencing and flashbacks).

In the present study, the post-central gyrus was identified as co-activated with the amygdala when subtracting the pre-treatment trauma script from the pre-treatment neutral script. Within this comparison, the remaining activation would be the effect of the traumatic nature of the script, all aspects of reading the cues and any effect of being inside the MRI scanner should be removed as those would be consistent across both conditions. This finding is consistent with the general role of the post-central gyrus, as participants were likely to be experiencing emotion and may have been more aware of their own bodily sensations, given the nature of the cues. Within the Human Brainnetome database, the primary somatosensory cortex has been associated with subjective emotional picture discrimination, interoception, emotion, reading, imagined movement and action as well as recall (Fan et al., 2016).

Within the current study during the pre-treatment autobiographical neutral script, the amygdala to whole brain analysis controlling for emotion over-modulation analysis identified the dorsolateral middle temporal gyrus as co-activated with the amygdala. The dorsolateral middle temporal gyrus is thought to be involved in action and observation, viewing, semantic monitoring, word generation, cognition and language (Fan et al., 2016). During this task participants when participants were experiencing symptoms of over-modulation, they may have been more likely to be attuned to the cues and process rather than being attuned to their bodily sensations and the scenarios presented.

Within this study, the precentral gyrus was identified as co-activated during the pre-treatment neutral script when controlling for emotion under-modulation. The precentral gyrus is thought to be active when reading, imagining movement, in studies involving perception, vision,

cognition, language and executing actions (Fan et al., 2016). This would suggest that during this task, those who experienced symptoms under-modulation were likely imagining the movements and may have actively been moving slightly, executing said actions within the scanner. This result is consistent with the identified roles of the precentral gyrus, as these behaviors would be present when re-experiencing an event.

The left dorsal dysgranular insula and left ventral agranular insula were both identified within the amygdala to whole brain analysis, when restricting the whole brain analysis to a masked region of the insula and pre-frontal areas, and when examining the post-treatment neutral script. The left dorsal dysgranular insula is thought to be activated in perception, pain, motor tasks and discrimination while the left ventral agranular insula is thought to be associated with cognition, emotion and rewards tasks (Fan et al., 2016). These areas of the insula may have been more activated within the neutral script as participants may have been attempting to work through their scripts, using their perception of the scenario during the question cues and may have been more attuned to their emotions. At this stage it is likely the neutral script was not eliciting strong negative emotions, but it may have been associated with areas of perception, cognition and some emotions or reward of being almost complete the program and the scanning.

The right cerebral cortex is involved with information processing and processing sensory information (Fan et al., 2016). This area was identified within the masked analysis examining the post-treatment trauma script. This is consistent as individuals were likely attempting to process and remember the event but were less likely to be emotional at post-treatment following the treatment, consistent with why they would be more likely to be processing and analyzing the information.

The last area identified was the right dorsal agranular insula. This area is associated with action, memory, cognition, pain and somesthesia (Fan et al., 2016). When examining the result of the masked analysis within the autobiographical trauma script, subtracting the pre-treatment from post-treatment scans, the right dorsal agranular insula was identified as co-activated with the amygdala. Within this comparison, the remaining activation should be the effect of the treatment on the traumatic script, with the effects of the cues and all other aspects of scanning removed. This would intuitively make sense as participants were likely more attuned to their bodily sensations than prior to treatment and were more likely to be remembering the events and scripts than overwhelmed with emotions.

4.3 Study Strengths

A strength of this study would be the generalizability to other patients. This study intentionally used exclusion criteria which would be centered on the safety of participants for participating in an MRI. This would allow for the population to be as typical of a patient group as possible, meaning patients were not excluded based on past treatments, current medical conditions (with the exception of non-MRI safe procedures/implants) or diagnosis. While this can be a study limitation (see below), it was intended to ensure the study would be useful within clinical populations. Many research studies follow such constraints that real world patients rarely fit into such neat categories, this study intended to allow for some interpretation and was designed to fit most patients. However, it should be cautioned that the small sample size would limit the generalizability.

Following on this theme, participants were able to choose which events they felt elicited the most emotion or would likely be events they would react to by over- or under-modulating.

Participants discussed possible events with the researchers and followed the set criteria to write the events but were able to choose what they felt was most traumatic or neutral. This has advantages over set common scripts as for example common neutral scripts may elicit negative or positive emotions for some participants but may be truly neutral for others. This would then defy the purpose of the script and would add variability to the interpretations. By allowing participants to choose their own and write their own scripts, many chose events that were quite emotionally upsetting to write and elicited the modulation symptoms from the onset, an indication of how they may react during the fMRI scan.

Additionally, the question cues designed to elicit further emotion were beneficial to this study. While other studies have had participants read the script, or used images to elicit emotion while scanning, these are not consistent measures across individuals and can allow for a variation of the types of emotional responses elicited. In using the question cue design, the scanning procedure was standardized across participants but was individually tailored. Participants were encouraged to think of the same scenario for extended periods, but had reminders or cues as to what to concentrate on.

The use of a control period (i.e., the time from orientation to start of treatment) helps to validate that changes from the start of treatment to end of treatment are due to the treatment itself rather than effects due to time, or regression to the mean. In having this control period, we were able to verify that symptoms did not significantly change in this period, however there were significant changes from pre- to post-treatment. While we were unable to gather functional images during the control period for logistical reasons (such as cost, and likelihood of dropout), the longitudinal design of this study did allow for more information surrounding the persistence

of symptoms. This longitudinal design addressed the concerns of other studies (i.e., Krause-Utz et al., 2014) by examine how changes to this symptomatology may be viewed neurobiologically.

4.4 Study Limitations

Although this study has many strengths, a significant limitation is the small sample size. Although generally there are smaller samples within fMRI studies in comparison to other types of research, the sample of 13 participants within this study limits the generalizability of findings. Initially, it was expected that 20 participants would participate, however due to recruitment and time constraints this number was lowered. Ideally, it would have been beneficial to recruit a larger sample size in order to detect more robust effects and to increase power within the study and to allow for other comparisons. This sample contained participants who exhibited symptoms of both over- and under- modulation in response to traumatic or stressful stimuli and simply looked at the continuum of modulation. Due to the small sample size it was not possible to sort participants into two groups for comparison (i.e., over modulators versus under modulators). Given a larger sample size, it would be beneficial to have an equal number of participants who experienced each method of emotion modulation.

Another potential limitation would be that participants were not screened for co-morbidities, or other illnesses. It would be beneficial to know whether there were confounds in terms of diagnosis, and what these may be. Common to both PTSD and BPD is the experience of trauma, which is common in other populations as well. In having further information regarding diagnosis, it may be easier to identify whether it is the complex trauma which results in changes in neurobiology, the emotional response to trauma or another aspect of the disorders. It would also be beneficial to know what treatments patients had encountered before entering the MHDTP, during the waitlist time period and whether there were changes to medications

throughout treatment. If this were the case, there could be a confound of medications, as participants may have been taking medications during the pre-treatment scan and then may have had changes to their prescriptions throughout treatment which could affect blood flow during the post-treatment scan. Similarly, menstrual cycle phase was not controlled for, and was not recorded. This may impact emotional response as well as functional connectivity during the mood induction procedure and should be taken into account in future research.

It is possible that the self-reported modulation during each of the scripts did not accurately represent what actually occurred. Although this is a common complaint among self-reported symptom scales, there are not many other ways to test for modulation. Some studies report heart rate as a possible objective measure, as individuals who over-modulate are less likely to have an increase in heart rate compared with those who under-modulate. However, some literature on Photoplethysmogram (PPG) devices within fMRI protocols suggests there is debate surrounding its accuracy, as PPGs can be sensitive to artifacts including ambient electromagnetic signals, temperature and motion or vibrations, thereby potentially reducing accuracy (Elgendi, 2012).

4.5 Future Directions

Future research examining emotion modulation using fMRI should seek to examine modulation in a number of contexts. While scripts are most commonly used within this field, other techniques to elicit these reactions may be beneficial to ensure the validity of the techniques and to gain further information about emotional responses in various contexts. It would also be beneficial to attempt to standardize the use of mood induction tasks so that studies may be compared more readily, and information can be interpreted easier across designs.

An important consideration for future analysis would be the use of a comparison group. While this study employed a control for the treatment, using a comparison for patients with BPD would allow for more understanding as to the origin of neurobiological changes. Many studies examining over- and under-modulation use populations with histories of trauma and rarely are there comparison groups employed. It would be beneficial to examine the differences between BPD and PTSD and healthy controls with and without trauma. This would help to explain whether the differing neurobiology may be due to certain types or experiences in trauma, emotional responses or may be due to another aspect of BPD or PTSD entirely. Within this vain, having more information on the types and recurrence of trauma may be beneficial in examining the emotional responses, as individuals who have experienced more trauma or perceive their trauma as more severe may have differing neurobiological and symptom related responses to these scenarios. Additionally, examining the effect of under and over-modulation should be employed within a sample of male participants. There is limited research to date examining dissociation broadly within male populations and less examining the differences between males and females. This would be an important area to consider in the future as there may be differences between each population and they therefor may have differing treatment needs.

Another area for further analysis would a follow-up post-treatment. While it is beneficial to know how participants change between the start of treatment and the end, given the structure of the 6-week intensive group it would be important to know if positive changes persist over time. While patients are enrolled within the MHDTP, there is a set structure and routine which is changed once patients are discharged. It may be beneficial to know what supports patients need following this discharge and how this affects their treatment progress.

Additionally, the use of a measure of structural connectivity (e.g., Diffusion Tensor Imaging (DTI)) in the future may add to the understanding of connectivity within this population. In including both structural and functional measures, it would allow researchers to gain insight to how the white matter structural connectivity relates to the functional connectivity of patients with BPD as well as to examine any possible changes over the course of treatments.

Also adding other seed regions as areas of interest to examine. An example of a possible seed region to be examined in the future would be the insula. The insula is comprised of separate areas which may be involved in interoception and emotion regulation so it would be important to fully examine this role to add to the literature surrounding emotion processing.

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Appendix A. Common Neutral Script

Common Neutral Script

I walked over and saw a basket of clean laundry. I could smell how fresh it was. I decided to fold the laundry one item at a time. In picking up the first item, I could feel its warmth. First, I picked up a grey shirt. I folded the shirt and placed it beside the basket. Next, I found a white sock. I searched the basket for the matching sock and put those on top of the shirt. I looked back in the basket and noticed another grey shirt. I folded this shirt. I noticed that the basket was almost empty. I picked up one of the last shirts and folded it. I placed the shirt with the others and reached for the last items in the basket, a set of matching socks. I picked up both socks and fold them together. These were the last items I placed on the side. Now that all my folding is finished, I put the items back in the basket.

Appendix B. Question Cues

Question Cues

Participants were first cued by a screen which read “You will now be presented with cues that will help you reflect more on the situation you just read.” Then the following prompts appeared on the screen, each cue was presented as the only item on screen for 30 seconds with the exception of the first prompt which was presented for 11 seconds, to accommodate for the length of the length of scanning (i.e., 6 minutes, 11 seconds).

Recall your script in detail. Imagine yourself back in this event.

Imagine in as much detail as possible everything you saw during the event.

Imagine in as much detail as possible everything you heard during the event.

Imagine in as much detail as possible everything you touched during the event.

Imagine in as much detail as possible everything you smelled during the event.

Imagine in as much detail as possible the bodily sensations you experienced during the event.

Imagine in as much detail as possible everything you thought during the event.

Imagine in as much detail as possible all the emotions you felt during the event.

Imagine in as much detail as possible everything you did during the event.

Imagine in as much detail as possible what you were thinking immediately after the event.

Imagine in as much detail as possible all the emotions you felt immediately after the event.

Imagine in as much detail as possible everything you did immediately after the event.

Imagine in as much detail as possible the bodily sensations you experienced immediately after the event.

Appendix C. CONSORT Flow Diagram

CONSORT Flow Diagram

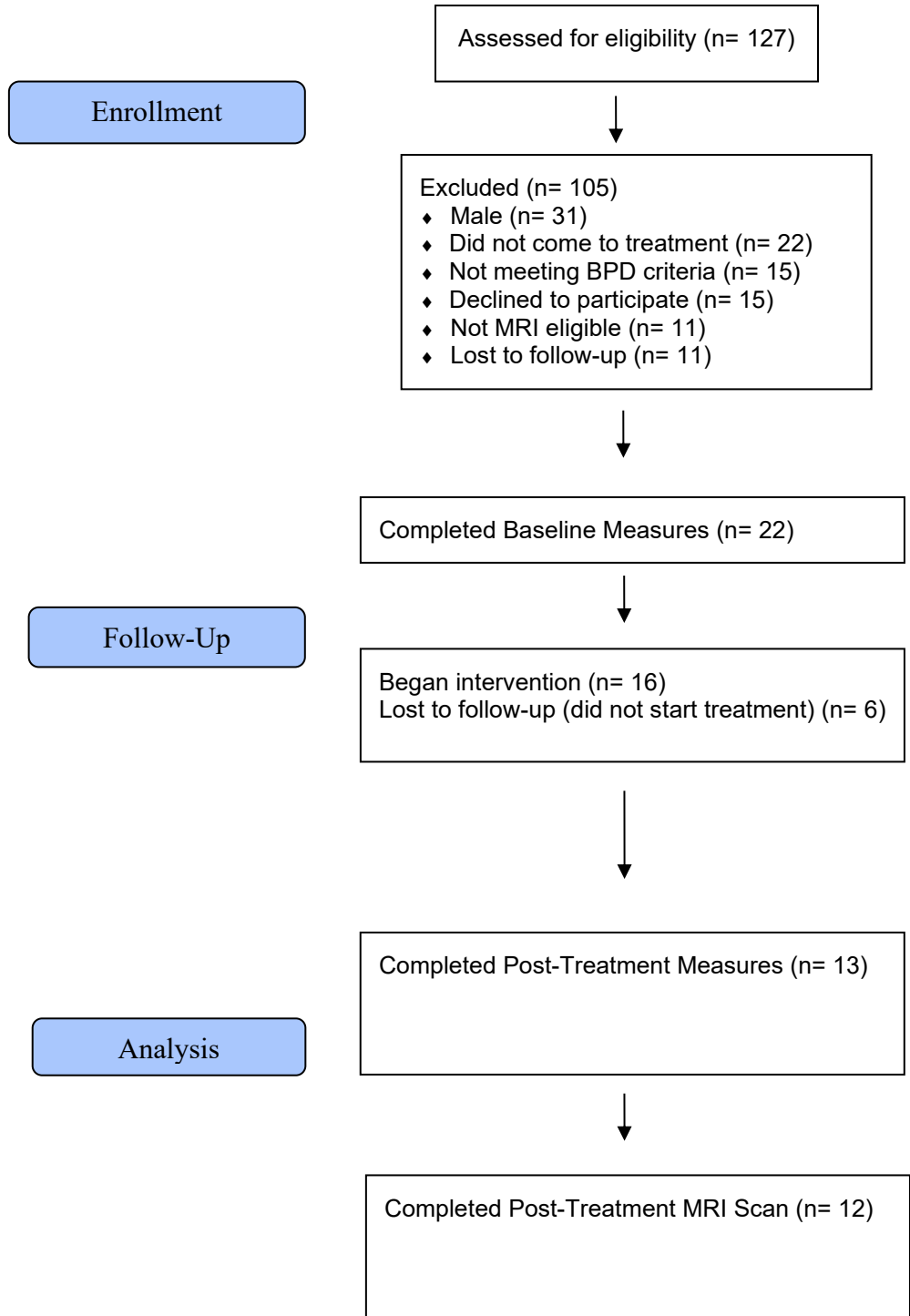


Table 1

Sample Descriptive Statistics

Demographic	<i>N</i>	Percent
Race		
Caucasian	11	84.6 %
Aboriginal	2	15.4 %
Education		
High School/ Equivalent	4	30.8 %
Bachelor's Degree	4	30.8 %
Some University	3	23.1 %
Vocational/ Technical	2	15.4%
Employment Status		
Employed Full-Time	6	46.2 %
On Disability	5	38.5 %
Part-Time Student	1	7.7 %
Unemployed	1	7.7. %
Marital Status		
Married/ Living with Partner	9	69.2 %
Single/ Never Married	3	23.1 %
Separated/ Divorced	1	7.7 %

Table 2

Symptom Differences Between Orientation Only and Treatment Completers

Measure	Treatment M (SD)	Waitlist M (SD)	t	p
Depression	25.85 (7.04)	30.44 (11.08)	-1.19	0.25
Anxiety	21.69 (9.89)	23.11 (8.67)	-0.35	0.73
Stress	26.92 (7.15)	26.00 (6.25)	0.31	0.76
Emotion Regulation	127.92 (21.30)	121.33 (14.92)	0.80	0.43
Depersonalization	33.13 (17.35)	32.31 (20.43)	0.10	0.82
Derealization	29.10 (20.87)	25.54 (18.40)	0.41	0.68
Flashbacks	36.82 (22.77)	28.98 (28.23)	0.72	0.48

Note. Independent samples t-test between those who completed only the waitlist time point and who completed all stages of treatment, based on scores at the waitlist time point.

Table 3

Symptom Differences Across All Time Points

Measure	Baseline M (SD)	Pre-Treatment M (SD)	Post-Treatment M (SD)	Wilks' Lambda F (p)	Effect Size η_p^2
Depression	25.85 (7.04)	20.92 (7.33)	12.15 (11.82)	7.16 (0.010)	.566
Anxiety	21.69 (9.89)	21.69 (8.44)	11.38 (9.78)	9.64 (0.004)	.637
Stress	26.92 (7.15)	26.15 (8.43)	14.54 (9.65)	7.22 (0.010)	.567
Emotion Regulation	127.92 (21.30)	130.85 (17.32)	82.38 (30.51)	14.34 (0.001)	.723
Depersonalization	33.13 (17.35)	33.78 (15.78)	12.93 (10.24)	16.91 (<0.001)	.755
Derealization	29.11 (20.87)	28.60 (16.22)	14.68 (18.07)	3.72 (0.058)	.404
Flashbacks	36.82 (22.77)	32.68 (18.19)	14.93 (16.39)	16.29 (0.001)	.748
Functional Resilience	202.20 (31.72)	199.40 (33.26)	259.40 (36.91)	7.391 (0.015)	.649

Note. Repeated Measures ANOVA for completer-only sample of N=13.

Table 4

Amygdala to Whole Brain Results Per Condition

Condition	Location	Coordinate of z-max (x, y, z)	Z-max	p value	Size (# voxels)
Pre- Treatment					
Neutral Script					
	Left Amygdala	-22, -4, -20	7.66	1.67×10^{-22}	2456
	Right Amygdala	20, -2, -16	7.65	4.1×10^{-21}	2239
Trauma Script					
	Nucleus Accumbens	-32, -10, -12	5.95	8.37×10^{-18}	1958
	Right Hippocampus	28, -20, -16	5.95	1.01×10^{-16}	1789
Post-Treatment					
Neutral Script					
	Left Amygdala	-26, -6, -18	6.71	3.27×10^{-18}	1807
	Right Amygdala	20, -8, -12	6.45	4.3×10^{-18}	1790
Trauma Script					
	Right Amygdala	26, 0, -18	6.59	3.98×10^{-17}	1863

Left Amygdala	-24, -8, -18	6.36	4.52×10^{-17}	1709
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Table 5

Amygdala to Whole Brain Results Across Conditions

Condition	Location	Coordinate of z-max (x, y, z)	Z-max	p value	Size (# voxels)
Pre-Treatment					
Neutral – Trauma					
	Post Central Gyrus	32, -36, 66	4.03	0.00171	175
	Post Central Gyrus	-50, -10, 58	4.03	0.00231	167

Table 6

Amygdala to Whole Brain Results Controlling for Over-Modulation

Condition	Location	Coordinate of z-max (x, y, z)	Z-max	p value	Size (# voxels)
Pre- Treatment					
Neutral Script					
	Left Amygdala	-22, -4, -20	6	2.25×10^{-8}	576
	Right Amygdala	20, -2, -16	6.95	5.96×10^{-8}	530
	Dorsolateral Middle Temporal Gyrus	-56, -58, 8	4	0.0166	123
Trauma Script					
	Nucleus Accumbens	-32, -10, -12	4.21	0.00862	156
	Right Amygdala	24, -4, -20	4.26	0.0135	143
Post- Treatment					
Neutral Script					
	Right Amygdala	26, -4, -20	5.71	1.05×10^{-8}	611
	Left Amygdala	-26, -6, -16	5.59	1.79×10^{-7}	491

Trauma
Script

Right Amygdala	22, -6, -18	5.66	1.79×10^{-6}	429
Left Amygdala	-24, -8, -18	5.03	9.3×10^{-6}	367

Table 7

Amygdala to Whole Brain Results Controlling for Under Modulation

Condition	Location	Coordinate of z-max (x, y, z)	Z-max	p value	Size (# voxels)
Pre- Treatment					
Neutral Script					
	Right Precentral Gyrus	56, -6, 34	4.56	3.16×10^{-10}	763
	Right Amygdala	20, -2, -16	5.23	3.34×10^{-5}	305
	Left Amygdala	-22, -4, -20	5.25	4.8×10^{-5}	293
	Left Postcentral Gyrus	-54, -26, 54	4.47	0.00971	137
Trauma Script					
	Left Amygdala	-28, -6, -16	4.67	0.00215	197
Post- Treatment					
Neutral Script					
	Right Amygdala	22, -4, -20	5.2	5.96×10^{-8}	555
	Left Amygdala	-26, -4, -18	5.33	1.25×10^{-6}	426

Trauma

Script

Right Amygdala	26, 0, -18	5.13	3.32×10^{-5}	319
Left Hippocampus	-22, -10, -20	5.15	8.96×10^{-5}	285

Table 8

Amygdala to Whole Brain Results with Masked Region

Condition	Location	Coordinate of z-max (x, y, z)	Z-max	p value	Size (# voxels)
Post-Treatment					
Neutral Script					
	Left Dorsal Dysgranular Insula	-32, 2, 10	3.77	0.0287	47
	Left Ventral Agranular Insula	-34, 16, -18	3.98	0.0376	42
Trauma Script					
	Right Cerebral Cortex	30, 6 -18	4.51	0.0042	27
Trauma Script					
Pre – Post Treatment	Right Dorsal Agranular Insula	40, 18, -2	3.4	0.0106	22