

Neuroimaging and Neurocognitive Assessment of PTSD and MDD in a South African  
Community Setting

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## Abstract

*Background:* There is growing evidence of abnormalities in neurocognition, neuroanatomy, and functional connectivity in posttraumatic stress disorder (PTSD) and major depressive disorder (MDD). However, there has been less work on individuals who suffer with comorbid PTSD and MDD. It is important to investigate the neurobiology of this overlap because of its prevalence, its associated morbidity, and the hope that it may shed more light on the mechanisms involved in each disorder, including the role of the prefrontal regions. This dissertation tests the hypothesis that women with PTSD and MDD display distinct patterns of neurocognitive impairment and associated brain dysfunction, relative to healthy controls, and these effects will be amplified in patients with both disorders.

*Methods:* This dissertation was undertaken within the Drakenstein Child Health Study, a study exploring child health determinants in mother-infant dyads from the Drakenstein district, Western Cape. Mothers (between 18 and 50 years) were recruited and divided into 4 groups: PTSD, MDD, PTSD with MDD, and healthy controls. Participants were assessed using the computerised NIH Toolbox, and paper and pencil neurocognitive tests. Domains assessed included memory, learning, and processing speed, and with particular focus on executive function and attention domains. Participants underwent resting-state functional imaging as well as structural brain imaging. Functional connectivity within and between cognitive control networks (salience network, dorsal attention network, and frontoparietal networks) and a default mode network were compared across the 4 groups. Neuroanatomical indices (cortical thickness, volume, and surface area) of 10 frontal cortical regions from the Desikan-Killiany atlas in Freesurfer 6 were analysed across the 4 groups.

*Results:* All three clinical groups demonstrated no group differences on measures of attention and executive function, diagnoses of PTSD and MDD were associated with more intrusive thoughts and delayed recall impairment, respectively. However, neurocognitive findings indicate that PTSD with comorbid MDD is not associated with greater neurocognitive dysfunction relative to mono-diagnostic groups. Abnormal resting-state connectivity was observed for the MDD group in the default mode network, and for both comorbid and MDD patient groups within frontoparietal networks. Abnormal salience network connectivity for the comorbid group was observed when examining performance on the Pattern Comparison Processing Speed test. No between-network connectivity group differences were observed. Surface area and volume

reductions of prefrontal regions were evident for PTSD and MDD, however, no volumetric and surface area differences were observed for the comorbid group.

*Conclusion:* In this sample of mothers from a low-middle income region, distinct patterns of neurocognitive dysfunction and impairment in PTSD, MDD, and PTSD with MDD were observed. However, contrary to hypotheses, comorbidity is not associated with greater dysfunction and impairment and the associations of PTSD and comorbid MDD are not amplified in this sample. These findings have implications for the development of treatment plans for patients diagnosed with PTSD, MDD, and PTSD with comorbid MDD, so that interventions are tailored in a way that is responsive to differences between these groups in the presentation of neurocognitive profile, brain function, and structure.

*Keywords:* neurocognition; neuroimaging; resting-state; structural; comorbidity

## **Chapter 1**

# **Neurocognitive assessment and neuroimaging of PTSD, MDD, and PTSD with MDD: a literature review**

Posttraumatic stress disorder (PTSD) and major depressive (MDD) are two of the most prevalent and burdensome of the common mental disorders, and they frequently occur together, further contributing to the high impairment associated with each. In recent decades, studies using neurocognitive testing and neuroimaging have shed light on the neurobiology of these two conditions. However, relatively little of this research has focused on PTSD with comorbid MDD. There is also a particular need for research on women and mothers with PTSD and MDD. This thesis aims to address these gaps, and so to pave the way to better treatment of these conditions, including better treatment of comorbid MDD and PTSD.

In this introductory chapter, I review the literature in this area. I begin by covering the neurocognitive research of PTSD, MDD, PTSD with MDD. I then go on to discuss neuroimaging studies, including both resting-state functional magnetic resonance imaging (rs-fMRI) and structural neuroimaging in PTSD, MDD, and PTSD with MDD. I consider both advances in our knowledge, as well as remaining gaps, and the importance of addressing them. This literature provides a rationale for subsequent chapters of this dissertation, which address the neurocognitive, resting-state functional MRI and structural neuroimaging of PTSD, MDD, and PTSD with MDD in mothers. I begin by briefly describing each of these conditions.

## **PTSD and MDD**

Posttraumatic stress disorder is now known as a trauma- and stressor-related disorder that may develop after exposure to a traumatic event- an event that is perceived to be a threat to one's body and/or mortality (American Psychiatric Association, 2013). According to the DSM-IV, in addition to experiencing a fear-inducing traumatic event, the patient needs to experience symptoms belonging to three symptom clusters in order to be diagnosed (American Psychiatric Association, 2000). These symptom clusters are: (a) re-experiencing/intrusions (recurrent recollections or dreams of the index event), (b) avoidance/numbing (avoidance of stimuli associated with the event), and (c) arousal (difficulty concentrating and sleeping, hypervigilance) (American Psychiatric Association, 2000). The DSM-5 has since changed the classification of PTSD from a trauma- and stress-related anxiety disorder, to a trauma- and stressor related disorder, thereby removing the disorder from the anxiety disorders. Furthermore, the DSM-5 criteria has removed the fear-based response to the index event, in addition to adding 3 new



symptoms to the DSM-IV symptom clusters (persistent and distorted cognitions about the event that leads the patient to blame themselves/others; persistent negative emotional state; and reckless/self-destructive behaviour) (American Psychiatric Association, 2013)<sup>1</sup>. In addition to these symptoms required for diagnosis, PTSD is also frequently associated with a number of neurocognitive deficits, such as memory impairments and executive dysfunction (Scott et al., 2015). These neurocognitive deficits are associated with impaired daily functions and quality of life (Insel, Morrow, Brewer, & Figueredo, 2006). This will be explored in detail below.

Major depressive disorder is a disorder that may be characterized by depressed mood, suicidality, anhedonia, reduced energy, a change in activity, appetite and sleep patterns (American Psychiatric Association, 2000). In order to be diagnosed with MDD, patients need to present with a minimum of 5 symptoms during the same two week period, and at least one of the symptoms must be depressed mood or loss of interest/pleasure (American Psychiatric Association, 2000). Meta-analyses have shown that MDD also presents with a variety of neurocognitive difficulties, such as difficulties with concentration and attention, as well as memory impairments (Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Lim et al., 2013; Rock, Roiser, Riedel, & Blackwell, 2014). Additionally, neurocognitive impairment in depression has been shown to be associated with social and occupational impairments (Evans, Iverson, Yatham, & Lam, 2014; McIntyre et al., 2013).

PTSD and MDD are common in community samples. For example, the National Comorbidity Survey conducted in the USA reported that lifetime PTSD prevalence estimates were approximately 7.8%, and women were twice as likely to develop lifetime PTSD than men (10.4% versus 5%, respectively) (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Furthermore, in South Africa, 3.5% of individuals exposed to a traumatic event will develop PTSD, based on data collected from a nationally represented sample (Atwoli et al., 2013). According to the National Comorbidity Survey Replication study, approximately 16% of the American sample develop lifetime MDD (Kessler et al., 2005). From a nationally representative sample, the South African Stress and Health (SASH) study, reported that approximately 9.8% of respondents develop lifetime MDD (Herman et al., 2009).

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<sup>1</sup> The DSM-IV criteria were utilised in this research as the DSM-5 had not yet been published, and materials had not been updated with the new criteria at the onset of the present study

Evidence suggests that PTSD and MDD are highly comorbid disorders, although exact prevalence estimates vary between studies and samples (Brady, Killeen, Brewerton, & Lucerini, 2000; Kaufman & Charney, 2000; O'Campo et al., 2006). For example, in the National Comorbidity Survey, conducted in USA, Kessler et al. (1995), found that of the 10.4% of women who presented with lifetime PTSD, 48.5% also presented with comorbid lifetime MDD. In a Dutch civilian sample, Maes, Mylle, Delmeire, and Altamura (2000) found that 26% of PTSD patients also presented with comorbid MDD. In community samples, PTSD with comorbid MDD is also common amongst female participants (Horesh et al., 2017; Rytwinski, Scur, Feeny, & Youngstrom, 2013; Stein & Kennedy, 2001). These studies provide strong evidence that PTSD and MDD are highly comorbid disorders. Moreover, comorbid samples present additional challenges as they have consistently shown to be treatment resistant (Campbell et al., 2007; Flory & Yehuda, 2015).

Comorbidity is important for a number of reasons. First, patients with comorbid PTSD and MDD may have a worse course, with greater functional impairment being reported for these samples (Blanchard, Buckley, Hickling, & Taylor, 1998; Nijdam, Gersons, & Olf, 2013). Second, patients with comorbid PTSD and MDD may be less likely to respond to treatment and are less likely to remit than PTSD patients (Blanchard et al., 1998; Campbell et al., 2007; Flory & Yehuda, 2015). Third, while studying any mental disorder in isolation may yield useful insights, given that comorbidity appears to be crucially characteristic of mental disorders, its investigation of the mechanisms involved in comorbidity is crucial, and may ultimately further contribute to our understanding of individual conditions.

Fortunately, there have been advances in understanding the neurocognition and neurocircuitry of both MDD and PTSD. In the next sections of this chapter, I will review each of these areas of work. The focus of the neuroimaging review will be on rs-fMRI and structural MRI studies. Although there is also important literature on other imaging modalities and measures, they are not the focus of the work here.

## **Review of neurocognitive impairments in patients with PTSD, MDD, and PTSD with comorbid MDD**

**Executive function.** Executive function (EF) is a broad term used to encapsulate a variety of complex neurocognitive processes. Executive functions are known as ‘higher-level’ processes, and these processes generally include functions that are important for daily functioning, such as inhibition, planning, problem-solving, set-switching, decision making, flexible thinking, and working memory (Alvarez & Emory, 2006; Diamond, 2013; Porter, Bourke, & Gallagher, 2007). Commonly utilised measures of executive functioning include the Tower of London (planning), Stroop test (inhibition), Wisconsin Card Sorting test (set-switching), Trail Making Test B (set-switching), and Digit Span Backwards (working memory).

**Executive function in PTSD.** Studies illustrate that PTSD is associated with a variety of executive function impairments, such as set-switching, working memory, and inhibition impairments. Set-switching has shown to be impaired in PTSD in a systematic review of 18 studies conducted by Polak, Witteveen, Reitsma, and Olf (2012). In this review, PTSD participants ( $n = 422$ ) performed significantly worse on the Trail Making Test B and Wisconsin Card Sorting test, relative to trauma exposed and healthy controls ( $n = 658$ ). This study also suggested that neurocognitive impairment differences were determined by factors such as type of trauma; for example, EF impairments were the most profound in PTSD participants who were exposed to war or combat trauma compared to trauma-exposed and -naïve controls (Polak et al., 2012). Olf and colleagues (2014) measured performance on various subdomains of executive function in PTSD (flexibility and set-switching, planning and working memory) and found that subjects with PTSD ( $n = 28$ ) performed worse on subdomains such as flexibility and set-switching. Stein, Kennedy, and Twamley (2002) found that in a sample of female interpersonal violence (IPV) survivors, the PTSD group ( $n = 17$ ) performed worse on a set-switching task when compared to controls ( $n = 22$ ), as well as the Stroop test (measuring inhibition). However, this study found no significant group differences on measures of working memory, such as the digit span backwards and Rey-Osterrieth Complex Figure Test. Contrary to these findings, working memory appeared to be significantly impaired in a sample of 56 female combat veterans with PTSD, relative to 53 healthy controls (Stricker, Keller, Castillo, & Haaland, 2015). Furthermore, this study observed relative impairments in an executive functions composite measure which included working memory and inhibition/switching components (tests such as

digit span backwards and Color-Word inhibition and switching) (Stricker et al., 2015). In an all-male sample of 37 veteran participants, it was found that inhibitory control was impaired in the PTSD group ( $n = 18$ ) relative to combat controls ( $n = 19$ ), while measures of executive function without inhibitory control (including set-switching and working memory) were not significantly different between groups (DeGutis et al., 2015). In a recent meta-analysis, Scott et al. (2015) reported that PTSD is associated with small to moderate executive function impairments ( $d = -0.45$ ), relative to a control group.

Evidence suggests that PTSD veteran samples tend to exhibit working memory deficits, irrespective of gender. Vasterling et al. (2002) found that male veterans with PTSD ( $n = 26$ ) tend to be less proficient than controls on working memory tasks. However, this study did not explore other EF subdomains. Research by Stricker et al. (2015) concurs with the above findings, as female veterans with PTSD ( $n = 56$ ) tended to perform worse on working memory tasks, relative to healthy controls ( $n = 53$ ). Flaks et al. (2014) reported that in a sample of Brazilian participants, the PTSD group ( $n = 81$ ) did not show impairments of set-switching, nor working memory. However, PTSD participants were impaired on the Stroop Test, indicating impairment with inhibition (Flaks et al., 2014).

**Executive function in MDD.** General executive dysfunction is commonly reported in MDD (Godard, Baruch, Grondin, & Lafleur, 2012; Lee et al., 2012; Lim et al., 2013; Snyder, 2013). McIntyre et al. (2013) reported moderate deficits of working memory in MDD, citing evidence that deficits larger than one standard deviation below the normative mean can be found in 20 to 30% of MDD participants. According to a meta-analysis by Snyder (2013), in a sample of 113 studies, working memory was impaired in MDD, in addition to impairments of inhibition, set-switching and updating. Furthermore, increased depression symptom severity led to increased executive dysfunction in general, rather than impairments in specific EF subdomains (Snyder, 2013). Impaired inhibition is frequently reported in the MDD literature (Degl'Innocenti, Ågren, & Bäckman, 1998; Hammar & Årdal, 2009; Rock et al., 2014), with MDD patients ( $n = 20$ ) unable to inhibit neutral information relative to controls (Gohier et al., 2009). According to a meta-analysis of 27 studies conducted by Bora, Harrison, Yücel, and Pantelis (2013), MDD was associated with impaired Stroop Test, Trail Making Test B, and digit span backwards tests, which implies that MDD was associated with inhibition, set-switching and working memory impairments.

**Executive function in PTSD with comorbid MDD.** There is a relative paucity of neurocognitive studies conducted on PTSD with comorbid MDD samples.

In a systematic review of 18 neurocognitive PTSD studies, Polak et al. (2012) reported that subgroup analyses indicated that more severe executive dysfunction was typically found in the PTSD group that had comorbid depression symptoms. This impairment was found on measures such as the Trail Making Test B and the digit span backwards (Polak et al., 2012).

Nevertheless, subsequent research suggests that comorbidity may have little effect on executive function. For example, in a comparison of medication-free patients, Scheiner et al. (2014) showed that all groups (MDD, and PTSD with comorbid MDD) performed comparably on the Wisconsin Card Sorting Test. These null findings may be, in part, due to the small sample of comorbid patients ( $n = 25$ ), and limited power to detect group differences in this study. This particular study (Scheiner et al., 2014b) seems to be the only published work that explicitly explores limited neurocognitive domains, including the attention domain, in a group of patients with PTSD and comorbid MDD.

In summary, it has been found that PTSD, MDD, and PTSD with comorbid MDD is associated with impaired executive functioning, particularly in subdomains such as set-switching, working memory, and inhibition.

**Attention.** While there is no consensus definition of what constitutes ‘attention’, it is generally agreed that attention is composed of 3 components: selective attention, sustained attention, and divided attention (Porter et al., 2007). Selective attention denotes tuning into incoming information (and ignoring competing information); sustained attention refers to focusing on a task for a length of time; and divided attention implies that more than one task at a time can be focused on (Porter et al., 2007).

**Attention in PTSD.** PTSD is associated with moderate deficits of attention, and impairment on attention measures is correlated with PTSD symptom severity (Gilbertson, Gurvits, Lasko, & Pitman, 1997; Qureshi et al., 2011; Scott et al., 2015). In a meta-analysis of 60 studies, Scott et al. (2015) reported that the PTSD group demonstrated attention deficits of a moderate effect size ( $d = -.5$ ) relative to the control group. Furthermore, attention impairment in combat veterans has been reported to be significantly correlated with PTSD symptom severity, as measured by CAPS total scores (Gilbertson et al., 1997). There is also evidence from a study

comparing current ( $n = 16$ ) versus lifetime PTSD ( $n = 22$ ) that patients with a current diagnosis are more impaired on attention, relative to trauma-exposed controls ( $n = 22$ ) (Eren-Kocak et al., 2009). With respect to performance in particular attention components, Vasterling, Brailey, Constans, and Sutker (1998) found that while the combat veteran PTSD group ( $n = 19$ ) performed poorly on attention measures relative to combat exposed controls ( $n = 24$ ), these deficits were restricted to sustained attention measures. Jenkins, Langlais, Delis, and Cohen (2000) found that in a sample of rape survivors, the PTSD group ( $n = 15$ ) performed significantly worse on measures of sustained and divided attention, relative to matched controls ( $n = 16$ ), however, no impairment was found on visuospatial selective attention.

**Attention in MDD.** Several meta-analyses report that MDD presents with pronounced general attention deficits (Lee et al., 2012; Lim et al., 2013; McIntyre et al., 2013; Porter et al., 2003; Rock et al., 2014). For example, Lee et al. (2012) reported that in their meta-analysis of 13 studies, the authors reported that a medium effect size (Hedge's  $g = 0.36$ ) was found between the MDD group that comprised of previously and currently depressed patients, and the control group in the attention domain. In a systematic review and meta-analysis of 24 MDD neurocognitive studies, Rock et al. (2014) found that MDD is associated with general attentional deficits of a moderate effect size ( $d = -0.65$ ), relative to controls. Lim et al. (2013) found that participants with MDD ( $n = 955$ ) exhibit impairments on both the forward digit span (standardised mean difference =  $-0.5$ ,  $p < 0.001$ ) and the continuous performance task (standardised mean difference =  $-0.69$ ,  $p = 0.01$ ), relative to controls ( $n = 7664$ ). Similarly, Godard et al. (2012) found that MDD participants ( $n = 13$ ) displayed deficits of sustained and divided attention when compared to bipolar participants ( $n = 11$ ), without differences in measures of general attention.

**Attention in PTSD with comorbid MDD.** There is little literature examining attention in PTSD with comorbid MDD. For example, Scheiner et al. (2014) reported that all groups, including the comorbid group, performed comparably across the attention measures and the results indicated normal range functioning (for all groups).

The evidence suggests that PTSD and MDD is associated with general attention impairments, as well as sustained and divided attention impairments. However, no attention impairments were found for patients with PTSD and comorbid MDD.

**Memory and learning in PTSD.** Current research indicates that PTSD is typically associated with impairments of verbal memory (Brewin, Kleiner, Vasterling, & Field, 2007; Johnsen & Asbjørnsen, 2008). For instance, in a meta-analysis of neutral memory in PTSD, Brewin et al. (2007) found small to moderate effect sizes in memory performances, when comparing the PTSD group ( $n = 660$ ) with a control group ( $n = 812$ ) consisting of both trauma naïve and trauma exposed controls. This study further found that across 27 studies, the PTSD group performed particularly poorly, relative to controls, on verbal memory tasks (Brewin et al., 2007). In a later memory-specific meta-analysis of 28 studies, Johnsen and Asbjørnsen (2008) indicated that PTSD participants ( $n = 667$ ) tend to have slower and less efficient verbal memory, with moderate effect sizes ( $d = 0.74$ ) relative to both healthy and trauma-exposed controls ( $n = 822$ ). When examining the neurocognitive differences between current and past PTSD, Eren-Kocak, Kilic, Aydin, and Hizli (2009) found that current PTSD ( $n = 16$ ) is associated with worse verbal memory than past PTSD ( $n = 15$ ) and trauma-exposed controls ( $n = 20$ ). Scott et al. (2015) demonstrated that PTSD is associated with moderate effect sizes for verbal memory ( $d = -0.46$ ), and a smaller effect size for visual memory ( $d = -0.29$ ). Moreover, evidence suggests that memory impairments in PTSD correlate with CAPS severity scores, with greater symptom severity correlating with poorer memory performance on the Wechsler Memory Scale general index, verbal index, visual index, as well as delayed recall index (Gilbertson et al., 1997).

Studies have consistently reported that PTSD is associated with impaired verbal learning relative to controls (Johnsen & Asbjørnsen, 2008; Johnsen, Kanagaratnam, & Asbjørnsen, 2008; Stricker et al., 2015). In a large meta-analysis by Scott et al. (2015), the learning domain was divided into verbal learning and visual learning. It was found that the PTSD group demonstrated moderate effect sizes ( $d = -.32$ ) for visual learning and verbal learning ( $d = -.46$ ) relative to controls (Scott et al., 2015). In a refugee sample, Johnsen et al. (2008) reported that PTSD ( $n = 21$ ) is associated with slower and less effective verbal learning compared to trauma-exposed controls ( $n = 21$ ). These findings of verbal learning deficits are similar to those in a sample of female war veterans, where significant verbal learning and memory impairments were found for the PTSD group ( $n = 56$ ) relative to healthy nonveteran controls ( $n = 53$ ) (Stricker et al., 2015).

Although a number of studies have reported that PTSD is associated with significant memory impairments, this finding has not been replicated in other studies. For instance, Neylan et al. (2004) was unable to find any significant differences between PTSD combat veterans and

controls on any measure of memory. This finding is similar to Stein et al. (2002), who reported that female interpersonal violence (IPV) victims with PTSD ( $n = 17$ ) did not exhibit differences on memory tasks. Furthermore, in a study using war veterans with PTSD ( $n = 80$ ), Crowell et al. (2002) also found no apparent differences between the currently distressed PTSD group ( $n = 80$ ) and normal control group ( $n = 80$ ) on neurocognitive measures, including learning and memory tasks such as the California Verbal Learning Test.

**Memory and learning in MDD.** Some meta-analyses have shown that MDD is associated with impaired memory function (Lim et al., 2013; Rock et al., 2014). These meta-analyses have generally found moderate memory deficits ( $SMD = -0.67$ ; *Cohen's d* ranged from -0.41 to -0.5, respectively); however, the range of memory dysfunction in MDD varies from study to study. For example, in a review, McIntyre et al. (2013) found that relative to controls, the MDD group exhibited pronounced memory deficits (small to moderate effect size).

Despite these findings, there is evidence suggesting that MDD is not associated with memory dysfunction. Porter et al. (2003) reported in a sample of medication-free MDD patients, no significant differences were observed between the MDD group ( $n = 44$ ) and healthy controls ( $n = 44$ ) on measures of verbal declarative memory (Porter et al., 2003). When examining verbal memory, Fossati, Amar, Raoux, Ergis, and Allilaire (1999) indicated that the MDD group ( $n = 20$ ) was not impaired, but instead performed at the same level as the IQ matched controls ( $n = 20$ ). Grant, Thase, and Sweeney (2001) found that MDD is not associated with any significant impairment on measures of memory (Hopkins Verbal Learning Test and WMS-R visual reproduction). In fact, they found that the MDD group ( $n = 123$ ) seemed to perform slightly better than healthy controls ( $n = 36$ ) on measures of immediate and delayed visual memory (measured by WMS-R verbal learning trials 2-3, and Hopkins Verbal Learning Test- delayed recall), however, these group differences were not statistically significant (Grant et al., 2001).

**Memory and learning in PTSD with comorbid MDD.** The literature has found reduced memory function in patients with PTSD and comorbid MDD. Nijdam et al. (2013) reported that comorbidity is associated with significant verbal learning deficits (of a moderate effect size) on the California Verbal Learning Test (CVLT), with the comorbid group ( $n = 84$ ) exhibiting significantly lower scores on the CVLT sum of trials, relative to PTSD only participants ( $n = 56$ ). Additionally, the comorbid group performed significantly worse on both the short-term cued recall and long-term free recall, relative to the PTSD only group (Nijdam et



al., 2013). In a recent study by Scheiner et al. (2014), participants with PTSD and comorbid MDD ( $n = 25$ ) performed consistently poorer on measures of learning and memory (namely the Buschke indices such as total recall, long and short-term retrieval, delayed recall, etc.) relative to the MDD-only group ( $n = 148$ ), and non-patient controls ( $n = 96$ ).

In summary, verbal memory deficits, as well as learning task impairment has been reported for PTSD, while MDD is associated with general memory deficits. Patients with PTSD and comorbid MDD exhibited reduced memory function and verbal learning deficits.

**Processing speed in PTSD.** Despite being an uncommonly measured domain in the PTSD literature, the consensus is that PTSD is associated with slower processing speed when compared to controls (Scott et al., 2015; Stricker et al., 2015; Twamley et al., 2009). For example, in a sample of 55 IPV survivors with PTSD, the PTSD group performed significantly worse (slower) than demographically similar controls ( $n = 20$ ) on measures such as D-KEFS Trail Making Test Visual Scanning, Number Sequencing, and Letter Sequencing (Twamley et al., 2009). Furthermore, it was found that greater PTSD symptom severity (as measured by Clinician Administered PTSD Scale (CAPS)) was associated with slower processing speed (Twamley et al., 2009), and more recent research by Stricker et al. (2015) concurs with this finding. In a recent meta-analysis by Scott et al. (2015), processing speed was calculated as having a moderate effect size ( $d = -.59$ ), implying that PTSD participants have moderate inefficiencies when processing information.

**Processing speed in MDD.** Moderate impairments of processing speed have been reported in the MDD literature (Lee et al., 2012; Lim et al., 2013; McDermott & Ebmeier, 2009; Snyder, 2013). In a meta-analysis examining the effects symptom severity has on neurocognitive impairments in MDD, McDermott and Ebmeier (2009) reported that processing speed is not only reduced in MDD, but increased symptom severity is related to poorer performance on processing speed measures. However, in a systematic review investigating currently depressed patients, Rock et al. (2014) reported that no significant differences between the MDD group and healthy controls on reaction time were observed ( $d = 0.07$ ).

**Processing speed in PTSD with comorbid MDD.** In a meta-analysis of 60 neurocognitive studies, Scott et al. (2015) reported that the addition of MDD symptoms to PTSD did not affect the magnitude of the reported effect sizes for each domain explored, including

processing speed. This suggests that the addition of MDD symptoms may not have an accumulative effect on certain neurocognitive domains.

### **Limitations of Previous Research**

This review has highlighted the inconsistencies found in the literature on the neurocognitive associations of PTSD, MDD, and PTSD with comorbid MDD. There are several possible reasons for these inconsistencies. Firstly, some of the contradictory findings may be a result of broad definitions of domains. Executive function, for example, includes a wide variety of functions, such as set-switching, planning, decision making, working memory, as well as flexible thinking (Alvarez & Emory, 2006; Diamond, 2013; Porter et al., 2007). However, these functions are not always classified as executive in nature. For instance, in their meta-analysis, Scott et al. (2015) include working memory measures under the attention domain instead of the executive function domain. Second, a potential confounding factor, related to the above point, is that some researchers choose to explore executive function as a global construct, while others have focused on certain subdomains of executive function, such as set-switching, and generalise impairments from their data to imply global executive dysfunction.

Thirdly, the heterogeneous sampling and diagnostic methods within the studies poses another issue. Investigators employ differing methods of grouping their participants, classifying participants as having PTSD or probable PTSD based on clinician administered assessments or self-report questionnaires, respectively. Clinician administered measures tend to be more stringent than self-report questionnaires and provide more homogeneous groups (Rosenthal & Rosnow, 2008). Related to this point, there is a bias towards using American male military samples or combat veterans in PTSD literature. There is a relative paucity of studies utilising female only samples, participant samples with a variety of trauma exposure, or studies from non-Western countries. Literature examining PTSD and MDD in South Africa has been scarce. These sampling biases may affect results and should be addressed.

Finally, an important aspect that has been overlooked in the literature is that very few studies utilised a four-group study design, with a healthy control group, to fully explore the neurocognitive associations of PTSD, MDD, and PTSD with comorbid MDD. By neglecting one of the four groups, it is not possible to determine whether PTSD with comorbid MDD exhibits impairments that are additive, or ‘greater than the sum of their parts’.

## **Neuroimaging of PTSD and MDD**

There have been important advances in the literature on neurobiology of PTSD and MDD. This is in part because advances in the field of neuroimaging have afforded us the opportunity to identify brain networks that are active while the brain is focused on a task or at rest. This, in turn, allows the elucidation of the potential networks and regions associated with neurocognitive tasks and functioning.

Executive dysfunction and attentional impairments are common sequelae in PTSD, MDD, and PTSD with comorbid MDD (Olf, Polak, Witteveen, & Denys, 2014; Scott et al., 2015; Snyder, 2013). It is therefore important to explore the functional networks associated with these neurocognitive domains, networks known as the cognitive control networks. Evidence suggests that resting-state network connectivity can serve as a proxy for functional networks that underlie neurocognitive abilities (Smith et al., 2009). While the intrinsic functional connectivity of cognitive control networks has been explored in PTSD and MDD samples, there has been little focus given to functional connectivity abnormalities in a sample of patients with PTSD and comorbid MDD. Additionally, the cognitive control networks and their connectivity with the default mode network have received little attention in this patient population.

### **Resting-State connectivity findings for PTSD, MDD, and PTSD with comorbid MDD**

Resting-state (RS) functional imaging is a tool that allows the mapping of large-scale networks in the brain (Buckner, Krienen, & Yeo, 2013). This method investigates the temporal relation of neural activity between brain regions based on fluctuations in the intensity of blood oxygen level dependent (BOLD) signal (Cole, Smith, & Beckmann, 2010; Greicius, Supekar, Menon, & Dougherty, 2009; Rosazza & Minati, 2011). During resting-state sequences, participants are instructed to lie still and not engage in any specific task for the duration of the scan. During these resting conditions, spontaneous low frequency activity (< 0.1 Hz) can be detected in a network of brain regions (Rosazza & Minati, 2011). These networks tend to reflect features of anatomical connectivity and organisation (Buckner et al., 2013), allowing researchers to draw tentative conclusions regarding structure and function of certain regions.

The two most common resting-state analytic approaches involve defining regions of interest (ROIs) using seeds, or independent component analysis (ICA) methods (Cole et al., 2010; Rosazza & Minati, 2011). ICA allows one to statistically identify large-scale, spatially

independent functional networks in the brain during rest (Beckmann, DeLuca, Devlin, & Smith, 2005). This is a model-free method that does not involve any prior assumptions (Cole et al., 2010). Conversely, the seed-based approach allows one to preselect a region of interest (ROI) and analyse connectivity between the average signal from the ROI and other seeds, or the whole brain, on a voxel-wise level (Rosazza & Minati, 2011). Global and local structural network characteristics are often derived using graph-theoretical methods when assessing the effect of psychopathology on connectivity between a large number of seeds (Sporns, 2013). For an analysis and review of the advantages and disadvantages of seed-based versus ICA-based approaches, please refer to Cole et al. (2010).

### **Commonly researched networks**

Certain large-scale networks have consistently been identified during resting-state imaging paradigms. One of the most commonly researched and studied large-scale network is the default mode network (DMN). This network is active while the brain is idle, and it has been reported that the DMN is involved in functions such as self-reflective thought, autobiographical memory, and mind-wandering (Menon, 2011). The default mode network consists of the following regions: the posterior cingulate, the ventromedial prefrontal cortex, the dorsal medial prefrontal cortex (PFC), the inferior parietal lobule, as well as the hippocampal formation (Buckner, Andrews-Hanna, & Schacter, 2008).

Other commonly researched networks include the bilateral frontoparietal networks (FPAR), the salience network (SN), and the dorsal attention network (DAN). Collectively known as task positive networks, given the increased BOLD activity in brain regions constituting these networks during the performance of executive function tasks in the MRI scanner, these networks all recruit prefrontal cortical regions (Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013), leading to their characterisation as cognitive control networks. The frontoparietal networks, sometimes referred to in the literature as the central executive network (CEN), includes the dorsolateral PFC, orbitofrontal cortex, anterior cingulate cortex, and the lateral posterior parietal cortex (PPC) (Niendam et al., 2012). This network is known to be involved in executive functions such as decision making, problem solving, inhibition, flexibility, planning, and manipulating information in working memory (Menon, 2011; Niendam et al., 2012). The salience network (SN) consists of the dorsolateral anterior cingulate cortex (dlACC) and the

anterior insular cortex, particularly in the right hemisphere. The SN is credited for filtering and integrating task-relevant information (Menon, 2011; Seeley et al., 2007). The dorsal attention network (DAN), consisting of the dlPFC, frontal eye fields, inferior precentral sulcus, and superior parietal lobule, engages attention towards external stimuli (Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010).

Evidence suggests that there is an antagonistic relationship between the DMN and the cognitive control networks, which Fox et al. (2005) describes as an ‘activation/deactivation dichotomy’. The DMN, a task negative network, exhibits decreased activity during task performance, while the cognitive control networks, task positive networks, exhibit increased activity during tasks (Fox et al., 2005; Liu et al., 2010). This antagonistic relationship has been found between the DMN and both frontoparietal and dorsal attention networks (Spreng et al., 2013). Further, Menon and Uddin (2010) postulate that the salience network acts as a switch between the DMN and the frontoparietal network. Once a stimulus has been detected, the DMN is disengaged by the salience network and the frontoparietal cognitive control networks (left and right) are then engaged (Menon & Uddin, 2010). Sridharan, Levitin, and Menon (2008) further postulate that it is the right fronto-insular cortex of the salience network that acts as the switch, as it activates the frontoparietal networks and salience network, while simultaneously deactivating the DMN. Contrary to the above, researchers such as Vincent, Kahn, Snyder, Raichle, and Buckner (2008) and Gao and Lin (2012) provide evidence suggesting that the switching function is performed by the frontoparietal network, rather than the salience network. Additionally, there is evidence suggesting that the above three networks (frontoparietal, salience, default mode) show abnormal connectivity in a multitude of psychiatric disorders, including MDD and PTSD (Menon & Uddin, 2010).

### **Resting-State Connectivity Findings in PTSD**

PTSD is associated with reduced functional connectivity of the default mode network (DMN), as seen using ICA methods (Bluhm et al., 2009b; Koch et al., 2016; Sripada et al., 2012a). In a recent meta-analysis of 14 resting-state studies, Koch et al. (2016) reported that PTSD consistently exhibited less connectivity within the DMN, relative to both traumatised and non-traumatised controls. Additionally, there was evidence of greater activity in the ventral ACC and the parahippocampus/amygdala, as well as greater connectivity within the salience network

(Koch et al., 2016). In a sample of male combat veterans, the PTSD group ( $n = 15$ ) exhibited less connectivity within the DMN relative to healthy controls ( $n = 15$ ) and combat-exposed controls ( $n = 15$ ) (Sripada et al., 2012a). In addition, significant group differences were found for the salience network, as the PTSD group showed greater connectivity within the salience network, as well as greater connectivity between the DMN and SN, relative to both control groups (Sripada et al., 2012a). Similar salience network results were reported by Bluhm et al. (2009b) in an all-female sample.

In a review of neuroimaging in anxiety studies, Peterson, Thome, Frewen, and Lanius (2014) reported that PTSD is associated with abnormal functional connectivity within the DMN and SN, with studies ( $n = 11$ ) finding both greater and less connectivity within these networks. Furthermore, greater PTSD symptom severity (measured using CAPS total score) was associated with greater functional connectivity within the default mode network (Peterson et al., 2014). However, the opposite effect was found for the salience network, where greater PTSD symptom severity was associated with less functional connectivity within the salience network (Tursich et al., 2015).

Using the seed-based approach, studies have found greater functional connectivity in midbrain regions such as the hippocampus and amygdala (Rabinak et al., 2011; Sripada, Wang, Sripada, & Liberzon, 2012b) in PTSD patients. In a sample of combat veterans, Rabinak et al. (2011) found that the PTSD group ( $n = 17$ ) exhibited stronger connectivity from the right amygdala to the posterior insula, relative to the combat-exposed control group ( $n = 17$ ). However, no group differences in amygdala-prefrontal connectivity were evident (Rabinak et al., 2011). Later research by Sripada et al. (2012b) in a veteran sample found similar results, and in addition, also reported less connectivity between the amygdala and the hippocampus. In a study of male combat veterans which included a group of patients with comorbid PTSD and MDD ( $n = 27$ ), it was observed that the PTSD group ( $n = 22$ ) displayed no functional connectivity between the (bilateral) insula and the left hippocampus when compared to the comorbid group (Kennis, Rademaker, van Rooij, Kahn, & Geuze, 2014). More recent research has shown that PTSD ( $n = 13$ ) is associated with poorer cingulum connectivity, relative to trauma exposed controls ( $n = 41$ ), in an all-female African American sample (Fani et al., 2016). These results remained after controlling for age, trauma exposure, and depressive symptoms (Fani et al., 2016). In a sample of US military veterans, Brown et al. (2014) reported that PTSD patients ( $n = 20$ ) displayed

stronger connectivity of the basolateral amygdala with the pregenual ACC/dorsomedial PFC and dorsal ACC, when compared to trauma-exposed controls ( $n = 22$ ). Additionally, the control group, relative to the PTSD group, demonstrated stronger connectivity between the basolateral amygdala and the left inferior frontal gyrus (Brown et al., 2014).

### **Resting-State Connectivity Findings in MDD**

Relative to controls, MDD is associated with greater functional connectivity within the DMN, which is frequently interpreted as reflecting the tendency for patients to engage in self-referential thought (Greicius et al., 2007; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015). Studies examining the salience network, dorsal attention network, and frontoparietal network indicate that these networks exhibit less within network functional connectivity in MDD, relative to controls (Kaiser et al., 2015). In a meta-analysis of 25 imaging studies, Kaiser et al. (2015) found that MDD is associated with hyperconnectivity within the DMN, as well as hyperconnectivity between regions of the DMN and frontoparietal networks, relative to healthy controls. MDD is characterised by hypoconnectivity within the FPAR, as well as hypoconnectivity between the frontoparietal network and the parietal regions of the dorsal attention network (DAN), relative to controls (Kaiser et al., 2015). Furthermore, MDD was also associated with hypoconnectivity between the salience network and midline regions of the DMN (Kaiser et al., 2015). However, Bluhm et al. (2009a) reported no group differences in connectivity within the DMN, referencing areas such as the medial PFC, subgenual ACC, thalamus, and parahippocampal gyri, when comparing MDD patients ( $n = 14$ ), relative to matched healthy controls ( $n = 15$ ).

In a review of executive function and prefrontal function in MDD, Rogers et al. (2004) reported that MDD was often associated with hypoactivation of the dlPFC and ACC, and hyperactivation of the orbitofrontal cortex (OFC). Moreover, the reduced connectivity within the dlPFC was associated with executive and prefrontal impairments (Rogers et al., 2004). A study by Ye et al. (2012) reported that MDD participants ( $n = 22$ ) exhibited greater functional connectivity of the dlPFC to the left dACC, left parahippocampal gyrus, and the thalamus, relative to age, gender, and education matched controls ( $n = 30$ ). In a sample of both in- and outpatients, Greicius et al. (2007) reported greater connectivity between the subgenual cingulate and thalamus for the MDD group ( $n = 28$ ) relative to healthy controls (Greicius et al., 2007).

Less resting-state connectivity in the salience network (anterior insula, dACC), vmPFC, temporal poles and amygdala was found in a sample of medication-free MDD patients ( $n = 19$ ) relative to gender matched controls ( $n = 19$ ) (Veer et al., 2010). Additionally, Satterthwaite et al. (2015) reported that MDD ( $n = 38$ ) was associated with diminished amygdala co-activation with the frontal regions, including the bilateral dlPFC and ACC, relative to the PTSD group ( $n = 50$ ) and demographically matched controls ( $n = 17$ ). Kaiser et al. (2015) reported abnormal connectivity within the dorsal attention network, with individual studies reporting both greater and less functional connectivity within the DAN in MDD relative to controls.

### **Resting-State Connectivity Findings in PTSD with MDD**

To date, there has been no imaging research that compares PTSD, MDD, PTSD with comorbid MDD, and healthy controls to determine the associated functional connectivity abnormalities of these disorders.

In a study using male combat veterans, less functional connectivity in the bilateral insula, as well as less functional connectivity in the left hippocampus was demonstrated by the PTSD with MDD group ( $n = 30$ ), relative to the PTSD only group ( $n = 25$ ). This finding suggests that salience network connectivity is reduced in patients with PTSD and comorbid MDD (Kennis et al., 2014). Furthermore, the comorbid group displayed greater functional connectivity between the subgenual ACC and the perigenual regions of the ACC, relative to the PTSD only group (Kennis et al., 2014). This study utilised two clinical groups (PTSD and PTSD+MDD groups) and no control group was used as a comparison group. In a more recent resting-state fMRI study, Zhu et al. (2016) reported that PTSD with comorbid MDD ( $n = 21$ ) is associated with a less connectivity between the basolateral amygdala and the orbitofrontal cortex when compared to PTSD only ( $n = 27$ ) and trauma exposed healthy controls ( $n = 34$ ). This study has further suggested that a comorbid diagnosis (PTSD+MDD) may be associated with alterations of functional connectivity in both the fear and reward systems (Zhu et al., 2016).

### **Structural imaging of PTSD, MDD, and PTSD with comorbid MDD**

Structural imaging studies explore aspects of neuroanatomy such as cortical surface area, volume, and thickness. Evidence suggests that neuroanatomical changes of particular regions are



evident in psychiatric disorders such as MDD and PTSD (Karl et al., 2006; Lorenzetti, Allen, Fornito, & Yücel, 2009; Morey et al., 2016; Schmaal et al., 2017).

### **Structural Imaging in PTSD**

Typically, structural imaging studies of PTSD tend to focus on key areas of the limbic system, with particular attention paid to the amygdala and hippocampus. These regions are associated with the fear response and memory, respectively (LeDoux, 2003; Tulving & Markowitsch, 1998). In an early review of the literature, in a sample of 7 MRI studies, Hull (2002) found that PTSD is associated with a reduction of hippocampal volume both bilaterally ( $n = 1$ ) and unilaterally ( $n = 3$ ). However, this review found two studies that showed no evidence of hippocampal volume reduction (Hull, 2002). In a series of meta-analyses, Karl et al. (2006) found that when comparing trauma-naïve participants with a PTSD group, the PTSD group demonstrated significantly smaller bilateral hippocampal volume. A meta-analysis, examining 13 studies, showed that the PTSD group exhibited left hippocampal volumes that were 6.9% smaller than controls, and right hippocampal volumes that were 6.6% smaller than controls (Smith, 2005). Furthermore, in more recent publications adults with PTSD display significantly smaller left amygdalae when compared to controls (Karl et al., 2006). In a recent multisite study, the PGC-ENIGMA PTSD working group (Morey et al., 2016) analysed data from 1868 participants (794 PTSD patients and 1074 trauma-exposed controls) and found that amygdala and hippocampus volumes were smaller in participants with current PTSD, relative to controls. The significant findings remained after controlling for age, sex and intracranial volume.

Frontal cortical regions have shown structural abnormalities in PTSD, particularly prefrontal cortical regions and the anterior cingulate cortex (Karl et al., 2006; Rauch et al., 2003; Shin, Rauch, & Pitman, 2006; Woodward, Schaer, Kaloupek, Cediël, & Eliez, 2009). In a review of the literature, Shin et al. (2006) report that medial prefrontal cortex volume reductions are evident in PTSD. Furthermore, in a biological review of PTSD, Pitman et al. (2012) noted that a number of studies have reported volumetric reductions of the rostral ventromedial PFC in PTSD. The anterior cingulate cortex and sub regions of the ACC have shown volumetric and thickness reductions in the PTSD literature. For example, in a series of meta-analyses, Karl et al. (2006) reported significantly smaller ACC volumes, of a moderate effect size, in the PTSD group relative to the trauma-exposed controls. Furthermore, caudal and rostral ACC cortical thickness

was smaller in a sample of combat-related PTSD patients ( $n = 50$ ) relative to trauma-exposed controls ( $n = 47$ ) (Woodward et al., 2009).

### **Structural Imaging in MDD**

In a meta-analysis of 64 structural imaging studies, Koolschijn et al. (2009) reported that the hippocampus is the brain structure most often studied in depression, and MDD is associated with reduced hippocampal volume relative to controls (Koolschijn et al., 2009). Additionally, it was found that amygdala size varied in relation to the duration of illness, and that depression was associated with hippocampal reductions (Lorenzetti et al., 2009). Similar findings were reported by Bremner et al. (2000) in a sample of medicated MDD patients ( $n = 16$ ) and matched controls ( $n = 16$ ). The MDD group exhibited 19% smaller left hippocampus relative to controls, and this result remained significant after controlling for whole brain volume (Bremner et al., 2000). Additionally, the MDD group exhibited larger amygdala volume relative to healthy controls; however, after controlling for brain size, this finding was no longer significant (Bremner et al., 2000).

Frontal cortical regions have been shown to be reduced in MDD, particularly the orbitofrontal cortex (OFC) and prefrontal cortex (PFC) volumes (Bremner et al., 2002; Koolschijn et al., 2009; Lorenzetti et al., 2009). In a review of 29 articles, Lorenzetti et al. (2009) reported that volumetric reductions of the OFC were evident in more severe patient groups, relative to controls (Lorenzetti et al., 2009). Later research by Bremner et al. (2002) revealed that the medial OFC was 32% smaller in the MDD group ( $n = 15$ ) relative to 20 healthy controls matched for age, gender, education, and handedness. In a large, multisite study, Schmaal et al. (2017) reported that the MDD group ( $n = 2148$ ) exhibited bilateral cortical thinning of frontal regions, such as the medial PFC, relative to healthy controls ( $n = 7957$ ).

In a structural imaging meta-analysis of 64 articles, Koolschijn et al. (2009) reported that MDD patients exhibit smaller ACC volumes relative to healthy controls (Cohen's  $d = -0.77$ ). Further, in a sample of first episode MDD patients ( $n = 20$ ), the caudal anterior cingulate cortex (cACC) volume was significantly reduced relative to age, sex, and education matched healthy controls ( $n = 22$ ) (Han et al., 2014). In a sample of 20 international data sets, Schmaal et al. (2017) reported reduced cortical thickness of rostral and caudal ACC regions in MDD ( $n = 2148$ ), relative to healthy controls ( $n = 7957$ ). Furthermore, Wagner et al. (2012) reported that

MDD patients ( $n = 30$ ) display lower cortical thickness of regions such as the posterior cingulate relative to age, gender, and education matched healthy controls ( $n = 30$ ). The posterior cingulate cortical thickness has also shown to be thinner in non-remitting MDD patients, relative to patients with remitted MDD, according to Järnum et al. (2011).

### **Structural Imaging in PTSD with MDD**

In a study examining PTSD and MDD respectively, Kroes, Rugg, Whalley, and Brewin (2011) reported that the structural cortical abnormalities associated with PTSD and MDD overlap. To date and to my knowledge, no other research has been conducted on this topic.

### **Limitations of previous imaging research**

Firstly, the above studies include heterogeneous sampling methods with different participant grouping methods. Some studies utilise clinician administered assessments, while others utilise self-report questionnaires. More stringent diagnostic criteria (namely clinician-based diagnoses) need to be employed to create homogeneous groups.

Second, due to the nature of imaging studies, relatively small sample sizes are found in the literature. For example, one MDD group consisted of 15 participants in Bremner et al. (2002), and the PTSD group consisted of 9 participants in Rauch et al. (2003). These small groups limit the power of such studies to detect group differences and yield imprecise estimates of the size of this effect.

Finally, no neuroimaging studies explicitly assess PTSD with comorbid MDD, particularly in a four-group design, including a healthy control group.

### **Objective of this dissertation**

To date, no published studies have assessed the neurocognitive deficits associated with PTSD, MDD, and PTSD with comorbid MDD, and a healthy control group. Neither is there research that has related these deficits to the intrinsic functional connectivity and neuroanatomy in these particular patients. By not utilising a four-group design, incorporating a healthy control group, studies are unable to accurately determine whether observed effects are of an ‘additive’ or ‘synergistic’ nature. ‘Additive’ findings would imply that the overall effect (of comorbidity) is the same as the sum of the individual disorders’ effects (PTSD and MDD, individually).

‘Synergistic’ findings would imply that the overall effect (of comorbidity) is greater than the sum of the individual effects of PTSD and MDD, combined. Furthermore, there is a relative paucity of research conducted on these disorders in female samples, in low-middle income countries, which leaves a large proportion of patients under-represented in the literature.

The present dissertation seeks to utilise a rigorous four-group study design to accurately estimate differences in the neurocognitive, functional, and structural correlates of frontal cortical brain regions in patients with PTSD, MDD, and PTSD with comorbid MDD, compared to healthy controls. This dissertation aims to determine whether PTSD with comorbid MDD is associated with greater impairments and dysfunction, relative to PTSD and MDD alone. Furthermore, utilising a female sample from a LMI country would allow greater representation in the literature. In the next chapter, the neurocognitive associations of PTSD, MDD, and PTSD with MDD will be assessed in a female sample from a low-middle income region of the Western Cape.

### **Context of this study**

Participants for this study were from Paarl, a low-middle income region of the Western Cape, South Africa. This study utilised participants from the Drakenstein Child Health Study (DCHS), a birth cohort study that examines child health outcomes in a sample of mother-infant dyads from two primary health care clinics (Zar et al., 2014). The first site, TC Newman, was a site that enrolled predominantly mixed-race participants, and the second, Mbekweni, enrolled African participants. All participants, including controls, were recruited from the local community and enrolled in the DCHS. Due to the high research burden, not all participants who underwent neurocognitive assessment were able to be scanned, and vice versa.

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## **Chapter 2**

### **Neurocognition of PTSD, MDD, and PTSD with MDD**



Chapter 1 reviewed the neurocognitive literature of PTSD, MDD, and the combination of the disorders. The present chapter focuses on the neurocognitive performance of mothers from a low-middle income country with either PTSD, MDD, or PTSD with comorbid MDD. This chapter will begin with a brief overview of the current literature and it will then go on to present findings from the present neurocognitive research, in an effort to address the gaps highlighted in Chapter 1.

## **Background**

As described in the first chapter of this thesis, much research has been conducted investigating the neurocognitive sequelae of PTSD and MDD, with the majority of studies measuring domains such as attention, processing speed, memory and executive function. Whereas some of these studies have indicated that both PTSD and MDD can lead to a variety of neurocognitive deficits, other studies were unable to find evidence of neurocognitive deficits in participants with PTSD or MDD. As the literature on neurocognitive performance in PTSD and MDD was reviewed in detail in the first chapter, what follows will be a concise summary of the current PTSD literature.

PTSD and MDD have both been reported in a number of peer-reviewed studies to be associated with mild to moderate executive functioning (EF) impairments, relative to both healthy and trauma-exposed controls (Polak et al., 2012; Scott et al., 2015; Stricker et al., 2015). For example, in a meta-analysis of 60 studies, Scott et al. (2015) reported that PTSD is associated with small to moderate executive functioning impairments ( $d = -0.45$ ), relative to healthy and trauma-exposed controls. Moreover, evidence for deficits in multiple aspects of executive function can be found for working memory, inhibition, flexibility, and set-switching in PTSD (Olf et al., 2014; Stein et al., 2002; Stricker et al., 2015) and MDD relative to healthy, non-clinical controls (Bora et al., 2013; Gohier et al., 2009; McIntyre et al., 2013). However, investigators have not always been able to replicate findings of executive dysfunction in PTSD (Flaks et al., 2014). In addition, executive dysfunction appears to be more severely compromised in patients with more severe MDD symptoms (Snyder, 2013). There is evidence that deficits in executive function performance in PTSD are further compromised in patients with depressive symptoms (Olf et al., 2014; Polak et al., 2012). Evidence for accumulative effects of depression on EF in PTSD is mixed, however, with Scheiner et al. (2014b) observing that both participant

groups (MDD, PTSD+MDD), performed similarly to controls on the Wisconsin Card Sorting Test, a measure of set shifting and problem solving.

The current literature suggests that PTSD and MDD are both associated with moderate deficits in attention, relative to healthy, non-clinical controls (Brandes et al., 2002; Eren-Kocak et al., 2009; Lee et al., 2012; Lim et al., 2013; Scott et al., 2015). Evidence for deficits of sustained and divided attention is common in both PTSD and MDD literature (Godard et al., 2012; Jenkins et al., 2000; Vasterling et al., 2002). However, very little research has explored the effects of PTSD and comorbid MDD on attention. Contrary to PTSD and MDD neurocognitive findings, Scheiner et al. (2014a) found that the comorbid group performed within the normal range on measures of attention, relative to healthy controls.

Peer-reviewed studies have reported a variety of memory deficits in PTSD and MDD, with the largest effects observed for verbal and visual memory relative to trauma-naïve healthy controls, and trauma-exposed controls (Brewin et al., 2007; Johnsen & Asbjørnsen, 2008; Lee et al., 2012; Lim et al., 2013; Rock et al., 2014; Scott et al., 2015). Additionally, PTSD has been associated with moderate deficits of short-term and long-term visual memory in this patient population (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; Scott et al., 2015). Patients with PTSD and comorbid MDD have shown verbal memory and learning deficits relative to healthy controls (Nijdam et al., 2013; Scheiner et al., 2014a).

Moderate processing speed impairments have been reported for PTSD patients (Scott et al., 2015; Stricker et al., 2015; Twamley et al., 2009), as well as MDD patients (Lee et al., 2012; Lim et al., 2013; McDermott & Ebmeier, 2009; Snyder, 2013), relative to healthy controls. Additionally, evidence suggests that processing speed is greatly compromised in patients with greater MDD symptom severity (McDermott & Ebmeier, 2009). However, there is little evidence to indicate that the addition of MDD symptoms to PTSD affects the magnitude of the reported effect size for processing speed (Scott et al., 2015).

## **Rationale**

The review of the research literature highlights heterogeneous neurocognitive performance findings across a number of domains for both PTSD and MDD, as well as a relative paucity of research in patients who present with comorbid diagnoses. Inconsistency in study findings could arise from numerous methodological inconsistencies (Danckwerts & Leathem, 2003), including

(a) varied sampling methods, (b) the use of an assortment of neuropsychological measures, (c) using a variety of diagnostic criteria, and (d) inconsistent definitions.

With regard to PTSD, the majority of research has been conducted in male combat veterans residing in the US and other developed nations (Danckwerts & Leathem, 2003). There is a lack of PTSD and MDD neurocognitive data in a South African context. Prevalence rates of PTSD and MDD in South Africa suggest that these disorders need more attention. Large numbers of people live with PTSD and/or MDD in South Africa (Atwoli et al., 2013), and although these local prevalence rates are lower than USA, for example, the prevalence of these disorders puts a burden on the already resource limited health care system. These clinically significant diagnoses influence daily activities, medication adherence, and response to treatment (Campbell et al., 2007; Insel et al., 2006). Due to relatively impoverished living conditions and high trauma rates, South Africans are vulnerable to psychological disorders such as MDD and PTSD (Abler et al., 2014; Lund et al., 2010).

In impoverished low-middle income regions, where resources are limited and there is heavy psychological burden on the healthcare system, research examining impairments mothers with PTSD, MDD, and PTSD with comorbid MDD experience is informative, and may provide the foundation for future research into interventions, coping strategies, and treatment plans.

Chapter 1 identified substantial variability in the neurocognitive tests used in studies of PTSD and MDD, potentially explaining inconsistent results. For example, some studies may use a measure of EF that taps into performance on a particular subdomain of EF, such as set-shifting. These results are often generalised to imply that there is global executive dysfunction. Moreover, some of the contradictory findings may be a result of broad definitions of domains, or lack of consensus about definitions. This is notably seen with the attention domain, for example.

A number of studies use self-report screening instruments (such as the Beck Depression Inventory II, or the PTSD Checklist) that may be subject to additional forms of bias compared to clinician-administered interviews and diagnoses (Rosenthal & Rosnow, 2008). In addition, investigators using these self-report screening instruments may be tempted to employ arbitrary and lenient cut-offs or thresholds in an attempt to uncover group differences.

Executive function plays an important role in day-to-day functioning (for example, planning, organising, and decision-making). Research has shown that executive function influences one's capacity for self-care and medication adherence (Insel, Morrow, Brewer, &

Figueredo, 2006). Executive dysfunction could affect quality of life, and this could translate to the care of others, in the case of mothers with executive dysfunction. Therefore, executive functioning should be carefully researched and explored. This would allow for better treatment and coping plans to be developed for those presenting with executive dysfunction.

Studies have highlighted that prefrontal regions tend to be particularly affected by disorders such as PTSD and MDD (Etkin, Gyurak, & O'Hara, 2013; Etkin & Wager, 2007; Rogers et al., 2004; Thomas & Elliott, 2009). Scott et al. (2015) suggest that alterations to the fronto-limbic circuitry may contribute to PTSD-associated neurocognitive deficits. Previous studies have linked decreased intrinsic connectivity in the frontal cortex to executive dysfunction in MDD (Rogers et al., 2004). Working memory and set-shifting are associated with the dorsolateral prefrontal cortex (dlPFC), and reduced activation of the dlPFC has been associated with executive and prefrontal impairments (Rogers et al., 2004). Therefore, exploring domains such as attention and executive function (domains that depend on prefrontal regions) is of particular importance.

Based on the heterogeneous nature of the findings reviewed above, as well as the general paucity of research in this area, there is an urgent need to further clarify the neurocognitive profiles of PTSD and MDD, with a particular emphasis on EF and attention. Moreover, participants with a dual diagnosis (PTSD and MDD) have been under-represented in the literature, and this gap in the literature needs to be addressed.

## **Aims and Hypotheses**

The primary aim of this study was to test the hypothesis that impairments in executive function and attention would be evident in mothers in a low-middle income country (LMIC) setting with PTSD and MDD, and that these deficits will be particularly apparent in participants with both disorders. In addition, an exploratory characterisation was conducted of group differences across the neurocognitive domains, including memory, learning, and processing speed domains. Based on the literature reviewed, the following hypotheses were formulated:

## **Hypotheses**

- Individuals with a sole diagnosis of PTSD or MDD will be impaired, relative to a healthy control group, with respect to executive function, attention, memory and learning, and

processing speed. These effects will be most apparent for domains that are particularly reliant on frontal cortical brain function, such as attention and EF.

- Comorbid PTSD and MDD will be associated with worse performance on all neurocognitive domains relative to controls. Differences in task performance between the comorbid and mono-diagnostic clinical groups, are predicted to reflect greater impairment in the comorbid group.
- With respect to particular components of EF, all the clinical groups will perform more poorly on measures of set-shifting, working memory and inhibition relative to controls.
- Greater PTSD symptom severity (in the PTSD and comorbid groups) will be associated with worse task performance, particularly with regards to EF and attention.

## **Methods**

### **Design and Ethics**

The present study was a cross-sectional study that was quantitative in nature. Ethical approval was received from the Human Research Ethics Committee at the University of Cape Town (HREC ref: 411/2013). The larger study (Zar, Barnett, Myer, Stein, & Nicol, 2014), in which this study was nested, received approval from the Health Science Faculty Ethics Committee of the University of Cape Town, and Stellenbosch University. All participants gave written consent before undergoing neurocognitive testing.

### **Participants**

Participants were recruited from two primary health care clinics (TC Newman clinic and Mbekweni clinic) that were associated with the Drakenstein Child Health Study (DCHS) in the Paarl area of the Western Cape (Zar et al., 2014). Inclusion criteria for the DCHS included: women over the age of 18 years, who were between 20 and 28 weeks pregnant, who presented to one of two health care clinics for antenatal care (TC Newman and Mbekweni clinics), and had no intention of moving out of the area within the following year, and were able to give written consent (Stein et al., 2015). The Drakenstein area was chosen for its high prevalence of trauma, stable population, and free public health system (Stein et al., 2015). All mothers who had enrolled in the Drakenstein Child Health study were eligible to take part in this study.

The following exclusion criteria were employed for the present study: any current or lifetime psychiatric disorder (other than MDD or PTSD) revealed by the Mini International Neuropsychiatric Interview (MINI), including psychosis; alcohol and/or substance dependence/abuse (revealed by the MINI); and inability to speak English. Participants were placed into one of four groups based on a diagnosis by a psychiatrist with extensive experience in this population: PTSD group; MDD group; PTSD+MDD group (also known as the comorbid group), and a control group of individuals without psychopathology. Controls were mothers from the Drakenstein Child Health Study who exhibited no psychopathology on the MINI.

### **Materials/Measures**

**Diagnoses.** All psychiatric interviews were conducted by a psychiatrist from the DCHS study. The 5<sup>th</sup> edition of the Mini International Neuropsychiatric Interview (MINI, Sheehan et al., 1998) was used to determine if participants had any psychopathology. This semi-structured interview screens for 17 axis 1 disorders using DSM-IV criteria. Not only is the MINI a concise instrument, it has been well validated and has good reliability for research settings (Sheehan et al., 1997; Sheehan et al., 1998).

PTSD symptom severity was measured utilising the Clinician Administered PTSD Scale (CAPS, Blake et al., 1995), which is a structured interview that measures both the frequency and intensity of PTSD symptoms. This interview has good internal consistency and has been well validated (Blake et al., 1995). According to Weathers, Ruscio, and Keane (1999), a strict scoring rule should be applied to confirm PTSD diagnosis, or to create homogeneous groups in research.

Due to the inclusion of lifetime PTSD diagnoses, CAPS assessments were undertaken to ensure that PTSD participants presented with moderate to severe PTSD symptoms and impairment at the time of neurocognitive assessment.

In this study, participants with current or lifetime PTSD (determined by the MINI) were placed in the PTSD group if their total CAPS score was more than, or equal to 45. Comparison of scoring rules by Weathers et al. (1999) and Orr (1997) indicate that a total CAPS score of  $\geq 45$  is strict enough to confirm the PTSD diagnosis, as well as creating a homogeneous group of participants. The MDD group consisted of mothers who were diagnosed as having current or lifetime depression on the MINI. The comorbid group consisted of mothers who had a diagnosis of current/lifetime PTSD, and current/lifetime MDD. All cases of current and lifetime depression

(including postpartum depression) were accepted, where other exclusion criteria were adhered to. Due to low numbers of current PTSD and MDD, lifetime diagnoses were included in the inclusion criteria. All participants in the comorbid group had a primary diagnosis of PTSD and a secondary diagnosis of MDD. The control group consisted of mothers who had no psychopathology (current and lifetime) on the MINI. Physical and psychological trauma exposure was not an exclusion criterion for the control group.

**Diagnostic criteria utilised.** At the time of this study, a number of diagnostic instruments, including the MINI, had not yet been updated and validated to include the new DSM V diagnostic criteria for PTSD. Accordingly, all diagnoses made using the MINI and CAPS were in keeping with the DSM-IV criteria. There are arguments both for and against the new diagnostic criteria for PTSD; however, this is beyond the scope of this research. See Hoge et al. (2016) and Friedman, Kilpatrick, Schnurr, and Weathers (2016) for full commentary.

### **Neurocognitive Assessment**

**NIH Toolbox.** The NIH Toolbox Cognition battery was used as the primary neurocognitive battery in this study. This particular battery was chosen due to the ease of administration with its short, but comprehensive measures. This computerised battery was recently developed to assess neurocognitive functioning across the lifespan, with the goal of becoming the “common currency” amongst researchers (Weintraub et al., 2013), and thereby allowing researchers to compare results across studies easily. For the present study, the measures assessing memory, attention, processing speed, and executive function were used, as well as two measures described by the authors of the Toolbox as “supplementary”. The measures that were utilised included the Dimensional Change Card Sort test (executive function/set-shifting), Flanker Control and Inhibition test (attention/executive function), the List Sorting Working Memory test (working memory), and the Pattern Comparison Processing Speed test (processing speed) (Weintraub et al., 2013). The supplementary measures included the Rey Auditory Verbal Learning test (memory/learning) and the Oral Symbol Digit test (processing speed). Published psychometric studies of the NIH Toolbox indicate that these measures are reliable, with Intraclass Correlation Coefficients ranging from 0.82 for the Pattern Comparison test, to 0.96 for the Flanker Control and Inhibition test (Weintraub et al., 2013). Tests that do not depend on verbal ability were given preference in the interests of cross-cultural comparability, as the NIH toolbox has not yet been

translated into the home languages of participants in the Drakenstein Child Health Study. As such, all measures were administered in English.

**Additional neuropsychological measures.** To date, no studies have been published using the NIH Toolbox within a South African context. Accordingly, a number of validated paper and pencil tests were included in the assessment in order to validate the NIH Toolbox results. The Wide Range Assessment of Memory and Learning (WRAML II) (Sheslow and Adams, 1990) was used as a measure of immediate and delayed memory recall. The Color Trails 1 and 2 tests (D'Elia, Satz, Uchiyama, & White, 1989) were used to assess psychomotor processing speed and executive functioning, respectively. The Color Trails Test 1 was used as a measure of psychomotor speed, while the Color Trails Test 2 was used as a measure of task-switching (Diamond, 2013; Porter et al., 2007). The Color Trails Test is ideal in the current research setting as it was developed to be free from cultural bias, and it can be administered nonverbally (D'Elia et al., 1989). The Color Trails Test includes an interference index (determined by subtracting Color Trails 1 time from Color Trails 2 time, then dividing by Color Trails 1 time), which helps obtain a purer measure of executive function by controlling for processing speed. The digit span (Wechsler, 1997) forwards was used as a measure of attention, and the digit span backwards was used as a measure of working memory/executive function. These additional measures have been used successfully in a South African research context on numerous occasions (for example, see Schoeman, Carey, and Seedat (2009)), and are frequently employed in PTSD and MDD research.

## **Procedure**

All participants were assessed at the 18-month postnatal DCHS visit at their primary health clinic. While the toddler was undergoing their clinical assessments, the mother completed the neurocognitive assessment. Neurocognitive testing typically took place in the morning, in a quiet room at the clinic. Participants began their assessment session by completing the paper and pencil tests (the WRAML II, Color Trails 1 and 2, and digit span, in that order). After these measures were completed, participants began the NIH Toolbox assessment. The NIH Toolbox was presented to the participant on a computer monitor, and participants were required to respond by pressing either the left or right arrow key on a keyboard. All task instructions were explained to the participants in English, and they were allowed to ask questions before



commencing the assessment. As per NIH Toolbox protocol, a practice example was given to the participants for each test prior to commencement of testing. After the example, the participant performed the task with no additional help or guidance. In totality, each neurocognitive assessment was approximately one-hour long.

To ensure that the examiner was blind to participant group designation, participants underwent a neuropsychiatric interview, conducted by a psychiatrist, a month later. This interview (which consisted of the MINI) determined in which group each participant belonged. If a preliminary diagnosis of PTSD was made, the CAPS was administered at a subsequent visit.

### **Data Analysis**

The data was analysed quantitatively using SPSS 24. As a preliminary analysis, bivariate correlations were run to explore the correlations between the paper and pencil tests and the NIH Toolbox measures. Convergent validity was assessed by computing correlations between the Toolbox measures and paper and pencil tests that test the same domains. Discriminant validity of the toolbox measures was assessed by computing correlations between Toolbox measures and paper and pencil tests of different domains. As a primary analysis, analysis of covariance tests (ANCOVA) were used to compare neurocognitive performance on the NIH Toolbox measures between groups. Age and education were included as covariates in the models. The education variable used in the analyses was a variable created to reflect years of education, rather than the NIH Toolbox education variable, which included education levels not found within the South African education system. Analyses were conducted using raw scores for all tests, except for two measures, the Dimensional Change Card Sort, and the Flanker Attention and Inhibition measure. Both of these tests generate a final score which combines the participant's accuracy and reaction time to create a computed score (Slotkin et al., 2012). These scores range from 0 to 10 in value. If a participant's accuracy score is less than or equal to 80%, the final score is the accuracy score. However, if a participant's accuracy score is greater than 80%, the participant's reaction time is combined with the accuracy score (Slotkin et al., 2012).

**Executive function composite score.** One of the objectives of the present dissertation was to identify differences in subdomains of executive function and global executive function. As a number of EF tasks were utilised in this study, an executive function composite score was created to determine associations between diagnoses of PTSD, MDD, and PTSD with comorbid

MDD and global executive function. The composite score was created by averaging scaled scores for each of the executive function measures, including the Dimensional Change Card Sort (set-shifting), Flanker Attention and Inhibition (inhibition), List Sorting Working Memory (working memory), Color Trails Test 2 (set-shifting), and digit span backwards (working memory).

**Additional analyses.** Additional analyses included hierarchical multiple regression models using CAPS total score as a predictor variable for neurocognitive performance. Age and education were added as further predictor variables in the second step. We were unable to explore depression symptom severity as a predictor for neurocognitive performance could not be explored (see Limitations).

**Multiple comparisons.** The Bonferroni method was used to correct for Type 1 error for ANCOVA tests of group differences in all 6 executive function and attention primary outcome measures in this study (adjusted alpha =  $.05/6 = .008$ ). No multiple comparisons procedure was employed for other outcomes compared between groups, however, given their exploratory nature.

## Results

A total of 200 participants were recruited for this study. Of the 200 participants, 25 participants were excluded from analysis for a variety of reasons, such as: no follow-up diagnostic criteria available ( $n = 9$ ), psychopathology or comorbid diagnoses other than PTSD or MDD ( $n = 13$ ), and subthreshold PTSD diagnosis ( $n = 3$ ). Thus, the total sample ( $n = 175$ ) was made up as follows: PTSD group  $n = 36$ ; MDD group  $n = 30$ ; PTSD+MDD group  $n = 23$ ; and control group  $n = 86$ . Of these participants, there were  $n = 4$  participants with current PTSD and  $n = 5$  with current MDD.

### Demographics

Demographics for the sample are presented in Table 1. There were no significant differences between the four groups on age ( $F(3, 171) = 1.74, p = .162$ ). There was, however, a significant difference between groups on education level ( $F(3, 171) = 4.04, p = .008$ ). Post hoc comparisons (Tukey's) indicated that the average level of education was significantly higher in the control

than the comorbid group ( $p = .009$ ). The effect size, calculated using eta squared, was .06, a moderate effect size (Rosenthal & Rosnow, 2008). The PTSD, MDD, and control groups were comparable with respect to education.

An independent samples t-test was run to determine whether there were differences between the PTSD group and the comorbid group on CAPS total score. The results indicate that there was a significant difference between the groups ( $t(57) = 0.001, p = .002$ ), with the comorbid group exhibiting greater mean CAPS scores ( $M = 85.8, SD = 18.4$ ), than the PTSD only group ( $M = 70.4, SD = 17.4$ ).

Table 1

<i>Demographic Data</i>						
	PTSD	MDD	PTSD+MDD	Control	<i>F/t</i>	<i>p</i>
	<i>n = 36</i>	<i>n = 30</i>	<i>n = 23</i>	<i>n = 86</i>		
Age mean ( <i>SD</i> )	28.86 (6.56)	28.17 (6.24)	30.7 (6.92)	27.56 (5.51)	1.73	.16
Education mean ( <i>SD</i> )	10.78 (2.76)	10.83 (2.32)	9.96 (2.4)	11.65 (1.96)	4.04	.008
CAPS total score ( <i>SD</i> )	70.44 (17.44)	NA	85.87 (18.49)	NA	-3.23	.002

### NIH Toolbox validity

Bivariate correlations were run comparing the NIH Toolbox measures (RAVLT, DCCS, Flanker Inhibition and Control, LSWM, Oral Symbol Digit, and Pattern Comparison Processing Speed test) with the paper and pencil tests (WRAML II, CT 1 and 2, and digit span forwards and backwards). The results indicate that the NIH Toolbox measures correlate well with the relevant paper and pencil tests (Table 2). On all Toolbox measures and the *WRAML II total, delayed recall*, and both *digit span forwards* and *backwards*, higher test scores indicate better performance, while on measures such as *WRAML II intrusions, Color Trails 1* and *2*, lower scores indicate better performance. Scores on the RAVLT were significantly and positively correlated with other verbal memory and learning measures, including the *WRAML II* total score ( $r = .61, p < .001$ ) and *digit span forwards* ( $r = .32, p < .001$ ). The DCCS correlated significantly and negatively with the *Color Trails 2* ( $r = -.52, p < .001$ ). Additionally, the Flanker Inhibition and Control test correlated significantly and negatively with the *Color Trails 2* ( $r = -.48, p <$

.001). The LSWM test correlated significantly and positively with the paper and pencil working memory measure, the *digit span backwards* ( $r = .36, p < .001$ ). The Oral Symbol digit correlated significantly and negatively with *Color Trails 1* ( $r = -.39, p < .001$ ), and the Pattern Comparison processing speed test correlated significantly and negatively with *Color Trails 1* ( $r = -.38, p < .001$ ). The *CT 2* test performance appeared relatively non-specific, correlating the highest of all pencil and paper tests with tests of both executive function (DCCS, Flanker Inhibition) and processing speed (Oral Symbol Digit). This is consistent with the conceptualisation of the *CT 2* as tapping into both of these domains (Mitrushina, Boone, Razani, & D'Elia, 2005). Nevertheless, the observation that relatively high correlations were observed between scores for tests of the same domain provides confidence in the validity of the NIH Toolbox measures for this particular research setting.

The correlations of Toolbox test scores with scores from paper and pencil tests of other domains, although statistically significant, were smaller than the correlations for tests of the same domain, as can be seen in Table 2, supporting the discriminant validity of the NIH Toolbox in this study sample.

Table 2

*NIH Toolbox correlations with paper and pencil tests*

NIH Toolbox measures	Paper and pencil tests				
	WRAML total	CT 1	CT 2	Digit F	Digit B
DCCS	.42**	-.3**	-.53**	.32**	.29**
Flanker Inhibition	.24**	-.24**	-.49**	.25**	.17*
LSWM	.36**	-.3**	-.5**	.36**	.28**
RAVLT	.61**	-.23**	-.3**	.33**	.28**
Oral Symbol digit	.39**	-.39**	-.59**	.29**	.23**
Pattern Comparison	.31**	-.38**	-.49**	.22**	.1

\* significant at  $p = .05$

\*\* significant at  $p < .001$

### **A priori findings: Neurocognitive Scores**

ANCOVAs were run on the neurocognitive measures, with group designation as the primary predictor variable, and using age and education as covariates. Interaction terms for group and age, as well as group and education were only included in the final model if models where these interactions were tested separately as predictors of test scores were statistically significant (at  $\alpha < 0.1$ ). This procedure was employed to maximise the power of the final models run to detect differences in test performance between groups. Where interactions were significant, scatterplots were created, and 1-tailed correlations were run between the test score and the significant covariate, within each group. As per convention, where interactions with group were detected, these were reported in preference to any group main effects. Neurocognitive test results can be found in Table 3.

### **Executive function measures**

#### *NIH Toolbox*

*Dimensional Change Card Sort test (DCCS)* - there was no significant interaction between the covariates and the independent variable; therefore, the interaction terms were removed from the model. The ANCOVA test showed that there was no group effect,  $F(3, 168) = .45, p = .72$ .

Across all groups, greater age and education were associated with poorer and better performance, respectively (at  $p < .001$ ). The final model explained almost 20% of the variability in test scores (adjusted  $R^2 = .186$ ).

*List Sorting Working Memory test (LSWM)* - Both covariates produced significant interaction terms and remained in the model. The comorbid group displayed a significant negative correlation between age and test performance ( $r = -.55; p = .003$ ) (see Figure 1). Higher levels of education were associated with better performance on the LSWM for the PTSD group ( $r = .52; p < .001$ ) and the MDD group ( $r = .35; p = .03$ ) only (see Figure 2). A relatively small portion of the variability in test scores were explained by the final model (adjusted  $R^2 = .106$ ).

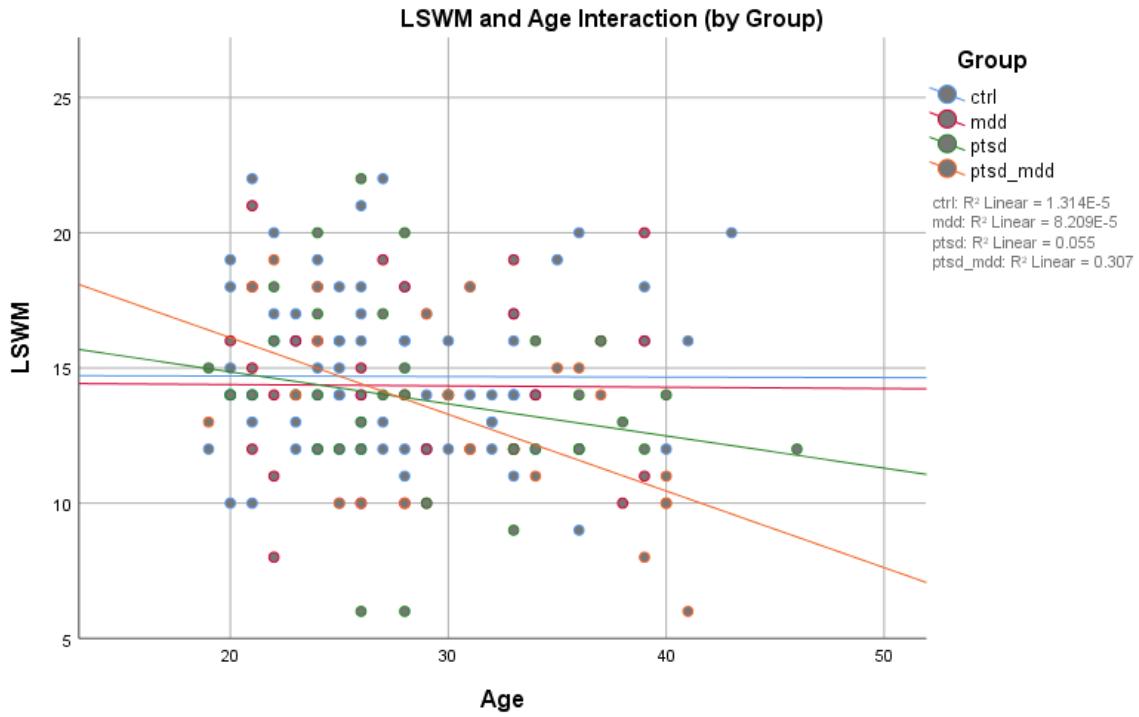


Figure 1. List Sorting Working Memory and Age Interaction

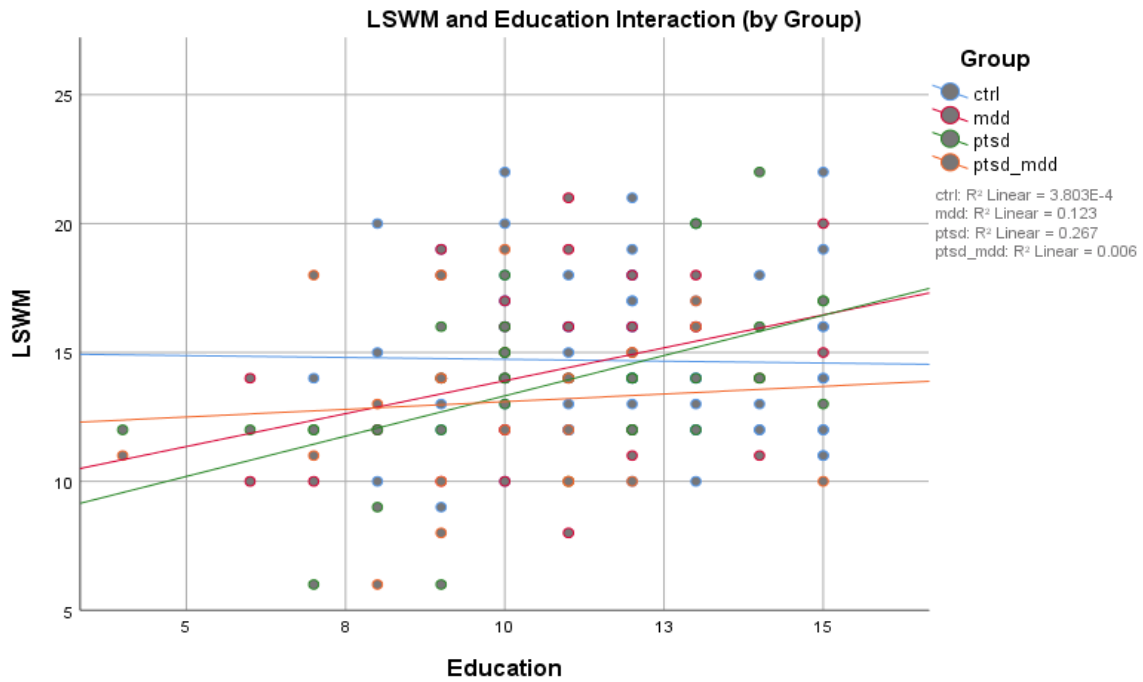


Figure 2. List Sorting Working Memory and Education Interaction

### *Paper and pencil tests*

*Color Trails 2 (CT 2)* - There were no significant interaction terms for the covariates; therefore, the interaction terms were removed from the final model. There was no significant group effect in the final model,  $F(3, 163) = .23, p = .61$ , and this model explained roughly 10% of the variability in test scores (adjusted  $R^2 = .098$ ).

*Digit Span Backwards* - The covariates did not produce significant interaction terms and were removed from the final model. The final ANCOVA indicated that there was no significant group effect,  $F(3, 163) = 0.23, p = .42$ , and less than 10% of the variability in test scores were explained by the final model (adjusted  $R^2 = .08$ ).

### *Executive Function composite score*

There were no significant interaction terms for age and education and were therefore removed from the final model. The final model showed that there was no group effect,  $F(3, 162) = 0.54, p = .216$ , and approximately a fifth of the variability in the test scores (adjusted  $R^2 = .206$ ) was explained by the final model.

## **Attention**

### *NIH Toolbox*

*Flanker Inhibition and Control* - There were no significant interactions for age and education, so the interaction terms were removed from the model. The final ANCOVA model showed that there was no significant group effect on this measure,  $F(3, 169) = 0.18, p = .91$ , and approximately 18% of the variability in test scores is explained by the final model (adjusted  $R^2 = .175$ ).

### *Paper and pencil tests*

*Digit Span forwards* - Age, but not education, produced a significant interaction term and remained in the final model ( $F(3, 160) = .2.61, p = .054$ ). There was a significant negative correlation between age and test score for the PTSD group ( $r = -.41, p = .011$ ), showing that increased age led to poorer digit span forwards results in the PTSD group (see Figure 3). No association was found for the other groups. The final model explained approximately 7% of the variance in test scores (adjusted  $R^2 = .072$ ).

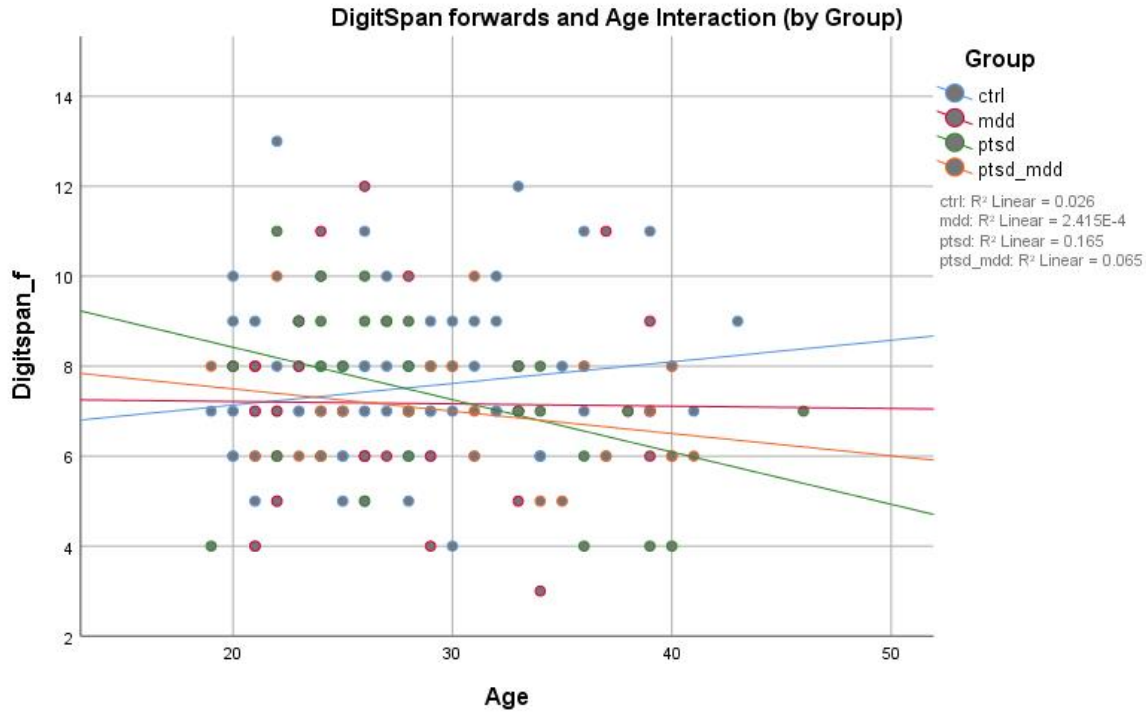


Figure 3. Digit Span Forwards and Age Interaction

## Memory and learning

### NIH Toolbox

*Rey Auditory Verbal Learning Test (RAVLT)* - Both age and education produced significant interaction terms and these terms were kept in the model. Age:  $F(3, 165) = 2.32, p = .077$ ; Education:  $F(3, 165) = 2.86, p = .039$ . Older age was negatively associated with performance on the RAVLT, but only in participants with PTSD (PTSD:  $r = -.32, p = .029$ ; PTSD+MDD:  $r = -.54; p = .004$ ) (see Figure 4). When examining the correlations between education level and RAVLT scores, the PTSD group showed the strongest positive correlation ( $r = .61, p < .001$ ), followed by the MDD group ( $r = .39, p = .018$ ), then the control group ( $r = .21, p = .027$ ) (see Figure 5). The comorbid group did not show a significant correlation. The final model explained less than a quarter of the variability of the test scores (adjusted  $R^2 = .223$ ).



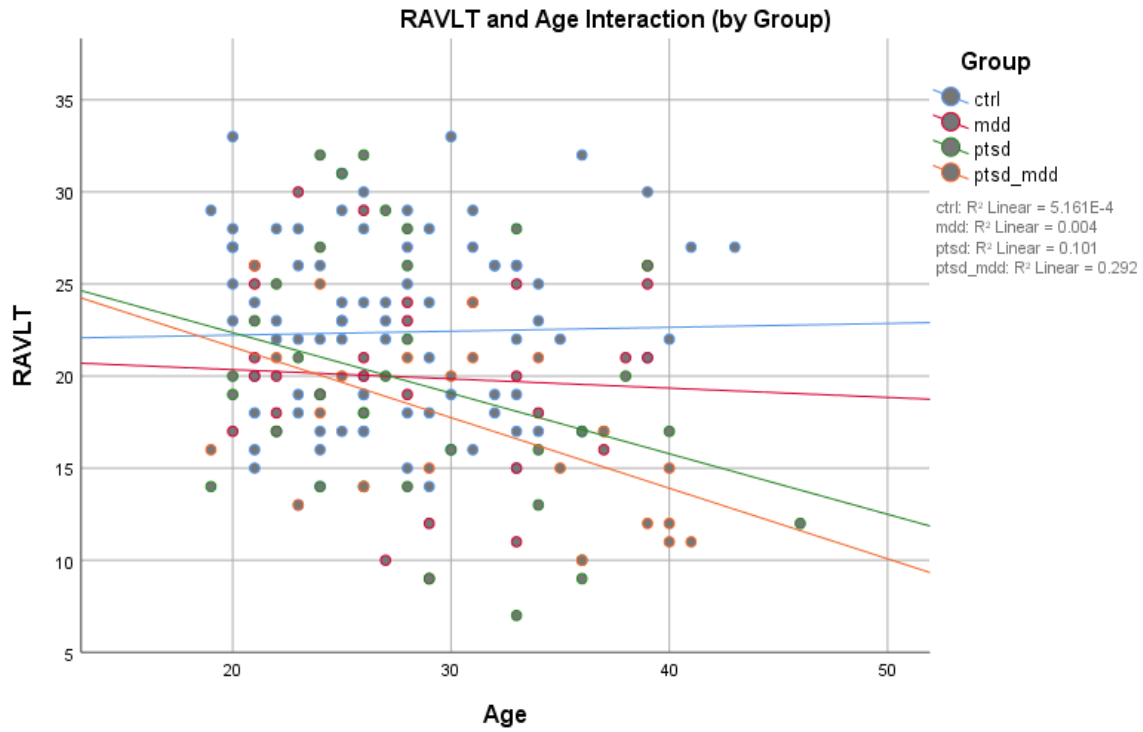


Figure 4. Rey Auditory Verbal Learning Test and Age Interaction

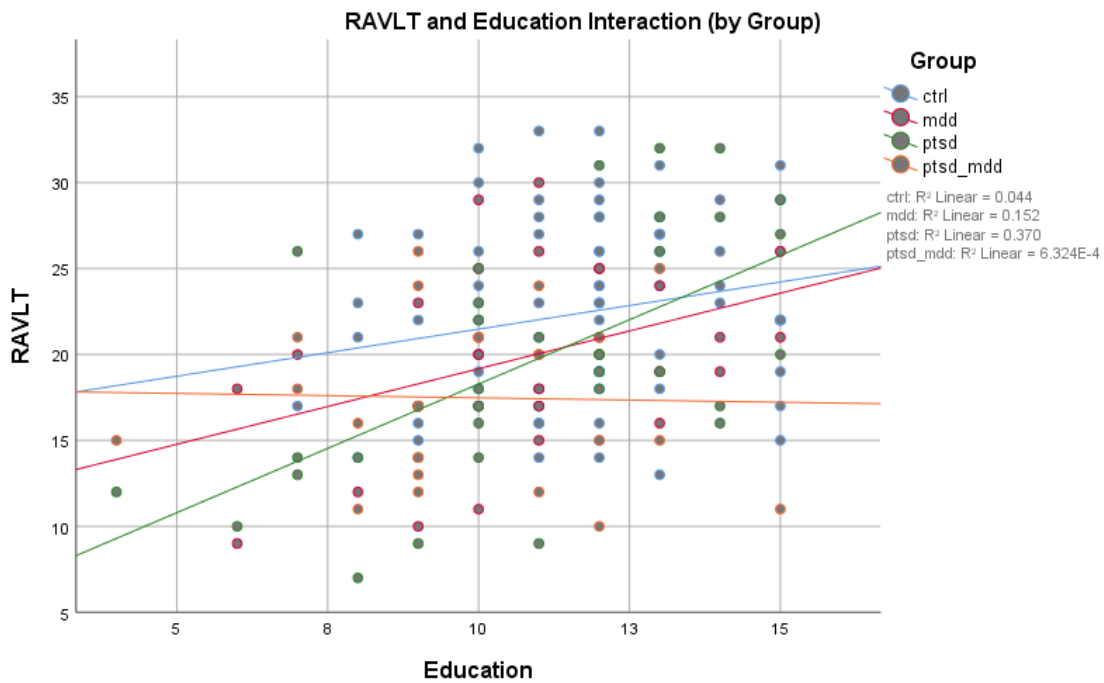


Figure 5. Rey Auditory Verbal Learning Test and Education Interaction

*Paper and pencil tests*

*WRAML II total* - The interaction term for education was significant and remained in the final model,  $F(3, 160) = 2.17, p = .094$ . The correlation between education level and WRAML II total score was positive and significant for the PTSD group ( $r = .66, p < .001$ ), comorbid group ( $r = .43, p = .023$ ), and the control group ( $r = .26, p = .008$ ), but not for the MDD group ( $r = .22, p = .124$ ) (see Figure 6). The final model explained 19% of the test score variance (adjusted  $R^2 = .19$ ).

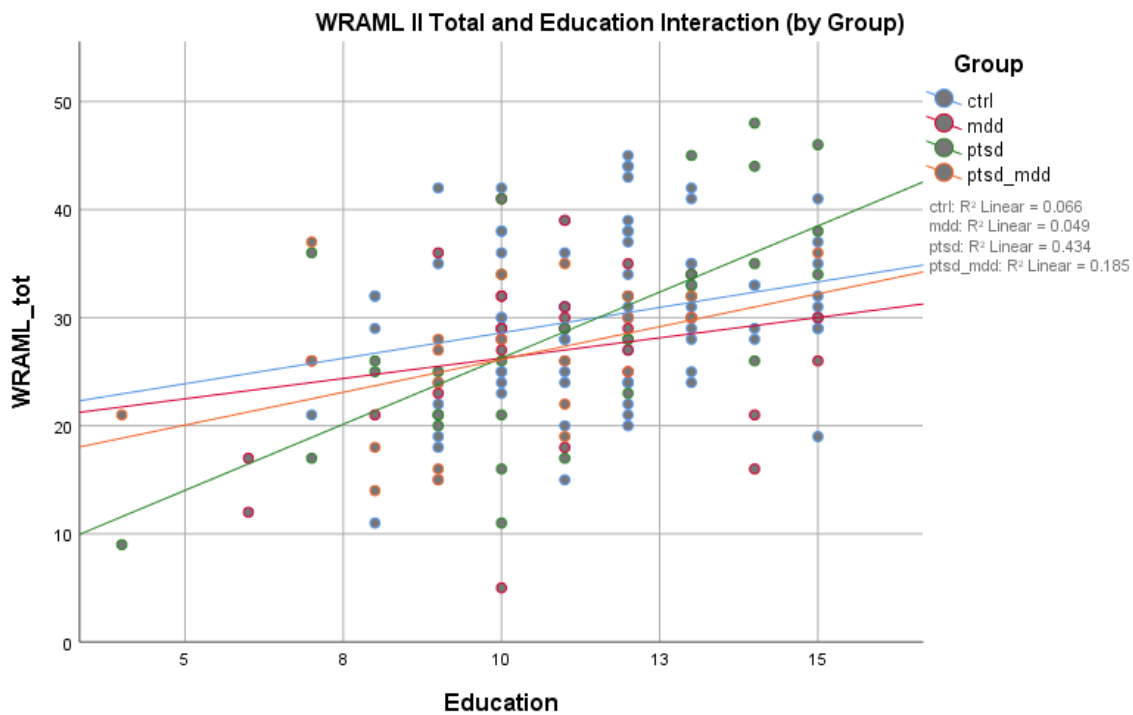


Figure 6. WRAML II Total Score and Education Interaction

*WRAML II delayed recall* – Neither age nor education produced significant interaction terms and were removed from the final model. The final ANCOVA model indicated that there was a group effect,  $F(3, 163) = 2.72, p = .046$ , and approximately 17% of the variance in test scores was explained by the final model (adjusted  $R^2 = .175$ ). Significant pairwise group differences were found between the control group and the MDD group ( $p = .01$ ) with the MDD group demonstrating significantly fewer recalled words. A significant pairwise group difference was

also found between the MDD group and the PTSD group,  $p = .017$ , with the MDD group exhibiting significantly fewer recalled words than the PTSD group. Comparable test performance was observed when comparing the control group and either of the PTSD groups (PTSD, comorbid).

*WRAML II intrusions* – Interaction terms for age and education were not significant, therefore they were removed from the model. The final ANCOVA model found a group effect,  $F(3, 163) = 3.46, p = .018$ . The final model explained almost 6% of the total variance in the intrusions test scores (adjusted  $R^2 = .058$ ). Significant pairwise group differences were found between the control group and PTSD group ( $p = .002$ ) with the PTSD group exhibiting significantly more intrusions than the control group. A pairwise comparison between the MDD group and PTSD group was approaching significance ( $p = .051$ ), with the PTSD group demonstrating more intrusions than the MDD group.

## **Processing speed measures**

### *NIH Toolbox*

*Oral Symbol Digit test* - The covariates did not produce significant interaction terms; thus, the interaction terms were not included in the final model. The final model indicated that there was no significant group effect,  $F(3, 167) = 1.03, p = .38$ , and approximately a quarter of the variance of test scores was explained by the final model (adjusted  $R^2 = .24$ ).

*Pattern Comparison Processing Speed test* - Age did not produce a significant interaction term and was therefore left out of the model. A significant education interaction effect was observed ( $F(3, 166) = 2.86, p = .038$ ) (see Figure 7). A significant group effect was observed in the final model,  $F(3, 166) = 3.01, p = .032$ . Post-hoc analysis revealed that level of education was significantly and positively correlated with test score for the PTSD group ( $r = .51, p < .001$ ) and the controls ( $r = .4, p < .001$ ). The final model explained almost a quarter of the variability of test scores (adjusted  $R^2 = .22$ ).

### *Paper and pencil tests*

*Color Trails 1 (CT1)* - Age and education did not produce significant interaction terms and the interaction terms were removed from the final model. The final ANCOVA model showed that

there was no significant group effect,  $F(3, 163) = 0.42, p = .388$ , with only a tiny portion of the variability in test scores explained by this model (adjusted  $R^2 = .009$ ).

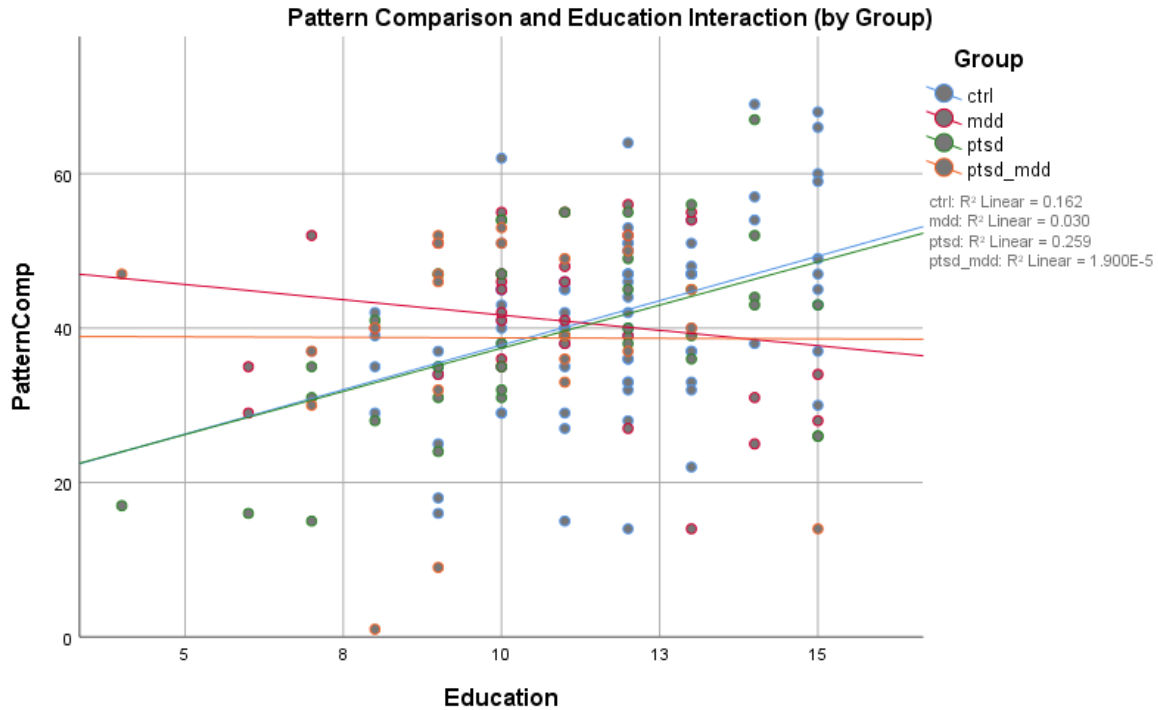


Figure 7. Pattern Comparison Processing Speed Test and Education Interaction

## Secondary findings

### Analysis of PTSD symptom severity as a predictor of neurocognitive test performance

**CAPS regression models.** Hierarchical multiple regression models were run investigating the effects CAPS total score, age and education have on test performance. The first model only contained CAPS total score, while the second model contained CAPS total score, age and education. This procedure was followed given concerns that the addition of covariates would jeopardise power to detect an association between PTSD severity and test performance in light of the relatively small group sizes used in this analysis. The following findings apply to participants belonging to the PTSD group and comorbid group combined.

## **Executive function**

### *NIH Toolbox*

*DCCS* – In model one, CAPS total score was significantly associated with performance on the DCCS ( $F(1, 56) = 4.08, p = .048$ ), and explained only 6.8% of the variance in DCCS scores. After adding age and education, the final model was significant ( $F(3, 54) = 4.79, p = .005$ ), with the total variance explained by the model increasing to 21%. Age and education explained a further 14.2% of the variance,  $R$  squared change = .142,  $F$  change ( $2, 54) = 4.87, p = .011$ . The final model explained almost a fifth of variability in test scores (adjusted  $R^2 = .166$ ), and education was significant,  $beta = .34, p = .009$ . With the addition of these covariates, CAPS total score was no longer a significant predictor ( $p = .16$ ).

*LSWM* – Model one showed that CAPS score was not significantly associated with test scores ( $F(1, 57) = .019, p = .89$ ). Total variance explained by model two as a whole was 23.8%, and this model was significant ( $F(3, 55) = 5.72, p = .002$ ). Adding age and education to the model explained 23.7% additional variance ( $R$  squared change = .237,  $F$  change = ( $2, 55) = 8.57, p < .001$ ). Almost a fifth of the variability in test scores was explained by the final model (adjusted  $R^2 = .196$ ). Both age and education were significant in the final model; Age  $beta = -.31, p = .012$ ; Education  $beta = .32, p = .012$ . However, CAPS total score was not a significant predictor ( $p = .27$ ) once the covariates were added to the model.

### *Paper and pencil tests*

*CT 2* – In the original model, CAPS total score was not significantly associated with performance on the Color Trails 2 ( $F(1, 52) = .58, p = .45$ ), and this model only accounted for 1.1% of the variance. Once age and education were added, the model became significant ( $F(3, 50) = 4.54, p = .007$ ), and total variance in test scores explained by the model as a whole was 21.4%. After adding age and education to the original model, the model explained a further 20.3%,  $R$  squared change = .203,  $F$  change ( $2, 50) = 6.46, p = .003$ . Approximately 16% of the variability in test scores was explained by the final model (adjusted  $R^2 = .167$ ). In the final model, age was significant,  $beta = .414, p = .002$ . Once the covariates were added to the model, CAPS total score was not a significant predictor ( $p = .61$ ).

*Digit span backwards* – In model one, CAPS total score was not significantly associated with test scores ( $F(1, 52) = 1.47, p = .231$ ), and accounted for only 2.7% of the total variance in

the original model. Adding age and education, the model explained a further 22.3% of the total variance,  $R$  squared change = .223,  $F$  change (2, 50) = 7.46,  $p < .001$ . Approximately 20% of the variability in test scores is explained by the final model (adjusted  $R^2 = .206$ ). In the final model, education was significant ( $beta = .495$ ,  $p < .001$ ), but CAPS total score was not ( $p = .69$ ).

*Executive function composite* – The original model showed that CAPS score was almost significantly associated with composite score ( $F(1, 52) = 3.43$ ,  $p = .07$ ) and accounted for 6.2% of the total variance. After adding age and education to the model, the model was significant, and total variance explained by the model as a whole was 35.1%,  $F(3, 50) = 9.02$ ,  $p < .001$ . After adding age and education to the model, 28.9% of the variance was further explained by these variables,  $R$  squared change = .29,  $F$  change (2, 50) = 11.14,  $p < .001$ . Over 30% of the variability in composite scores was explained by the final model (adjusted  $R^2 = .312$ ), and both education and age emerged as significant predictors of the composite scores ( $beta = .44$ ,  $p < .001$  versus  $beta = -.24$ ,  $p = .047$ , respectively), however, CAPS total was not significant ( $p = .25$ ).

## **Attention**

### *NIH Toolbox*

*Flanker* – The original model demonstrated that CAPS total score was not significantly associated with Flanker test scores ( $F(1, 57) = 3.36$ ,  $p = .072$ ), but after adding age and education, the model became significant ( $F(3, 55) = 4.56$ ,  $p = .006$ ), and 19.9% of the variance was explained by the model as a whole. Age and education explained an additional 14.4% of the variance,  $R$  square change = .14,  $F$  change (2, 55) = 4.93,  $p = .011$ . Approximately 15% of the variability in test scores was explained by the final model (adjusted  $R^2 = .156$ ), and age was significant,  $beta = -.25$ ,  $p = .045$ . CAPS total score was not a significant predictor,  $p = .24$ .

### *Paper and pencil tests*

*Digit span forwards* – Model one did not show a significant association between CAPS total score and digit span forwards scores ( $F(1, 52) = .56$ ,  $p = .46$ ), however, model two found a significant association between CAPS total score, age, education, and test score ( $F(3, 50) = 4.38$ ,  $p = .008$ ). Total variance explained by model two as a whole was 20.8%. Adding age and education explained a further 19.7% of the variance,  $R$  squared change = .197,  $F$  change (2, 50) = 6.23,  $p = .004$ . The final model explained 16% of the variability in test scores (adjusted  $R^2 =$

.16). In the final model, age is significant ( $beta = -.28, p = .032$ ), as well as education ( $beta = .28, p = .037$ ), but CAPS total score was not significant,  $p = .84$ .

## **Memory and learning**

### *NIH Toolbox*

*RAVLT*- The original model, CAPS total score was not significantly associated with test performance ( $F(1, 57) = .005, p = .94$ ). The model became significant after adding age and education ( $F(3, 55) = 8.04, p < .001$ ), and total variance explained by model two as a whole was 30.5%. Age and education explained a further 30.5% of the variance, after controlling for CAPS total score,  $R$  squared change = .305,  $F$  change (2, 55) = 12.05,  $p < .001$ . Over a quarter of the variability in test scores was explained by the final model (adjusted  $R^2 = .26$ ). In the final model, age ( $beta = -.32, p = .008$ ) and education ( $beta = .4, p < .001$ ) were significant predictors, but CAPS total score was not significant ( $p = .21$ ).

### *Paper and pencil tests*

*WRAML II total* – Model one showed that CAPS total score was not significantly associated with WRAML total score ( $F(1, 52) = .033, p = .86$ ). Model two became significant after adding age and education ( $F(3,50) = 11.21, p < .001$ ), and 40.2% of the variance was explained by the model as a whole. Age and education explained an additional 40.2% of the variance,  $R$  squared change = .402,  $F$  change (2, 50) = 16.79,  $p < .001$ . A large portion of the variability of test scores was explained by model two (adjusted  $R^2 = .36$ ), and education was significant;  $beta = .581, p < .001$ . CAPS total score was not a significant predictor ( $p = .3$ ) once the covariates were added to the model.

*WRAML II delayed* – CAPS total score was not significantly associated with test scores ( $F(1, 52) = .63, p = .432$ ). After adding age and education, the model became significant ( $F(3, 50) = 6.9, p < .001$ ), and total variance explained by the model as a whole was 29.3%. Adding age and education explained an additional 28.1% of the total variance,  $R$  squared change = .281,  $F$  change (2, 50) = 9.93,  $p < .001$ . A quarter of the variability of the test scores were explained by the final model (adjusted  $R^2 = .25$ ). In the final model, the beta value for education was significant,  $beta = .52, p < .001$ , however, CAPS total score was not a significant predictor ( $p = .9$ ).

*WRAML II intrusions* – Model one showed that CAPS score was not significantly associated with number of intrusions ( $F(1, 52) = 2.75, p = .103$ ), but after adding age and education, the model became significant ( $F(3, 50) = 1.3, p = .285$ ), and total variance explained by the model as a whole was 7.2%. Adding age and education to the model explained a further 2.2% of the total variance,  $R$  squared change = .022,  $F$  change =  $(2, 50) = .59, p = .556$ . Only a small portion of the variability in intrusion score was explained by model two (adjusted  $R^2 = .017$ ), and CAPS total score, age and education were not significant predictors.

## **Processing speed**

### *NIH Toolbox*

*Oral symbol digit* – In the first model, CAPS total score was not significantly associated with test scores ( $F(1, 55) = 2.81, p = .099$ ). However, after adding age and education, the model became significant ( $F(3, 55) = 11.69, p < .001$ ), and total variance explained by the model as a whole was 39.8%. Adding age and education to the model explained an additional 35% of the variance,  $R$  squared change = .35,  $F$  change =  $(2, 53) = 14.4, p < .001$ . A large proportion of the variability in test scores was explained by the final model (adjusted  $R^2 = .36$ ), and both age and education were significant, with age recording a larger beta value. Age  $beta = -.44, p < .001$ ; education  $beta = .32, p = .006$ . CAPS total score was not a significant predictor once the covariates were added to the model ( $p = .4$ )

*Pattern comparison* – CAPS total score was not significantly associated with test scores, as shown by model one ( $F(1, 57) = .32, p = .573$ ). However, adding age and education to the model showed a significant association ( $F(3, 55) = 9.17, p < .001$ ). Adding age and education to the original model explained an additional 32.8% of the variance,  $R$  squared change = .328,  $F$  change =  $(2, 55) = 13.52, p < .001$ . Almost 30% of the variability of test scores was explained by the final model (adjusted  $R^2 = .297$ ), and age was significant ( $beta = -.506, p < .001$ ), whereas CAPS was not a significant predictor ( $p = .77$ ).

### *Paper and pencil tests*

*CT 1* – The original model demonstrated that CAPS score was not significantly associated with Color Trail 1 time ( $F(1, 52) = 1.31, p = .258$ ). However, after adding age and education, the model remained non-significant ( $F(3, 50) = 1.73, p = .173$ ), and 9.4% of the total variance was



explained by the model as a whole. Adding age and education to the model explained a further 7%,  $R$  squared change = .07,  $F$  change (2, 50) = 1.92,  $p$  = .15. Only 4% of the variability in test scores was explained by the final model (adjusted  $R^2$  = .04), and age was approaching significance in the model,  $p$  = .056. After adding the covariates, CAPS total score was not a significant predictor,  $p$  = .28).

NEUROCOGNITIVE ASSESSMENT OF PTSD AND MDD

Table 3

*Means, Standard Deviations, and ANCOVA Test Statistics for Neurocognitive Tests*

<i>NIH Toolbox measures</i>	PTSD <i>n</i> = 36	MDD <i>n</i> = 30	PTSD+MDD <i>n</i> = 23	Control <i>n</i> = 86	<i>F</i>	<i>p</i>
DCCS	-0.14 (1.12)	0.05 (1.23)	-0.39 (1.1)	0.15 (0.79)	0.45	.72
List sorting WM	13.81 (3.34)	14.34 (3.42)	13.09 (3.54)	14.69 (2.9)	2.29	.08
Flanker	6.82 (1.17)	6.78 (1.24)	6.44 (1.14)	6.97 (1.02)	0.18	.91
RAVLT	19.44 (6.79)	19.93 (5.32)	17.48 (4.9)	22.38 (5.13)	2.13	.09
Oral symbol digit	62.24 (17.13)	58.07 (14.83)	54.7 (14.52)	63.69 (14.72)	1.03	.38
Pattern comparison	39.14 (12.12)	41.03 (10.63)	38.74 (14.16)	41.6 (11.21)	3.02	.032*
<b><i>Additional measures</i></b>						
Color Trails 2 time	122.19 (32.94)	116.62 (33.03)	127.95 (43)	118.62 (36.8)	0.23	.88
CT interference index	0.65 (0.57)	0.68 (0.57)	0.82 (0.5)	0.73 (0.57)	0.47	.71
Digit span backwards	4.09 (1.49)	4.21 (1.42)	3.77 (1.44)	4.16 (1.59)	0.23	.88
Digit span forwards	7.34 (1.86)	7.17 (2.12)	6.95 (1.36)	7.5 (1.66)	2.38	.07
WRAML total score	28.78 (9.99)	26.83 (7.9)	26.14 (6.91)	30.15 (7.18)	1.97	.12
WRAML intrusions	3.31 (2.75)	2.31 (2.28)	2.36 (1.92)	1.85 (1.72)	3.46	.018*
WRAML delayed recall	8.28 (3.29)	6.69 (2.36)	7.05 (2.65)	8.5 (2.54)	2.72	.046*
Color Trails 1 time	4.31 (0.29)	4.24 (0.24)	4.24 (0.27)	4.23 (0.35)	0.42	.74
<b><i>Composite score</i></b>						
EF composite	-0.018 (0.69)	-0.029 (0.69)	-0.317 (0.73)	0.105 (0.59)	0.54	.65

Notes. \*  $p < .05$

## Discussion

The aim of the present study was to test the hypothesis that neurocognitive deficits would be evident in a sample of mothers with PTSD and MDD in a LMIC setting, and that these would be particularly apparent for executive function and attention domains. The results of this study are discussed in relation to specific hypotheses are presented below, followed by a general discussion of the implications of these findings.

The first hypothesis was that *individuals with a sole diagnosis of PTSD or MDD will be impaired, relative to a healthy control group, with respect to executive functioning, attention, memory and learning, and processing speed. We expect these effects to be most apparent for domains that are particularly reliant on frontal cortical brain function, such as attention and EF.*

In the present sample, very specific neurocognitive impairments were found, rather than general neurocognitive dysfunction. ANCOVA analyses indicated that there were significant group differences on the processing speed measure, as well as on the measures of intrusions and delayed recall. It is notable that there was a group effect on the Pattern Comparison processing speed test, yet no group effect was observed on the other measures of processing speed. It may be that the Pattern Comparison test is more sensitive to visuospatial deficits rather than processing speed only, but this will be explored further later.

On the WRAML II, relative to healthy controls, the PTSD group exhibited greater intrusions, which suggests that PTSD is associated with greater intrusive recollections compared to healthy controls. Further, with regard to WRAML II delayed recall, the MDD group displayed the poorest delayed recall results, with significantly fewer words recalled for the MDD group relative to the control group.

The second hypothesis was that *comorbid PTSD and MDD will be associated with worse performance on all neurocognitive domains relative to controls. Where differences occur between the comorbid and mono-diagnostic clinical groups, we predict impairment to be worse in the comorbid group.*

Where differences were observed on the processing speed measure, the comorbid group displayed the greatest impairment relative to the control group, highlighting that PTSD with comorbid MDD is associated with slower processing speed, relative to controls.

Neurocognitive impairment was not always worse in the comorbid group when compared to the mono-diagnostic groups, for example on the measure of delayed and immediate recall (WRAML II).

The third hypothesis was that, *with respect to particular components of EF, all the clinical groups will perform more poorly on measures of set-shifting, working memory and inhibition relative to controls.*

In examining the subdomains of executive function, including working memory, ANCOVA analyses indicated there were no significant group differences on any of the subdomain measures. The mono-diagnostic groups did not demonstrate impairment on executive functioning tasks relative to the control group; however, a significant positive correlation was observed between education level and working memory scores in both the PTSD and MDD groups. A significant negative correlation between age and working memory was observed in the comorbid group, relative to the remaining groups.

The final hypothesis was that *greater PTSD symptom severity will be associated with worse task performance, particularly with regards to EF and attention*

PTSD symptom severity and its association with neurocognitive function in the PTSD and comorbid groups was measured using hierarchical multiple regression. The analyses showed that CAPS total score was significantly associated with the set-switching measure (Dimensional Change Card Sort), implying that increased PTSD symptom severity in the PTSD and comorbid group is associated with impaired set shifting. This association was not apparent when the relationships between task performance and both subject age and education were considered. Significant associations were not found between PTSD symptom severity (for the PTSD group as well as the comorbid group) and neurocognitive performance on the remaining tasks.

However, a trend-level association was observed between PTSD symptom severity and the EF composite score, indicating worse performance in the PTSD and comorbid groups in participants with more severe PTSD symptoms.

The present study found that there were no significant differences between any of the groups on executive functioning measures such as the *Color Trails Tests*, digit span, as well as the working memory measure (List Sorting Working Memory). Similar findings were reported by Stein et al. (2002), with the PTSD group and control group performing comparably on

measures such as Trail Making Test, the digit span, as well as measures of memory. As in this study, Stein et al. (2002) employed a female-only sample with high levels of interpersonal violence (IPV) related trauma. Johnsen and Asbjørnsen (2008) support the theory that different samples exhibit different neurocognitive findings, as they found that larger effect sizes of impairment on neurocognitive domains for male combat veterans than female participants with exposure to sexual or physical abuse. The general lack of group differences on executive function, attention, and memory observed in this study could indicate that there is a degree of resilience in the sample. As these participants are exposed to high levels of gang violence, interpersonal violence, and difficult day-to-day living conditions (Abler et al., 2014; Lund et al., 2010), it is possible that the participants in this sample have built up resilience as a protective factor. This resilience is possibly helping the participants perform better than PTSD and MDD samples from different living conditions.

Contrary to predictions, the present study found that MDD is not associated with significant impairments in domains (attention, processing speed) where deficits have typically been reported in the MDD literature (Lee et al., 2012; Snyder, 2013). Instead, the present MDD group only exhibited delayed recall impairments. This discrepancy may be due to the nature of the sample employed in this study. This sample of female participants from a low-middle income country, with trauma exposure differs from the majority of studies whose samples stem from western countries with little to no trauma exposure in their middle-income settings.

Importantly, the present study found that covariates such as age and education explained a significant portion of the variability in test scores. When controlling for CAPS total score, age makes the biggest unique contribution to domains such as attention and processing speed, while education makes the largest contribution to the memory/learning domain, and the combination of age and education affects executive function. This finding is consistent with literature suggesting that both age and education influence neurocognitive domains such as executive function and attention (Constantinidou, Christodoulou, & Prokopiou, 2012; Perbal, Droit-Volet, Isingrini, & Pouthas, 2002). Evidence suggests that lower education levels are associated with poorer executive function performance (Constantinidou et al., 2012), and older age is associated with poorer attention and slower processing speed (Perbal et al., 2002). The findings from the present study concur with the literature.

Examining the interactions of age and education on group differences showed that relative to controls, older age was associated with worse performance on measures of

learning (RAVLT), attention (digit span forwards), and executive function (LSWM) in participants diagnosed with PTSD (PTSD and comorbid groups). No effect of age was found for the MDD group on these tasks. Further, education tends to have a protective effect on the mono-diagnostic groups on the auditory verbal learning measure (RAVLT). Higher levels of education were associated with better working memory performance, as assessed using the LSWM, for the mono-diagnostic groups, but not the comorbid group, compared to controls. This finding suggests that the protective effect of education is reduced for the comorbid group.

Consistent with current literature and diagnostic criteria, the PTSD group demonstrated significant levels of intrusions, based on the WRAML II intrusions results (Brandes et al., 2002; DeGutis et al., 2015). This finding indicated that the PTSD group exhibited a greater number of intrusive recollections than the MDD and control groups in the present study. This finding was expected given the re-experiencing/intrusions symptom cluster diagnostic criteria for PTSD. This finding suggests that intrusive thoughts experienced by PTSD patients may not be restricted to intrusive trauma-related thoughts but may rather be related to all thoughts that require a degree of inhibition. However, the comorbid group performed similarly to the MDD group regarding number of intrusive recollections. Both the MDD group and comorbid group experienced fewer intrusive recollections relative to the PTSD group. This suggests that MDD symptoms may be ameliorating intrusive thoughts and responses in PTSD with comorbid MDD.

It was hypothesised that the comorbid group would perform the worst of the three clinical groups on the neurocognitive measures. Of all the neurocognitive tests, the present study found that comorbidity is associated with significantly reduced processing speed on the Pattern Comparison test. Instead, higher levels of education exhibited a protective effect on the mono-diagnostic groups, which was not observed in the comorbid group. The finding that education level did not modulate working memory performance in the comorbid group, whereas it did in the mono-diagnostic groups, suggests that the neurocognitive impairments on these working memory measures may not be more severe in the comorbid group.

Scott et al. (2015) suggest that the neurocognitive deficits associated with PTSD may be due to alterations to the fronto-limbic circuitry. Evidence suggests that prefrontal regions (such as the dlPFC) are affected in disorders such as PTSD and MDD (Etkin et al., 2013; Etkin & Wager, 2007; Rogers et al., 2004; Thomas & Elliott, 2009). For instance, decreased intrinsic connectivity in the frontal cortex has been linked to executive dysfunction in depression

(Rogers et al., 2004). Working memory and set-shifting are associated with the dorsolateral prefrontal cortex (dlPFC), and reduced dlPFC has been associated with executive and prefrontal impairments (Rogers et al., 2004). In a review, Etkin et al. (2013) reported that imaging studies mirror the neuropsychological studies for both PTSD and MDD regarding EF dysfunction and deficits in activation of the cognitive control networks (prefrontal regions associated with executive functions). Therefore, examining domains such as attention and executive functioning (domains that depend on prefrontal regions) in this sample is of particular importance, especially with regard to treatment adherence and daily functioning.

### **Limitations**

A number of important limitations of this work deserve acknowledgement.

First, this study was cross-sectional in nature, and due to this, it is not possible to establish the causality of the relationship observed between age and neurocognitive function.

Second, the NIH Toolbox was used as the primary neurocognitive assessment measure. Although the NIH Toolbox has been well validated and standardized, it has not, to this date, been officially validated in a South African population. However, according to Weintraub et al. (2013), the NIH Toolbox was developed to become a ‘common currency’ for researchers, and it can be used across a range of populations. Moreover, this study established preliminary evidence of concurrent validity of the NIH Toolbox in a South African sample, suggesting that the NIH Toolbox is a sufficient tool to utilise in a South African context. However, as the NIH Toolbox is computerised, participants in low income regions with little-to-no computer experience may find using a computer during assessment daunting. A potential issue, for all neurocognitive research, is that the measures used to assess a particular domain may actually be measuring more than one domain, or a number of subdomains (Austin, Mitchell, & Goodwin, 2001). This makes teasing apart the relevant domains affected difficult. For example, Harvey et al. (2004) suggests that executive function measures tend to include many functions (for example, set-shifting tasks include attention and aspects of memory functioning too), which makes executive dysfunction difficult to tease out.

A third limitation is the sample size. Despite every effort to increase the size of the clinical groups, a large proportion of participants ( $n = 13$ ) were excluded based on alcohol and/or substance abuse or dependence. Research has consistently shown that alcohol abuse negatively affects neurocognitive functioning (Bates, Bowden, & Barry, 2002; Brown, Tapert, Granholm, & Delis, 2000), and therefore it remained an exclusion criterion. Unfortunately, alcohol and substance abuse are a common feature of the Western Cape

region. Research by Parry et al. (2005) reported that 24.2% of women in the Western Cape are current drinkers. Further, research by Petersen Williams, Jordaan, Mathews, Lombard, and Parry (2014) determined that alcohol was the most common substance used overall, and methamphetamine was found to be the most commonly used illicit drug. Indeed, substance abuse in the Drakenstein region of the Western Province is very common and seems to be in line with similar research in the region (Stein et al., 2015). The Drakenstein sample has highlighted the alcohol and drug issue in the region. With this issue in mind, the results from the present study can only be generalised to non-substance-abusing women from a LMIC.

A potential confounding issue is the combination of current and lifetime diagnoses in the clinical groups. Low numbers of participants with only diagnoses of current PTSD and/or MDD diagnoses necessitated the inclusion of participants with lifetime diagnoses. The heterogeneous nature of the clinical groups' diagnoses may therefore be masking neurocognitive dysfunction in this sample.

Due to the high research burden on participants in the DCHS, a clinician-administered measure for depression symptom severity was not included. BDI-II data was collected by the main DCHS study at the 18-month post-natal visit as a substitute. However, it was apparent that there were many issues with the data; for example, there was a large proportion of missing data and incomplete questionnaires, as well as a proportion of participants lost to follow-up. An unusually high proportion of participants scoring zero on the measure was also found. These inconsistencies led to the decision to exclude the BDI-II data, as it was decided that the data was not accurate and did not represent the sample correctly. Investigating the association between MDD symptom severity and neurocognitive performance, utilising a measure such as the Hamilton Depression Rating Scale or the Montgomery-Asberg Depression rating scale, is therefore an important topic for further research.

Education levels significantly differed between groups, with the comorbid group displaying the lowest average education level. Education was controlled for in the analyses, however, if there is an absolute minimum level of education that needs to be achieved to detect a modulating effect of education, this may be a problem for the comorbid group.

Socioeconomic variables, such as type of employment and level of employment and medication use, were not collected in this study. Due to this, neurocognitive functioning could not be examined in relation to employment in LMI settings, for example. Future research should endeavour to collect these data in order to determine whether employment affects neurocognitive functioning, and to fully examine neurocognitive abilities in patients with PTSD, MDD, and PTSD with comorbid MDD.



The final limitation is that this study utilised an all-female sample. While this may be seen as a potential limitation, it must be noted that women are twice as likely as men to develop PTSD (Foa & Street, 2001). Furthermore, research has indicated that women are more susceptible to developing depression than men (Kessler, 2003; Nolen-Hoeksema, 2001). Additionally, the vast majority of current research focuses on male combat veterans. By using an entirely female sample, it reduces the sample bias in the literature. However, future studies should consider using a more generalizable sample by including men in the sample.

### **Conclusions**

This research set out to explore the effects PTSD, MDD, and PTSD with comorbid MDD has on the neurocognitive profile of mothers in a South African community setting, with a particular interest in domains associated with prefrontal regions (for example, executive functioning and attention). The results indicated that PTSD, MDD, and PTSD with comorbid MDD present with limited neurocognitive dysfunction in this particular sample. Taking into account the limitations, the present study determined that factors such as age and education affect test performance to differential degrees. The PTSD groups were particularly vulnerable at an older age to deficits in verbal learning, working memory, and attention. Higher levels of education were associated with better verbal learning and working memory performance for both the PTSD and MDD group, suggesting the importance of research into the value of psycho-educational or neurocognitive remediation interventions in these populations. Furthermore, results indicated that MDD is associated with delayed memory recall impairments, while PTSD with comorbid MDD is associated with inferior processing speed. The findings from this study indicated that while overt executive dysfunction was not associated with psychiatric classification, greater PTSD symptom severity may impact set-shifting and resilience to intrusive cognitions in the PTSD and comorbid groups. The findings from the present study could guide future research, as well as inform potential treatment plans for the above disorders.

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## **Chapter 3**

### **Resting-state functional connectivity in PTSD, MDD, and PTSD with MDD**

Chapter 1 illustrated that executive dysfunction and attentional impairments are common sequelae in PTSD, MDD, and PTSD with comorbid MDD (Olf et al., 2014; Scott et al., 2015; Snyder, 2013). It is therefore important to explore the functional networks associated with these neurocognitive domains, networks known as the cognitive control networks. Evidence suggests that resting-state network connectivity can serve as a proxy for functional networks that underlie neurocognitive abilities (Smith et al., 2009). While the intrinsic functional connectivity of cognitive control networks has been explored in PTSD and MDD samples, there has been little focus given to functional connectivity abnormalities in a sample of patients with PTSD and comorbid MDD. Additionally, the cognitive control networks and their connectivity with the default mode network have received little attention in this patient population.

### **Resting-State fMRI in Research**

Resting-state (RS) functional imaging is a method that investigates the temporal relation of neural activity between brain regions based on fluctuations in the intensity of blood oxygen level dependent (BOLD) signal and allows one to map large-scale networks in the brain (Buckner et al., 2013; Cole et al., 2010; Greicius et al., 2009; Rosazza & Minati, 2011). Spontaneous low frequency activity (< 0.1 Hz) can be detected in a variety of brain regions or networks during resting conditions (Rosazza & Minati, 2011), and these networks tend to reflect features of anatomical connectivity and organisation, allowing researchers to draw tentative conclusions regarding structure and function of certain regions (Buckner et al., 2013).

The default mode network (DMN), dorsal attention network (DAN), salience network (SN), and bilateral frontoparietal networks (FPAR) are robust resting-state networks that are frequently reported in the scientific literature. Researchers highlight an antagonistic relationship between the “task negative” default mode network and the “task positive” cognitive control networks (salience network, dorsal attention network, and frontoparietal networks), which has been described as an ‘activation/deactivation dichotomy’ by Fox et al. (2005). The DMN exhibits decreased activity during task performance, while the cognitive control networks exhibit greater activity during tasks (Fox et al., 2005; Liu et al., 2010). It is argued that the salience network acts as a switching mechanism between the default mode network and the frontoparietal network (Menon & Uddin, 2010). Sridharan et al. (2008) further postulate that the right fronto-insular cortex of the SN is a key region of this switching mechanism, as it activates the frontoparietal networks and the dorsal anterior cingulate in the

saliency network, while simultaneously deactivating the DMN. Furthermore, Menon (2011) review evidence supporting the theory that abnormal connectivity between three networks (frontoparietal, saliency, and default mode networks) underlie a multitude of psychiatric disorders, including MDD and PTSD. Contrary to the above, it has been argued by others that the switching function is performed by the frontoparietal network, rather than the saliency network (Gao & Lin, 2012; Vincent et al., 2008).

### **Resting-State Connectivity in PTSD**

Current evidence suggests that PTSD is associated with less functional connectivity within the DMN and the saliency network, relative to controls (Bluhm et al., 2009a; Koch et al., 2016; Sripada et al., 2012a). PTSD has been associated with greater connectivity relative to controls between the DMN and SN (Sripada et al., 2012a). Additionally, greater functional within-network connectivity of midbrain regions such as the hippocampus and amygdala has been found in PTSD samples, relative to controls (Rabinak et al., 2011; Sripada et al., 2012b).

### **Resting-State Connectivity in MDD**

MDD has shown to be associated with greater connectivity within the DMN, relative to controls (Greicius et al., 2007; Kaiser et al., 2015). Moreover, according to a large resting-state meta-analysis, the saliency network, dorsal attention network, and frontoparietal network exhibit reduced within-network connectivity in MDD, relative to controls (Kaiser et al., 2015). In a meta-analysis of 25 resting-state fMRI in MDD studies, Kaiser et al. (2015) reported that MDD was associated with less connectivity between the frontoparietal network and the parietal regions of the dorsal attention network (DAN), as well as abnormal connectivity within the dorsal attention network, relative to healthy controls. Nevertheless, individual studies included in the Kaiser et al. (2015) meta-analysis reported both greater and reduced functional connectivity (FC) within the DAN in MDD relative to controls (Kaiser et al., 2015). In a review, Rogers et al. (2004) reported that MDD was often associated with hypoactivation of the dlPFC and ACC, core regions of the cognitive control networks. Reduced connectivity within the dlPFC in MDD patients was associated with executive and prefrontal impairments in MDD in Rogers et al. (2004).

### **Resting-State Connectivity in PTSD with MDD**

A resting-state fMRI study of male combat veterans with PTSD and comorbid MDD reported that the comorbid group ( $n = 30$ ) exhibited reduced salience network connectivity relative to the PTSD only group ( $n = 25$ ) (Kennis et al., 2014). Furthermore, the comorbid group exhibited less functional connectivity (FC) between the bilateral anterior insula and left hippocampus relative to the PTSD only group (Kennis et al., 2014). The comorbid group also displayed greater functional connectivity between the subgenual ACC and the perigenual regions of the ACC, relative to the PTSD only group (Kennis et al., 2014). This study did not utilise a control group, so it is not possible to draw accurate conclusions regarding the effect a comorbid diagnosis has on resting-state functional connectivity.

To the best of my knowledge, there are no published studies that compare resting-state FC in healthy individuals with that found in patients diagnosed with PTSD only, MDD only, and in patients with both disorders. Utilising such a four-group design with a healthy control group makes it possible to accurately determine whether PTSD with comorbid MDD is associated with an additive effect on resting-state functional connectivity, or whether comorbidity has a synergistic effect, whereby connectivity abnormalities are ‘greater than the sum of their parts’.

### **Rationale**

Chapter 1 highlighted the paucity of research and literature investigating the intrinsic functional connectivity of resting-state networks (DMN, DAN, SN, FPAR) in PTSD with comorbid MDD, despite the frequent co-occurrence of these conditions. I was not able to find a single study utilising a four-group design in this patient population, which limits our ability to accurately characterise the nature of resting-state connectivity abnormalities found in patients with comorbid PTSD and MDD.

PTSD imaging studies tend to use participants with specific trauma exposure, with American combat veterans (predominantly males) being the most commonly utilised group of participants in the PTSD imaging literature. In addition, control groups in these studies are almost exclusively made up of trauma-exposed participants. By utilising a female sample from a LMI country with a range of trauma exposure, as well as using a control group consisting of both trauma-exposed and naïve participants, we are in a position to obtain a more generalisable understanding of intrinsic FC abnormalities in PTSD and MDD.

Investigating executive function and the functional connectivity of prefrontal brain regions associated with higher order neurocognitive control processes in these populations is particularly important. Intrinsic functional connectivity in prefrontal cortical regions such as the dorsolateral prefrontal cortex (dlPFC) and the ventrolateral prefrontal cortex (vlPFC), have been implicated in executive functions such as working memory, inhibition, and set-shifting (Miller & Cohen, 2001; Rogers et al., 2004). Moreover, neurocognitive dysfunction associated with prefrontal regions has been reported in both the PTSD and MDD literature (Etkin, Gyurak, & O'Hara, 2013; Etkin & Wager, 2007; Rogers et al., 2004; Satterthwaite et al., 2015; Thomas & Elliott, 2009). Day-to-day tasks such as planning, organising, and decision-making are tasks that rely on executive function (Diamond, 2013), and research has shown that executive function influences one's ability to adhere to treatment plans, and self-care (Insel, Morrow, Brewer, & Figueredo, 2006). Accordingly, a study of abnormalities in resting-state functional connectivity of prefrontal brain regions in PTSD and MDD, and their association with executive dysfunction in this patient population would allow for better treatment plans to be developed for patients with disorders associated with executive dysfunction, such as PTSD and MDD, and may also help monitor their response to these interventions.

### **Aims and hypotheses**

The aim of the present study was to determine the extent to which abnormalities are observed in connectivity of resting-state brain networks associated with neurocognitive control, including executive functioning and attention in female patients from a LMI setting diagnosed with PTSD, MDD, and PTSD with comorbid MDD. Cognitive control networks of interest included the default mode network (DMN), salience network (SN), dorsal attention network (DAN), and the frontoparietal (FPAR) networks.

The following hypotheses were tested:

#### **PTSD versus Controls**

- The PTSD group will display reduced connectivity within the DMN, compared to the control group
- The PTSD group will display greater connectivity within the SN, relative to controls
- The PTSD group will display greater connectivity between the DMN and SN, compared to controls

### MDD versus Controls

- The MDD group will exhibit greater connectivity within the DMN, as well as greater connectivity between the DMN and both the FPAR and the DAN, relative to controls
- The MDD group will display less connectivity within the FPAR, compared to controls
- The MDD group will display abnormal connectivity within the dorsal attention network, as well as between the FPAR and DAN, as well as the SN and DMN, compared to controls

### PTSD with MDD versus Controls

There is insufficient data at present to make predictions regarding the functional connectivity in PTSD with comorbid MDD patients. However, based on the available literature, I predict that the comorbid group will display abnormal connectivity within the SN compared to controls.

I hypothesized that poorer task performance in the clinical groups compared to healthy controls would be associated with group differences in connectivity between networks. Finally, I also tested whether PTSD symptom severity could be regarded as a confounding factor in explaining group differences in strength of intrinsic functional connectivity between PTSD participants and comorbid participants.

## **Methods**

### **Design and ethics**

This study was cross-sectional in nature. Ethical approval was received from the Human Research Ethics Committee at the University of Cape Town (HREC ref: 411/2013). The larger Drakenstein Child Health Study (DCHS) (Zar, Barnett, Myer, Stein, & Nicol, 2014), in which this study was nested, received ethical approval from the Health Sciences Human Research Ethics committees of the University of Cape Town, as well as Stellenbosch University. Before participating, all participants gave voluntary written consent.

### **Participants**

As explained in Chapter 2, this entirely female sample was recruited from two primary health clinics (TC Newman clinic and Mbekweni clinic) in the Paarl region of the Western Cape,

and were enrolled in the Drakenstein Child Health Study (DCHS) (Zar et al., 2014). For the present study, participants were recruited at the 18-month postnatal visit, after undergoing neurocognitive assessment (see chapter 2) and neuropsychiatric interviews (Mini International Neuropsychiatric Interview and Clinician Administered PTSD Scale). Exclusion criteria for this study included: 1) loss of consciousness longer than 30 minutes, 2) inability to speak English, 3) current/lifetime alcohol and/or substance dependence or abuse, 4) psychopathology, including psychosis, other than PTSD and/or MDD, 5) traumatic brain injury, 6) standard MRI exclusion criteria, such as claustrophobia and presence of ferromagnetic objects in the participant's body. Psychological and physical trauma exposures were not exclusion criteria for the control group.

### **Materials and Diagnoses**

**Diagnoses.** As explained in Chapter 2, diagnoses were made by a psychiatrist from the DCHS using the MINI (5<sup>th</sup> edition) (Sheehan et al., 1998) and, where applicable, the CAPS (Blake et al., 1995). To confirm the initial diagnosis of PTSD using the MINI, as well as measure PTSD symptom severity, the CAPS was used. The CAPS measures both the intensity and frequency of PTSD symptoms (Blake et al., 1995). The scoring rule suggested by Weathers, Ruscio, and Keane (1999) and Orr (1997) was utilised to diagnose PTSD in this sample. This scoring method requires a total CAPS score greater or equal to 45 to confirm a PTSD diagnosis, and has demonstrated reliability against gold-standard diagnostic instrument (namely, the SCID PTSD module) (Weathers et al., 1999). Due to the inclusion of lifetime PTSD diagnoses, CAPS assessments were undertaken to ensure that participants with lifetime PTSD experienced moderate to severe PTSD symptoms at the time of scanning.

Participants were placed into groups based on a diagnosis made by a psychiatrist with extensive experience with this population. Mothers who had a current/lifetime PTSD diagnosis formed the PTSD group, participants who had a current/lifetime MDD diagnosis were part of the MDD group, and participants who had current/lifetime PTSD and MDD formed the comorbid group. Due to low numbers of current PTSD and MDD, lifetime diagnoses were included to increase the sample size, to increase power. Additionally, all cases of current and lifetime depression (including postpartum depression) were included, where other exclusion criteria were adhered to. The comorbid group participants had a primary diagnosis of PTSD and a secondary diagnosis of MDD. The control group consisted of participants from the DCHS who had no current or lifetime psychopathology on the MINI.

## Data Acquisition

Scans took place at the Cape University Body Imaging Centre (CUBIC) at Groote Schuur Hospital at the University of Cape Town (3T Magnetom Skyra (Siemens)), as well as at Tygerberg Hospital at Stellenbosch University (3T Magnetom Allegra Syngo (Siemens)). The scanning session at both centres began with a 10-minute high resolution MPRAGE structural scan which allowed the participants to acclimatise to the scanner and settle. Scans were acquired at Groote Schuur Hospital using a 32-channel head coil and at Tygerberg Hospital with a four-channel head coil. At Groote Schuur Hospital, a whole-brain multi-echo T1-weighted gradient echo echo-planar images (36 slices, TR = 2530 ms, TE = 1.69, 3.55, 5.41, 7.27 ms, FOV = 256×256 mm, 1.0x1.0x1.5 mm voxels, slice thickness = 1.5 mm, inter-slice gap = 1mm). Following this, participants underwent an 8-minute resting-state scan, prior to which participants were instructed to keep their eyes open and focus on a fixation cross on a screen for the duration of the scan. The following parameters were used at the University of Cape Town scanner to obtain resting-state data: TR = 2000ms, TE = 30 ms, 3.8x3.8x4.0 mm voxels, slice thickness = 4.0 mm, flip angle = 77 degrees, FOV = 240×240mm, 172 sagittal slices). Structural scans at Stellenbosch University were acquired using the following parameters: 128 slices, TR = 2000ms, TE = 1.53, 3.21, 4.89, 6.57 ms, FOV = 256x256 mm, 1.0x1.0x1.5 mm, slice thickness = 1.5 mm. The resting-state sequence at Tygerberg hospital employed the following parameters: TR = 2000ms, TE = 30 ms, 3.8x3.8x4.0 mm voxels, slice thickness = 4.0 mm, flip angle = 77 degrees, FOV = 240×240mm, 172 sagittal slices). Echo planar imaging fieldmaps were acquired immediately prior to the resting-state functional sequences at both scanner sites.

## Preprocessing Pipeline

The *fMRIPrep* preprocessing pipeline was utilized for the resting-state data set (Esteban et al., 2018). This pipeline is robust to potential input dataset idiosyncrasies (for example, missing acquisitions) and quality checking of preprocessing results allows transparency (Esteban et al., 2018).

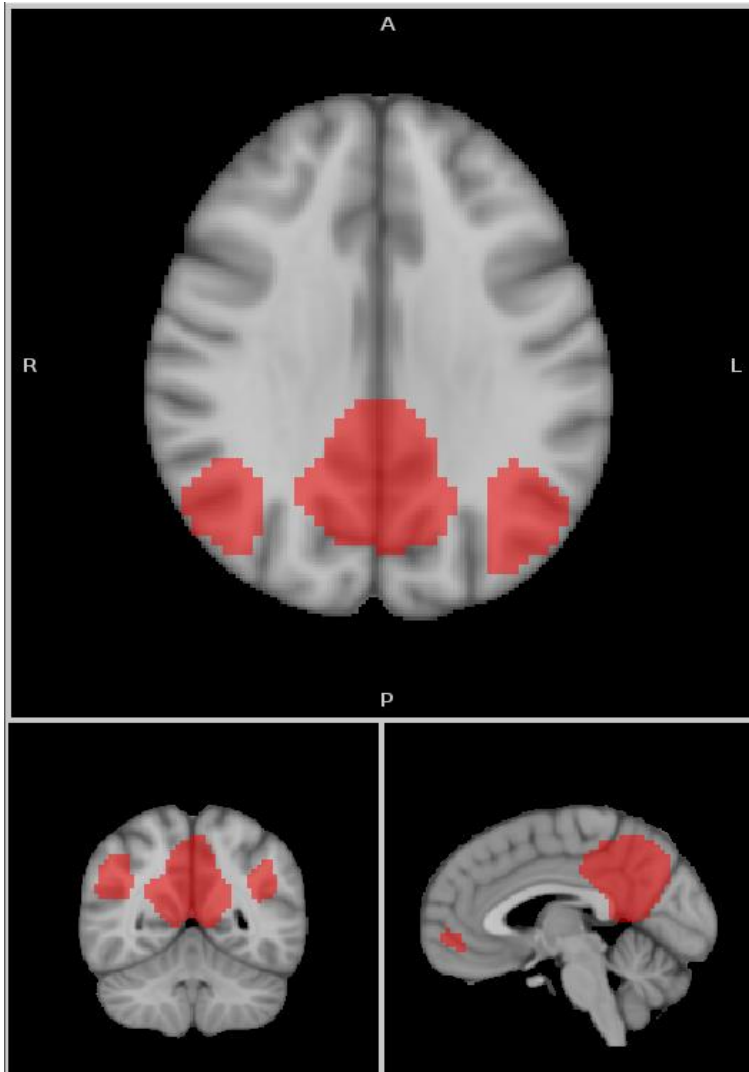
Using the custom *fMRIPrep* methodology, a reference volume and its skull-stripped version were generated. To correct for susceptibility distortions, a deformation field was estimated based on a fieldmap that was co-registered to the BOLD reference for the scans from roughly half of the participants for whom both magnitude and phase difference acquisitions were acquired. For the remainder of the participants, fieldmap acquisitions were erroneously restricted to phase difference images only. For these participants, the unique



functionality afforded by the *fMRIPrep* to estimate a deformation field utilising the participant-specific T1 anatomical sequence was utilised (Esteban et al., 2018). Based on the estimated susceptibility distortion, an unwarped BOLD reference was calculated for a more accurate co-registration with the anatomical reference (T1w reference). Head-motion parameters (transformation matrices and six corresponding rotation and translation parameters) were estimated with respect to the BOLD reference before spatiotemporal filtering. BOLD runs were slice-time corrected. The BOLD time-series were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. Next, non-steady state volumes were removed, and spatial smoothing was applied, with an isotropic, Gaussian kernel of 6mm FWHM (full-width half-maximum). Following this, motion artifacts were identified by running the ICA AROMA algorithm on the pre-processed BOLD in MNI space time-series (Pruim et al., 2015). Components corresponding to motion were subsequently removed from the BOLD time-series, in a "non-aggressive" manner which preserved common covariance shared between components (Esteban et al., 2018). The BOLD time-series were subsequently resampled to MNI152NLin2009cAsym standard space. Following pre-processing with *fMRIPrep*, a general linear regression model, as implemented by AFNI's 3dDeconvolve, was run on each participant's RS BOLD dataset. Global white matter and CSF signals were regressed out, as part of this model, utilising subject-specific white matter and CSF masks, as were constant, linear, squared, and cubic trends in the data. A band pass filter (0.01- 0.1 Hz) was applied to the data, as the final step in the processing pipeline.

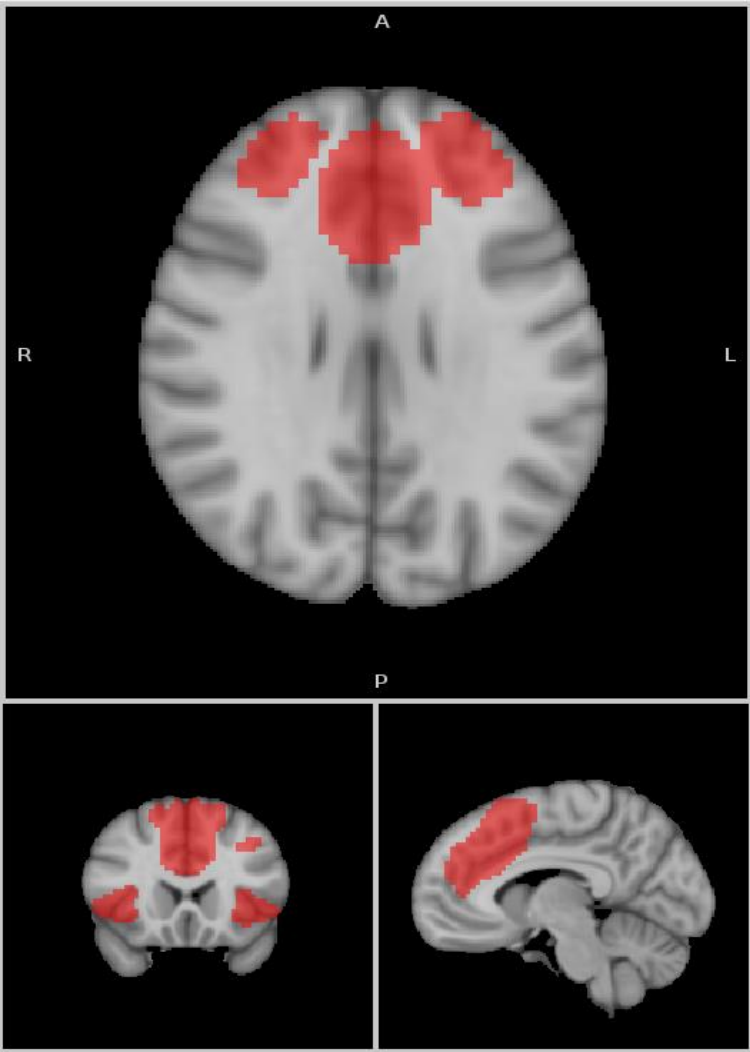
To assess network connectivity, masks were created for networks of interest (left and right frontoparietal, default mode, dorsal attention, and salience networks) based on components extracted using group ICA. For this purpose, FSL's melodic tool was applied to the smoothed output of ICA-AROMA, concatenated across the 28 healthy control participants, with dimensionality set to 25 components. Networks were visually inspected and identified using methods outlined by Allen et al. (2011) and Smith et al. (2009). Network masks were created by thresholding voxels at  $Z = 4$ , and restricting clusters to those containing at least 100 2mm isotropic voxels. Seeds for masks were created by placing spheres of 6mm radius at peak voxels in the clusters. In addition, for the SN masks, localised peak voxels within the largest cluster, that extended across the bilateral insula and basal ganglia, were identified that corresponded to the right and left anterior insula. This was necessary given how key the anterior insula is to the SN. A seed was also centred at the peak voxel for this cluster. Once the BOLD signal had been averaged across voxels within each of

the networks, the averaged BOLD signal was correlated between the networks across all the participants in each group. Following this, the correlation coefficients were compared between groups to determine if group differences in network connectivity were found.



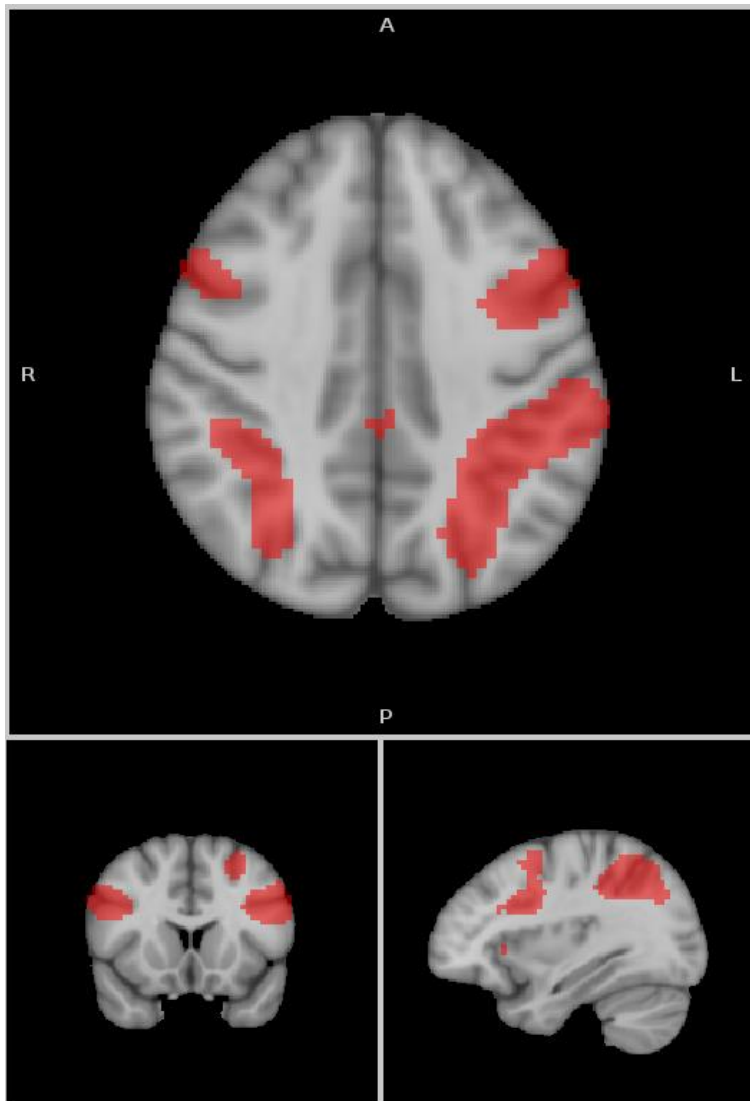
Default mode network (DMN) mask.

MNI co-ordinates: -3 -53 31



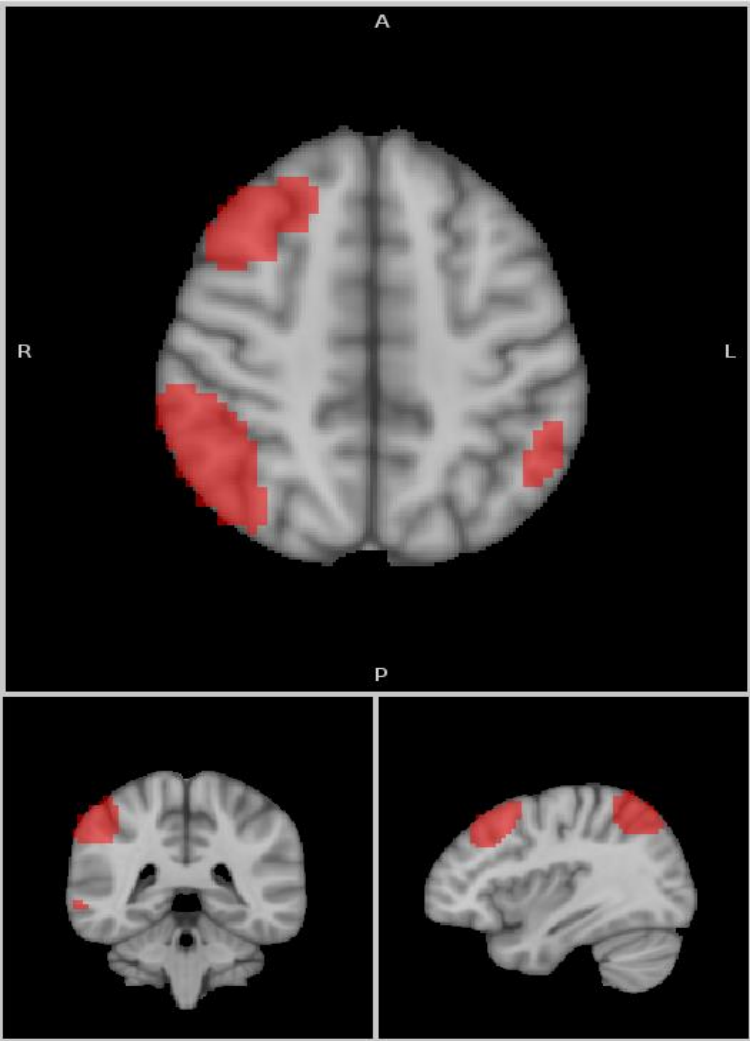
Salience network (SN) mask.

MNI co-ordinates: -7 20 28



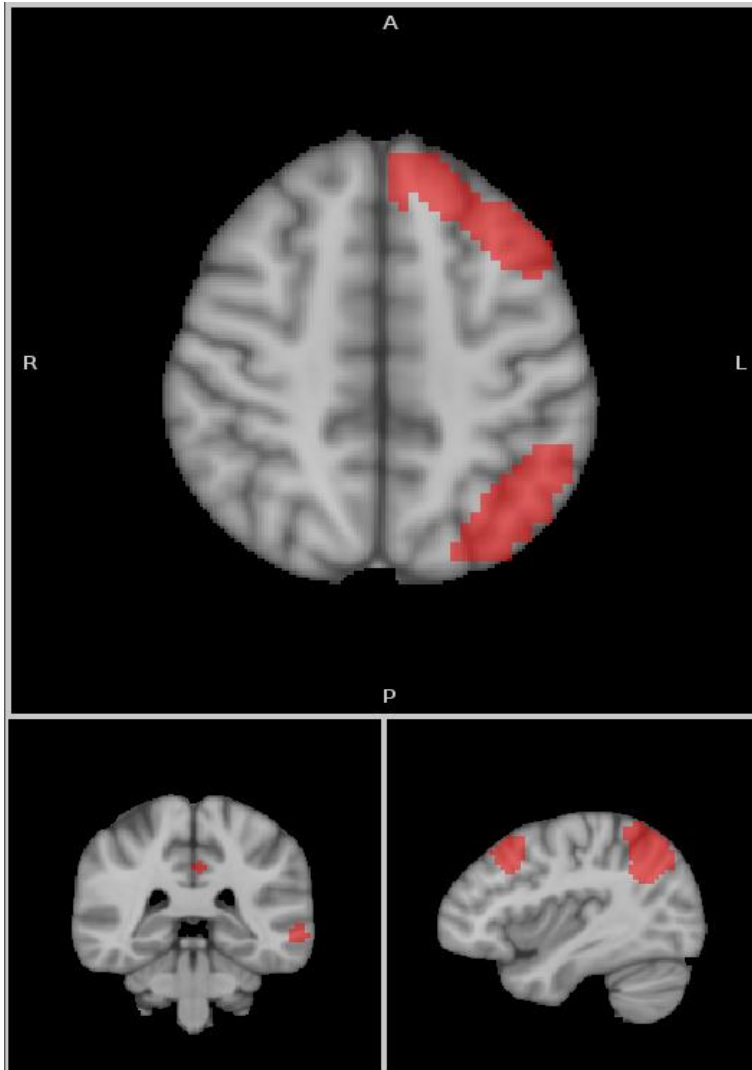
Dorsal attention network (DAN) mask.

MNI co-ordinates: -33 15 39



Right frontoparietal network (R FPAR) mask.

MNI co-ordinates: 37 -40 48



Left frontoparietal network (L FPAR) mask.

MNI co-ordinates: -38 -37 48

### Data Analysis

Group differences on demographic variables were assessed using ANOVA tests. To determine whether there were differences between the two PTSD groups on CAPS total severity scores, an independent two-tailed t-test was utilised. All bivariate analyses were conducted using SPSS 24.

**Primary analyses.** Primary statistical analyses involved testing study hypotheses using a series of multivariate linear regression models (MVM). These models were applied to Fisher Z transformed within-network correlation matrices created using 3dNetCorr, to determine whether there were group differences in connectivity within the DMN, DAN, SN, right frontoparietal, and left frontoparietal networks, after adjusting for age and average

motion displacement during the scan. Group differences in connectivity were identified with multivariate models created using AFNI's FATCAT (Taylor, Chen, Cox, & Saad, 2016; Taylor & Saad, 2013), a suite of tools that provides an intuitive interface to the AFNI 3dMVM script. Five separate models were run, one for each network, to test group differences in connectivity between seeds constituting the network. In addition, a BOLD time-series for each network was obtained by averaging the time-series for each of the network seeds, with these global networks used as input to a multivariate model of group differences in between-network connectivity estimates.

Since two scanners were utilised in this study, scanner was initially included as a covariate in each of the models, to check for scanner effects. If there was no scanner effect, the scanner covariate was removed from the model and the model run again. If there was a significant scanner effect, pair-wise comparisons between seed or networks where significant differences in connectivity as a function of scanner site were observed (at  $p < 0.1$ ) were removed. A new analysis was run for network pairs where connectivity was not scanner dependent. In instances in which the omnibus model results indicated a significant effect of group on network connectivity, post hoc comparisons generated by FATCAT were run for seed-pairs for which connectivity was moderated by group assignment.

**Secondary analyses.** Secondary analyses included running models to test for total CAPS score interactions with network connectivity (both within and between). The first model checked for scanner effects. If there was no scanner effect, the next model included a group and CAPS total score interaction term. If this term was not significant, the model was run again to test for a CAPS total score main effect. Additionally, models were run utilising the scores from neurocognitive tests (from Chapter 2) that displayed significant group differences and/or interactions with CAPS. Neurocognitive scores included the Dimensional Change Card Sort (DCCS), Pattern Comparison Processing Speed test, WRAML II intrusions, and WRAML delayed recall.

## Results

### Participants

Of the 112 participants recruited for this study,  $n = 8$  were excluded from the analyses. Participants were excluded based on incomplete diagnostic information ( $n = 3$ ), subthreshold PTSD diagnosis ( $n = 1$ ), and alcohol abuse ( $n = 1$ ). Further exclusion criteria include faulty skull stripping ( $n = 1$ ) and bad quality T1 images ( $n = 2$ ). A further 19 participants were removed due to excessive motion. A total of 85 participants were included in the final

analyses. Group sizes were as follows: PTSD  $n = 22$ ; MDD  $n = 18$ ; PTSD+MDD  $n = 17$ ; control  $n = 28$ . Of these participants,  $n = 3$  were diagnosed with current PTSD, and  $n = 3$  were diagnosed with current MDD. The descriptive statistics for the groups can be found in Table 1.

### **Descriptive Statistics**

One way Analysis of Variance (ANOVA) tests found no significant differences between the groups on both age ( $p = .08$ ) and education ( $p = .39$ ). T-tests indicated that CAPS scores were significantly larger in the comorbid group than the PTSD group on average ( $M = 89.4$ ,  $SD = 15.3$  versus  $M = 69.1$ ,  $SD = 18.9$ , respectively,  $t(37) = -3.62$ ,  $p = .001$ , two-tailed).

### **A priori primary analyses**

#### **Within-network connectivity**

**DMN.** A significant group effect was observed for DMN connectivity, with the MDD group exhibiting greater positive connectivity, relative to controls. There was no scanner effect ( $\chi^2 = 2.4$ ,  $p = .12$ ), therefore the model was run with the scanner covariate removed. The final model indicated that there were significant network connectivity differences with group ( $\chi^2 = 5.65$ ,  $p = .017$ ), and post hoc pairwise group comparisons indicated that differences in connectivity were primarily observed for the MDD group, relative to the other groups, with seeds where connectivity differences were most apparent including the ACC, precuneus, and hippocampal gyrus. Average correlations for these seed-pairs can be seen in Table 2.

**SN.** A scanner effect was detected ( $\chi^2 = 5.9$ ,  $p = .015$ ), therefore scanner and two seed-pairs (insula and right middle frontal gyrus; right anterior insula and left anterior insula) were removed from the final model.

**DAN.** Scanner produced a significant effect ( $\chi^2 = 6.1$ ,  $p = .014$ ) and seven seed-pairs were removed from the final model (left dlPFC and right dlPFC; left dlPFC and left inferior temporal gyrus; left dlPFC and left middle frontal gyrus; left precuneus and left cingulate gyrus; right dlPFC and left middle frontal gyrus; right middle temporal gyrus and left cingulate gyrus; left middle frontal gyrus and right middle frontal gyrus).

**Right FPAR.** There was no scanner effect ( $\chi^2 = 2.42$ ,  $p = .12$ ), therefore the final model excluded the scanner covariate. The final model indicated that there was a significant



association with group ( $\chi^2 = 4.4, p = .036$ ), and post hoc pairwise comparisons indicated that differences were observed primarily for the comorbid group, relative to all the other groups, in seed-pairs with connectivity with the dlPFC and inferior parietal regions. These differences can be seen for each seed-pair in Table 3.

**Left FPAR.** A scanner effect was detected ( $\chi^2 = 4.61, p = .032$ ), therefore the final model removed the scanner covariate, as well as seed-pairs that were dependent on scanner (left middle frontal gyrus and right cerebellum; left supramarginal gyrus and right cerebellum; left precuneus and right inferior parietal lobule). The final model indicated that there was a near significant network connectivity association with group ( $\chi^2 = 3.83, p = .0504$ ), with the MDD group exhibiting less connectivity within L FPAR regions relative to the other groups. Post hoc analyses were run due to the close trend level association. Post hoc comparisons indicated that reductions were observed, primarily for the MDD group, with seed-pairs that included connections with the middle frontal gyrus and the inferior frontal gyrus. Average correlations for these regions can be found in Table 4.

#### **Between-network connectivity**

There was no scanner effect ( $\chi^2 = 2.78, p = .095$ ), therefore the scanner covariate was removed from the final model. No significant group effect was observed for between-network connectivity ( $\chi^2 = 0.78, p = .38$ ).

Table 1  
*Sample demographics*

	PTSD <i>n</i> = 22	MDD <i>n</i> = 18	PTSD+MDD <i>n</i> = 17	Control <i>n</i> = 28	<i>F/t</i>	<i>p</i> value
Age ( <i>SD</i> ) <sup>a</sup>	31.1 (8.1)	28.2 (7.6)	30.4 (7.1)	26.1 (6.2)	2.34	.08
Education ( <i>SD</i> ) <sup>b</sup>	10.7 (2.9)	10.9 (1.8)	10.2 (1.9)	11.4 (1.8)	1.01	.39
CAPS total severity score <sup>c</sup>	69.1 (18.9)	NA	89.4 (15.3)	NA	3.62	.001

<sup>a</sup> based on 85 participants

<sup>b</sup> based on 77 participants

<sup>c</sup> based on 39 participants

## Secondary analyses

### CAPS total score models – within-network analyses

**DMN.** No effect of scanner was observed in the model of the association of CAPS score with DMN connectivity ( $\chi^2 = 3.49, p = .06$ ). The second model indicated that there was no significant interaction between group and total CAPS score ( $\chi^2 = 0.34, p = .56$ ), therefore the analysis was run without the interaction term. The final model indicated that there was a significant effect for CAPS total score on DMN connectivity ( $\chi^2 = 4.5, p = .038$ ). Post hoc analysis indicated that higher CAPS scores were associated with greater connectivity between the precuneus and the right posterior cingulate seeds ( $p = .01$ ), indicating that greater PTSD symptom severity is associated with greater connectivity of the DMN in the PTSD and comorbid groups.

**R FPAR.** No scanner effect was observed in the model of association of CAPS score and R FPAR connectivity ( $\chi^2 = 0.69, p = .4$ ). The second model indicated that there was no significant group and CAPS total score interaction ( $\chi^2 = 1.29, p = .25$ ), therefore the analysis was run without the interaction term. The final model indicated that there was no effect of CAPS total score on right frontoparietal connectivity ( $\chi^2 = 0.52, p = .47$ ).

**L FPAR.** No scanner effect was detected in the first model ( $\chi^2 = 3.49, p = .062$ ), and the second model indicated that there was an interaction for group and CAPS total score ( $\chi^2 = 7.1, p = .008$ ). Post hoc analysis did not indicate significant pairwise interaction effects for any seed-pairs, however a number of subthreshold effects were observed. Post hoc analysis indicated that the comorbid group, relative to the PTSD group, exhibited greater subthreshold connectivity effects for the left precuneus.

**SN.** A significant scanner effect was observed ( $\chi^2 = 5.38, p = .02$ ), and two seed-pairs (right anterior insula – left anterior insula; right anterior insula – posterior cingulate) were removed from the subsequent analyses. There was no significant interaction between group and CAPS total score ( $\chi^2 = 0.87, p = .35$ ), therefore the interaction term was removed from the model. The final model indicated that there was no effect of CAPS on salience network connectivity ( $\chi^2 = 1.569, p = .21$ ).

**DAN.** No scanner effect was observed ( $\chi^2 = 2.22, p = .14$ ) and there was no significant interaction between CAPS total score and group ( $\chi^2 = 0.58, p = .48$ ), therefore the interaction

term was removed from the final model. The final model indicated that there was no significant association between CAPS total score and dorsal attention network connectivity ( $\chi^2 = 1.41, p = .23$ ).

### **Between-network connectivity**

No scanner effect was observed in the model of association of CAPS score and between-network connectivity ( $\chi^2 = 0.146, p = .7$ ). The interaction term in the model was not significant ( $\chi^2 = 1.97, p = .16$ ); therefore, it was removed from the final model. The final model indicated that there was no significant association between CAPS total score and between-network connectivity in this sample ( $\chi^2 = 1.06, p = .3$ ).

### **Neurocognitive scores and between-network connectivity**

**DCCS.** The final model observed a significant interaction between group and DCCS score ( $\chi^2 = 3.85, p = .049$ ), indicating the combined effects of group and DCCS performance on connectivity between the 5 networks were significant. Post hoc analysis indicated that group status moderated connectivity for a number of pairwise network comparisons. Between the DMN and SN, the controls exhibited a strong negative correlation between task performance and network connectivity ( $r = -0.58, p = .016$ ). A similar strong negative correlation was found for the controls between the R FPAR and SN ( $r = -0.62, p = .01$ ), relative to the clinical groups. The controls exhibited a very strong negative correlation between connectivity between L FPAR and SN, and task performance ( $r = -0.8, p < .001$ ). Although the connectivity between L FPAR and DAN and task performance was flagged as significant, there were no significant group correlations. However, controls exhibited a trend towards significance ( $r = -0.46, p = .07$ ).

**Pattern Comparison Processing Speed test.** The final model indicated a significant interaction between group and Pattern Comparison scores ( $\chi^2 = 9.04, p = .003$ ) indicating the combined effects of group and task performance on connectivity between the 5 networks were significant. Although there was a significant interaction between task performance and network connectivity between the DMN and the R FPAR, no significant group correlations were found. Between the DMN and L FPAR, the comorbid group exhibited a strong negative correlation ( $r = -0.64, p = .013$ ). Controls exhibited a subthreshold positive correlation between the DMN and L FPAR ( $r = .45, p = .08$ ). A significant negative correlation between the two frontoparietal networks' connectivity and task performance was observed for the

PTSD with comorbid group ( $r = -0.68, p = .007$ ). The MDD group exhibited a strong negative correlation between the R FPAR and SN ( $r = -0.68, p = .01$ ).

**WRAML II intrusions.** There was no significant interaction effect between group and WRAML intrusion scores ( $\chi^2 = 0.095, p = .76$ ).

**WRAML II delayed recall.** The model indicated that there was no significant interaction between group and WRAML delayed recall scores ( $\chi^2 = 2.84, p = .09$ ).

Table 2

*Average correlations for DMN seed-pairs where intrinsic connectivity was moderated by group*

Seed-pair	Control	Comorbid	MDD	PTSD	Difference	<i>t</i> statistic	<i>p</i> value
ACC - left precuneus	.38 (.31)	.22 (.28)	.34 (.34)	.43 (.26)	Comorbid < CTRLS Comorbid < PTSD	2.23 -2.29	.028 .025
ACC - left hippocampal gyrus	.13 (.26)	.19 (.16)	.29 (.31)	.3 (.21)	CTRLS < MDD CTRLS < PTSD	-2.03 -2.28	.045 .025
Precuneus - left hippocampal gyrus	.58 (.28)	.4 (.25)	.51 (.36)	.55 (.22)	Comorbid < CTRLS	2.61	.01
Right angular gyrus - left hippocampal gyrus	.31 (.28)	.44 (.25)	.53 (.16)	.41 (.25)	CTRLS < MDD	-2.47	.015
Right angular gyrus - right hippocampal gyrus	.29 (.23)	.39 (.17)	.46 (.21)	.31 (.27)	CTRLS < MDD	-2.33	.022
Left precuneus - left hippocampal gyrus	.25 (.32)	.42 (.24)	.5 (.22)	.42 (.26)	CTRLS < MDD	-2.72	.007
Left precuneus - right precuneus	.4 (.24)	.4 (.17)	.51 (.21)	.38 (.24)	PTSD < MDD	2.06	.042
Right posterior cingulate - right hippocampal gyrus	.4 (.24)	.43 (.23)	.56 (.17)	.48 (.26)	CTRLS < MDD	-2.37	.019
Right posterior cingulate - right precuneus	.49 (.21)	.57 (.12)	.67 (.12)	.57 (.19)	CTRL < MDD	-3.09	.027

Table 3

*Average correlations for R FPAR seed-pairs where intrinsic connectivity was moderated by group*

Seed-pair	Control	Comorbid	MDD	PTSD	Difference	<i>t</i> statistic	<i>p</i> value
Right dlPFC - right inferior parietal	.44 (.33)	.55 (.26)	.32 (.21)	.31 (.34)	MDD < Comorbid PTSD < Comorbid	2.43	.017
Right dlPFC - right middle frontal	.19 (.3)	.39 (.36)	.17 (.25)	.26 (.27)	CTRLS < Comorbid MDD < Comorbid	-2.07	.041
Right inferior parietal - right middle temporal gyrus	.27 (.34)	.47 (.33)	.19 (.21)	.29 (.38)	MDD < Comorbid	2.64	.009
Right inferior parietal - left inferior parietal	.53 (.22)	.56 (.22)	.38 (.25)	.41 (.28)	MDD < CTRLS PTSD < CTRLS MDD < Comorbid	2.3 2.11 2.1	.024 .038 .039
Right inferior parietal - left, right cingulate gyrus	.34 (.29)	.49 (.25)	.32 (.13)	.35 (.29)	MDD < Comorbid	2.21	.029
Right middle temporal gyrus - left inferior parietal	.23 (.25)	.39 (.18)	.16 (.29)	.27 (.26)	CTRLS < Comorbid MDD < Comorbid	-2.09	.039
Left inferior parietal - left, right cingulate gyrus	.27 (.22)	.41 (.25)	.15 (.3)	.27 (.23)	MDD < Comorbid	2.71	.008
					MDD < Comorbid	2.98	< .001

Table 4

*Average correlations for L FPAR seed-pairs where intrinsic connectivity was moderated by group*

Seed-pair	Control	Comorbid	MDD	PTSD	Difference	<i>t</i> statistic	<i>p</i> value
Left middle frontal gyrus - left middle temporal gyrus	.489 (.22)	.38 (.35)	.2 (.24)	.41 (.25)	MDD < CTRLS	3.65	< .001
					MDD < Comorbid	2.1	.038
					MDD < PTSD	-2.47	.015
Left middle frontal gyrus - left precuneus	.3 (.25)	.19 (.29)	.11 (.18)	.27 (.24)	MDD < CTRLS	2.43	.017
					MDD < PTSD	-2.01	.047
Left middle frontal gyrus - right inferior parietal lobule	.33 (.24)	.27 (.24)	.07 (.24)	.17 (.22)	MDD < CTRLS	3.43	< .001
					PTSD < CTRLS	2.31	.023
					MDD < Comorbid	2.31	< .001
Left inferior frontal gyrus - left precuneus	.05 (.26)	.09 (.25)	-.06 (.32)	.11 (.19)	MDD < Comorbid	2.12	.036
					MDD < PTSD	-2.43	.016
Left inferior frontal gyrus - right inferior parietal lobule	.13 (.24)	.07 (.35)	-.028 (.26)	.15 (.19)	MDD < CTRLS	2.01	.047
					MDD < PTSD	-2.15	.033



## Discussion

The present study set out to determine the intrinsic functional connectivity associations of PTSD, MDD, and PTSD with comorbid MDD in a sample of mothers from a LMI region. Networks associated with neurocognitive domains such as attention and executive function were of particular interest.

There was no evidence in this study for an association of diagnostic group with intrinsic connectivity between DMN and cognitive control networks. Nevertheless, the results from the present study provide some support for the hypotheses that diagnoses of PTSD and MDD, individually, are associated with abnormal intrinsic functional connectivity within the DMN and cognitive control networks, and these have implications for symptom severity and executive function. The nature of group differences for each network, and the relationship of network connectivity to PTSD symptom severity and executive function, will be discussed below.

### Default Mode Network (DMN)

The present study found evidence for greater positive connectivity within the DMN for the MDD group than controls, as hypothesised. This finding extended to comparisons to both groups of participants diagnosed with PTSD, as well. This finding is in accordance with numerous MDD resting-state studies and a 25-study meta-analysis reporting hyperconnectivity of the DMN in MDD patients (Greicius et al., 2007; Kaiser et al., 2015). In the present study, particular seed-pair connections have been highlighted, many of which are connections to the bilateral hippocampal gyrus. For example, the present study observed that regions such as the bilateral anterior cingulate, right angular gyrus, left precuneus, and right posterior cingulate are hyperconnected to the bilateral hippocampal gyrus in MDD. Previous research has reported that the hyperconnectivity within these DMN regions is related to the increased rumination and self-referential thought, commonly observed in MDD patients (Bluhm et al., 2009a; Cavanna & Trimble, 2006; Kaiser et al., 2015).

Contrary to my hypotheses, the present findings suggest that PTSD is not associated with less functional connectivity within the DMN, relative to controls (or clinical groups). There was no evidence to suggest that the comorbid group exhibited abnormal functional connectivity of the DMN, relative to controls, or the mono-diagnostic groups. However, additional analyses found that greater PTSD symptom severity was associated with increased connectivity between the bilateral precuneus and the right posterior cingulate of the DMN,

suggesting that increased PTSD symptom severity is associated with greater connectivity within in the DMN for participants with PTSD and PTSD with comorbid MDD. This finding is contrary to literature, where PTSD and PTSD symptom severity is associated with less connectivity within the DMN (Peterson et al., 2014; Sripada et al., 2012a).

### **Right Frontoparietal Network (R FPAR)**

Although not hypothesised, PTSD with comorbid MDD was associated with greater within-network connectivity for the right frontoparietal network. Greater connectivity within this network was exhibited by the comorbid group, relative to controls and the mono-diagnostic groups (see Table 3). Furthermore, the MDD group consistently exhibited less connectivity within the right FPAR network regions relative to controls.

The comorbid group consistently displayed greater connectivity between regions that are typically involved with higher order neurocognitive functions. Furthermore, PTSD with comorbid MDD was associated with greater connectivity of frontal regions such as the dlPFC, inferior parietal lobule, and the middle temporal gyrus, and these regions are associated with neurocognitive functions such as set-switching, planning, and decision-making (Elliott, 2003).

Relative to controls, the MDD group exhibited less connectivity within the right inferior parietal and left inferior parietal seed-pair. This finding is consistent with published research reporting reduced within-network connectivity of the frontoparietal network in MDD (Kaiser et al., 2015). Interestingly, PTSD symptom severity (for both PTSD groups) was not associated with within-network connectivity of the R FPAR, given that the comorbid group exhibited greater PTSD symptom severity as well as hyperconnectivity within the R FPAR.

### **Left Frontoparietal Network (L FPAR)**

There was a trend towards a group effect for the left frontoparietal network, and post hoc analysis indicated that, relative to controls and the PTSD groups, the MDD group consistently exhibited less connectivity of regions within the left frontoparietal network (see Table 4). This finding supports the hypothesis suggesting that this network would exhibit abnormal connectivity. An MDD resting-state meta-analysis (Kaiser et al., 2015) reported reduced functional connectivity within the frontoparietal networks, therefore it was expected and hypothesised that the present MDD sample would display reduced connectivity within this network.

The greatest difference was evident between controls and MDD, where controls exhibited greater connectivity than the MDD group. The PTSD groups also displayed sizeable group differences in connectivity, relative to the MDD group, however no group effect was observed for the comorbid group. Despite evidence for less connectivity between the left inferior frontal gyrus and the left precuneus, and the left inferior parietal lobule, group differences in strength of connectivity was not statistically significant, rendering interpretation problematic.

Although no group effect for the PTSD group was observed, additional analyses indicated that CAPS total score was associated with L FPAR connectivity. Post hoc analysis failed to observe significant pairwise interaction effects, although subthreshold effects were observed for the left precuneus, with greater connectivity observed between the precuneus and supramarginal gyrus, as well as the precuneus and the inferior parietal lobule. These findings were observed for the PTSD and comorbid MDD group. This finding suggests that greater PTSD symptom severity is associated with greater connectivity within the precuneus for both the PTSD and comorbid groups.

### **Dorsal Attention Network (DAN)**

Within-network analyses failed to find significant group differences between any of the groups compared for the DAN. This finding is not consistent with published evidence for abnormal functional connectivity in patients with MDD in the DAN (Kaiser et al., 2015). Nevertheless, absence of evidence for a group effect is not evidence for absence of differences in DAN connectivity in patient groups. Failure to detect group differences may be partly due to the removal of seven seed-pairs that demonstrated sensitivity to scanner site, from the DAN analysis, which may have muted potential group effects. Furthermore, additional analyses found that PTSD symptom severity was not associated with DAN connectivity for both the PTSD and comorbid groups.

### **Salience Network (SN)**

This study found no evidence for a group effect for the SN, contrary to the postulated hypotheses and numerous publications suggesting altered connectivity within the salience network (Kaiser et al., 2015; Kennis et al., 2014; Sripada et al., 2012a). For example, studies report that PTSD exhibits greater within-network connectivity relative to controls (Sripada et al., 2012a), as well as abnormal within-network connectivity in PTSD with comorbid MDD (Kennis et al., 2014). The present study found no evidence suggesting that PTSD with

comorbid MDD is associated with greater functional connectivity abnormalities, relative to controls and the mono-diagnostic groups. Furthermore, additional analyses revealed that no association was observed between SN connectivity and PTSD symptom severity (PTSD and comorbid groups).

### **Between-network findings**

The present study hypothesised that PTSD would be associated with greater connectivity between the DMN and SN, while MDD would be associated with greater connectivity between the DMN and FPAR, as well as DMN and DAN. Further, it was postulated that MDD would be associated with abnormal connectivity between the FPAR and DAN, as well as SN and DMN. However, the present study found no evidence suggesting significant between-network connectivity, indicating that the clinical groups do not exhibit group differences between-networks. Importantly, the comorbid group did not exhibit greater functional connectivity abnormalities relative to controls and the mono-diagnostic groups. Furthermore, PTSD symptom severity was not associated with between-network connectivity, indicating that the PTSD and comorbid groups are not associated with abnormal connectivity between any of the chosen networks.

As part of additional analyses, I predicted that differences in connectivity between networks would be informative with respect to neurocognitive test scores that demonstrated group differences, as reported in Chapter 2. When examining the association between task performance and network connectivity, significant interactions were observed between group status and both set-switching ability, as assessed using the DCCS, as well as processing speed, as assessed using the Pattern Comparison Processing Speed test, in relation to network connectivity. No significant interactions were found for the WRAML II intrusions or WRAML II delayed recall tests. With regard to DCCS results, reduced connectivity between the DMN and SN, the R FPAR and SN, the L FPAR and SN, and L FPAR and DAN was observed. The controls consistently exhibited significant negative correlations for these network pairs and task performance, except for the L FPAR and DAN pair, where a subthreshold effect was observed. These findings indicated that greater network connectivity is associated with reduced task performance, particularly with respect to the above network combinations. The clinical groups did not exhibit significant correlations for network connectivity and task performance.

For the Pattern Comparison Processing Speed test, it was observed that better task performance was associated with greater connectivity between the DMN and R FPAR, the

DMN and L FPAR, both frontoparietal networks, and R FPAR and SN. In this analysis, the frontoparietal networks were consistently indicating greater connectivity, which is consistent with the literature as the frontoparietal networks are involved with higher-cognitive functions (Elliott, 2003). PTSD with comorbid MDD was associated with strong negative connectivity of the frontoparietal networks, indicating that task performance was inversely correlated with network connectivity. Additionally, the MDD group exhibited a strong negative correlation between network connectivity (between FPAR and SN) and performance on the Pattern Comparison test, relative to controls.

In an attempt to determine the functional connectivity of PTSD, MDD, and PTSD with comorbid MDD in a sample of LMI mothers, the present study highlights a number of findings that are consistent with recent publications, as well as a number of novel findings not yet reported in the literature. This study was not able to find support for the hypothesis that the comorbid group would exhibit abnormal connectivity within the salience network. Instead, the present study found that the comorbid group exhibited greater within-network functional connectivity of the right frontoparietal network, relative to the mono diagnostic groups and controls. Consistently, the dlPFC seed-pairs displayed greater connectivity, relative to controls and the single diagnosis groups. The dlPFC has been implicated in neurocognitive functions such as working memory, inhibition, and set-shifting (Elliott, 2003; Miller & Cohen, 2001). However, when analyses were run utilising neurocognitive scores from the inhibition measure (WRAML II intrusions); no significant group effect was found for the R FPAR.

The present study identified DMN functional connectivity abnormalities, with evidence highlighting greater connectivity for the MDD group within numerous seed-pairs of the DMN. This finding is supported by many published studies (Greicius et al., 2007; Kaiser et al., 2015). Furthermore, there was trending evidence for group differences in left frontoparietal network connectivity, due to relatively weak positive correlations for numerous seed-pairs in this network in the MDD group.

Notably, within-network group differences were absent for the salience network, as well as the dorsal attention network. A potential reason for the lack of findings in this sample is that the sample comprised of mothers from a LMI region of the Western Cape who have experienced a variety of trauma types. Previous resting-state studies, particularly PTSD studies, have been conducted on male war veterans, who experienced a single trauma type (Danckwerts & Leathem, 2003). For instance, in a meta-analysis of PTSD risk factors,

Brewin, Andrews, and Valentine (2000) reported that military samples differ from civilian samples in that gender effects are rarely seen in military samples, whereas they are seen in civilian samples. Additionally, trauma severity and intensity is often greater in military samples, relative to civilian samples (Brewin et al., 2000). Alternatively, the present sample could be more resilient than published samples. For example, the South African Stress and Health study (SASH) reported PTSD prevalence rates that are lower than American PTSD prevalence rates (3.5% versus 7.8%, respectively), despite greater trauma exposure in South Africa (Herman et al., 2009; Kessler et al., 1995). This illustrates that South African samples appear to be more resilient to trauma, but additional research is required.

Of importance, this study failed to identify any PTSD specific within- or between-network findings. This is contrary to the majority of PTSD resting-state publications. However, additional analyses were run to determine whether there was an association for within-network connectivity and PTSD symptom severity for the PTSD and comorbid groups, combined. Findings suggest that greater PTSD severity was associated with increased within-network connectivity of the DMN, particularly between the precuneus and the posterior cingulate cortex for the PTSD and comorbid groups. Similar findings were found for the L FPAR, however no significant pairwise interaction effects were observed. Nevertheless, subthreshold effects were observed which suggested greater connectivity of the left precuneus in the L FPAR.

The precuneus has been reported to be involved in a range of higher-order neurocognitive functions (Cavanna & Trimble, 2006). In a review of a variety of imaging studies, Cavanna and Trimble (2006) report that the precuneus is involved in functions such as internal mentation, self-processing tasks, and processing intentions related to the self. These functions are very similar to the self-referential thought and internal mentation commonly exhibited by MDD patients (American Psychiatric Association, 2013; Kaiser et al., 2015).

When examining the association between task performance and between-network connectivity, a number of differences were observed between networks, which supported the hypotheses of the present study. For example, with regard to the DCCS, a set-shifting measure, the results indicate that controls exhibit strong negative correlations between network connectivity and task performance, while the clinical groups do not.

Furthermore, connectivity between the left and right frontoparietal networks was positively associated with performance on the Pattern Comparison Processing Speed test for participants diagnosed with PTSD and comorbid MDD. This finding may be connected to the

increased within-network connectivity observed in the comorbid group for the R FPAR in the primary group analyses. It may indicate that greater connectivity within (and between) the frontoparietal networks are required as a compensatory mechanism for participants with PTSD and comorbid MDD.

With regard to task performance, for both the DCCS and Pattern Comparison Processing Speed test, the salience network seems to exhibit faulty functioning in the clinical groups, as it can be seen that there is an absence of an association between task performance and between-network connectivity in the clinical groups.

### **Limitations**

Several research limitations need to be emphasised. First, this study had a cross-sectional design; therefore, it cannot establish the causality of the relationship between psychiatric disorders and intrinsic functional connectivity of the networks examined.

Second, due to reasons beyond the control of the study, two separate scanners were used during this study. Every effort was made to statistically control for these scanner effects, nevertheless where analyses indicated a scanner effect, results should be interpreted with caution.

As Chapter 2 highlights, due to utilising a LMI female sample, results from this study may not accurately reflect the associations of PTSD, MDD, or PTSD with comorbid MDD on intrinsic resting-state networks in mixed gender populations, or higher income populations.

### **Conclusions**

The present study reports findings that support some of the hypotheses. Within-network connectivity differences were evident for the DMN and R FPAR, and subthreshold effects were observed for the L FPAR. No evidence was found for abnormal within-network connectivity for the DAN and SN in the present sample. The present study supports the hypothesis that PTSD symptom severity would be associated with network connectivity. Set-switching and processing speed were also associated with between-network connectivity, as hypothesised. However, the present study provides evidence suggesting that PTSD with comorbid MDD is associated with greater connectivity within the right frontoparietal network, relative to the mono-diagnostic groups and controls, which has not yet been reported in the literature. As there is very limited resting-state imaging research of PTSD with comorbid MDD, these findings are the first of its kind and may pave the way for future

research. The present study found no evidence of abnormal between-network intrinsic functional connectivity in a sample of mothers from a LMI setting.



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## **Chapter 4**

### **Structural brain imaging in PTSD, MDD, and PTSD with MDD**

Empirical evidence suggests that PTSD and MDD are characterised by alterations of volume and cortical thickness of brain structures (Karl et al., 2006; Lorenzetti et al., 2009). However, the neuroanatomy of patients with PTSD and comorbid MDD has not been reported in the literature. Examining abnormalities in cortical thickness, surface area, and volume in psychiatric disorders such as PTSD and MDD may reveal biomarkers for the disorders and may have important implications for clinical neuroscience (Han et al., 2006). These structural measures also provide powerful tools for studying and understanding the biological basis of psychiatric disorders (Fischl & Dale, 2000).

The previous chapter highlighted that MDD is associated with greater within-network connectivity of the default mode network, PTSD with comorbid MDD is associated with greater functional connectivity within the right frontoparietal network, and no specific within-network findings were observed for PTSD. Empirical evidence illustrates that frontal cortical regions belonging to the above networks are particularly affected in these psychiatric patient populations. The present chapter aims to explore the neuroanatomy of these frontal regions in these patient populations, with a particular focus on whether PTSD with comorbid MDD amplifies the structural abnormalities found in either PTSD or MDD.

## **Background**

Recent literature has illustrated an overlap of structural brain abnormalities in PTSD and MDD (Kroes et al., 2011). Despite the extensive PTSD and MDD structural imaging research, there is little similar research conducted on patients with PTSD and comorbid MDD.

### **Structural Imaging in PTSD**

Areas of the limbic system (amygdala and hippocampus) are the focus of the majority of structural imaging research in PTSD, as these regions are heavily implicated in the fear response and memory, respectively (Etkin & Wager, 2007; LeDoux, 2003; Smith, 2005; Tulving & Markowitsch, 1998). Studies consistently report reduced (bilateral) hippocampal and amygdala volume in PTSD patients relative to controls (Hull, 2002; Karl et al., 2006; Morey et al., 2016). In a series of structural imaging meta-analyses, PTSD was associated with significantly smaller left amygdalae relative to healthy controls ( $r = -.14$ ), whilst the right amygdala showed no significant reductions when compared to healthy controls (Karl et

al., 2006). In a recent multisite study of a sample of 794 PTSD participants, the PGC-ENIGMA group explored the amygdala and hippocampal associations with PTSD. This study found that the amygdala and hippocampus was smaller relative to controls. These significant differences remained after controlling for age, sex, and intracranial volume. Furthermore, a large effect ( $d = -0.31$ ) indicated volumetric reductions of the hippocampus in female participants (Morey et al., 2016).

Studies have further shown that PTSD is associated with reductions in regions such as the prefrontal cortex (PFC), a region thought to be the seat of executive functions (Diamond, 2013; Karl et al., 2006; Kroes et al., 2011; Pitman et al., 2012; Rauch et al., 2003). In a structural imaging review, Shin et al. (2006) reported medial PFC volume reductions in PTSD. Evidence suggests that cortical thickness of the medial PFC is also reduced in PTSD ( $n = 20$ ) relative to healthy controls ( $n = 20$ ) (Bing et al., 2013). Further, in a biological review of PTSD, Pitman et al. (2012) reported that volumetric reductions of the rostral ventromedial PFC in PTSD are common.

Reductions of the anterior cingulate cortex and its sub regions are also commonly reported in the PTSD literature (Karl et al., 2006; Kroes et al., 2011; Rauch et al., 2003). For example, in an all-female sample, Rauch et al. (2003) found that the pregenual ACC and the subcallosal cortical volume is reduced in a sample of current PTSD patients ( $n = 9$ ), relative to trauma-exposed controls ( $n = 9$ ). However, the dorsal ACC exhibited no significant volumetric differences in the PTSD group relative to controls (Rauch et al., 2003). In a sample of combat-related PTSD patients ( $n = 50$ ), PTSD was associated with reduced mean cortical thickness across the whole brain, as well as reduced rostral and caudal ACC cortical thickness, relative to combat-exposed controls ( $n = 47$ ) (Woodward et al., 2009).

### **Structural Imaging in MDD**

The hippocampus is the most often studied structure in the MDD literature, with the majority of studies reporting that MDD is associated with reduced hippocampal volume ( $d = -0.37$ ) (Koolschijn et al., 2009). In a study by Bremner et al. (2000), it was reported that the left hippocampus was smaller in the MDD group ( $n = 16$ ), relative to gender and handedness matched controls ( $n = 16$ ), and this result remained significant after controlling for whole brain volume. Contrary to the findings of the studies of PTSD, no evidence of amygdala reductions in MDD relative to controls was found in a meta-analysis of 64 structural imaging studies (Koolschijn et al., 2009).

Further, significantly thinner cortex has been reported in cortical-limbic regions such as the orbitofrontal cortex (OFC), superior temporal lobe, and the insula cortex in MDD ( $n = 23$ ) relative to healthy controls ( $n = 26$ ) (Järnum et al., 2011). Koolschijn et al. (2009) further reported frontal region volume reductions, particularly of the ACC (left:  $d = -1.11$ ; right:  $d = -0.62$ ), orbitofrontal cortex ( $d = -0.43$ ), and prefrontal cortex (PFC) ( $d = -0.34$ ) in an MDD group relative to controls. Similar findings were reported in a review by Lorenzetti and colleagues (2009), where it was reported that severely depressed patients exhibited significant volume reduction of the OFC (Lorenzetti et al., 2009). Research by Bremner et al. (2002) revealed that the medial OFC was 32% smaller in the (medicated) MDD group ( $n = 15$ ) when compared to age, gender, education, and handedness matched controls ( $n = 20$ ). Further, Wagner et al. (2012) reported that MDD patients exhibited reduced cortical thickness of fronto-cingulate and temporal regions, with the MDD group ( $n = 30$ ) displaying decreased cortical thickness of the PFC and ACC, relative to age, gender, and education matched healthy controls ( $n = 30$ ). In a sample of Korean first episode MDD patients, the MDD group exhibited reduced cortical volume of the caudal middle frontal gyrus and the medial orbitofrontal gyrus, relative to controls (Han et al., 2014). Most recently, in a large multisite study, Schmaal et al. (2017) reported that MDD ( $n = 2148$ ) is associated with cortical thinning of frontal regions, such as mPFC, and the rACC, in addition to the posterior cingulate, insula, and right inferior parietal, relative to healthy controls ( $n = 7957$ ).

### **Structural Imaging in PTSD with Comorbid MDD**

In a study examining PTSD and MDD respectively, Kroes et al. (2011) reported that the brain abnormalities associated with PTSD ( $n = 24$ ) and MDD ( $n = 29$ ) tend to overlap, and this may be due to the PTSD group and MDD group reporting similar levels of depression (Kroes et al., 2011). To date, no research has been conducted on this topic utilising a comorbid group, or a four-group design.

There is a paucity of structural imaging literature examining cortical thickness and total surface area in PTSD, MDD, and PTSD with comorbid MDD patient groups. The majority of literature focuses on volumetric findings in these patients.

### **Rationale**

Chapter 1 highlighted a number of gaps in knowledge that need addressing to clarify whether PTSD with comorbid MDD has a synergistic or additive effect on neuroanatomy. Synergistic



findings would indicate that the comorbid group would display structural reductions that are greater than the combined reductions found in PTSD and MDD, respectively. Additive findings would indicate that the comorbid group would display structural reductions similar to those found in PTSD and MDD, individually. While Kroes et al. (2011) reported that PTSD and MDD respectively exhibit similar structural abnormalities, there is no further literature to support this finding. Current studies neglected to utilise a comorbid group in analyses and therefore structural abnormalities associated with PTSD with comorbid MDD have not been determined to date.

Furthermore, numerous PTSD imaging studies are conducted on (American) military samples, which leaves a substantial group of PTSD patients (female participants in low-middle income countries with a variety of trauma types, etc.) underrepresented in the literature. Additionally, there are no structural imaging studies of PTSD and MDD in a South African context. Although these prevalence rates are not as high as in America, the prevalence of these disorders, and the frequent co-occurrence of the two disorders in South African populations suggests that this topic needs more attention as these disorders place a large burden on resource scarce healthcare (Atwoli et al., 2013).

### **Aims and Hypotheses**

The aim of this study is to characterise structural abnormalities associated with PTSD, MDD, and PTSD with comorbid MDD in a sample of LMI mothers. Associations of diagnostic group with frontal cortical volume, thickness, and surface area metrics were of particular interest. Based on the literature review, and findings from analysis of neurocognitive and resting-state fMRI abnormalities in this thesis, the following hypotheses will be tested:

### **Hypotheses**

- Anterior cingulate and superior frontal cortical thickness, volume, and surface area reductions will be evident in the mono-diagnostic groups (PTSD and MDD) , relative to controls.
- The MDD only group will display surface area, volume, and thickness reductions of the precuneus and the posterior cingulate (regions associated with the default mode network), relative to controls.
- Where differences are observed, the comorbid group will exhibit greater reductions of cortical surface area, thickness, and volume, relative to the mono-diagnostic groups.

## Methods

The sample for this study is identical to the sample utilised in the previous chapter.

Information regarding ethics, participants, and materials used in this study can be found in the methods section of Chapter 3.

### Data Acquisition

Imaging took place at two venues: The Cape University Body Imaging Centre (CUBIC) at Groote Schuur Hospital at the University of Cape Town (3T Magnetom Skyra (Siemens)), and Tygerberg Hospital at Stellenbosch University (3T Magnetom Allegra Syngo (Siemens)). Whole-brain T1-weighted multi-echo MPRAGE gradient echo echo-planar images (128 slices, TR = 2530 ms, TE = 1.69, 3.55, 5.41, 7.27 ms, FOV = 256×256 mm, 1.0x1.0x1.5 mm voxels, slice thickness = 1.5 mm, inter-slice gap = 1mm) and corresponding fieldmaps were acquired using a 3T Magnetom Skyra (Siemens) full body scanner with a 32 channel head coil at the University of Cape Town. Multi-echo MPRAGE structural scans at Stellenbosch University, using a four-channel coil, were acquired using the following parameters: 128 slices, TR = 2000ms, TE = 1.53, 3.21, 4.89, 6.57 ms, FOV = 256x256 mm, 1.0x1.0x1.5 mm, slice thickness = 1.5 mm.

### Data Processing

Data were processed using Freesurfer 6 (<http://surfer.nmr.mgh.harvard.edu/>), a program that produces a reliable cortical thickness measurement (Han et al., 2006). Data were processed using the method described in an article by Desikan et al. (2006). Briefly, each participant's scan underwent motion correction, was normalized for intensity, then resampled (to 1x1x1mm). The skull was stripped, with the images subsequently segmented to identify gray and white matter. The cortex was then segmented into 34 gyral-based neuroanatomical regions (Desikan et al., 2006).

### Data Analysis

Group differences on demographic variables were analysed utilising ANOVAs and t-tests, using SPSS 24.

**Primary analyses.** Frontal regions associated with neurocognitive domains such as attention and executive function, as well as regions falling within DMN and cognitive control networks were the primary focus of the analyses. This included the following regions defined by the Desikan-Killiany atlas and analysed by hemisphere: the caudal and rostral anterior

cingulate (ACC), superior frontal and superior parietal cortex, inferior parietal cortex, posterior cingulate, precuneus, caudal middle frontal and rostral middle frontal cortices, and the insula. ANCOVAs were run on the structural indices, with group designation as the primary predictor variable, and age and education as covariates. Interaction terms for group and age, as well as group and education were only included in the final model if models where these interactions were tested separately as predictors of test scores were statistically significant (at  $\alpha < 0.1$ ). This method was utilised to maximise the power of the final models. Significant interactions remained in the final model and scatterplot graphs were created to establish the effect of these interactions on structural indices. Where interactions were significant, 1-tailed Pearson correlations were run between the structural outcome and the significant covariate, within each group.

**Secondary analyses.** Secondary analyses included correlating PTSD symptom severity (PTSD and comorbid groups) with structural metrics, using CAPS total score. Two-tailed Pearson correlations were utilised.

**Multiple comparisons.** Due to multiple comparisons being conducted, the Bonferroni method was used to correct for Type 1 error for the ANCOVA tests of group differences. A total of 60 analyses will be run, therefore alpha was set at ( $p = .05/60 = .0008$ ).

## Results

### Participants

Out of the 112 participants recruited for this study,  $n = 8$  were excluded, leaving a total of  $n = 104$  to be included in analyses. Participants were excluded due to incomplete diagnostic information ( $n = 3$ ), subthreshold PTSD diagnosis ( $n = 1$ ), and other psychopathology (alcohol abuse) ( $n = 1$ ). One participant was excluded for faulty skull stripping and  $n = 2$  were excluded for bad quality T1 images. Three participants were excluded due to excessive motion; however, these participants were also excluded based on the above exclusion criteria. Final groups were as follows: PTSD  $n = 22$ ; MDD  $n = 27$ ; PTSD+MDD  $n = 19$ ; control  $n = 36$ . Of these participants,  $n = 3$  were diagnosed with current PTSD and  $n = 3$  were diagnosed with current MDD.

**Descriptive statistics.** Descriptive statistics for the sample can be found in Table 1. The results indicated that the groups were comparable with respect to age ( $p = .21$ ) and education ( $p = .38$ ). A two-tailed t-test showed significant group differences for CAPS total

score between the PTSD group ( $M = 69.1$ ,  $SD = 18.9$ ) and the PTSD with comorbid MDD group ( $M = 87.1$ ,  $SD = 15.9$ ),  $t(39) = -3.28$ ,  $p = .002$ .

### **A priori primary analyses**

Means and standard deviations for left and right hemisphere surface area, cortical volume and cortical thickness can be found in Tables 2 to 7.

#### **Left hemisphere surface area**

**Caudal ACC.** Neither age, nor education produced significant interaction terms; therefore, these terms were removed from the final model. The final model indicated no significant group effect ( $F(3, 98) = 1.33$ ,  $p = .27$ ). Partial  $\eta^2$  indicated that a small to moderate proportion of caudal ACC surface area variance was explained by group (partial  $\eta^2 = .039$ ).

**Caudal Middle Frontal.** No significant interaction was found for age or education, therefore the final model, without these interaction terms, indicated that surface area was significantly smaller for PTSD and MDD groups, but not for the comorbid group, relative to controls ( $F(3, 98) = 2.79$ ,  $p = .044$ ). Partial  $\eta^2 = .079$ , indicating a moderate amount of variance in caudal middle frontal surface area was explained by group.

**Inferior Parietal.** Age and education did not produce significant interaction terms; therefore, they were removed from the final model. The final model indicated that there was no significant group effect ( $F(3, 98) = 0.17$ ,  $p = .92$ ). Very little variance of the inferior parietal variance was explained by group (partial  $\eta^2 = .005$ ).

**Posterior Cingulate.** Age did not produce a significant interaction; however, education did ( $p = .004$ ), therefore the education interaction remained in the final model. The comorbid group displayed a significant positive correlation between education and posterior cingulate surface area ( $r = .43$ ;  $p = .033$ ), whereas the PTSD group exhibited a significant negative correlation between education and posterior cingulate surface area ( $r = -.54$ ,  $p = .004$ ). A large portion of the variability in surface area was explained by the final model (partial  $\eta^2 = .131$ ). A scatterplot (Figure 1) was created to visually assess the effect education has on posterior cingulate surface area.

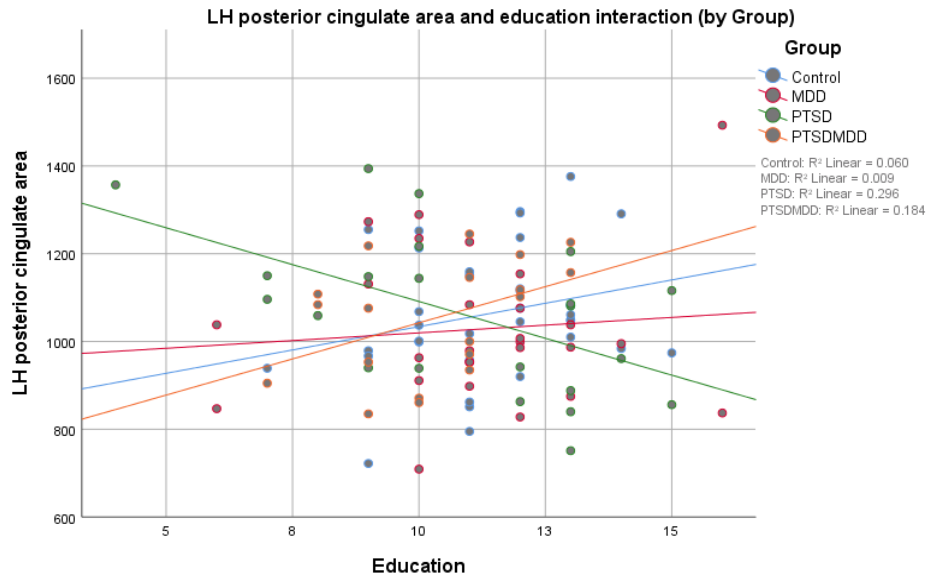


Figure 1. Scatterplot of posterior cingulate surface area and education interaction

**Precuneus.** There was no significant interaction for age, but the education interaction was significant ( $p = .065$ ). None of the groups exhibited a significant correlation between precuneus surface area and education. A moderate proportion of variability in precuneus surface area was explained by the final model (partial  $\eta^2 = .072$ ). Figure 2 illustrates the interaction between precuneus surface area and education.

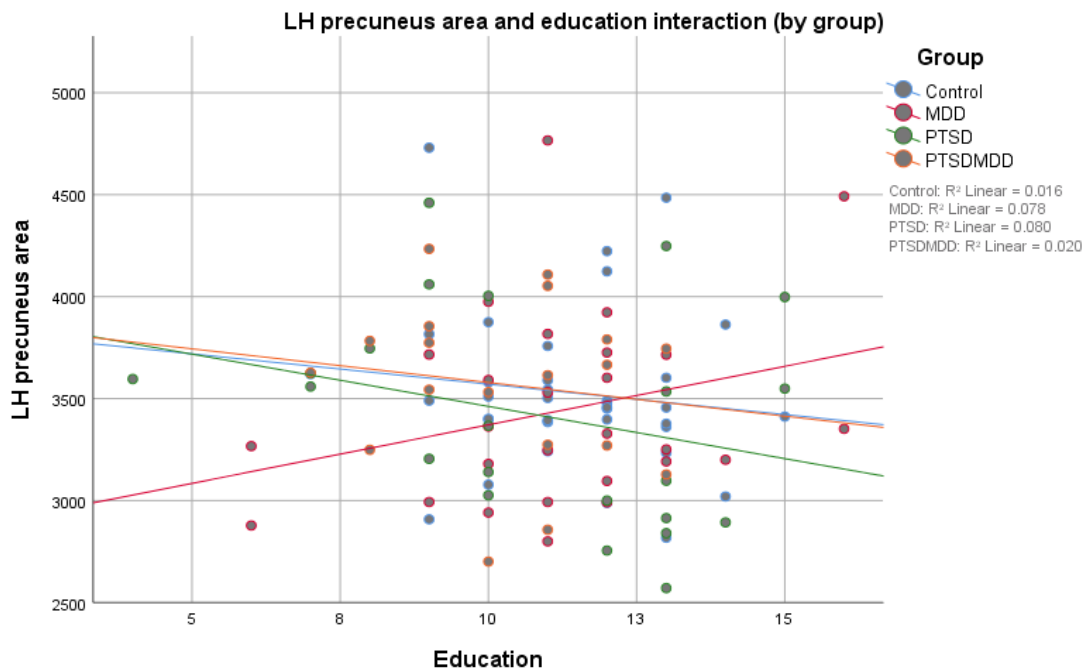


Figure 2. Scatterplot of precuneus surface area and education interaction

**Rostral ACC.** Both age and education failed to produce significant interaction terms and were therefore removed from the final model. The final model indicated that there was no significant group effect ( $F(3, 98) = 1.75, p = .16$ ) and a small to moderate amount of variability in rostral ACC surface area was explained by the model (partial  $\eta^2 = .051$ ).

**Rostral Middle Frontal.** Only education produced a significant interaction ( $p = .002$ ) and the interaction term remained in the model. The control group exhibited a significant positive correlation between rostral middle frontal surface area and education level ( $r = .325, p = .026$ ), while the PTSD group exhibited a significant negative correlation between surface area and education ( $r = -.486, p = .011$ ). Partial  $\eta^2$  indicated that a large amount of the rostral middle frontal variability was explained by the final model (partial  $\eta^2 = .137$ ). The interaction between rostral middle frontal surface area and education can be seen in Figure 3.

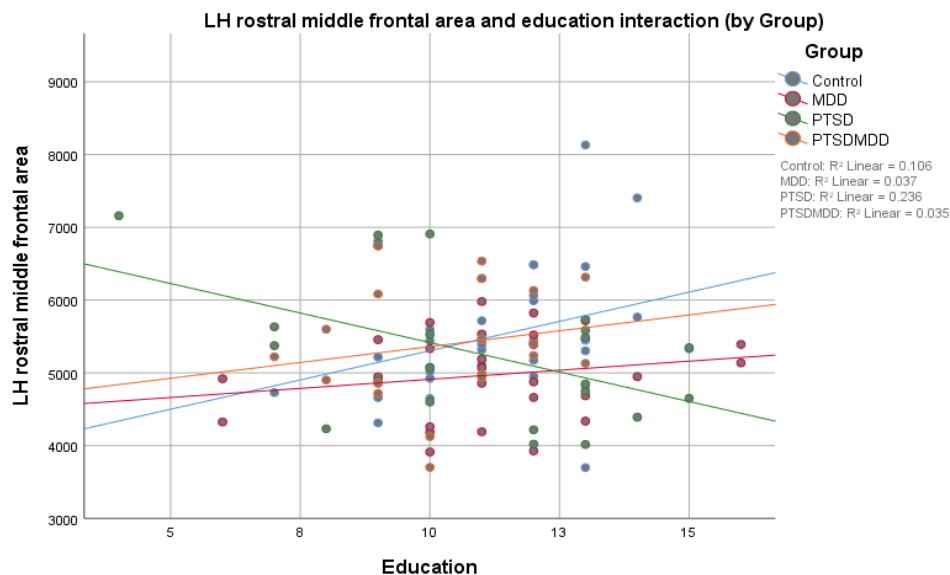


Figure 3. Scatterplot of rostral middle frontal surface area and education interaction

**Superior Frontal.** Age did not produce a significant interaction, however, there was a significant interaction with education ( $p = .028$ ), and the education interaction term remain in the final model where a significant group effect was found ( $F(3, 95) = 3.11, p = .03$ ). The comorbid group displayed a significant positive correlation between superior frontal surface area and education ( $r = .403, p = .043$ ), while the PTSD group exhibited a significant negative correlation between surface area and education level ( $r = -.394, p = .035$ ). A moderate portion of the variability in superior frontal surface area variability was explained by the final model (partial  $\eta^2 = .09$ ). Figure 4 highlights the interaction between superior frontal surface area and education.

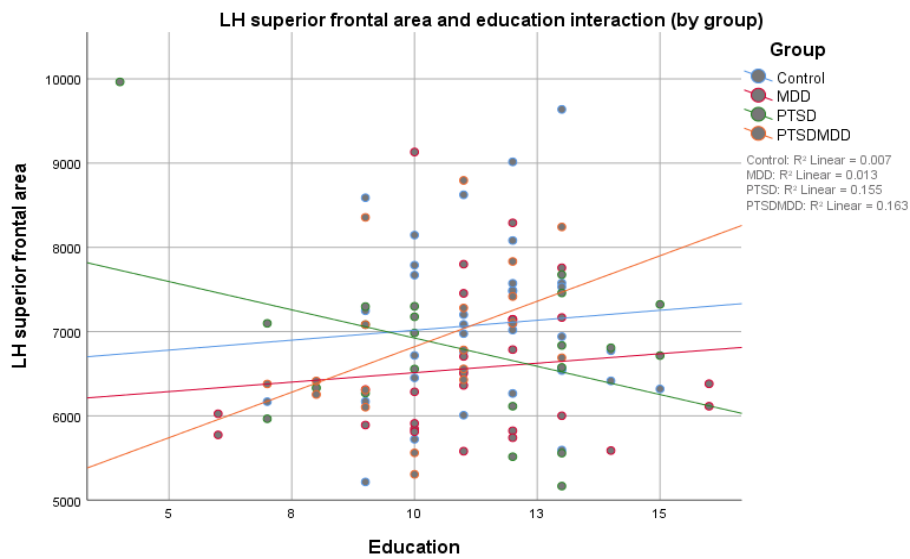


Figure 4. Scatterplot of superior frontal surface area and education interaction

**Superior Parietal.** Both age ( $p = .057$ ), and education ( $p = .044$ ) produced significant interactions and both interaction terms remained in the final model. PTSD exhibited a significant negative correlation between age and superior parietal surface area ( $r = -.372$ ,  $p = .044$ ). PTSD with comorbid MDD was associated with a subthreshold negative correlation between age and superior parietal surface area ( $r = -.37$ ,  $p = .06$ ). MDD was associated with a significant positive correlation between education and superior parietal surface area ( $r = .504$ ,  $p = .004$ ). The final model explained a large proportion of the variability of superior parietal surface area (partial  $\eta^2 = .12$ ). A scatterplot (see Figure 5) was created to visually inspect the relationship between education and superior parietal surface area. Figure 6 illustrates the interaction between age and superior parietal surface area.

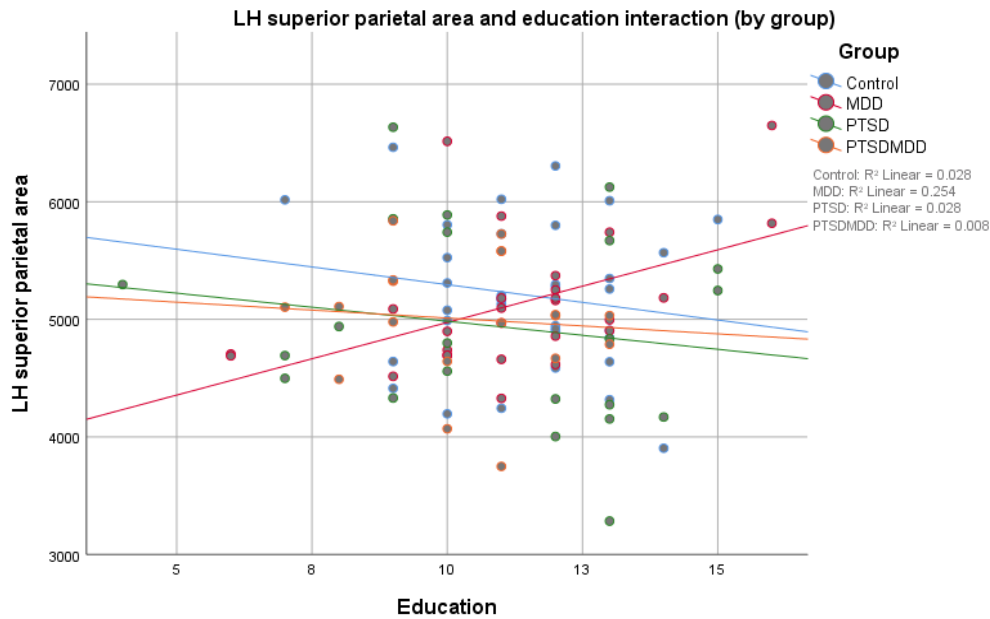


Figure 5. Scatterplot of superior parietal surface area and education interaction

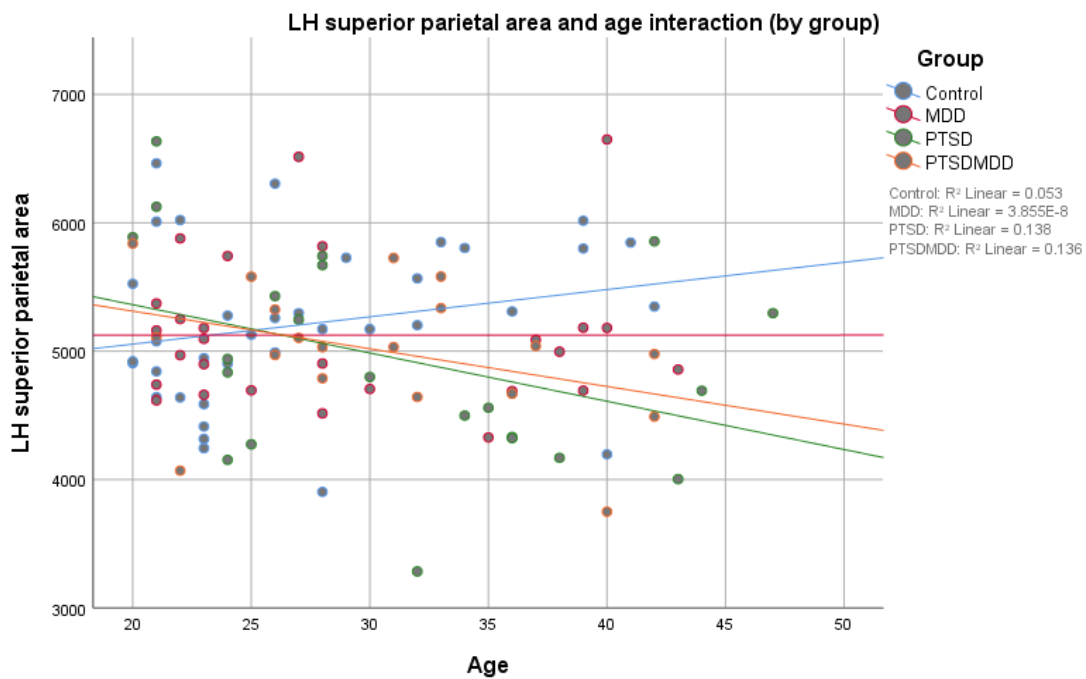


Figure 6. Scatterplot of superior parietal surface area and age interaction

**Insula.** Education was the only covariate to produce a significant interaction term ( $p = .006$ ), and therefore remained in the final model. The PTSD group exhibited a significant negative correlation between insula surface area and education level ( $r = -.567, p = .003$ ). The final model explained a large amount of the variability in insula surface area (partial  $\eta^2 = .128$ ).



After removing the outlier from the analysis, the effect was still observed ( $r = -.41, p = .033$ ).

Figure 7 illustrates the relationship between education and insula surface area.

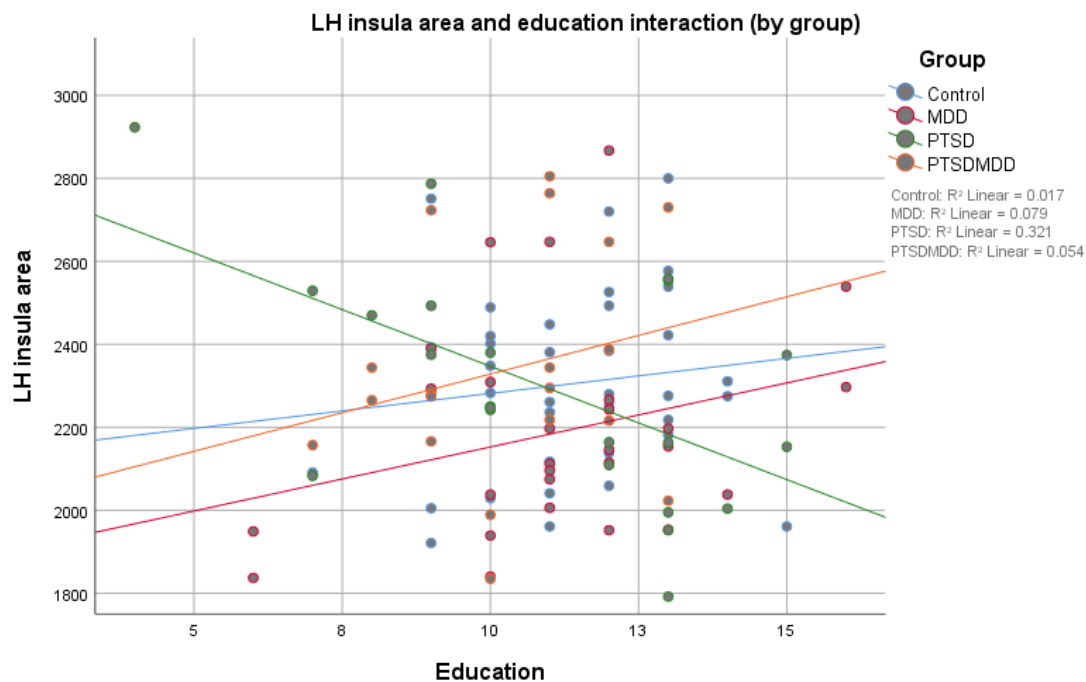


Figure 7. Scatterplot of insula surface area and education interaction

### Left hemisphere volume

**Caudal ACC.** Age and education did not produce significant interactions and were removed from the final model. The final model indicated no significant group effect ( $F(3, 98) = 1.98, p = .12$ ). Partial  $\eta^2 = .057$  indicated a moderate amount of the variance of caudal ACC mean volume was explained by group.

**Caudal Middle Frontal.** The covariates did not produce significant interaction terms and were therefore removed from the final model. The final model indicated no significant group effect ( $F(3, 98) = 1.29, p = .28$ ) and a small to moderate amount caudal middle frontal volume variance is explained by group (partial  $\eta^2 = .038$ ).

**Inferior Parietal.** Both age and education interaction terms were removed from the final model as they did not produce significant interactions. The final model indicated that there was no significant group effect ( $F(3, 98) = .6, p = .62$ ). Group explained a small portion of inferior parietal variance (partial  $\eta^2 = .018$ ).

Table 1

*Sample demographics*

	PTSD	MDD	PTSD+MDD	Control	<i>p</i> value	Group contrast
	<i>n</i> = 22	<i>n</i> = 27	<i>n</i> = 19	<i>n</i> = 36		
Age ( <i>SD</i> ) <sup>a</sup>	31.1 (8.1)	28.8 (7.5)	30.5 (6.7)	27.4 (6.7)	.18	NA
Education ( <i>SD</i> ) <sup>b</sup>	10.7 (2.9)	11.2 (2.4)	10.3 (1.8)	11.4 (1.8)	.21	NA
CAPS total severity score <sup>c</sup>	69.1 (18.9)	NA	87.1 (15.9)	NA	.002	Comorbid > PTSD

<sup>a</sup> based on 104 participants

<sup>b</sup> based on 97 participants

<sup>c</sup> based on 41 participants

**Posterior Cingulate.** Age did not produce a significant interaction term, but education did ( $p = .005$ ), therefore the final model included the education interaction term. A significant positive correlation was found for the controls between posterior cingulate volume and level of education ( $r = .29, p = .043$ ), as well as for the comorbid group ( $r = .45, p = .026$ ). The PTSD group exhibited a significant negative correlation between education level and posterior cingulate volume ( $r = -.39, p = .037$ ). The final model explained a large proportion of the variability in posterior cingulate volume (partial  $\eta^2 = .128$ ). Figure 8 illustrates the relationship between posterior cingulate volume and education level.

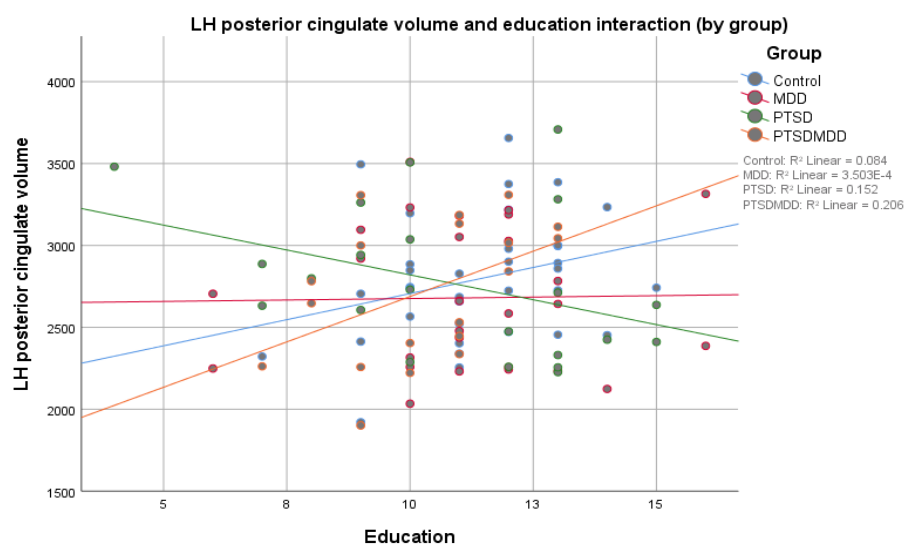


Figure 8. Scatterplot of posterior cingulate volume and education interaction

**Precuneus.** There were no significant interactions for age or education, and these interaction terms were removed from the final model. The final model found no significant group effect,  $F(3, 98) = .17, p = .91$ . A small portion of precuneus variability was explained by group (partial  $\eta^2 = .005$ ).

**Rostral ACC.** The covariates did not produce significant interactions; therefore, the interaction terms were removed from the final model. The final model found no significant group effect,  $F(3, 98) = .77, p = .51$ . Partial  $\eta^2$  indicated that a small amount of rostral ACC volume variance was explained by group (partial  $\eta^2 = .023$ ).

**Rostral Middle Frontal.** Education produced a significant interaction ( $p = .014$ ), but age did not. The controls exhibited a significant positive correlation between rostral middle frontal volume and education ( $r = .376, p = .012$ ). The final model accounted for a moderate to large

amount of variability of rostral middle frontal volume (partial  $\eta^2 = .106$ ). The relationship between rostral middle frontal volume and education can be seen in Figure 9.

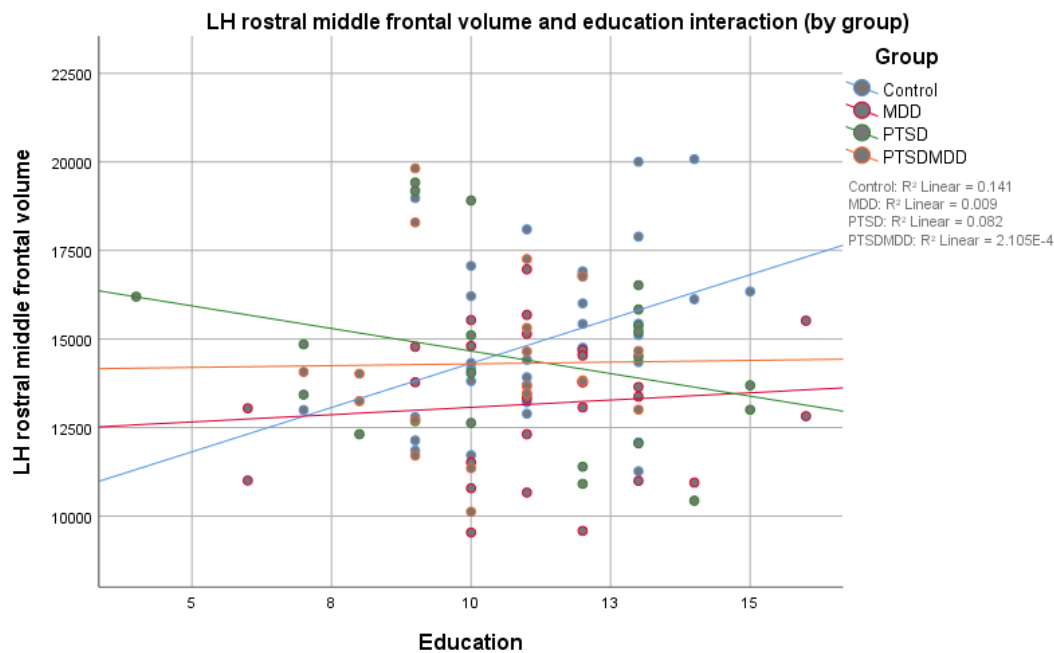


Figure 9. Scatterplot of rostral middle frontal volume and education

**Superior Frontal.** No significant interactions were found for age or education. The final model indicated that there was no significant group effect ( $F(3, 98) = 2.03, p = .11$ ). A moderate proportion of superior frontal variance was explained by group (partial  $\eta^2 = .058$ ).

**Superior Parietal.** Age produced a significant interaction term ( $p = .05$ ) and remained in the final model; however, education did not produce a significant interaction term. PTSD exhibited a strong negative correlation between age and superior parietal volume ( $r = -.557, p = .004$ ). The comorbid group exhibited a subthreshold negative correlation between age and superior parietal volume ( $r = -.35, p = .07$ ). The final model accounted for a moderate proportion of the variability of superior parietal volume (partial  $\eta^2 = .07$ ). Figure 10 highlights the relationship between superior parietal volume and age.

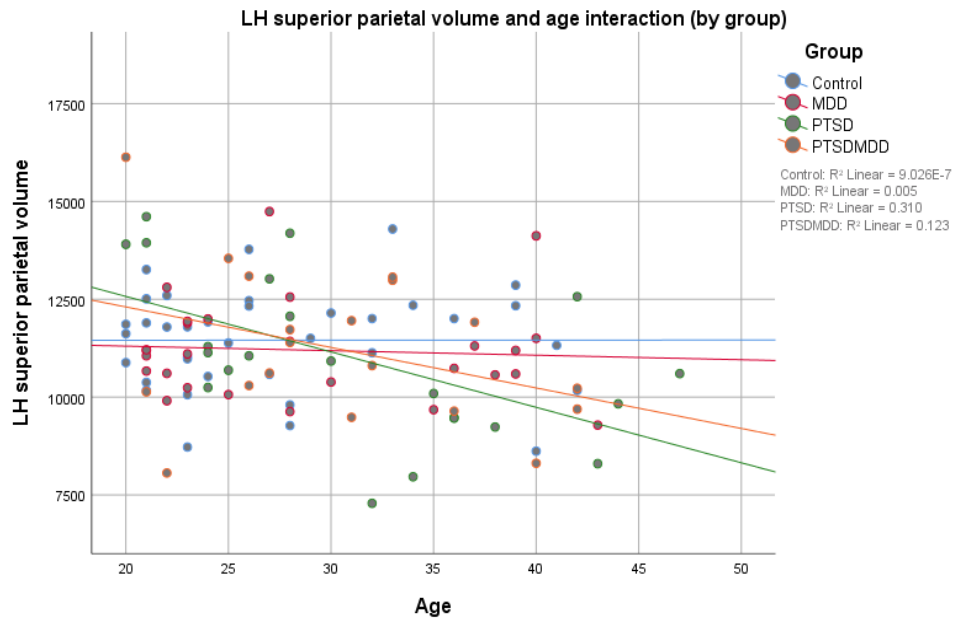


Figure 10. Scatterplot of superior parietal volume and age interaction

**Insula.** Age did not produce a significant interaction term. Education produced a significant interaction term ( $p = .024$ ) and the term remained in the final model. None of the groups exhibited a significant correlation between education and insula volume, however, the PTSD group exhibited a trend towards significance ( $r = -.342, p = .06$ ). The final model explained a moderate to large proportion of variability in insula volume (partial  $\eta^2 = .11$ ). The relationship between insula volume and education can be seen in Figure 11.

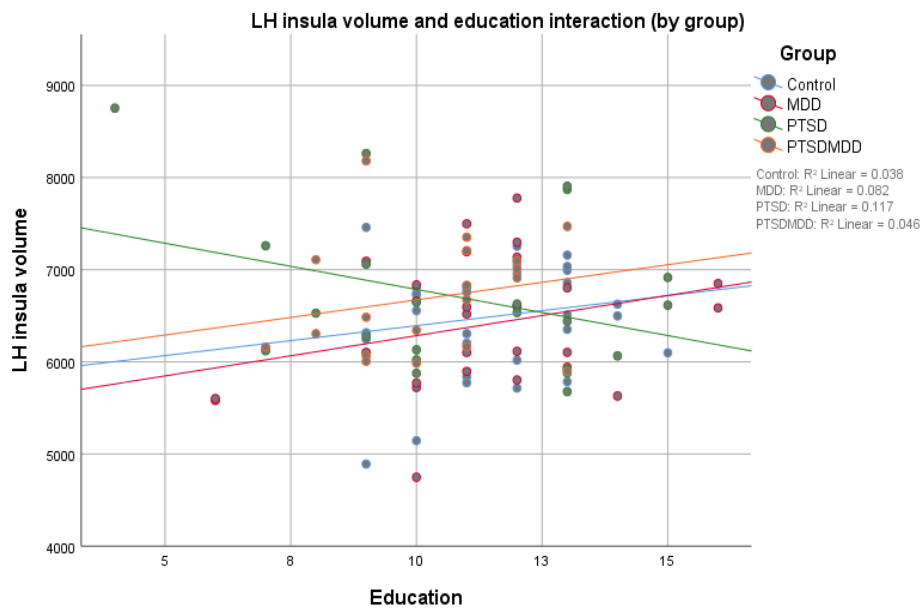


Figure 11. Scatterplot of insula volume and education interaction

### **Left hemisphere cortical thickness**

Age and education did not produce significant interaction terms for any of the region models, therefore these interaction terms were removed from all final region models.

**Caudal ACC.** The final model indicated that there was no significant group effect ( $F(3, 98) = .66, p = .58$ ). Partial  $\eta^2 = .02$ , indicating that group explained a small proportion of caudal ACC thickness variance.

**Caudal Middle Frontal.** The final model indicated that there was no significant group effect,  $F(3, 98) = .94, p = .43$ . A small proportion of caudal middle frontal thickness variance was explained by group (partial  $\eta^2 = .028$ ).

**Inferior Parietal.** The final model found no significant group effect ( $F(3, 98) = 1.88, p = .14$ ) and a moderate proportion of inferior parietal thickness variance was explained by group (partial  $\eta^2 = .054$ ).

**Posterior Cingulate.** No significant group effect was evident in the final model,  $F(3, 98) = .31, p = .82$ , and a small proportion of posterior cingulate variance was explained by group (partial  $\eta^2 = .009$ ).

**Precuneus.** No significant group effect was observed in the final model ( $F(3, 98) = .72, p = .54$ ). Partial  $\eta^2 = .021$ , indicating a small proportion of precuneus thickness variance was explained by group.

**Rostral ACC.** The final model did not produce a significant group effect,  $F(3, 98) = .98, p = .41$ , and a small proportion of rostral ACC variance was explained by group (partial  $\eta^2 = .029$ ).

**Rostral Middle Frontal.** No significant group effect was observed in the final model,  $F(3, 98) = 1.21, p = .31$ , and a small portion of rostral middle frontal thickness variance was explained by group (partial  $\eta^2 = .036$ ).

**Superior Frontal.** The final model indicated no significant group effect ( $F(3, 98) = 1.35, p = .26$ ). A small proportion of superior frontal variance was explained by group (partial  $\eta^2 = .04$ ).

**Superior Parietal.** There was no significant group effect in the final model,  $F(3, 98) = .59, p = .62$ . Partial  $\eta^2$  indicated that a small proportion of superior parietal variance was explained by group (partial  $\eta^2 = .018$ ).

**Insula.** The final model observed no significant group effect,  $F(3, 98) = .52, p = .67$ , and a small amount of insula thickness variance was explained by group (partial  $\eta^2 = .016$ ).

## Right hemisphere surface area

**Caudal ACC.** Education was the only covariate to produce a significant interaction term ( $p = .016$ ) and remained in the final model. PTSD was associated with a significant negative correlation between caudal ACC surface area and education ( $r = -.495, p = .01$ ). The final model indicated that a moderate proportion of the variability of caudal ACC surface area was explained by group (partial  $\eta^2 = .101$ ). The relationship between caudal ACC surface area and education can be seen in Figure 12.

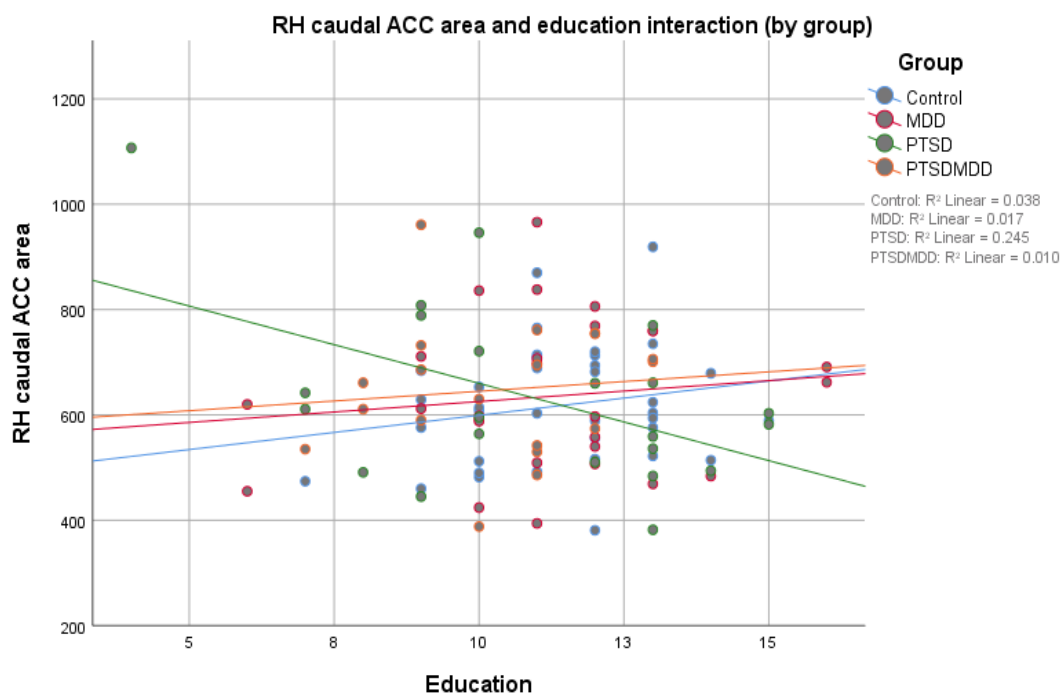


Figure 12. Scatterplot of caudal ACC surface area and education interaction.

**Caudal Middle Frontal.** Age and education did not produce significant interaction terms, therefore were removed from the final model. The final model found no significant group effect ( $F(3, 98) = 2.1, p = .11$ ). A moderate proportion of variance in caudal middle frontal surface area was explained by group (partial  $\eta^2 = .059$ ).

**Inferior Parietal.** Age did not produce a significant interaction term and was removed from the final model. Education produced a significant interaction term ( $p = .004$ ) and remained in the final model. The MDD group exhibited a moderate positive correlation between inferior parietal surface area and education ( $r = .367, p = .03$ ), whereas the PTSD group exhibited a significant negative correlation ( $r = -.465, p = .015$ ). Group explained a large proportion of

the variability of inferior parietal surface area (partial  $\eta^2 = .116$ ). Figure 13 illustrates the relationship between inferior parietal surface area and education.

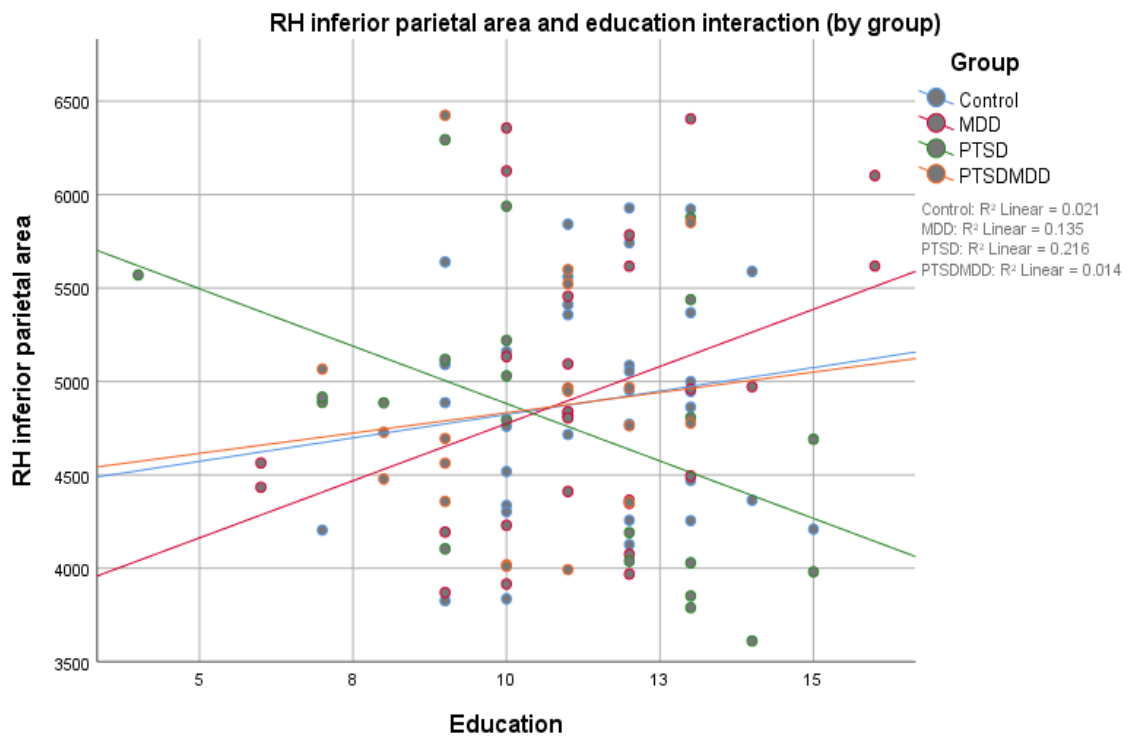


Figure 13. Scatterplot of inferior parietal surface area and education interaction

**Posterior Cingulate.** Education produced a significant interaction term ( $p = .003$ ) and remained in the final model, while age did not produce a significant interaction term. The PTSD group displayed a significant negative correlation between education and posterior cingulate surface area ( $r = -.553, p = .004$ ). Group explained a large proportion of the variability of posterior cingulate surface area (partial  $\eta^2 = .124$ ). The relationship between posterior cingulate surface area and education can be seen in Figure 14.



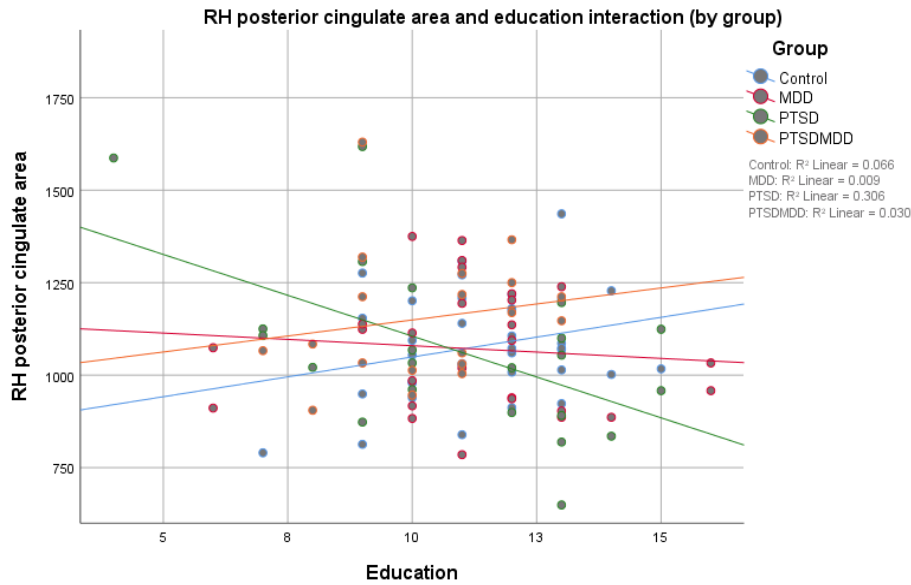


Figure 14. Scatterplot of posterior cingulate surface area and education interaction

**Precuneus.** A significant interaction term was found for education ( $p = .001$ ), but not age. The MDD group exhibited a significant positive correlation between education and precuneus surface area ( $r = .42, p = .014$ ), while the PTSD group exhibited a significant negative correlation ( $r = -.44, p = .02$ ). Group explained a large proportion of the variability of precuneus surface area (partial  $\eta^2 = .153$ ). Figure 15 represents the relationship between education and precuneus surface area.

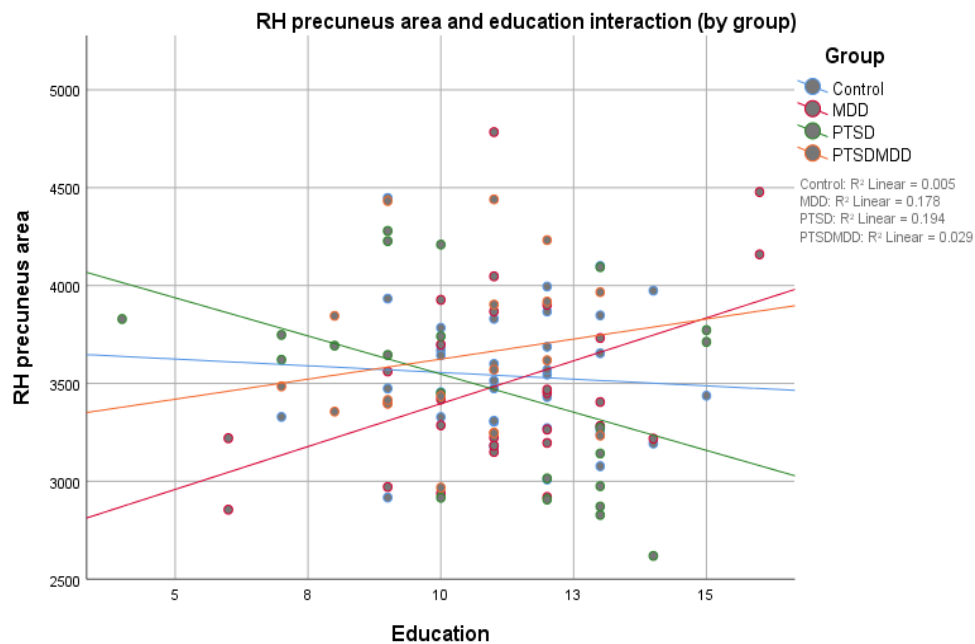


Figure 15. Scatterplot of precuneus surface area and education interaction

**Rostral ACC.** Age did not produce a significant interaction term; however, education produced a significant interaction term ( $p = .026$ ) and the term remained in the final model. The PTSD group exhibited a significant negative correlation between rostral ACC surface area and level of education ( $r = -.45, p = .018$ ). A large proportion of the variability of rostral ACC surface area was explained by group (partial  $\eta^2 = .115$ ). Figure 16 illustrates the relationship between rostral ACC surface area and education.

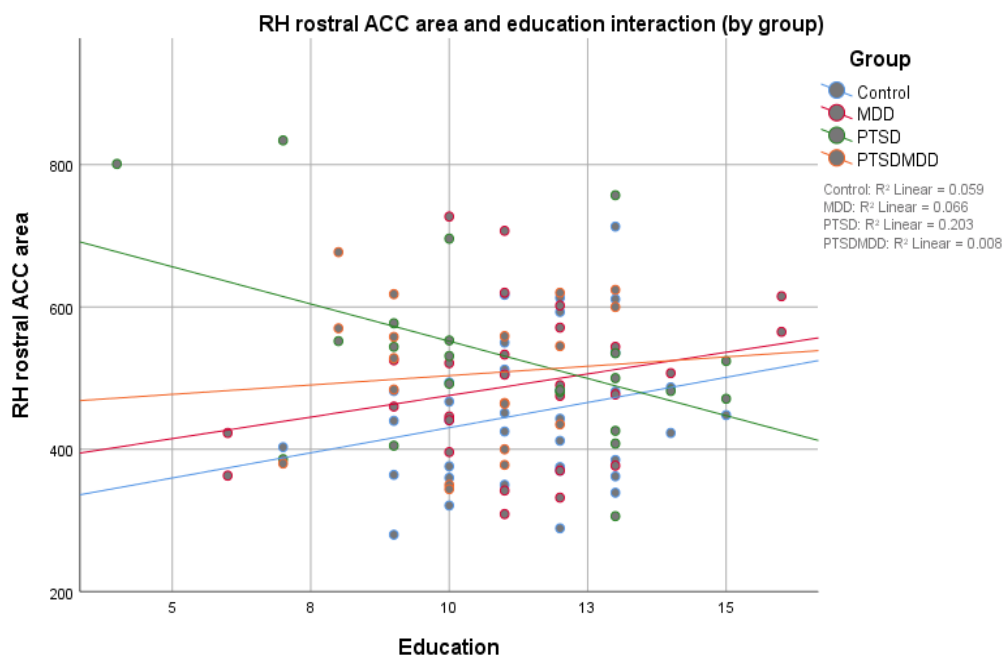


Figure 16. Scatterplot of rostral ACC surface area and education interaction

**Rostral Middle Frontal.** There was a significant interaction for education ( $p = .057$ ) which remained in the final model. The controls exhibited a significant positive correlation between rostral middle frontal surface area and education ( $r = .29, p = .043$ ), while the PTSD group exhibited a significant negative correlation ( $r = -.376, p = .042$ ). A moderate portion of the variability of rostral middle frontal surface area was explained by group (partial  $\eta^2 = .063$ ). A scatterplot highlighting the relationship between rostral middle frontal surface area and education can be seen in Figure 17.

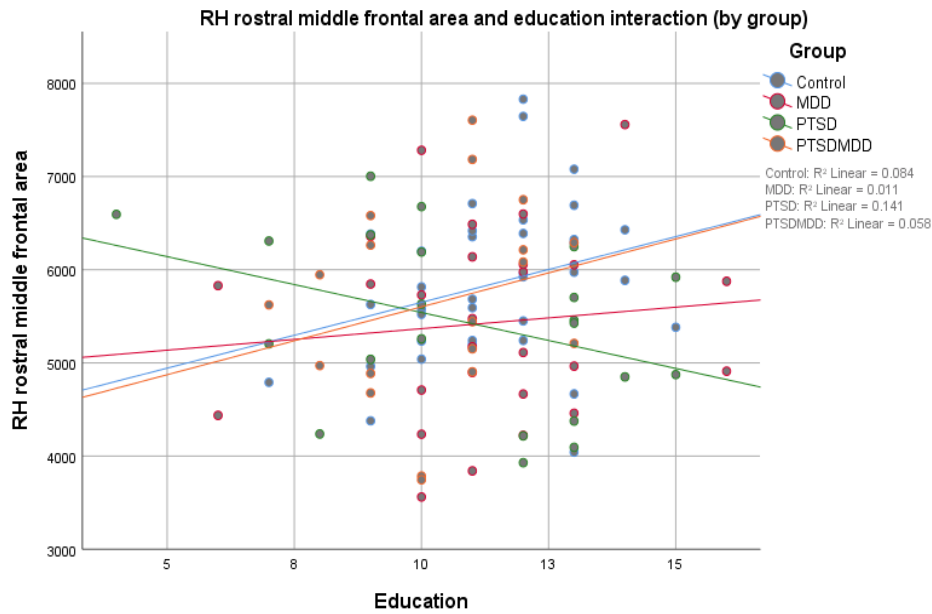


Figure 17. Scatterplot of rostral middle frontal surface area and education interaction

**Superior Frontal.** Age did not produce a significant interaction and was removed from the final model. There was a significant interaction for education ( $p = .022$ ) which remained in the final model. The PTSD group exhibited a significant negative correlation between superior frontal surface area and education ( $r = -.519, p = .007$ ). Group explained a moderate portion of the variability of superior frontal surface area (partial  $\eta^2 = .089$ ). Figure 18 illustrates the relationship between education and superior frontal surface area.

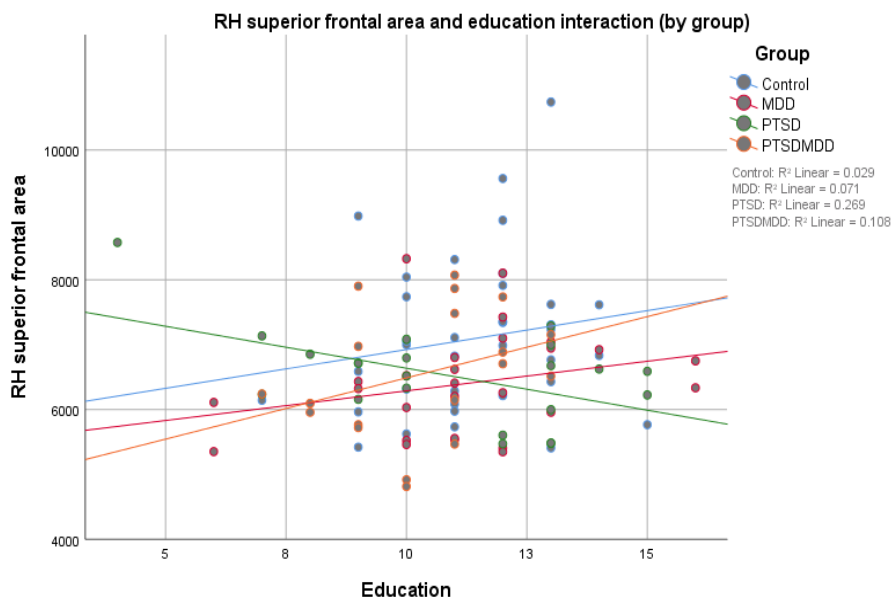


Figure 18. Scatterplot of superior frontal surface area and education interaction

**Superior Parietal.** A significant interaction term was found for education ( $p = .071$ ) which remained in the final model. Age did not produce a significant interaction term. None of the four groups exhibited a significant correlation between superior parietal surface area and education. A moderate proportion of the variability in superior parietal surface area was explained by group (partial  $\eta^2 = .058$ ). The relationship between superior parietal surface area and education can be seen in Figure 19.

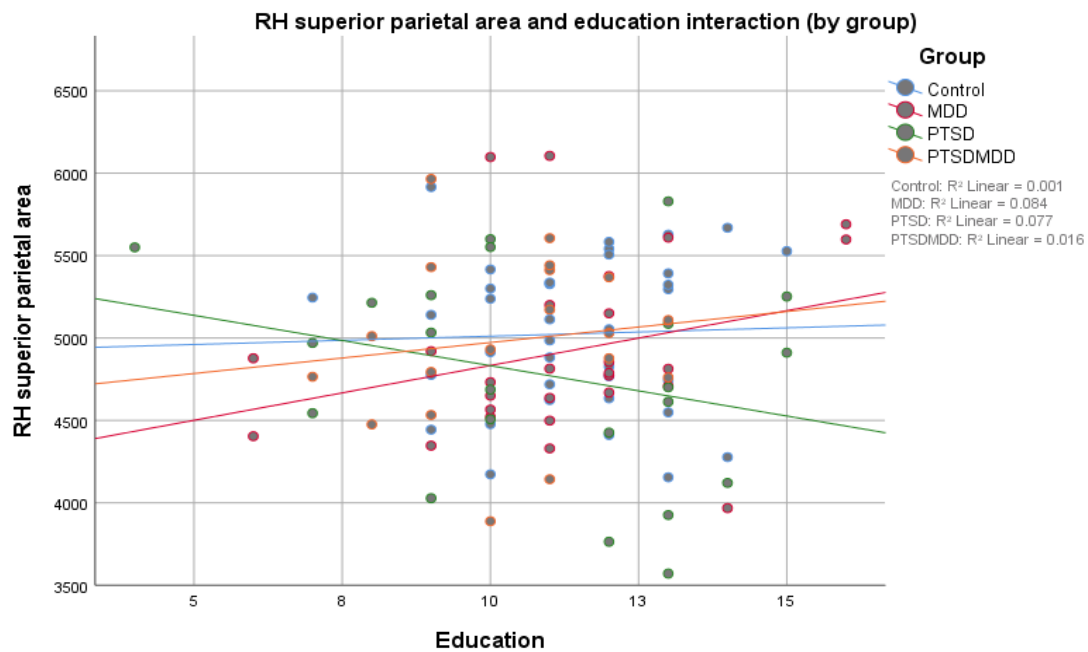


Figure 19. Scatterplot of superior parietal surface area and education interaction

**Insula.** Education produced a significant interaction term ( $p = .02$ ) and remained in the final model. The MDD group exhibited a significant positive correlation between insula surface area and education ( $r = .372$ ,  $p = .028$ ). The PTSD group exhibited a trend towards significance ( $r = -.352$ ,  $p = .054$ ). Group explained a large proportion of insula surface area variability (partial  $\eta^2 = .116$ ). Figure 20 highlights the relationship between education and insula surface area.

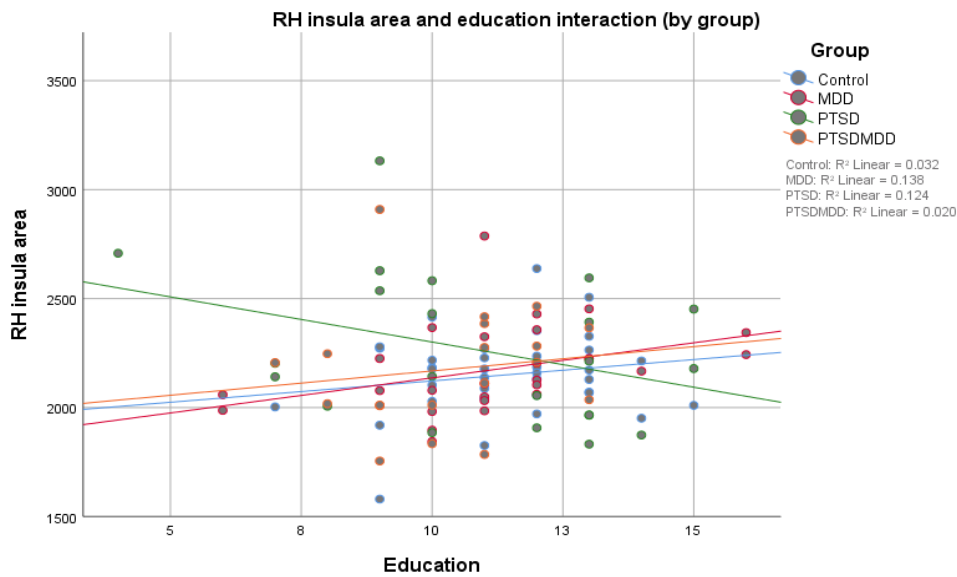


Figure 20. Scatterplot of insula surface area and education interaction

### Right hemisphere volume

**Caudal ACC.** Age did not produce a significant interaction term and was removed from the final model, while a significant interaction term was produced by education ( $p = .08$ ). The PTSD group exhibited a trend towards significance ( $r = -.352, p = .054$ ). Group explained a moderate proportion of caudal ACC volume variability (partial  $\eta^2 = .065$ ). Figure 21 illustrates the relationship between caudal ACC volume and education.

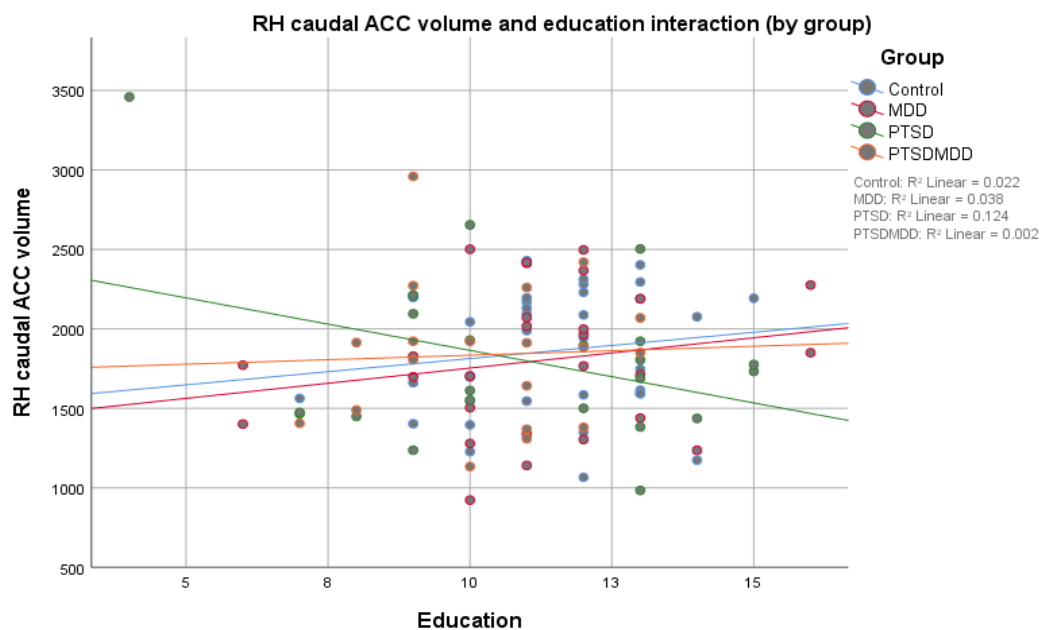


Figure 21. Scatterplot of caudal ACC volume and education interaction

**Caudal Middle Frontal.** Neither age nor education produced significant interaction terms and were therefore removed from the final model. The final model indicated MDD exhibited reduced caudal middle frontal volume, relative to controls ( $F(3, 98) = 2.69, p = .051$ ). Partial  $\eta^2 = .076$ , indicating that group explained a moderate portion of caudal middle frontal volume variance.

**Inferior Parietal.** Education produced a significant interaction term ( $p = .02$ ) and remained in the final model, while age did not. Controls exhibited a significant positive correlation between inferior parietal volume and education ( $r = .295, p = .04$ ), while the MDD group exhibited a trend towards significance ( $r = .316, p = .054$ ). Group explained a moderate proportion of the variability of inferior parietal volume (partial  $\eta^2 = .104$ ). Figure 22 illustrates the relationship between inferior parietal volume and education.

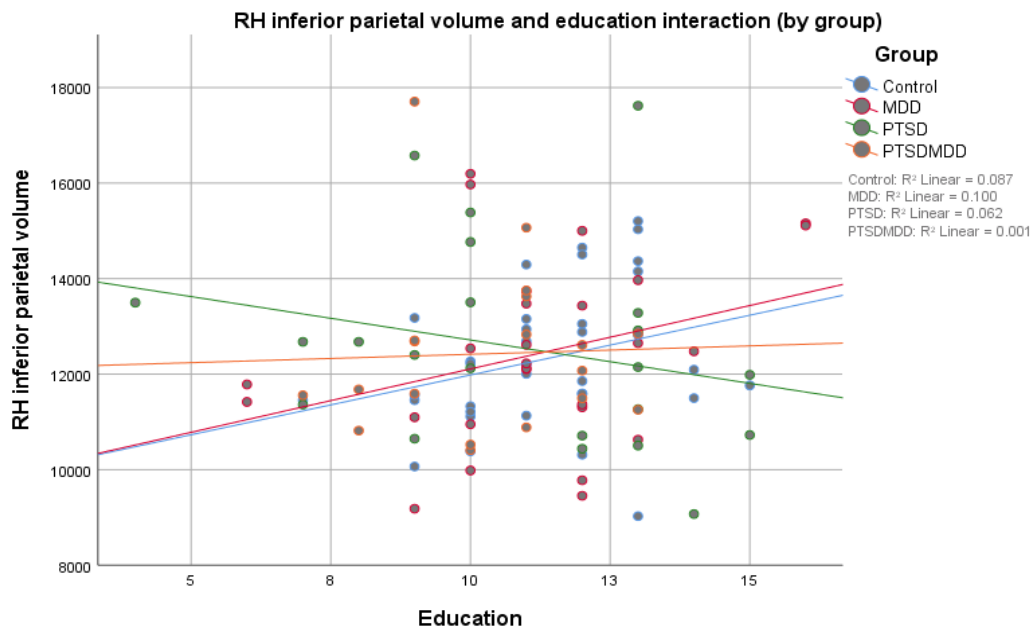


Figure 22. Scatterplot of inferior parietal volume and education interaction

**Posterior Cingulate.** A significant interaction term was found for education ( $p = .002$ ) but not for age. Controls exhibited a significant positive correlation between posterior cingulate volume and education ( $r = .357, p = .016$ ), while the PTSD group exhibited a significant negative correlation ( $r = -.438, p = .021$ ). Group explained a large proportion of posterior cingulate volume variability (partial  $\eta^2 = .13$ ). Figure 23 illustrates the relationship between posterior cingulate volume and education.

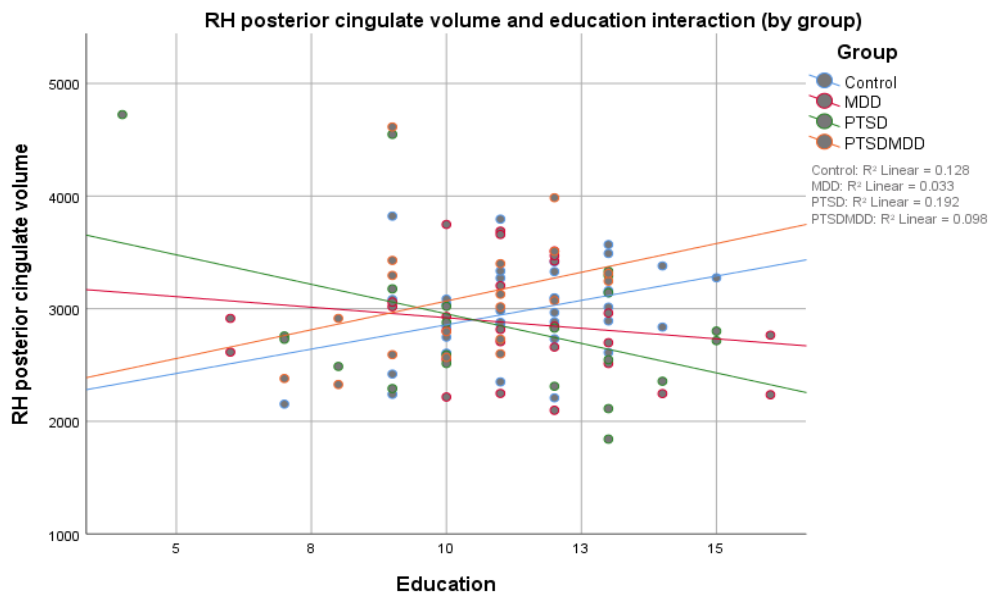


Figure 23. Scatterplot of posterior cingulate volume and education interaction

**Precuneus.** Education produced a significant interaction term ( $p = .03$ ) and remained in the final model. None of the four groups exhibited a significant correlation between precuneus volume and education, however, the MDD group exhibited a trend towards significance ( $r = .313$ ,  $p = .056$ ). Group explained a moderate proportion of precuneus volume variability (partial  $\eta^2 = .09$ ). Figure 24 illustrates the relationship between precuneus volume and education level.

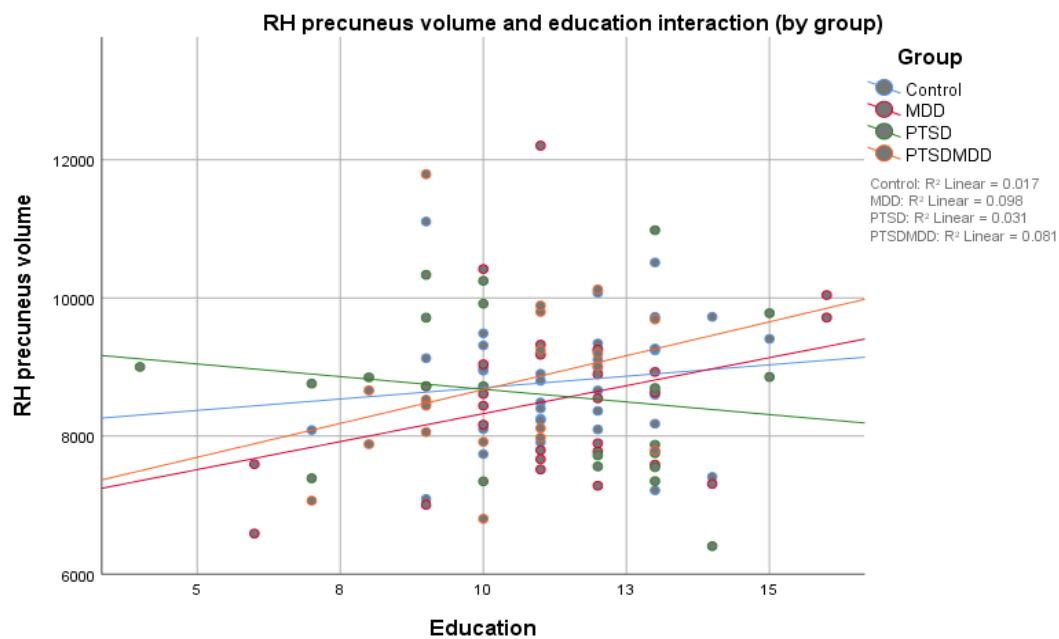


Figure 24. Scatterplot of precuneus volume and education interaction

**Rostral ACC.** Neither age nor education produced significant interaction terms, so these terms were removed from the final model. The final model indicated that there was no significant group effect ( $F(3, 98) = 1.46, p = .23$ ), and group explained a small to moderate proportion of rostral ACC volume variance (partial  $\eta^2 = .043$ ).

**Rostral Middle Frontal.** Education produced a significant interaction term and remained in the final model. Controls exhibited a significant positive correlation between rostral middle frontal volume and education ( $r = .458, p = .003$ ), whereas the clinical groups did not. Group explained a moderate proportion of rostral middle frontal volume variability (partial  $\eta^2 = .073$ ). Figure 25 illustrates the relationship between rostral middle frontal volume and education level.

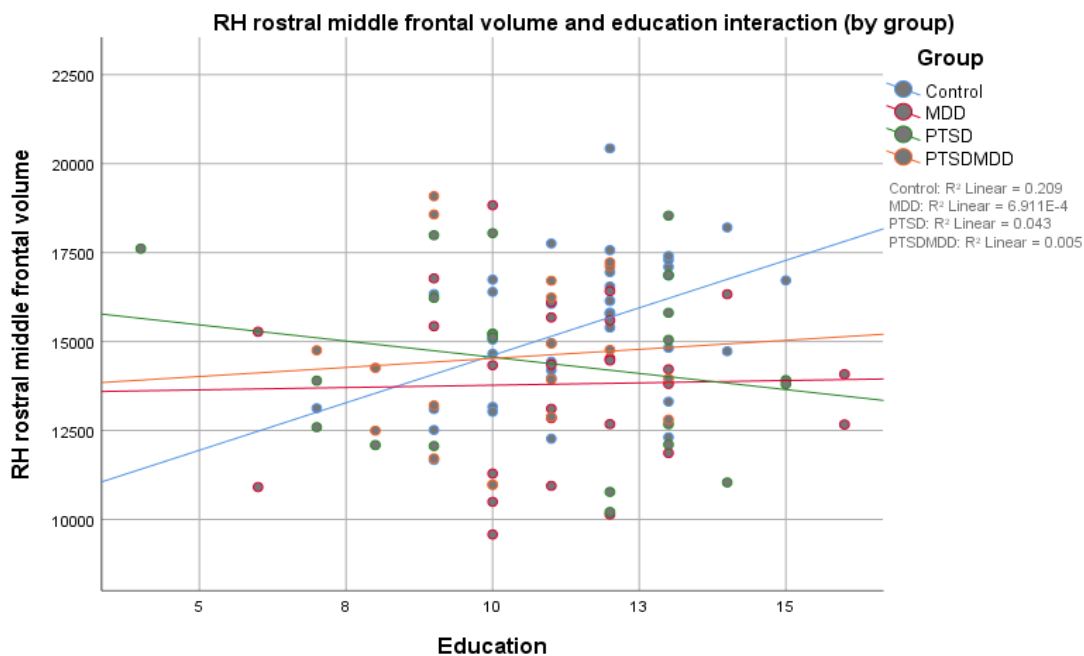


Figure 25. Scatterplot of rostral middle frontal volume and education interaction

**Superior Frontal.** Age and education did not produce significant interaction terms and these terms were removed from the final model. The final model indicated the MDD group exhibited reduced volume of the superior frontal cortex, relative to controls, while the PTSD groups did not exhibit significant reductions relative to controls ( $F(3, 98) = 2.71, p = .049$ ). Group explained a moderate proportion of superior frontal volume variance (partial  $\eta^2 = .077$ ).

**Superior Parietal.** Neither age nor education produced significant interaction terms and the terms were removed from the final model. The final model did not find a significant group



effect,  $F(3, 98) = .73, p = .54$ . A small proportion of superior parietal variance was explained by group (partial  $\eta^2 = .022$ ).

**Insula.** Age and education did not produce significant interaction terms and these terms were removed from the final model. The final model did not display a group effect,  $F(3, 98) = 2.19, p = .09$ . Group explained a moderate proportion of insula volume variance (partial  $\eta^2 = .063$ ).

### **Right hemisphere cortical thickness**

Age and education did not produce significant interaction terms for any of the below models. Therefore, these interaction terms were removed from the final model.

**Caudal ACC.** There was no significant group effect in the final model ( $F(3, 98) = .58, p = .63$ ). Partial  $\eta^2 = .017$ , indicating a small portion of caudal ACC variance being explained by group.

**Caudal Middle Frontal.** No group effect was observed in the final model ( $F(3, 98) = .64, p = .59$ ). A small proportion caudal middle frontal variance was explained by group (partial  $\eta^2 = .019$ ).

**Inferior Parietal.** The final model indicated no group effect ( $F(3, 98) = 1.29, p = .28$ ). Group explained a small to moderate proportion of inferior parietal variance (partial  $\eta^2 = .038$ ).

**Posterior Cingulate.** No significant group effect was detected in the final model,  $F(3, 98) = .65, p = .59$ . Partial  $\eta^2 = .019$ , indicating that group accounted for a small proportion of posterior cingulate variance.

**Precuneus.** The final model did not exhibit a group effect ( $F(3, 98) = .28, p = .84$ ) and a small proportion of the variance was explained by group (partial  $\eta^2 = .009$ ).

**Rostral ACC.** The final model observed a trend towards a group effect ( $F(3, 98) = 2.6, p = .056$ ). Group explained a moderate proportion of rostral ACC thickness variance (partial  $\eta^2 = .074$ ).

**Rostral Middle Frontal.** No significant group effects were found in the final model,  $F(3, 98) = 1.5, p = .21$ , and group accounted for a small to moderate proportion of rostral middle frontal thickness variance (partial  $\eta^2 = .045$ ).

**Superior Frontal.** The final model provided no evidence of a group effect ( $F(3, 98) = .91, p = .44$ ). Group explained a small proportion of superior frontal variance (partial  $\eta^2 = .027$ ).

**Superior Parietal.** No group effect was detected in the final model,  $F(3, 98) = .94, p = .42$ . A small proportion of the variance was explained by group (partial  $\eta^2 = .028$ ).

**Insula.** The final model did not find a significant group effect,  $F(3, 98) = .99, p = .4$ . Partial  $\eta^2 = .029$ , indicating a small portion of variance was explained by group.

## Secondary analyses

### PTSD symptom severity correlations

**Left hemisphere surface area.** Two-tailed Pearson correlations indicated that CAPS total score was not significantly correlated with left hemisphere area. This suggests that PTSD symptom severity for the PTSD and comorbid group does not affect left hemisphere surface area.

**Left hemisphere volume.** Correlations indicated that CAPS total score was not significantly correlated with left hemisphere volume. There was a subthreshold finding supporting a weak negative association between PTSD symptom severity and volume of the left superior frontal cortex ( $r = -.275, p = .08$ ) for the PTSD and comorbid groups.

**Left hemisphere thickness.** Two regions indicated significant negative correlations between CAPS total score and left hemisphere cortical thickness: inferior parietal ( $r = -.512, p = .001$ ) and precuneus ( $r = -.415, p = .007$ ). There was a subthreshold effect for the superior parietal ( $r = -.28, p = .076$ ). These moderately negative correlations indicate that greater PTSD severity (in the PTSD and comorbid group combined) is associated with reduced cortical thickness of the above regions.

**Right hemisphere surface area.** Two-tailed Pearson correlations indicated no significant correlations between CAPS total score and right hemisphere surface area, indicating PTSD symptom severity does not affect right hemisphere surface area for the PTSD and comorbid group combined.

**Right hemisphere volume.** The results indicated no significant correlations between CAPS total score and right hemisphere volume, indicating that RH volume is not affected by PTSD symptom severity in both PTSD and PTSD with comorbid MDD.

**Right hemisphere thickness.** Three regions indicated significant negative correlations between CAPS total score and right hemisphere cortical thickness: inferior parietal ( $r = -.46, p = .002$ ), the posterior cingulate ( $r = -.309, p = .002$ ), and the precuneus ( $r = -.363, p = .02$ ). A subthreshold effect was observed for the superior frontal cortex ( $r = -.295, p = .061$ ). These significant negative correlations indicated that PTSD symptom severity is associated with reduced cortical thickness of the inferior parietal cortex, posterior cingulate cortex, and the precuneus in the combined PTSD and comorbid group.

Table 2

*Left hemisphere surface area means and standard deviations*

Region	Control	MDD	PTSD	PTSD+MDD	<i>p</i> value	Group
	<i>n</i> = 36	<i>n</i> = 27	<i>n</i> = 22	<i>n</i> = 19		Contrast
Caudal ACC	558.9 (136.2)	509.2 (136.6)	582.3 (133.7)	548.4 (116.6)	0.27	NA
Caudal Middle Frontal	2303.6 (451.8)	2053.9 (313.9)	2061.6 (319.8)	2226.9 (407.3)	0.044	Control > MDD
Inferior Parietal	4221.8 (412.4)	4244.8 (590.3)	4124.8 (744.5)	4224.9 (565.9)	0.92	NA
Posterior Cingulate	1063.5 (148.5)	1028.3 (169.6)	1062.3 (176.9)	1053.1 (133)	.004*	NA
Precuneus	3529.4 (398.9)	3441.7 (473.4)	3417.6 (519.9)	3568.7 (405.9)	.067*	NA
Rostral ACC	623.5 (114.7)	648.3 (150.1)	701.9 (192.3)	721.3 (187.9)	0.16	NA
Rostral Middle Frontal	5529 (846.6)	4972.9 (595.4)	5276.7 (956.7)	5389.1 (810)	.003*	NA
Superior Frontal	7082.7 (965.8)	6567.8 (902.8)	6807.7 (975.4)	6889 (928.2)	.03*	NA
Superior Parietal	5211.5 (620.1)	5124.9 (566.7)	4942.8 (819.6)	5002.9 (533.5)	.008*	NA
Insula	2305.3 (224.6)	2190.4 (254.2)	2299.9 (276.3)	2340.2 (276.9)	.004*	NA

\* model with significant interaction terms

Table 3

*Left hemisphere cortical volume means and standard deviations*

Region	Control <i>n</i> = 36	MDD <i>n</i> = 27	PTSD <i>n</i> = 22	PTSD+MDD <i>n</i> = 19	<i>p</i> value
Caudal ACC	1655.6 (496.4)	1424.4 (459.3)	1730.5 (464.3)	1599.4 (441.4)	0.12
Caudal Middle Frontal	5946.4 (1097.6)	5435.9 (919.4)	5594.6 (865)	5826.7 (1158.2)	0.28
Inferior Parietal	10375.4 (1024.8)	10455.9 (1592.7)	10677.2 (2111.8)	10607.7 (1530.8)	0.62
Posterior Cingulate	2795 (376.6)	2680.1 (433.5)	2767.9 (447)	2723.3 (423.5)	.004*
Precuneus	8451 (971.2)	8227.2 (1044.8)	8235.2 (1257.7)	8341.3 (1143.2)	0.91
Rostral ACC	2110.9 (425.2)	2119.9 (471.6)	2250.4 (581.1)	2282.6 (517.3)	0.51
Rostral Middle Frontal	15011.6 (2278.1)	13171.9 (1985.6)	14440.9 (2553.2)	14304.1 (2384)	.011*
Superior Frontal	21434.3 (2828.7)	19808 (3007.8)	21126.2 (2833.6)	20425.5 (2602.1)	0.12
Superior Parietal	11454.1 (1290.6)	11199.8 (1270.4)	10994.4 (2061.6)	11214.1 (1981.9)	.073*
Insula	6483.3 (566.9)	6391.1 (706.1)	6699.4 (839.8)	6697.1 (619.1)	.011*

\* model with significant interaction terms

Table 4

*Left hemisphere cortical thickness means and standard deviations*

Region	Control <i>n</i> = 36	MDD <i>n</i> = 27	PTSD <i>n</i> = 22	PTSD+MDD <i>n</i> = 19	<i>p</i> value
Caudal ACC	2.76 (0.26)	2.68 (0.19)	2.77 (0.26)	2.75 (0.35)	0.58
Caudal Middle Frontal	2.51 (0.18)	2.52 (0.17)	2.58 (0.19)	2.5 (0.14)	0.43
Inferior Parietal	2.35 (0.17)	2.3 (0.11)	2.38 (0.14)	2.33 (0.15)	0.14
Posterior Cingulate	2.46 (0.13)	2.48 (0.18)	2.44 (0.19)	2.44 (0.11)	0.82
Precuneus	2.32 (0.15)	2.29 (0.13)	2.3 (0.16)	2.24 (0.12)	0.55
Rostral ACC	2.89 (0.23)	2.95 (0.27)	2.86 (0.29)	2.8 (0.26)	0.41
Rostral Middle Frontal	2.46 (0.16)	2.41 (0.15)	2.46 (0.15)	2.41 (0.13)	0.31
Superior Frontal	2.76 (0.19)	2.74 (0.14)	2.79 (0.17)	2.69 (0.15)	0.26
Superior Parietal	2.12 (0.14)	2.01 (0.11)	2.1 (0.15)	2.1 (0.16)	0.62
Insula	2.89 (0.19)	2.93 (0.21)	2.91 (0.14)	2.86 (0.19)	0.67

Table 5

*Right hemisphere surface area means and standard deviations*

Region	Control <i>n</i> = 36	MDD <i>n</i> = 27	PTSD <i>n</i> = 22	PTSD+MDD <i>n</i> = 19	<i>p</i> value
Caudal ACC	617.5 (114)	635.2 (142.6)	634.6 (169.9)	647.3 (127.5)	.017*
Caudal Middle Frontal	2204.6 (515.7)	1928.1 (334.5)	2100.7 (409.1)	2103.3 (388.8)	0.11
Inferior Parietal	4893.1 (587.3)	4924.1 (770)	4775.5 (758.4)	4846.5 (644.3)	.008*
Posterior Cingulate	1078.9 (143.4)	1071 (164.6)	1067.3 (229.1)	1154.7 (172.1)	.005*
Precuneus	3536.9 (329.6)	3503.8 (479.6)	3480.3 (507.6)	3637.2 (418.8)	.001*
Rostral ACC	450.1 (99.3)	490.5 (109.2)	533.8 (133.3)	505.2 (103.3)	.009*
Rostral Middle Frontal	5846 (832.9)	5424 (1007.2)	5436.9 (914.7)	5648 (1048.2)	0.104
Superior Frontal	7092 (1199.5)	6400 (791.2)	6525.1 (715.1)	6548.3 (994.5)	.03*
Superior Parietal	5025.3 (460.8)	4914.7 (531)	4779.3 (630)	4984.8 (508.8)	.124*
Insula	2149.7 (188.6)	2175.7 (199.9)	2264.8 (337.3)	2175.3 (275.4)	.008*

\* model with significant interaction terms

Table 6

*Right hemisphere cortical volume means and standard deviations*

Region	Control <i>n</i> = 36	MDD <i>n</i> = 27	PTSD <i>n</i> = 22	PTSD+MDD <i>n</i> = 19	<i>p</i> value	Group Contrast
Caudal ACC	1859.5 (382.8)	1800.3 (450.8)	1807.5 (539.1)	1837.9 (446.9)	.092*	NA
Caudal Middle Frontal	5780.1 (1268.6)	4991.1 (882.5)	5593.8 (1070.8)	5558.9 (1099.4)	0.051	Control > MDD
Inferior Parietal	12330.7 (1453.4)	12434.6 (1940.9)	12558.7 (2095.3)	12427.3 (1757.3)	.015*	NA
Posterior Cingulate	2977.8 (414.5)	2874 (478.1)	2863.6 (686.4)	3100.6 (564.1)	.004*	NA
Precuneus	8793.4 (867.1)	8522.7 (1197.4)	8614.2 (1189.9)	8735.3 (1191.8)	.029*	NA
Rostral ACC	1557.1 (360.9)	1591.3 (388.6)	1781.7 (467.9)	1653.6 (424.2)	0.229	NA
Rostral Middle Frontal	15355.8 (1996.2)	13805 (2309.6)	14402.3 (2511.2)	14559.3 (2409.4)	.064*	NA
Superior Frontal	20714.5 (3248.9)	18731 (2253.5)	19803.7 (2294.4)	19086.9 (2863.5)	0.049	Control > MDD
Superior Parietal	11097.7 (1281.3)	10575.2 (1358.4)	10581.8 (1837.8)	11007.5 (1783.5)	0.54	NA
Insula	6210.8 (599.5)	6420.7 (627.3)	6648.9 (914.6)	6286.6 (826.4)	0.095	NA

\* model with significant interaction terms

Table 7

*Right hemisphere cortical thickness means and standard deviations*

	Control	MDD	PTSD	PTSD+MDD		Group
Region	<i>n</i> = 36	<i>n</i> = 27	<i>n</i> = 22	<i>n</i> = 19	<i>p</i> value	Contrast
Caudal ACC	2.65 (0.24)	2.58 (0.26)	2.57 (0.26)	2.59 (0.25)	0.63	NA
Caudal Middle Frontal	2.49 (0.19)	2.43 (0.19)	2.49 (0.18)	2.46 (0.13)	0.59	NA
Inferior Parietal	2.36 (0.18)	2.33 (0.09)	2.39 (0.12)	2.34 (0.16)	0.28	NA
Posterior Cingulate	2.48 (0.17)	2.47 (0.14)	2.46 (0.16)	2.41 (0.13)	0.58	NA
Precuneus	2.33 (0.11)	2.32 (0.11)	2.32 (0.13)	2.29 (0.11)	0.84	NA
Rostral ACC	2.97 (0.25)	2.81 (0.26)	2.81 (0.24)	2.83 (0.29)	0.056	Control > MDD
Rostral Middle Frontal	2.41 (0.17)	2.31 (0.16)	2.38 (0.19)	2.34 (0.16)	0.21	NA
Superior Frontal	2.71 (0.19)	2.66 (0.17)	2.72 (0.2)	2.65 (0.16)	0.44	NA
Superior Parietal	2.11 (0.13)	2.05 (0.11)	2.1 (0.15)	2.1 (0.15)	0.42	NA
Insula	2.92 (0.15)	2.94 (0.19)	2.91 (0.11)	2.87 (0.14)	0.4	NA



## Discussion

The present study set out to determine whether cortical structures differed between the PTSD group, MDD group, PTSD with comorbid MDD group, and healthy controls in a sample of mothers from a LMI region of the Western Cape. Cortical thickness, volume, and surface area of regions associated with neurocognitive domains and resting-state networks explored in Chapters 2 and 3, respectively, were measured and compared between groups.

The first hypothesis was that *anterior cingulate and superior frontal cortical thickness, volume, and surface area reductions will be evident in patients with MDD and PTSD, relative to controls.*

Given the literature regarding structural abnormalities of the ACC in MDD and PTSD, it was hypothesised that this region would show reductions in both mono-diagnostic groups. The present study measured the surface area, volume, and cortical thickness of the caudal and rostral ACC and found no significant group differences in either of these regions. There was a trend towards significance for the rostral ACC right hemisphere thickness metric, where the MDD group exhibited reduced cortical thickness, relative to controls. The MDD group exhibited volume reductions of the superior frontal cortex, particularly in the right hemisphere, relative to controls. Additionally, a subthreshold negative correlation was observed for CAPS total score and right hemisphere thickness for the superior frontal cortex. This suggests that the observed volume and thickness reductions are not restricted to MDD only. Trauma severity and MDD appear to be associated with reduced superior frontal cortical thickness and volume, which indicates an overlap or similarity of structural abnormalities in PTSD and MDD. The above findings support the hypothesis and are further supported by the literature (Koolschijn et al., 2009; Kroes et al., 2011; Lorenzetti et al., 2009; Schmaal et al., 2017).

The second hypothesis was that *the MDD group will display surface area, volume, and thickness reductions of the precuneus and the posterior cingulate (regions associated with the default mode network), relative to controls.*

In chapter 3, the MDD group exhibited hyperconnectivity within the DMN. The present study assessed whether MDD was associated with structural abnormalities of regions associated with the DMN, namely the ACC, precuneus, and posterior cingulate. Although MDD was not associated with significant structural abnormalities of the ACC, precuneus, or posterior

cingulate, there is evidence that surface area of the left precuneus was reduced in MDD with lower education levels.

The third hypothesis was that, *where differences are observed, the comorbid group will exhibit greater reductions of cortical surface area, thickness, and volume.*

The present study observed group differences for regions such as the left hemisphere caudal middle frontal (surface area), right hemisphere superior frontal (volume), and a trend towards group differences for right hemisphere caudal middle frontal (volume) and right hemisphere rostral ACC (cortical thickness). For these regions, the MDD group consistently exhibited the smallest indices, relative to the controls, who exhibited the largest (see Tables 2 to 7). The comorbid group did not exhibit significant reductions for these significant regions, and therefore did not exhibit an accumulative effect regarding structural abnormalities in the present sample.

The present sample exhibited a distinct profile of structural abnormalities. Particularly, MDD was associated with left hemisphere caudal middle frontal cortex surface area reductions, as well as right hemisphere superior frontal cortex volume reductions. The MDD group was further associated with subthreshold volume reductions of the caudal middle frontal (right hemisphere) and right hemisphere rostral ACC thinning. These findings support the hypotheses for the present study and are further supported by a meta-analysis of 64 structural studies (Koolschijn et al., 2009), which reported large volume reductions of frontal regions in MDD samples. Frontal regions, such as the caudal middle frontal gyrus, have been reported to be involved in higher-order functions of neurocognitive control, such as reward-based association learning (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Reductions in these regions would suggest impairment of neurocognitive control.

During analyses it became apparent that covariates such as age and education significantly interacted with structural indices. Upon closer inspection, it was found that where interactions occurred, education produced significant interaction terms ( $n = 23$ ) more consistently than age ( $n = 2$ ). This is contrary to evidence suggesting that age affects cortical volume and thickness, leading to reductions of the cortex (Jernigan et al., 2001; Salat et al., 2004). This lack of evidence for an age effect may be due to the restricted variability in age of the participants, as well as relatively young average age of the groups. The PTSD group exhibited negative associations between years of formal education and structural metrics for a number of the regions assessed. Visual inspection of scatterplots revealed that PTSD was

associated with greater surface area and volume at lower levels of education, relative to controls, MDD, and the comorbid group, who exhibited the opposite trend. Further, reduced surface area and volume was evident at higher levels of education in the PTSD group. This was in stark contrast to the remaining three groups who exhibited greater surface area and volume at higher education levels. The remaining groups (MDD and comorbid group), including controls, displayed interactions in the expected direction (greater levels of education associated with greater surface area and volume), which suggests that higher education has a protective effect on controls and MDD participants. As low levels of education are a risk factor for developing PTSD, participants with higher levels of education who still develop PTSD may have 'worse' PTSD, leading to greater surface area and volume differences. There may be other vulnerabilities not explored in this study that may be underlying these reductions. These education effects were not observed in the MDD group or the comorbid group. This may suggest that MDD symptoms may be ameliorating the effects of PTSD on cortical structure, however, there is no available literature to support this.

Furthermore, the present study did not find any significant group differences related to cortical thickness for any region. This finding contradicts numerous publications suggesting that PTSD and MDD, respectively, present with cortical thinning of particular regions (Karl et al., 2006; Koolschijn et al., 2009; Schmaal et al., 2017). Interestingly, when running the analyses on both left and right hemisphere cortical thickness values, it became evident that covariates such as age and education did not produce interaction terms for any of the region models, suggesting that age and education did not have an effect on cortical thickness in the present sample.

However, during secondary analyses, when examining the effect of PTSD symptom severity on structural metrics, a trend emerged where CAPS total score was negatively correlated with cortical thickness for some frontal regions. In the combined group of PTSD and PTSD with comorbid MDD, greater PTSD symptom severity was associated with cortical thickness reductions in the bilateral inferior parietal cortex, the bilateral precuneus, as well as the right posterior cingulate. Interestingly, these regions are commonly reduced in MDD literature (Järnum et al., 2011; Schmaal et al., 2017; Wagner et al., 2012).

The findings for the present study are consistent with, and support, the findings from Chapter 3. The abovementioned regions coincide with networks explored in Chapter 3, mainly the default mode network (DMN). Moreover, the correlations between CAPS score and structural metrics observed in the present chapter is similar to the CAPS finding in Chapter 3. In the present study, CAPS score was associated with significant negative

correlations for regions belonging to the DMN (posterior cingulate, precuneus, etc). Chapter 3 illustrated that greater CAPS score was associated with greater connectivity between the precuneus and posterior cingulate.

The present study reported a specific profile of structural abnormalities in MDD, and findings of PTSD symptom severity for both PTSD groups combined are evident. However, there is no evidence from the present study to suggest that PTSD with comorbid MDD exhibits greater structural abnormalities, relative to controls and the mono-diagnostic groups, as hypothesised. In fact, apart from the subthreshold effects seen for age and LH superior parietal area and volume, the present study did not find any comorbid-specific findings. This suggests that PTSD with comorbid MDD does not present with additive or synergistic effects.

### **Limitations**

Like others, this study was not without its limitations. Chapter 3 limitations apply to this study as the sample and methods are the same.

### **Conclusions**

Despite the limitations of this study, the findings suggest that the clinical groups exhibited a specific profile of structural abnormalities, relative to healthy controls. Additionally, it was found that education level significantly interacted with structural indices, with the PTSD group exhibiting a relative distinct negative association between level of education and cortical surface area and volume. Furthermore, the present study provides no evidence suggesting that PTSD with comorbid MDD is associated with greater reductions of surface area, volume, and cortical thickness, relative to controls or the mono-diagnostic groups. These findings of structural abnormalities could be utilised as biomarkers for these conditions and could aid in differentiating between the disorders.

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**Chapter 5**  
**Discussion and conclusions**

## **Introduction**

Posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) have consistently been reported to be associated with specific neurocognitive impairments, particularly in attention and executive dysfunction, as well as with intrinsic functional connectivity and structural abnormalities (Kaiser et al., 2015; Karl et al., 2006; Lee et al., 2012; Scott et al., 2015). However, little is known about the neurocognitive, functional connectivity, and structural imaging of patients with both PTSD and MDD, and this gap is important to fill for a number of reasons, including the high prevalence and impairment associated with this comorbidity.

The present dissertation therefore set out to compare participants with PTSD, MDD, primary PTSD with comorbid MDD, and healthy controls, on neurocognitive performance, resting-state functional connectivity, as well as the cortical volume, thickness and surface area of the brain. Recruitment of such a broad range of contrasting participants was possible because of access to the Drakenstein Child Health Study, a birth cohort study conducted on mother-infant dyads (Zar et al., 2014), in a region where there is a substantial amount of exposure to trauma (Abler et al., 2014), and so high rates of conditions such as PTSD and MDD (Lund et al., 2010).

Chapter 1 reviewed the literature on neurocognitive, resting-state intrinsic functional connectivity, and structural MRI in PTSD, MDD, and PTSD with MDD. The review illustrated that PTSD was associated with executive dysfunction, particularly for set-switching, working memory, and inhibition. Domains such as attention, processing speed, and verbal memory are also impaired in PTSD. MDD was associated with moderate deficits of executive function (particularly working memory and inhibition), attention, processing speed, and memory. The review further highlights that the neurocognitive associations of these disorders are heterogeneous, and it highlighted the paucity of research conducted on patients with both PTSD and MDD.

With regard to the functional and structural imaging literature, no studies were found at the time of this dissertation that included a group with PTSD and comorbid MDD. Chapter 1 highlighted that few studies explore PTSD with comorbid MDD, and even fewer studies utilise a four-group study design with healthy controls. Therefore, it is not possible to accurately determine from the literature whether PTSD with comorbid MDD reflects an additive effect of both diagnoses, a different profile compared to mono-diagnostic groups, or whether comorbidity has a synergistic effect, whereby abnormalities are ‘greater than the sum



of their parts', or an additive effect, whereby the overall effect (of PTSD with comorbid MDD) is the same as the sum of the individual disorders' effects (PTSD and MDD).

PTSD and MDD have been shown to be highly prevalent across clinical and community populations, and these two disorders are highly comorbid (Atwoli et al., 2013; Kessler et al., 2005; Kessler et al., 1995). PTSD with comorbid MDD is known to be associated with treatment resistance (Campbell et al., 2007; Flory & Yehuda, 2015). Due to the prevalence of these disorders, the inconsistencies in the literature, as well as the general lack of research conducted on patients with PTSD with comorbid MDD, studying the neurocognitive, resting-state functional connectivity, and structural abnormalities of these disorders could further shed light on each of the disorders.

### **Neurocognitive findings**

It was hypothesised that the PTSD and MDD groups would exhibit attention and executive function deficits. Although there was no overt evidence suggesting executive dysfunction or attentional impairments in this sample, a significant association was found between the working memory measure (List Sorting Working Memory) and level of education for the mono-diagnostic groups. Furthermore, PTSD symptom severity (PTSD and comorbid group combined) was associated with set-switching test scores (Dimensional Change Card Sort (DCCS)) after correcting for the influence of education and age differences, and a subthreshold statistical association was seen between higher trauma severity score from the CAPS and the executive function composite score. These findings provide preliminary evidence that greater PTSD symptom severity is associated with greater executive dysfunction, particularly for set-shifting for the combined PTSD and comorbid groups.

The PTSD group exhibited more intrusive recollections when performing the WRAML II delayed recall task, relative to all other groups. Impairments of this nature were expected given the re-experiencing/intrusions symptom clusters for PTSD diagnosis (American Psychiatric Association, 2000, 2013). This finding suggests that the intrusive recollections experienced by PTSD patients are not restricted to trauma related thoughts but may extend to thoughts involved in day-to-day functioning. Furthermore, this finding suggests inhibitory deficits may characterise patients with PTSD, and may underlie intrusive responses (Carrion & Wong, 2012). The finding that only the PTSD group exhibits these deficits, while the comorbid group and MDD group does not, implies that different aspects of brain function are being affected in patients with both PTSD and MDD.

The neurocognitive literature for MDD suggests that MDD is associated with reduced executive function, as well as impaired attention and learning (Lee et al., 2012; Rock et al., 2014). The present dissertation failed to find significant MDD differences for domains such as executive function and attention. However, the MDD group did exhibit significant delayed recall impairments, as measured by the WRAML II.

The results reported in Chapter 2 suggest that PTSD with comorbid MDD is associated with impairment in specific neurocognitive domains, rather than general impairment across all neurocognitive domains. The neurocognitive profile in this group also differs from that exhibited by the mono-diagnostic groups. Contrary to hypotheses, the comorbid group did not exhibit neurocognitive deficits or impairments on measures of executive function, attention, or memory and learning. However, the comorbid group was associated with processing speed impairments, relative to controls. The fact that the comorbid group demonstrates a distinct profile from the other groups, and not merely a difference in extent of impairment within the same domains, suggests that comorbid diagnosis of these conditions have a synergistic, and not additive, effect on neurocognitive ability.

The only neurocognitive study of comorbid PTSD and MDD explored attention and executive function in these patients (Scheiner et al., 2014). It was reported that the comorbid group (as well as the MDD group) exhibited similar performance on attention and executive function measures, relative to the controls (Scheiner et al., 2014). The results from Scheiner and colleagues (2014) were replicated by this sample as the comorbid group did not exhibit greater differences on measures of attention or executive function, relative to controls and the mono-diagnostic groups. This is the first time that comparisons of PTSD with comorbid MDD on processing speed have been reported. The finding on differences in processing speed as a function of MDD comorbidity in PTSD is therefore a novel contribution to the scientific and clinical literature in this area.

This dissertation examined the concurrent validity of the NIH Toolbox by utilising a number of standardised paper and pencil tests to determine whether the NIH Toolbox was a suitable battery for the South African sample. This is, to date, the first analysis examining concurrent validity of NIH Toolbox in a South African setting. The findings indicated that utilising the NIH Toolbox was a feasible choice in the present research setting. However, there are caveats. Concurrent validity was only determined for the performance-based measures of the NIH Toolbox, as the language-based measures were not utilised and assessed in this dissertation (due to the NIH Toolbox not being translated into the participants' home languages). Additionally, participants in low income regions with little or no computer

experience may feel uncertain or anxious during the assessment when presented with a tablet or computer set up. In some cases, additional computer tutelage prior to assessment commencement may be required in some research settings. Additionally, the NIH Toolbox is no longer a cost-free neurocognitive battery, which may influence researchers' choice in future, particularly in resource-constrained settings.

### **Resting-state functional connectivity findings**

Resting-state analyses indicated that MDD was associated with greater functional connectivity within the DMN, and less functional connectivity within the frontoparietal networks, as predicted, based on the literature (Kaiser et al., 2015). The DMN has been implicated in functions such as self-referential thought, memory, ruminative thought, and recollection of prior experiences (Raichle, 2015). Not only is the finding of greater connectivity within the DMN network for the MDD group consistent with the ruminative symptoms experienced by MDD sufferers (Spasojević & Alloy, 2001), it may also underlie the delayed recall impairments observed in this group, given the DMN's role in memory and recollection.

Participants with PTSD and comorbid MDD exhibited greater connectivity within the right frontoparietal network, relative to controls and the mono-diagnostic groups. Regions exhibiting greater connectivity within the R FPAR include: dlPFC, middle frontal and middle temporal, as well as inferior parietal. These particular regions have been demonstrated to be involved in the manipulation of information in working memory (Elliott, 2003; Mazoyer et al., 2001). This could explain deficits observed in the comorbid group on performance on the Pattern Comparison processing speed test, as the Pattern Comparison Processing Speed test requires information to be manipulated in working memory.

During secondary analyses, when examining the associations of PTSD symptom severity (based on the PTSD and comorbid groups combined) on network connectivity, it was illustrated that greater symptom severity was associated with greater connectivity within the DMN and L FPAR for the comorbid group. Peterson et al. (2014) report similar findings related to PTSD symptom severity and DMN connectivity, with their sample exhibiting greater DMN connectivity in relation to PTSD symptom severity. The comorbid group exhibited greater functional connectivity of the precuneus, within both of these networks, relative to the PTSD group. Research suggests that the precuneus plays a role in higher order neurocognitive functions and self-processing tasks (tasks that require thinking about one's self) (Cavanna & Trimble, 2006). These functions are comparable to self-referential thought,

commonly exhibited by MDD patients. In contradiction to the conclusion reached on the basis of group comparisons on the neurocognitive test battery, this observation appears to support an additive effect, rather than a synergistic effect, of MDD symptoms on the presentation of PTSD.

When examining network connectivity and neurocognitive performance, it was found that greater connectivity within both frontoparietal networks was associated with performance on the processing speed measure (the measure on which the comorbid group exhibited greater impairments). This finding was evident for the PTSD with comorbid MDD group.

Consistent with hypotheses, PTSD with comorbid MDD was associated with abnormal salience network connectivity for task performance. Greater connectivity between the frontoparietal networks and salience network predicted better performance on the Pattern Comparison Processing Speed test and the Dimensional Change Card Sort test. Greater between-network connectivity of the SN and FPAR networks was exhibited by the PTSD with comorbid MDD group for both of the tasks above. The salience network is credited for filtering and monitoring relevant information and stimuli (Menon, 2011; Seeley et al., 2007), and may serve as a switching mechanism between the DMN and task positive networks

### **Structural findings**

When investigating structural abnormalities, MDD was associated with caudal middle frontal surface area reductions and superior frontal volume reductions, relative to controls. Furthermore, PTSD symptom severity (analysed using PTSD and comorbid participants) was negatively correlated with cortical thickness of bilateral inferior parietal and precuneus, as well as the right posterior cingulate. These regions correspond with the DMN, which supports the findings of PTSD symptom severity correlating with greater within-network connectivity of the DMN, reported in Chapter 3. Furthermore, effects were primarily seen for education rather than age in this sample, with greater education being associated with reduced surface area or volume in the PTSD group, contrary to the other groups. In contradiction, where effects of education were observed for comorbid PTSD and MDD, MDD, and control groups, greater education was associated with increased surface area or volume. Lack of education is a recognised risk factor for developing PTSD, with higher levels of education seeming to protect individuals exposed to trauma from developing PTSD (Brewin et al., 2000). One possibility is that the more educated individuals with PTSD may be particularly vulnerable to negative sequelae associated with PTSD, as they developed PTSD despite being at low risk

for developing the condition. The nature of these vulnerabilities would seem to be a fruitful avenue of future research.

The present dissertation reported few structural abnormalities for PTSD with comorbid MDD. Subthreshold effects were observed for age and left hemisphere superior parietal surface area and volume, indicating greater volumetric reductions of this particular region with greater age in participants with PTSD and comorbid MDD. Koenigs, Barbey, Postle, and Grafman (2009) report that damage to the superior parietal cortex is associated with information manipulation impairments, particularly in working memory; however, working memory impairments were not observed.

The present dissertation found evidence suggesting a distinct profile of impairment for patients with PTSD and comorbid MDD in a low-middle income female sample. It was expected that the comorbid patients would exhibit greater deficits or impairments relative to controls and the mono-diagnostic groups, given the limited available literature and symptom severity outcomes. However, this dissertation found that the comorbid group does not present with structural cortical abnormalities, indicating that participants with PTSD and comorbid MDD do not exhibit additive or synergistic reductions of cortical volume, surface area, and/or thickness.

### **General findings**

On demographic variables such as age and education, the comorbid group in this project was comparable to the mono-diagnostic groups and controls. However, on symptom severity scales, such as the CAPS, the comorbid group exhibited greater symptom severity relative to the mono-diagnostic groups. This finding is in line with convergent literature of symptom severity in PTSD with comorbid MDD patients (Gros, Price, Magruder, & Frueh, 2012). This finding suggests that greater symptom severity may confound group differences involving the comorbid group, a possibility that I set out to test in this dissertation.

Chapter 2 and Chapter 4 reported that PTSD individuals with more education tended to perform more poorly on neurocognitive measures (Chapter 2) and exhibit cortical thinning (Chapter 4), relative to controls. The literature repeatedly states that higher levels of education were associated with better cognitive performance, for example (Van Hooren et al., 2007), and no literature, to date, explicitly reports an association between greater education and cortical thinning, for example. The present dissertation's findings, although counterintuitive, may point to a cognitive reserve, where there is a delay before the functional and cognitive expression of an illness is observed (Julkunen et al., 2010). This can be seen in

a sample of Alzheimer's disease patients, where individuals with higher levels of education may display more severe cortical atrophy, relative to those with lower levels of education (Julkunen et al., 2010). This cognitive reserve could be reflected in the PTSD participants of this sample.

Notably, psychiatric classification of PTSD was not associated with large abnormalities in neurocognitive performance and resting-state fMRI connectivity, as evident from Chapters 2 and 3. PTSD-specific results were obtained in secondary analyses, however, when utilising CAPS total score, a measure of PTSD symptom severity. This suggests that utilising symptom severity, rather than a categorical classification, may be a more sensitive method to observe the effects of psychological trauma on executive function and associated brain networks. It also suggests that the heterogeneous nature of the clinical groups may be masking these effects (see Limitations).

### **PTSD and MDD overlap**

In trying to explain the high comorbidity rates between PTSD and MDD, investigators have pointed to significant overlap of PTSD and MDD symptoms (Biehn et al., 2013; Gros et al., 2012). Numerous researchers have argued that the broad symptom criteria for PTSD include many symptoms related to mood disorders, like MDD (Elhai et al., 2015). The shift to DSM-5 diagnostic criteria further fuelled this argument, as PTSD diagnostic criteria were changed to include a broad cluster of additional symptoms, some of which include symptoms such as sleep disturbances, difficulty concentrating, and anhedonia, which are commonly observed in MDD (American Psychiatric Association, 2013; Elhai et al., 2015). For example, in a study of 672 military soldiers with combat-related trauma, Elhai et al. (2015) reported that PTSD's dysphoria symptoms were strongly related to MDD's somatic and non-somatic symptoms. This study further reported that dysphoria symptoms matched MDD symptoms such as restlessness and fatigue, known as vegetative symptoms, as well as affective MDD symptoms, such as depressed mood and feelings of worthlessness (Elhai et al., 2015). Researchers argue that the similarity of diagnostic symptoms between the two disorders, particularly of the dysphoria symptoms, may be the reason for the high comorbidity rates amongst the two disorders (Elhai et al., 2015; Gros et al., 2012).

Studies have reported similar findings for PTSD and MDD participants in the neuroimaging and neurocognitive literature (Kroes, Rugg, Whalley, & Brewin, 2011a; Scheiner et al., 2014a). Although one might expect an additive effect of diagnosis in the comorbid group for neurocognitive impairment and underlying brain indices, whereby the

impairments of PTSD and MDD are seen in PTSD with comorbid MDD, a recent meta-analysis of 60 neurocognitive studies by Scott et al. (2015), it was reported that the addition of MDD symptoms to a PTSD diagnosis did not affect the magnitude of the observed impairments. One alternative possibility that has not been explored is that, instead of an additive effect, there may be a synergistic effect of comorbidity in PTSD with comorbid MDD, whereby the neurocognitive and brain findings are greater than the sum of the impairments found in PTSD and MDD combined. The current dissertation set out to tease these possibilities apart.

### **Implications for mothers**

The findings from this dissertation may have implications for mothers, particularly mothers from low-middle income regions. Mothers with MDD have shown to present with memory impairments, while mothers with PTSD and comorbid MDD present with processing speed impairments. With this information, clinics and health care professionals could better explain potential difficulties mothers in LMI regions experience. Coping strategies and treatment adherence plans can be developed for mothers who have memory or executive functioning impairments, to ensure that mothers can function as best as they can when caring for their children. Additionally, the findings may provide the foundation for interventions and treatment plans for mothers with PTSD, MDD, or PTSD with MDD.

### **Why are different findings observed in the present research relative to published studies?**

A number of findings reported in this investigation are contrary to that reported in the literature. For example, differences were not observed for the clinical groups on neurocognitive measures of attention and executive functioning. The clinical groups did not perform more poorly on executive functioning subdomains (set-switching, inhibition, etc.) than controls. Furthermore, the clinical groups did not exhibit an association between the DMN and the cognitive control networks. Structural reductions were not observed by the clinical groups on key frontal regions.

There are a number of potential reasons for this. Reasons that could account for these differences include, firstly, that this dissertation utilised a sample that is very different from the standard samples used in published research. An overwhelming proportion of PTSD studies tend to use male military samples where the participants experience a single trauma type (Danckwerts & Leathem, 2003). The present dissertation utilised a female sample that

have experienced a multitude of trauma types, with high levels of interpersonal violence (IPV) trauma prevalent in the communities (Koen et al., 2016). Johnsen and Asbjørnsen (2008) support the notion that trauma differences between psychiatric samples may affect neurocognitive outcomes. In their meta-analysis, stronger neurocognitive effects were observed in male military samples ( $d = 0.82$ ) relative to female participants with exposure to sexual or physical abuse ( $d = 0.54$ ) (Johnsen & Asbjørnsen, 2008). Further support for the possibility that gender and trauma differences could explain why the present sample differs from those reported elsewhere comes from the observation that similar neurocognitive results were reported in a study conducted on a sample of women with PTSD due to interpersonal violence exposure (Stein et al., 2002). Stein et al., (2002) reported that the PTSD group and controls performed comparably on measures of executive function, such as Trail Making Test, digit span, and measures of memory. Likewise, the present dissertation, utilising a similar sample with predominantly IPV exposure, did not find evidence that PTSD was associated with differences in performance on measures of executive function and working memory.

Differences may have been observed due to the present sample being from a LMI region of a non-Western, underdeveloped country, whilst the majority of published studies have been conducted on Western, or developed, populations. Some evidence suggests that PTSD samples from less developed countries may perform similarly to controls on neurocognitive measures. For example, in a Brazilian sample, Flaks and colleagues (2014) reported that the PTSD group performed similarly to both trauma-exposed and healthy controls on neurocognitive measures. The present dissertation reported similar findings across the individual chapters, with the mono-diagnostic groups performing similarly to controls.

Equivalent task performance in the PTSD and control groups in this thesis may also indicate a degree of resilience in this sample, as these participants are exposed to difficult day-to-day living conditions, such as gang violence and interpersonal violence (Abler et al., 2014; Lund et al., 2010). It is possible that prolonged exposure to these trying living conditions may have led participants to develop a degree of resilience as a protective factor. Prevalence studies have shown that South African samples tend to exhibit more resilience than American samples, despite greater trauma exposure in South Africa. The South African Stress and Health study (SASH) reported PTSD prevalence rates that are lower than American PTSD prevalence rates (3.5% versus 7.8%, respectively) (Herman et al., 2009; Kessler et al., 1995), despite very high rates of trauma exposure in South Africa (Abler et al.,



2014; Lund et al., 2010). Resilience in the present sample may be muting the potential impairments and abnormalities seen in PTSD and MDD samples.

This research utilised a combined control group of trauma-exposed and trauma-naïve participants. I have argued in this dissertation that a control group that combines trauma-exposed and unexposed participants is more representative of the population from which the participants originate, given evidence that when compared to PTSD, trauma-exposed and trauma-naïve controls exhibit different profiles of neurocognitive impairments and functional connectivity abnormalities (Malarbi, Abu-Rayya, Muscara, & Stargatt, 2017; Stark et al., 2015). A potential issue for all neurocognitive research, is that the measures used to assess a particular domain may actually be measuring more than one domain, or a number of subdomains (Austin, Mitchell, & Goodwin, 2001). It is therefore difficult to tease apart impairments in the relevant domains affected. For example, Harvey et al. (2004) suggests that executive function measures tend to include many other neurocognitive functions, making executive dysfunction difficult to tease out. For instance, set-switching tasks include functions such as attention and working memory. Accordingly, if a participant has attention deficits, he/she may display demonstrate impairments on the set-switching task, whilst otherwise possessing intact executive function.

Neurocognitive findings from the present dissertation may differ from published articles due to utilising differing neurocognitive batteries. The present dissertation utilised the NIH Toolbox, a comprehensive, computerised battery which was developed to become a research tool and a ‘common currency’ amongst researchers (Weintraub et al., 2013).

Contrary to literature, Chapter 4 highlighted that age did not influence the structural metrics. According to the literature, greater age is associated with cortical reductions and thinning (Jernigan et al., 2001; Salat et al., 2004). However, the present dissertation’s lack of evidence for an age effect may be due to the relatively young mean age for the individual groups. As the participants were between the ages of 18 and 49 years, the restricted variability in age range may be too narrow to reflect any potential age effects in this sample.

### **Limitations of this dissertation**

Several methodological limitations should be acknowledged. Firstly, this dissertation was cross-sectional in nature, and due to this, it was not possible to establish the causality of the relationship observed between psychiatric diagnosis and neurocognitive function, intrinsic functional connectivity, or neuroanatomical integrity.

The present research utilised DSM-IV diagnostic criteria, instead of the most recent DSM-5 criteria. In the early stages of the studies, when enrolment and assessment had started, the DSM-5 was still being compiled. Once the DSM-5 had been released, the diagnostic measures used in this research (mainly the MINI and CAPS) had not yet been updated and validated with the new DSM-5 criteria. With this potential confound in mind, the DSM-IV diagnostic criteria were utilised throughout this research to remain consistent, to create groups as homogeneous as possible, and to use as many validated diagnostic measures as possible. There are arguments both for and against the DSM-5 diagnostic criteria for PTSD; however, this is beyond the scope of this research. Hoge et al. (2016) and Friedman, Kilpatrick, Schnurr, and Weathers (2016) give commentary on this topic.

The surprisingly low number of participants with current diagnoses in this sample necessitated the inclusion of participants with lifetime diagnoses. The heterogeneous nature of the clinical groups' diagnoses may therefore be masking the full extent of neurocognitive and functional abnormalities in this sample. Given the literature suggesting that current PTSD is associated with greater neurocognitive impairments, relative to participants with past PTSD (Eren-Kocak et al., 2009), for example, it would be beneficial for future research to separate current and lifetime diagnoses when running analyses.

The present dissertation could have benefited from the use of a clinician administered depression measure such as the Hamilton Depression Rating Scale or the Montgomery-Asberg Depression rating scale. However, due to the high research burden placed on the DCHS participants, it was not possible to include such scales. BDI-II data was collected at the 18-month time point, however, due to participants lost to follow-up, a high proportion of incomplete BDI-II questionnaires (almost one-third), the remaining data pool was too small to utilise. Due to the lack of power, MDD symptom severity was not explored in relation to neurocognitive performance, resting-state connectivity, and structural abnormalities.

Despite every effort to increase the clinical group sample sizes, a large proportion of participants were excluded based on psychopathology such as alcohol and/or substance abuse or dependence. Research has consistently shown that neurocognitive functioning is negatively affected by alcohol abuse (Bates, Bowden, & Barry, 2002; Brown, Tapert, Granholm, & Delis, 2000), and it therefore remained an exclusion criterion for all studies in this dissertation. Unfortunately, alcohol and substance use is a common feature of the Western Cape region, where 24.2% of women from the Western Cape are current drinkers (Parry et al., 2005). Indeed, the motivation for the significance of the Drakenstein Child Health Study, from which the cohort in this dissertation represents a sub-sample, highlighted

how alcohol and drug abuse is an issue in the region (Stein et al., 2015). With this issue in mind, the results from the present dissertation can only be generalised to non-substance-abusing women from a LMI country. Furthermore, utilising a female-only sample may be considered a potential limitation; however, research has indicated that women are twice as likely as men to develop PTSD (Foa & Street, 2001), and more susceptible to developing MDD, relative to men (Kessler, 2003; Nolen-Hoeksema, 2001). As the majority of PTSD research focuses on male combat veterans, utilising an entirely female sample reduces sample bias in the literature.

Due to unforeseen circumstances, two different scanners were used during this study. Every effort was made to ensure that scanning sequences and sessions remained as similar as possible. Chapter 3 illustrated that there were significant scanner effects for some of the resting-state networks. Scanner effects were controlled for; nevertheless, the results need to be interpreted with care.

This dissertation could have benefited from the inclusion of a variety of additional variables. For example, socioeconomic variables, such as type of employment and medication usage, were not collected in this study. Due to this, neurocognitive functioning could not be examined in full, with regard to socioeconomic variables. Future research should endeavour to collect these data in order to determine whether these variables affect neurocognitive functioning and the neuroanatomy of patients with PTSD, MDD, and PTSD with comorbid MDD in LMI women.

As this sample is a particular subset of mothers, the sample is not fully representative of all mothers. However, the data obtained from the study may shed light on the potential difficulties experienced by mothers, particularly in low-middle income regions. Moreover, the results may not be generalisable to male-only samples, however, the current PTSD literature is skewed towards male combat veterans, and there is a paucity of female-only samples in the PTSD literature. Additionally, the results may not be generalisable to females from higher income regions, or women without children, but it may elucidate findings that may influence interventions, coping strategies, and treatment plans for mothers with these disorders.

### **Directions for future research**

As there is currently limited imaging research focusing on PTSD with comorbid MDD, there are a number of opportunities for future research, especially with regard to structural neuroimaging.

As both PTSD and MDD are highly prevalent in clinical and civilian samples, future research should endeavour to build upon the present research to help develop better treatment plans or alternative treatment adherence plans, as research has shown that these patients are particularly treatment resistant. These plans would help lessen the burden on primary health care resources, particularly in low-middle income regions.

The neurocognitive findings, especially with regard to education, reveal the importance of further research examining the value of psycho-educational or neurocognitive remediation interventions in patients with these disorders in these LMI settings. These interventions could be used in conjunction with treatment plans to create a holistic treatment approach. Future research should investigate the effects of education and low levels of education have on neurocognitive, functional intrinsic connectivity, and structural cortical abnormalities in women from low-middle income regions, as this dissertation has reported results contrary to the literature.

Future research could further explore resting-state networks in patients with PTSD and comorbid MDD. As these networks underlie higher-order neurocognitive functions, they could be used as diagnostic markers, separating MDD patients from complex PTSD cases. Future research could utilise resting-state methods to target frontal networks and their connectivity to develop improved interventions for patients with these disorders.

More PTSD research needs to be conducted on samples from marginalised population sectors in non-Western LMIC settings, given how vulnerable these communities are to psychological trauma. Studies in Western societies would focus usefully on PTSD resulting from a variety of trauma types, and PTSD in women as well as men. This would give a more generalisable and holistic overview of the disorders.

### **Conclusions**

Several important findings should be highlighted. Firstly, the present dissertation reports a distinct profile of impairment and abnormalities for PTSD, MDD, and PTSD with comorbid MDD. This distinct profile of impairment is contrary to the impairment across all neurocognitive domains that is illustrated in the literature as this sample of female

participants did not exhibit overt deficits on attention, working memory, or executive function tasks.

Second, as the findings from each chapter has consistently shown, PTSD symptom severity was a better indicator of impairment and dysfunction in the present dissertation than categorical, diagnostic classification. This dimensional approach to psychopathology should be utilised in future research as it elucidates more subtle results from data as categorical approaches cannot account for sources of variance, for example.

Furthermore, the present sample indicated that MDD was associated with aberrant resting-state connectivity within the DMN and L FPAR, as well as structural abnormalities that are in line with those reported in the literature. MDD was also associated with greater structural abnormalities, and the findings have been consistent with literature.

The present dissertation attempted to determine whether PTSD with comorbid MDD presented with greater impairment or abnormalities more reflective of synergistic effects, relative to the mono-diagnostic groups. In some regards, PTSD with comorbid MDD has shown to create an additive effect, while in other instances, it shows more of a synergistic effect. For example, PTSD symptom severity associations with within-network connectivity reflects an additive effect of comorbidity, while the neurocognitive performance profile of the comorbid groups reflects a synergistic effect. As there is no research on resting-state imaging in PTSD with comorbid MDD, the findings presented in the extant dissertation reflect novel knowledge that may influence further research into resting-state networks in this treatment resistant patient group. Furthermore, the implications for the synergistic effect of comorbid PTSD/MDD extends to treatment plans, suggesting that treatments cannot simply increase dosage, for example, as the implications are not additive or accumulative. Rather these patients may require distinct and unique treatment plans, relative to patients with PTSD or MDD alone.

The present dissertation reports novel information regarding the neurocognitive, resting-state functional connectivity, and structural association of PTSD with comorbid MDD. These findings have a number of implications for both the research laboratory and clinic.

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