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A NEUROIMAGING ANALYSIS OF WORKING MEMORY UPDATING IN POSTTRAUMATIC STRESS DISORDER

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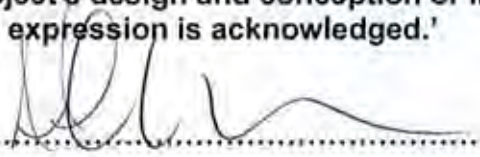
Signed 

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ABSTRACT

Posttraumatic stress disorder (PTSD) is an anxiety disorder in which there are disturbances in arousal, fear regulation, and concentration and attention. Prominent neural models have focused on the fear-based phenomena of the disorder, but do not account for neuropsychological disturbances, of which reduced working memory is an example. Reduced working memory in PTSD has been observed previously and may be a cognitive cost of the processing load imposed by disorder symptomatology (the cognitive cost hypothesis). This thesis aimed to understand the neural correlates of disturbed working memory in PTSD. Studies used a 1-back working memory updating task in conjunction with behavioural and functional neural measures via event-related potential (ERP) and functional magnetic resonance imaging (fMRI) paradigms in PTSD, trauma-exposed control, and non-trauma-exposed control participants. The potential confounding contributions of trauma exposure, depressive symptoms and psychotropic medication use were also controlled. Study 1 found degraded working memory processing on ERP measures (reduced amplitude of the P3b) specific to PTSD, which was also related to severity of re-experiencing symptoms (P3b latency). Using fMRI, Study 2 found reduced activation in bilateral dorsolateral prefrontal cortex (dlPFC) and left anterior cingulate cortex (ACC) during the task that was specific to PTSD. PTSD symptom clusters were generally inversely associated with activation in dlPFC and ACC during the task. These findings are consistent with the proposed importance of these brain regions to normal working memory. They are also consistent with the cognitive cost hypothesis. Positive associations were observed between precuneus activation and avoidance and arousal symptoms, possibly reflecting disturbed operation of the default mode brain network. Study 3 found (via fMRI) that greater pre-treatment task-concurrent activation in dlPFC, ACC and inferior parietal cortex was

associated with better PTSD response to cognitive behavioural therapy, a treatment proposed by researchers to require working memory integrity. This was independent of depressive symptoms and psychotropic medication use. Together, these studies provide evidence of neural dysfunction in working memory updating in PTSD, independent of contributions from depressive symptoms and medication to these deficits. The current findings point to extensions of fear-based neural models to capture the array of PTSD phenomena.

LIST OF ABBREVIATIONS

μV	Microvolt
ACC	Anterior cingulate cortex
ANOVA	Analysis of variance
BOLD	Blood oxygenation level dependent signal
BRID	Brain Resource International Database
CAPS	Clinician Administered PTSD Scale
CIDI	Composite International Diagnostic Interview
cm	centimetre
CR	Conditioned response
CS	Conditioned stimulus
DASS	Depression Anxiety Stress Scales
dlPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
EEG	Electroencephalogram
EOG	Electro-oculogram
ERP	Event-related potential
fMRI	functional magnetic resonance imaging
FOV	Field of View
IFG	Inferior frontal gyrus
Inf Temp	Inferior temporal
IPC	Inferior parietal cortex
ISI	Interstimulus interval
LTM	Long-term memory
Med	Medial
mm	millimetre
MNI	Montreal Neurological Institute
ms	Millisecond
NTE control	Non-trauma-exposed control
OFC	Orbitofrontal cortex
PCC	Posterior cingulate cortex
PET	Positron emission tomography
pr	Partial correlation
PTSD	Posttraumatic stress disorder
ROI	Region of Interest
rTMS	repetitive transcranial magnetic stimulation
SCR	Skin conductance response
sd	Standard deviation
SMA	Supplementary motor area
SMG	Supramarginal gyrus
SPC	Superior parietal cortex
Sup	Superior
TE	Time to echo
TE control	Trauma-exposed control
TR	Repetition time
UR	Unconditioned response
US	Unconditioned stimulus
vlPFC	Ventrolateral prefrontal cortex
vmPFC	Ventromedial prefrontal cortex

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. Chapter 1: Introduction

1.1 Overview

Posttraumatic stress disorder (PTSD) affects over one million Australians (Ewing, 2008). Prevailing models of PTSD have focused on the neurobiological mechanisms of fear-based phenomena (Rauch, Shin, & Phelps, 2006). In contrast, much less attention has been given to understanding the neural bases of the neurocognitive features of the disorder. Working memory difficulty is one such example. Indeed, working memory difficulty is common in PTSD (Vasterling & Brailey, 2005) and may negatively impact post-trauma recovery and response to treatment (Brewin, 2005; Vasterling & Verfaellie, 2009). As such, the overarching aim of this thesis is to better characterise the neural basis of working memory difficulty in PTSD. This introduction outlines behavioural and neural evidence for reduced working memory functioning in PTSD and proposes that this may be a cognitive cost of the disorder. The potential confounding factors of non-specific impact of trauma exposure, depressive symptoms and use of psychotropic medication are also detailed. An outline of the current research program follows.

1.2 Clinical features of PTSD

The current Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association (APA), 2000) defines PTSD as an anxiety disorder that may develop following a traumatic event in which an individual experiences, witnesses or is confronted with actual or threatened death or serious physical injury to self or other, and experiences a sense of fear, helplessness, or horror. It is composed of three symptom clusters: re-experiencing symptoms (e.g., flashbacks, intrusive thoughts); avoidance symptoms (e.g., avoidance of thoughts or activities, emotional numbing), and symptoms of increased arousal (e.g., sleep and concentration disturbances). To qualify for a PTSD

diagnosis, the individual must have at least one re-experiencing symptom, three avoidance symptoms, and two arousal symptoms, which must be present for at least four weeks following the trauma, and result in significant distress or impairment in social, occupational, interpersonal or other functioning.

1.3 Arousal dysregulation and its contribution to features of PTSD

Arousal dysregulation is a core pathogenic process in PTSD (Kolb, 1987). It is hypothesised that extreme sympathetic arousal at the time of trauma may prompt overconsolidation of trauma memories via cortical release of stress-related neurotransmitters, including norepinephrine and epinephrine (Cahill & McGaugh, 1996; Pitman, 1988, 1989). Moreover, as a result of classical conditioning (explained more fully in Section 1.5) and stress sensitisation processes, subsequent confrontation with trauma reminders results in excessive sympathetic arousal, which may manifest as the intrusive phenomena characteristic of PTSD (Kolb, 1987; Pitman, Shalev, & Orr, 2000; Post, Weiss, & Smith, 1995). Consistent with these proposals, PTSD patients exhibit exaggerated peripheral arousal responses (including heart rate, skin conductance and facial electromyogram) to personalised trauma reminders relative to individuals with a similar trauma history but without PTSD (Orr, Pitman, Lasko, & Herz, 1993; Pitman, Orr, Forgue, de Jong, & Claiborn, 1987). Further, people who eventually develop PTSD display elevated resting heart rates (Bryant, Harvey, Guthrie, & Moulds, 2000; Shalev et al., 1998) and respiration rates (Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2008) in the initial days after trauma.

1.4 Neurocognitive disturbances in PTSD

Given the memory-related features of PTSD (e.g., flashbacks, psychogeneic amnesia, trauma-related nightmares), much neurocognitive research on the disorder has

focused on aberrant memory functioning. Indeed, some theorists have characterised PTSD as a disorder of memory (McNally, 2006). Disturbed autobiographical memory in PTSD is well supported (Brewin, 2008; Brewin, Kleiner, Vasterling, & Field, 2007; Harvey, Bryant, & Dang, 1998; Sutherland & Bryant, 2007), which may manifest as difficulty with explicit recall as well as reduced recall specificity (McNally, 2006; McNally, Litz, Prassas, Shin, & Weathers, 1994). Additionally, studies examining information processing in PTSD have revealed disturbances in attention, including attentional bias to threat-associated stimuli (Buckley, Blanchard, & Neill, 2000); this bias has been demonstrated through modified Stroop (Harvey, Bryant, & Rapee, 1996; McNally et al., 1987) (but see Kimble, Frueh, & Marks, 2009), dot-probe (Bryant & Harvey, 1997), and eye-tracking paradigms (Bryant, Harvey, & Gordon, 1995). There is also electrophysiological evidence (via event-related potentials) of impaired processing of emotionally neutral stimuli in PTSD (Felmingham, Bryant, Kendall, & Gordon, 2002; McFarlane, Weber, & Clark, 1993).

Also, in keeping with patient reports of difficulties with concentration and attention (McNally, 2006; Vasterling & Brailey, 2005), investigators have examined the neuropsychological integrity of attention and working memory in PTSD. For the sake of reviewing the following findings, working memory is considered the ability to hold and manipulate a limited amount of information in mind for a limited time (Smith & Jonides, 1999). However, working memory is a complex construct and is reviewed more comprehensively in Section 1.7. Individuals with PTSD from either civilian or combat-related trauma perform more poorly than those without PTSD on standardised neuropsychological working memory tasks (e.g., Digit Span and Spatial Span subtests from the Wechsler Memory Scale battery) (Gilbertson et al., 2006; Koso & Hansen, 2006; Lagarde, Doyon, & Brunet, 2010; Samuelson et al., 2006; Vasterling, Brailey,

Constans, & Sutker, 1998; Vasterling et al., 2002). These findings are complemented by laboratory-based tasks of working memory (e.g., the n-back task; outlined in Section 1.8), which have demonstrated longer reaction times and worse performance accuracy in PTSD compared to healthy controls (Clark, Moores, et al., 2001; Galletly, Clark, McFarlane, & Weber, 2001; Galletly, McFarlane, & Clark, 2008; Veltmeyer et al., 2009; Veltmeyer et al., 2006; Weber et al., 2005). However, degraded working memory performance in PTSD is not a consistent finding (e.g., Moores et al., 2008; Stein, Kennedy, & Twamley, 2002; Twamley, Hami, & Stein, 2004), possibly because trauma exposure and comorbid depressive symptoms may contribute to observed working memory decrements in PTSD (Barrett, Green, Morris, Giles, & Croft, 1996; Brandes et al., 2002; Horner & Hamner, 2002) (but see Gilbertson et al., 2006). This issue is addressed more fully in Section 1.12.

1.5 The fear conditioning model of PTSD

Arguably the most influential model for the persistence of PTSD is the fear conditioning model (Pitman et al., 2000; Yehuda & LeDoux, 2007). This model suggests that PTSD results from a failure to extinguish a conditioned fear response acquired at the time of the traumatic event. Within this conceptualisation, a traumatic event (the unconditioned stimulus; US) provokes a fear response (unconditioned response; UR). Previously neutral stimuli present during the traumatic event become trauma reminders (conditioned stimuli; CS), prompting re-experiencing of the fear response (the conditioned response; CR) when encountered by the PTSD patient. Failure to extinguish the conditioned fear response is thought to result in ongoing conditioned fear responses and intrusive memories (Pitman et al., 2000). This model has strong support from evidence of enhanced psychophysiological responses to trauma reminders in PTSD (Orr, Metzger, & Pitman, 2002).

Following the fear conditioning model of PTSD, findings from animal research on the neural bases of fear conditioning and extinction have informed development of fear-based neural models of PTSD. One such model, the fear circuitry model of PTSD, is outlined below.

1.6 Neurobiology of PTSD - the prevailing fear circuitry model

The fear circuitry model of PTSD is informed by substantial research using animal models to understand the brain bases of fear conditioning and extinction, which has received convergent support from human neuroimaging and lesion-based studies (Rauch et al., 2006; Shin & Handwerger, 2009; Shin, Rauch, & Pitman, 2006). This model describes the fear-based phenomena of PTSD as a product of insufficient regulation by the ventromedial prefrontal cortex (vmPFC) (including the rostral portion of anterior cingulate cortex; ACC) and the hippocampus, and of a hyperactive response to threat in the amygdala. Amygdala hyperactivity underlies the excessive fear and hyperarousal responses of the disorder, while insufficient regulation from the vmPFC explains the failure to extinguish fear responding after extrication from the traumatic event, and therefore the perpetuation of re-experiencing symptoms to trauma reminders. Insufficient hippocampus activity explains the generalisation of fear responding across context and failure to identify safe contexts, while reduced rostral ACC activity contributes to the disrupted recall/contextualisation of fear memory.

Supporting the fear circuitry model, lesion-based and cell recording animal studies have shown that amygdala nuclei are integral to the acquisition and expression of conditioned fear (Campeau & Davis, 1995; Collins & Paré, 2000; Cousens & Otto, 1998; LeDoux, Cicchetti, Xagoraris, & Romanski, 1990; Maren, 2000; Quirk, Repa, & LeDoux, 1995; Zimmerman, Rabinak, McLachlan, & Maren, 2007). Similar such

paradigms have shown that vmPFC enables the retention and expression of the fear extinction memory (Lebron, Milad, & Quirk, 2004; Milad & Quirk, 2002), likely via modulatory projections to the amygdala (Quirk & Mueller, 2008; Sotres-Bayon, Bush, & LeDoux, 2004; Sotres-Bayon, Corcoran, Peters, & Sierra-Mercado, 2008). Hippocampal activity appears important in modulating the contextual expression of fear memory and extinction memory (Corcoran, Desmond, Frey, & Maren, 2005; Hobin, Ji, & Maren, 2006), though specific mechanisms are not well understood (Bouton, Westbrook, Corcoran, & Maren, 2006). Human neuroimaging studies in normals and in PTSD patients support the role of the amygdala in the acquisition of conditioned fear, and the vmPFC and hippocampus in extinction memory (Kalisch, Korenfeld, et al., 2006; Milad et al., 2009; Milad et al., 2007; Phelps, Delgado, Nearing, & LeDoux, 2004). The fear circuitry model is supported by additional imaging findings in PTSD, which show exaggerated amygdala response to threat and symptom provocation, along with reduced vmPFC and hippocampus activity (Bremner, Narayan, et al., 1999; Bremner, Staib, et al., 1999; Shin et al., 2004; Shin et al., 2005). Thus, the fear circuitry model of PTSD is supported by convergent human and animal evidence using fear-based paradigms. (For more comprehensive reviews beyond the scope of the current thesis see Lanius, Bluhm, Lanius and Pain (2006), Rauch et al. (2006), Quirk and Mueller (2008) and Milad, Rauch, Pitman and Quirk (2006)).

A limitation of the fear conditioning model of PTSD, and the associated neurobiological model, is that they do not directly account for the presence of working memory difficulties in PTSD. An additional mechanism is required to extend these models to account for the presence of these symptoms.

1.7 Working memory and its importance to PTSD

1.7.1 Theoretical models of working memory

Working memory is typically considered to be composed of processes that enable the temporary storage and manipulation of information in the service of higher cognition such as planning, problem-solving, language comprehension and reasoning (e.g., Chein & Fiez, 2010; Jonides, Lacey, & Nee, 2005; Repovs & Baddeley, 2006). However, there is no universal agreement on a model of working memory, nor its mechanisms (Conway, Jarrold, Kane, Miyake, & Towse, 2007). Nevertheless, certain commonalities regarding the properties of working memory are evident among many of these models. That is, they typically agree that working memory is a limited capacity system as a result of functional restrictions, such that cognitive performance is constrained when limits are reached; that it is composed of multiple processes (such as updating, inhibition, monitoring and shifting) rather than being a unitary construct; that it functions to support higher cognition; and that it relies upon some form of cognitive control processes (variously referred to as "controlled attention", "executive attention", "attentional focus" or the "central executive") (Conway et al., 2007; Conway, Moore, & Kane, 2009; Kintsch, Healy, Heagrty, Pennington, & Salthouse, 1999; Miyake & Shah, 1999; Shah & Miyake, 1999). Understood in this light, working memory can be defined as "...those mechanisms or processes that are involved in the control, regulation and active maintenance of task-relevant information in the service of complex cognition... [with] capacity limits that reflect multiple factors and may even be an emergent property of the multiple processes and mechanisms involved. Working memory is closely linked to LTM [long-term memory] and its contents consist primarily of currently activated LTM representations..." (p.450, Miyake & Shah, 1999). Supporting this definition, recent confirmatory factor analysis, structured equation modelling, and

functional brain imaging approaches indicated that working memory variation is best accounted for by both attentional control and storage processes (Kiss, Watter, Heisz, & Shedden, 2007; Unsworth & Spillers, 2010).

1.7.2 Updating as a core process within working memory

While there is disagreement on the specific processes that constitute working memory (e.g., for contrasting views see McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010; Oberauer, Süß, Wilhelm, & Wittman, 2003), there is good evidence for updating as a crucial process of working memory. Working memory updating can be defined as the revision of information held within working memory, allowing the entry of new information and the replacement of old irrelevant information (Kessler & Meiran, 2008; Morris & Jones, 1990). It is considered to optimise use of the limited capacity resources of working memory (De Beni & Palladino, 2004), and it is implicitly or explicitly included in various theoretical models of working memory (e.g., Baddeley, 1996; O'Reilly, Braver, & Cohen, 1999; Oberauer & Kliegl, 2006). Latent variable and structured equation modelling analyses have shown a strong relationship between performance on putative working memory tasks and tasks considered to predominantly tap the updating process (Ecker, Lewandowsky, Oberauer, & Chee, 2010; Miyake et al., 2000; Schmiedek, Hildebrandt, Lövdén, Wilhelm, & Lindenberger, 2009). Also, because updating explains a significant proportion of unique variance in working memory task performance, it is considered a useful probe of working memory functioning as it can be easily operationalised (Miyake et al., 2000). Additionally, tasks designed to predominantly tap updating have suggested that it possesses two of the key properties outlined above as integral to working memory – association with higher cognition and capacity limitation (Carretti, Cornoldi, De Beni, & Romano, 2005; Chen & Li, 2007; Friedman et al., 2006; Montojo & Courtney, 2008; Passolunghi &

Pazzaglia, 2005). Finally, there is functional overlap in the brain areas that are activated during working memory updating tasks, and other putative tasks of working memory (Clark et al., 2000; Collette & Van der Linden, 2002; Collette et al., 2007; Owen, McMillan, Laird, & Bullmore, 2005; Postle, 2006; Smith & Jonides, 1999; Wager & Smith, 2003). Taken together, such evidence suggests that updating is integral to working memory functioning given their empirically supported relationship and similarity in terms of properties these faculties exhibit and overlap in supporting brain areas. Furthermore, this suggests that tasks designed to tap updating can be considered to probe broader working memory functioning.

1.7.3 Working memory as a limited capacity process – the impact of cognitive load

In keeping with the definition of working memory as being of limited capacity, research has indicated that increases in information processing requirements can have an adverse impact upon working memory performance in normals, observed operationally as increasing reaction time and poorer accuracy (increasing number of omission and/or commission errors). Reduced working memory performance from increasing information processing requirements has been achieved by increasing the amount of neutral information to be stored and manipulated (Callicott et al., 1999; Chen, Mitra, & Schlaghecken, 2008; Cohen et al., 1997; Eldreth et al., 2006; Ellis, Silberstein, & Nathan, 2006; Jaeggi, Buschkuehl, Perrig, & Meier, 2010; Jansma, Ramsey, Coppola, & Kahn, 2000; Jonides et al., 1997; Kiss et al., 2007; McEvoy, Smith, & Gevins, 1998; Sambataro et al., 2010; Veltman, Rombouts, & Dolan, 2003; Yun, Krystal, & Mathalon, 2010), by increasing the number of sequential or simultaneous operations required (Leung, Oh, Ferri, & Yi, 2007; Montojo & Courtney, 2008), or by having the individual perform a secondary irrelevant task in parallel with the primary working memory task (Anderson, Mannan, Rees, Sumner, & Kennard,

2010). Also, these load-induced performance declines appear to last over time. For example, performing a high-load working memory task can degrade subsequent performance on lower load tasks of the same type relative to baseline performance levels (Yun et al., 2010). Also, Paskavitz et al. (2010) observed that prolonged performance of a working memory task degrades over time. Thus, due to the capacity constraints of the working memory system, increases in processing load may impose a cognitive cost, observable as declining performance accuracy.

1.7.4 The cognitive cost hypothesis – degraded working memory as a cognitive cost of PTSD phenomenology

On the premise that working memory is dependent on available resources, it is likely that depleted working memory capacity is a potential cost of the intrusive and anxiety-provoking symptoms of PTSD. Numerous theorists have proposed that ongoing intrusions of trauma memory and the resulting distress absorb limited cognitive resources, which degrades a range of cognitive functioning in PTSD (Aikins et al., 2009; Brewin, 2005; Brewin & Beaton, 2002; Nixon, Cain, Nehmy, & Seymour, 2009; Shipherd & Beck, 1999). A major rationale for the hypotheses proposed in this thesis is that behavioural and neural indices of working memory in PTSD will reflect deficits associated with depleted cognitive resources that are secondary to PTSD symptoms.

Additionally, there is evidence that attempts to suppress thoughts and manage distressing memories and affect may also degrade working memory functioning by absorbing processing capacity that would otherwise be devoted to working memory processing. This is germane to PTSD, given the prominence of thought suppression as a coping strategy in the aftermath of trauma (Brewin, 2008; Wenzlaff & Wegner, 2000). Indeed, Brewin (2005) has noted in PTSD "...it is quite possible that neuropsychological

deficits are secondary to reductions in processing capacity brought about by effortful avoidance of specific thoughts and images...[that] may affect the course of the disorder and response to treatment" (p. 280).

Further, there is also evidence that working memory limitations may influence thought intrusions. Lower working memory capacity has been associated with greater number of thought intrusions during directed suppression conditions (Brewin & Beaton, 2002; Brewin & Smart, 2005). Moreover, self-reported cognitive failures have been positively correlated with thought intrusions in normals (Verwoerd & Wessel, 2007), and self-reported thought intrusions associated with negative life events predict lower working memory performance (Klein & Boals, 2001). In line with one of the proposed roles of working memory as a means of protecting against task-irrelevant interference (Engle, 2002; Engle, Kane, & Tuholski, 1999), it is plausible that larger working memory capacity may act as a buffer against thought intrusions. In this context, it is worth noting that the prevailing model of thought suppression posits that working memory capacity is the key factor in determining suppression-related intrusions (Wenzlaff & Wegner, 2000).

Understood in this way, **the degraded working memory performance observed in PTSD may be a cognitive cost of the disorder, such that ongoing processing of trauma memory and attempts to suppress involuntary thoughts and flashbacks degrade working memory functioning** (Aikins et al., 2009; Brewin, 2005, 2008; Brewin & Beaton, 2002; Nixon et al., 2009; Shipherd & Beck, 1999). Indeed, these features may be the pathological equivalent of the detrimental impact of increasing cognitive load on working memory performance which has been modelled in normals (Paskavitz et al., 2010; Yun et al., 2010; Wenzlaff & Wegner, 2000). This cognitive cost hypothesis is consistent with findings that working memory performance is

negatively correlated with PTSD symptom severity (Brandes et al., 2002; Gilbertson et al., 2006; Sutker, Vasterling, Brailey, & Allain, 1995), that chronicity of PTSD symptoms is associated with reduced neuropsychological performance (Marx et al., 2009), that individuals with PTSD process threat-related information at the expense of processing threat-neutral material (Stanford, Vasterling, Mathias, Constans, & Houston, 2001), and that traumatic thought intrusions in PTSD have been shown to increase when cognitive capacity is taxed by directed suppression of neutral material or personally relevant trauma-related information (Aikins et al., 2009; Shipherd & Beck, 1999).

1.8 Neural bases of normal working memory

Lesion and functional imaging studies show that normal working memory is supported by a broad network of frontoparietal brain areas. This includes dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), ACC, parietal areas such as superior parietal cortex (SPC) and inferior parietal cortex (IPC), and other sensory processing areas, the involvement of which varies by task modality (Collette & Van der Linden, 2002; Conway et al., 2009; Jonides et al., 2005; Klingberg, 2006; Postle, 2006; Scheibel & Levin, 2004; Smith & Jonides, 1999; Wager & Smith, 2003). The current brief review of the neural bases of working memory focuses on dlPFC, ACC and IPC. The evidence reviewed here is based primarily on studies that have utilised the following working memory tasks – the delayed match to sample task, the complex span task, and the n-back task. The delayed match to sample task requires information to be actively maintained in working memory over a brief delay in the absence of external cues with a decision about whether the held information matches a subsequently presented stimulus. The complex span task requires information to be actively maintained while performing a concurrent operation (e.g., holding a word in mind while judging the meaning of the sentence from which it comes). The n-back task

requires a judgement as to whether a presented stimulus matches that presented ‘n’ items back in a list of sequentially presented items, therefore requiring active maintenance and continuous updating of stimulus identity. Functional neuroimaging studies using these tasks were selected for review as they tap storage, manipulation and updating processes, and thus conform to working memory as defined in Section 1.7.1.

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) monitor brain activity by measuring changes in regional cerebral bloodflow and blood oxygenation levels, respectively. Such imaging methods have shown increased activity over baseline across dlPFC, IPC and ACC during complex span tasks and n-back tasks (Collette & Van der Linden, 2002; Collette et al., 2007; Osaka et al., 2003; Owen et al., 2005), as well as during storage-based tasks in which concurrent interference tasks must be performed (Anderson et al., 2010; Gruber & von Cramon, 2001; Klingberg, O'Sullivan, & Roland, 1997).

The updating process is also associated with activation in these areas when performing the 1-back version of the n-back task, the design of which emphasises use of the updating process (described in more detail in Section 1.13.2). During performance of this task, participants activate dlPFC and IPC bilaterally, and the left/midline ACC in response to non-targets (Clark et al., 2000; Clark et al., 2003; Moores et al., 2008).

Lesion studies provide convergent evidence for the role of dlPFC, ACC and IPC in working memory. Lesions to dlPFC result in increased susceptibility to distraction while retaining information over a brief delay (Chao & Knight, 1995), while lesions to lateral PFC, ACC and right parietal cortex have been associated with degraded n-back task performance relative to healthy controls (Ravizza, Behrmann, & Fiez, 2005; Tsuchida & Fellows, 2009). Further, lesions in the white matter pathways

interconnecting dlPFC, ACC and IPC have been associated with degraded performance on a verbal numeric working memory task in multiple sclerosis patients (Sepulcre et al., 2009).

Convergent findings have also been found in repetitive transcranial magnetic stimulation (rTMS) studies. This technique allows temporary disruption of functioning in cortical areas during task performance to test their functional relevance to the process of interest (Postle et al., 2006). rTMS applied specifically to dlPFC or IPC resulted in performance decrements on verbal and visuospatial n-back working memory tasks (Mottaghy, Döring, Müller-Gärtner, Töpper, & Krause, 2002; Oliveri et al., 2001; Sandrini, Rossini, & Miniussi, 2008).

Anatomical evidence and functional connectivity analyses suggest that dlPFC, ACC and IPC may act as a network in support of working memory. There are anatomical interconnections between dlPFC and each of ACC and posterior parietal regions (Funahashi, 2007; Petrides & Pandya, 1999). Consistent with these connections, there is positively correlated functional connectivity between dlPFC and ACC during complex span tasks, using either visuoverbal, visuonumeric or spatial stimuli, the strength of which increases with better performance (Kondo, Morishita, et al., 2004; Kondo, Osaka, & Osaka, 2004; Osaka et al., 2003). Positively correlated functional connectivity is also evident between dlPFC and IPC during working memory updating on the 1-back working memory task (Shaw et al., 2009).

In summary, working memory theorists have proposed a frontoparietal network which functions to support working memory, with dlPFC, ACC, and IPC as key nodes, though other areas such as vlPFC and SPC are also involved (Collette and van der Linden, 2002; Conway & Kane, 2007; Jonides et al., 2005; Klingberg et al., 2006;

Postle, 2006; Scheibel & Levin, 2004; Smith & Jonides, 1999; Wager & Smith, 2003). Functionally, the dlPFC has been proposed to subserve an executive control function to assist in manipulation of information or interference control processes that may be observable during the working memory delay period (D'Esposito & Postle, 1999; Postle, 2006; Smith & Jonides, 1999). The ACC may act to provide additional attention control when task demands increase (Kondo, Morishita, et al., 2004; Kondo, Osaka, et al., 2004; Osaka, Komori, Morishita, & Osaka, 2007; Osaka & Osaka, 2007; Osaka et al., 2003). The IPC may act to hold stimulus-response representations which can be prioritised and selected by dlPFC to guide appropriate responding (Clark et al., 2000; Curtis & D'Esposito, 2003; Hester, D'Esposito, Cole, & Garavan, 2007).

It should be noted that there is evidence for lateralisation in working memory based on material type, with verbal and object information left lateralised and spatial information right lateralised (D'Esposito et al., 1998; Jonides et al., 2005). However, this appears modulated by task demands, such that strict left lateralisation of verbal material is less likely when working memory processes additional to maintenance are required (Wager & Smith, 2003). As such, bilateral activation for verbal material may be expected when working memory tasks require manipulation of information. This is consistent with observations of bilateral activation of dlPFC and IPC in normals during the 1-back working memory task (Clark et al., 2000; Clark et al., 2003; Moores et al., 2008).

1.9 Neural correlates of capacity limitation in working memory

In keeping with the capacity limitations of working memory, corresponding changes in brain activation and working memory performance have been observed with increases in the amount of information to be processed during task performance. This

increase in cognitive load has frequently been operationalised as increasing the number of items to be actively maintained and updated during the n-back task. Such increases in cognitive load have been associated with increased activation in dlPFC, ACC and IPC with increased performance accuracy at lower load levels (1-back to 2-back) (Callicott et al., 1999; Jansma et al., 2000). However, at higher load levels (3-back and higher), there was reduced dlPFC activity (Callicott et al., 1999). This decline in dlPFC activity is sustained through performance on subsequent working memory tasks, along with reduced ACC and IPC activation (Yun et al., 2010), complementing observations of relative cognitive performance declines on tasks that follow intensive practice on high interference working memory tasks (Persson, Welsh, Jonides, & Reuter-Lorenz, 2007).

Thus, increasing processing load on the cognitive system can reduce both working memory performance and activation in supporting brain regions. As already noted, reduced working memory functioning in PTSD may be a cognitive cost of the demanding nature of symptoms. It follows that there may also be reduced activation in dlPFC, ACC and IPC in PTSD during working memory processing.

1.10 Working memory-based evidence for degraded brain function in PTSD

1.10.1 Neuroimaging evidence

Using brain imaging approaches such as PET and fMRI, Clark and colleagues have reported reduced brain functioning in PTSD compared to controls, during working memory updating in word-based 1-back working memory tasks. Across a series of studies, they found reduced dlPFC, ACC and IPC activity during working memory updating in PTSD with concurrent decrements in performance measures (increased reaction time and/or omission errors) compared to healthy controls, (Clark, McFarlane, et al., 2001; Clark et al., 2003; Moores et al., 2008). Specifically, these reduced

activations were observed in the middle frontal gyrus of the dlPFC and the supramarginal gyrus of the IPC (Clark, McFarlane, et al., 2001; Clark et al., 2003), though reduced activity was also present in adjacent areas within each of dlPFC and IPC (Moores et al., 2008). There does not appear to be a laterality effect, with left lateralised reductions observed by Clark and colleagues (Clark, McFarlane, et al., 2001; Clark et al., 2003), and bilateral reductions observed by Moores et al. (2008) despite use of similar tasks.

1.10.2 Evidence from event-related potential studies

Convergent evidence for degraded working memory processing in PTSD versus controls has been found in studies of event-related potentials (ERP). The ERP is a scalp-recorded voltage deflection, extracted from the ongoing electroencephalogram (EEG) by signal averaging. It is time-locked to a particular physical or mental event and provides information at a millisecond timescale. It is composed of several components, each defined by positive or negative polarity, latency, scalp distribution and its relation to experimental variables. The latency of these components can provide information on the time course of particular cognitive processes, while their amplitude provides information on the extent of neural resource allocation (Duncan et al., 2009; Humphrey & Kramer, 1994; Opitz, 2003; Soltani & Knight, 2000). Two such components that have been examined in the context of working memory in PTSD are P3b and N2.

Amplitude of the P3b component has been the focus in most PTSD working memory research. The P3b is a large positive amplitude potential with peak latency typically in the 300-700 ms range post-stimulus and a parietal scalp distribution (Hartikainen & Knight, 2003). P3b amplitude is considered to be positively related to allocation of cognitive processing capacity, as performance of secondary tasks (particularly with

increasing perceptual demands) results in reduced P3b amplitudes during primary task performance (Nieuwenhuis, Aston-Jones, & Cohen, 2005; Polich, 2007) (but see Kok, 2001). The latency of the P3b appears to be a measure of stimulus classification speed, and is therefore considered to index the speed with which resources are allocated to stimulus processing (Polich, 2003). This is evidenced by increased P3b latency along with increased reaction times to target stimuli on auditory oddball (a discrimination task) and visual discrimination tasks as stimulus discrimination difficulty is increased (Donchin, Karis, Bashore, Coles, & Gratton 1986; Katayama & Polich, 1998; Magliero, Bashore, Coles, & Donchin, 1984; McCarthy & Donchin, 1981). Collectively, findings from studies using either lesion-based, intracranial recording studies or ERP source localisation approaches, suggest direct contribution to P3b from the temporoparietal junction (including areas of IPC), and frontal areas (Hartikainen & Knight, 2003; Lenartowicz, Escobedo-Quiroz, & Cohen, 2010; Linden, 2005; Nieuwenhuis et al., 2005; Polich, 2003; Polich, 2007; Polich & Criado, 2006; Weber et al., 2005), all possibly driven by the locus coeruleus (Nieuwenhuis et al., 2005). It should be noted, however, that conclusively determining exact neural sources of ERP generation is difficult given the diffuse nature of recording at the scalp and the likely overlap between individual components (Kok, 2001).

In their context updating theory, Donchin and colleagues (Donchin, 1981; Donchin & Coles, 1988) proposed that P3b reflects updating of a contextual model of the environment held in mind, the amplitude of which is proportional to available cognitive resources (but for alternative views see Kok, 2001; Nieuwenhuis et al., 2005; Polich, 2007). Accordingly, larger P3b amplitude has been observed during working memory tasks that require constant stimulus updating compared to those in which no updating is

required (Chen et al., 2008; Clark, Orr, Wright, & Weber, 1998; Lenartowicz et al., 2010; Weber et al., 2005).

The N2 component has also been examined in the context of working memory, though mostly with regard to PTSD. The N2 is a negative potential, which typically peaks 180-350 ms post-stimulus and has a frontal locus (Folstein & Van Petten, 2008; Patel & Azzam, 2005). The latency of this component is related to stimulus discrimination difficulty in normals, such that longer latency reflects increased stimulus discrimination difficulty and stimulus categorisation time (Näätänen & Picton, 1986; Naatanen, Teder, Alho, & Lavikainen, 1992; Ritter, Simson, Vaughan, & Friedman, 1979). It is noted that such findings on N2 characteristics have typically been observed with respect to target stimuli on the oddball task rather than during working memory processing.

Use of the 1-back working memory updating task in both visual and auditory modalities has found degraded brain functioning in PTSD as measured by ERPs. Specifically, individuals with PTSD exhibited reduced P3b amplitude when engaged in working memory updating for tone stimuli (Galletly et al., 2001; Galletly et al., 2008)[1] and visually presented word and letter stimuli compared to healthy controls (Clark, McFarlane, et al., 2001; Veltmeyer et al., 2009; Veltmeyer et al., 2006; Weber et al., 2005)[2]. Galletly et al. (2001) also found significantly delayed N2 latency while updating tone stimuli in PTSD compared to controls. These studies have typically found such ERP alterations at midline electrode sites, along with altered performance measures that indicated reduced functioning of working memory updating (longer reaction time and

[1] P3b amplitude reduction to non-targets in PTSD versus controls was at trend level in Galletly et al. (2001).
[2] Despite variation in naming conventions across these studies for the working memory updating component, the current thesis refers to this as P3b for consistency and because observed components conform to the temporal and topographic characteristics described above for P3b.

more omission errors in PTSD than controls). As such, reduced P3b amplitude and increased N2 latency on the 1-back task may be indicators of poorer working memory updating and supporting stimulus discrimination processes. In particular, as P3b amplitude reflects working memory updating (Donchin, 1981; Donchin & Coles, 1988), the size of which is positively associated with the extent of allocated cognitive resources (Nieuwenhuis et al., 2005; Polich, 2007), this reduced P3b amplitude in PTSD may reflect reduced allocation of cognitive resources to working memory updating (Veltmeyer et al., 2009; Weber et al., 2005). Also, such ERP alterations may suggest degraded functioning in the frontal and posterior brain areas thought to contribute to these ERPs (Folstein & ven Petten, 2008; Hartikainen & Knight, 2003; Lenartowicz et al., 2010; Linden, 2005; Nieuwenhuis et al 2005; Patel & Azzam, 2005; Polich, 2003, 2007; Polich & Criado, 2006; Weber et al., 2005). Such findings converge with research that has found reduced P3b amplitude and delayed N2 latency in PTSD compared to controls on tasks of attentional processing, such as the oddball paradigm (Boudarene & Timsit-Berthier, 1997; Charles et al., 1995; Felmingham et al., 2002; McFarlane et al., 1993) (but see Kimble, Kaloupek, Kaufman, & Deldin, 2000).

1.10.3 Reduced neural functioning during working memory updating as a cognitive cost of PTSD phenomenology

The cognitive cost hypothesis of reduced working memory functioning in PTSD would predict an association between increased PTSD symptom severity and poorer neural functioning during working memory processing. Correlational findings are in line with this hypothesis. For example, an inverse association between re-experiencing symptom severity in PTSD and P3b amplitude has been observed during working memory updating (Weber et al., 2005). Also, Weber et al. (2005) observed P3b amplitude was inversely related to avoidance symptoms. These authors interpreted these

findings as "...evidence that intrusion and avoidance are related to withdrawal of working memory resources from stimulus information processing..." (p. 40). Complementing this, PTSD re-experiencing score was positively correlated with P3 latency to non-target stimuli on a sustained attention task (a continuous performance task) (Shucard, McCabe, & Szymanski, 2008), suggesting increased re-experiencing severity was associated with reduced speed of cognitive resource allocation for stimulus processing (as per Polich, 2003). It is emphasised that this was not a working memory task and that the observed non-target P3 was likely a P3a (Shucard et al., 2008), thus not reflective of working memory updating. However, these authors speculated that increased P3a latency in that study reflected generally delayed processing of stimuli. As such, their findings are aligned with the proposal that PTSD phenomena can adversely affect cognitive processing.

Recent fMRI findings on operation of the default mode network (DMN) in PTSD are relevant here. The DMN is a network of brain regions including posterior cingulate cortex (PCC), precuneus, posterior lateral cortices and ventromedial and dorsomedial PFC, active when an individual is not engaged in goal-directed behaviour (Gusnard & Raichle, 2001; Koch et al., 2010; Raichle et al., 2001). DMN activity likely reflects self-referential and contemplative processing, and stimulus-independent thought (Gusnard & Raichle, 2001; Mason et al., 2007). Both suppression of DMN activity and activation of task-relevant areas reflect allocation of attentional resources, which enable adequate cognitive task performance, including working memory (Bluhm et al., 2010; Fransson, 2006; Sambataro et al., 2010). Furthermore, instability in the DMN may reduce cognitive resource availability for task-relevant processing and interfere with processing in task-relevant neural areas, thereby degrading working memory processing (Sambataro et al., 2010; Sonuga-Barke & Castellanos, 2007). DMN instability has been

observed in PTSD at rest in the form of reduced functional connectivity between a PCC/precuneus region and other DMN areas compared to healthy controls (Bluhm et al., 2009). Also, compared to healthy controls, individuals with PTSD were unable to adequately disengage the DMN and engage an executive control network when required to switch to a working memory updating task from a passive viewing fixation task (Daniels et al., 2010). Importantly, DMN instability at rest in acutely traumatised individuals is related to current PTSD symptom severity (Lanius, Bluhm, et al., 2010). One possibility is that disturbed DMN functioning in PTSD may be associated with the cognitive cost that PTSD symptomatology may impose on working memory processing.

It is noted that some ERP and fMRI-based PTSD studies failed to find significant associations between neural measures of working memory updating and PTSD symptomatology (Moores et al., 2008; Veltmeyer et al., 2009). In part, this may reflect an impact of accompanying depressive symptoms (see Section 1.12.2 below), or heterogeneity in PTSD symptom profile, which can vary over time (McFarlane, 2000) and/or by PTSD subtype (e.g., the dissociative subtype versus the re-experiencing/hyperaroused subtype) (Lanius et al., 2006; Lanius, Vermetten, et al., 2010).

1.11 Working memory and treatment outcome

Cognitive behavioural therapy (CBT) is the psychological treatment of choice for PTSD and is commonly applied (Bisson & Andrew, 2007; Foa, Keane, Friedman, & Cohen, 2008; Mendes, Marcelo Feijó, Paula, Cristiane de Medeiros, & Jair de Jesus, 2008). Though this is an effective treatment, a substantial proportion (30-50%) of PTSD patients do not achieve clinically significant improvement (Bradley, Greene, Russ, Dutra, & Westen, 2005). Importantly, CBT requires sufficient cognitive resources in

order to engage in the extinction learning and cognitive restructuring elements that form part of this treatment. Sufficient working memory capacity is proposed as a critical enabler here (Brewin & Beaton, 2002; Brewin & Smart, 2005; LeDoux, 2002; Vasterling & Verfaellie, 2009). As such, reduced functioning of working memory and supporting neural processing may limit the ability of PTSD patients to benefit from CBT.

Understanding the neural mechanisms of response to psychological intervention for anxiety disorders may contribute to treatment refinement (Linden, 2006). Work to date has indicated that greater fear-related activity in ventral limbic areas prior to treatment predicts a poorer PTSD response to CBT (Bryant, Felmingham, et al., 2008). Further, better verbal memory in PTSD is also predictive of better response to CBT (Wild & Gur, 2008). However, the association between PTSD response to such treatment and neural markers of working memory functioning is yet to be examined. Such investigation is warranted as it may contribute to treatment refinement and improvement of current treatment response rates.

1.12 Potential influences on reduced working memory updating in PTSD

There are two outstanding issues in the current working memory literature in PTSD that may be important confounds in the current findings. These are the potential impact of trauma exposure itself and accompanying depressive symptoms on working memory functioning in PTSD. These issues warrant examination and empirical investigation to determine the extent to which working memory decrements and associated neural functioning can be attributed specifically to PTSD symptoms. Examining the potential contribution of psychotropic medication use is also warranted.

1.12.1 The impact of trauma exposure

PTSD researchers have noted the utility of including both trauma-exposed non-PTSD and non-trauma-exposed control groups in neurocognitive research to distinguish the contribution of trauma exposure from that of PTSD diagnosis (Brewin, 2008; Duke & Vasterling, 2005; Kimble et al., 2000; Kimble, Fleming, Bandy, & Zambetti, 2010; Kimble et al., 2009). This is especially important given findings that reduced concentration can occur following trauma in the absence of PTSD (Foa, Riggs, & Gershuny, 1995), and that combat deployment has been associated with decline on measures of sustained attention, learning and memory, independent of PTSD symptoms (Vasterling et al., 2006). Moreover, previous research has shown that trauma exposure is associated with reduced grey matter volume in areas such as PFC, ACC and hippocampus in non-PTSD trauma-exposed individuals compared to those not exposed to trauma (Ganzel, Kim, Glover, & Temple, 2008; Karl, Schaefer, et al., 2006). This suggests an independent association between trauma exposure and brain integrity. Also, Kimble et al. (2010) found that reduced P3b amplitude to oddball targets was not associated with PTSD symptom severity after accounting for trauma history when both of these factors were measured continuously in a sample of military cadets. Indeed, meta-analysis has suggested that trauma-exposure is associated with reduced P3b amplitude to oddball targets independent of PTSD (except at electrode site Pz) (Karl, Malta, & Maercker, 2006). However, trauma-exposed control groups have not been used in previous behavioural and neurofunctional investigation (either ERP or fMRI) of working memory updating in PTSD (Clark et al., 2001, 2003; Galletly et al., 2001; Galletly et al., 2008; Moores et al., 2008; Veltmeyer et al., 2006; Veltmeyer et al., 2009; Weber et al., 2005), making it unclear whether the associated decrements observed in PTSD are due to PTSD pathology or are a non-specific effect of trauma exposure.

Comparing PTSD groups to trauma-exposed and non-trauma-exposed controls would help elucidate the specific impact of PTSD on behavioural and neural measures of working memory functioning, as distinct from that of trauma exposure.

1.12.2 The impact of depressive symptoms

It is also unclear whether the working memory-related data reported above are specific to PTSD or are more attributable to the accompanying depressive symptoms. Major Depressive Disorder (MDD) and PTSD have significant diagnostic overlap and are highly comorbid, with PTSD-depression comorbidity estimates of 13-65% (Creamer, Burgess, & McFarlane, 2001; Jeon et al., 2007; Kessler, Chiu, Demler, & Walters, 2005; Pietrzak, Goldstein, Southwick, & Grant; Sareen et al., 2007). Parallel to findings in PTSD, studies examining cognitive functioning in depression have found worse performance on neuropsychological and laboratory-based tasks of working memory functioning compared to controls (Austin, Mitchell, & Goodwin, 2001; Landro, Stiles, & Sletvold, 2001; Rose & Ebmeier, 2006) (but see Matsuo et al., 2006). Complementing this, reduced P3b amplitude to oddball targets has also been observed in MDD (Kawasaki, Tanaka, Wang, Hokama, & Hiramatsu, 2004; Kemp et al., 2009; Kemp et al., 2010). Further, depressed individuals have shown worse working memory updating performance than controls during n-back and wordlist-based working memory updating tasks (Harvey et al., 2004; Joormann & Gotlib, 2008). Interestingly, Joorman & Gotlib (2008) observed that reduced working memory updating performance in MDD associated with greater self-reported rumination, consistent with research on the detrimental impact of cognitive load on working memory (see Section 1.7.3).

Functional neuroimaging studies have indicated dysfunction in the same brain areas during working memory processing in MDD as in PTSD. Individuals with current or

remitted MDD have exhibited dysfunction in dlPFC, ACC and IPC during verbal and spatial n-back tasks, evident as lower neural efficiency (i.e., activation in these areas increases in a manner that was absent in healthy controls in order to maintain a stable level of working memory performance) (Fitzgerald et al., 2008; Harvey et al., 2005; Matsuo et al., 2006; Walsh et al., 2007). Also, reduced functional connectivity between dlPFC and IPC, and aberrant ACC functional connectivity with prefrontal regions, during working memory processing has been observed in individuals with MDD compared to healthy controls (Vasic, Lohr, Steinbrink, Martin, & Wolf, 2008). Moreover, reduced resting state metabolism in dlPFC and ACC in MDD has been commonly reported (Dougherty & Rauch, 2007). Additionally, theoretical brain models of MDD overlap with areas of apparent working memory updating-related brain dysfunction in PTSD. For example, Mayberg (1997, 2003) has proposed that failed integration between dorsal and ventral brain areas contribute to depressive symptomatology, with the dlPFC, ACC and IPC as key nodes of dysfunction.

Despite PTSD groups having higher levels of depressive symptoms than control groups in some studies examining PTSD working memory functioning (Weber et al., 2005), this differential has not always been accounted for (Clark et al., 2001; Galletly et al., 2001; Galletly et al., 2008; Veltmeyer et al., 2006; Veltmeyer et al., 2009; Weber et al., 2005). Importantly, studies examining attentional processing in the oddball task or probing working memory with standardised neuropsychological tasks have shown that accounting for depressive symptoms removes group differences initially attributed to PTSD diagnosis (Metzger, Orr, Lasko, & Pitman, 1997) and PTSD symptoms (Brandes et al., 2002). Thus, there is a need to control for the effect of depressive symptomatology in examining PTSD working memory functioning.

1.12.3 The impact of psychotropic medication

There is evidence that use of psychotropic medication (hereafter referred to as medication use), such as benzodiazepines and tricyclic antidepressants, can degrade working memory and concentration in normals (Mintzer & Griffiths, 2007; Stein & Strickland, 1998). Further, medication use may affect supporting brain functioning. For example, sub-acute administration of selective serotonergic reuptake inhibitors (SSRI) in normals has been associated with reduced ACC activity during working memory processing (though no more than ±1 sd unit) (Rose, Simonotto, Spencer, & Ebmeier, 2006). This converges with work that has indicated that SSRIs reduced resting-state ACC metabolism in depressive patients (Drevets, Bogers, & Raichle, 2002). Given the commonality of medication use in PTSD (Lanius, Brewin, et al., 2010), it is possible that medication factors may contribute to alterations in behavioural and neural measures of working memory.

Although the impact of medication use on behavioural and ERP measures of working memory in PTSD has received some examination, findings are somewhat mixed. Veltmeyer et al. (2009) found only PTSD patients using medication exhibited reduced P3b amplitude (at trend level) compared to controls. There was no significant difference in this measure between unmedicated PTSD patients and controls. This is consistent with a previous finding that showed that covarying for medication status diluted P3b amplitude differences between PTSD and controls from significance to trend level (Veltmeyer et al., 2006). Such findings suggest that medication use may contribute to degraded working memory processing in PTSD. Contrasting this are findings of P3b amplitude reduction and increased omission errors and reaction time in unmedicated PTSD groups compared to controls on working memory updating tasks (Galletly et al., 2001; Galletly et al., 2008; Weber et al., 2005). Additionally, Metzger et

al. (1997) observed a normalising effect of medication use on P3b amplitude alterations to oddball targets in PTSD. Also, reduced activity in dlPFC, ACC and IPC has been observed during working memory updating in PTSD after controlling for medication use (Moores et al., 2008) (but see Section 3.1 for a discussion of this finding). Moreover, degraded performance on neuropsychological working memory tasks has been observed in PTSD relative to controls independent of medication use (Vasterling et al., 2002). Also, Gilbertson et al. (2006) found worse performance on neuropsychological working memory tasks in non-trauma-exposed individuals at higher familial risk for PTSD compared to those with lower familial risk for PTSD, independent of medication use. In part, some of this inconsistency in findings may reflect differences in samples, tasks and the potential impact of depressive symptoms and trauma exposure. In general, the impact of medication use on brain functioning within PTSD is largely unknown (Friedman, 2005; Lanius, Brewin, et al., 2010). Notably, Lanius, Brewin et al. (2010) recommend recruitment, and separate analyses, of both medicated and unmedicated participants in neuroimaging research to allow generalisation of findings to the larger PTSD population. Thus, including both medicated and unmedicated PTSD participants may help clarify aspects of working memory reduction specific to PTSD, while enabling generalisation of results to the broader PTSD population.

1.13 Overview of the current research program

1.13.1 Aim

The overarching aim of the current research program was to better characterise the neural bases of degraded working memory updating in PTSD, whilst controlling for the effects of trauma exposure, accompanying depressive symptoms and medication use.

Both ERPs and fMRI, in conjunction with a 1-back working memory updating task, were utilised to measure working memory updating-related brain functioning in PTSD, as per previous research (Clark et al., 2001; Clark et al., 2003; Daniels et al., 2010; Galletly et al., 2001; Galletly et al., 2008; Moores et al., 2008; Weber et al., 2005;Veltmeyer et al., 2006; Veltmeyer et al., 2009). Importantly, the effect of trauma exposure was controlled in the study design by utilising two control groups – a trauma-exposed non-PTSD (TE) control group and a non-trauma-exposed (NTE) control group. This enabled the identification of characteristics that were either specific to PTSD (observable in significant differences between the PTSD group compared to both control groups) or a generalised impact of trauma exposure (observable as a difference between the NTE control group compared to both the PTSD and TE groups, in the absence of a difference between the latter two groups). Comorbid depressive symptoms were controlled statistically. To distinguish the contribution of medication use from PTSD in working memory updating alterations, analyses in each study were performed using a full PTSD sample (composed of unmedicated participants and medication users) and were repeated using an unmedicated PTSD subsample (with age- and gender-matched controls where appropriate).

1.13.2 The 1-back working memory updating task

The current studies utilised the 1-back version of the n-back task, adapted from Veltmeyer et al. (2006) and Veltmeyer et al. (2009). In this task letters are presented sequentially. This task requires a button press when a letter is the same as that immediately prior (the target). Critically, it requires target identity to be updated whenever a letter (the non-target) is dissimilar to that immediately prior. Thus, it is the processing of non-targets that is of primary interest to examining working memory updating (Weber et al., 2005).

It is acknowledged that the construct validity and reliability of the n-back task as a measure of working memory has been debated (Jaeggi et al., 2010; Jarrold & Towse, 2006; Kane, Conway, Miura, & Colflesh, 2007). However, the 1-back version of this task was selected for the following reasons: (a) it has been used in previous ERP and imaging-based working memory research in PTSD (Clark et al., 2003; Moores et al., 2008; Veltmeyer et al., 2006; Veltmeyer et al., 2009); (b) the brain regions activated during n-back performance overlap with those activated during other working memory tasks (Clark et al., 2000; Collette & van der Linden, 2002; Collette et al., 2007; Osaka et al., 2003; Owen et al., 2005; Postle, 2006; Smith & Jonides, 1999; Wager & Smith, 2003); (c) it predominantly taps the updating process (Harvey et al., 2004), which is a relatively circumscribed process within working memory (Miyake et al., 2000), and important to broader working memory functioning (as outlined in Section 1.7.2); and (d) it allows relatively precise operational definition of updating (Miyake et al., 2000).

1.13.3 Operational definition of working memory updating

Working memory updating was operationally defined as memory that is required for one trial of the 1-back task, but not for subsequent trials (adapted from Dalley, Cardinal, & Robbins, 2004). This was measured by accuracy of responding (number of omission errors and number of commission errors) and reaction time following presentation of a stimulus requiring a response (target stimuli). Updating-related brain functioning was measured by examining ERPs and fMRI blood oxygenation level dependent (BOLD) signal in response to presentation of non-target stimuli as these stimuli prompt the need to update the item held in mind in order to successfully perform the task (Weber et al., 2005). Target stimuli function to index task compliance and performance (Weber et al., 2005). As such, functional brain measures to target stimuli were not analysed and are

not presented in the current studies as the focus of the current research program was on working memory updating.

1.13.4 Overview of current studies

Study 1 (Chapter 2) utilised the 1-back task along with ERPs to determine the specificity of previously observed reductions in P3b amplitude and increases in N2 latency to PTSD, independent of trauma exposure and depressive symptoms. It also examined the association between PTSD symptom clusters and measures of working memory updating, as per the cognitive cost hypothesis of reduced working memory functioning as a result of PTSD.

Study 2 (Chapter 3) utilised fMRI with the 1-back task to determine which of the previously observed areas of working memory-related hypofunction in PTSD (i.e., dlPFC, ACC and IPC) are specific to the disorder, independent of the effects of trauma exposure and depressive symptoms. Study 2 also examined the association between brain activation in the aforementioned areas and PTSD symptom clusters.

Finally, Study 3 (Chapter 4) aimed to examine how activation in these specific brain areas predicted outcome following treatment, again independent of depressive symptoms.

All studies examined the impact of medication use by conducting all analyses with a full PTSD sample (composed of medication-free participants and medication users), which were repeated using an unmedicated PTSD subsample (and age- and gender-matched controls where required by analyses).

2. Chapter 2: Behavioural and ERP-based measures of working memory updating in PTSD

2.1 Introduction

Findings of reduced P3b amplitude and increased N2 latency in PTSD during stimulus discrimination tasks, such as the oddball task (Boudarene & Timsit-Berthier, 1997; Charles et al., 1995; Felmingham et al., 2002; McFarlane et al., 1993; Metzger et al., 2009; Metzger et al., 1997; Stanford et al., 2001; Veltmeyer et al., 2005), have implications for working memory functioning in PTSD. Consistent with theoretical views that P3b amplitude reflects allocation of cognitive resources to working memory updating (Donchin, 1981; Donchin & Coles, 1988), P3b amplitude reductions may indicate degradation of such processes. Indeed, McFarlane et al. (1993) proposed that the P3b amplitude reductions to oddball targets in PTSD may represent "a reduced impact of attended stimuli on working memory structures," (p. 317). Accordingly, ERPs have been utilised to examine the temporal dynamics of working memory updating in PTSD.

Examination of working memory updating in PTSD has utilised variants of the verbal 1-back working memory updating paradigm, which requires continuous updating of target identity. Utilising verbal and tone-based variants of this task in both auditory and visual modalities, Clark and colleagues have found reduced parietal P3b amplitude to non-target stimuli in PTSD compared to non-traumatised controls (Clark, McFarlane, et al., 2001; Galletly et al., 2001; Galletly et al., 2008; Veltmeyer et al., 2009; Veltmeyer et al., 2006; Weber et al., 2005)[3]. These ERP alterations were accompanied by increased reaction time and omission errors, suggestive of degraded working

[3] P3b amplitude reduction to non-targets in PTSD versus controls was at trend level in Galletly et al. (2001)

memory updating in PTSD relative to controls. Also, Galletly et al. (2001) found prolonged N2 latency in a tone-based version of this task, which was interpreted as increasing difficulty with stimulus discrimination. These alterations in N2 latency and P3b amplitude during working memory updating tasks in PTSD converge with similar observations in individuals with PTSD while processing target stimuli in stimulus discrimination tasks, such as the oddball paradigm (Felmingham et al., 2002; McFarlane et al., 1993; Metzger et al., 2009; Veltmeyer et al., 2005), and is consistent with the idea of generally degraded information processing in individuals with PTSD (e.g., Buckley et al., 2000). Behavioural and ERP findings of degraded working memory updating in PTSD are consistent with the cognitive cost hypothesis. Correlational findings are also in line with this hypothesis. For example, re-experiencing symptom severity is inversely related to P3b amplitude during working memory updating in PTSD, coincident with poorer task performance compared to controls (Weber et al., 2005). Moreover, Weber et al. (2005) found that avoidance was inversely related to P3b amplitude (in the presence of hyperarousal symptoms). This was interpreted as evidence for an association between re-experiencing and avoidance and withdrawal of processing resources from working memory updating. This is consistent with proposals that P3b amplitude is positively related to the extent of cognitive resources allocated for working memory updating (Donchin, 1981; Donchin & Coles, 1988). Furthermore, Veltmeyer et al. (2009) found a positive relationship between number of omission errors during working memory processing and re-experiencing symptom severity (though this only occurred in medicated PTSD participants and these authors failed to find associations between P3b measures and PTSD symptoms). It is emphasised that causation cannot be inferred from these correlational findings.

However, as outlined in Section 1.12, ERP research on working memory processing in PTSD has not controlled for the potential confounds of the trauma exposure itself and depressive symptoms that accompany PTSD. Moreover, there have been variable findings on the impact of medication upon behavioural and ERP measures of working memory updating in PTSD.

In view of the above, the current study utilised a previously employed working memory updating paradigm (Veltmeyer et al., 2006; Veltmeyer et al., 2009), while measuring behavioural performance and temporal aspects brain function (via ERP analysis) in individuals with PTSD compared to trauma-exposed (TE) and non-trauma-exposed (NTE) control groups. As per previous research (Clark, McFarlane, et al., 2001; Galletly et al., 2001; Galletly et al., 2008; Veltmeyer et al., 2009; Veltmeyer et al., 2006; Weber et al., 2005)[4], it was hypothesised that the PTSD group would have reduced working memory updating functioning on behavioural measures (increased reaction time, omission errors, and commission errors) and ERP measures (reduced P3b amplitude and prolonged N2 latency to non-target stimuli). To examine if findings were consistent with the cognitive cost hypothesis, the association between PTSD symptom clusters and robust alterations in measures of working memory updating was also investigated. The impact of depressive symptoms was examined by conducting all analyses prior to, and again after, accounting for the contribution of depressive symptoms. To control for any potential impact of medication use, all analyses were repeated in a subsample of medication-free PTSD participants (with matched trauma-exposed and non-trauma-exposed controls for group difference analyses).

[4] Some of these studies found degraded PTSD working memory performance on only one behavioural measure.

2.2 Methods

2.2.1 Participants

Eighty nine participants were recruited from the Traumatic Stress Clinic, Westmead Hospital, and Department of Psychology, Flinders University, in collaboration with the Brain Resource International Database (BRID) (Gordon, Cooper, Rennie, Hermens, & Williams, 2005). PTSD diagnosis was determined according to DSM-IV criteria (APA, 2000) by use of the Composite International Diagnostic Interview (CIDI) (Kessler & Üstün, 2004). Participants were divided into three groups on the basis of their CIDI responses: those who met diagnostic criteria for PTSD (PTSD; n=30), those who were exposed to a Criterion A stressor but did not meet PTSD diagnosis or report any Criterion B re-experiencing symptoms (trauma-exposed (TE) control; n=29), and healthy controls who had not been exposed to a Criterion A stressor (non-trauma-exposed (NTE) control; n=30). No participants in the TE control group met criteria for avoidance. All groups were matched for age, gender and years of education. Depressive symptoms were assessed with the 21-item version of the Depression Anxiety Stress Scales (DASS) (Lovibond & Lovibond, 1995). To determine severity and frequency of PTSD symptoms in participants with PTSD, the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995) was administered. Participants were excluded if they had: current substance abuse or alcohol abuse or dependence, history of traumatic brain injury or neurological condition, a significant medical condition, or history of psychosis (determined by clinical interview). All TE and NTE control participants were primary English speakers and were free from personal and familial history of mental illness, physical brain injury, traumatic brain injury, history of stroke or other neurological disorder, history of serious medical condition, history of drug addiction and heavy marijuana and alcohol use, or history of genetic disorders. Of the PTSD group, seven

participants reported current or previous MDD, determined on the basis of semi-structured interview with the CIDI. Within the PTSD group, 10 people were using selective serotonin reuptake inhibitors, two were people using serotonin-noradrenergic reuptake inhibitors, three were using tricyclic anti-depressants, one was using tetracyclics, one was using benzodiazepines, one was using acetylcholinesterase inhibitors, and one was using anti-epileptics. Prior to testing, all participants abstained from alcohol for at least 24 hours and abstained from nicotine and caffeine for at least four hours.

2.2.2 Procedure

2.2.2.1 Research protocol

Written informed consent was provided by all participants prior to participation. On the day of testing, participants completed questionnaires detailing demographic information and medication status. They also completed the DASS questionnaire. An initial assessment was performed by clinical psychologists to diagnose PTSD and depression using the CIDI; the PTSD group was also administered the CAPS. After collection of demographic and clinical information, participants completed the working memory updating task. Prior to task commencement, participants' visual acuity was checked by means of a Snellen chart.

2.2.2.2 Task

The current study used a 1-back working memory updating task employed in previous ERP studies (Veltmeyer et al., 2006; Veltmeyer et al., 2009). Participants viewed a series of white letters (B, C, D, G) presented sequentially on a black background for 200 ms with a constant 2500ms interstimulus interval. There were 85

stimuli in total: 65 non-target letters (those letters that were not repetitions of previous letters), and 20 pseudo-randomly presented target letters (i.e., repetitions of the previous letter). Participants were instructed to simultaneously press two buttons (with the index finger of each hand) to the second of two consecutive presentations of the same letter (targets) (see Figure 2.1). Speed and accuracy of responding were equally emphasised. Non-target stimuli did not require a button-press response. Participants were provided with brief practice prior to data collection to ensure they understood task requirements. Participants performed the task while seated in a sound- and light-attenuated room. Standardised pre-recorded task instructions were delivered to participants through a computer via headphones. Letter stimuli were presented via computer monitor.

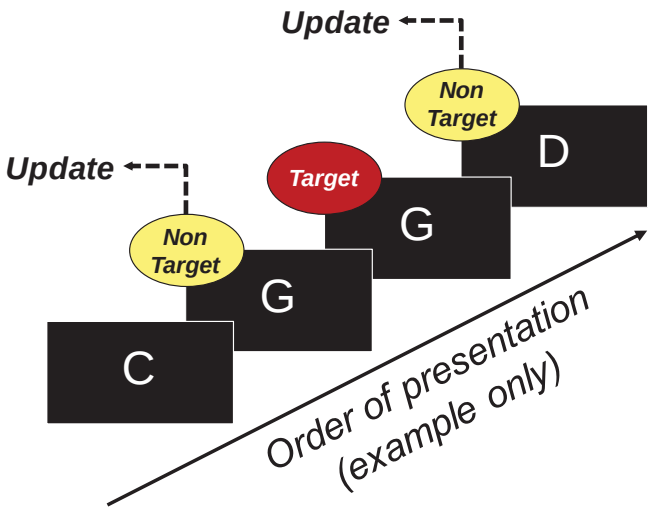

Figure 2.1. Example order of letter presentation during the 1-back task.

In this example the first G is a non-target and prompts updating as it is dissimilar to the preceding stimulus (C), but requires no button press response. The second G is a target as it is a repeat of the preceding stimulus and requires a button press response. The D is a non-target and requires updating as it is dissimilar to the preceding letter (G) and requires a button press response.

2.2.3 Apparatus

2.2.3.1 EEG recording

A QuickCap (Neuroscan) was fitted to each participant to record brain activity. This recorded data from 26 scalp sites (Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz, O2) according to the 10-20 International system. Subsequent analyses were limited to data recorded at midline sites (Fz, Cz, Pz) in accordance with previous research (Galletly et al., 2001; Felmingham et al., 2002; Metzger et al., 2002; Shucard et al., 2008). Hemispheric effects were not investigated following variable laterality of ERPs and associated neural measures with respect to working memory updating to non-target stimuli in PTSD (Galletly et al., 2001; Veltmeyer et al., 2009; Weber et al., 2005). Data were recorded relative to the average of linked mastoids (A1 and A2 electrode sites). Horizontal eye movements were recorded via electrodes 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded via electrodes 3mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid. Skin resistance was maintained at < 5 kOhms. Scalp and electro-oculogram (EOG) potentials were amplified and digitized through a continuous recording system (NuAmps, SCAN 4.3) with a 500 Hz sampling rate. The system had a frequency response of DC to 100 Hz, above which there was attenuation by 40dB per decade. Data were EOG corrected offline, following the procedure used by Gratton, Coles and Donchin (1983).

2.2.4 ERP analysis

ERP data to non-target stimuli were extracted from the electroencephalogram (EEG) recorded during the working memory updating task. Each epoch was filtered with a low-pass Tukey filter with a bandwidth of 25 Hz and a cutoff of 35Hz, above which no

signal was passed. Single trials were then averaged to generate ERPs at each recording site. N2 and P3b latency and amplitude peaks were selected from a window of -300 to 700 ms, relative to a pre-stimulus baseline average from -300 ms to 0 ms, at each recording site. A specified algorithm preselected N2 and P3b latency and amplitude peaks. N2 was defined as the peak negative amplitude between 160 to 400ms post-stimulus (as per Galletly et al., 2001), and P3b was defined as the peak positive amplitude between 300 to 700ms post-stimulus (as per Veltmeyer et al., 2009). Peak data were visually inspected and corrected by hand when required.

2.2.5 Data analysis

2.2.5.1 General analysis – group difference analyses

Behavioural data were analysed using univariate analysis of variance (ANOVA). In each ANOVA, Group (PTSD, TE control, NTE control) was the predictor. Separate ANOVAs were run for reaction time, number of omission errors (the number of failures to button press on presentation of target stimuli), and number of commission errors (the number of button presses made in response to non-target stimuli during the task), each of which acted as the outcome variable.

ERP data were inspected prior to analysis for artifact-rejected missing values and outliers (2.5 standard deviations from the group mean). Artifact-rejected missing values (1.0%) and outliers (2.6%) were replaced with the group mean for the relevant variable. ERP data were analysed with a series of repeated measures ANOVAs with Group (PTSD, TE control, NTE control) as the between-subjects factor and Site (Fz, Cz, Pz) as the within-subjects factor. Separate repeated-measures ANOVAs were conducted for amplitude and latency data for the N2 and P3b components in response to non-targets, each of which acted as the outcome variable. Violations of sphericity were corrected

with the Greenhouse-Geisser epsilon. Follow-up tests were conducted using the Sidak correction for multiple comparisons.

2.2.5.2 Impact of depressive symptoms – group difference analyses

To determine the contribution of depressive symptoms to group differences on behavioural measures, hierarchical ANOVAs were conducted separately for each of the outcome variables – reaction time, number of omission errors, and number of commission errors. To determine the contribution of depressive symptoms to group differences on ERP responses, hierarchical repeated measures ANOVAs were conducted separately for each of the outcome variables – N2 amplitude, N2 latency, P3b amplitude, P3b latency. Site (Fz, Cz, Pz) was the within-subjects factor for analyses of ERPs. In each hierarchical analysis, the continuous depressive symptom predictor variable (DASS depressive symptom score) was entered prior to the Group (PTSD, TE control, NTE control) predictor variable.

2.2.5.3 Impact of psychotropic medication – group difference analyses

To control for the influence of psychotropic medication, each analysis was repeated on a subsample of PTSD participants who were not using psychotropic medication, with age-and gender-matched participants from each control group (n=11 per group).

2.2.5.4 Correlational analyses

Separate simple linear regression analyses were performed to examine the association between each PTSD symptom cluster (Criterion B re-experiencing, Criterion C avoidance, Criterion D arousal) and each behavioural and ERP measure that showed robust alterations in PTSD in the group difference analyses (i.e., those that were significantly altered in the PTSD group after controlling for depressive symptoms

and/or medication use). This was done to minimise type I error. The statistical threshold was Bonferroni adjusted accordingly. In each case, CAPS cluster score was the predictor variable and the behavioural or ERP measure of interest was the outcome variable. To examine the impact of depressive symptoms on the association between each CAPS cluster score and each selected measure of working memory updating in participants with PTSD, hierarchical regression analyses were conducted in which the continuous depressive symptom predictor variable (DASS depressive symptom score) was entered before the CAPS cluster predictor of interest. In each case, the behavioural or ERP measure of interest was the outcome variable.

As for examination of group differences, these simple linear and hierarchical regression analyses were repeated in an unmedicated PTSD subsample.

2.3 Results

2.3.1 Demographic and clinical data

Demographic and clinical data for all participants are summarized in Table 2.1. The TE control group had significantly longer time since trauma than the PTSD group [$F(1,57)=10.91$, $p=0.002$] [5]. The PTSD group recorded higher depressive symptom scores on the DASS than both control groups [$F(2,86)=71.59$, $p<0.001$].

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[5] For all group difference analyses that follow, parallel analyses were also performed to control for the difference in years since trauma between the PTSD and TE control groups. These used a subsample of participants from the PTSD and TE control groups matched for years post-trauma, with age- and gender-matched NTE controls (n=13 per group). These analyses did not significantly alter the main pattern of findings.

Table 2.1: Demographic and clinical data for participant groups

	PTSD - full sample	**PTSD - unmedicated sample**	**Trauma-exposed Controls**	**Non-Trauma exposed Controls**
n	30	11	29	30
Male	14	5	14	14
Female	16	6	15	16
Age$^{\Delta}$	44.9 (10.6)	45.7 (12.6)	47.10 (13.2)	43.77 (11.6)
Handedness – left	1	0	0	2
Handedness – right	29	11	29	28
Years of education$^{\Delta}$	13.1 (3.1)	14 (3.0)	14.8 (2.6)	13.6 (2.6)
Years since trauma$^{\Delta}$	10.0 (11.1)	12.8 (13.6)	21.1 (14.6)	-
DASS-D score$^{\Delta}$	20.9 (11.6)	18.7 (12.6)	1.6 (2.2)	2.5 (3.0)
CAPS B re-experiencing score$^{\Delta\dagger}$	21.7 (7.2)	18.1 (3.8)	-	-
CAPS C avoidance score$^{\Delta\dagger}$	35.8 (7.1)	33.9 (7.2)	-	-
CAPS D arousal score$^{\Delta\dagger}$	26.6 (6.5)	21.4 (7.0)	-	-
Trauma Type				
Motor vehicle / industrial acc.	2	-	2	-
Assault	19	9	17	-
Fire / natural disaster	2	-	3	-
Witness injury or killing	7	2	7	-

Δ Group means (standard deviations appear in parentheses); † CAPS cluster score represents sum of PTSD symptom frequency and intensity scores; DASS-D – DASS depressive symptom scale; acc – accident.

2.3.2 Behavioural performance data

Table 2.2 presents a summary of the behavioural data and associated group difference findings. There was an overall difference in average reaction time to target stimuli across groups [$F(2,86)=6.41$, $p=0.003$] and in number of omission errors [$F(2,86)=5.14$, $p=0.008$]. Tukey post-hoc tests showed that, compared to both control groups, the PTSD group exhibited significantly longer average reaction time to target letters [TE control: $p=0.008$; NTE control: $p=0.007$] and made significantly more omission errors [TE control: $p=0.010$; NTE control: $p=0.039$]. There were no significant

group differences on commission errors [$F(2,86)=0.60$, $p=0.6$]. Control groups were equivalent on all measures.

Table 2.2: Behavioural data for all groups and significance of omnibus between-group differences before controlling for depressive symptoms and after controlling for depressive symptoms

	PTSD - Full Sample	TE Controls	NTE Controls	Before Controlling for Depressive Symptoms	Controlling for Depressive Symptoms
Reaction time $^{\Delta}$	580.1 (126.9)	497.4 (84.2)	497.7 (91.6)	**†@	ns
No. omission errors $^{\Delta}$	1.9 (-1.6)	0.9 (-0.9)	1.0 (-1.3)	**†@	ns
No. commission errors$^{\Delta}$	0.4 (-0.6)	0.4 (-0.5)	0.6 (-0.6)	ns	ns

Δ Group means (standard deviations appear in parentheses); ns=not significant; **$p<0.01$; † indicates PTSD group > TE control group; @ indicates PTSD group > NTE control group; reaction time in ms.

2.3.3 ERP data

2.3.3.1 Site main effect

The N2 component had a frontal maximum [$F(1.61, 138.06)=14.81$, $p<0.001$], and peak latency increased towards the anterior of the brain [$F(2,172)=88.83$, $p<0.001$]. The P3b was maximal parietally [$F(1.73,148.63)=77.80$, $p<0.001$]. There was no difference in P3b latency between sites [$F(2,172)=2.32$, $p=0.101$].

2.3.3.2 Group main effect

Table 2.3 presents mean values for amplitude and latency of non-target ERP components for each group, along with a summary of associated omnibus group difference findings. Representative waveforms for each group to non-target stimuli are presented in Figure 2.2. The following data refer to ERPs averaged across midline sites (Fz, Cz, Pz). There were no group differences on N2 amplitude [$F(2,86)=0.53$, $p=0.590$]. There was a significant overall difference in N2 latency across groups [$F(2,86)=5.98$, $p=0.004$], with the PTSD group showing significantly longer N2 latency than the NTE control group ($p=0.004$) and a trend towards a longer N2 latency than the TE control group ($p=0.052$). Groups differed significantly on P3b amplitude [$F(2,86)=8.88$, $p<0.001$] with the PTSD group having significantly smaller P3b amplitude than both the TE control group ($p<0.001$) and the NTE control group ($p=0.019$). This effect was significant at all midline sites, except for the parietal site where the PTSD group showed smaller P3b amplitude than the TE control group only, as shown by a significant Group x Site interaction [$F(3.46,148.63)=3.88$, $p=0.007$]. There were no significant group differences on P3b latency [$F(2,86)=0.20$, $p=0.821$]. The control groups were equivalent on all measures.

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Table 2.3: Mean amplitude and latency for N2 and P3b ERPs (all groups) and significance of omnibus between-group differences before controlling for depressive symptoms and after controlling for depressive symptoms

	PTSD	TE Controls	NTE Controls	Before Controlling for Depressive Symptoms	Controlling for Depressive Symptoms
N2 Amplitude				ns	ns
Fz	-1.0 (-3.9)	0.1 (-3.8)	-0.7 (-3.6)		
Cz	0.6 (-3.5)	1.6 (-3.4)	0.4 (-2.8)		
Pz	1.1 (-3.3)	1.3 (-3.8)	1.5 (-2.8)		
N2 Latency				**@	ns
Fz	243.1 (33.2)	233.7 (33.9)	225.9 (-30.9)		
Cz	235.6 (32.3)	218.4 (22.8)	210.1 (-24.0)		
Pz	203.6 (27.3)	188.0 (21.7)	188.5 (-22.6)		
P3b Amplitude				***#^	ns
Fz	5.3 (-2.9)	10.1 (-5.1)	9.2 (-4.3)		
Cz	7.9 (-3.7)	14.0 (-6.5)	11.3 (-4.8)		
Pz	10.7 (-4.0)	13.8 (-5.8)	12.8 (-4.8)		
P3b Latency				ns	ns
Fz	416.1 (49.8)	404.9 (50.5)	407.2 (-48.6)		
Cz	408.6 (52.1)	408.0 (46.7)	394.2 (-57.5)		
Pz	393.9 (63.9)	400.3 (49.2)	396.6 (-63.6)		

ns=not significant; ** $p<0.01$; *** $p<0.001$; @ indicates PTSD group > NTE control group; # indicates PTSD group < TE group; ^ indicates PTSD group < NTE control group; amplitude in μV; latency in ms; standard deviation in parentheses.

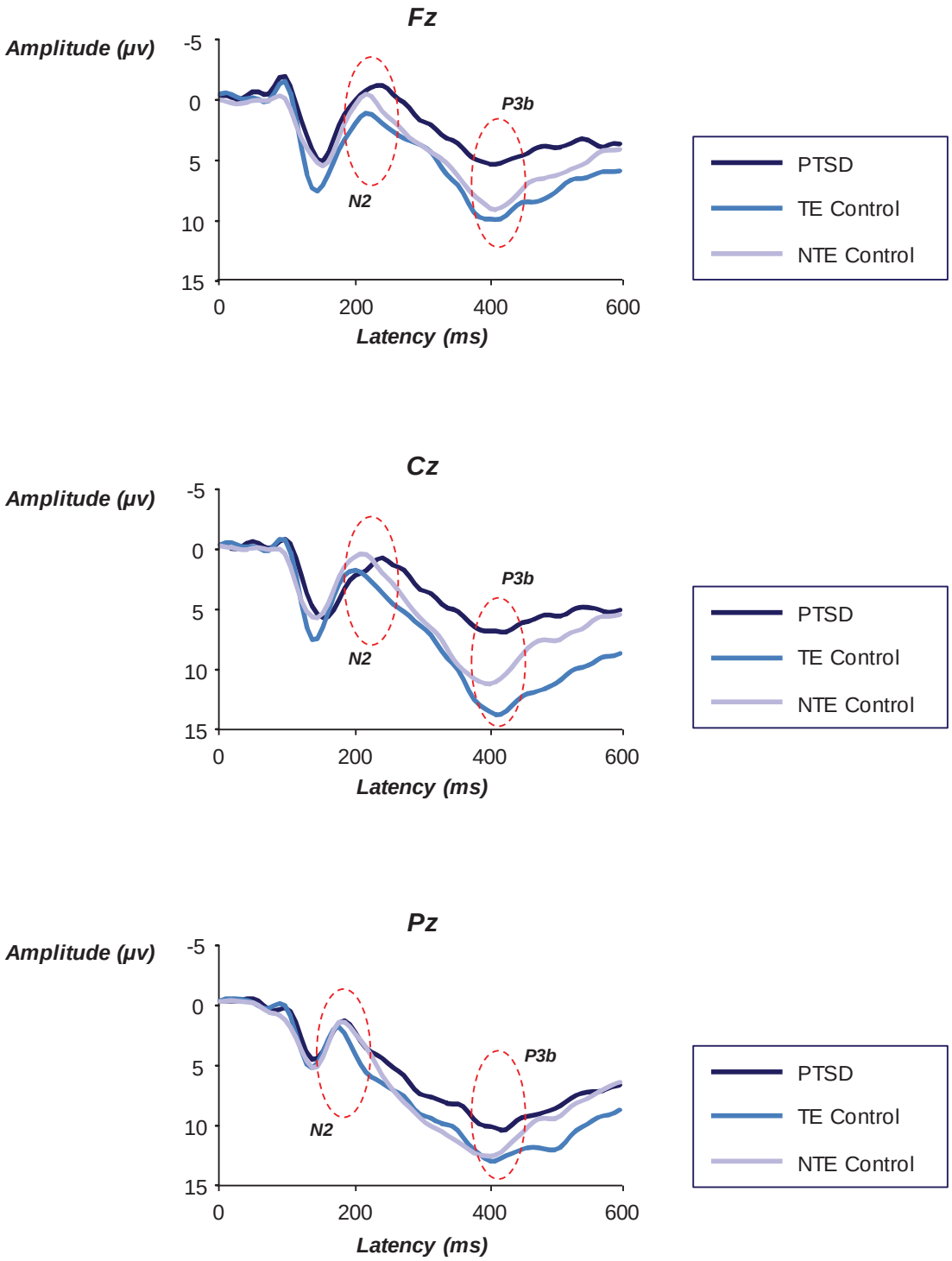

Figure 2.2. Group average ERP waveforms for the PTSD group, TE and NTE control groups to non-target stimuli at midline sites (full sample).

2.3.3.3 Group differences after controlling for depressive symptoms

After controlling for depressive symptoms, there were no significant group differences on any of the behavioural measures [Reaction time: $F(1,86)=1.95$, $p=0.166$; Omission errors: $F(1,86)<0.01$, $p=0.983$; Commission errors: $F(1,86)=3.06$, $p=0.084$] (see Table 2.2), nor on amplitude or latency measures of N2 [Amplitude: $F(2,68)=0.353$, $p<0.704$; Latency: $F(2,68)=0.798$, $p<0.455$], P3b [Amplitude: $F(2,68)=1.411$, $p<0.251$; Latency: $F(2,68)=0.167$, $p<0.846$] (see Table 2.3).

2.3.4 Control analysis – behavioural and ERP data in the unmedicated subsample

2.3.4.1 Behavioural data

Departing from the previous analyses, there were no group differences on any of the behavioural measures prior to controlling for depressive symptoms [reaction time: $F(2,30)=0.73$, $p=0.487$; omission errors: $F(2,30)=1.30$, $p=0.289$; commission errors: $F(2,30)=0.20$, $p=0.818$]. These remained non-significant after controlling for depressive symptoms.

2.3.4.2 Non-target ERP data

Site effects[6] to non-target stimuli were similar to previous analyses for each of N2 and P3b. N2 was maximal frontally [$F(1.516,45.483)=9.48$, $p=0.001$], with peak latency increasing in towards the anterior of the brain [$F(2,60)=29.55$, $p<0.001$]. P3b showed a parietal maximum [$F(1.553,46.59)=36.60$, $p<0.001$]. There was no between-group difference for N2 latency [$F(2,30)=2.96$, $p=0.067$]. P3b amplitude was significantly different across groups [$F(2,30)=4.73$, $p=0.016$], with the PTSD group showing significantly lower amplitude than the TE control group ($p=0.025$). All these group

[6] Site effects are for analyses prior to controlling for depressive symptoms.

difference findings are those before controlling for depressive symptoms. Contrary to the previous analyses, the group difference on P3b amplitude was maintained after accounting for depressive symptoms [$F(2,21)=10.97$, $p=0.001$]. There were no other significant group differences on ERP measures after controlling for depressive symptoms.

2.3.5 Associations between measures of working memory updating and CAPS cluster scores

The association between CAPS cluster scores and behavioural measures was not examined as there was no alteration on any behavioural measure in the PTSD group relative to the control groups, independent of depressive symptoms or medication use.

Regarding the association between ERP measures and CAPS cluster scores, only the P3b component was selected for analyses as there were robust alterations in this component in PTSD relative to the control groups after controlling for depressive symptoms and medication use. The latency and amplitude of the P3b were examined separately for their association with each CAPS cluster score. Accordingly, a statistical threshold of $p<0.025$ (Bonferroni adjusted) was used. These relationships were only examined at site Pz as this was where P3b was maximal. This was done to limit the number of analyses and minimize type I errors. Within the full PTSD group, greater re-experiencing symptom score was associated with increased P3b latency prior to accounting for depressive symptoms ($r(20)=0.505$, $p=0.023$). However, after accounting for depressive symptoms, this association was only marginally significant ($pr(17)=0.48$, $p=0.036$)[7]. The relationship between re-experiencing symptoms and P3b latency to non-targets both before and after accounting for depressive symptoms is presented in Figure

[7] *pr* represents partial correlation.

2.3. There were no other significant associations between CAPS cluster scores or P3b measures in the full PTSD sample, either before or after controlling for depressive symptom score.

There were no significant associations between CAPS cluster scores and P3b measures within the unmedicated PTSD subsample, either before or after partialling out depressive symptoms.

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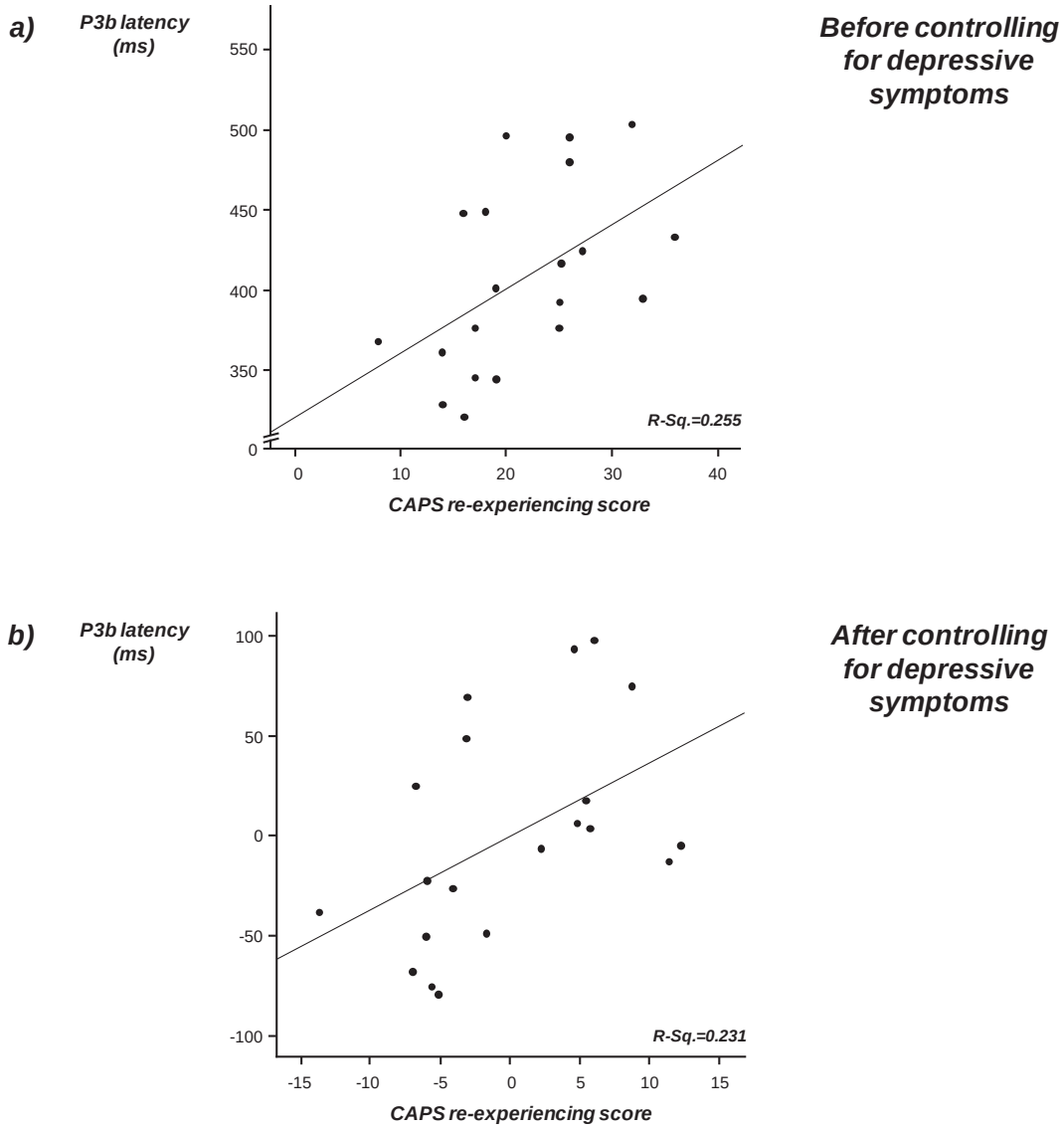

Figure 2.3. Plots of the association between CAPS re-experiencing score and P3b latency to non-target stimuli for the full PTSD group before and after controlling for depressive symptoms.

a) Bivariate plot before accounting for depressive symptoms; b) Partial regression plot represents the relationship between CAPS re-experiencing score and P3b latency after partialling out the contribution of DASS depressive symptom score (i.e., residuals of regressing P3b latency against CAPS re-experiencing score versus residuals of regressing DASS depressive symptom score against CAPS re-experiencing score).

2.4 Discussion

This study provides novel evidence on the impact of PTSD and depressive symptoms on working memory updating, measured both by task performance and ERPs. The key findings of this study were that deficits in working memory updating on behavioural and ERP measures in PTSD were largely removed after controlling for depressive symptoms. However, this impact of depressive symptoms was not evident after controlling for medication use, suggesting that the effect of depressive symptoms may be influenced by medicated PTSD participants.

Behaviourally, the PTSD group showed significantly increased reaction time to targets and increased errors of omission than both control groups. There were no group differences in the number of commission errors, a finding consistent with previous research (Galletly et al., 2001; Veltmeyer et al., 2009; Veltmeyer et al., 2006; Weber et al., 2005). This may reflect low task difficulty shown in the low mean number of commission errors across groups.

Consistent with behavioural findings, group differences on ERPs indicated reduced cognitive processing of stimuli associated with working memory updating in the PTSD group relative to both control groups. Of primary interest in the current task were ERPs to non-target stimuli, as these are the stimuli which probe working memory updating (Weber et al., 2005). As predicted, the PTSD group showed longer N2 latency and reduced P3b amplitude than both control groups (with a trend level N2 latency difference between the PTSD and the TE control groups).

Findings of degraded task performance and ERPs in PTSD relative to controls converge with previous examination of such measures during working memory updating. Prolonged N2 latency and reduced P3b amplitude in PTSD relative to controls

have been observed on 1-back working memory tasks and on affectively neutral auditory oddball tasks (Clark et al., 2001; Felmingham et al., 2002; Galletly et al., 2001; Galletly et al., 2008; McFarlane et al., 1993; Veltmeyer et al., 2006; Veltmeyer et al., 2009; Weber et al., 2005). This is consistent with the proposal that individuals with PTSD have depleted cognitive resources to deploy for tasks requiring cognitive engagement (Aikins et al., 2009; Brewin & Beaton, 2002; Brewin & Holmes, 2003).

The current findings extend previous research in two ways. First, by including a trauma-exposed control group, degraded behavioural performance and ERP responses were shown to be specific to PTSD, rather than being a generalized effect of trauma exposure. This was indicated by the pattern of results where the PTSD group was significantly different from both control groups on behavioural and ERP measures, while there was no significant difference on these measures between the control groups. The current PTSD-specific P3b amplitude reduction during working memory updating accords with meta-analytic findings that suggested PTSD-specific P3b amplitude reduction (at the parietal electrode site Pz) during attentional processing of neutral stimuli in the oddball task (Karl, Malta, et al., 2006).

A contribution of PTSD diagnosis to degraded P3b measures of cognitive processing independent of trauma exposure appears to contrast with findings from Kimble et al. (2010). During an auditory oddball task, these authors found that trauma history predicted reduced P3b amplitude to target stimuli in a sample of military cadets. Further, they noted that PTSD symptom scores did not contribute to P3b reductions after considering the contribution of trauma history[8]. In part, differences between current findings and those of Kimble et al. (2010) may reflect differences in analysis

[8] Kimble et al. (2010) noted the same pattern with respect to P3a amplitude reductions to novel distractors, in which the contribution of dissociative symptoms was also significant.

approach. Whereas the current study examined the relative contribution of trauma exposure and PTSD in a categorical manner, Kimble et al. (2010) adopted a dimensional approach, measuring trauma history and PTSD symptoms as continuous variables. In general, such dimensional approaches may be more stable and reliable than categorical measurement (Watson, 2009). As such, replication of current findings using a dimensional approach to measurement of trauma exposure and PTSD symptoms is required. This would help clarify the robustness or otherwise of current findings.

Second, these group differences on behavioural and ERP measures were removed after controlling for depressive symptoms. This raises the possibility that the observed differences may be accounted for by differences in level of depressive symptoms rather than PTSD per se. However, such a conclusion is tempered by the pattern of findings in the analyses using the unmedicated PTSD subsample (discussed further below). The effect of depressive symptoms accords with previous depression research. For example, individuals with MDD perform more poorly on neuropsychological tasks of working memory compared to controls (Austin et al., 2001; Landro et al., 2001; Rose & Ebmeier, 2006) and have reduced P3b amplitude to oddball targets (Kawasaki et al. 2004; Kemp, Pe Benito et al. 2009; Kemp et al., 2009), similar to performance in PTSD (Charles et al., 1995; Felmingham et al., 2002; McFarlane et al., 1993; Metzger et al., 2009). The current findings suggest that the depressive symptoms within PTSD may be contributing substantially to the degraded cognition observed in this disorder. This proposal accords with previous evidence that controlling for depressive symptoms removed group differences in cognitive performance originally accounted for by PTSD symptoms and diagnosis (Brandes et al., 2002; Metzger et al., 1997). That depressive symptoms play a role in degraded cognitive functioning within PTSD is consistent with confirmatory factor analyses that have found a unique dysphoric factor within PTSD,

strongly related to depressive symptoms (Grant, Beck, Marques, Palyo, & Clapp, 2008; Simms, Watson, & Doebbelling, 2002).

Greater PTSD re-experiencing symptom intensity was associated with longer P3b latency during working memory updating in the full PTSD sample. This suggests that greater re-experiencing was associated with slower allocation of cognitive resources to working memory updating in PTSD (Katayama & Polich, 1998; Polich, 2003). Such an association between increased re-experiencing symptoms and disrupted cognitive processing in PTSD is consistent with previous findings on tasks of memory, attention and working memory updating in PTSD (Vasterling et al., 1998; Weber et al., 2005). It also accords with the cognitive cost hypothesis that cognitive load associated with intrusive and distressing thoughts and emotions depletes resources for cognitive functioning (Aikins et al., 2009; Brewin & Smart, 2005). Note that the association between P3b latency and re-experiencing fell to marginal significance after accounting for depressive symptoms. This may suggest that depressive symptoms contributed to this relationship, a possibility consistent with the occurrence of intrusive phenomena within depression (Brewin, 2008; Christopher & MacDonald, 2005). However, this may have also represented a type II error as a result of low power from the small sample (n=11). Notably, the strength of the relationship between re-experiencing and P3b latency was similar both before and after controlling for depressive symptoms. Replication with a larger sample is required to better understand the impact of depressive symptoms on the relationship between re-experiencing and ERP measures of working memory updating in PTSD.

Analyses using the unmedicated PTSD subsample showed no group differences on any behavioural or ERP measures with the exception of reduced P3b amplitude in the PTSD group compared to trauma-exposed controls. This was true in the absence of

controlling for depressive symptoms. This suggests that medication use may have contributed to some of the altered working memory updating measures in the full PTSD sample. Notably, analysis with the unmedicated PTSD subsample *prior* to controlling for depressive symptoms yielded a pattern of findings strikingly similar to those found *after* accounting for depressive symptoms in the full sample analysis. That is, after controlling for medication use (by removing medicated PTSD participants), there were no group differences on behavioural measures or N2 latency. Thus, it may be that the medicated PTSD participants were driving the apparent contribution of depressive symptoms to reduced working memory updating observed in the full PTSD sample. In line with this, it is noted that 15 of the 19 medicated PTSD participants were using anti-depressant medication. Moreover, the reduced P3b amplitude within the unmedicated PTSD subsample persisted after controlling for depressive symptoms. This suggests no contribution of depressive symptoms to reduced P3b amplitude in PTSD in the absence of medication use. Finally, the unmedicated PTSD group failed to show the positive correlation between re-experiencing symptoms and P3b latency observed in the full sample analysis. While this may suggest that medication use contributed to this relationship in the full PTSD sample, a type II error cannot be ruled out due to low power from the small size (n=7) of this subsample. Re-examination with a larger sample is required to clarify the impact of medication on this relationship and its general contribution to working memory updating in PTSD, independent of depressive symptoms.

The current findings on the impact of medication contrast those of Veltmeyer et al. (2009) who observed reaction time increases and (trend-level) P3b amplitude reductions during working memory updating in medicated, but not unmedicated, PTSD patients. It also contrasts Metzger et al.'s (1997) finding of a normalising effect of psychotropic

medication use on P3b amplitude during oddball target detection in PTSD. Such discrepancy may reflect P3b amplitude fluctuation over time (Neylan et al., 2003). It may also reflect possible differences between these studies in types of medications used, possible use of concurrent psychotherapy, and trauma severity, all of which warrant consideration in determining the contribution of medication use to PTSD brain function (Lanius, Brewin, et al., 2010). Variation in other factors such as duration of medication use, dose, and time since trauma may also contribute. These factors should be carefully controlled in future ERP research on working memory updating in PTSD.

Several methodological limitations require acknowledgement. First, depressive symptoms were indexed as a continuous self-report measure rather than as a binary diagnostic variable. There is evidence for both a dimensional and categorical impact of depression on ERP markers of attention (Kemp et al., 2009). Given the comorbidity between PTSD and major depression (Creamer et al., 2001; Jeon et al., 2007; Kessler et al., 2005; Pietrzak et al.; Sareen et al., 2007), it may have been greater comorbidity in the PTSD group than the controls that explained the impact of depressive symptoms, rather than greater expression of depressive symptoms per se. However, continuous symptom measurement of depressive symptoms is more stable and reliable than categorical approaches (Watson, 2009). Comparison of clinically depressed and non-depressed PTSD groups to control groups would help elucidate the contribution of depression to degraded working memory updating in PTSD. Second, the PTSD participants experienced their traumatic events more recently than the TE control participants. Time since trauma should be carefully matched in future studies. Moreover, larger sample sizes and careful control for medication use could better elucidate the impact of medication on the temporal dynamics of working memory processing in PTSD. This could help distinguish the impact of medication use from that

of depressive symptoms. Additionally, it is possible that limiting analyses to single electrode sites for each brain region (frontal, central, parietal) allowed entry of spurious effects at single electrode sites. Future ERP research could overcome this by averaging signals across an electrode "montage" composed of multiple electrode sites for each brain region, as recommended by Kimble et al. (2010). Also, the working memory updating task did not contain a baseline condition in which target identity remained constant, and so target updating processes could not be isolated from target storage processes. However, it is emphasised that the direction of reduced P3b amplitude and increased N2 latency in PTSD observed in the current study (prior to accounting for depressive symptoms) is consistent with previous research in which such a baseline condition was used (Galletly et al., 2001; Galletly et al., 2008; Weber et al., 2005; Veltmeyer, 2006, 2009). Finally, the CAPS was not administered to TE control subjects. Thus, the relationship between PTSD symptomatology and working memory updating in a subsyndromal sample could not be examined.

2.5 Summary and implications for the research program

In summary, the present findings suggest that working memory updating is specifically degraded within PTSD, independent of the generalised effect of trauma exposure. This was evidenced by degraded task performance and alteration of temporal measures of brain function. This may be partly attributable to the depressive symptoms that exist within this diagnosis, though other aspects of PTSD symptomatology, such as re-experiencing, may also contribute. Moreover, psychotropic medication use also appears to contribute to some, though not all, of the reduced working memory functioning in PTSD. Importantly, medication use may contribute to the apparent effect of depressive symptoms.

While this study provided evidence for altered temporal dynamics of working memory updating in PTSD, identifying the specific brain loci that contribute to degraded working memory processing requires use of imaging techniques with higher spatial resolution than ERPs. Such investigation may shed light on the disturbed neural networks which underlie degraded working memory processing in PTSD. This is investigated in the study outlined in the next chapter.

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3. Chapter 3: An fMRI-Based Analysis of Working Memory in PTSD

3.1 Introduction

While a broad network of brain regions supports normal working memory functioning, imaging and lesion-based work in normals has indicated a central role for the dorsolateral prefrontal cortex (dlPFC), anterior cingulate (ACC) and inferior parietal cortex (IPC) (Conway et al., 2007; Jonides et al., 2005; Postle, 2006; Scheibel & Levin, 2004; Smith & Jonides, 1999). The aim of the current study was to determine the functional integrity of these areas during working memory updating in PTSD, whilst controlling for the independent contribution of trauma exposure, depressive symptoms and medication use.

Previous functional neuroimaging research has found that individuals with PTSD exhibited reduced activity in dlPFC, IPC and ACC accompanied by increased reaction times and omission errors compared to non-traumatised control groups during word- or letter-based 1-back working memory updating tasks (Clark, McFarlane, et al., 2001; Clark et al., 2003; Moores et al., 2008). Moreover, the pattern of functional connectivity between frontal and parietal areas during working memory updating appears disrupted in PTSD compared to those without the disorder, suggesting network-related disruption in addition to disruption of isolated neural loci (Shaw et al., 2009; Shaw et al., 2002). However, there does not appear to be a consistent pattern of laterality effects (for a more detailed review, see Section 1.10.1).

The reduced functioning of brain areas in PTSD observed during working memory updating may represent a cognitive cost of the disorder. This is in line with proposals that PTSD symptoms and ongoing attempts to process traumatic thoughts absorb processing capacity, which results in degraded cognition (Aikins et al., 2009; Nixon et

al., 2009), and working memory in particular (Brewin & Beaton, 2002). Indeed, PTSD symptom severity is inversely related to performance on neuropsychological tasks of working memory (Brandes et al., 2002; Gilbertson et al., 2006; Sutker et al., 1995) that ostensibly require integrity of frontoparietal functioning (Koenen et al., 2001; Vasterling et al., 1998). Furthermore, efforts to suppress traumatic thoughts (a Criterion C avoidance symptom) may tax functioning in dlPFC, ACC and IPC, all of which are activated during thought suppression in normals (Anderson et al., 2004; Butler & James, 2010)[9]. These areas are sensitive to cognitive load, and show sustained reductions in working-memory related activity after cognitive load limits are exceeded (Callicott et al., 1999; Yun et al., 2010). As such, reduced functioning in these areas may be the neural corollary of the reduced cognitive processing capacity thought to result from ongoing suppression of traumatic thoughts in PTSD (Aikins et al., 2009; Brewin & Beaton, 2002:Brewin, 2005 #1431; Shipherd & Beck, 1999).

Building on the premise that PTSD symptomatology may degrade brain functioning in working memory-related brain areas, inverse relationships between PTSD symptom severity and activation in brain regions that support working memory could be expected. The only study to have investigated this (Moores et al., 2008) failed to find any such associations. However, that study did not control for the potential contribution of depressive symptoms. Also, due to low sample size, the potential impact of using medication was controlled by means of analysis of covariance. This approach has been criticised in cases where there is non-random group assignment and the covariate (in that case, medication status) is systematically related to the grouping variable (in that case, PTSD diagnostic status) (Miller & Chapman, 2001). Given the non-random assignment to PTSD or non-PTSD groups and the commonality of medication use in

[9] These researchers utilised memory suppression paradigms, considered a proxy for thought suppression as it requires suppression of unwanted material from consciousness.

PTSD (Lanius, Brewin, et al., 2010), these factors may have affected results in that study. Therefore, it is important to investigate the association between PTSD symptom severity and working memory updating-related brain functioning, while controlling for the potential impact of medication use in an experimental, rather than statistical, manner. Additionally, as noted in Section 1.12, the potential independent contributions of trauma exposure and depressive symptoms have not been examined in functional neuroimaging studies of working memory in PTSD.

The current study was designed to better characterise the nature of brain functioning during working memory updating in PTSD in key regions of the working memory network. This was examined using a version of the 1-back working memory updating task used in Study 1, modified for use with fMRI. Importantly, experimental and statistical control was incorporated to isolate findings to PTSD, independent of the potential contributions of trauma exposure, depressive symptoms and use of medication. In keeping with the research presented above, it was hypothesised that people with PTSD would exhibit less brain activation in each of dlPFC, ACC and IPC during working memory updating compared to both trauma-exposed and non-trauma-exposed control groups. Furthermore, it was expected that severity of each PTSD symptom cluster (re-experiencing, avoidance and arousal) would be inversely related to brain activation in each of these brain regions, following the proposal that such reduced brain activation may be a cognitive cost of resource-depleting symptoms of PTSD. To examine the impact of depressive symptoms, all analyses were conducted prior to, and again after, accounting for the contribution of depressive symptoms. To control for any potential impact of medication use, all analyses were repeated in a subsample of medication-free PTSD participants and matched trauma-exposed and non-trauma-exposed controls.

3.2 Methods

3.2.1 Participants

Fifty five participants were recruited from the Traumatic Stress Clinic, Westmead Hospital, in collaboration with the Brain Resource International Database (BRID) (Gordon et al., 2005). PTSD diagnosis was determined according to DSM-IV criteria (APA, 2000) by use of the Composite International Diagnostic Interview (CIDI) (Kessler & Üstün, 2004). Participants were divided into three groups on the basis of their CIDI responses: those who met diagnostic criteria for PTSD (PTSD; n=20), those who were exposed to a Criterion A stressor but did not meet PTSD diagnosis or report any re-experiencing symptoms (trauma-exposed (TE) control; n=18), and healthy controls who had not been exposed to a Criterion A stressor (non-trauma-exposed (NTE) control; n=17). No participants in the TE control group met full criteria for avoidance. All groups were matched for age and gender. Depressive symptoms were assessed with the 21-item version of the Depression Anxiety Stress Scales (DASS) (Lovibond & Lovibond, 1995). The Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995) was administered to participants with PTSD to determine severity and frequency of PTSD symptoms. Participants were excluded if they had: current substance abuse or alcohol abuse or dependence, history of traumatic brain injury or neurological condition, a significant medical condition, or history of psychosis (determined by clinical interview). All control participants were primary English speakers and were free from personal and familial history of mental illness, physical brain injury, traumatic brain injury, history of stroke or other neurological disorder, history of serious medical condition, history of drug addiction and heavy marijuana and alcohol use, or history of genetic disorders. Of the PTSD group, 12 participants reported current MDD. Within the PTSD group, six people were using SSRIs, and one person

was using tetracyclics. Prior to testing, all participants abstained from alcohol for at least 24 hours and abstained from nicotine and caffeine for at least 4 hours.

3.2.2 Procedure

3.2.2.1 Research protocol

Written informed consent was provided by all participants prior to participation. On the day of testing, participants completed questionnaires detailing demographic information and medication status. They also completed the DASS questionnaire. An initial assessment was performed by clinical psychologists to diagnose PTSD and depression using the CIDI. Participants with PTSD were then administered the CAPS. After clinical and demographic information was collected, participants completed the working memory updating task. Prior to task commencement, participants' visual acuity was checked by means of a Snellen chart.

3.2.2.2 Task

The current study employed a 1-back working memory updating task as used by Veltmeyer et al. (2006) and Veltmeyer et al. (2009), adapted for use with fMRI. Participants viewed a series of letters (B, C, D, G) presented sequentially in two different colours (yellow, white) on a black background. The task required participants to simultaneously press a response box with their left and right thumbs (to counterbalance for motor activity) to the second of two consecutive presentations of the same letter (targets) when presented in yellow. These were the only stimuli requiring a response. Participants were instructed to make no response to letters presented in white (white letters served as a 'perceptual' baseline). Speed and accuracy of responding were equally emphasised. There were 125 stimuli in total, of which 20 were target letters

(i.e., repetitions of the previous yellow letter). In yellow, there were 21 Bs, 22 Cs, 21 Ds and 21 Gs. In white, there were 10 of each letter. Letters were presented in a pseudorandom sequence with the constraint that targets were separated from each other by at least two letters. Participants were provided with brief practice prior to data collection to ensure they understood task requirements. Standardised pre-recorded task instructions were delivered to participants via MRI-compatible headphones.

3.2.3 Apparatus

3.2.3.1 fMRI recording

Participants were placed on the MRI scanner table and viewed a headcoil-mounted mirror, onto which visual stimuli were projected from an external projector (Sanyo Pro-X Multivers, Tokyo, Japan), 60 Hz maximum. Each stimulus was presented for 200ms, with an inter-stimulus interval (ISI) of 3500ms (a slight increase over the ISI of Study 1, to allow for the repetition time (TR) of fMRI). Stimulus onset was jittered by ±200ms within the ISI to ensure that stimulus onset did not always coincide with the same brain slice starting position. An event-related design was used. In total, 128 T2-weighted volumes (including 3 dummy measurements) depicting blood oxygenation level dependent (BOLD) signal were acquired with a VISION Plus 1.5 Tesla scanner (Siemens Magnetom) fitted with a standard quadrature headcoil. T2-weighted images were acquired using an echoplanar sequence, comprised of 15 non-contiguous 6mm slices (with 10% gap) acquired parallel to the intercommissural (AC-PC) line, with time to echo (TE) = 40ms, flip angle 90-degree; field of view (FOV) 24 cm x 24 cm^2, matrix size 128 x 128.

3.2.4 fMRI analysis

Prior to data analysis, all T2-weighted volumes were realigned, unwarped and spatially normalized into standardized Montreal Neurological Institute (MNI) space and smoothed with a Gaussian kernel (full width at half maximum 8mm). Image preprocessing and statistical analysis for fMRI data were performed using the Statistical Parametric Mapping program (SPM2, Wellcome Department of Neurology, London, UK). A hemodynamic-convolved event-related model was created, corresponding to target and non-target stimuli, and a high-pass filter (cut-off period of 128 seconds) was applied to remove low frequency fluctuation in the BOLD signal. To determine activation related to working memory updating, BOLD signal change was analysed for the contrast of yellow non-target stimuli minus passively viewed white stimuli for each participant. This contrast was used for all analyses.

3.2.5 Data analysis

3.2.5.1 General analysis

Behavioural data (reaction time to targets, omission errors, commission errors) were recorded but were not usable due to a computer malfunction. As such, these data were not analysed and are not reported.

Group differences in fMRI BOLD signal response (hereafter referred to as activation) to working memory non-targets were conducted using a series of ANOVAs with Group (PTSD, TE, NTE) as the between-subjects factor and activation to non-target stimuli as the outcome variable. These were run separately for each significant voxel cluster. Note that only two groups could be examined per ANOVA due to a constraint of the analysis software. Preliminary ANOVA revealed significantly more

years post-trauma in the TE control group than the PTSD group [$F(1,36)=4.11$, $p=0.050$]. Therefore, years post-trauma was controlled in analyses in which differences between these groups were examined.

Group difference analyses were conducted on both a region of interest (ROI) basis to test a priori hypotheses, and a whole brain basis to identify significant activation in non-hypothesised areas. For ROI analyses, a statistical threshold of $p<0.01$ (small volume corrected) was used with an extent threshold of greater than or equal to 15 voxels. The WFU Pickatlas (Version 1.02, Wake Forest University, School of Medicine Winston-Salem, North Carolina) was used to conduct the ROI analysis (Maldjian, Laurienti, Kraft, & Burdette, 2003; Tzourio-Mazoyer et al., 2002). ROI analysis was conducted on three regions, informed by current hypotheses – dlPFC (including lateral portions of the superior frontal gyrus (excluding internal medial superior frontal grey matter) as defined by Tzourio-Mazoyer et al. (2002) and middle frontal gyrus as defined by Petrides and Pandya (1999); ACC (limited rostrally by the paracingulate sulcus and caudally by the white matter of the corpus callosum, and including the subgenual cingulate region (BA25); and IPC (including the supragmarginal gyrus (SMG) and angular gyrus, and a superior portion of cortex between the SMG and angular gyrus). These analyses were conducted in each hemisphere, giving a total of six regions. As per Bryant et al. (Bryant et al., 2005), ACC subregions were operationally defined as follows: rostral ACC was the area of ACC anterior and superior to the genu of the corpus callosum with posterior boundary y = + 30mm; dorsal ACC was the area of ACC superior to the corpus callosum between y = 0 and +30mm; and ventral ACC was the ACC subregion inferior to the genu of the corpus callosum, below z = 0mm. For whole brain analyses, a statistical threshold of $p<0.001$ uncorrected for multiple comparisons was used with an extent threshold of greater than or equal to 15 voxels.

For participants with PTSD, separate simple linear regression analyses were performed to examine the association between each PTSD symptom cluster (Criterion B re-experiencing, Criterion C avoidance, Criterion D arousal) and brain activation during working memory updating. In each analysis, CAPS cluster score was the predictor variable and activation to non-target stimuli was the outcome variable. Analyses were run separately for each significant voxel cluster. ROI analyses used a statistical threshold of $p<0.0083$ (Bonferroni corrected for multiple comparisons) and an extent threshold of greater than or equal to 15 contiguous voxels. For whole brain analyses, a statistical threshold of $p<0.001$ uncorrected for multiple comparisons was used, along with an extent threshold of greater than or equal to 15 voxels.

3.2.5.2 Impact of depressive symptoms

To determine the contribution of depressive symptoms to potential group differences in activation during working memory updating, each between-group analysis was repeated as a hierarchical regression model with group-averaged DASS depressive symptom score entered into the model as a continuous predictor before the Group variable. To index the association between each PTSD symptom cluster and brain activation during working memory updating after accounting for the contribution of depressive symptoms, hierarchical regression analyses were performed in which the continuous depressive symptom predictor variable (mean DASS depressive symptom score for the PTSD group) was entered before the CAPS cluster predictor of interest. Activation to non-target stimuli was the outcome variable in all analyses. Analyses were run separately for each significant voxel cluster.

3.2.5.3 Impact of medication

To control for the impact of medication on activation to non-targets, all between-groups and regression analyses above were repeated on a subsample of unmedicated individuals with PTSD (n=13), after removing PTSD participants (n=7) who were using medication. Group difference analyses used TE and NTE control samples (each n=13) matched for age and gender. The impact of comorbid depressive symptoms was examined in the same manner as in the full sample analysis.

3.3 Results

As noted in Section 1.13.3 only data associated with presentation of non-target stimuli are presented here, as these probe working memory updating. As Study 1 found that depressive symptoms accounted for the predominance of findings suggesting reduced working memory updating in PTSD, all data presented in this chapter are those conducted after accounting for the impact of depressive symptoms as this is of primary interest.

3.3.1 Demographic and clinical data

Demographic and clinical data are presented in Table 3.1. The PTSD group recorded significantly higher depressive symptoms on the DASS than both control groups [$F(2,52)=23.22$, $p<0.001$].

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Table 3.1: Demographic and clinical data for participant groups

	PTSD - full sample	**PTSD - unmedicated subsample**	**Trauma-exposed Controls**	**Non-Trauma exposed Controls**
n	20	13	18	17
Male	9	5	11	7
Female	11	8	7	10
Age$^{\Delta}$	37.1 (9.7)	36.3 (10.9)	32.8 (14.4)	31.1 (11.9)
Handedness – left	0	0	2	3
Handedness – right	20	13	16	14
Years of Education$^{\Delta}$	13.7 (2.5)	13.3 (2.8)	14.7 (2.6)	14.2 (4.6)
Years since trauma$^{\Delta *}$	5.4 (6.5)	4.8 (5.9)	10.7 (9.4)	-
DASS-D score$^{\Delta ***}$	21.0 (11.0)	19.5 (11.8)	5.8 (6.8)	4.8 (5.2)
CAPS B re-experiencing$^{\Delta}$†$^{@}$	21.0 (7.8)	20.2 (8.3)	-	-
CAPS C avoidance$^{\Delta}$†$^{@}$	29.9 (8.9)	31.3 (10.4)		
CAPS D arousal$^{\Delta}$†$^{@}$	25.4 (7.1)	24.2 (7.9)		
Trauma Type				
Motor vehicle / industrial acc.	6	2	4	-
Assault	12	11	7	-
Fire / natural disaster	-	-	6	-
Witness injury or killing	-	-	2	-

Δ Group means. Standard deviations appear in parentheses. $p \leq 0.05$*; $p \leq 0.001$***; † CAPS cluster score represents sum of PTSD symptom frequency and intensity scores; $^{@}$ CAPS data were unavailable for two participants at the time of analysis, therefore mean CAPS cluster scores and standard deviations for the full PTSD sample and the unmedicated PTSD subsample are based on n=18 and n=12, respectively; acc – accident.

3.3.2 Full sample analysis

3.3.2.1 Group difference analysis

The following activation differences refer to those observed during presentation of non-target stimuli. The location, voxel cluster size and statistical values for all significant between-group activation differences are presented in Table 3.2. On ROI analyses, compared to the TE control group, the PTSD group showed significantly less activation in dlPFC bilaterally and in left rostroventral ACC. Similarly, the PTSD group showed significantly less activation than the NTE control group in bilateral dlPFC. Compared to the NTE controls, the TE control group showed significantly greater activation in right dlPFC. See Figure 3.1 (*a* to *d*) for loci of peak activation differences between groups (ROI analyses).

On whole brain analysis the PTSD group showed significantly greater activation in right inferior orbitofrontal cortex (OFC), but significantly reduced activation in left superior medial frontal and left superior orbitofrontal regions than TE controls. The PTSD group also showed reduced activation compared to TE controls in left rostroventral ACC at the same location as found in the ROI analysis. There were no activation differences on whole brain analyses between the PTSD group and the NTE controls. The only activation difference between the control groups was greater activation in TE controls than NTE controls in the right dlPFC, in line with ROI analyses.

Table 3.2: Sites of peak activation differences between groups in the presence of working memory non-targets in the full sample after accounting for depressive symptoms (ROI and whole brain analyses)

Contrast, Brain region	Hemisphere	MNI coordinates x	y	z	Voxels	z	p
TE > PTSD							
Region of interest							
dlPFC	L	-16	52	10	236	3.28	0.001
	R	20	62	8	268	2.82	0.002
ACC	L	-14	42	-4	284	3.38	<0.001
Whole brain							
Frontal							
Sup.med. frontal	L	-6	54	12	69	3.57	<0.001
Superior OFC	L	-26	52	-4	21	3.49	<0.001
ACC	L	-14	42	-4	17	3.38	<0.001
PTSD > TE							
Region of interest	-	-	-	-	-	-	-
Whole brain							
Frontal							
Inferior OFC	R	46	36	-14	48	3.95	<0.001
NTE > PTSD							
Region of interest							
dlPFC	L	-22	56	12	205	3.27	0.001
	R	22	62	10	90	2.85	0.002
Whole brain	-	-	-	-	-	-	-
PTSD > NTE							
Region of interest	-	-	-	-	-	-	-
Whole brain	-	-	-	-	-	-	-
TE > NTE							
Region of interest							
dlPFC	R	26	46	46	233	2.96	0.002
Whole brain							
Frontal							
dlPFC	R	48	36	34	22	4.16	<0.001
NTE > TE							
Region of interest	-	-	-	-	-	-	-
Whole brain	-	-	-	-	-	-	-

dlPFC – dorsolateral prefrontal cortex; ACC – anterior cingulate cortex; IPC – inferior parietal cortex; OFC – orbitofrontal cortex Sup – superior; med – medial; OFC – orbitofrontal cortex; PTSD – PTSD sample; TE – trauma-exposed control; NTE – non-trauma-exposed control; L – left; R – right.

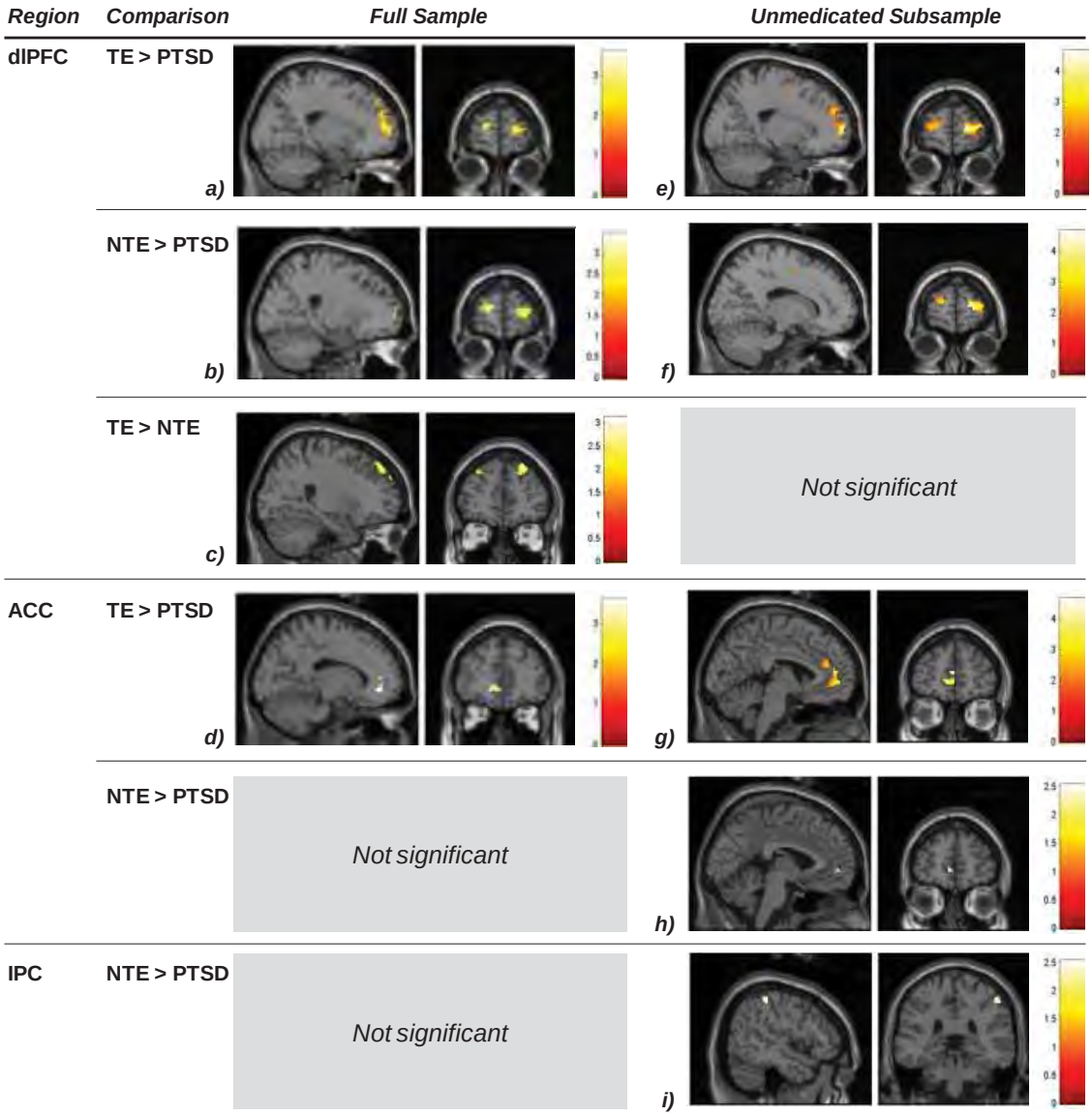

Figure 3.1. Sites of peak activation differences between participant groups during the working memory updating task after controlling for depressive symptoms (ROI analyses).

Regions of significant group difference in the full sample (a to d) and the unmedicated subsample (e to i). dlPFC – dorsolateral prefrontal cortex; ACC – anterior cingulate cortex; IPC – inferior parietal cortex; PTSD – PTSD sample: TE – trauma-exposed control; NTE – non-trauma-exposed control.

3.3.2.2 CAPS-BOLD associations

Outliers (values >2.5 sd from the mean) were removed to avoid erroneous influence on analyses. Outliers represented <1.7% of all values. Hierarchical regression analyses were based on a PTSD sample of n=18 as CAPS data were unavailable for two

participants at the time of analysis. As recommended by Tabachnick & Fidell (2007), the associations between areas of peak activation and each CAPS cluster score are presented as partial correlations (*pr*) as this reflects the unique association between these variables after removing the variance that both of these variables share with DASS depressive symptom score. Associated coordinates of peak activation to working memory non-targets, voxel cluster size and statistical values are presented in Table 3.3. Selected associations between sites of peak activation and CAPS cluster scores are presented in Figure 3.2 (*a* to *c*).

Re-experiencing symptom score showed no significant association with activation in any brain regions on either a ROI or whole brain basis.

On a ROI basis, avoidance score was positively correlated with activation in each of right dlPFC [$pr(15)=0.63$; $p<0.008$], left ventral ACC [$pr(14)=0.67$; $p<0.008$] and left IPC [$pr(15)=0.66$; $p<0.005$]. However, there was an inverse association between avoidance score and activation in left dorsal ACC [$pr(15)=–0.66$; $p<0.005$] and right IPC [$pr(15)=–0.63$; $p<0.008$]. On whole brain analyses, avoidance score correlated positively with activation in right precuneus [$pr(14)=0.84$; $p<0.001$], left inferior OFC [$pr(15)=0.73$; $p=0.001$] and bilateral cerebellum [left: $pr(15)=0.73$; p=0.001; right: $pr(14)=0.76$; $p=0.001$].

In ROI analyses, arousal score was inversely related to activation in right dlPFC [$pr(13)=–0.74$; $p<0.005$] and left rostral ACC [$pr(13)=–0.68$; $p<0.008$]. On a whole brain basis, arousal score correlated positively with activation in right precuneus [$pr(14)=0.83$; $p<0.001$].

Table 3.3: Sites of peak activation in the presence of working memory non-targets significantly associated with CAPS cluster scores in the full PTSD sample after accounting for depressive symptoms (ROI and whole brain analyses)

Association, Brain region	Hemisphere	MNI coordinates (mm) x	y	z	Voxels	z	p
Positive association with re-experiencing score							
Region of interest	-	-	-	-	-	-	-
Whole brain	-	-	-	-	-	-	-
Negative association with re-experiencing score							
Region of interest	-	-	-	-	-	-	-
Whole brain	-	-	-	-	-	-	-
Positive association with avoidance score							
Region of interest							
dlPFC	R	14	26	58	49	2.71	<0.008
ACC	L	-2	28	-10	95	3.20	<0.008
IPC	L	-30	-66	40	88	2.81	<0.005
Whole brain							
Frontal							
iOFC	L	-2	28	-12	16	3.33	0.001
Parietal							
Precuneus	R	6	-52	40	23	4.31	<0.001
Other nuclei							
Cerebellum	L	-20	-34	-24	21	3.34	0.001
	R	14	-36	-18	24	3.74	0.001
Negative association with avoidance score							
Region of interest							
ACC	L	-2	16	30	83	2.89	<0.005
IPC	R	58	-46	52	68	2.63	<0.008
Whole brain	-	-	-	-	-	-	-
Positive association with arousal score							
Region of interest	-	-	-	-	-	-	-
Whole brain							
Parietal							
Precuneus	R	10	-56	38	306	4.60	<0.001
Negative association with arousal score							
Region of interest							
dlPFC	R	18	50	2	142	2.68	<0.005
ACC	L	-14	46	0	348	3.09	<0.008
Whole brain	-	-	-	-	-	-	-

dlPFC – dorsolateral prefrontal cortex; ACC – anterior cingulate cortex; IPC – inferior parietal cortex; iOFC – inferior orbitofrontal cortex; R – right; L – left.

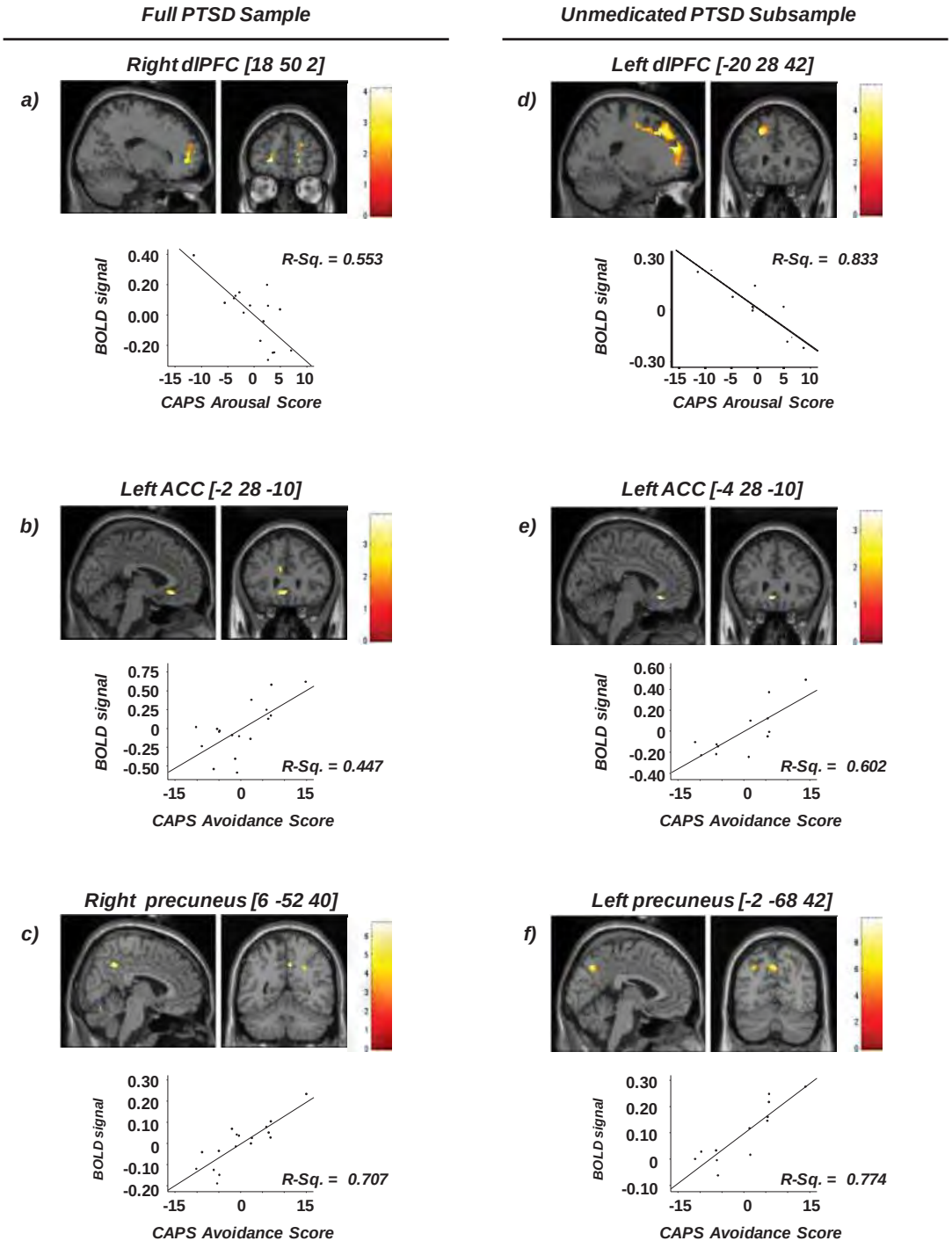

Figure 3.2. Example plots of peak activation (BOLD signal) to non-target stimuli by CAPS arousal and avoidance scores, with corresponding activation regions.

Partial regression plots of association between activation to non-targets with CAPS arousal and avoidance scores in the full PTSD sample (a to c) and the unmedicated PTSD subsample (d to f). Partial regression plots represent the relationship between brain activation and CAPS cluster score after partialling out the contribution of DASS depressive symptom score (i.e., residuals of regressing activation against CAPS cluster score versus residuals of regressing DASS depressive symptom score against CAPS cluster score). Plots and r-squared value were produced in SPSS. dlPFC – dorsolateral prefrontal cortex; ACC – anterior cingulate cortex.

3.3.3 Control analysis – unmedicated subsample analyses

3.3.3.1 Group difference analysis

All areas of peak activation, voxel cluster size and associated statistical values are presented in Table 3.4. On ROI analyses, the PTSD group showed significantly less activation in bilateral dlPFC and left rostral ACC compared to TE controls during the working memory updating task. Similarly, the PTSD group showed significantly less activation than NTE controls in bilateral dlPFC, left rostroventral ACC and right IPC. See Figure 3.1 (*e* to *i*) for sites of peak activation differences between groups (ROI analyses).

On whole brain analyses, the PTSD group showed significantly less activation than the TE group in right dlPFC, left superior medial frontal cortex and middle OFC bilaterally. Compared to NTE controls, the PTSD group showed less activation in bilateral dlPFC, in line with the ROI analysis above, left superior medial frontal cortex, middle OFC at midline, right superior temporal pole and the right hippocampus, but greater activation in right inferior OFC.

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Table 3.4: Sites of peak activation differences between groups in the presence of working memory non-targets in the unmedicated subsample after accounting for depressive symptoms (ROI and whole brain)

		MNI coordinates					
Contrast, Brain region	Hemisphere	x	y	z	Voxels	z	p
TE > PTSD							
Region of interest							
dlPFC	L	-16	52	12	896	3.35	<0.001
	R	20	62	8	423	3.96	<0.001
ACC	L	-4	52	12	612	3.79	<0.001
Whole brain							
Frontal							
dlPFC	R	20	62	8	46	3.96	<0.001
Sup. med. frontal	L	-8	52	12	255	4.12	<0.001
Middle OFC	L	-44	50	-8	16	3.30	<0.001
	R	4	54	-4	265	3.75	<0.001
PTSD > TE							
Region of interest	-	-	-	-	-	-	-
Whole brain	-	-	-	-	-	-	-
NTE > PTSD							
Region of interest							
dlPFC	L	-22	56	12	257	3.95	<0.001
	R	16	64	10	205	4.07	<0.001
ACC	L	-2	54	-2	61	2.78	0.003
IPC	R	50	-34	56	37	2.43	0.008
Whole brain							
Frontal							
dlPFC	L	-22	56	12	53	3.95	<0.001
	R	16	64	10	68	4.07	<0.001
Sup. med. frontal	L	-4	64	14	16	3.81	<0.001
Middle OFC	M	0	56	-8	67	4.08	<0.001
Temporal							
Sup. temporal pole	R	62	4	-6	31	3.77	<0.001
Hippocampus	R	34	-22	-8	15	3.26	0.001
PTSD > NTE							
Region of interest	-	-	-	-	-	-	-
Whole brain							
Frontal							
Inferior OFC	R	46	32	-16	36	3.77	<0.001

OFC – orbitofrontal cortex; med – medial; sup – superior; R – right; L – left; M – midline. Note there was no comparison between TE and NTE controls in the unmedicated subanalysis as this would have artificially reduced power from the equivalent comparison in the full sample analysis. Moreover, controlling for medication use in these samples was unnecessary as none of these participants were medication users.

3.3.3.2 CAPS-BOLD associations

Outliers (values >2.5 sd from the mean) were removed to avoid erroneous influence on analyses. Outliers represented <1% of all values. Hierarchical regression analyses were based on an unmedicated PTSD subsample of n=12 as CAPS data were unavailable for one of the unmedicated participants at the time of analysis. As for the full sample, associations between areas of peak activation (BOLD signal) and each CAPS cluster score are presented as partial correlations (*pr*), after removing variance shared by each of these variables with DASS depressive symptom score (Tabachnick & Fidell, 2007). Associated coordinates of peak activation during the working memory updating task, voxel cluster size and statistical values are presented in Table 3.5. Selected associations between sites of peak activation and CAPS cluster scores are presented in Figure 3.2 (*d* to *f*).

Re-experiencing score was inversely related to activation in right dlPFC [*pr*(9)=–0.84; $p<0.005$] on a ROI basis. This was also evident on a whole brain basis [*pr*(9)=–0.84; $p=0.001$]. There were no other significant associations between re-experiencing score and brain activation.

On a ROI basis, avoidance score was correlated positively with activation in left ventral ACC [*pr*(9)=0.78; $p<0.008$], but inversely with activation in right rostral ACC [*pr*(9)=–0.78; $p<0.005$]. On a whole brain basis, avoidance score was positively associated with left precuneus activation [*pr*(9)=0.88; $p<0.001$].

Arousal score was inversely related to activation in left dlPFC [*pr*(9)=–0.91; $p<0.005$] and left IPC [*pr*(9)=–0.83; $p<0.005$] on a ROI basis. The inverse relationship with dlPFC was also present on a whole brain basis [*pr*(9)=–0.91; $p=0.001$]. Further, on whole brain analyses, arousal score correlated positively with activation in the pars

triangularis region of the left inferior frontal gyrus (IFG) [$pr(9)=0.95$; $p<0.001$] and in the left hippocampus [$pr(9)=0.83$; $p=0.001$], but inversely with right inferior temporal gyrus activation [$pr(9)=–0.90$; $p<0.001$].

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Table 3.5: Sites of peak activation in the presence of working memory non-targets significantly associated with CAPS cluster scores in the unmedicated PTSD subsample after accounting for depressive symptoms (ROI and whole brain)

		MNI coordinates (mm)					
Association, Brain region	Hemisphere	x	y	z	Voxels	z	p
Positive association with re-experiencing score							
Region of interest	-	-	-	-	-	-	-
Whole brain	-	-	-	-	-	-	-
Negative association with re-experiencing score							
Region of interest							
dlPFC	R	28	58	8	397	3.94	<0.005
Whole brain							
Frontal							
dlPFC	R	28	58	8	99	3.94	0.001
Positive association with avoidance score							
Region of interest							
ACC	L	-4	28	-10	35	2.76	<0.008
Whole brain							
Parietal							
Precuneus	L	-2	-68	42	129	4.76	<0.001
Negative association with avoidance score							
Region of interest							
ACC	R	12	36	2	550	3.55	<0.005
Whole brain	-	-	-	-	-	-	-
Positive association with arousal score							
Region of interest	-	-	-	-	-	-	-
Whole brain							
Frontal							
IFG (pars tri)	L	-54	14	28	67	5.27	<0.001
Temporal							
Hippocampus	L	-36	-34	-10	20	3.53	0.001
Negative association with arousal score							
Region of interest							
dlPFC	L	-20	28	42	1201	3.29	<0.005
IPC	L	-52	-40	38	43	2.65	<0.005
Whole brain							
Frontal							
dlPFC	L	-20	28	42	28	3.29	0.001
Temporal							
Inf Temp	R	64	-56	-6	39	4.37	<0.001

dlPFC – dorsolateral prefrontal cortex; ACC – anterior cingulate cortex: IPC – inferior parietal cortex; IFG (pars tri.) = inferior frontal gyrus (pars triangularis); Inf Temp – inferior temporal; L = left; R = right.

3.4 Discussion

All findings presented here are those after controlling for the contribution of depressive symptoms. As hypothesised, there was significantly less activation in key areas of the working memory brain network in the full PTSD sample composed of both medicated and unmedicated individuals compared to both control groups during the working memory updating task. That is, during the working memory updating task individuals with PTSD showed significantly less activation in dlPFC bilaterally than both trauma-exposed and non-trauma-exposed controls, with significantly lower activation in the rostroventral portion of left ACC compared to trauma-exposed controls, also evident on whole brain analyses. This suggests that lower activation in these areas in PTSD during the task may not be solely attributable to trauma exposure. Furthermore, that these differences were present after accounting for depressive symptoms and that they remained in the subsample of PTSD patients composed only of individuals not using medication, suggests that they are associated with unique aspects of PTSD pathology and not attributable to depressive symptoms or medication use. The robustness of these lesser prefrontal activations in the unmedicated PTSD sample was evidenced by their presence in the whole brain analyses (in right dlPFC compared to trauma-exposed controls; and in bilateral dlPFC compared to non-trauma-exposed controls).

Reduced activation in dlPFC and ACC in PTSD compared to controls during the working memory updating task is consistent with previous brain imaging research. Use of verbal 1-back working memory updating paradigms similar to that used in the current study has indicated reduced dlPFC and ACC activation in PTSD (Clark et al., 2003; Moores et al., 2008), as well as aberrant functioning within the working memory brain network in which these areas feature (Shaw et al., 2009; Shaw et al., 2002). The current

study complements and extends these previous findings by showing that this pattern of reduced activation was associated with PTSD, over and above the contribution of trauma exposure, depressive symptoms and medication use.

A point of divergence from previous research was the failure to find robustly reduced IPC activation to non-targets in either hemisphere in PTSD relative to the control groups in the full sample. However, in the subsample analysis composed only of unmedicated individuals, there was significantly less activation in right IPC in PTSD during the task compared to non-trauma-exposed controls. That the IPC activation difference was present only in the unmedicated sample may suggest that medication was influencing IPC functioning in PTSD. This potential explanation can be better examined in future research by utilising larger samples as well as examining differences in IPC functioning between controls, and discrete medicated and unmedicated PTSD samples.

Activation differences between the control groups during the working memory updating task were limited to right dlPFC regions, with the trauma-exposed controls exhibiting greater activation than individuals not exposed to trauma. This was evident on both region of interest and whole brain analyses, suggesting robustness of the effect in the current sample. Enhanced dlPFC activity during the current task in trauma-exposed individuals may represent a resilience factor protecting against PTSD. Such an idea is consistent with the proposed importance of potent prefrontal cortical functioning as a resilience factor in the aftermath of trauma (Charney, 2004; New et al., 2009) and twin-based research suggesting that better neurocognitive functioning may protect against PTSD onset (Gilbertson et al., 2006). This hypothesis could be better investigated with appropriate longitudinal research in which working memory-related

brain functioning is recorded prior to trauma exposure. The notion of resilience factors is discussed further in Section 5.2.3.

Whole brain analyses also revealed altered brain functioning in PTSD in areas outside the hypothesised working memory neural network during the working memory updating task. There was less activation in left superior medial frontal cortex, but greater activation in right inferior OFC in PTSD compared to trauma-exposed controls in the full sample. In the unmedicated sample, the PTSD group showed less activation in left superior medial frontal cortex and middle OFC compared to both control groups. The unmedicated PTSD subsample also showed less activation in right superior temporal pole and right hippocampus, but increased activation in right inferior OFC, relative to non-trauma-exposed controls. The current findings concerning OFC and superior medial frontal cortex during the working memory updating task are consistent with functional neuroimaging and lesion-based evidence implicating these areas in working memory (Barbey, Koenigs, & Grafman, 2010; Levens & Phelps, 2010; Seeley et al., 2007). This is covered in more detail in Section 5.2.3. In conjunction with the ROI findings showing reduced task-concurrent activation in PTSD in dlPFC and ACC, these results suggest altered functioning within distributed nodes of the working memory network, in line with previous work (Moores et al., 2008; Shaw et al., 2009).

Associations between PTSD symptom intensity and task-concurrent activation in a priori working memory-related brain regions were generally as hypothesised in the full PTSD sample. As expected, increased avoidance symptoms were associated with reduced activation in ACC (in the left dorsal subregion) and in IPC on the right. In line with this, increased arousal symptoms were associated with reduced activation in right dlPFC and ACC (in the left rostral subregion). Notably, the inverse relationship of avoidance symptoms with ACC activation, and of arousal symptoms with dlPFC

activation, persisted in the unmedicated PTSD subsample. (Though it is acknowledged that each of these relationships diverged slightly from its counterpart in the full sample; in the unmedicated sample avoidance symptoms were inversely related to activation in right rostral ACC, compared to left dorsal ACC in the full sample; and arousal symptoms related inversely to dlPFC activation on the left in the unmedicated sample, whereas this was on the right in the full sample). This suggests that these relationships were not a result of medication use. These findings were complemented by inverse relationships between re-experiencing symptoms and right dlPFC activation, and between arousal symptoms and left IPC activation, in the unmedicated PTSD subsample

This pattern of findings accords with the cognitive cost hypothesis that PTSD symptomatology imposes a processing load that reduces cognitive processing (Aikins et al., 2009; Nixon et al., 2009), and working memory in particular (Brewin & Beaton, 2002). It is also in keeping with observations of reduced activity in dlPFC, ACC and IPC under conditions of high processing load during working memory processing (Callicott et al., 1999; Yun et al., 2010). Indeed, that the inverse association between arousal and ACC was evident in rostral and dorsal subregions is interesting in light of research indicating dorsal ACC activation during memory suppression in normals (Anderson et al., 2004; Butler & James, 2010). The cognitive cost hypothesis would predict that ongoing suppression (an avoidance symptom) should result in reduced working memory processing. This may be reflected in reduced activation in ACC during a working memory task, given the detrimental impact of excessive processing load on activation in this area (Yun et al., 2010). Thus, the inverse relationship between avoidance and ACC activation during the current task may have reflected the cost imposed on this region by suppression. It is noted that this task was not explicitly affective, and so there was no apparent reason for suppression during the task;

nonetheless, avoidance scores may reflect tendencies of ongoing suppression, which may be resource depleting. Furthermore, the robust inverse association between arousal symptoms and task-concurrent activation in dlPFC converges with the proposal that anxiety may interfere with cognitive processing by reducing dlPFC activity and increasing activity in the amygdala (Bishop, 2007), an area associated with arousal processing (Williams et al., 2001) that exhibits disturbed functioning in PTSD (Rauch et al., 2006; Rauch et al., 2000).

The above pattern of inverse associations of PTSD symptom clusters with activation in dlPFC and ACC during the task, is also broadly consistent with the group difference analyses, which showed overall reduced activation in these regions in PTSD compared to the control groups. The reason for the inverse relationship between arousal and dlPFC activation occurring in different hemispheres in the full PTSD sample and unmedicated PTSD subsample is unclear and requires further research. Also, it is unclear why re-experiencing was not associated with task-concurrent activation in any regions in the full PTSD sample. While one interpretation may be that medication eased the burden of re-experiencing symptoms on brain activation, this requires further research.

Divergent from the above inverse relationships between PTSD symptom clusters and brain activation in a priori working memory-related regions, were the *positive* relationships between avoidance symptoms and activation in these areas. This was observed in right dlPFC, left IPC and left ventral ACC in the full sample, the last of which was also evident in the unmedicated PTSD subsample. The reason for this pattern of findings is unclear. One possibility is that this reflected dissociative-type avoidance symptoms of detachment and emotional numbing; these dissociative phenomena display

distinct neurobiological correlates from more “positive” PTSD symptoms (Lanius et al., 2006; Lanius, Vermetten, et al., 2010). This point is discussed further in Section 5.2.3.

Whole brain analyses in the full sample also revealed positive relationships between avoidance symptoms and task-concurrent activation in left inferior OFC and bilateral cerebellum. In the unmedicated PTSD subsample, greater arousal symptoms were associated with greater activation in left inferior frontal gyrus and in the left hippocampus, but with lower activation in right inferior temporal gyrus. However, the most robust whole brain findings concerned symptom associations with task-concurrent activation in precuneus. Arousal symptoms were positively associated with right precuneus activation in the full sample. Avoidance symptoms showed the same association with right precuneus activation, which persisted in the unmedicated sample, though only evident in the left hemisphere. The current findings concerning the precuneus are interesting in light of its involvement in the default mode network (DMN) (Cavanna & Trimble, 2006) (but see Ding, Van Hoesen, Cassell, & Poremba, 2009)), the operation of which appears disturbed in PTSD (Bluhm et al., 2009). The DMN is a network of areas active when an individual is not engaged in goal-directed behaviour (Gusnard & Raichle, 2001; Koch et al., 2010; Raichle et al., 2001). Compromised DMN integrity (in acutely traumatised individuals) is associated with current (and future) PTSD symptom severity (Lanius, Bluhm, et al., 2010), and is evident during working memory processing in PTSD (Daniels et al., 2010). As such, current findings may indicate disturbed DMN functioning in the current sample. This point and potential implications are addressed in detail in Section 5.2.3.

The current study has several limitations. All behavioural data were lost due to a computer malfunction. Therefore it could not be determined how patterns of brain activity in PTSD relative to controls reflected alterations in working memory updating

in the current study. However, the currently observed pattern of reduced activity in working memory-related neural areas in PTSD is consistent with prior research in which degraded working memory updating performance was observed in PTSD (Clark et al., 2003; Moores et al., 2008). Secondly, investigation of brain activation differences across the three groups was conducted using a series of ANOVAs in which only two groups could be compared at a time. This was due to a limitation of the analysis program used to examine these data. Type I error may have occurred as a result. Future research could better examine the impact of PTSD as distinct from trauma exposure by utilising three groups as per the current study, but conducting analyses in which all groups can be compared at once. With regard to the group difference findings, there was no correction for multiple comparisons over the brain, meaning type I error may have occurred. However, it is noted that the broad pattern of group differences is in line with investigation by other research groups (Clark et al., 2003; Moores et al., 2008). Finally, medication use may have been confounded with level of depressive symptoms in the current sample. Most of the psychotropics used in the current sample were anti-depressants. Thus, removing medicated individuals may have removed a substantial portion of explanatory variance from the depressive symptoms predictor variable. This may have accounted for the persistent association between PTSD and brain activation in the unmedicated PTSD sample, independent of depressive symptoms. Replicating current findings with a larger sample in which groups can be distinguished in terms of depressive symptoms, PTSD and medication use would help clarify this issue.

3.5 Summary and implications for the research program

Notwithstanding the limitations above, the current study suggests that individuals with PTSD show less brain activation than controls during a working memory updating task in key regions of the supporting executive brain network – namely, bilateral dlPFC

and left rostroventral ACC. This appears to be independent of trauma exposure, comorbid depressive symptoms and use of psychotropic medication. Moreover, there appeared to be aberrant functioning in PTSD in a wider network of brain areas, including superior medial frontal and orbitofrontal areas. Potentially, the cognitive load imposed by PTSD symptoms may contribute to this degraded brain functioning, a proposal supported by robust inverse relationships between arousal symptoms and dlPFC activation, and between avoidance and ACC activation. In contrast to this, there was a robust positive relationship between avoidance symptoms and left ventral ACC activation, though the reason for this is unclear. Finally, positive relationships between precuneus activation and avoidance and arousal symptoms may reflect disturbed DMN activity.

Importantly, working memory is considered necessary for successful engagement in psychological treatment (Brewin & Smart, 2005). By extension, this assumes that functional integrity in supporting neural areas may be associated with treatment outcome. This possibility is explored in the following chapter.

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4. Chapter 4: Working memory predictors of PTSD response to CBT: an fMRI study

4.1 Introduction

Cognitive behavioural therapy (CBT) is a common psychological treatment for PTSD (Mendes et al., 2008) and is recommended by international treatment review panels (e.g., Bisson & Andrew, 2007; Foa et al., 2008). CBT is typically composed of exposure to conditioned fear stimuli associated with the trauma and/or cognitive restructuring, along with psychoeducation and anxiety management techniques. Exposure is based on extinction learning principles (Rothbaum & Davis, 2003). These principles stipulate that reduced conditioned responding (e.g., re-experiencing symptoms) to conditioned stimuli (e.g., cues present at the time of the traumatic event) results from repeated confrontation of these stimuli in the absence of an unconditioned stimulus (i.e., the traumatic event). As such, exposure enables diminished fear responding by requiring the individual with PTSD to repeatedly confront personally relevant trauma-related stimuli in safe controlled contexts for sufficient duration that distress reduces (Rothbaum & Schwartz, 2002). This may take the form of repeatedly recounting the traumatic memory as though it were being relived and/or repeated confrontation with trauma-associated stimuli *in vivo*. Typically, this is followed by post-hoc discussion or "processing" of the trauma-associated material present during the exposure session (Rothbaum & Davis, 2003). Cognitive restructuring involves identification, interrogation and modification of maladaptive appraisals about the self, the world and the future in relation to the trauma in order to foster adaptive emotional responding and reduce PTSD symptoms.

There is strong research evidence for the effectiveness of these techniques in CBT to treat PTSD in terms of magnitude of symptom reduction from pre-treatment levels and diagnostic recovery (Harvey, Bryant, & Tarrier, 2003; Mendes et al., 2008; Ponniah & Hollon, 2009; Roberts, Kitchiner, Kenardy, & Bisson, 2009). However, despite the effectiveness of this therapeutic approach, approximately 30 to 50% of PTSD patients do not achieve clinically significant improvement (Bradley et al., 2005). As such, understanding factors that influence response to CBT would be helpful to inform clinical management and may help improve these response rates.

Understanding the neural mechanisms of response to psychological intervention for anxiety disorders may contribute to treatment refinement (Linden, 2006). Work to date has revealed an association between activity in limbic areas, such as rostral and ventral ACC and amygdala, during fear processing and reduction in PTSD severity following CBT (Bryant, Felmingham, et al., 2008; Felmingham et al., 2007). Specifically, better treatment response was associated with increased rostral ACC activity, but reduced amygdala activity, during fear processing from pre-treatment to post-treatment (Felmingham et al., 2007). Complementing this, pre-treatment activation in bilateral amygdala during fear processing predicted a poorer response to treatment (Bryant, Felmingham, et al., 2008). Such findings are consistent with the role of the amygdala in fear expression, rostral ACC (as part of ventromedial PFC) in fear extinction (LeDoux, 2002; Milad et al., 2006; Rauch et al., 2006; Shin & Handwerger, 2009; Shin & Liberzon, 2010), and extinction learning as the theoretical basis for exposure therapy within CBT (Rothbaum & Davis, 2003). However, exposure only constitutes one element of CBT. As cognitive restructuring in CBT is a form of emotion regulation (as per Gross & Thompson, 2007), and as dlPFC, ACC and IPC are implicated in emotion regulation (Campbell-Sills et al., 2011; Ochsner, Bunge, Gross, & Gabrieli, 2002;

Ochsner et al., 2004) and working memory (e.g., Collette & Van der Linden, 2002; Collette et al., 2007; Osaka et al., 2003; Owen et al., 2005)), this suggests that sufficient working memory functioning may be a factor in adequate response to CBT.

Successful CBT is thought to require intact neurocognitive functioning and sufficient working memory capacity. This facilitates engagement in session, free from the interference of intrusive PTSD symptoms (Brewin & Beaton, 2002; Brewin & Smart, 2005; LeDoux, 2002), allows access to and management of the trauma memory, and enables the mental flexibility necessary for cognitive restructuring (Vasterling, Grande, Graefe, & Alvarez, 2010; Vasterling & Verfaellie, 2009). Such proposals are consistent with emotional processing theory, which stipulates that recovery from trauma requires activation of the fear memory structure and incorporation of new adaptive information (Foa & Kozak, 1986; Rauch & Foa, 2006). Two points follow from the assumed importance of working memory to CBT. Firstly, this suggests that general cognitive functioning is related to PTSD response to CBT. Supporting this, better pre-treatment verbal memory ability predicts greater PTSD symptom reduction following CBT (Wild & Gur, 2008). Secondly, it suggests that adequate functioning in working memory circuitry may be necessary for successful treatment of PTSD with CBT. This is true of other types of psychopathology in which there is cognitive interference from disorder-related phenomena. For example, greater pre-treatment dlPFC activation during n-back working memory processing is associated with greater symptom reduction following CBT for schizophrenia (Kumari et al., 2009). However, the association between working memory-related brain functioning and treatment outcome in PTSD has not been investigated.

In examining the association between functioning in working memory circuitry and PTSD response to CBT, it is important to control for the potential influence of

depressive symptoms and use of psychotropic medication (hereafter referred to as medication). With regard to depression, pre-treatment activity in dlPFC, ACC and IPC is related to outcome from CBT in major depressive disorder (MDD). That is, greater resting state activity and phasic responses in these areas to negatively valenced stimuli at pre-treatment are associated with better response to CBT in MDD (Costafreda, Khanna, Mourao-Miranda, & Fu, 2009; Fu et al., 2008; Kennedy et al., 2007; Siegle, Carter, & Thase, 2006). Regarding medication use, despite some divergence in the brain mechanisms by which medication and psychotherapy may exert their therapeutic effects (Fu et al., 2008; Goldapple et al., 2004; Kennedy et al., 2007; Linden, 2006; Martin, Martin, Rai, Richardson, & Royall, 2001; Mayberg et al., 1997; Nemeroff et al., 2006), there appears also to be some overlap. Due to the paucity of research on the functional neural effects of medication in PTSD (Lanius, Brewin, et al., 2010), much of this research is based on MDD samples. For example, adequate pre-treatment functioning in dlPFC and ACC either at rest, during working memory processing, or while processing negative material, appears necessary for successful MDD response to anti-depressant medication (Davidson, Irwin, Anderle, & Kalin, 2003; Kennedy et al., 2007; Marquand, Mourao-Miranda, Brammer, Cleare, & Fu, 2008; Mayberg et al., 1997; Walsh et al., 2007). Moreover, MDD symptom reduction following anti-depressant pharmacological treatment has been associated with increased ACC activity from pre-treatment levels in response to negative pictures (Davidson et al., 2003). Thus, there appears to be overlap in the brain areas implicated in treatment response to both psychotherapy and medication. Taken together, these findings suggest that controlling for depressive symptoms and medication use would be helpful to avoid these factors being confounded in examining the association between brain functioning in PTSD and response to CBT.

The current study was designed to examine the association between functioning in key working memory neural areas prior to CBT and treatment outcome in PTSD, controlling for depressive symptoms and medication use. Following the proposed importance of working memory to CBT success (Brewin & Beaton, 2002; Brewin & Smart, 2005; LeDoux, 2002; Vasterling et al., 2010; Vasterling & Verfaellie, 2009), and the role of dlPFC, ACC and IPC in supporting working memory (e.g., Collette & Van der Linden, 2002; Collette et al., 2007; Osaka et al., 2003; Owen et al., 2005), greater activity at pre-treatment in each of these brain areas during a working memory updating task was hypothesised to predict better PTSD response to CBT.

4.2 Methods

4.2.1 Participants

Thirteen treatment-seeking participants were recruited for the study from the Traumatic Stress Clinic, Westmead Hospital. PTSD diagnosis and comorbidity was determined according to DSM-IV criteria (APA, 2000) by use of the Composite International Diagnostic Interview (CIDI) (Kessler & Üstün, 2004). The Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995) was administered to determine overall PTSD severity. Depressive symptoms were assessed prior to treatment with the 21-item version of the Depression Anxiety Stress Scales (DASS) (Lovibond & Lovibond, 1995). PTSD participants were excluded if they had current substance abuse, history of a neurological condition, or psychosis. Eight participants had co-morbid MDD, two participants had a panic disorder, two participants had obsessive-compulsive disorder and one had social phobia. Four participants were medicated with antidepressant medication (SSRIs), which was not altered during the course of the study.

4.2.2 Procedure

4.2.2.1 Research and treatment protocol

Written informed consent was provided by all participants prior to participation. The working memory updating task was completed by participants prior to treatment. On the day of testing, participants completed questionnaires detailing demographic information and medication status. They also completed the DASS questionnaire. An initial assessment was performed by clinical psychologists to diagnose PTSD and screen for comorbid psychiatric disorders using the CIDI. Participants were administered the CAPS at pre-treatment and again 6 months following the completion of treatment by clinical psychologists who were independent of the treatment program. After clinical and demographic information was collected, participants completed the working memory updating task. Prior to task commencement, participants' visual acuity was checked by means of a Snellen chart. Following completion of the working memory updating task, participants received weekly sessions of CBT over eight weeks. CBT comprised psychoeducation, imaginal exposure, cognitive restructuring and relapse prevention (see Bryant, Moulds, Guthrie, Dang, & Nixon, 2003).

4.2.2.2 Task

The current study employed the same 1-back working memory updating task employed in Study 2. Full details of the task are outlined in Section 3.2.2.2.

4.2.3 Apparatus

4.2.3.1 fMRI recording and fMRI analysis

Details of fMRI recording and fMRI analysis conducted prior to data analysis are the same as for Study 2. Full details of these procedures are outlined in Sections 3.2.3.1 and 3.2.4, respectively.

4.2.4 Data analysis

4.2.4.1 General analysis

Behavioural data (reaction time to targets, omission errors, commission errors) were recorded but were not usable due to a computer malfunction. As such, these data were not analysed and are not reported.

To remove the impact of differences in pre-treatment PTSD severity on post-treatment CAPS Total scores, residual change scores were calculated by regressing post-treatment CAPS Total score on pre-treatment CAPS Total score (as per Raes, Williams, & Hermans, 2009). Hereafter, this is referred to as post-treatment PTSD severity and represents the indicator of treatment response, measured six months after completion of treatment. As such, higher post-treatment PTSD severity indicates poorer treatment response, whereas lower post-treatment PTSD severity indicates better treatment response.

Simple linear regressions were used to examine the association between fMRI BOLD signal (hereafter referred to as activation) to working memory non-targets at pre-treatment (the predictor variable) and post-treatment PTSD severity (the outcome variable). These were run separately for each significant voxel cluster. These analyses were conducted on both a region of interest (ROI) basis to test a priori hypotheses, and a

whole brain basis to identify significant activation in non-hypothesised areas that were associated with post-treatment PTSD severity.

The WFU Pickatlas (Version 1.02, Wake Forest University, School of Medicine Winston-Salem, North Carolina) was used to conduct the ROI analysis (Maldjian et al., 2003; Tzourio-Mazoyer et al., 2002). ROI analysis was conducted on three regions, informed by current hypotheses – dlPFC (including lateral portions of the superior frontal gyrus (excluding internal medial superior frontal grey matter) as defined by Tzourio-Mazoyer et al. (2002) and middle frontal gyrus as defined by Petrides and Pandya (1999); ACC (limited rostrally by the paracingulate sulcus and caudally by the white matter of the corpus callosum, and including the subgenual cingulate region (BA25); and IPC (including the supragmarginal gyrus (SMG) and angular gyrus, and a superior portion of cortex between the SMG and angular gyrus). These analyses were conducted in each hemisphere, giving a total of six regions. As per Bryant et al. (2005), ACC subregions were operationally defined as follows: rostral ACC was the area of ACC anterior and superior to the genu of the corpus callosum with posterior boundary y = + 30mm; dorsal ACC was the area of ACC superior to the corpus callosum between y = 0 and +30mm; and ventral ACC was the ACC subregion inferior to the genu of the corpus callosum, below z = 0mm. ROI analyses used a statistical threshold of $p<0.0083$ (Bonferroni corrected for multiple comparisons) and an extent threshold of greater than or equal to 15 contiguous voxels. For whole brain analyses, a statistical threshold of $p<0.001$ uncorrected for multiple comparisons was used with an extent threshold of greater than or equal to 15 voxels.

4.2.4.2 Impact of depressive symptoms

To determine the contribution of depressive symptoms to the association between pre-treatment brain activation and post-treatment PTSD severity, each analysis above was repeated as a hierarchical regression model. This placed group-averaged DASS depressive symptom score in the model as a continuous predictor before the predictor variable of activation to non-targets at pre-treatment. Post-treatment PTSD severity was the outcome variable in all analyses. Analyses were run separately for each significant voxel cluster.

4.2.4.3 Impact of medication

To control for the impact of medication on the association between pre-treatment activation to working memory non-targets and post-treatment PTSD severity, all analyses were repeated after removing PTSD participants (n=4) who were using medication. This left a PTSD subsample of n=9 unmedicated individuals. The impact of comorbid depressive symptoms was examined as per the full sample analysis.

4.3 Results

As with Study 2, all results on the association between activation to working memory non-targets and post-treatment PTSD severity presented in this study are those after accounting for the impact of depressive symptoms. As working memory updating is the construct of interest, only activation data associated with presentation of non-target stimuli are presented here.

4.3.1 Demographic and clinical data

Demographic and clinical data are presented in Table 4.1. There was significant reduction in CAPS Total score from pre-treatment to post-treatment (measured six

months following treatment completion) in the full PTSD sample [$t(12)=4.48$, $p=0.001$] and in the unmedicated subsample [$t(8)=6.22$, $p<0.001$].

Table 4.1: Demographic and clinical data for the full PTSD sample and the unmedicated PTSD subsample

	PTSD - full sample	**PTSD - unmedicated subsample**
n	13	9
Male	5	3
Female	8	6
Age$^{\Delta}$	40.4 (10.2)	39.1 (10.9)
Handedness - right	13	9
Years of education$^{\Delta}$	13.5 (2.5)	10.9 (2.6)
Years since trauma$^{\Delta}$	6.4 (7.2)	5.5 (6.8)
Pre-treatment CAPS score$^{\Delta}$	74.4 (20.0)	73.1 (23.8)
Post-treatment CAPS score$^{\Delta}$	33.3 (31.8)	26.6 (24.1)
DASS-D score$^{\Delta}$	22 (3.0)	21.8 (12.4)
Trauma type		
Motor vehicle / industrial accident	6	3
Assault	7	6

Δ Group means. Standard deviations appear in parentheses.

4.3.2 fMRI data

4.3.2.1 Full sample analysis

Outliers (values >2.5 sd from the mean) were removed to avoid erroneous influence on analyses. Outliers represented <1% of all values. As recommended by Tabachnick & Fidell (2007), the associations between areas of peak activation at pre-treatment and post-treatment PTSD severity are presented as partial correlations (*pr*) as this reflects the unique association between these variables after removing the variance that both of these variables share with DASS depressive symptom score. Associated coordinates of

peak activation to working memory non-targets, voxel cluster size and statistical values are presented in Table 4.2. On ROI analyses, activation in rostral portions of the dlPFC bilaterally [left: *pr*(10)=0.81, *p*<0.005; right: *pr*(10)=0.82, *p*=0.001], and the left IPC [*pr*(10)=0.72, *p*=0.008] were positively associated with post-treatment PTSD severity. However, there was an inverse relationship between post-treatment PTSD severity and activation in the more caudal portion of dlPFC bilaterally [left: *pr*(10)=–0.84, *p*<0.005; right: *pr*(10)=–0.86, *p*<0.001] and the right dorsal ACC [*pr*(10)=–0.93, *p*<0.001] (see Figure 4.1 (*a* and *b*) for selected associations between sites of peak activation and post-treatment PTSD severity).

On whole brain analyses, post-treatment PTSD severity correlated positively with activation in each of the right dlPFC [*pr*(9)=0.92, *p*<0.001], right inferior frontal operculum [*pr*(10)=0.89, *p*<0.001], the middle occipital gyrus bilaterally [left: *pr*(10)=0.91, *p*<0.001; right: *pr*(10)=0.86, *p*<0.001], left cuneus [*pr*(10)=0.88, p<0.001], the left calcarine fissure [*pr*(10)=0.92, *p*<0.001] and the right cerebellum [*pr*(10)=0.86, *p*<0.001]. Post-treatment PTSD severity was inversely related to activation in left superior medial frontal cortex [*pr*(10)=–0.91, *p*<0.001], right inferior frontal operculum [*pr*(10)=–0.85, *p*<0.001], left supplementary motor area (SMA) [*pr*(10)=–0.90, *p*<0.001], bilateral precentral gyrus [left: *pr*(10)=–0.80, *p*<0.001; right: *pr*(10)=–0.89, *p*<0.001], right middle cingulate cortex [*pr*(10)=–0.87, *p*<0.001], left superior parietal cortex [*pr*(10)=–0.86, *p*<0.001] and right cuneus [*pr*(10)=–0.89, *p*<0.001].

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Table 4.2: Regions in which peak activation in the presence of working memory non-targets was significantly associated with post-treatment PTSD severity for the full PTSD sample after partialling out depressive symptoms (ROI and whole brain analyses)

		MNI coordinates (mm)					
Association, Brain region	Hemisphere	x	y	z	Voxels	z	p
Positive association							
Region of interest							
dlPFC	L	-22	58	30	298	3.71	<0.005
	R	26	58	30	363	3.35	0.001
IPC	L	-36	-74	50	36	2.90	0.008
Whole brain							
Frontal							
dlPFC	R	32	56	30	41	4.09	<0.001
Inf. frontal operculum	R	56	10	54	18	4.15	<0.001
Occipital							
Middle occipital cortex	L	-34	-92	20	97	4.39	<0.001
	R	52	-70	24	80	3.76	<0.001
Cuneus	L	-6	-90	38	36	3.89	<0.001
Calcarine	L	-4	-92	2	161	4.59	<0.001
Other nuclei							
Cerebellum	R	24	-76	-22	26	3.92	<0.001
Negative association							
Region of interest							
dlPFC	L	-22	0	52	340	3.36	<0.005
	R	20	20	38	785	3.59	<0.001
ACC	R	6	14	26	1456	4.55	<0.001
Whole brain							
Frontal							
Sup.med. frontal cortex	L	-1	34	36	151	4.21	<0.001
Inf. frontal operculum	R	56	14	18	30	3.65	<0.001
Supp. motor area	L	-8	-6	62	34	4.04	<0.001
Precentral gyrus	L	-56	12	34	159	4.83	<0.001
	R	30	-18	58	35	4.03	<0.001
Limbic							
Middle cingulate cortex	R	12	24	40	201	3.91	<0.001
Parietal							
Paracentral gyrus	L	-10	-36	-66	28	4.18	<0.001
Superior parietal cortex	L	-18	-60	58	25	3.90	<0.001
Occipital							
Cuneus	R	14	-76	40	43	3.85	<0.001

dlPFC – dorsolateral prefrontal cortex; ACC – anterior cingulate cortex; IPC – inferior parietal cortex; Sup – superior; inf- inferior; med – medial; Supp – supplementary; L – left; R- right.

4.3.2.2 Control analysis – unmedicated subsample analyses

There were no outliers (values >2.5 sd from the mean) on variables within the unmedicated PTSD subsample analyses. As for the full sample, associations between areas of peak activation at pre-treatment and post-treatment PTSD severity are presented as partial correlations (*pr*), after removing variance shared by each of these variables with DASS depressive symptom score (Tabachnick & Fidell, 2007). Associated coordinates of peak activation during the working memory updating task at pre-treatment, voxel cluster size and statistical values are presented in Table 4.3. For the unmedicated PTSD subsample, ROI analyses revealed no significant positive correlations between post-treatment PTSD severity and activation in any a priori regions. However, there were significant inverse correlations between post-treatment PTSD severity and activation in left dlPFC [$pr(6)=–0.85$, $p<0.008$], right dorsal ACC [$pr(6)=–0.97$, $p<0.001$], and right IPC [$pr(6)=–0.91$, $p<0.005$] (see Figure 4.1 (*c* and *d*) for selected relationships).

On whole brain analyses, post-treatment PTSD severity correlated positively with activation in the left fusiform [$pr(6)=0.96$, $p<0.001$], left parahippocampal gyrus [$pr(6)=0.96$, $p<0.001$], and left cerebellum [$pr(6)=0.96$, $p<0.001$]. There was an inverse correlation between post-treatment PTSD severity and activation in right dlPFC [$pr(6)=–0.92$, $p=0.001$], left precentral gyrus [$pr(6)=–0.95$, $p<0.001$], and left middle cingulate cortex [$pr(6)=–0.94$, $p<0.001$].

Table 4.3: Regions in which peak activation in the presence of working memory non-targets was significantly associated with post-treatment PTSD severity for the unmedicated PTSD subsample after partialling out depressive symptoms (ROI and whole brain analyses)

		MNI coordinates (mm)					
Association, Brain region	Hemisphere	x	y	z	Voxels	z	p
Positive association							
Region of interest	-	-	-	-	-	-	-
Whole brain							
Temporal							
Parahippocampal gyrus	L	-18	0	-26	70	3.88	<0.001
Occipital							
Fusiform	L	-40	-62	-12	59	4.22	<0.001
Other nuclei							
Cerebellum	L	-2	-44	-12	64	4.04	<0.001
Negative association							
Region of interest							
dlPFC	L	-16	34	32	89	3.09	<0.008
ACC	R	6	14	28	215	4.14	<0.001
IPC	R	48	-36	48	505	3.59	<0.005
Whole brain							
Frontal							
dlPFC	R	36	36	36	16	3.41	0.001
Precentral gyrus	L	-56	12	36	44	3.99	<0.001
Limbic							
Middle cingulate cortex	L	-10	-16	44	41	3.95	<0.001

dlPFC – dorsolateral prefrontal cortex; ACC – anterior cingulate cortex; IPC – inferior parietal cortex; L – left; R – right.

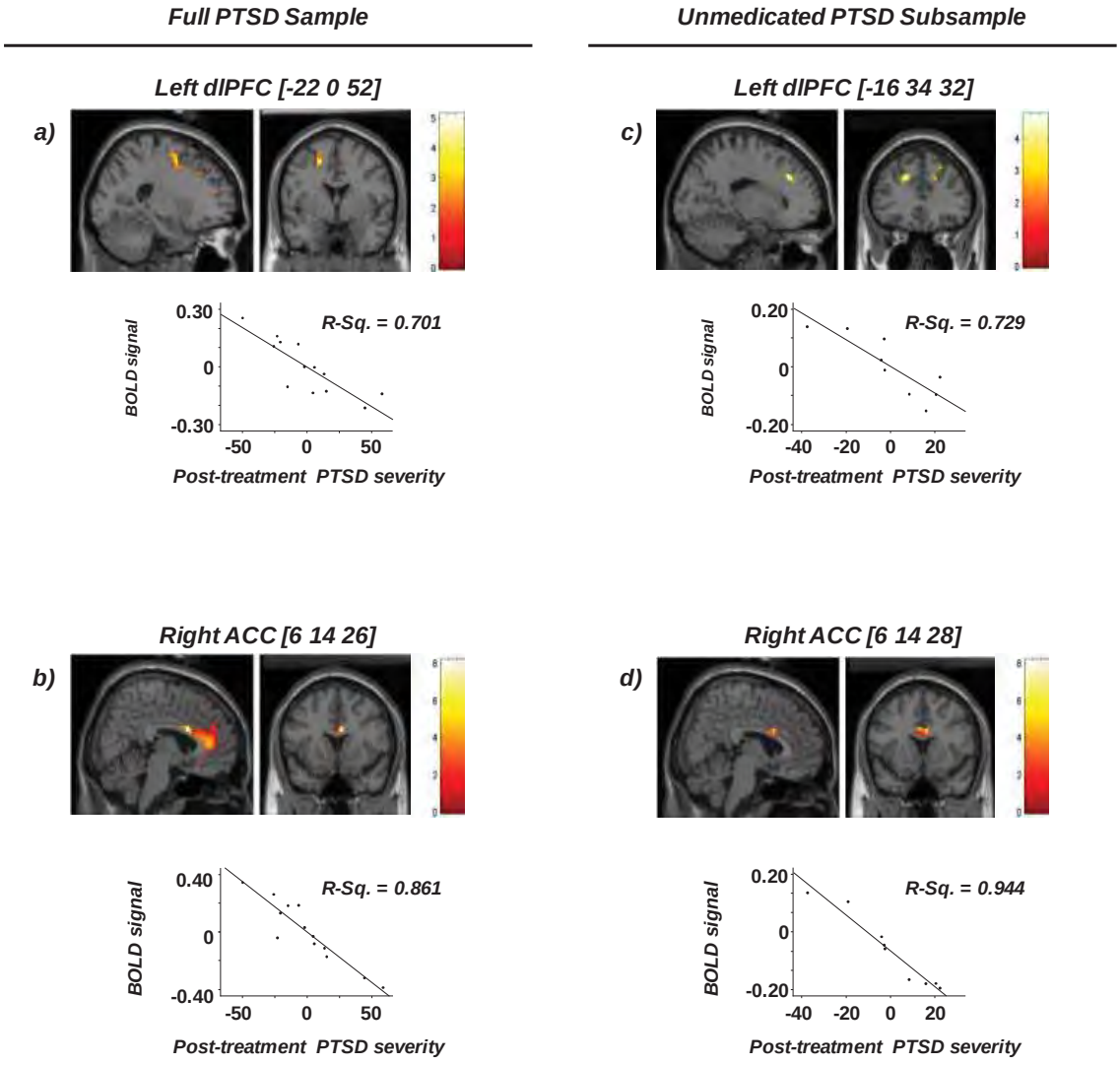

Figure 4.1. Example plots of peak activation (BOLD signal) to non-target stimuli at pre-treatment and post-treatment PTSD severity, with corresponding activation regions.

Plates (a) and (b) are for the full PTSD sample; plates (c) and (d) are for the unmedicated PTSD subsample. All plots are partial regression plots. Partial regression plots represent the relationship between brain activation and post-treatment PTSD severity after partialling out the contribution of DASS depressive symptom score (i.e., residuals of regressing activation against post-treatment PTSD severity versus residuals of regressing DASS depressive symptom score against post-treatment PTSD severity). Plots and r-squared values were produced in SPSS. dlPFC – dorsolateral prefrontal cortex; ACC – anterior cingulate cortex.

4.4 Discussion

All findings presented in this section are those after accounting for depressive symptoms. The findings of the current study are novel in that they represent the first identification of a cognitively based brain predictor of treatment response in PTSD. As hypothesised, greater pre-treatment activation of key frontoparietal regions during a working memory updating task predicted better PTSD response to CBT, indicated by lower PTSD severity measured 6 months following the completion of treatment. Importantly, this association was present after controlling for the contribution of depressive symptoms and medication use. Specifically, greater bilateral dlPFC activation during the working memory updating task was related to better treatment response in the full sample, a relationship that was preserved in left dlPFC in the unmedicated subsample. The contribution of right ACC activity was robust, with greater activation in a dorsal portion of ACC associated with better treatment response in the full sample and the unmedicated subsample. The right IPC showed the same association in the unmedicated sample. Moreover, greater activity in an extended frontoparietal working memory network (including superior medial frontal and superior parietal regions) was associated with better response to CBT in the full sample, though this was absent in the unmedicated subsample.

The current results are in line with previous identification of performance-based neurocognitive predictors of PTSD response to CBT (Wild & Gur, 2008) and working memory-based neural predictors of CBT response in other psychopathologies (Kumari et al., 2009). Moreover, by identifying a working memory updating-based neural predictor of PTSD response to CBT, these findings converge with the proposed importance of working memory to psychological treatment (Brewin & Beaton, 2002; Brewin & Smart, 2005; LeDoux, 2002; Vasterling & Verfaellie, 2009). Therefore, it

may be that a minimum capacity to engage working memory at a neural level is required for successful response to CBT in PTSD. If so, the deficient working memory functioning observed in PTSD both behaviourally (Gilbertson et al., 2006; Koso & Hansen, 2006; Lagarde et al., 2010; Samuelson et al., 2006; Vasterling et al., 1998; Vasterling et al., 2002) and neurally (Clark, McFarlane, et al., 2001; Clark et al., 2003; Moores et al., 2008; Shaw et al., 2009; Shaw et al., 2002), may act as an impediment to the success of CBT for some people. Following the cognitive cost hypothesis that degraded working memory operation may be a cognitive cost of PTSD phenomenology (Aikins et al., 2009; Brewin, 2005; Brewin & Beaton, 2002; Shipherd & Beck, 1999; Nixon et al., 2009), it is possible that PTSD severity may act to limit the success of CBT for some patients.

In addition to the above findings, analyses on the full sample showed that poorer response to CBT was associated with greater activation in bilateral dlPFC (though more rostral than the dlPFC areas that predicted better treatment response), left IPC and additional frontal, occipital visual processing areas and cerebellar areas (evidenced by positive correlations between post-treatment PTSD severity and pre-treatment activation in these areas). A possible interpretation is that this reflects a compensatory effect of medication. However, the following reasoning cautions against this. Firstly, there were only four medicated participants in the full sample of 13, meaning activation in these participants alone would be responsible for any medication effect; although unlikely, this may account for the finding. Secondly, whole brain analyses showed that greater activation in temporal, occipital and cerebellar areas in the *unmedicated* subsample was associated with poorer response to CBT. A medication effect in these areas is apparently not feasible. Understanding the reason for the association between greater activity in these areas and poorer treatment outcome in PTSD requires further research.

Current findings should be considered preliminary in view of several limitations. As with Study 2, behavioural data were lost due to a computer malfunction. The lack of behavioural data means that it cannot be determined that the brain activation associated with treatment outcome necessarily reflected working memory updating. Therefore, any inference about the association between brain functioning and working memory updating in the current study, and its relation to treatment outcome in PTSD, is indirect and requires empirical examination in studies in which functional neuroimaging and performance data are collected. Secondly, there was no alternative treatment to CBT. As such, the specificity of task-concurrent neural functioning to predict outcome from CBT cannot be determined. Also, Frewen, Dozois and Lanius (2008) recommend that psychotherapy-related neuroimaging research include non-psychiatric control groups against which to compare the baseline neural functioning of the clinical group. This would enable determination of the representativeness of the clinical group's working memory updating-related neuroimaging profile with regard to previous research. These researchers also recommend inclusion of a waitlist control group against which the active treatment group can be compared. Both types of control were absent in the current study. This limits the generalisability of current findings and the extent to which the observed association between pre-treatment brain functioning and post-treatment PTSD severity can be ascribed to the impact of treatment. Fourthly, the partial r-values of the association between task-concurrent brain activation and treatment outcome were relatively high, particularly when compared to the more moderate values observed in other neural treatment prediction research (e.g., Bryant, Felmingham, et al., 2008). This may be an artefact of limited variation within the small sample, particularly in the unmedicated PTSD group. Therefore, replication with a larger sample is required. Finally, the current study measured the association between pre-treatment task-

concurrent brain activation and PTSD severity measured 6 months following treatment. Investigating the association between pre-treatment brain activation and PTSD severity at longer time points following treatment may provide further information on the robustness of current findings.

4.5 Summary and implications for the research program

The current study showed that greater activation in regions of a frontoparietal network during a working memory updating task predicted better treatment outcome in PTSD following CBT, independent of depressive symptoms and medication use. In particular, greater task-concurrent activation in dlPFC, ACC and IPC before treatment was associated with better treatment response to CBT. These findings converge with the proposed importance of working memory to engagement in CBT and the role of these neural areas in normal working memory. Importantly, the present findings dovetail with the role of fear circuitry in predicting treatment outcome in PTSD (Bryant, Felmingham, et al., 2008; Felmingham et al., 2007), as well as circuits implicated in working memory functioning and emotion regulation (Campbell-Sills et al., 2011; Collette & Van der Linden, 2002; Collette et al., 2007; Ochsner et al., 2002; Ochsner et al., 2004; Osaka et al., 2003; Owen et al., 2005). Potential implications of this overlap are taken up in the General Discussion that follows in the next chapter.

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5. Chapter 5: General Discussion

5.1 Summary of findings

This research program investigated working memory updating in PTSD using behavioural, electrophysiological and functional neuroimaging measures. Importantly, it controlled for the potential contribution of trauma exposure and depressive symptoms, while also attempting to control for psychotropic medication use. This chapter summarises these findings, discusses potential theoretical implications and presents possible directions for future research.

Study 1 investigated the pattern of altered working memory updating in PTSD using behavioural measures and event-related potentials (ERPs). The full PTSD sample (composed of both unmedicated individuals with PTSD and those who were medication users) showed degraded working memory updating on these measures compared to both trauma-exposed and non-trauma-exposed controls. This suggests that the observed alterations were specific to PTSD, and not a generalised effect of trauma exposure. Specifically, PTSD participants exhibited longer reaction time and more omission errors than control groups. They also showed delayed N2 latency and reduced P3b amplitude during working memory updating. All group differences in the full sample on behavioural measures and ERPs were removed after controlling for depressive symptoms, suggesting a contribution of depressive symptoms to degraded working memory updating in PTSD. Also, prior to controlling for depressive symptoms, reduced P3b amplitude was the only altered measure of working memory updating in unmedicated PTSD individuals compared to the control groups. This suggests that medication use contributed to the degraded behavioural and N2 latency measures of working memory updating in the full PTSD sample. Furthermore, depressive symptoms

did not appear to account for reduced P3b amplitude in unmedicated PTSD participants. Finally, regression analyses within the full PTSD sample revealed that greater intensity of re-experiencing symptoms was associated with longer P3b latency during working memory updating, though this fell to marginal significance after controlling for depressive symptoms.

Study 2 used fMRI to investigate key areas of working memory circuitry in PTSD compared to controls. After controlling for depressive symptoms, PTSD participants showed less activation in bilateral dorsolateral prefrontal cortex (dlPFC) compared to both trauma-exposed and non-trauma-exposed control groups, and less activation in left rostroventral anterior cingulate (ACC) compared to trauma-exposed controls. The same pattern was observed when controlling for the effect of medication use in addition to depressive symptoms, except that reduced ACC activation in the PTSD group relative to trauma-exposed controls was restricted to the rostral subregion. This pattern of findings suggests that reduced activation in these areas during the working memory updating task is associated with unique aspects of PTSD. Reduced activation in inferior parietal cortex (IPC) in PTSD was only observed after controlling for both depressive symptoms and medication use in comparison to non-trauma-exposed controls. There was also altered activation in PTSD in a broader set of brain regions after controlling for depressive symptoms. Included in these were reduced activation in left superior medial frontal gyrus and left superior and middle orbitofrontal cortex (OFC), with enhanced inferior OFC activation, before and after controlling for medication use. With respect to the control groups, the trauma-exposed controls showed greater activity in right dlPFC compared to non-trauma-exposed controls.

Regression analyses within Study 2 revealed significant relationships between PTSD symptom clusters and brain activation during the working memory updating task, after

partialling out the effect of depressive symptoms. Robust inverse associations between avoidance symptoms and ACC activation, and between arousal symptoms and dlPFC activation, were evident in the current work. These were present in both the full PTSD sample and the unmedicated PTSD subsample, suggesting that these effects were not due to medication use. These findings were complemented by inverse relationships between re-experiencing symptoms and right dlPFC activation, and between arousal symptoms and left IPC activation, in the unmedicated PTSD subsample. Diverging from this, avoidance symptoms were positively related to activation in right dlPFC, left IPC and left ventral ACC in the full PTSD sample. The positive association between avoidance symptoms and left ventral ACC activation persisted in the unmedicated sample. While activity in other brain regions was also related to each PTSD symptom cluster, particularly notable was the precuneus. Right precuneus activation was positively related to avoidance and arousal symptoms before controlling for the impact of medication use, with left precuneus activation positively related to avoidance after controlling for medication use.

Study 3 determined patterns of activation in key frontoparietal regions during the working memory updating task at pre-treatment that were associated with PTSD treatment outcome from CBT, after controlling for depressive symptoms. Greater bilateral dlPFC activation was associated with better PTSD response to CBT, with left dlPFC retaining this association after controlling for medication use. The contribution of bilateral ACC was robust, with greater dorsal ACC activity associated with better PTSD response to CBT, both before and after controlling for medication use. Greater right IPC activity was also associated with better CBT response after controlling for medication use. Furthermore, greater activity in regions of an extended frontoparietal working memory network (including superior medial frontal and superior parietal

regions) was related to better PTSD response to CBT, though not in unmedicated PTSD individuals.

5.2 Evidence for reduced working memory updating in PTSD

5.2.1 Behavioural measures

Behavioural data were only available for Study 1, following loss of behavioural data in Studies 2 and 3 due to computer malfunction. Behavioural data showed worse performance in the PTSD group on the working memory updating task than both the trauma-exposed and non-trauma-exposed control groups. This was evidenced by longer reaction times and greater number of omission errors in the PTSD group when required to respond to working memory targets. This reduced working memory performance converges with previous studies that have shown worse performance in individuals with PTSD than controls on standardised neuropsychological working memory tasks (e.g., Digit Span and Spatial Span subtests from the Wechsler Memory Scale) (Gilbertson et al., 2006; Koso & Hansen, 2006; Lagarde et al., 2010; Samuelson et al., 2006; Vasterling et al., 1998; Vasterling et al., 2002). The current findings also agree with previous research that used similar versions of the 1-back working memory updating task to that used in this research. Across these 1-back studies, PTSD participants demonstrated longer reaction times and increased omission errors than healthy controls (Clark, McFarlane, et al., 2001; Galletly et al., 2001; Galletly et al., 2008; Veltmeyer et al., 2009; Veltmeyer et al., 2006; Weber et al., 2005)[10]. However, the current research program extends these previous 1-back findings by showing reduced working memory updating performance specific to PTSD, independent of a generalised impact of trauma exposure itself.

[10] Some of these studies found degraded working memory performance in PTSD on only one of these measures.

Importantly, PTSD-specific deficiencies on behavioural measures were not present after independently controlling for the effects of depressive symptoms and medication use. This suggests that one or both of these factors may affect behavioural indices of working memory processing in PTSD. This possibility is consistent with previous findings that reduced working memory and concentration has been associated with depression (Austin et al., 2001; Landro et al., 2001; Rose & Ebmeier, 2006) and use of some psychotropic medication (Mintzer & Griffiths, 2007; Stein & Strickland, 1998). This implies that it is important to consider both of these factors when examining PTSD-specific alterations in working memory performance measures. The issues of depressive symptoms and medication use in research on working memory in PTSD are covered more fully in Sections 5.4.2 and 5.4.3, respectively.

5.2.2 ERP measures

There was reduced P3b amplitude and prolonged N2 latency during working memory updating in PTSD compared to both trauma-exposed and non-trauma-exposed controls. Reduced P3b amplitude in PTSD during working memory updating is consistent with previous research that has examined this construct in PTSD using visuoverbal and tone-based 1-back tasks (Clark, McFarlane, et al., 2001; Galletly et al., 2001; Galletly et al., 2008; Veltmeyer et al., 2009; Veltmeyer et al., 2006; Weber et al., 2005).

Importantly, current findings extend working memory updating ERP research in PTSD by showing that reduced P3b amplitude and increased N2 latency was specific to PTSD, and not a generalised effect of trauma exposure. Also, the current findings of prolonged N2 latency in PTSD during working memory updating are novel in the context of the visuoverbal 1-back task. Previous ERP research on working memory

updating in PTSD has only examined this component in the auditory domain (Galletly et al., 2001; Galletly et al., 2008). That prolonged N2 latency co-occurred with P3b amplitude reduction in the visuoverbal 1-back task underlines the robustness of the altered temporal dynamics of working memory processing in PTSD. These findings also complement previous work using the oddball paradigm, which found similar N2 latency increases and P3b amplitude reductions to target stimuli (Charles et al., 1995; Felmingham et al., 2002; McFarlane et al., 1993; Metzger et al., 2009; Veltmeyer et al., 2005). In sum, these findings suggest altered temporal dynamics of general attentional functioning in PTSD.

The ERP alterations in PTSD found in the current work, and also in previous research, likely represent degraded cognitive processing. Indeed, P3b amplitude is considered to represent the amount of cognitive resources allocated to cognitive processing (Nieuwenhuis et al., 2005; Polich, 2007), including updating (Chen et al., 2008; Clark et al., 1998; Donchin, 1981; Donchin & Coles, 1988; Lenartowicz et al., 2010; Weber et al., 2005). The latency of the N2 component is considered positively related to difficulty of stimulus discrimination (McFarlane et al., 1993; Naatanen, 1992). On this basis, reduced P3b amplitude and increased N2 latency in PTSD suggest reduced allocation of resources and increased difficulty with discriminating non-target from target stimuli during working memory updating. This temporal evidence for degraded working memory updating converges with the above reduction in behavioural performance in PTSD during this task. Taken together, these behavioural and temporal brain data indicate degraded working memory processing in PTSD.

Consistent with degraded ERP measures of working memory updating in PTSD was the positive association between re-experiencing symptoms and P3b latency within the full PTSD sample in Study 1. As P3b latency represents the speed with which cognitive

resources are allocated to cognitive processing (Polich, 2003), this suggests heightened re-experiencing in PTSD is associated with slower allocation of resources to working memory updating. This is consistent with previous findings suggesting re-experiencing is associated with disrupted resource allocation to working memory updating in PTSD. For example, Weber et al. (2005) found that re-experiencing was inversely related to P3b amplitude in PTSD during working memory updating. These authors interpreted these findings as indicating an association between the cognitive load resulting from re-experiencing symptoms and reduction of working memory resources from stimulus processing.

It is noted that the failure to find an association between P3b amplitude during working memory updating and PTSD symptom clusters contrasts with findings of Weber et al. (2005). As noted in the paragraph above, these authors found an inverse association between P3b amplitude during working memory updating and re-experiencing and avoidance symptom intensity in PTSD. The failure to find such associations in the present work may reflect differences between these studies in terms of PTSD symptom profile, which may vary by subtype and/or over time (Lanius et al., 2006; Lanius, Vermetten, et al., 2010; McFarlane, 2000). It may also reflect varying power between studies. There is a need for replication across studies to determine the robustness of associations between different components of PTSD and ERPs reflecting working memory.

As with behavioural measures, most ERP alterations that appeared specific to PTSD were accounted for by depressive symptoms and medication use. Such findings are consistent with research that has indicated ERP alterations during attentional processing in MDD (Kawasaki et al., 2004; Kemp et al., 2009; Kemp et al., 2010) and in the presence of medication use (at trend level) (Veltmeyer et al., 2006). This highlights the

importance of considering such factors when using ERPs to probe working memory functioning in PTSD.

A notable exception to the moderating impact of depressive symptoms and medication use on ERP measures of working memory updating was the PTSD reduction in P3b amplitude. Depressive symptoms only accounted for reduced P3b amplitude in the full sample, composed of both medication-free and medication-using PTSD participants. Reduced P3b amplitude was evident in unmedicated PTSD participants, and remained after controlling for depressive symptoms in this subsample. This pattern suggests that medicated PTSD participants may have influenced the moderating influence of depressive symptoms on P3b amplitude reduction in the full PTSD sample. The issues of depressive symptoms and medication use are discussed below in Sections 5.4.2 and 5.4.3, respectively.

5.2.3 fMRI measures

fMRI findings revealed a robust pattern of reduced activity in bilateral dlPFC and left rostroventral ACC during the 1-back task. This pattern appeared specific to PTSD (as it was not evident in trauma-exposed controls). Further, unlike the behavioural and ERP data, this pattern of findings was present after controlling for depressive symptoms, and remained largely the same once controlling for medication status. These reductions in bilateral dlPFC and left rostroventral ACC activation during the 1-back task are consistent with evidence in normals that has shown the importance of these areas to normal working memory processing (Collette & Van der Linden, 2002; Collette et al., 2007; Osaka et al., 2003; Owen et al., 2005; Postle, 2006; Smith & Jonides, 1999). Moreover, these results accord with previous brain imaging work that collectively found reduced dlPFC and ACC activity in PTSD during working memory

updating in PTSD (Clark, McFarlane, et al., 2001; Clark et al., 2003; Moores et al., 2008). These findings extend previous research in two important ways: 1) by revealing that they are specific to PTSD, rather than being a result of trauma exposure itself; and 2) they are not accounted for by depressive symptoms. The failure to find robust reductions in IPC activation during the working memory updating task in PTSD deviates from previous research (Clark, McFarlane, et al., 2001; Clark et al., 2003; Moores et al., 2008). That the IPC activity reduction in PTSD was present in the unmedicated sample, but not the full PTSD sample, may reflect the impact of medication use and is discussed in more detail in Section 5.4.3.

Altered activation in PTSD was also observed in various brain regions outside the hypothesised regions of the working memory network. In particular, these included superior medial frontal cortex and OFC compared to controls, though the pattern of differences was variable. With regard to the superior medial frontal cortex, this region showed reduced activation during the 1-back task in PTSD compared to both control groups in both the full sample and the unmedicated subsample (except with respect to non-trauma-exposed controls in the full sample). This region is adjacent to dlPFC and ACC (Mai, Assheuer, & Paxinos, 2004; Tzourio-Mazoyer et al., 2002), forms part of an "executive-control network" required for directing attention (Seeley et al., 2007), and is functionally implicated in working memory processing (Seeley et al., 2007). Therefore, this pattern of reduced activation may be further evidence for disturbed working memory processing in PTSD.

Activation patterns within OFC in PTSD were mixed, with areas of greater and reduced activation in PTSD compared to controls, all after controlling for depressive symptoms. The reduced activation in left superior OFC compared to trauma-exposed controls in the full sample, and in middle OFC in PTSD compared to both control

groups in the unmedicated sample the during working memory updating task is consistent with lesion-based evidence for OFC involvement in normal working memory functioning (Barbey et al., 2010) and reciprocal connections between OFC and each of dlPFC and ACC (Kringelbach & Rolls, 2004). In particular, the pattern of findings with respect to middle OFC suggests that this reduced activation is not solely attributable to any of trauma exposure, depressive symptoms or medication use. In contrast to this, there was greater right inferior OFC activation in PTSD (compared to trauma-exposed controls in the full sample, and compared to non-trauma-exposed controls in the unmedicated subsample). Altered recruitment of inferior OFC during working memory updating in PTSD has been observed previously (Shaw et al., 2009), though the functional significance of this is unclear. Moreover, whether this increased inferior OFC activation is attributable to PTSD, trauma exposure and/or medication use cannot be discerned from the current pattern of findings. Future research is required to better understand the robustness and functional significance of enhanced inferior OFC activation for working memory processing in PTSD.

It was notable that the trauma-exposed control group showed greater activity in right dlPFC during the working memory updating task, compared to non-trauma-exposed controls and individuals with PTSD. This suggests that trauma exposure without PTSD was associated with enhanced dlPFC activation during the working memory updating task. This enhanced activity may have represented a resilience factor against PTSD in the aftermath of trauma. This idea is consistent with previous proposals that potent prefrontal activity may protect against development of PTSD after exposure to extreme stress (Charney, 2004; New et al., 2009). In keeping with this, monozygotic twin research has suggested that reduced performance on neuropsychological tests of working memory may be a premorbid risk factor for PTSD following trauma exposure

(Gilbertson et al., 2006). Specifically, this project found that working memory performance was equivalent between combat-exposed individuals with PTSD and their identical co-twins who had neither combat exposure nor PTSD themselves; and the working memory performance of these combat-unexposed individuals was significantly worse than both the combat-exposed and combat-unexposed members of the non-PTSD twin pairs. However, determining whether the currently observed enhanced right dlPFC activity in the trauma-exposed group may represent a resilience factor requires longitudinal research that assesses individuals prior to, and following, a trauma. This would delineate whether increased dlPFC activity is a premorbid resilience factor or an acquired characteristic of trauma. It is also recognised that differences between trauma-exposed and non-trauma-exposed controls may be attributed to a range of factors associated with vulnerability to trauma exposure, the exposure itself, or factors related to consequences of exposure that were not measured in the current research.

PTSD symptoms showed varying associations with brain activation during the working memory updating task, focused mainly in dlPFC, ACC, and precuneus. The inverse relationships between each of arousal and re-experiencing symptoms with dlPFC activity, and between avoidance and (rostral and dorsal) ACC activity, is consistent with the cognitive cost hypothesis that PTSD symptomatology represents a load that degrades cognitive processing (Aikins et al., 2009; Brewin, 2005, 2008; Brewin & Beaton, 2002; Nixon et al., 2009; Shipherd & Beck, 1999). These findings are also in keeping with work in normals showing that dlPFC and ACC are vulnerable to the effects of increased processing load, possibly underlying reduced working memory performance (Callicott et al., 1999; Persson et al., 2007; Yun et al., 2010).

In contrast to the above inverse relationships between PTSD symptomatology and activation in dlPFC and rostral and dorsal ACC, avoidance symptoms were *positively*

associated with activation in right dlPFC, left IPC and left ventral ACC in the full PTSD sample. The positive relationship with left ventral ACC activity persisted in the unmedicated PTSD subsample. A possible explanation for this finding may be that it reflects dissociative-type avoidance symptoms (e.g., emotional numbing, detachment). The dissociative subtype of PTSD has been characterised with a neurobiological profile of enhanced prefrontal and ACC activation (Lanius, Vermetten, et al., 2010). Thus, the currently observed positive association between avoidance symptoms and brain activation may have reflected the presence of these dissociative-type symptoms and their possible association with enhanced activity in prefrontal and ACC areas. However, this is speculative and there are several caveats. Lanius, Vermetten et al. (2010) characterise the dissociative subtype as showing enhanced activity in medial PFC and rostral ACC, whereas the current findings were focused in ventral ACC, dlPFC and IPC. Moreover, there was no measure of dissociation in the current study and the extent of numbing and detachment during the task were not measured. Better understanding of the meaning and robustness of this positive association requires replication with larger samples in which such symptoms can be explicitly measured. Importantly, the differential roles of avoidance and dissociative tendencies during working memory updating need to be investigated.

The positive association between precuneus activation and PTSD symptom clusters is interesting in light of recent findings concerning functioning of the default mode network (DMN) in PTSD, in which the precuneus is a component (Cavanna & Trimble, 2006; but see Ding et al., 2009). The DMN is a network of brain regions composed of posterior cingulate cortex (PCC), precuneus, posterior lateral cortices and ventromedial and dorsomedial PFC (Gusnard & Raichle, 2001; Koch et al., 2010; Raichle et al., 2001). This network is active in the absence of goal-directed behaviour and is

considered to underlie self-referential and contemplative processing (Gusnard & Raichle, 2001; Mason et al., 2007; Raichle et al., 2001). Adequate suppression of DMN activity in favour of neural networks that support goal-directed processing is necessary when an individual is required to perform a task (Sambataro et al., 2010). Bluhm et al. (2009) found reduced functional connectivity between a PCC/precuneus region and other regions of the DMN in PTSD compared to healthy controls while at rest. Furthermore, these researchers subsequently found that current PTSD symptom severity was positively correlated with the extent of functional connectivity between a PCC/precuneus region and bilateral rostroventral ACC[11] in acutely traumatised individuals (Lanius, Bluhm, et al., 2010), an area also found to show lower levels of activity during the working memory updating task in PTSD in the present study. Finally, when required to switch between a fixation task and a working memory updating task, individuals with PTSD failed to properly disengage the DMN and to adequately engage the executive control network activated by controls during the updating task (Daniels et al., 2010). That activation in precuneus (central to the DMN) was present during the working memory updating task in PTSD in the current research may have reflected insufficient disengagement of the DMN.

Interestingly, Sambataro et al. (2010) observed that in older (compared to younger) normals, poorer working memory performance was associated with reduced functional connectivity within the DMN and reduced ability to disengage this network in favour of task-relevant regions, such as dlPFC and ACC. They proposed that such neural changes may reflect attentional fluctuation and performance decrements. They noted that "both adequate suppression of activity within the DMN as well as activation in task-related regions are critical for the allocation of attentional resources necessary for the

[11] This area was described as perigenual ACC in Lanius, Bluhm, et al. (2010).

performance of a cognitive task... Instability of the DMN can affect the availability of attentional resources and... result in poorer WM [working memory] performance when resources are limited...” (pp. 848-849). Further, commenting on the above findings of Lanius, Bluhm et al. (2010), Daniels et al. (2010) have noted that “the integrity of the default mode network is compromised in PTSD and...the extent of these deficits reflects clinical measures of PTSD” (p.259). On that basis, the positive association observed in the current work between precuneus activation and severity of avoidance and arousal symptoms may have reflected neural resource reallocation to symptom processing, resulting in reduced activity in working memory-related brain regions. However, this is speculative and cannot be determined from the current correlational findings. This idea could be tested by monitoring changes in precuneus activity and performance measures in response to symptom provocation in the context of working memory processing. Moreover, functional connectivity analyses are required to examine how changes in the correlated activity between precuneus and task-positive brain regions during working memory processing are related to PTSD symptom expression. Finally, there is evidence for precuneus involvement in working memory processing (Postle, 2006). Therefore, it is possible that the current association between precuneus activation and PTSD symptoms was not reflective of DMN functioning.

5.3 The cognitive cost hypothesis – degraded working memory as a cognitive cost of PTSD

The presence of group difference and correlational findings across behavioural, ERP and fMRI measures conforms to the cognitive cost hypothesis that degraded working memory processing may be a cognitive cost of PTSD symptomatology. The evidence from ERP measures of reduced cognitive resource allocation to working memory processes converges with the poorer working memory performance currently observed

in PTSD. Consistent with this, that greater severity of re-experiencing symptoms was associated with longer P3b latency during working memory updating suggests that these symptoms were associated with disturbed allocation of processing resources to working memory, as per Weber et al. (2005). The inverse associations across re-experiencing, avoidance and arousal symptoms with dlPFC and rostral and dorsal ACC activity during the 1-back task may have reflected the cognitive load imposed by these symptom processes, leaving fewer resources for cognitive processes. The observed PTSD-specific activity reductions in dlPFC and ACC during the task may have reflected this imposition of cognitive load and absorption of processing resources by PTSD symptoms. While the positive relationships between avoidance and activity in dlPFC, ACC and IPC are counter to the cognitive cost hypothesis, the reason for this is currently unclear, though dissociative-type avoidance symptoms may have contributed. The positive association between precuneus activation and PTSD symptom clusters may also have reflected processes that contributed to this depleted resource availability, by withdrawing resources that would otherwise have been available for processing in working memory-related neural areas.

It is emphasised that proposals concerning the effect of PTSD symptoms on brain functioning in the current work are speculative and that causality cannot be inferred from these correlational data. Future research that examines the effect of symptom provocation on behavioural and neural measures of working memory in PTSD, along with functional connectivity analyses, is necessary to test this proposal. Such work should also consider the functional implications of possibly altered activity in additional regions such as OFC, superior medial regions and precuneus, which are currently unclear.

5.4 Summary of the impact of moderating factors on reduced working memory updating in PTSD

5.4.1 The general impact of trauma exposure

Previous research has shown that trauma, in the absence of psychopathology, can affect brain integrity and cognitive processes. For example, trauma exposure is associated with reduced grey matter volume in areas such as PFC, ACC and hippocampus in non-PTSD trauma-exposed individuals compared to those not exposed to trauma (Ganzel et al., 2008; Karl, Schaefer, et al., 2006). Consistent with the potential of trauma to affect brain integrity were the current observations of enhanced right dlPFC activity during the working memory updating task in trauma-exposed controls compared to both individuals with PTSD and non-trauma-exposed controls. Findings concerning the effect of trauma exposure, as distinct from PTSD, upon neuropsychological functioning have been somewhat equivocal. A recent ERP study found no independent additional contribution of continuously measured PTSD symptoms to attentional processing on an oddball task after accounting for trauma history in a sample of military cadets (Kimble et al., 2010). In line with this are observations of reduced performance on sustained attention and working memory tasks in trauma-exposed groups, regardless of PTSD status, compared to healthy controls (Stein et al., 2002). In contrast, Marx et al. (2009) found that Iraq war deployment (a proxy for trauma exposure) and neuropsychological functioning were only related when considering PTSD severity in military personnel one year after return from deployment, not on immediate return. In part, these differences may reflect variation in samples, tasks, measures, analysis approaches, differences in trauma type and intensity, and time post-trauma. Importantly, such variability highlights the need for experimental control to help distinguish the impact of trauma exposure from PTSD upon neuropsychological

functioning. In line with this, trauma researchers have collectively noted the utility of including both trauma-exposed and non-trauma-exposed control groups in research that examines neuropsychological functioning in PTSD (Brewin, 2008; Duke & Vasterling, 2005; Kimble et al., 2000; Kimble et al., 2010; Kimble et al., 2009). Up to this point, these groups had not been included together within a single neuroimaging investigation of working memory processes in PTSD.

By including both trauma-exposed and non-trauma-exposed control groups, the current findings extend previous research on the neurofunctional investigation of working memory in PTSD. This enabled identification of degraded measures of working memory that were specific to PTSD, independent of the effects of trauma exposure. The current pattern of findings across behavioural and ERP measures, with fMRI findings that were consistent with these, suggested degraded working memory processing in PTSD over and above the impact of trauma exposure alone. The robustness of these findings could be tested by applying the experimental design across samples, tasks and measures. Also, examining the contribution of trauma exposure (versus PTSD) by using continuous measures would be helpful, given the sensitivity of such approaches to variation not always observable with categorical measures (Kimble et al., 2010; Watson et al., 2009).

5.4.2 The contribution of depressive symptoms

The contribution of depressive symptoms to reduced working memory updating in PTSD varied by the measure of working memory updating employed. The effect of depressive symptoms was most pronounced on behavioural and ERP measures, on which depressive symptoms accounted for degraded working memory functioning in PTSD. This may indicate that such measures are susceptible to the known impact of the

psychomotor slowing and cognitive slowing effects of depression (Gualtieri, Johnson, & Benedict, 2006; Sobin & Sackeim, 1997). However, after considering the impact of medication use, the P3b amplitude reduction in PTSD was not accounted for by depressive symptoms. This implies that medication use may have influenced the effect of depressive symptoms on working memory updating measures in the full PTSD sample. Thus, while depressive symptoms contributed to some alteration in the temporal dynamics of working memory updating in PTSD, they did not completely account for the reduced P3b amplitude. Reduced activity in the key working memory-related areas of dlPFC and ACC during the working memory updating task was not accounted for by depressive symptoms. Moreover, PTSD symptomatology was associated with altered functioning in key nodes of the frontoparietal working memory network, independent of depressive symptoms. Taken together, these findings suggest that depressive symptoms contribute to some, but not all, of the degraded working memory processing in PTSD. These findings also emphasise the importance of using a variety of measures across behaviour, electrophysiology and functional neuroimaging when examining the association between symptomatology and degraded cognitive processing.

It is noted that where depressive symptoms had an effect on working memory updating measures, this does not indicate an absent effect of PTSD. Rather, it may suggest that depressive symptoms within PTSD are accounting for those particular changes. Depressive symptoms feature within PTSD diagnostic criteria (e.g., withdrawal from significant activities, restricted affective range, concentration difficulty). Also, factor analyses have shown that MDD and PTSD share a common dysphoric factor (Grant et al., 2008; Simms et al., 2002). By extension, this may suggest that aspects of altered working memory updating in PTSD not accounted for by depressive symptoms are due to unique non-depressive symptoms of PTSD.

5.4.3 The contribution of psychotropic medication use

There is a paucity of research on the impact of medication use on cognitive functioning and functional neuroimaging findings in PTSD (Friedman, 2005; Lanius, Brewin, et al., 2010). Previous research on the confounding effects of medication use on working memory in PTSD has been somewhat mixed. Some researchers have noted degraded working memory on behavioural and functional neural measures in PTSD, independent of medication (Clark et al., 2003; Galletly et al., 2001; Galletly et al., 2008; Moores et al., 2008; Weber et al., 2005), while other findings suggest a role for medication in such deficiency on working memory measures (Veltmeyer et al., 2006; Veltmeyer et al., 2009). (See Section 1.12.3 for a detailed review). However, Veltmeyer and colleagues did not control for the potential contribution of trauma exposure or depressive symptoms.

By controlling for these factors, the current research may provide some preliminary clarification. After accounting for medication use, the most robust findings in the current work specific to PTSD were reduced P3b amplitude, along with reduced activation in dlPFC and ACC. Additionally, there was broad consistency in the findings of inverse relationships of arousal symptoms with dlPFC activation, avoidance symptoms with rostral and dorsal ACC activation, and the positive association between avoidance symptoms and activation in precuneus and left ventral ACC, all of which were evident in the full PTSD sample and the unmedicated PTSD subsample. The current conclusions are tempered, however, by the small size of the unmedicated PTSD subsamples. As such, inferences about the potential impact of medication use are preliminary and should be treated with caution.

The current findings on the impact of psychotropic medication contrast those of Veltmeyer et al. (2009) who observed reaction time increases and (trend-level) P3b amplitude reductions during working memory updating in medicated, but not unmedicated, PTSD patients. It also contrasts Metzger et al.'s (1997) finding of a normalising effect of psychotropic medication use on P3b amplitude during oddball target detection in PTSD. Such discrepancy may reflect P3b amplitude fluctuation over time (Neylan et al., 2003). It may also reflect possible differences between these studies in types of medications used, possible use of concurrent psychotherapy, trauma severity, and sample characteristics, all of which warrant consideration in determining the contribution of medication use to PTSD brain functioning (Lanius, Brewin et al., 2010). Variation in other factors such as duration of medication use, dose and time since trauma may also contribute. These factors should be carefully controlled in future research on working memory updating in PTSD.

It is noted that different classes of psychotropics were used within PTSD samples in the current studies. Small sample size precluded examination of class-specific effects of medication on working memory updating. It is possible that these drug classes may affect working memory measures in different ways due to variation in their pharmacological mechanisms of action (Julien, 2001). Future studies are required to distinguish the specific effects of distinct drug classes on working memory updating in PTSD.

5.4.4 Summary

In summary, current findings suggest that degraded working memory updating in PTSD is not a generalised effect of trauma exposure. Moreover, while depressive symptoms and medication use appeared to contribute to some reduced working memory

functioning, PTSD contributes uniquely. This was most observable on neural measures that suggested reduced allocation of cognitive resources to the updating process and reduced activity in specific neural areas of the working memory network, namely dlPFC and ACC, which were also associated with disorder symptomatology.

5.5 Implications for CBT for PTSD

In line with the proposed importance of working memory to psychological treatment (Brewin & Beaton, 2002; Brewin & Smart, 2005; LeDoux, 2002; Vasterling & Verfaellie, 2009), greater task-concurrent activation in key working memory regions at pre-treatment was associated with better response to CBT. Specifically, greater pre-treatment activity in dlPFC and dorsal ACC during the working memory updating task was related to better PTSD response to CBT, independent of depressive symptoms. This pattern of findings was largely the same in PTSD samples composed of both unmedicated participants and medication users or solely unmedicated participants, though greater IPC activity was associated with better treatment response in the unmedicated sample only. This similarity of findings between the mixed medication status and unmedicated groups is encouraging as it suggests these findings may be generalised to the broader population of individuals with PTSD in which medication use is common (Lanius, Brewin, et al., 2010). However, it is acknowledged that only 4 of 13 participants in the full PTSD sample in Study 3 were medicated, which may be an under-representation.

The current findings complement and extend previous work, which has shown that better verbal memory performance predicts PTSD response to CBT (Wild & Gur, 2008). Taken together, these findings suggest the possibility of using neurocognitive markers to identify clients potentially at risk for poor treatment response. In the case of

working memory, this may be the use of neuropsychological tests of working memory that reflect integrity of supporting neural functioning.

In addition to their role in working memory, the predictive value of dlPFC and dorsal ACC (and possibly IPC) to treatment response may reflect their role in emotion regulation processes, such as cognitive reappraisal of negatively valenced stimuli (Campbell-Sills et al., 2011; Ochsner et al., 2002; Ochsner & Gross, 2008; Ochsner et al., 2004). These researchers showed that these areas are active during cognitive reappraisal of negative material in normals. Such processes underpin cognitive restructuring in CBT, as per the emotion regulation process model of Gross and Thompson (2007). Thus, activation in these regions observed during the working memory updating task before treatment may have reflected sufficient functioning in areas subsequently required by therapeutic elements of CBT to enable satisfactory treatment response. Moreover, these findings may also highlight the importance that frontal regulatory areas play in regulating fear processing activity in ventral limbic regions (Hartley & Phelps, 2010; Schiller & Delgado, 2010). Indeed, the current findings are complemented by previous findings that greater fear processing activity in ventral limbic regions prior to treatment predicted poor PTSD response to CBT (Bryant, Felmingham, et al., 2008). Thus, adequate PTSD response to CBT may require not only sufficient working memory and dorsal area functioning, but also sufficient ability to engage top-down emotion regulation processes to manage ventral limbic regions.

The current findings may suggest avenues of investigation for improving PTSD response rates to CBT. This would be helpful in view of the large proportion of individuals with PTSD (30 to 50%) who do not show significant improvement following such intervention (Bradley et al., 2005). Examining modification to standard CBT delivery to cater for degraded working memory functioning in PTSD may be

helpful. Secondly, it may be worth investigating ways to prime working memory functioning in PTSD prior to initiating CBT and to investigate the impact on treatment response rates. However, it is acknowledged that this last point makes an assumption about mechanism that cannot be determined from the correlational design of the current study. Importantly, it is also noted that current findings are based solely on neural markers of treatment response (due to the absence of companion behavioural data) and cannot speak to altered working memory functioning directly.

5.6 Possible implications for the fear circuitry model of PTSD

While fear conditioning and fear circuitry models have utility for explaining the fear-based phenomena of PTSD, it has been argued that such models cannot account for other features of PTSD (Brewin, 2005; Brewin, 2008; Brewin & Holmes, 2003), amongst which are disturbed working memory and concentration. The current findings on the altered activity in working memory-related neural loci in PTSD, coupled with findings on the neural bases of top-down control of affective processing, may provide a springboard from which future research could extend this neurobiological model. The current work found reduced activity in dlPFC and ACC (and less robustly in IPC) in the context of a working memory updating task in PTSD; it is interesting that these areas are also implicated in cognitive control of affective processing. For example, dlPFC, dorsal ACC and IPC are activated in normals when required to downregulate affective responses to aversive stimuli by reappraisal or suppression (Campbell-Sills et al., 2011; Ochsner et al., 2002; Ochsner & Gross, 2005, 2008; Ochsner et al., 2004; Phan et al., 2005). This dovetails with the current findings that greater activation in these areas during the 1-back task prior to treatment was associated with better response to CBT, a treatment that requires cognitive control of affective processing in the form of cognitive restructuring. In relation to the fear circuitry model, this suggests that processing

resources within working memory brain regions potentially contribute to the integrity of inhibitory control networks (mPFC) within the fear circuitry model. Furthermore, that the areas supporting the cognitive control of affective responses are disturbed in PTSD agrees with the prominence of affect dysregulation in this disorder (Frewen & Lanius, 2006). With reference to the cognitive cost hypothesis, this suggests that PTSD symptomatology may absorb processing resources that subsequently reduces the capacity for cognitive control of symptom expression. This is consistent with findings in normals of reduced prefrontal appraisal-related activation when cognitive resources are absorbed by cognitively demanding parallel tasks (Bishop, 2007; Kalisch, Wiech, Critchley, & Dolan, 2006). Importantly, a recent neural model of fear regulation that explicitly links the dlPFC to fear circuitry (Hartley & Phelps, 2010; Schiller & Delgado, 2010) may provide a means of bridging current findings with the fear circuitry model. This is outlined in Section 5.8 along with possible future research directions.

5.7 Limitations and future directions

5.7.1 Measurement of function

The current research examined the temporal dynamics of working memory processing in PTSD with ERPs, whilst separately investigating the spatial bases of this process with fMRI. The absence of source localisation analyses prevented determination of the neural generators of the currently observed ERP alterations in PTSD. Therefore, it was not possible to determine the anatomical convergence between altered neural activity observed using fMRI and alterations in ERPs. Future work could better understand the nature of this overlap by concurrently measuring ERPs and fMRI BOLD signal during task processing. Complementing this with ERP source localisation would also be helpful. Relatedly, ERPs were only measured at midline sites, preventing

examination of topographical variation in ERP alterations in PTSD. Analysis of more extensive electrode arrays is necessary to examine topographic variation in observed ERP differences. Also, while the fMRI BOLD signal likely reflects neuronal activity (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001), it cannot detect whether this activity is excitatory or inhibitory (Savoy & Gollub, 2004).

Peripheral autonomic measures (e.g., skin conductance responses; SCR) were not obtained in the current research. Previous research has found that neuroimaging profiles in PTSD during attentional processing are modulated by engagement of arousal networks as measured by SCR (Felmingham et al., 2009). Given the proposed association between disordered arousal and reduced working memory processing in PTSD (Vasterling et al., 2002), such arousal-based variation in neuroimaging profiles may have been present but undetectable in the current study. Future research should incorporate peripheral arousal measures to examine potential variability in neuroimaging profiles of working memory in PTSD.

Structural brain data were not collected in the current studies. There is evidence for reduced structural volumes in specific regions in PTSD, including ACC and portions of dlPFC (Eckart et al., 2010; Kasai et al., 2008; Woodward et al., 2006; Yamasue et al., 2003). It is possible that structural alterations in these regions could impact working memory performance in PTSD, given the role of these regions in normal working memory processing (Collette & Van der Linden, 2002; Collette et al., 2007; Osaka et al., 2003; Owen et al., 2005; Postle, 2006; Smith & Jonides, 1999). Relating potential structural alterations to variation in working memory performance measures and functional profiles in these regions in PTSD may provide a more complete understanding of the neural underpinnings of reduced working memory processing in PTSD.

While current fMRI analyses identified reduced activation in specific neural regions, functional connectivity analyses were not performed. Functional connectivity analyses are used to examine the correspondence between activity changes in distributed brain loci (Das et al., 2005). Such analyses provide a network view of brain functioning, thus complementing analyses that examine relative activation differences within single regions. While functional connectivity analyses have been conducted on working memory updating in PTSD, (Shaw et al., 2002; Shaw et al., 2009), these have not controlled for the contribution of trauma exposure or depressive symptoms. Employing functional connectivity analyses while controlling for these potential confounds will provide a network view of working memory dysfunction that is more specific to PTSD.

Finally, the loss of behavioural data from studies using fMRI meant that it was not possible to determine whether observed neural activity alterations necessarily reflected the updating process. It has been noted that behavioural data are necessary to give meaning to interpretation of neural activity data (Postle & Feredoes, 2010). As such, replication is necessary in which behavioural data can be collected and reviewed in conjunction with fMRI.

5.7.2 Task-related limitations

The current 1-back working memory task was used to examine the updating function of working memory. The task tapped the updating function by varying target identity, determined by any consecutive repeat of a letter stimulus. However, there was no condition in which target identity remained fixed, which emphasised storage over updating processes. Comparison of measures between such conditions is necessary to isolate the updating function from storage processes. Thus, current measures likely reflected a combination of these processes. However, current findings were directionally

consistent with previous working memory updating research in PTSD in which updating was isolated in the manner just described (Clark et al., 2001; Clark et al., 2003; Moores et al., 2008; Weber et al., 2005). Also, the working memory updating task did not tap all aspects of cognitive functioning. Replication of current results across tasks that tap additional aspects of cognitive and executive functioning would help determine the extent of the impact of PTSD/depressive symptomatology and medication use on a broader range of cognitive functions.

On a related note, it may be argued that the 1-back task reflected attention rather than working memory. In response, it is noted that working memory is a multi-faceted construct and some theorists have explicitly described attention as being an underlying component (e.g., Engle et al., 1999; Kane & Engle, 2002). As such, it may be that altered performance during the task as a result of deficient attentional processes may still be reflective of deficient working memory.

The current research examined the association between PTSD symptom clusters and functional measures of working memory updating to examine if findings were in line with the cognitive cost hypothesis of PTSD. This was a relatively “passive” means of examining this association. That is, because the current work used non-affective stimuli and did not adopt symptom provocation procedures, there was no manipulation of the load on the working memory system. Examining the effect of symptom provocation on neural and behavioural measures of working memory would provide a more “phasic” complement to current findings. This would provide additional information to further understanding of the pathophysiology of degraded working memory in PTSD. It could also act as a means of examining the robustness of the cognitive cost hypothesis.

5.7.3 Sample-related limitations

Current PTSD sample sizes limited the inferences that could be drawn with respect to the impact of medication use on working memory functioning. While subanalysis using an unmedicated PTSD group was possible, samples were not sufficiently large to enable comparison of medicated and unmedicated PTSD subsamples. Such comparison has been recommended in PTSD neuroimaging research in order to better understand underlying pathophysiological mechanisms and how these may be affected by medication use (Lanius, Brewin, et al., 2010). Moreover, unmedicated PTSD sample sizes were small, which limited power and posed risk of type II error.

The PTSD samples in the current research program had significantly shorter duration since their trauma than the trauma-exposed control groups. These differences were controlled in the current analyses (methodologically in Study 1 by running control analyses in which PTSD and trauma-exposed control groups were matched for years post-trauma; and statistically when examining differences on spatial measures of brain functioning during the working memory task). Future research that carefully matches groups on years post-trauma would be helpful to verify the robustness of current findings. However, this factor was not controlled in analyses that examined the association between neural functioning and PTSD symptom clusters, nor in those examining the predictive value of pre-treatment neural activity during the working memory updating task and subsequent response to CBT. It is possible that this may have contributed to the observed strong associations in these aforementioned analyses, as the presentation and underlying biological bases of PTSD may change over time (Duke & Vasterling, 2005; McFarlane, 2000; McFarlane, Yehuda, & Clark, 2002). Future research should consider this factor by controlling for the impact of years post-trauma

on the association between symptomatology and neural measures of working memory functioning.

5.7.4 Design and analysis-related limitations

A limitation of the current research program was the failure to examine potential gender differences in the functional working memory profile in PTSD. Gender may be an important factor in PTSD, as demonstrated by the higher prevalence of PTSD in females compared to males (Olff, Langeland, Draijer, & Gersons, 2007). Moreover, there is evidence for different neurobiological responses to fear in women compared to men (Felmingham et al., 2010; Williams et al., 2005), as well as gender-specific modulatory effects of emotion on neural functioning during working memory tasks (Koch et al., 2007).

The omission of a measure of dissociation is a limitation of the current research. Recent research has suggested distinct neurobiological profiles for dissociative and re-experiencing/hyperarousal PTSD subtypes (Lanius et al., 2006; Lanius, Vermetten, et al., 2010). The Dissociative subtype may be an example of emotion overmodulation in which there is dorsal ACC and medial PFC hyperactivity; while the re-experiencing/hyperarousal subtype represents emotion undermodulation in which there is rostral ACC and vmPFC hypoactivity, with amygdala hyperactivity (Lanius, Vermetten, et al., 2010). Furthermore, dissociation may contribute to the attentional disturbances observed in PTSD (Kimble et al., 2010). The potential impact of dissociation on the neural profile of working memory updating in PTSD (possibly due to different demands on cognitive capacity), and the potential for variation here between the dissociative and re-experiencing/hyperarousal subtypes, should be considered in future research.

The current study measured depressive symptoms from the Depressive symptoms subscale of the Depression Anxiety Stress Scales (DASS; Lovibond & Lovibond, 1995). While the DASS is a valid and reliable instrument for measuring depressive symptoms in clinical and non-clinical populations (Brown, Chorpita, Korotitsch, & Barlow, 1997; Henry & Crawford, 2005), recent evidence has suggested a ceiling effect on the depressive symptom subscale (Page, Hooke, & Morrison, 2007). Such a ceiling effect may have masked variance in depressive symptoms in the PTSD sample. This may have contributed to findings that were specifically ascribed to PTSD after controlling for depressive symptoms. However, the distribution of depressive symptom scores on this measure in the current studies suggests that this is unlikely. Future research should include alternative measures for depressive symptoms, such as the Beck Depression Inventory (Beck, Rush, Shaw, & Emery, 1979) to overcome potential ceiling effects of the DASS. On a related note, the effect of depressive symptoms was measured continuously and controlled statistically in the current work. While such continuous measures are reliable and valid (Watson, 2009), the current results cannot speak to the contribution of comorbid diagnosis of MDD in PTSD. Future work that compares a PTSD group without MDD to a group composed of individuals with PTSD and comorbid MDD would be a useful complement to the current findings.

The design used to examine the association between neural measures during the 1-back task and each of current symptomatology and post-treatment symptom measures means that a causal mechanism cannot be determined. With respect to the association between current symptom levels and neural functioning, examining changes in neural measures during working memory processing after symptom provocation would assist here. With respect to treatment, examining the impact on treatment outcome of manipulating activity in circumscribed areas (for example, by repetitive transcranial

magnetic stimulation), and comparing pre- and post-treatment brain functioning, may be useful in this regard.

The current research used a categorical approach to examine the potential generalised impact of trauma exposure on degraded working memory in PTSD. However, continuous measures of trauma exposure may provide a more sensitive probe of this contribution as they capture more variability in the construct (Kimble et al., 2010). Future work that utilises this approach would be helpful in determining the robustness of the current findings with respect to the impact of PTSD as distinct from trauma exposure.

Finally, the use of a cross-sectional design precludes discerning whether working memory updating deficits are a consequence of the disorder or a risk factor for its onset. There is evidence that reduced hippocampal volume (Gilbertson et al., 2002) and lower intellectual ability (Macklin et al., 1998) confer risk for PTSD. Prospective studies that index working memory (via performance and neural measures) prior to trauma exposure (e.g., in military or emergency response personnel) and relate this to post-trauma working memory performance and neural patterns would clarify the extent to which working memory factors are a risk factor or a function of PTSD.

5.8 Integrating fear circuitry and working memory models

In view of the overlap between areas that support working memory and top-down affective control, a recent model of fear regulation may provide a means by which future research could extend the fear circuitry model in PTSD. Schiller and Delgado (2010) and Hartley and Phelps (2010) proposed that dlPFC exerts top-down control over fear circuitry (namely the amygdala) via projections to vmPFC in order to manage fear responding. This is consistent with findings that activation of dlPFC (and dorsal

ACC) during affect regulation is inversely related to amygdala activity, and co-occurs with reduced subjective ratings of negative affect in normals (Ochsner et al., 2002; Phan et al., 2005). By functionally integrating the dlPFC with fear circuitry, this model provides a bridge between fear circuitry and working memory circuitry. Indeed, work on the behavioural and neural impact of emotionally distracting material during cognitive processing in traumatised samples is consistent with this model. For example, during an oddball task, combat veterans high on PTSD symptomatology showed enhanced activity in ventral limbic (vmPFC and periamygdala regions) to emotional distractors, but attenuated activity in dlPFC and IPC to neutral target stimuli, compared to those lower on PTSD symptoms (Pannu Hayes, LaBar, Petty, McCarthy, & Morey, 2009). Also, presentation of trauma-related distractors in the delay period of a working memory task caused greater activity in ventral emotional processing areas, disrupted dlPFC activity, and disrupted working memory performance in PTSD participants more than in controls (Morey et al., 2009)[12]. These findings suggest that use of appropriate neuroimaging and analysis approaches, coupled with paradigms that compare PTSD and appropriate control participants on cognitive control in the presence of affective and non-affective stimuli may be a useful means to build and test a neural model of PTSD extending beyond fear circuitry. Complementing such approaches with functional connectivity analyses and symptom provocation paradigms in the context of working memory processing may also be useful here. This remains a goal for future research.

Additionally, future work that seeks to extend and test neurobiological models of PTSD would be well served by considering DMN functioning in PTSD. As already noted, there is disturbed resting state DMN functioning in PTSD (Bluhm et al., 2009), which is related to current and future PTSD severity in acutely traumatised individuals

[12] These researchers noted that the disruption in dlPFC activity during the working memory task occurred in response to both trauma-related and neutral distractor stimuli.

(Lanius, Bluhm, et al., 2010). Also, there is a failure to adequately disengage the DMN and to engage the executive control network in PTSD when required to switch from a passive viewing task to an active working memory updating task (Daniels et al., 2010). With reference to research in normals, this disturbed DMN functioning may contribute to reduced allocation of cognitive resources for working memory processing, manifesting as reduced working memory performance (Sambataro et al., 2010). That activation in precuneus (part of the DMN) during the 1-back task was positively associated with PTSD symptom clusters in the current work, is consistent with these earlier findings in that it may reflect failed disengagement of the DMN. Future work that seeks to extend neurobiological models of PTSD could examine the importance of DMN functioning by including paradigms that involve switching from a passive resting state to active fear processing and regulation; importantly, this framework could facilitate integration of working memory and affect processing aspects of PTSD.

5.9 Conclusions

This research identified a specific neurobiological profile suggestive of reduced working memory processing in PTSD. Importantly, controlling for the contributions of trauma exposure and depressive symptoms helped determine specificity of findings to PTSD. This is a novel addition to the field of neurocognitive functioning in this disorder. The work also provided guidance as to the potential contribution of medication use, though additional work is required to understand this impact more clearly. It also identified methodological issues that can be addressed in future research. Importantly, by identifying specific brain regions that may contribute to reduced working memory processing in PTSD, this work provides a potential starting point from which to extend current neurobiological models of PTSD. Future work that utilises paradigms to

simultaneously examine neurocognitive functioning, fear processing and fear regulation in PTSD hold promise for an improved understanding of PTSD neurobiology.

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APPENDIX

Consent Form – Study 1

Consent Form – Study 2

Consent Form – Study 3

Consent Form – Study 1

The University of New South Wales and Westmead Hospital

CONSENT FORM: Examination of Working Memory Updating in Posttraumatic Stress Disorder (Behavioural and ERP assessment)

Aim: The aim of this assessment is to better understand the role of your brain in your responses to trauma

Method: An EEG scalp cap will be placed on your head. This cap measures your brain activity. You will be asked to perform a brief task in which you will need to watch and respond to letters that appear on a computer screen in front of you. The specific task instructions will tell you how to perform the task. The procedure should last about 60 minutes.

Risks: This procedure should contain no risks to you. It is non-invasive and requires you only to watch the screen and respond to the letters by pressing a button when necessary. You may decide not to participate in this assessment or choose to stop at any time after it starts. All information collected during the experiment will be kept confidential. It will be seen by the researcher and possibly by the supervisor. A clinical psychologist is available to discuss any issues that may arise from this procedure.

I acknowledge that I have read the above information and I am satisfied that it has been properly explained to me. I have been given the opportunity to ask questions about the procedure and any possible risks. I understand that I can withdraw at any time without any negative impact on any treatment that I may receive through this service. I agree that the data gathered during the course of this study may be published, provided that neither my name nor any other identifying information is used.

Participant signature: Date:

Participant Name (please print):

Independent Witness signature:

If you would like to talk about your participation in the study, please contact Adrian Allen (researcher) on 9385 3595 or Professor Richard Bryant (supervisor) on 9385 3640.

Consent Form – Study 2

The University of New South Wales and Westmead Hospital

CONSENT FORM: Examination of Working Memory Updating in Posttraumatic Stress Disorder (Behavioural and fMRI assessment)

Aim: The aim of this assessment is to better understand the role of your brain in your responses to trauma

Method: You will be placed inside an MRI scanning machine in which you will lie on your back and wear headphones. You will be asked to perform a brief task in which you will need to watch and respond to letters that appear on a small mirror in front of you. The specific task instructions will tell you how to perform the task. The procedure should last about 60 minutes.

Risks: This procedure should contain no risks to you. It is non-invasive and requires you only to watch the mirror and respond to the letters by pressing a button when necessary. You may decide not to participate in this assessment or choose to stop at any time after it starts. All information collected during the experiment will be kept confidential. It will be seen by the researcher and possibly by the supervisor. A clinical psychologist is available to discuss any issues that may arise from this procedure.

I acknowledge that I have read the above information and I am satisfied that it has been properly explained to me. I acknowledge that my body contains no metal plates or screws that would prevent me from participating. I have been given the opportunity to ask questions about the procedure and any possible risks. I understand that I can withdraw at any time without any negative impact on any treatment that I may receive through this service. I agree that the data gathered during the course of this study may be published, provided that neither my name nor any other identifying information is used.

Participant signature: Date:

Participant Name (please print):

Independent Witness signature:

If you would like to talk about your participation in the study, please contact Adrian Allen (researcher) on 9385 3595 or Professor Richard Bryant (supervisor) on 9385 3640.

Consent Form – Study 3

The University of New South Wales and Westmead Hospital

CONSENT FORM: Working memory predictors of treatment response in Posttraumatic Stress Disorder (Behavioural and fMRI assessment)

Aim: The aim of this assessment is to better understand the role of your brain in your responses to trauma and psychological treatment

Method: You will be placed inside an MRI scanning machine in which you will lie on your back and wear headphones. You will be asked to perform a brief task in which you will need to watch and respond to letters that appear on a small mirror in front of you. The specific task instructions will tell you how to perform the task. The procedure should last about 60 minutes. In the following 8 weeks you will participate in a program of cognitive behaviour therapy for your posttraumatic stress disorder. This will be administered by a clinical psychologist.

Risks: This procedure should contain no risks to you. It is non-invasive and requires you only to watch the mirror and respond to the letters by pressing a button when necessary. You may decide not to participate in the scanning procedure or choose to stop at any time after it starts. You will still be able to continue with treatment if you do this. All information collected during the experiment will be kept confidential. It will be seen by the researcher and possibly by the supervisor. A clinical psychologist is available to discuss any issues that may arise from this procedure.

I acknowledge that I have read the above information and I am satisfied that it has been properly explained to me. I acknowledge that my body contains no metal plates or screws that would prevent me from participating. I have been given the opportunity to ask questions about the procedure and any possible risks. I understand that I can withdraw at any time without any negative impact on my treatment through this service. I agree that the data gathered during the course of this study may be published, provided that neither my name nor any other identifying information is used.

Participant signature: Date:

Participant Name (please print):

Independent Witness signature:

If you would like to talk about your participation in the study, please contact Adrian Allen (researcher) on 9385 3595 or Professor Richard Bryant (supervisor) on 9385 3640.