NEUROPSYCHOLOGICAL FUNCTION AND FUNCTIONAL IMPAIRMENT IN PTSD

INVESTIGATING NEUROPSYCHOLOGICAL FUNCTIONING, FUNCTIONAL IMPAIRMENT, AND COGNITIVE REMEDIATION IN POSTTRAUMATIC STRESS DISORDER

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Lay Abstract

Posttraumatic stress disorder (PTSD) is a mental health condition that develops after exposure to a traumatic event. It is associated with reduced functioning in important areas of life, including social relationships, work performance, and self-care. PTSD is also associated with reduced cognitive functioning in areas such as memory, planning, and organization. This thesis focuses on examining variables that may be related to these difficulties, including specific symptoms such as difficulty managing emotions and difficulties remaining in the present moment (dissociation). We also investigate a treatment program, Goal Management Training (GMT), aimed at teaching skills to improve cognitive and daily functioning. By understanding what contributes to cognitive functioning and functional difficulties in individuals with PTSD and by providing evidence for a treatment that can improve these difficulties, we hope to improve the lives of individuals with PTSD.

Abstract

Posttraumatic stress disorder (PTSD) is associated with significant functional impairments and disruptions in cognitive functioning. Functional recovery and remediation of cognitive difficulties are oft over-looked treatment targets in this population, despite their significant contribution to the burden of PTSD to the individual and to society. Existing literature suggests that functional impairment and cognitive dysfunction may not respond to first-line treatments for PTSD. Thus, the focus of this thesis was to examine symptom dimensions associated with cognitive dysfunction and functional impairment among individuals with PTSD, and to investigate a novel approach to cognitive remediation, Goal Management Training (GMT), in this population. Study one in this thesis is a review in which we identified a strong relation between dissociative symptoms and neuropsychological functioning, transdiagnostically and among individuals with PTSD. The hypothesis that dissociative symptoms would be strongly related to functional impairment among individuals with PTSD was explored in study two. We found that dissociative symptoms mediated the relation between PTSD symptoms and functional impairment among a sample of military members, veterans, and first responders with PTSD. Study three identified that emotion regulation difficulties and dissociative symptoms most strongly predicted functional impairment among civilians with PTSD and high rates of exposure to childhood abuse and neglect. In study four we investigated the effectiveness of a cognitive training program, Goal Management Training (GMT), in improving cognitive functioning, clinical symptoms, and functional impairment among inpatients with PTSD. Participation in GMT was associated with

improved cognitive functioning and increased ability to engage in goal directed behaviours when highly emotional. This thesis highlights the importance of assessing emotion regulation difficulties and dissociative symptoms in order to target functional impairment and cognitive dysfunction among individuals with PTSD. Moreover, it provides evidence for a potential treatment approach to ameliorate these difficulties.

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List of Abbreviations

ACC	Anterior Cingulate Cortex
ACE	Adverse Childhood Experience
ACE-Q	Adverse Childhood Experiences Questionnaire
ACTH	Adrenocorticotropic Hormone
ADHD	Attention Deficit Hyperactivity Disorder
AI	Anterior Insular Cortex
AH	Auditory Hallucinations
AM	Autobiographical Memory
ANOVA	Analysis of Variance
ANP	Apparently Normal Parts
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BLA	Basolateral Amygdala
BPD	Borderline Personality Disorder
CAPS-5	Clinician Administered PTSD Scale for DSM 5
CBT	Cognitive Behavioural Therapy
CEN	Central Executive Network
CFQ	Cognitive Failures Questionnaire
CI	Confidence Interval
CMA	Centromedial Amygdala
COWAT	Controlled Oral Word Association Task
CPT	Cognitive Processing Therapy
CPT 3.0	Conners' Continuous Performance Test – Third Edition
CTQ	Childhood Trauma Questionnaire
CVLT-II	California Verbal Learning Test II
dACC	Dorsal Anterior Cingulate Cortex
DA	Divided Attention
DASS	Depression Anxiety Stress Scale
DERS	Difficulties in Emotion Regulation Scale
DEX	Dysexecutive Questionnaire
DID	Dissociative Identity Disorder
DKEFS	Delis Kaplan Executive Functioning System
DMN	Default Mode Network
DPD	Depersonalization Disorder
DSM-IV-TR	Diagnostic and Statistical Manual, Fourth Edition, Text Revision

DSM-5	Diagnostic and Statistical Manual, Fifth Edition
DVC	Dorsal Vagal Complex
dlPFC	Dorsolateral Prefrontal Cortex
EF	Executive Function
EM	Episodic Memory
EMDR	Eye-movement Desensitization and Reprocessing
EP	Emotional Parts
GAD	Generalized Anxiety Disorder
GMT	Goal Management Training
HC	Healthy Controls
HPA-axis	Hypothalamic-Pituitary-Adrenal Axis
ICN	Intrinsic Connectivity Network
IM	Implicit Memory
IPV	Intimate Partner Violence
IQ	Intelligence Quotient
LPAG	Lateral Periaqueductal Gray
MDD	Major Depressive Disorder
MDI	Multiscale Dissociation Inventory
M.I.N.I.	Mini International Neuropsychiatric Interview
mPFC	Medial Prefrontal Cortex
NIS	Neutral Identity State
NMDA	Glutamate
OCD	Obsessive Compulsive Disorder
PAG	Periaqueductal Gray
PCC	Posterior Cingulate Cortex
PCL-5	PTSD Checklist for DSM 5
PE	Prolonged Exposure
PFC	Prefrontal Cortex
PHQ-9	Patient Health Questionnaire 9
PPC	Posterior Parietal Cortex
PS	Processing Speed
PTSD	Posttraumatic Stress Disorder
PTSD+DS (or PTSD-DS in chapter 2)	Dissociative Subtype of PTSD
QOL	Quality of Life
RBANS	Repeatable Battery of Neuropsychological Status
SE	Standard Error
SN	Saliance Network

TAS	Toronto Alexithymia Scale
TAU	Treatment As Usual
TBI	Traumatic Brain Injury
TIS	Trauma Identity State
ToM	Theory of Mind
TSST	Trier Social Stress Test
VLPAG	Ventrolateral Periaqueductal Gray
VM	Verbal Memory
VS	Visuospatial Functioning
VSM	Visuospatial Memory
VVC	Ventral Vagal Complex
WAIS-IV	Wechsler Adult Intelligence Scale - IV
WASI-II	Wechsler Abbreviated Scale of Intelligence – II
WHODAS	World Health Organizaion Disability Assessment Schedule
WM	Working Memory
WTAR	Wechsler Test of Adult Reading

Declaration of Academic Achievement

This thesis contains a total of six chapters: Chapters 2 is a review article and chapters 3 through 5 are empirical articles. Chapter 1 provides a background to the material presented in the review chapter and empirical chapters, and chapter 6 discusses the main conclusions, limitations, and future directions.

The review presented in Chapter 2 was conceived by Drs. Margaret McKinnon and Ruth Lanius. J. Boyd conducted the literature review and wrote the initial draft of the manuscript. Dr. McKinnon and J. Boyd are joint first authors on this paper. Drs. McKinnon, R. Lanius, U. Lanius, Frewen, Jetly, and Richardson provided critical revisions. This paper was submitted to and published in *Neurosychologia* in July 2016.

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The research presented in chapter 5 was supported by the Homewood Research Institute, the J.P. Bickell Foundation, and a research studentship from the Research Institute at St. Joseph's Healthcare Hamilton. Dr. McKinnon and J. Boyd collaborated on the conception and design of the project. J. Boyd, C. O'Connor and A. Protopopescu completed data collection and testing of all participants. C. O'Connor ran the study treatment groups. J. Boyd conducted all data analyses and wrote the initial manuscript. Drs. McKinnon, Lanius, Rhind, and Jetly provided critical feedback and revisions for the manuscript. Chapter 5 was submitted to and published in the journal *Chronic Stress* in April 2019.

Chapter 1: General Introduction

This thesis examines neuropsychological functioning and functional outcomes in individuals with posttraumatic stress disorder (PTSD) and the implementation of a novel approach to address these issues among this population. PTSD has an estimated lifetime prevalence of 8% to 9% in North America (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Van Amerigen, Mancini, Patterson, & Boyle, 2008) and is characterized by a distinct set of symptoms that occur following exposure to a traumatic event or prolonged and repeated exposure to traumatic events (e.g., childhood abuse) where an individual experiences, witnesses, learns about, or is exposed to the aversive details of, actual or threatened death, serious injury, or sexual violence (APA, 2013). Symptoms include intrusions (e.g., unwanted memories, nightmares, flashbacks), avoidance of internal (e.g., memories, feelings) or external (e.g., people, places, situations) reminders of the trauma, negative alterations in cognitions and mood (e.g., increased negative emotions, decreased positive emotions, changes in beliefs), and alterations in arousal and reactivity (e.g., hypervigilance, sleep difficulty) (APA, 2013). In addition, approximately 15-30% of individuals with PTSD also experience significant dissociative symptoms of depersonalization (feeling outside of, or as if you do not belong to your own body) and derealization (feeling as though things around you are strange or unfamiliar), and are classified as having the dissociative subtype of PTSD (PTSD+DS) (Armour, Karstoft, & Richardson, 2014; Bennett, Modrowski, Kerig, & Chaplo, 2015; Hansen, Ross, & Armour, 2017; Lanius, Brand, Vermetten, Frewen, & Spiegel, 2012; Stein et al., 2013; Wolf et al., 2012). Critically, PTSD and PTSD+DS are associated with reduced

neuropsychological functioning (McKinnon*, Boyd*, et al., 2016 (chapter two); Scott et al., 2015; Woon, Farrer, Braman, Mabey, & Hedges, 2017) and impairments in day-to-day functioning (Boyd et al., 2018* (chapter three); Boyd et al., 2019a* (chapter four); Johansen, Wahl, Eilertsen, Weisaeth, & Hanestad, 2007; Olatunji, Cisler, & Tolin, 2007; Stein et al., 2013; Westphal et al., 2011). Indeed, PTSD is associated with impairments in workplace performance (e.g., absenteeism) (Kessler, 2000) and social functioning, reduced physical and mental-health related quality of life (Johansen et al., 2007; Olatunji et al., 2007; Pagotto et al., 2015), and high use of medical care services (Amaya-Jackson et al., 1999; Greenberg et al., 1999).

Despite knowledge of the significant functional limitations associated with PTSD, limited work to date has investigated symptoms associated with functional impairment beyond those captured by the DSM-IV-TR criteria for PTSD. This is particularly important given that previous work has established that functional impairment continues to affect individuals following treatment for PTSD or remission of PTSD symptoms (Murphy et al., 2016; Westphal et al., 2011), suggesting that it may be necessary to look beyond those symptoms targeted by the majority of first-line psychotherapies for PTSD in order to understand factors contributing to functional impairment in this population. Investigation of the role of dissociative symptoms and emotion regulation difficulties in predicting functional impairment among individuals with PTSD is a focus of this thesis, given the growing literature associating PTSD+DS with increased disease severity and functional impairment in comparison to PTSD (Stein et al., 2013; Tanner et al., 2019) (possibly via an association with cognitive impairment as explored in chapter two of this

thesis) and previous findings that DSM-IV-TR symptoms consistent with emotion regulation difficulties (e.g., emotional numbing) have been most consistently associated with functional impairment in PTSD (Breslau, Reboussin, Anthony, & Storr, 2005; Malta, Levitt, Martin, Davis, & Cloitre, 2009). As noted above, PTSD is also associated with significant alterations in neuropsychological functioning, which has in turn been associated with reduced day-to-day functioning among individuals with this disorder (Geuze, Vermetten, De Kloet, Hijman, & Westenberg, 2009; Wrocklage et al., 2016). Thus, in addition to exploring symptom profiles associated with functional impairment, this thesis examines a novel approach to remediating cognitive dysfunction and functional impairment among individuals with PTSD.

The overall aim of this thesis is to evaluate the hypothesis that dissociative symptoms and emotion regulation difficulties contribute significantly to functional impairment among individuals with PTSD and to evaluate the hypothesis that cognitive dysfunction and functional impairment can be ameliorated via a cognitive remediation approach, Goal Management Training (GMT), that may have effects not only on cognitive functioning, but also on symptoms of dissociation and emotion dysregulation. This introduction provides an overview of what this thesis examines, divided into three sections to provide a concise summary of literature relevant to the four manuscripts presented hereafter. The first section provides a summary of neuropsychological functioning in PTSD and PTSD+DS, as reviewed in chapter two. The second section provides a summary of functional impairment in PTSD and PTSD+DS as is discussed in chapters three and four. The third section summarizes the literature on cognitive

remediation in PTSD and other affective disorders and the fourth section provides a review of the cognitive remediation strategy employed in chapter four, GMT (Levine et al., 2000; 2011).

1.1 Cognitive functioning in PTSD

Cognitive functioning in PTSD represents a growing area of interest over the past several decades. To date, a handful of systematic reviews and meta-analyses have noted modest, but clear, impairments in cognitive functioning among individuals with PTSD when compared with trauma exposed controls and non-trauma exposed controls (Aupperle, Melrose, Stein, & Paulus, 2012; Johnsen & Asbjørnsen, 2008; Polak, Witteveen, Reitsma, & Olff, 2012; Qureshi et al., 2011; Scott et al., 2014; Woon et al., 2017). Impairments have emerged most prominently in domains of cognition including verbal memory, processing speed, attention, working memory, and executive functioning. For example, a recent meta-analysis reported medium effect size impairments in verbal learning, processing speed, and working memory (Cohen's d = -0.50 - -0.62) and small effect size impairments in verbal memory, executive functioning, visual learning and visual memory (Cohen's d = -0.29 - -0.46) among individuals with PTSD relative to trauma exposed and non-trauma exposed control groups (Scott et al., 2015). Interestingly, recent work indicates that executive functioning impairments may be present regardless of the severity of PTSD symptoms (i.e., both individuals with low symptom severity and those with high symptom severity exhibit executive functioning impairment), suggesting that cognitive impairment should be considered among individuals with PTSD, regardless of the severity of their presentation (Woon et al., 2017).

There has been some debate in the literature as to whether cognitive dysfunction in PTSD develops as a consequence of the traumatic experience and resultant symptomatology, or whether cognitive dysfunction may be a pre-existing vulnerability to the development of PTSD (Marx, Doron-Lamarca, Proctor, & Vasterling., 2009; Gilbertson, Gurvits, Lasko, Orr, & Pitman, 2001; Gilbertson et al., 2006; Parslow & Jorm, 2007; Vasterling et al., 2018, 2002). Recent work suggests a bidirectional relationship between PTSD symptom severity and memory processes among combat veterans. Whereas increases in PTSD symptom severity from pre- to post-deployment are associated with reduced proficiency of visual learning and memory and verbal memory, worse pre-deployment visual learning is associated with more severe post-deployment PTSD symptoms (Vasterling et al., 2018). Taken together, these results suggest that higher levels of pre-trauma cognitive functioning may be protective against the development of PTSD and that post-trauma PTSD symptom severity may contribute to cognitive functioning impairments, particularly in memory processes. Notably, in this study, traumatic brain injury (TBI) (largely reported as mild in nature) was not associated with measures of cognitive functioning impairments (Vasterling et al., 2018). Given the relation between PTSD symptom severity and post-trauma cognitive functioning, it is clinically useful to understand which symptoms contribute specifically to impairments in cognitive functioning among individuals with PTSD. This is particularly important in light of research indicating that impaired cognitive functioning in PTSD is associated with reduced treatment response (Crocker et al., 2018; Wild & Gur, 2008), possibly due to a decreased ability to attend to and encode information during cognitively demanding

therapies such as cognitive behavioural therapy (CBT). This understanding becomes more critical when considering that impaired cognitive functioning is also associated with poor functional outcomes among individuals with PTSD (Foa, Keane, Friedman, & Cohen, 2008; Geuze et al., 2009; Silverberg et al., 2017; Wrocklage et al., 2016) and findings that functional impairments persist following treatment or remission of PTSD symptoms (Murphy et al., 2016; Westphal et al., 2011). Thus, treatment of symptoms associated with impaired cognitive functioning in PTSD may be a significant factor in achieving functional recovery and remediation of cognitive dysfunction in this population.

Limited work to date has investigated which symptom domains among individuals with PTSD are most associated with cognitive impairment, yielding mixed findings (Aase et al., 2017; Dretsch et al., 2012; Judah, Renfroe, Wangelin, Turner, & Tuerk, 2018; Leskin & White, 2007; Olff, Polak, Witteveen, & Denys, 2014; Wrocklage et al., 2016). For example, whereas some studies report that emotional numbing symptoms are associated with impairments in executive functioning (Olff et al., 2014; Wrocklage et al., 2016) and verbal memory (Aase et al., 2017), other studies identify hyperarousal symptoms as important in predicting working memory (Judah et al., 2018), executive functioning and information processing speed (Wrocklage et al., 2016). Additional studies found that the relation between PTSD symptoms and cognitive impairment can be explained, in part, by depressive symptoms (Dretsch et al., 2012; Olff et al., 2014). Importantly, these studies do not assess symptoms that reach beyond those conceptualized within the traditional diagnostic framework of PTSD, but that may be particularly important in our understanding of impaired cognitive functioning in this population,

including symptoms of dissociation and emotion regulation difficulties. Indeed, dissociative symptoms have received increasing attention as a potential clinical mechanism for cognitive dysfunction transdiagnostically and within PTSD samples (e.g., De Bellis, Woolley, & Hooper, 2013; DePrince, Weinzierl, & Combs, 2009; Minshew & D'Andrea, 2015b; Rivera-Vélez, González-Viruet, Martínez-Taboas, & Pérez-Mojica, 2014; Roca, Hart, Kimbrell, & Freeman, 2006; Twamley et al., 2009) and are present to a significant degree among those with PTSD+DS (Armour et al., 2014; Bennett et al., 2015; Hansen et al., 2017; Lanius et al., 2012; Stein et al., 2013; Wolf, et al., 2012). Furthermore, dissociative symptoms have been found to be transdiagnostic in nature, presenting among individuals with trauma-related disorder (e.g., PTSD, borderline personality disorder) as well as other affective disorders (e.g., major depressive disorder) and anxiety-related disorders (e.g., panic disorder) (Belli, Ural, Vardar, Yesilyurt, & Oncu, 2012; Marquez, Segui, Garcia, Canet, & Ortiz, 2001; McKinnon et al., 2016*; Parlar, Frewen, Oremus, Lanius, & Mckinnon, 2016). They have further been demonstrated to be associated with impaired cognitive functioning and functional impairment transdiagnostically (McKinnon et al., 2016; Tanner et al., 2019).

Interestingly, there is emerging evidence that emotion regulation difficulties may also be related to cognitive dysfunction in this population. Although emotion regulation difficulties are captured to some extent within the DSM 5 diagnostic criteria for PTSD (e.g., symptoms such as difficulty experiencing positive emotions or the persistent experience of negative emotions) they also include symptoms such as difficulty accessing emotion regulation strategies, understanding emotions, and acting impulsively in response

to strong emotions (Gratz & Roemer, 2004). Emotion regulation difficulties have been identified both as a pre-trauma vulnerability for posttraumatic stress symptoms (Bardeen, Kumpula, & Orcutt, 2013) and as being associated with higher posttruamtic stress symptoms pos-trauma (Ehring & Quack, 2010; Boden et al., 2013). Emotion regulation and executive functioning are considered strongly related, where it is theorized that executive functioning underlies effective emotion regulation (Hofmann, Schmeichel, & Baddeley, 2012). To date, however, the relation between emotion regulation difficulties and cognitive functioning impairments has not been explored among individuals with PTSD.

Accordingly, in a wide-ranging narrative review presented in chapter two, we take a transdiagnostic approach to examine the relation between dissociative symptoms and cognitive functioning among a wide variety of clinical and non-clinical populations, including those with PTSD. We also explore potential mechanisms by which dissociative symptoms may exert their deleterious effects on cognition. Although we do not explore the relation between emotion regulation and impaired cognitive functioning among those with PTSD in the current thesis, we do explore the influence of emotion regulation difficulties on functional impairment among individuals with PTSD in chapters three and four, an effect which may be related to impaired executive functioning. Future studies will be needed to explore this relation.

1.2 Functional Impairment in PTSD

Before reviewing the literature on functional impairment among individuals with PTSD, it is important to acknowledge that functional impairment has not been well-

defined within the literature and that there are conflicting definitions (Ustun & Kennedy, 2009). For example, the DSM refers to functional impairment as limitations in social, occupational, and other important areas of life, but does not identify additional areas or clearly define limitations (Ustun & Kennedy, 2009). In comparison, the WHO's international classification of functioning, disability, and health (ICF) refers to functioning as a neutral term encompassing all body functions including body functions (physiological functions), body structures (anatomical parts of the body), activity (execution of tasks or actions by an individual) and participation (involvement in a life situation) (WHO, 2001) and defines disability as activity limitations and participation restrictions that are caused by the interaction between the individual and their health condition and environmental or personal factors (WHO, 2001). Ustun & Kennedy (2009) also point out that the issue of disability or impairment is further complicated by the distinction between these constructs and severity of illness whereby individuals assume that increased severity of illness is synonymous with increased disability. Functional consequences of a disorder can be distinguished from illness severity by examining what a patient has difficulty doing rather than the severity of their symptoms. Finally, quality of life although related to functioning or functional impairment, is also a distinct concept which can be defined as an individual's impression of the "goodness" of multiple aspects of their life, including sense of fulfillment or satisfaction in areas such as work or personal relationships (Theofilou, 2013).

Improving our understanding of functional impairment among individuals with PTSD is critical on both an individual and a societal level. Estimates of lost work

productivity among those with PTSD are similar to that of individuals with Major Depressive Disorder, leading to approximately 0.8 days of missed work per month and 2.8 days per month of reduced work productivity (Kessler, 2000). Moreover, PTSD is associated with significant economic burden, where a recent study in Northern Ireland estimated the total annual cost of PTSD to be £200,779,165 or $246,637,126 (USD) after accounting for service visits, medication, productivity losses and presenteeism (working while ill leading to reduced productivity) (Ferry et al., 2015). Impairments in functioning remain difficult to ameliorate among individuals with affective disorders, including those with PTSD. For example, in a sample of primary care patients with PTSD, patients with a history of PTSD but no current PTSD continued to experience significantly reduced mental health-related quality of life in comparison to trauma-exposed controls, suggesting that functional impairment may persist beyond symptomatic recovery in this disorder (Westphal et al., 2011). Although some studies report an improvement in functioning following psychotherapy for PTSD (Galovski, Monson, Bruce, & Resick, 2009; Monson et al., 2012), others have reported that increased supports may be necessary to target functional impairment among individuals with PTSD (Murphy et al., 2016). In particular, among an inpatient treatment sample of veterans with PTSD, Murphy et al. (2016) reported that worse functional impairment immediately following treatment was predictive of higher PTSD symptoms at 6 and at 12 months post-treatment, leading to the hypothesis that if functional recovery is not achieved following treatment, PTSD symptoms may be more severe post-treatment. Moreover, in a meta-analysis comparing effectiveness of psychotherapies for PTSD, evidence was deemed insufficient or low

regarding the effect of psychotherapies on disability or functional outcomes for therapies including cognitive processing therapy, exposure therapies and eye-movement desensitization and reprocessing and mixed (exposure plus cognitive restructuring) cognitive behavioural therapies (Cusack et al., 2016). Taken together, these findings suggest that functional impairment is not adequately measured or assessed in treatment studies and that current treatments may not lead to sufficient recovery of functioning among individuals with PTSD.

1.2.1. PTSD Symptom Dimensions and Functional Impairment

Work to date investigating functional impairment among individuals with PTSD has focused primarily on investigation of symptoms captured by the diagnostic criteria for PTSD as defined in the DSM-IV-TR, including re-experiencing, avoidance/numbing, and hyperarousal (APA, 2000). Here, previous work indicates that the avoidance/numbing cluster of symptoms is most strongly associated with functional impairment among individuals with PTSD including among community samples (Breslau et al., 2005), victims of terrorism (Malta et al., 2009; North et al., 1999), and military members or veterans (Rona et al., 2009; Shea, Vujanovic, Mansfield, Sevin, & Liu, 2010) (although others have found symptoms of hyperarousal or re-experiencing to be most related to functioning (Heir, Piatigorsky, & Weisæth, 2010; Maguen, Stalnaker, McCaslin, & Litz, 2009; Norman, Stein, & Davidson, 2007)). However, avoidance and emotional numbing have been conceptualized as representing distinct symptoms and are presented as such in DSM 5 (Asmundson, Stapleton, & Taylor, 2004) leading to the identification of numbing symptoms as being more closely tied to functional impairment among individuals with

PTSD (Breslau et al., 2005; Malta et al., 2009). Emotional numbing (or restricted range of affect) may be part of a larger cluster of symptoms reflective of emotion regulation difficulties.

1.2.2. Emotion Dysregulation and Functional Impairment in PTSD

Findings that emotional numbing is closely tied to functional impairment are consistent with more recent findings that alterations in the mood and cognition symptom (including symptoms reflecting restricted positive affect and increased negative affect) cluster are most closely related to functional impairment (Ross, Murphy, & Armour, 2018) and previous findings that emotion regulation difficulties are predictive of functional impairment among women with PTSD and a history of childhood sexual or physical abuse after accounting for overall PTSD symptom severity (Cloitre, Miranda, Stovall-McClough, & Han, 2005). Among individuals with PTSD, those who have experienced significant childhood abuse are at risk for increased levels of emotion dysregulation as is evidenced by an established body of literature associating childhood abuse, emotion dysregulation, and PTSD symptomatology (Cloitre, Stovall-McClough, Zorbas, & Charuvastra, 2008; Ehring & Quack, 2010; Stevens et al., 2013). Thus, symptoms of emotion regulation difficulties may be important contributors to functional impairment among individuals with PTSD, particularly those with a history of childhood abuse. Accordingly, chapter three of this thesis investigates the hypothesis that emotion regulation difficulties contribute significantly to functional impairment in an inpatient sample of civilians with PTSD and high rates of exposure to childhood abuse.

1.2.3. Dissociative Symptoms and Functional Impairment in PTSD

Dissociative symptoms may also be a key predictor of functioning among individuals with PTSD and PTSD+DS. As noted above, PTSD+DS has been associated with increased disease severity and functional impairment in comparison to PTSD (Stein et al., 2013; Tanner et al., 2019). In particular, dissociative symptoms have been associated with increased symptom severity, depressive and alcohol abuse symptoms, and psychiatric comorbidity among individuals with PTSD resulting from military service or combat exposure, incarcerated youth, motor vehicle accident survivors, physical or sexual assault victims, and victims of childhood abuse (Bennett et al., 2015; Blevins, Weathers, & Witte, 2014; Tsai, Armour, Southwick, & Pietrzak, 2015; Waelde, Silvern, & Fairbank, 2005; Wolf, Lunney, et al., 2012; Wolf, Miller, et al., 2012). Moreover, there is an established body of literature implicating dissociative symptoms in reduced cognitive functioning among individuals with PTSD (reviewed by McKinnon, Boyd, et al., 2016; chapter two of this thesis). In particular, dissociative symptoms are associated with worse working memory, attention, verbal memory and executive functioning among individuals with PTSD (Kaplow, Hall, Koenen, Dodge, & Amaya-Jackson, 2008; Minshew & D'Andrea, 2015; Morgan, Doran, Steffian, Hazlett, & Southwick, 2006; Rivera-Vélez et al., 2014; Roca et al., 2006; Twamley et al., 2009). Given the relation between cognitive functioning and functional outcomes among PTSD samples (Ainamani, Elbert, Olema, & Hecker, 2017; Geuze et al., 2009; Wrocklage et al., 2016), it is possible that dissociative symptoms are associated with increased functional impairment via their relation to reduced cognitive functioning. In chapters three and four, we explore the impact of dissociative symptoms on functioning in civilian and military/first responder populations,

respectively, in order to evaluate the hypothesis that dissociative symptoms contribute significantly to functional impairment among individuals with PTSD. Notably, the data for chapters three and four of this thesis were collected utilizing the same retrospective chart review approach but look at different subsets of the collected data (e.g., civilians in chapter four and military members, veterans, and first responders in chapter three), thus these papers contain substantially similar methodology sections.

1.3 Remediation of Cognitive and Functional Difficulties in PTSD

Despite knowledge that 1) PTSD is associated with cognitive functioning impairments, and 2) cognitive impairments in PTSD are associated with increased functional impairment and reduced treatment effectiveness, very limited work has investigated therapeutic approaches to cognitive remediation among individuals with PTSD. This contrasts significantly with the large literature base exploring cognitive remediation approaches among other psychiatric disorders, such as schizophrenia and to a lesser extent, major depressive disorder (Motter et al., 2016; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). To date, four studies have investigated the efficacy of cognitive remediation approaches among individuals with PTSD, with two being published in the last six months, demonstrating the nascent nature of this literature (Bomyea, Stein, & Lang, 2015; Clausen et al., 2019; Fonzo et al., 2019; Saunders et al., 2015). Notably, all of these studies have employed computerized training programs which have been criticized for a lack of generalizability to everyday functioning (Barlati, Deste, De Peri, Ariu, & Vita, 2013; Prikken, Konings, Lei, Begemann, & Sommer, 2018). Further, although some have reported improvements in domains of cognition associated

with executive functioning (e.g., working memory) among individuals with affective disorders (e.g., MDD) (Meusel et al., 2013), a recent meta-anlaysis found that computerized training programs have not been associated with improvements in executive functioning among individuals wth MDD (Motter et al., 2016). Saunders et al. (2015) combined computer-based working memory training with transcranial direct current stimulation in a case series with four patients and found clinically (but not statistically) significant improvements on tests measuring attention, working memory, verbal memory, and visual memory. Bomyea et al. (2015) studied an eight-session computerized cognitive training program aimed at reducing proactive interference (the inability to inhibit irrelevant or unwanted information from entering working memory) among individuals with PTSD in comparison with a control condition (using training with low impact on proactive interference). Here, participants in the active treatment condition reported reduced re-experiencing symptoms and performed better on a working memory task in comparison to those in the control condition (Bomyea et al., 2015).

Consistent with concerns regarding generalizability of computer-based training programs noted in other populations (Barlati et al., 2013; Motter et al., 2016), two more recent studies have failed to find significant effects of computerized training programs on cognitive or clinical outcomes in PTSD. Clausen et al. (2019) examined a computerized executive function training program among male combat veterans with full or partial PTSD and combat-exposed controls (as a normative comparison group), where participants in the PTSD group were randomized to the training condition or a placebo condition (word games). Here, they reported that both the active and control condition

participants reported reductions in PTSD and depressive symptoms and while the treatment group demonstrated improvements on Lumosity training tasks, no significant effects were found for standardized assessments of neuropsychological function, neurobehavioural symptoms, or brain activation (Clausen et al., 2019). Similarly, Fonzo et al. (2019) reported the results of two randomized clinical trials investigating an internet-delivered cognitive and affective remediation training program among individuals with acute PTSD (recruited from the emergency department) and those with chronic PTSD who were randomized to receive either a training program aimed at improving affective bias toward negative, threatening, or trauma-related stimuli (positive emotion recognition, resisting negative emotion distraction) and cognitive capacities (attention, working memory, task shifting, processing speed) or control conditions which were playing online games or daily reading of internet news or lifestyle articles. Here, the authors failed to find significant effects of training on cognitive processes in either the acute or chronic PTSD groups. Further, although they found an increase in the speed at which individuals in the treatment condition with chronic PTSD could identify fearful faces, this was not associated with any changes in PTSD symptoms (Fonzo et al., 2019).

Thus, to date, research investigating potential cognitive remediation programs among individuals with PTSD has focused on the use of computerized cognitive training programs with limited success, suggesting poor generalizability and clinical utility of these approaches among individuals with PTSD. These types of training programs often consist of "bottom-up" or restitution-based approaches that focus on training of basic skills (e.g., attention via skill-drill exercises) and advancing to more complex skills. In

contrast, top-down approaches that begin with remediation of complex skills (e.g., executive function or problem solving) with the aim of improving downstream skills (e.g., attention, memory) and generalizing to real-world functioning (Barlati et al., 2013) may be more appropriate.

1.4 Goal Management Training

Goal Management Training (GMT) is one such "top-down" approach to cognitive remediation that aims to teach strategies that assist individuals in regaining executive control and improving the ability to engage in goal-directed behaviours (i.e., behaviours that lead to the achievement of an identified goal) (Levine et al., 2000). GMT is a group-based therapy typically consisting of nine weekly 2-hour sessions, taught in a step-by-step manor where patients learn skills such as "stopping" the automatic pilot, monitoring working memory, identifying goals, monitoring progress toward achieving goals, decision making, and balancing competing goals (Levine et al., 2000). GMT achieves ecological validity by having participants complete daily skills practice to achieve real-life goals and includes discussion and troubleshooting of skills practice during group sessions. Notably, GMT has been proven effective in various psychiatric and non-psychiatric populations both as a stand-alone treatment and when combined with psychotherapy (Stamenova & Levine, 2018).

GMT is based theoretically on the assertion that the sustained attention system is critical to the maintenance of higher order goals and the simultaneous inhibition of automatic processes (Robertson & O'Connell, 2012). Disruptions in this system are hypothesized to lead automatic processes to override higher order goals leading to

disruptions in executive functioning. Furthermore, executive functioning and emotion regulation are inextricably linked, whereby disruptions in executive function may lead to disproportional allocation of cognitive resources to affect regulation and lead to the use of ineffective emotion regulation strategies (Diamond, 2013; Morillas-Romero, Tortella-Feliu, Balle, & Bornas, 2015). Thus, remediation of executive functions is expected to lead not only to improved cognitive functioning and functional outcomes, but also to improved ability to regulate intense emotions among individuals with PTSD. Furthermore, dissociative symptomatology is also related significantly to executive functioning, as reviewed in Chapter two of this thesis (McKinnon et al., 2016). Here, we discuss the shared neural underpinnings of dissociative phenomena and higher-order cognitive operations, leading to competition for shared processing resources and reduced cognitive functioning among individuals experiencing significant dissociative symptoms. Thus, the resumption of active self-monitoring of both internal processes (e.g., working memory) and external processes (e.g., goal directed behaviours) encouraged via skills taught in GMT may also lead to reductions in dissociative symptomatology.

GMT has been validated in populations noted to experience cognitive difficulties similar to those seen in PTSD, including executive functioning difficulties and difficulties with memory, attention, working memory, and processing speed, including individuals who have experienced TBI (Krasny-Pacini, Chevignard, & Evans, 2014; Levine et al., 2000; 2011), older adults (Levine et al., 2007; van Hooren et al., 2007), those with attention deficit hyperactivity disorder (In de Braek, Dijkstra, Ponds, & Jolles, 2012), polysubstance abuse (Alfonso, Caracuel, Delgado-Pastor, & Verdejo-García, 2011), and

spina bifida (Stubberud, Langenbahn, Levine, Stanghelle, & Schanke, 2014). In a recent meta-analysis, GMT was reported to have significant benefits on standardized executive function tests and tasks meant to simulate every-day functioning at post-treatment and follow-up (small-medium effect size), as well as a small effect size improvement on self-reported executive function at post-treatment, although this was not sustained at follow-up (Stamenova & Levine, 2018). Small to medium effect size improvements were also found on measures of working memory and long-term memory (Stamenova & Levine, 2018).

Despite its documented effectiveness in neurological and some psychiatric populations, GMT has not yet been investigated as a cognitive remediation approach among individuals with PTSD. It represents a novel, contrasting intervention approach to the issue of cognitive and functional impairment in PTSD (and affective disorders more generally). In Chapter five of this thesis we investigate the feasibility and effectiveness of GMT in reducing cognitive difficulties and improving functioning in an inpatient sample of individuals with PTSD. We also examine the impact of this intervention on clinical symptomatology associated with PTSD and related to executive functioning and functional impairment, including emotion regulation difficulties.

Overall, our understanding of cognitive and functional impairments among individuals with PTSD has been limited by an investigation of PTSD as described in DSM-IV-TR. Therefore, the aim of this research program was to expand our understanding of functional and cognitive impairments in order to characterize the contributions of symptoms captured of emotion regulation difficulties and dissociative

symptomatology which are both hypothesized to be significantly related to cognition and functioning. Moreover, this thesis makes a significant contribution to growing efforts to address cognitive and functional impairments in PTSD by providing preliminary evidence for a cognitive remediation approach, GMT, in ameliorating such difficulties among individuals with PTSD.

Chapter 2: A review of the relation between dissociation, memory, executive functioning and social cognition in military members and civilians with neuropsychiatric conditions

Chapter Link

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Dissociative symptomatology is characterized by a detachment from the present moment and alterations in consciousness, and is strongly associated with trauma-related psychopathology. Dissociative symptoms have also been associated with reduced neuropsychological functioning among individuals with PTSD and transdiagnostically. This chapter is a review of the relation between dissociative symptomatology and neuropsychological functioning across psychiatric populations and also provides a proposed neurobiological model to understand the relation between dissociation and neuropsychological functioning.

A review of the relation between dissociation, memory, executive functioning and social cognition in military members and civilians with neuropsychiatric conditions

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ABSTRACT

Dissociative experiences, involving altered states of consciousness, have long been understood as a consequence or response to traumatic experiences, where a reduced level of consciousness may aid in survival during and after a traumatic event. Indeed, the dissociative subtype of post-traumatic stress disorder (PTSD-DS) was added recently to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Dissociative symptoms are present across a host of neuropsychiatric conditions, including PTSD, psychotic spectrum illnesses, anxiety and mood disorders. Transdiagnostically, the presence of dissociative symptoms is associated with a greater illness burden and reduced treatment outcomes. Critically, dissociative symptoms are related to impaired performance on measures of attention, executive functioning, memory, and social cognition and may contribute to the widespread cognitive dysfunction observed across psychiatric illnesses. Despite this knowledge, the relation between dissociative symptoms and reduced cognitive function remains poorly understood. Here, we review the evidence linking dissociative symptoms to cognitive dysfunction across neuropsychiatric disorders. In addition, we explore two potential neurobiological mechanisms that may underlie the relation between dissociative symptoms and cognitive dysfunction in trauma-related neuropsychiatric conditions. Specifically, we hypothesize that: 1) functional sensory deafferentation at the level of the thalamus as observed in the defense cascade model of dissociation may underlie reduced attention and arousal leading to progressive cognitive dysfunction and; 2) altered functional connectivity between key brain networks

implicated in cognitive functioning among may represent a critical neurobiological mechanism linking dissociative symptoms and cognitive dysfunction in patients with PTSD-DS and transdiagnostically.

Keywords: Dissociation; Trauma; Memory; Executive functioning; Social cognition; Intrinsic networks

Highlights

- The relation between dissociation and cognitive dysfunction is reviewed
- Functional sensory deafferentation at the level of the thalamus may lead to progressive cognitive dysfunction
- Altered functional connectivity between key intrinsic neural networks may underlie cognitive dysfunction
- Clinical and treatment implications are discussed

1.0 Introduction

Dissociation refers to a disturbance in the normal integration of consciousness, memory, identify, emotion, perception, body representation, motor control, and behaviour (APA, 2013). Whereas some theoretical frameworks describe dissociative experiences as involving a division within the sense of self (van der Hart et al., 2004; 2006), others highlight altered states of consciousness surrounding dissociative experiences (Cardeña and Carlson, 2011; Frewen and Lanius, 2015; Holmes et al., 2005; Putnam, 1997; Spiegel et al., 2013; Steele et al., 2009). Core symptoms of dissociation include disengagement (not paying attention or "spacing out"), emotional constriction, memory disturbances, depersonalization (feeling outside of and as if you do not belong to your own body), derealization (feeling as though things around you are not real) and identity dissociation (Briere et al., 2005; Dell and Lawson, 2009; Lanius et al., 2012; Spiegel et al., 2013). Dissociative experiences have been conceptualized as lying on a continuum from normal integration of consciousness followed by depersonalization/derealization through to identity fragmentation (Bernstein and Putnam, 1986; Bremner and Marmar, 1998; Putnam, 1997b). One recent theory suggests that dissociative experiences may be separated into two distinct forms, involving detachment (e.g., altered states of consciousness) and compartmentalization (e.g., inability to control deliberately processes such as memory) (Holmes et al., 2005). Other researchers have noted the distinction between altered states of consciousness and structural dissociation (e.g., divisions in personality), while noting that the two may co-occur in trauma-related disorders (Steele et al., 2009). Regardless of theoretical orientation, trauma has long been recognized as an

antecedent to dissociative symptoms where in the early 20th century Pierre Janet first described dissociation as the most direct defense against overwhelming traumatic experiences (Janet, 1901). Indeed, the trauma model of dissociation suggests that dissociation is a psychobiological response to threat or danger that allows an organism to engage in automized behaviour, enhancing analgesia, depersonalization, and removal of oneself from traumatic or catastrophic experiences with the aim of enhancing survival during and after the event (Dalenberg et al., 2012). Accordingly, dissociation allows for psychological escape when physical escape is not possible (Putnam, 1997). In addition to their association with traumatic life events, dissociative symptoms are frequently associated with disrupted development of attachment relationships (Dutra et al., 2009; Liotti, 2006, 2004; Schore, 2002, 2009).

Dissociation is associated classically with trauma-related disorders following both civilian and military trauma exposure, including borderline personality disorder (BPD) (Bremner, 2005; Meares, 2012; Vermetten and Spiegel, 2014; Winter et al., 2015), dissociative disorders (Brand et al., 2012; Dell and O'Neil, 2009; Spiegel et al., 2013; Van der Hart et al., 2006) and post-traumatic stress disorder (PTSD) (Bremner and Brett, 1997; Dalenberg and Carlson, 2012; Ginzburg et al., 2006; Lanius et al., 2010, 2012; Stein et al., 2013; Wolf et al., 2012a, 2012b). In response to recent work indicating that a subset of approximately 15 -30 % of patients with PTSD present with symptoms of depersonalization and derealization (Armour et al., 2014; Blevins et al., 2014; Frewen et al., 2015; Lanius et al., 2010, 2012; Putnam et al., 1996; Spiegel et al., 2013; Steuwe et al., 2012; Tsai et al., 2015; Wolf et al., 2012a, 2012b), the recently revised Diagnostic and

Statistical Manual of Mental Disorders (DSM-5) now includes a dissociative subtype of PTSD (PTSD-DS). Notably, dissociative symptomatology can also present in syndromes less frequently associated with trauma including major depressive disorder (MDD) (Bob et al., 2008; Molina-Serrano et al., 2008; Mula et al., 2007; Sar et al., 2013), anxiety disorders (Ball et al., 1997; Marquez et al., 2001; Mula et al., 2007; Sierra et al., 2012), obsessive compulsive disorder (OCD) (Belli, 2014; Belli et al., 2012; Rufer et al., 2006a; Semiz et al., 2014; Watson et al., 2004), bipolar disorder (Hariri et al., 2015; Mula et al., 2009; Oedegaard et al., 2008), alcohol and drug abuse and dependence (Evren et al., 2011, 2008, 2007; Tamar-Gurol et al., 2008) and schizophrenia (Haugen and Castillo, 1999; Holowka et al., 2003; Sar et al., 2010; Spitzer et al., 1997; Yu et al., 2010). Taken together, the widespread appearance of dissociative symptoms suggests high rates of trauma exposure across neuropsychiatric conditions and points to the need for careful assessment of dissociation as a transdiagnostic psychiatric symptom.

Given that dissociation is associated with a disrupted integration of consciousness, memory, and behaviour, involving symptom clusters of memory disturbance and disengagement, it follows that individuals who experience dissociative symptoms would experience disruptions in cognitive function, affecting memory, attention, and executive functioning. This observation is in line with widespread reports of cognitive dysfunction across psychiatric disorders associated with dissociative symptoms, including schizophrenia (Millan et al., 2012; Wykes et al., 2011), MDD (Marazziti et al., 2010; Millan et al., 2012; Rock et al., 2013), bipolar disorder (Lee et al., 2014; Millan et al., 2012), OCD (Shin et al., 2014), and both civilian and combat-related PTSD (Aupperle et

al., 2012; Millan et al., 2012; Polak et al., 2012; Scott et al., 2014). Notably, although the results of one systematic review pointed towards greater cognitive dysfunction among individuals with combat-related as compared to civilian PTSD (Polak et al., 2012), a recent quantitative meta-analysis reported no differences in severity of cognitive dysfunction across trauma etiologies (Scott et al., 2014). Critically, poor cognitive functioning is thought to contribute to the development and maintenance of these disorders, where, for example, executive dysfunction impacts negatively on response to pharmacological and non-pharmacological treatments for psychiatric disorders including mood disorders and PTSD (Dunkin et al., 2000; Polak et al., 2012; Wild and Gur, 2008) (but see Walter et al. (2010)). Here, the ability to engage in and successfully complete treatment relies heavily on higher-order cognitive processes. Indeed, leading treatment interventions for affective disorders, including PTSD and depression (e.g. cognitive behavioural therapy), rely heavily upon cognitive processing resources (e.g. working memory; attention) that are impacted negatively by these conditions.

A growing body of evidence points towards a relation between dissociative symptoms, including altered states of consciousness and identity fragmentation, and cognitive dysfunction in trauma-related psychiatric conditions. Specifically, dissociative symptoms have been linked to reduced attention, executive functioning, and memory performance in healthy individuals (Amrhein et al., 2008; Bergouignan et al., 2014; Brewin et al., 2013; Bruce et al., 2007; Freyd et al., 1998; Olsen and Beck, 2012), trauma-exposed individuals from the general (Cromer et al., 2006) and military populations (Morgan et al., 2006), and in military and civilian psychiatric samples, including

individuals with PTSD (Chae et al., 2011; De Bellis et al., 2013; DePrince et al., 2009; Kaplow et al., 2008; Minshew and D'Andrea, 2015; Rivera-Vélez et al., 2014; Roca et al., 2006; Twamley et al., 2009), BPD (Haaland and Landrø, 2009; Winter et al., 2015), MDD (Parlar et al., 2016), DID (Dorahy et al., 2006, 2005, 2002), and DPD (Guralnik et al., 2007, 2000). The nature of the relation between dissociation and cognitive dysfunction, however, remains poorly elucidated.

Our primary objective was therefore to review emerging evidence supporting the link between dissociative symptoms and cognitive dysfunction among healthy individuals and military and civilian samples with trauma-related neuropsychiatric conditions. In addition to surveying the results of studies involving participants with civilian or military-related PTSD, we examine findings across the broad range of psychiatric conditions that are associated with dissociative symptoms. Here, we begin by reviewing the evidence for PTSD-DS, as well as for considering dissociation as a transdiagnostic feature across psychiatric conditions. The evidence linking dissociation to cognitive dysfunction is then identified. We next introduce a neurobiological model of dissociation that provides a partial explanation for the emergence of cognitive dysfunction in patients with dissociation. A secondary aim of this review is to propose a model linking dissociation and cognitive dysfunction to alterations in connectivity among three key brain networks, the default mode network (DMN), central executive network (CEN), and salience network (SN) that are consistently reported altered in psychiatric disorders. Accordingly, we propose a model where alterations among these key brain networks proposed to underlie psychopathology across psychiatric disorders (Menon, 2011) contribute to

reduced cognitive functioning in individuals who experience high levels of dissociation. Specifically, reduced coupling between the networks responsible for orienting individuals to internal and external stimuli (the SN) and the executive control (CEN) and self-referential processing networks (DMN) may be a key neurobiological mechanism by which dissociation and cognitive dysfunction are linked. We also examine the role of brainstem regions, including the periaqueductal gray (PAG) in an attempt to elucidate the relation between functional connectivity between neural regions involved in defensive responses and basic emotional processing and those implicated in higher emotional and cognitive brain networks.

2.0 Evidence for the Dissociative Subtype of PTSD

Over the past decade, a significant body of research has emerged pointing towards a dissociative subtype of PTSD, leading to the recent addition of this subtype to the DSM 5 (APA, 2013). Early work, including that of Putnam et al. (1996), indicated that a subset of individuals with PTSD experienced chronically higher levels of dissociation (see also Ginzburg et al., 2006). Building on this seminal work, Lanius et al. (2010) proposed a neurobiological model of PTSD-DS, characterized primarily by symptoms of derealization, depersonalization, and tonic hypoarousal that contrasted with the more typical symptoms of re-experiencing and hyperarousal that feature predominately in the majority of cases of PTSD. Subsequent latent class and confirmatory factor analyses have indicated that approximately 15-30% of individuals with PTSD experience symptoms of depersonalization and derealization that are consistent with the dissociative subtype (Armour et al., 2014; Bennett et al., 2015; Blevins et al., 2014; Frewen et al., 2015;

Spiegel et al., 2013; Steuwe et al., 2012; Tsai et al., 2015; Wolf et al., 2012a, 2012b) Critically, increased disease severity (e.g., elevated risk of 12-month suicidality), earlier age of onset, and poorer functional outcomes have been reported in this subtype (Stein et al., 2013). Indeed, dissociative symptoms are associated with elevated rates of suicidal ideation, self-harm and multiple suicide attempts, with multiple suicide attempts significantly associated with dissociative status even after controlling for diagnoses such as PTSD and BPD (Foote et al., 2008).

2.0.1 Impact of dissociative symptoms on treatment response

Dissociative symptoms also appear predictive of treatment response. In a recent study, levels of dissociation present at initial assessment following an acute trauma were the only significant predictor of treatment response at one and three months follow-up (Price et al., 2014). Indeed, among individuals with BPD, pre-treatment dissociative symptomatology predicted reduced symptom improvement following treatment with dialectical behavioural therapy (Kleindienst et al., 2011). In addition, a recent study indicated that whereas more frequent experiences of depersonalization and derealization were associated with non-response to treatment with eye movement desensitization reprocessing therapy, factors including avoidance, hyperarousal, and intrusion were not (Bae et al., 2016). These findings may be a consequence of detachment and avoidance, symptoms related to PTSD-DS, and associated reductions in cognitive and affective processing of trauma in its aftermath. Interestingly, Sar (2015) has proposed the concept of a “dissociative depression” where recovery from the dissociative aspects of the illness is associated with relief of depressive symptoms. This potential subtype of depression is

thought to be treatment resistant, and is associated with an earlier onset, increased suicidality and somatic complaints. Interestingly, a recent study investigating the efficacy of exposure therapy compared with present-centered therapy for female veterans and active duty members of the military with PTSD found a small but significant difference in treatment response (collapsed across treatment types) between those with versus without PTSD-DS. Here, individuals with the non-dissociative subtype of PTSD showed a 10-point greater improvement in clinician administered PTSD scale (CAPS) score compared to individuals with PTSD-DS. However, the authors questioned the clinical significance of this difference and raised doubts that PTSD-DS is a contraindication for the use of exposure therapy in the treatment of PTSD (Wolf et al., 2015; see also Cloitre et al., 2012; Resick et al., 2012). Similar reports that dissociative symptoms do not impact negatively on treatment outcome have been made elsewhere (Hagenaars et al., 2010; Speckens et al., 2006). Importantly, in the Wolf et al. (2015), Hagenaars et al. (2010), and Speckens et al. (2006) studies, the authors focused on measures of trait dissociation, rather than state dissociation experienced at the time of treatment sessions, where trait dissociation refers to the tendency of the individual to dissociative over time, and state dissociation refers to acute dissociative experiences. Indeed, it is measures of state dissociation that have shown to interrupt emotional learning in individuals with BPD, a type of learning crucial for effective learning in cognitive behavioural therapies (Ebner-Priemer et al., 2009). As such, future studies will be necessary to examine the effects of state dissociation directly before and during treatment sessions on treatment outcome.

2.0.2 Dissociative symptomatology and immune system functioning

Neurobiological studies of PTSD-DS continue to underscore the observation that depersonalization and derealization represent distinct responses from re-experiencing/hyperarousal reactivity in persons with PTSD (Lanius et al., 2010, 2012, 2006; Nicholson et al., 2015). Specifically, reliving responses are thought to be mediated by a failure of prefrontal inhibition or top-down control of limbic regions, while depersonalization and derealization responses are thought to be mediated by increased prefrontal inhibition of limbic regions. These findings are mirrored in the reactivity of the hypothalamic-pituitary-adrenal axis (HPA axis) among individuals with PTSD. Specifically, roughly half of female PTSD patients exposed to a Trier Social Stress Test (TSST) were classified as HPA-axis non-responders in that they did not exhibit an expected increase in cortisol levels in response to the TSST. Critically, HPA-axis non-responders also showed significantly higher levels of trauma-related dissociative symptoms as compared to PTSD HPA-axis responders. These findings represent the first empirical evidence of differences in HPA-axis reactivity among individuals with PTSD in relation to dissociative symptomatology (Zaba et al., 2015). Similarly, recent work by Quevedo et al. (2012) reported a flattening of the cortisol awakening response among pre- or early-pubertal youth who had been institutionalized (e.g., orphanages) early in life that was no longer apparent when mid-late pubertal post-institutionalized youth were tested. These findings are of interest given the well-established role of early childhood adverse experiences and disrupted attachment in the development of dissociative psychopathology (Carlson et al., 2009), while also suggesting that pre-pubertal alterations in HPA-axis function may be re-programmed through puberty (Quevedo et al., 2012). By contrast,

increased salivary cortisol in response to exposure to trauma-related material was noted in a sample of individuals with PTSD who had been raped and who described coping strategies including emotional shut-down and immobilization responses (processes that have been linked to dissociation) as compared to those with PTSD who had not been raped but had equivalent symptom severity (Gola et al., 2012). Additional research will be required to determine the directionality of the relation between cortisol and dissociative symptoms among individuals with PTSD. Notably, immune responses, including markers of inflammation, have also been implicated in PTSD (Passos et al., 2015).

Interestingly, among individuals with depression, higher levels of traumatic stress-related symptoms and somatoform dissociation has been related to higher levels of interleukin-6 (Bob et al., 2010). Similarly, among individuals with unipolar depression, tumour necrosis factor alpha has been related to dissociation, but not to depressive or PTSD symptoms (Bizik et al., 2011). Further, in a recent meta-analysis, multiple inflammatory biomarkers, including interleukin-6, tumour necrosis factor-alpha, and c-reactive protein, were associated with trauma exposure among a heterogeneous psychiatric sample (although dissociation was not investigated as a factor here) (Tursich et al., 2014). Critically, both elevated cortisol (Brown et al., 2013; Lara et al., 2013) and increased inflammatory markers (Bermejo et al., 2008; Guerreiro et al., 2007; Patanella et al., 2010; Peng et al., 2013; Yaffe et al., 2003) have been related to cognitive dysfunction in healthy controls and patient populations, highlighting another potential link between dissociative processes and cognitive dysfunction.

2.0.3 Neuroimaging and dissociative symptomatology

Recent work has begun to elucidate differences in functional connectivity within and between intrinsic connectivity networks (ICNs) in relation to dissociative symptomatology among individuals with PTSD. ICNs refer to brain networks made up of brain regions that are temporally and functionally connected. Three key ICNs have been implicated in psychiatric disorders as well as in understanding higher cognitive function (Menon, 2011). These include the central executive network (CEN), salience network (SN), and the default mode network (DMN). The CEN consists of two main nodes, the dorsolateral prefrontal cortex (dlPFC) and the posterior parietal cortex (PPC), and is involved in the active maintenance and manipulation of information in working memory and executive functioning (Habas et al., 2009; Koechlin and Summerfield, 2007; Miller and Cohen, 2001; Petrides, 2005; Seeley et al., 2007). The SN is anchored by the dorsal anterior cingulate cortex (dACC) and the anterior insular cortex (AI), and is important for the detection, integration, and filtering of internal and external stimuli (Dosenbach et al., 2007; Lovero et al., 2009; Seeley et al., 2007; Sridharan et al., 2008). Finally, the DMN is made up of cortical midline structures and the lateral parietal lobes, with anchors in the posterior cingulate cortex (PCC) and the medial prefrontal cortex (mPFC). In contrast to the CEN, the DMN is generally deactivated during cognitive tasks and is involved in self-related processes, autobiographical memory, and social cognition (Amodio and Frith, 2006; Buckner et al., 2008; Greicius et al., 2003; Qin and Northoff, 2011; Raichle et al., 2001; Spreng et al., 2009).

Importantly, higher levels of dissociative symptoms were associated with greater connectivity of the dlPFC with the DMN among women with PTSD as a result of early life trauma (Bluhm et al., 2009), suggesting inappropriate recruitment of CEN brain regions to the DMN. Moreover, reduced connectivity between DMN regions (e.g., dorsal anterior and posterior DMN regions and ventromedial PFC and right perigenual ACC with DMN) as well as between the CEN and ventral anterior DMN, was associated with depersonalization/derealization symptoms among individuals with PTSD related to childhood trauma, suggesting reduced synchrony between and within brain networks. Finally, recent work investing functional connectivity of ICNs during supra- and sub-liminal threat processing revealed increased functional connectivity of the ventrolateral PFC with the CEN as a function of dissociative subtype status among individuals with PTSD (Rabellino et al., 2015). Recent work has identified further heightened insular connectivity of the left basolateral amygdala complex among individuals with PTSD-DS compared to individuals with PTSD without the dissociative subtype, where higher symptoms of depersonalization and derealization were predictive of increased insular connectivity with the left basolateral amygdala (Nicholson et al., 2016), suggesting increased connectivity within the SN. Here, the authors posit that the basolateral amygdala may attenuate the activity of the anterior insula via GABA-ergic connections, leading to reduced arousal and interoceptive awareness, alertness, and emotional processing as seen in PTSD-DS (Nicholson et al., 2016).

In addition, Daniels et al., (2015) reported recently that patients with the PTSD-DS exhibited increased grey matter volume in the right precentral gyrus, a brain region

involved in fear-related motor neurocircuitry (Williams et al., 2001). Daniels et al. (2015) also noted that increased volume in the right middle frontal gyrus, a region shown previously to contribute to downregulation of emotional arousal (Dorfel et al., 2014) was positively correlated with dissociative symptoms. Finally, compared to individuals with PTSD without the dissociative subtype, individuals with PTSD-DS show greater connectivity of the amygdala to prefrontal regions involved in emotion regulation (i.e., the bilateral basolateral amygdala (BLA) and left centromedial amygdalar (CMA) regions with the middle frontal gyrus and bilateral CMA with the medial frontal gyrus) and with regions involved in consciousness, awareness, and proprioception (i.e., the left BLA with the superior parietal lobe and cerebellar culmen and the left CMA to the dorsal posterior cingulate and precuneus) (Nicholson et al., 2015). Thus, these findings, along with those described above by Nicholson et al. (2016), indicate that altered connectivity of the amydala complex may be related to the distinct symptom and neurobiological profile of PTSD-DS. Thus, emerging work indicates that functional connectivity within and between ICNs may differentiate individuals with PTSD-DS from those with PTSD without the dissociative subtype. Taken together, the empirical evidence reviewed here favours recognition of PTSD-DS at the symptom, neurobiological, endocrine and immunological levels.

2.1 Dissociation Transdiagnostically

2.1.1 Dissociation in anxiety disorders

Although a large body of evidence supports the relation between dissociative symptomatology and trauma-related disorders (Dalenberg and Carlson, 2012; Gershuny and Thayer, 1999; Lanius et al., 2012; Spiegel, 1984; Spiegel et al., 2013; Stein et al., 2013; Vermetten and Spiegel, 2014; Vermetten et al., 2007; Winter et al., 2015) there is also significant evidence of dissociation across a host of other psychiatric conditions that are less often considered trauma-related. Dissociative symptoms, specifically depersonalization/derealization, occur transdiagnostically, rather than representing disease-specific processes. For example, among anxiety disorders, symptoms of depersonalization have been reported in panic disorder, agoraphobia, and social phobia (Mula et al., 2007). Interestingly, among a sample of individuals with panic disorder and other anxiety disorders (social phobia; generalized anxiety disorder; OCD; specific phobia), whereas individuals who experienced symptoms of depersonalization had higher rates of comorbidity with depression and personality disorder symptoms (Ball et al., 1997), individuals with panic disorder and higher levels of depersonalization exhibited poorer functional outcomes and greater illness severity (Marquez et al., 2001). Similarly, both panic disorder and social phobia are frequently comorbid with depersonalization disorder (Simeon et al.,2003). Moreover, among individuals with bipolar I and II disorder, symptoms of depersonalization were associated with comorbid panic disorder (Mula et al., 2009). Additional studies reveal that dissociative symptoms are present in OCD and are correlated with increased disease severity (Belli et al., 2012; Rufer et al., 2006a), treatment non-compliance and reduced treatment effectiveness (Rufer et al., 2006b; Semiz et al., 2014). Belli et al. (2012) reported further that approximately 14% of

a sample of individuals with OCD met criteria for a comorbid dissociative disorder. Indeed, it has been proposed that dissociative symptoms may constitute a specific subtype of OCD, where symptoms of checking and obsessive intrusions are the main features of the disorder (Watson et al., 2004).

2.1.2 Dissociation in mood disorders

Although less empirical work exists to support a relation between dissociative symptomatology and depression, depersonalization in MDD has been linked tentatively to a longer duration of depressive symptoms and a reduction in treatment efficacy (Nuller, 1982). In addition, a recent study reported that dissociative symptoms were present in individuals with both MDD and bipolar type II disorder, with higher levels of symptoms observed in patients with bipolar type II disorder (particularly on one item measuring identity fragmentation) and in patients who reported a cyclothymic temperament (Oedegaard et al., 2008). Similarly, in a recent factor analysis, Hariri et al., (2015) reported that approximately 20% of individuals with a bipolar disorder experience dissociative symptoms, including identity fragmentation, amnesia and depersonalization/derealization symptoms. Whereas all symptom dimensions were associated with an earlier age of illness onset, amnesia and depersonalization/ derealization symptoms were associated with a longer illness duration. Finally, overall dissociative symptoms were associated with the presence of childhood trauma (Hariri et al., 2015).

Interestingly, in a recent study, 4.1% of women in a community sample were found to have a current major depressive episode involving a comorbid dissociative disorder (termed dissociative depression) that was associated with higher levels of suicidality and childhood sexual abuse than in non-dissociative depressed women (Sar et al., 2013). Recent work from our group has indicated that levels of dissociative symptoms are higher in trauma-exposed individuals with a primary diagnosis of MDD than in healthy controls (Parlar et al., 2016). Indeed, dissociative symptoms have been theoretically linked to the restricted range of emotional experience seen in depression (e.g., anhedonia), particularly given that emotional constriction has been identified as a facet of dissociative experiences (Briere et al., 2005). Finally, traumatic experiences are highly prevalent in mood and anxiety disorders, where in a recent sample of 2000 persons with mood and anxiety disorders, 91.2% of reported having experienced a potentially traumatic or bothersome life event (Spinhoven et al., 2014).

2.1.3 Dissociation in alcohol and substance disorders

Similarly, studies in alcohol and drug abuse/dependency populations report the presence of comorbid dissociative symptoms (Evren et al., 2011, 2008, 2007; Tamar-Gurol et al., 2008) in these conditions. Specifically, among a sample of drug-dependent individuals, 26% had a comorbid dissociative disorder, predicted by past suicide attempts and childhood emotional abuse (Tamar-Gurol et al., 2008). One additional study reported that among individuals with alcohol use disorders, approximately 9% had a comorbid dissociative disorder (Evren et al., 2007). In a pattern similar to that reported in mood disorders, dissociative pathology has been associated with increased suicidality and past

suicide attempts, childhood emotional and sexual abuse and neglect, self-harm behaviours, and increased severity of anxiety, depression and alcoholism related symptoms (Evren et al., 2008, 2007).

2.1.3 Dissociation in psychotic-spectrum illness

Symptoms of dissociation also emerge in psychotic-spectrum illness, and voice hearing is increasingly recognized within the symptomatology of dissociative experiences. For example, in a sample of individuals with schizophrenia, approximately 15% were diagnosed with a comorbid dissociative disorder (Yu et al., 2010). The authors of these studies acknowledge that exposure to traumatic experiences may contribute to the emergence of dissociative symptoms in OCD and schizophrenia (Belli, 2014; Belli et al., 2012; Rufer et al., 2006b; Semiz et al., 2014; Yu et al., 2010). It is also important to note the association between early psychological trauma histories and voice hearing where a recent review suggested that voice hearing in individuals with trauma-related disorders does not differ significantly from individuals with schizophrenia (Longden et al., 2012). Moreover, individuals with dissociative disorders were more likely to experience hearing voices before reaching the age of 18 and were more likely to experience hearing both child and adult voices in comparison to individuals with psychotic-spectrum disorders, who generally report hearing adult voices exclusively (Dorahy et al., 2009). Finally, in a sample of individuals with chronic PTSD, approximately half reported experiencing auditory hallucinations (AH); these individuals also experienced higher levels of pathological dissociation in comparison to participants who did not experience AH (Anketell et al., 2010). Indeed, a recent meta-analysis has confirmed a strong relation

between voice hearing and the presence of dissociative symptoms (Pilton et al., 2015). Future research will be required, however, to disentangle the clinical and neurobiological factors that differentiate voice hearing associated with dissociative symptomatology and voice hearing related to psychotic disorders.

3.0 Evidence for the relation between dissociation and neuropsychological functioning

3.1 Dissociation and neuropsychological functioning in the general population

Dissociative tendencies are not isolated to psychiatric disorders but are also present in the general population (albeit to a lesser extent) (Kihlstrom et al., 1994; Ross et al., 1991). Here, a large body of evidence supports the relation between the presence of dissociative experiences and decrements in neuropsychological functioning. Both chronic dissociation and state dissociation have been associated with reduced performance on measures of attention, executive functioning, and memory (Amrhein et al., 2008; Brewin et al., 2013; Bruce et al., 2007; Giesbrecht et al., 2004; Olsen and Beck, 2012). In studies differentiating healthy individuals by levels of dissociative symptoms, or the extent to which individuals have dissociative experiences in their day-to-day lives, individuals higher in dissociation performed worse on tasks assessing executive function (Amrhein et al., 2008; Giesbrecht et al., 2004), divided attention (Olsen and Beck, 2012a), verbal memory (Amrhein et al., 2008; Devilly et al., 2007) (but see Giesbrecht and Merckelbach, 2009), episodic memory (Olsen and Beck, 2012) and working memory (Amrhein et al., 2008). Similarly, higher levels of dissociation are associated with worse performance on

executive functioning tasks (Freyd et al., 1998), and are associated with greater self-reported difficulties in executive function (Bruce et al., 2007).

In contrast, a smaller number of studies have suggested that dissociative traits may enhance neuropsychological functioning among healthy individuals. For example, in two studies from the same group, individuals who scored higher in dissociation performed better on measures of verbal working memory span and on a n-back task (De Ruiter et al., 2004; Veltman et al., 2005). The authors of these studies suggest that dissociative tendencies may confer a unique information processing style that contributes to this enhanced performance. Similarly, DePrince and Freyd (2004, 2001, 1999) described a directed forgetting task where participants were instructed to attend to some words and forget others; persons higher in dissociation recalled fewer trauma-related words but more neutral words when asked to recall all presented words (regardless of whether they had been directed to forgot or remember them. Further, in their 1999 study, Deprince and Freyd reported that high dissociators showed greater interference in a selective attention condition of the Stroop task compared to low dissociators, while the opposite pattern held for a divided attention condition of the Stroop task. These findings were not replicated in subsequent studies, however (Devilly et al., 2007; Giesbrecht and Merckelbach, 2009). Notably, in a recent study investigating state-based dissociation in healthy controls, where dissociation was induced using a mirror-gazing protocol, higher levels of dissociation were associated with a shorter digit span (working memory) and greater deterioration in story recall following a delay (Brewin et al., 2013).

3.2 Dissociation and episodic memory in the general population

Dissociative responses may instantiate further symptoms of dissociative amnesia through episodic memory deficits associated with symptoms of depersonalization and derealization. The encoding of experiences in long-term memory requires a "sense of bodily self", where events are experienced from the perspective of one's own body (Bergouignan et al., 2014). Accordingly, dissociative "out-of-body" experiences may interrupt the encoding and integration of environmental details into episodic memory. Indeed, in a recent key study of healthy individuals, participants underwent induction of out-of-body and in-body experiences while engaging in a simulated social interaction involving enactment of real-life events with an actor. One week later, participants showed significantly less episodic recall of events encoded during the out-of-body condition as compared to in-body experiences, including reduced spatial and temporal recall (Bergouignan et al., 2014). In a separate sample, the same authors reported contrasting patterns of recruitment of the left posterior hippocampus, with differential activation during retreival of out-of-body events as compared to in-body events experienced two weeks previously. Specifically, for in-body events, participants showed strong activation of the left posterior hippocampus during initial retrieval trials, with progressively less recruitment of this region for further trials. By contrast for out-of-body events, reduced initial recruitment of the left posterior hippocampus was observed, with increasing recruitment over further trials (e.g., following reproduction of the event). These findings demonstrate the necessity of sensory integration from an embodied perspective, or the experiencing of life events from within one's own body (rather than from an observer persepctive as seen in depersonalization), in the encoding of episodic or autobiographical

memories, a process likely to be disrupted by dissociative processes both at the behavioural and neural level. Critically, these findings are consistent with evidence of disrupted episodic and autobiographical memory among individuals with high levels of pathological dissociation (e.g., Chae et al., 2011; Roca et al., 2006).

3.3 Dissociation and neuropsychological functioning among individuals exposed to trauma

The association between dissociation and cognitive performance has also been supported in studies of patients with trauma-related disorders and among trauma-exposed individuals. Here, pathological dissociation has been linked to neurocognitive vulnerabilities or impairments across various conditions. In one recent study of adults with PTSD stemming from childhood sexual abuse, impaired performance on indices of verbal and visual memory was strongly correlated with higher levels of dissociation (Rivera-Vélez et al., 2014). Similarly, among children with PTSD due to abuse or neglect, higher levels of dissociation were associated with worse performance on measures of attention (De Bellis et al., 2013). Among a community sample of children, both dissociative symptoms and trauma-exposure status, accounted for unique proportions of the variance in a model predicting executive functioning performance that also included, anxiety, socioeconomic status, and potential traumatic brain injury (DePrince et al., 2009). Further, among a sample of foster children, higher levels of trait dissociation were related to worse performance on measures of response inhibition and auditory attention (Cromer et al., 2006). Moreover, Chae et al. (2011) reported that among traumatized children, trauma symptoms were associated with reduced accuracy on an interview

measuring recall for a play activity that had occurred three days prior only among those who were identified as high dissociators. Another recent study indicated that the presence of dissociative symptoms immediately following disclosure of sexual abuse by children predicted parent-reported attentional dysfunction, as measured 8 – 36 months later. Here, PTSD symptoms were only indirectly related to attention dysfunction through their relation to dissociation (Kaplow et al., 2008). These findings are of particular relevance given that dissociation is understood as a psychobiological response to threat and danger that occurs in both children and adults (Dalenberg et al., 2012). Accordingly, disruptions in cognitive function as a result of dissociative symptoms arising from early traumatic experiences may continue to have detrimental impacts on the lives of impacted individuals through key developmental periods well into adulthood, as demonstrated by Rivera-Vélez et al's study (2014). By contrast, in a study investigating neuropsychological dysfunction following a recent trauma, peri-traumatic dissociation (dissociation that occurred during the event) was not associated with impaired performance on tasks assessing visuospatial memory and attention among individuals with high levels of PTSD symptoms (Brandes et al., 2002). Notably, these cognitive impairments were no longer significant when depressive symptoms were controlled for, a finding that may be accounted for by high collinearity (i.e., symptom overlap) between depressive and PTSD symptoms.

The impact of dissociation on cognitive functioning has also been examined in members of the military and in women who have experienced intimate partner violence (IPV). Specifically, recent work among active military personnel who were asked to

complete a visual memory task under stressful conditions (i.e., after a mock interrogation in a mock prisoner of war camp) demonstrated that baseline state dissociation and history of traumatic stress predicted reduced performance on the visual memory task (Morgan et al., 2006). Similarly, among veterans with PTSD, those with a comorbid dissociative disorder demonstrated greater deficits on measures of attention, autobiographical memory, and verbal memory than those with PTSD alone (Roca et al., 2006). Finally, in studies of women with PTSD as a result of IPV or treatment seeking women exposed to IPV, those with more severe dissociative symptoms performed worse on a task of reasoning (Twamley et al., 2009), and on a measure of explicit verbal memory for threat-related (but not trauma-related) stimuli (Minshew and D'Andrea, 2015).

Dissociative symptoms have been linked further to neuropsychological dysfunction in other trauma-related disorders, including BPD and dissociative disorders. For example, among individuals with BPD, pathological dissociation was associated with reduced functioning on measures of attention, verbal memory, working memory, and executive functioning relative to healthy control performance. Conversely, relative to healthy controls, individuals with BPD without pathological dissociation showed impairment on measures of executive functioning only (Haaland and Landrø, 2009) (but see Cloitre et al., 1996). In a pattern similar to that found in healthy populations, state dissociation among individuals with BPD (induced using script-driven imagery of an autobiographical memory) was associated with reduced inhibitory control for emotional stimuli and a trend toward reduced verbal memory performance when compared to performance amoung individuals with BPD who did not undergo dissociation induction

and who performed similarly to healthy controls (Winter et al., 2015). Similarly, Guralnik et al. (2007) found that higher levels of dissociative symptoms among individuals with depersonalization disorder were associated with slowed processing speed and heightened distractibility. Previous work from this group also revealed that lower levels of performance on measures of visuospatial functioning and verbal memory predicted DPD status (Guralnik et al., 2000). Similarly, reduced cognitive inhibition and slower processing speed has also been reported in individuals with DID in response to emotionally negative contexts (Dorahy et al., 2006, 2005, 2002). Finally, work from our group has identified a relation between dissociative symptoms (depersonalization and derealization) and cognitive performance in trauma-exposed individuals with MDD, where higher levels of dissociation were related to worse performance on tasks measuring cognitive flexibility, sustained attention, and short-term and delayed memory (Parlar et al., 2016).

3.4 Episodic Memory in Dissociative Identity Disorder

Recent work has pointed to the presence of autobiographical memory disturbance among individuals with DID, a disorder where an individual's sense of self is experienced as fragmented or divided into different "parts". For example, in one model, "emotional parts" (EPs) that have access to traumatic memories are differentiated from "apparently normal parts" (ANPs) that inhibit or avoid access to traumatic memories and thus enable daily life functioning (also referred to as the “trauma identity state” (TIS) and “neutral identity state” (NIS), respectively) (Van der Hart et al., 2006; van der Hart et al., 2004). In comparison to the TIS, the NIS is thought to act as a protective state, avoiding access

or response to traumatic memories (Reinders et al., 2006), a process that may render the ANP amnesic for these memories. Indeed, inter-identity amnesia is a clinical hallmark of DID (Bryant, 1995; Elzinga et al., 2003; Schlumpf et al., 2014; Reinders et al., 2012), yet mixed findings are reported in the literature when this association is investigated objectively. For example, in a directed forgetting experiment involving patients with DID who were able to alternate between identity states yet have no conscious awareness between states, Elzinga et al. (2003) reported intact cued recall of stimuli that were encoded in the same identity state as was present at encoding (e.g., no directed forgetting effect with participants recalling equal number of to-be-remembered and to-be-forgotten stimuli), but impaired cued recall when participants were in a different, amnestic, identity state than was present at encoding (e.g., directed forgetting effect with participants recalling fewer to-be-forgotten stimuli compared to to-be-remembered stimuli). Conversely, other studies report a transfer of information between identity states, for both explicit verbal memory (Huntjens et al., 2007) and implicit procedural (Huntjens et al., 2005a) and recognition memory (Huntjens et al., 2012) assessments. Notably, two studies failed to find differences in memory transfer between identity states in DID patients and control participants simulating DID-like amnesia, further rendering interpretation of these findings unequivocal (Huntjens et al., 2006, 2005b). Notably, a recent study reported reduced autobiographical memory specificity for emotionally-valenced events [(i.e., overgeneral memory consisting of primarily semantic associates, extended memories (memories for extended time periods rather than specific events) and categorical memories (memories referring to a whole class of events)] similar to that seen in PTSD

(Ono et al., 2015) among individuals with DID, regardless of their identity state (Huntjens et al., 2014) (but see also Barlow, 2011).

Recent studies have identified further differential patterns of psychobiological response to trauma-related memories when in a trauma identity state as compared to a neutral identity state. For example, Reinders et al. (2006) reported increased activation of brain areas involved in somatosensory processes and negative emotional states (e.g., insular cortex) when the trauma identity state was presented with a traumatic memory script as compared to a neutral memory script; no such difference was reported for the NIS. Similarly, Reinders et al. (2014) reported differential patterns of brain activation in response to trauma-related script-driven imagery as compared to neutral scripts. Here, as compared to the trauma identity state, the neutral identity state showed increased activation of the prefrontal cortex in response to trauma scripts as compared to neutral scripts, and greater activation in posterior association areas, and hippocampal gyri in response to trauma scripts (demonstrating emotional overmodulation). By contrast, the trauma identity state showed increased activation of the amygdala and insula in response to trauma scripts as compared to neutral scripts, and greater dorsal striatum activation in response to trauma scripts when compared with the neutral identity state (emotional undermodulation) (Reinders et al., 2014). Notably, this pattern of brain activity is similar to that seen in patients with the PTSD-DS during presentation of trauma-related scripts (Lanius et al., 2010, 2012, 2006).

3.5 Preliminary work supporting the relation between neuropsychological function and dissociative symptoms in military trauma exposed individuals

Unpublished work from our group links further the presence of dissociative symptoms to cognitive dysfunction in military samples. We recruited twenty military-combat-exposed males through operational stress injury referrals made by military providers. Diagnosis of PTSD and PTSD symptom severity were determined using the CAPS (Blake et al., 1995), where it was found that fourteen participants had a current diagnosis of PTSD related to military trauma, three were considered to be in remission from PTSD, and three had no current or past diagnosis of PTSD and were considered to be resilient. Participants also completed self-report measures of depression, anxiety, and dissociative symptoms, as well as childhood trauma history. The Repeatable Battery of the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998) was used to determine participants' neuropsychological status, measuring Immediate Memory (short-term memory), Visuospatial/Constructional, Language, Attention, and Delayed Memory.

Whereas no significant correlations were found between RBANS scores and CAPS, nor with the self-report indices of depression, anxiety, or childhood trauma history, the immediate memory subscale of the RBANS was significantly correlated with severity of dissociative symptoms, specifically, Multiscale Dissociation Inventory (MDI) (Briere, 2002) total scores ($\rho = -0.48$, $P = 0.031$), and scores on the disengagement ($\rho = -0.60$, $P = 0.005$), derealization/depersonalization ($\rho = -0.56$, $P = 0.01$), and memory impairment ($\rho = -0.47$, $P = 0.036$) subscales (see Table 1). These results indicate that higher levels of dissociative symptomatology are associated with worse performance on a measure of short-term verbal memory. Critically, other factors, such as illness severity and level of trauma exposure putatively associated with cognitive dysfunction following

trauma exposure showed no such relation. Taken together, these data suggest that dissociation contributes to impaired memory performance in military-trauma exposed populations.

3.6 Dissociative symptomatology and social cognition

Social cognition, involving the ability to use, encode, and store information about others that we gain from social interactions (Brothers, 1990; Adolphs, 2001), is disrupted across a host of psychiatric conditions, including schizophrenia (Savla et al., 2013), mood disorders (Cusi et al., 2010, 2013, 2012a, 2012b, 2011; McKinnon et al., 2010), borderline personality disorder (Domes et al., 2009), and PTSD (Nazarov et al., 2014, 2015; Parlar et al., 2014; Steuwe et al., 2015) Critically, alterations in social cognitive functions relying upon the joint contribution of cognitive and affective processing resources (McKinnon and Moscovitch, 2007; McKinnon et al., 2007) known to be disrupted in neuropsychiatric illness may contribute to the impairments in interpersonal functioning (e.g., relations with family and friends) seen in these conditions.

Recent work indicates that dissociation may contribute to deficits in social cognition among individuals with PTSD and schizophrenia. Specifically, in a recent study of women with PTSD stemming from childhood abuse, we found impaired performance on a theory of mind (ToM) task tapping the ability to identify kinship interactions (e.g., who is the parent and who is the child) and requiring participants to take on the perspectives of others and understand their emotions, intentions, and behaviours. Critically, the degree of ToM impairment in this sample was also related to the severity of

dissociative symptoms present, including disengagement, memory disturbance and identity dissociation (Nazarov et al., 2014). In the same study, slower response time on the Reading the Eyes in the Mind Task, a ToM task where participants are asked to discriminate complex emotions depicted through the eyes, was associated with heightened symptoms of dissociation, including disengagement, memory disturbance and identity dissociation (Nazarov et al., 2014). Similarly, in a related study involving the same sample, we found that reduced ability to recognize emotions conveyed through speech was associated with heightened symptoms of dissociation and greater severity of childhood abuse (Nazarov et al., 2015). These findings are consistent with a recent study among individuals with schizophrenia and schizoaffective disorder where dissociative symptoms were the strongest predictor of performance on an emotion recognition task, over and above the impact of positive and negative symptoms of schizophrenia, cognitive symptoms, symptoms of PTSD, and the impact of social desirability bias (Renard et al., 2012).

Interestingly, an individual's response to socially complex scenarios may vary with their dissociative state. Here, Frewen and Lanius (2015) describe the case of a male patient with high levels of dissociative symptoms who had experienced childhood sexual, physical, and emotional trauma. Interestingly, his responses to complex moral reasoning dilemmas, including whether or not a prescribed course of action was ethical and what course of action he might choose in response to the dilemma varied radically from one week to the next. Moreover, on a task where he was required to interpret a social scenario, he reported amnesia for his response from the previous week upon being

queried again at a second session (in line with inter-identity amnesia as discussed in section 3.1). Notably, we did not find a relation between dissociation and moral reasoning performance in a sample of women with PTSD stemming from childhood abuse (Nazarov et al., submitted). Nonetheless, this case study suggests that an individual's responses to social cognitive tasks may vary depending on the dissociative state present. Future work will be required to confirm this hypothesis.

3.7 Interim summary: Neuropsychological function and dissociation

Table 2 provides a summary of studies that have examined the relation between dissociative symptoms and cognitive function indexed by cognitive domain and psychiatric condition. Among healthy controls, trauma-exposed individuals, and in trauma-related psychiatric populations both chronic and state dissociation have been associated with reduced performance in a wide variety of cognitive domains, including attention, executive functioning, working memory, immediate and delayed verbal and visual memory, autobiographical, and episodic memory. Although there is conflicting evidence from a number of studies suggesting enhanced cognitive performance among individuals higher in dissociation, these findings are constrained to indices of working memory and verbal memory performance (Cloitre et al., 1996; De Ruiter et al., 2004; Elzinga et al., 2007, 2000; Veltman et al., 2005). Here, it has been suggested that an enhanced ability to elaborate coupled with the ability to divide attention between multiple streams of information may improve working memory in highly dissociative individuals (De Ruiter et al., 2004; Elzinga et al., 2000). Taken together, however, the evidence in favour of the association between neuropsychological dysfunction and dissociative

symptoms or traits among healthy controls and civilian trauma-related psychiatric populations appears stronger than that suggesting that dissociation confers a beneficial effect on neuropsychological functioning. Moreover, recent provocative work from our group has identified dissociation as the single clinical correlate of neuropsychological functioning (short-term memory) in a small sample of individuals exposed to military trauma.

Episodic memory also appears affected by dissociation, specifically among individuals with the most severe dissociative disorder, DID. Here, it has been suggested that trauma identity states are privy to trauma-related memories that their "normal" identity counterparts are not (Bryant, 1995; Elzinga et al., 2003; Reinders et al., 2012; Schlumpf et al., 2014). Although reports are mixed as to whether these subjective memory impairments hold up when tested objectively (Elzinga et al., 2003; Huntjens et al., 2012, 2006, 2005a, 2005b), differences in psychophysiological and neural functioning between states when processing traumatic or emotional stimuli (e.g., Reinders et al., 2006, 2014) support the authenticity of DID patients' subjective reports of autobiographical memory deficits. Moreover, these patients demonstrate overgeneral recall of autobiographical memories regardless of their identity state (Huntjens et al., 2014).

Importantly, the impact of dissociation on neuropsychological functioning does not appear to be limited to purely cognitive domains, but also extends to social cognition. Specifically, recent work from our group has identified a relation between reduced functioning on measures of prosody and theory of mind and higher levels of dissociative

symptomatology among women with PTSD (Nazarov et al., 2015, 2014). These findings are similar to those reported among individuals with schizophrenia-spectrum disorders (Renard et al., 2012). Poor social or interpersonal functioning is a hallmark of many psychiatric disorders, including PTSD (Charuvastra and Cloitre, 2008; Lanius et al., 2011; Olatunji et al., 2007), mood disorders (Romera et al., 2010; Wells et al., 1989), and schizophrenia (Couture, 2006; Fett et al., 2011) and is associated with reduced treatment efficacy (Sotsky et al., 1991). As such, identifying factors related to deficits in social cognition may help to target treatment approaches related to interpersonal and social functioning, thereby improving functional outcomes.

A number of authors suggest that dissociation contributes to reduced cognitive functioning as the result of its interference with the integration of perceptual and other forms of incoming information (e.g., Freyd et al., 1998; Kaplow et al., 2008). For example, Dorahy (2006) has described a dissociative processing style associated with a learned strategy for dealing with perceived or actual threat. Here, individuals may redirect awareness away from threatening stimuli or fail to integrate multiple streams of encoded information following a traumatic event. Although this processing style may be protective in the face of a traumatic event or during its aftermath, it may become maladaptive if adopted as a general processing strategy, thus leading to reductions in neuropsychological function among individuals who experience high levels of dissociation. Indeed, cognitive functions (e.g., cognitive control) and dissociation may depend on shared processing resources, thus competing for these resources when simultaneously activated, and leading to the disruption of cognitive operations (e.g., attention, memory). Despite this apparent

link between dissociation and reduced neuropsychological functioning, the biological underpinnings of this relation remain largely unexplored.

Importantly, the majority of studies reviewed here focus on trait dissociation rather than state dissociation. Critically, measures of trait dissociation demonstrate good test-retest reliability (Bernstein and Putnam, 1986; Dell, 2006; Dubester and Braun, 1995). Given that dissociative states are transient, however, one might expect cognitive functioning in individuals with these symptoms to change as a function of their dissociative state. Indeed, studies investigating neuropsychological functioning following induction of dissociative states have revealed reduced functioning on measures of executive functioning and verbal memory among BPD patients (Winter et al., 2015), and on measures of episodic memory (Bergouignan et al., 2014) among healthy individuals. Moreover, strikingly different responses to a task assessing moral reasoning in an individual with high levels of dissociative symptomatology from one week to the next were reported by our group, in addition to amnesia for the individual's previous response (Frewen and Lanius, 2015). These results suggest that in addition to the deleterious impact of chronic or trait dissociation on cognitive functioning, state dissociation might also be expected to also impact negatively on cognitive functioning. As such, future studies should examine neuropsychological functioning as a function of state dissociation.

4.0 Neurobiological model of dissociation

Neurobiological models linking trauma exposure to the development of dissociation provide one explanatory mechanism for cognitive dysfunction in individuals

with dissociation, where the presence of dissociative states in humans exposed to trauma have been linked to more primitive animal defensive responses. Here, the defense cascade model of dissociation proposes that state dissociation occurs on a continuum (Nijenhuis et al., 1998; Schauer and Elbert, 2010). Such phylogenetically old states of arousal are mediated by a common neural pathway involving the PAG, hypothalamus, amygdala, and sympathetic and vagal nuclei (Kozlowska et al., 2015; Lanius et al., 2014) (see figures 1 and 2). In this model, initial responses to confrontation with threat are thought to be accompanied by an orienting response characterized by bradycardia and inhibition of the startle response (Schauer and Elbert, 2010). Importantly, threat-related stimuli are first processed via the superior colliculus (through direct projection from the retina), a midbrain structure closely linked to the PAG (see below), that plays a crucial role in spatial attention, orienting and target selection prior to processing at the cortical level (Lanius et al., 2014; Merker, 2007; Panksepp, 1998). Flight or fight follows, characterized by prolonged discharge of the sympathetic division of the autonomic nervous system, leading to a generalized sympathetic response including increased heart rate and vasoconstriction of peripheral blood vessels (Schauer and Elbert, 2010), as well as activation of the adrenal medulla to release catecholamines (e.g., noradrenaline amplifying the sympathetic response (Porges, 2011). Concomitant activation of the lateral PAG via direct projection from the amygdala and limbic forebrain activate motor patterns of fight or flight (Carrive, 1993; Keay and Bandler, 2001; Kozlowska et al., 2015; LeDoux et al., 1988; Rizvi et al., 1991). At the same time, cortical loops in the basal ganglia and cerebellum are activated to modulate basic motor patterns consistent with

context and defense strategies (Kozlowska et al., 2015; Lanius et al., 2014). Notably, the fight or flight response involves non-opioid (endocannabinoid-mediated) analgesia evoked by the lateral PAG (Keay and Bandler, 2001; Kozlowska et al., 2015). Critically, in cases where the organism determines it has little to no chance of survival, unresponsive immobility or death feigning may occur in an attempt to decrease predator interest, which may lead to tonic or collapsed immobility (Kozlowska et al., 2015; Schauer and Elbert, 2010). This type of response is initiated through tonic immobility, where activation of tactile sensory, proprioceptive and visceral afferents are coupled with fear (i.e., when an animal is struggling with a predator). Here, higher-order judgment is not involved, but rather, these processes rely on phylogenetically old regions of the brain (such as the VLPAG) and occur in organisms without a highly developed cerebral cortex, such as insects and birds (Gallup and Rager, 1996). The ventrolateral PAG (VLPAG) receives signals from muscle and visceral tissues via the dorsal horn of the spinal cord and the parabrachial and vagal sensory nuclei, triggering tonic immobility (Kozlowska et al., 2015). The VLPAG acts as a brake for the lateral PAG, inhibiting fight-or-flight motor patterns. Withdrawal of sympathetic activity and activation of parasympathetic activity occur as the organism becomes increasingly unresponsive to sensory stimulation, including pain, representing the beginning of functional sensory deafferentation at the level of the cortico-sensory pathways (e.g., reduced integration of auditory, visual, proprioceptive, and somatosensory information from the thalamus to cortical sensory processing areas), thereby providing a means of modulating or shutting down overwhelming sensory information, and mimicking death or “death-feigning” ensues

(Schauer and Elbert, 2010). Withdrawal of sympathetic activation and increased parasympathetic activation is further associated with vasodilation and a precipitous drop in heart rate and blood pressure, a pattern mimicked in vasovagal syncope (or fainting) (Fenton et al., 2000).

Similarly, the polyvagal theory (Porges, 2011, 2003, 2001) details three response systems related to the autonomic nervous system, where the vagal complex of the parasympathetic nervous system is divided into two branches, the dorsal vagal complex (DVC) and ventral vagal complex (VVC) that work in concert with the sympathetic nervous system, depending on the environmental context. Specifically, the VVC is involved social communication, calming, self-soothing, and bonding and is inhibitory to the sympathetic nervous system and HPA-axis activity via the "vagal brake" and includes myelinated pathways that originate in the nucleus ambiguous. This system is active when the organism deems the environment to be safe. In contrast, in threatening situations, the vagal brake may be released, leading to discharge of the sympathetic nervous system and initiation of fight or flight patterns. Porges (2011, 2003, 2001) also describes immobilization, or death feigning responses that occur when fight or flight is not an option (e.g., under life-threatening circumstances). These responses are mediated by the DVC, which is the most phylogenetically old system and is comprised of unmeyelinated fibers that originate in the dorsal motor nucleus of the vagus and provide inhibitory input to the sinoatrial node of the heart (the pacemaker) and when upregulated, may lead to immobilization, bradycardia, apnea and cardiac arrest. Critically, whereas the dorsal motor nucleus is in close communication with the VLPAG, a critical component of

immobility or shut-down responses described above, the sympathetic nervous system communicates with the lateral PAG and thus carries out motor patterns of fight or flight (Porges, 2007).

Notably, thalamic pathways may play a central role in shutdown or immobility responses, where they are involved in the relay of sensory information from the periphery to the cerebral cortex (Kandel et al., 2000) and the regulation of arousal (Schiff, 2008). Accordingly, Schauer and Elbert (2010) suggest that regulation of thalamic activity may allow an organism to shut down peripheral sensory mechanisms in order to enter a state of collapsed immobility. Collapsed immobility is mediated by the same neural networks as tonic immobility, however, para-sympathetically mediated bradycardia leads to hypoxia, disrupting signals from the brain stem that maintain muscle tone and leading to compromised consciousness (Koslowska et al., 2015). Opioid-mediated analgesia is activated in these states via the PAG and the rostral ventromedial medulla pain circuit (Kozlowska et al., 2015). Finally, in extreme situations, a final stage of response may be mediated by a shut-down of peripheral vagal activity and a vasovagal response leading to fainting or flaccid immobility (Schauer and Elbert, 2010) (see figures 1 and 2). Notably, although these responses occur during acute stress or trauma exposure, they also continue post-trauma among individuals with trauma-related psychopathology in response to trauma-related cues in the internal or external environment, thus representing learned processes and a continuation of defensive posturing normally observed under threat. Here, Kozlowska and colleagues (2015) described defensive mind-body states as fixed

action patterns that are repeated or reactivated by environmental triggers, including motor patterns, autonomic responses and opioid mediated analgesia (e.g., Van der Kolk, 2001).

Accordingly, functional sensory deafferentation mediated by reduced integration of sensory information via the thalamus to the cortex may underlie symptoms of depersonalization and derealization, given that these pathways are central to cohesive perceptual and sensory experiences, and thus embodiment of conscious experience. In the case of individuals with the PTSD-DS, functional sensory deafferentation may be maintained, despite the absence of overt threat. Specifically, Schauer and Elbert (2010) describe re-enactment of defense stages, including tonic and collapsed immobility, in response to internal (e.g., intrusion symptoms) or external environmental trauma cues. Here, associated decrements in attention and arousal would be expected to give rise to progressive cognitive dysfunction and result in diminished availability of cognitive resources. It is important here to consider the role of autonomic arousal in cognition. Stress-cognition relationships have been conceptualized as an inverted u-shaped curve, where increasing levels of arousal are thought to lead to enhanced cognitive performance to some optimal level, after which increased arousal may have deleterious effects on cognition, as in the Yerkes-Dodson Law (Cohen, 2011; Yerkes and Dodson, 1908). More recent conceptualizations integrate dimensions such as task difficulty, cognitive appraisal and individual coping mechanisms into this model (Deffenbacher, 1994). Morever, recent work has confirmed that acute stress impairs performance on tasks requiring higher-order cognitive resources (e.g., executive functioning) with associated reductions in prefrontal cortex activation (e.g., dlPFC) (Arnsten, 2009). Indeed, high levels of catecholamine

release (e.g., dopamine and noradrenaline), which also follows an inverted u-shaped curve in response to stress, appears to lead to reduced neuronal firing in the prefrontal cortex (Arnsten, 2009).

Among individuals with PTSD, the thalamus may also play a key role in the interplay between dissociative symptoms and cognitive functioning where altered thalamic sensory processing is postulated to underlie or enable dissociative symptoms (Krystal et al., 1998; Lanius et al., 2014). Indeed, the thalamus is crucial to the integration of sensory information in the cortex, amygdala, and hippocampus (Amaral and Cowan, 1980; Kandel et al., 2000; Krystal et al., 1998; McCormick, 1992; Turner and Herkenham, 1991). Critically, among healthy populations, dissociative states may occur during exposure to very high or very low levels of sensory stimulation (Krystal, 1988; Krystal et al., 1998). Krystal et al. (1998) suggest that the role of the thalamus in trauma-related and possibly dissociative processes is supported by the presence of receptors for neurotransmitters previously implicated in the induction of post-traumatic (e.g., flashbacks) and dissociative symptoms in thalamic networks, including the noradrenergic (Buzsáki et al., 1991; McCormick and Wang, 1991) and glutamatergic receptors (McCormick, 1992). Indeed, whereas responses to trauma have been linked to the noradrenergic system (Bremner et al., 1996a, 1996b; Krystal et al., 1989), ketamine (a glutamate (NMDA) receptor antagonist) has been shown to induce detachment and withdrawal as well as sensory distortions and illusions (Krystal et al., 1994). Krystal et al. (1998) further link alterations in sensory processing via the thalamus and dissociative states with attentional changes, where they cite work reporting alterations in reported

locus of attention (e.g., to peripheral sensory stimuli or internal mental processes) among dissociated individuals (Carlson and Putnam, 1989). Taken together, Krystal et al. (1998) hypothesize that extensive activation monoamine systems under conditions or stress (e.g., dissociation) may lead interference with, rather than enhancement of sensory processing.

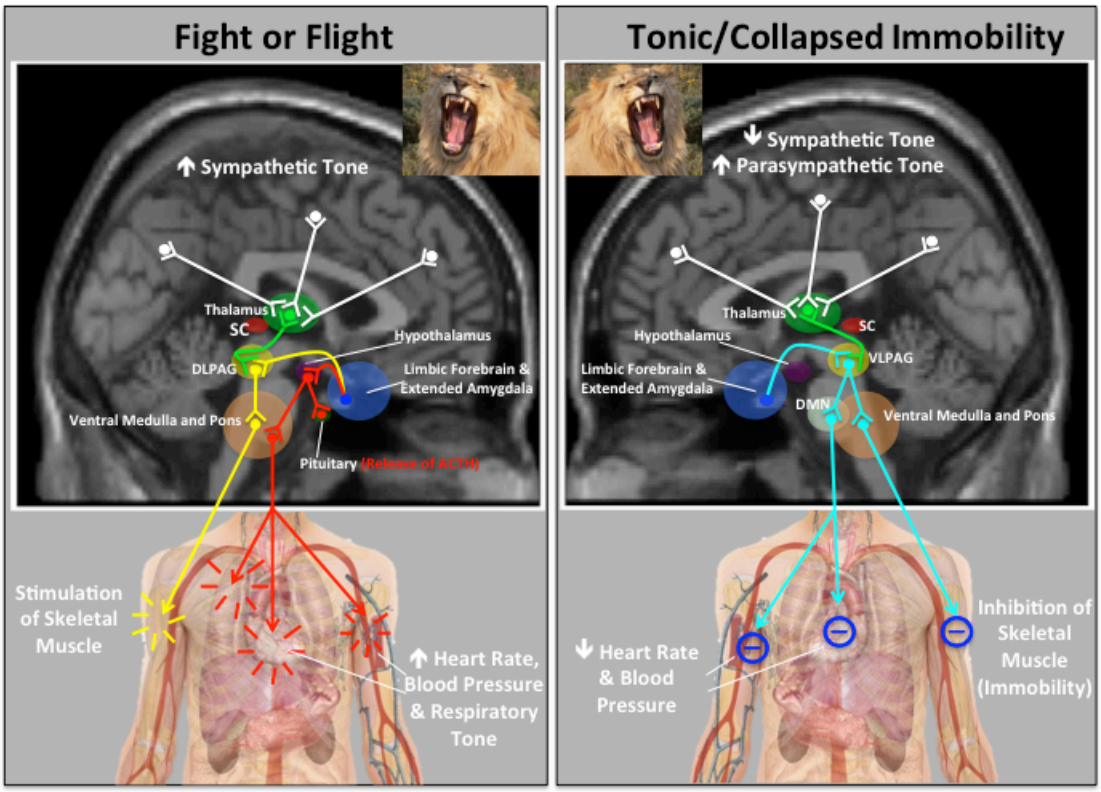

Figure 1. This figure is based on ideas presented in Kozlowska et al. (2015). Responses to a stressful stimulus (e.g., the tiger) as in animal models are represented here as they might appear in the human brain. Fight or flight response: Information from the limbic forebrain and amygdala mediate somatomotor activation (yellow pathway) via the lateral periaqueductal gray (LPAG) leading to downstream activation of skeletal muscles via premotor centers in the pons and medulla. Autonomic activation (red pathway) via the sympathetic nervous system is mediated by the hypothalamus leading to increased heart rate and vascular resistance via the pons and medulla, while activation of the pituitary causes a release of ACTH and downstream cortisol with concomitant increased sympathetic tone. Tonic/collapsed immobility: Information from the limbic forebrain and amygdala activates the ventrolateral periaqueductal gray (VLPAG), which acts as a break for the LPAG, leading to reduced sympathetic tone. Activation of the vagal pathway from the dorsal motor nucleus (DMN) in the brainstem opposes sympathetic activation. Downstream projections of the VLPAG via the ventral medulla mediate immobility.

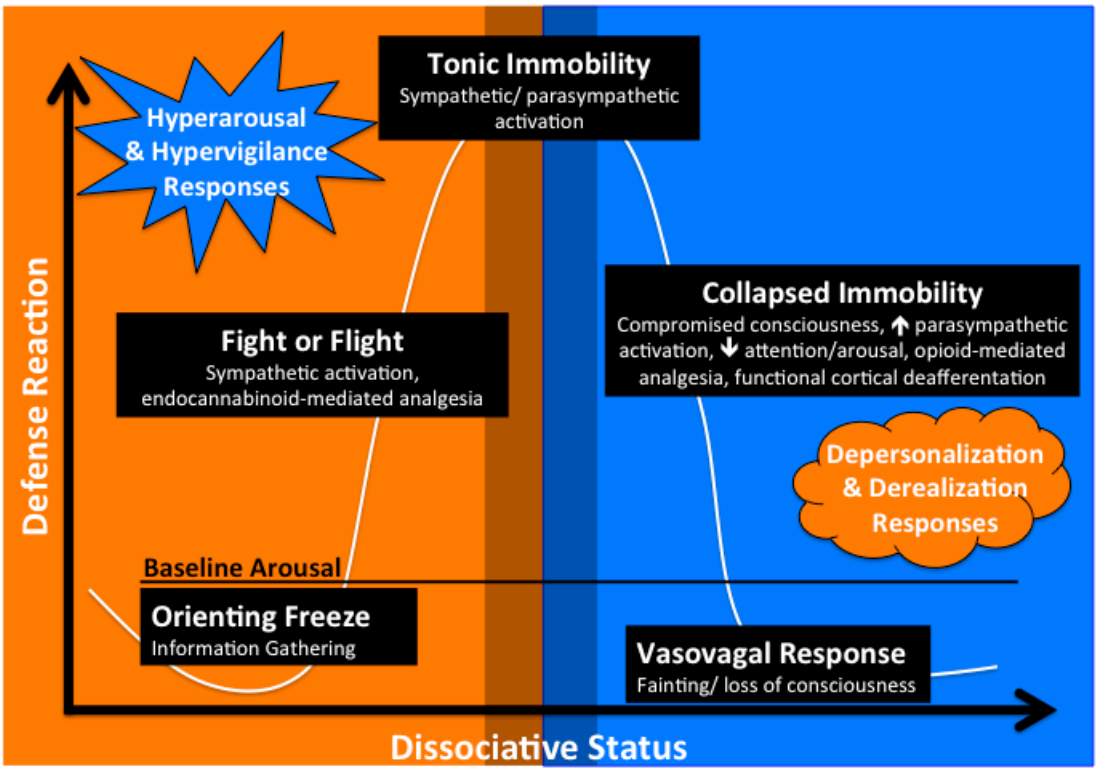

Figure 2: Adapted with permission *Zeitschrift für Psychologie / Journal of Psychology*2010; Vol. 218(2):109–127, p.111 ©2010 Hogrefe Publishing, www.hogrefe.com. Illustration of the defense cascade model demonstrating dissociative states occur on a continuum along with the defense reaction adopted by the organism following confrontation by threatening stimuli. During the hyperarousal/hypervigilance stage (marked in orange), an initial orienting freezing response facilitates information gathering (accompanied by bradycardia). This is followed by fight or flight (accompanied by sympathetic activation and endocannabinoid-mediated analgesia (da Silva et al., 2012; Keay and Bandler, 2001), then tonic immobility, mediated both by sympathetic and parasympathetic activation leading into the dissociative response (dark shaded area in center of image), when chance of survival is deemed low. On the dissociative side of the continuum (marked in blue), collapsed immobility occurs, consisting of compromised consciousness, increased parasympathetic activation, decreased attention and arousal, decreased muscle tension, and opioid-mediated analgesia (Kozlowska et al., 2015). In extreme situations, a vasovagal response may occur, leading to fainting or loss of consciousness.

4.1 Neuroimaging findings supporting neurobiological model of dissociation

More recent work has reported that individuals with hyperarousal and flashback/reliving showed less activation of the thalamus as compared to those with depersonalization/derealization responses during responses to trauma scripts (Lanius et al., 2006). As such, the nature of the relation between thalamic activity and dissociative symptomatology remains an important focus of future research. Notably, in keeping with this model, D'Andrea et al. (2013) recently described two patterns of psychophysiological response to startle probes among trauma exposed individuals with PTSD symptomatology. Specifically, participants who reported state dissociation after startle, had a PTSD diagnosis, and varied exposure to trauma, showed initial reduced heart rate acceleration and reduced skin conductance (that remained low throughout the task), while also exhibiting decreasing heart rate deceleration with concomitant increasing heart rate acceleration as the task progressed. Conversely, participants who did not meet criteria for PTSD, had lower trauma exposure (e.g., later in life, single trauma) and who did not demonstrate state dissociation in response to startle showed decreased heart rate acceleration and skin conductance as the task continued along with stable heart rate deceleration. D'Andrea et al. (2013) postulate that one potential explanation for the response pattern seen in the high-trauma, dissociative group is activation of a shut-down of defensive responses, where the individual engages in passive immobilization and withdrawal of resources. These findings are consistent with previous reports of an absence of heart-rate increase in response to traumatic scripts among patients with PTSD and comorbid dissociative symptoms (Lanius et al., 2002), and of depressed skin

conductance and heart rate when recalling a trauma among rape victims high in peri-traumatic dissociation (Griffin et al., 1997). Moreover, in a recent study, Sack et al. (2012) reported reduced heart-rate reactivity and attenuated reductions in parasympathetic cardiac activity in response to a trauma script among individuals reporting high levels of acute dissociative symptoms as compared to those reporting low dissociative symptoms. Finally, in a large scale study including 1461 military veterans, a logistic regression model for predicting current PTSD status that included baseline heart rate, heart rate in response to trauma-related audio-visual cues, and electromyogram and skin conductance response to trauma scripts was successful in identifying two thirds of participants (Keane et al., 1998). Here, it is possible that the remaining one third of participants with PTSD were not characterized by heightened physiological arousal in response to trauma stimuli, a pattern similar to that seen in PTSD-DS. Finally, heightened parasympathetic activity, as seen in tonic and collapsed immobility, may be associated with reduced sensory perception, where among healthy males, higher pain sensitivity was associated with lower parasympathetic activity (Koenig et al., 2015). Further work is required to determine whether heightened parasympathetic activity is associated with reduced sensory perception among healthy individuals.

Among individuals with PTSD, neurobiological evidence points to differing patterns of neural activation among individuals who exhibit hyperarousal or re-experiencing reactivity (similar to the "fight or flight" response (see figures 1 and 2)) in comparison to those who experience dissociative symptomatology (similar to unresponsive immobility, as above) (Bremner, 1999; Lanius et al., 2010, 2012, 2006,

2002). Specifically, functional neuroimaging studies indicate that individuals who reported re-experiencing a traumatic memory in response to script provocation with concomitant psychophysiological hyperarousal exhibit reduced activation in the medial prefrontal and rostral anterior cingulate cortex, accompanied by increased amygdala reactivity. These reliving responses are therefore thought to be mediated by a failure of prefrontal inhibition or top-down control of limbic regions. By contrast, individuals who reported symptoms of depersonalization and derealization (without concomittant psychophysiological hypoarousal) showed increased activation in the rostral anterior cingulate cortex and the medial prefrontal cortex, suggesting that depersonalization/derealization responses are mediated by midline prefrontal inhibition of the limbic regions (Frewen and Lanius, 2006; Lanius et al., 2010, 2012).

4.2 Opioid-mediated contributions to neurobiological model of dissociation

Critically, as noted by Kozlowska et al. (2015), dissociative responses (i.e., tonic collapsed immobility (see figures 1 and 2)) are associated with opioid-mediated analgesia via the PAG and ventromedial medulla pain circuit, where opioids are involved in triggering immobility (Fanselow, 1986; Makino et al., 2000), suppressing vocal responses to threat (Lanius et al., 2014), down-regulation of the hypothalamic mediated sympathetic responses to stress (Drolet et al., 2001). Opioid receptors are present in high volumes in the thalamus (Henriksen and Willoch, 2008), and opioids have been linked to sensory perception, including pain and non-pain related somatosensory perception (Mueller et al., 2010) and physiological arousal, two key roles of thalamic nuclei. Accordingly, we posit that opioid-mediated alterations in thalamic activity may underlie, in part, the altered

sensory integration and arousal levels associated with states of collapsed immobility and dissociative symptoms. Indeed, stressful situations elicit the release of endogenous opioids, as is seen in stress-induced analgesia (van der Kolk et al., 1989) and endogenous opioid secretion following exposure to trauma-related stimuli has been reported among individuals with PTSD, whose self-reported responses included emotional blunting (Van der Kolk, 2001). Further, a study measuring endogenous β-endorphin secretion in the cerebrospinal fluid of combat veterans with PTSD reported significantly higher levels of β-endorphin in the PTSD group compared with controls and negative correlation between β-endorphin levels and PTSD intrusion and avoidant symptoms (Baker et al., 1997). Although not assessed in this study, the inverse relationship between intrusion and avoidant symptoms and plasma β-endorphin levels may be related to an opioid-mediated vulnerability to dissociative states. Moreover, exposure to trauma-related stimuli has been reported to induce a naloxone (opioid antagonist) reversible increase in pain threshold among individuals with PTSD (Pitman et al., 1990). Finally, a handful of studies report successful reductions in dissociative symptoms, including depersonalization, following treatment with opioid-receptor antagonists (e.g., naloxone and naltrexone) among individuals with depersonalization disorder (Nuller et al., 2001; Simeon and Knutelska, 2005), and BPD (Bohus et al., 1999; Schmahl et al., 2012; but see Philipsen et al., 2004). Future work should aim to identify whether stress-induced analgesia or the presence of endogenous opioids among individuals with PTSD is related specifically to symptoms associated with the dissociative subtype, including depersonalization and derealization. Moreover, additional study is required to determine whether reductions in pain

sensitivity, as seen in highly dissociative individuals (Bekrater-Bodmann et al., 2015; Ludascher et al., 2007; Schmahl et al., 2014), are subserved by the endogenous opioid system.

Opioid receptors are present throughout the cortex and limbic system (Le Merrer et al., 2009) and opioids have been implicated in memory disturbance in the animal literature (Itoh et al., 1994; Ma et al., 2007; Ukai et al., 1997; Zhu et al., 2011). Specifically, treatment with opioid agonists have been reported to interfere with acquisition (Spain and Newsom, 1991; Zhu et al., 2011) and retrieval (Zhu et al., 2011) of spatial memories, and disrupt working memory (Itoh et al., 1994), avoidance learning (Aguilar et al., 1998; Ukai et al., 1997), and spatial recognition memory (Ma et al., 2007). Importantly, opioid receptor antagonists have been reported to reverse the effects of opioid agonists (Ukai et al., 1997; Zhu et al., 2011), and even facilitate memory performance (Canli et al., 1990; Gallagher et al., 1983). These findings are mirrored in human populations, where treatment with naltrexone (opioid receptor antagonist) improved recognition memory following stress induction by physiologically arousing stimuli as compared to a matched placebo condition (Katzen Perez et al., 2001). Among individuals receiving opioid treatment for pain management in cancer, opioid use has also been associated with reduced performance on measures of reaction time, attention, and episodic memory, related to initial dosing or dose increases (Kurita et al., 2009; Lawlor, 2002). Similar findings have been reported among individuals with chronic pain, where those using opioid-analgesics for pain management showed greater impairment on tests of

spatial memory, cognitive flexibility, and working memory (Schiltenwolf et al., 2014) (but see Hojsted et al. (2012)).

Critically, not only do opioids interfere with memory acquisition and retrieval, but they also interfere with hippocampal neurogenesis, where chronic administration of morphine leads to reduced hippocampal neurogenesis and cell proliferation (Eisch et al., 2000; Kahn et al., 2005; Mandyam et al., 2004). By contrast, mice who were knocked out for the mu opioid receptor showed enhanced neurogenesis as evidenced by increased number of hippocampal progenitor cells and increased volume and neuron number in the dentate gyrus (Harburg et al., 2007). These findings were mirrored in a recent study among individuals with PTSD with and without comorbid DID, where the authors reported smaller global and subfield hippocampal volume among the PTSD-DID group and smaller subfield hippocampal volume correlated with dissociative symptoms in both PTSD groups (Chalavi et al., 2015) (but see Nardo et al., 2013). Moreover, a study by Liberzon et al. (2007) revealed alterations in central mu-opioid receptor binding following psychological trauma, where men with combat-related PTSD and combat-trauma-exposed men without PTSD demonstrated lower mu-opioid receptor binding in the extended amygdala/ventral pallidum, thalamus, nucleus accumbens, insula, dorsal ACC, and mPFC, but higher mu-opioid receptor binding in the oribitofrontal cortex (with even higher binding among trauma-exposed controls) and subgenual ACC relative to controls. In addition, the PTSD group showed reduced binding in the rostral ACC relative to both control groups. Critically, the up-regulation of mu-opioid receptors in the orbitofrontal cortex as a function of military trauma exposure may contribute to the

effects of endogenous opioids on cognitive functioning among individuals with PTSD-DS. Future work should aim to identify differences in opioid receptor availability and binding in individuals with PTSD-DS as compared to those with PTSD.

Taken together, functional sensory deafferentation at the level of the cortico-sensory pathways may contribute further to patterns of cognitive dysfunction in patients with high levels of dissociation. Here, the development and maintenance of functional sensory deafferentation may limit access to cortical processing resources including those required for memory encoding and retrieval, attention and executive functioning. Moreover, poor integration of sensory experiences would be expected to contribute further to deficits in most aspects of cognitive functioning where sensory input is requisite to the majority of cognitive control operations. Concomitant activation of the endogenous opioid system during states of thalamic-mediated sensory deafferentation and collapsed immobility or dissociation may further compromise cognitive functioning through opioid-mediated memory disturbances and reduced neurogenesis and neuroplasticity (see figure 3).

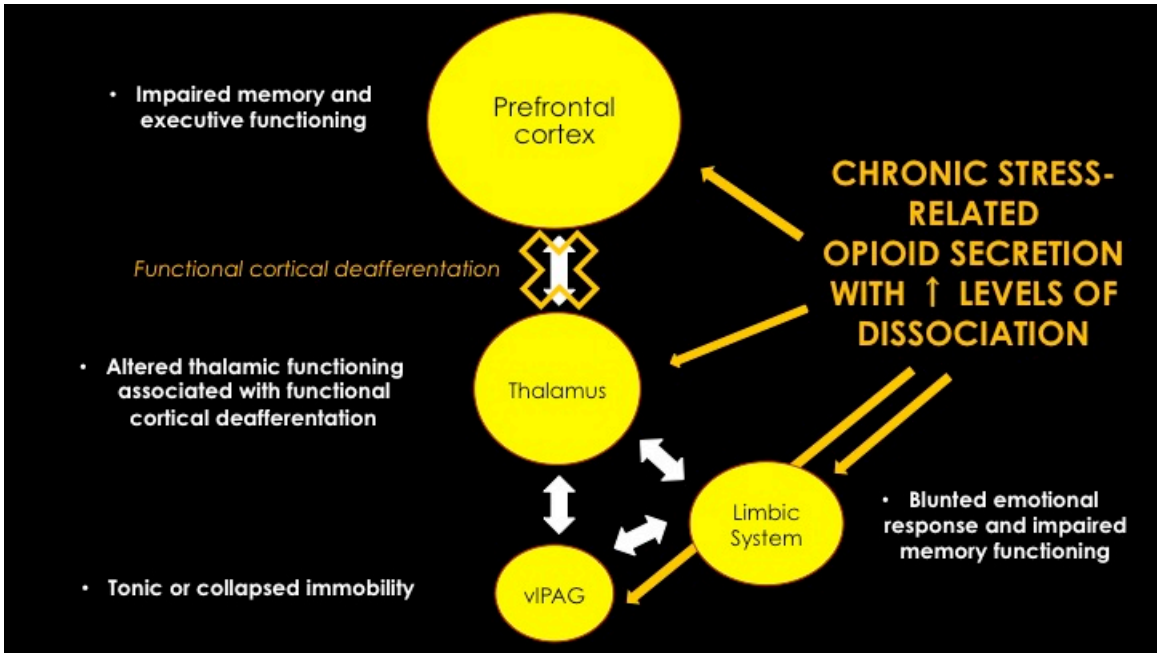

Figure 3: During states of tonic or collapsed immobility, stress-induced release of endogenous opioids via the periaqueductal gray (PAG) triggers immobility (Fanselow et al., 1986), suppression of vocal responses (Kalin et al., 1998), and down-regulation of the hypothalamic-mediated sympathetic response (e.g., fight or flight) (Drolet et al., 2001). Here, endogenous opioids are postulated to mediate functional cortical deafferentation, given the diffuse distribution of opioid receptors throughout the limbic system, thalamus, and prefrontal cortex (Le Merrer et al., 2009), and their influence on sensory perception (Mueller et al., 2010), arousal, memory (e.g., Zhu et al., 2011) and executive functioning (Kurita et al., 2009; Lawlor, 2002). Specifically, we hypothesize that endogenous opioids may mediate functional sensory deafferentation via their actions on thalamic nuclei, leading to reduced sensory integration with associated decrements in memory and executive functioning at the level of the prefrontal cortex. Endogeneous opiods are also postulated to be involved in blunted emotional responses and impaired memory functioning via reciprocal projections between the vlPAG and limbic structures, and between thalamic nuclei and limbic structures.

5.0 Altered brain connectivity among trauma exposed populations: A potential link between dissociative status and cognitive dysfunction

As outlined above, emerging evidence points to a link between dissociative symptoms and alterations in resting-state functional connectivity within and between these neural networks and other brain regions among trauma-related psychiatric

populations. For example, among women with PTSD as a result of early life trauma, higher levels of dissociation were associated with increased connectivity of the dlPFC (a main node of the CEN) with the DMN (Bluhm et al., 2009). In addition, in women with BPD and a history of trauma, increased levels of dissociative symptoms were associated with increased functional connectivity of the amygdala (which has been associated with the SN (Seeley et al., 2007)) with the dlPFC (Krause-Utz et al., 2014a). An additional study of the same population revealed that higher levels of state dissociation are associated with increased connectivity of the amygdala with the right ACC, right thalamus, and left insula when confronted with negative stimuli in an emotional working memory task where prolonged reaction times were also observed (Krause-Utz et al., 2014b). A related study showed increased activity in limbic brain regions, including the amygdala, hippocampus, insula, and ACC during performance on the same task, however, higher levels of state dissociation present at the beginning of the experiment correlated negatively with activation in the amygdala, hippocampus, ACC, and insula, suggesting reduced emotional responding among individuals experiencing dissociation (Krause-Utz et al., 2012). In another study investigating functional connectivity of the DMN in women with BPD, women who scored higher on a measure of trait dissociation showed attenuated fMRI signal decrease in the DMN in response to a "painful" stimulus during a functional imaging task where participants were instructed to rate the severity of pain (Kluetsch et al., 2012). The authors of this study suggest that a reduced ability to down-regulate DMN activity during task performance may contribute to the poor attentional and inhibitory control observed in this population.

Interestingly, a related study identified distinct connectivity profiles for specific symptom profiles of PTSD. Specifically, in women with chronic PTSD as a result of childhood maltreatment, higher severity of hyperarousal was associated with reduced connectivity within the salience network. In addition, increased severity of dissociative symptoms (specifically, depersonalization and derealization) was associated with reduced connectivity of the right perigenual ACC and the ventromedial prefrontal cortex with the DMN and reduced connectivity between the dorsal anterior and posterior regions of the DMN and between the CEN and ventral anterior DMN (Tursich et al., 2015). Rabellino et al (2015) also examined functional connectivity of ICNs during supra- and subliminal threat processing among individuals with PTSD and PTSD-DS (Rabellino et al., 2015). Here, the authors reported altered functional connectivity within the CEN, particularly, increased functional connectivity of the vlPFC with the CEN in PTSD-DS as compared to individuals with PTSD without the dissociative subtype. The authors speculate that this hyperconnectivity within the CEN may contribute to the increased top-down inhibition of limbic regions seen in PTSD-DS (Frewen and Lanius, 2006; Lanius et al., 2010, 2012). Finally, in unpublished preliminary work from our group, we found anterior insular uncoupling with the right CEN as a function of increasing levels of dissociation, including depersonalization and derealization, as measured by the well-validated MDI.

The limited but provocative evidence for the impact of dissociative symptomatology on functional connectivity in ICNs sheds light on potential neural mechanisms underlying the association between dissociation and cognitive dysfunction. Specifically, the three aforementioned ICNs are inextricably linked to higher-order

cognitive processes (Menon, 2011), and alterations in these networks as a function of dissociative symptomatology would be expected to impact negatively on cognitive functioning in these populations. For example, inappropriate recruitment of regions associated with the network involved in cognitively complex tasks (CEN) to the network responsible for self-referential thinking (DMN), as was reported by Bluhm et al. (2009), may interfere with cognitive function through disruption of the focused activity of the CEN. Increased connectivity of brain regions involved in emotional processing (e.g., the amygdala) with those central to higher-order cognitive processes (e.g., dlPFC) (Krause-Utz et al., 2014a) may also disrupt activity in these regions resulting in cognitive dysfunction (e.g., in working memory). Moreover, hyperconnectivity within regions associated with the SN (e.g., amygdala with right ACC and left insula) in response to emotionally negative stimuli in association with state dissociation may result in a reduced ability to attend to external cognitive demands in the face of competing emotional stimuli (Krause-Utz et al., 2014b). Critically, hyperconnectivity within the CEN may result in increased top-down inhibition of limbic regions thought to underlie depersonalization/derealization symptoms and reduce the availability of the CEN for use in other cognitively demanding tasks (Rabellino et al., 2015). Finally, our preliminary, unpublished work, points towards uncoupling of the anterior insula with the CEN as underlying, in part, the impact of dissociative symptoms on cognitive dysfunction given the critical role of the anterior insula in coordinating switching between the CEN and DMN (Goulden et al., 2014; Sridharan et al., 2008) and thus engaging appropriate attentional, working memory, and higher cognitive processes.

Indeed, this proposal is supported by work from our group indicating that individuals with PTSD inappropriately recruited task-negative brain networks (e.g., increased functional connectivity within the DMN) during a working memory task, as compared to healthy controls who demonstrated increased functional connectivity of DMN nodes with areas associated with the SN and CEN, suggesting a greater ability to down-regulate the DMN and activate the CEN and SN during working memory tasks among controls (Daniels et al., 2010). Here, a reduced ability to appropriately recruit task-positive networks (CEN) for tasks requiring working memory may be associated with an inability to switch between the DMN and CEN and thus reduced cognitive capacity. Although Daniels et al. (2010) did not directly assess the relation between these alterations and dissociative symptomatology, these findings coupled with those of Bluhm et al. (2009) suggest that inappropriate recruitment of task-negative brain networks and a potential inability to switch between networks in response to cognitively demanding tasks in association with dissociative symptomatology may be a significant contributor to cognitive dysfunction the populations discussed here. Taken together, aberrant functional connectivity within and between these networks, and reduced ability to appropriately activate task-relevant networks may be related to reduced cognitive control in association with dissociative symptoms. Future work should aim to confirm the relation of dissociative symptomatology and the ability to switch between task positive, and task negative networks.

6.0 General Discussion and Conclusions

Dissociation has been understood as a response to traumatic experiences since the beginning of the 20th century (Janet, 1901); however, its' associations with increased disease severity, poor prognosis, and reduced functional and cognitive outcomes has only begun to be elucidated over the past several decades. More recent work points to a relation between altered patterns of brain activity and connectivity and the presence of dissociative symptoms.

The concept of a PTSD-DS is supported by evidence from studies using latent class and confirmatory factor analysis, where approximately 15-30% of individuals with PTSD can be classified as belonging to a dissociative subtype featuring symptoms of depersonalization and derealization (Armour et al., 2014; Blevins et al., 2014; Frewen et al., 2015; Spiegel et al., 2013; Steuwe et al., 2012; Tsai et al., 2015; Wolf et al., 2012a, 2012b). Evidence of distinct patterns of neural activity (Frewen and Lanius, 2006; Lanius et al., 2010, 2012) and of endocrine (Gola et al., 2012; Zaba et al., 2015) response systems among individuals with PTSD with high levels of dissociative symptomatology provide further evidence for the dissociative subtype. Importantly, dissociation is not a phenomenon linked exclusively to trauma-related disorders, including PTSD, BPD (Meares, 2012; Vermetten and Spiegal, 2014; Winter et al., 2015) and dissociative disorders (Brand et al., 2012). Instead, dissociative symptomatology or comorbid dissociative disorders are observed across numerous psychiatric conditions, including panic disorder, agoraphobia and social phobia (Ball et al., 1997; Marquez et al., 2001; Mula et al., 2007; Simeon et al., 2003), MDD (Nuller, 1982; Parlar et al., 2016), bipolar

disorder (Oedegaard et al., 2008), OCD (Belli, 2014; Belli et al., 2012; M. Rufer et al., 2006a, 2006b), and schizophrenia (Yu et al., 2010). Transdiagnostically, heighted dissociative symptoms are associated with increased disease severity (Belli et al., 2012; Rufer et al., 2006a; Stein et al., 2013), elevated risk of suicidality (Stein et al., 2013), the presence of suicidal ideation and self-harm behaviours (Foote et al., 2008), increased pain threshold and reduced pain perception (related to self-harm behaviours) (Bekrater-Bodmann et al., 2015; Ludascher et al., 2007; Schmahl et al., 2014) poor functional outcomes (Stein et al., 2013), and reduced treatment efficacy (Bae et al., 2016; Kleindienst et al., 2011; Price et al., 2014; Rufer et al., 2006b; Semiz et al., 2014; Spitzer et al., 2007).

In this review, we have identified a significant body of evidence linking dissociative symptomatology to reduced neuropsychological functioning among healthy individuals and individuals suffering from psychiatric conditions. Specifically, evidence linking heightened dissociative symptoms to reduced performance on measures assessing a broad range of cognitive functions including executive functioning, attention, working memory, immediate and delayed verbal and visual memory, autobiographical memory, and episodic memory has been reported among controls and in trauma-related psychiatric populations (Amrhein et al., 2008; Brewin et al., 2013; Bruce et al., 2007; Giesbrecht et al., 2004; Olsen and Beck, 2012a) [but see (Cloitre et al., 1996; De Ruiter et al., 2004; Elzinga et al., 2007, 2000; Veltman et al., 2005) and section 3.3 above for a discussion of conflicting evidence]. Preliminary work from our group, reviewed here, also provides evidence for a link between dissociative symptomatology and poor short-term memory

performance among military trauma-exposed individuals. Differing patterns of episodic memory recall between dissociative states have been reported in individuals with DID (Bryant, 1995; Elzinga et al., 2003; Schlumpf et al., 2014; Reinders et al., 2012), as has overgeneral autobiographical memory recall (Huntjens et al., 2014; Barlow et al., 2011). Moreover, evidence for the relation between neuropsychological dysfunction and dissociative symptomatology extends beyond purely cognitive domains to the realm of social cognition, where higher levels of dissociation have been related to worse performance on measures of prosody (Nazarov et al., 2015), theory of mind (Nazarov et al., 2014), and emotion recognition (Renard et al., 2012).

Although dissociation may be confused with attention, it is critical to consider dissociation as an orthoganal construct, with dissociable neural and behavioural correlates reviewed here. In cases where dissociative processes and cognitive operations compete for shared processing resources and their underlying neural networks, disruption of each may occur, with the evidence reviewed here pointing sharply to disruption across multiple cognitive domains. Future work will be required to deconstruct carefully the concept of dissociation to identify specifically those facets of its presentation most likely to be associated with disruption of cognitive performance (see Lanius et al., 2012 and Bryant, 2007 for a discussion). One other critical avenue for future work will be to compare directly the impact of state dissociation at the time of testing to the impact of trait dissociation on cognitive dysfunction, as well as to compare directly hetrogeneous samples of trauma-exposed individuals (e.g., military versus civilian trauma). Despite knowledge of a clear relation between dissocaitive symptomatology and cognitive

function, however, the neurobiological mechanisms underlying this association remain to be unidentified.

Here, we propose further a neurobiological model linking altered states of arousal, as in the defense cascade model of dissociation (Schauer and Elbert, 2010; Kozlowska et al., 2015), to reduced cognitive functioning among highly dissociative individuals (see figure 3). Specifically, we argue that functional sensory deafferentation at the level of cortico-sensory pathways may, in part, underlie cognitive dysfunction among highly dissociative individuals, where reduced integration of sensory experiences, mediated by thalamic relay sites, may interfere with cognitive functioning in these populations. We have also identified the deleterious effect of opioid-mediated analgesia on memory and point to the impact of opioid dysregulation on neurogenesis and neuroplasticity. Future work will be necessary to elucidate further the relation between opioids, cognitive dysfunction, and thalamic sensory integration among individuals with dissocaitive disorders via prospective, longitudinal methodology.

We have presented a model linking altered connectivity within, and between, three resting state ICNs crucial for higher-order cognitive processes and consistently linked to psychopathology (Menon, 2011), with dissociative symptomatology in PTSD and other trauma-related disorders. Specifically, we posit that dissociative psychopathology and cognitive dysfunction may be linked through inappropriate recruitment of brain regions associated with task positive networks (CEN) to task negative networks (DMN) (as reported by Bluhm et al., 2009). Critically, preliminary work from our group has identified insular uncoupling with the CEN and DMN as a

function of dissociative symptomatology that we hypothesize to be associated with a reduced ability to switch between task-positive and task-negative networks in response to external demands. Further, increased connectivity of emotionally-driven brain regions to nodes of the CEN as a function of dissociative symptomatology (Krause-Utz et al., 2014a) may lead to reduced cognitive capacity. Finally, hyperconnectivity within the SN in response to emotionally negative stimuli (Krause-Utz et al., 2014b) may be related to a reduced ability to attend to external cognitive demands in the face of competing emotional demands leading to impaired cognitive function. Future work will be necessary to determine directly the relation between connectivity within and between these resting state networks, dissociative symptomatology, and cognitive dysfunction in order to confirm these hypotheses. Specifically, it will be critical to investigate the ability of individuals displaying dissociative symptomatology to recruit task-positive networks in cognitively demanding environments and their ability to utilize key nodes of the SN (e.g., the anterior insula) in order to achieve fluid switching.

Further work will also be required to gain an understanding of the longitudinal course of dissociative symptomatology following exposure to trauma, leading up to the development of illness and following individuals through the course of their illness. Here, it remains unknown how dissociative symptoms present longitudinally, and further, how underlying neural, cognitive, and physiological changes may mediate the increased disease severity, treatment resistance, and functional impairment observed among individuals with high levels of dissociative psychopathology. Specifically, prospective, longitudinal studies should investigate the development of cognitive dysfunction among

individuals with dissociative psychopathology in relation to the functioning of the CEN, SN, and DMN. Given the association between dissociative symptomatology and reduced treatment efficacy (Bae et al., 2015; Price et al., 2014; Rufer et al., 2006b; Semiz et al., 2014), future work should also focus on identifying treatments aimed specifically at individuals with high levels of dissociative symptoms. It will be of particular importance to investigate the efficacy of treatments aimed at reducing cognitive dysfunction, such as cognitive remediation therapies that have proven effective in other psychiatric populations (Bowie et al., 2013; Deckersbach et al., 2010; Elgamal et al., 2007; Kurtz, 2012; Wykes et al., 2011) but have scarcely been applied to trauma-related psychiatric disorders. It will also be crucial to identify interventions that target simultaneously dissociative symptomatology and cognitive dysfunction and seek to remediate the functioning of large-scale brain networks. As reviewed by our group, these interventions may include cognitive remediation, mindfulness, and neurofeedback-based approaches Lanius et al., (2015). In addition, it will be important to determine more precisely the impact of dissociation on treatment effectiveness, where conflicting reports have arisen as to the impact of dissociation on treatment (e.g., Bae et al., 2015; Price et al., 2014; Wolf et al., 2015)), and other reports where no difference is noted between highly dissociative and low-dissociative individuals. Notably, these studies have focused on the impact of dissociation measured retrospectively, including symptom frequency and severity over the last month, indices that are prone to measurement error and non-specificity. It will be necessary here to determine the impact of state dissociation experienced immediately preceding and during therapy. Finally, we have reviewed the transdiagnostic nature of

dissociative symptomatology. On balance, it is imperative that clinicians and researchers assess adequately dissociation and consider carefully treatment approaches given the detrimental effects of this symptom profile on disease severity, treatment efficacy and cognitive functioning, with associated decrements in real-world, functional outcomes.

Table 1. Results of correlational analysis between RBANS scores and clinical variables including PTSD symptom severity, anxiety and depressive symptoms, trauma exposure, and dissociation in a sample of military combat-exposed individuals.

Clinical Measure	**r or ρ**	**RBANS Total**	**RBANS Immediate Memory**	**RBANS visuospatial/ constructional**	**RBANS Language**	**RBANS Attention**	**RBANS Delayed Memory**
CAPS (Previous Month)	r	0.13	-0.29	0.36	-0.26	0.21	0.17
BAI	r	0.06	0.001	0.18	-0.27	0.09	0.03
BDI	r	0.26	-0.05	0.35	-0.19	0.38	0.19
CTQ (Total)	ρ	0.14	0.44	-0.02	0.09	-0.14	0.18
MDI (Total)	ρ	-0.11	**-0.48***	0.07	-0.01	0.20	-0.23
Disengagement	ρ	-0.13	**-0.60****	0.17	-0.11	0.17	-0.23
Depersonalization/ Derealization	ρ	-0.23	**-0.56***	-0.03	-0.06	0.12	-0.33
Emotional Constriction	ρ	-0.06	-0.28	-0.02	0.11	0.15	-0.11
Memory Impairment	ρ	-0.05	**-0.47***	0.19	0.08	0.16	-0.21
Identity Dissociation	ρ	-0.23	-0.29	-0.22	-0.36	-0.01	-0.16

* $P<.05$; ** $P<.01$

Table 2. Summary of studies examining the relation between dissociative symptoms and cognitive functioning separated by cognitive domain and psychiatric condition. Positive results denote studies supporting the relation between dissociative symptoms and cognitive dysfunction. Whereas negative results denote studies that do not support such a relation, mixed results provide some support for this relation.

Population	Study	*N*	Cognitive Domains	Positive or Negative	Relevant Findings
Healthy Controls	Amrhein et al., 2008	17 High Dissociators, 17 Low Dissociators	VM, WM, EF	Positive	Poorer performance on measures of VM and WM and increased perseveration among high dissociators
	Bergouignan et al., 2014	32 HC	EM	Positive	Significantly reduced recall of episodic events encoded in an induced out-of-body condition compared to a within-body condition
	Brewin et al., 2013	60 HC	VM, WM, Att	Positive	Experimentally induced dissociation led to greater deterioration in VM between immediate and delayed recall and worse performance on a digit span test (WM)
	Bruce et al., 2007	65 HC	WM, EF	Positive	Individuals with higher trait dissociation reported significantly more EF difficulties; no objective differences were found
	DePrince and Freyd, 1999	28 High Dissociators, 28 Low Dissociators	VM	Mixed	Under a divided attention condition, high dissociators recalled more neutral and fewer trauma words as compared to low dissociators who showed the opposite pattern. High dissociators showed greater interference in a selective attention condition of the Stroop task compared to low dissociators. The opposite pattern held for a divided attention condition of the Stroop task.

DePrince and Freyd, 2001	28 High Dissociators, 28 Low Dissociators	VM	Mixed	In a divided attention directed forgetting task, high dissociators recalled fewer trauma-related words and more neutral words compared to low dissociators
de Ruiter et al., 2004	119 HC	WM	Negative	High dissociative students had higher WM span than medium or low dissociative students.
Devilly et al., 2007	23 Low Dissociators, 14 High Dissociators	VM	Positive	No significant interaction effects between high and low dissociators were found on a directed forgetting task in regard to condition (i.e., divided or selective attention) or stimulus type (trauma vs. neutral words). Lower recall for to-be-remembered words and increased commission errors was noted in high dissociators compared to low dissociators
Freyd et al., 1998	40 High Dissociators, 40 Low Dissociators	EF	Positive	High dissociators showed increased interference on a task of response inhibition (Stroop) in comparison to low dissociators
Giesbrecht et al., 2004	185 HC	EF	Positive	Disruptions in EF were related to higher trait dissociation
Giesbrecht and Merckelbach, 2009	22 High Dissociators, 24 Low Dissociators	VM, EF	Negative	No significant differences emerged between groups on verbal recall tasks, all participants recalled more emotional than neutral words. High dissociators showed trend level reductions in response time on an emotional stroop task under divided and selective attention conditions and for both trauma and neutral words compared to low dissociators.
Olsen and Beck, 2012	27 High Dissociators; 27 Low Dissociators	DA, IM, EM	Positive	High dissociators demonstrated reduced scores on a DA task, reduced IM for trauma-related stimuli, and greater EM detail for neutral stimuli but lower EM detail for trauma stimuli in comparison to low dissociators

	Veltman et al., 2005	11 High Dissociators, 10 Low Dissociators	WM	Negative	High dissociators performed significantly better on WM tasks
Trauma-Exposed	Cromer et al., 2006	24 Foster-care Children	EF, Att	Positive	Significant relation between dissociation and response inhibition and attention tasks among foster-care children
	DePrince et al., 2009	110 Children	WM, EF, Att	Positive	Parent reported dissociative symptoms and trauma exposure status accounted for unique proportions of the variance in the prediction of EF
	DePrince and Freyd, 2004	24 High Dissociators; 21 Low Dissociators	VM	Mixed	In a directed forgetting task, higher dissociators recalled fewer trauma-related words and more neutral words compared to low dissociators under divided attention conditions
	Morgan et al., 2006	184 Military Personnel	VSM	Positive	Baseline dissociation and history of traumatic stress predicted performance on a VSM task under stressful conditions
PTSD	Chae et al., 2011	322 Abused Children	IQ, Lang, VM, VSM, EM	Positive	Trauma symptoms were associated with reduced EM among children reporting high levels of dissociative symptomatology, but not those reporting low levels of dissociative symptomatology
	De Bellis et al., 2013	38 maltreated children, 60 maltreated + PTSD, 104 HC	Att, Lang, VS, VM, VSM, EF	Positive	Dissociative symptoms were negatively correlated with Att scores
	Kaplow et al., 2008	156 Abused Children	Att	Positive	Sexually abused children who reported dissociative symptoms upon disclosure of abuse are at increased risk of developing parent-reported attentional problems 8-36 months later
	Minshew and D'Andrea, 2015	27 PTSD	IM, VM	Positive	Higher dissociative symptoms were related to reduced explicit recall of threat-related (but not trauma-related) word stimuli

	Rivera-Vélez et al., 2014	12 PTSD, 12 HC	VM, WM, EF, Att	Positive	Dissociative symptoms negatively correlated with VM and VSM measures
	Roca et al., 2006	10 PTSD + dissociative disorder, 17 PTSD only	IQ, Att, VM, VSM, EF, AM	Positive	Greater deficits on measures of Att, AM, and VM in PTSD + dissociative disorder group compared to PTSD only group
	Twamley et al., 2009	55 PTSD, 20 HC	EF, VS, VM	Positive	Among PTSD group, those with greater levels of dissociative symptoms performed worse on a reasoning task (EF)
	Brandes et al., 2002	14 PTSD, 14 Trauma-exposed control	WM, EM, Att, VSM	Negative	Group differences in performance on measure of VSM and Att remained significant after controlling for peri-traumatic dissociation
MDD	Parlar et al., 2016	23 MDD, 20 HC	VSM, VM, PS	Positive	Among a sample of trauma exposed individuals with MDD, higher levels of derealization symptoms were associated with reduced VSM and VM and higher levels of depersonalization symptoms were associated with reduced performance on measures of PS.
BPD	Cloitre et al., 1996	24 BPD + childhood abuse, 24 BPD only, 24 HC	VM	Negative	Dissociative symptomatology was positively correlated with recall for "to-be-remembered" words in a directed forgetting task
	Haaland and Landrø, 2009	40 BPD, 20 HC	Att, WM, EF, VM, VSM, IQ	Positive	BPD + pathological dissociation was related to worse performance on measures of Att, VM, WM, and EF compared to controls. BPD without pathological dissociation performed worse only on measures of EF compared with controls
	Winter et al., 2015	40 BPD, 20 HC	EF, VM	Positive	Dissociation induction was associated with reduced EF (inhibitory control) in an emotional Stroop task among BPD patients for emotional stimuli and a trend toward reduced free recall for presented words among the BPD + dissociation induction group compared to the BPD control group (no

					dissociation induction). The BPD control group performed similarly to controls on both measures.
DID	Elzinga et al., 2007	16 DID, 16 HC	WM	Negative	Enhanced WM performance with increased task load in DID patients as compared to HCs
	Dorahy et al., 2005	11 DID, 11 MDD, 11 HC	WM	Positive	Reduced cognitive inhibition in DID group in an emotionally negative context and a significant correlation between response speed to negative stimuli and dissociative symptoms was reported
	Dorahy et al., 2006	12 DID, 12 GAD, 12 HC	WM	Positive	Reduced cognitive inhibition in an anxiety provoking (emotionally negative) context in DID group
	Dorahy et al., 2002	20 DID, 20 HC, 20 MDD	WM	Positive	An absence of cognitive inhibition (negative priming effect) in a DID group compared to a HC group who showed a trend toward negative priming. The psychiatric comparison group (MDD) also failed to show negative priming. A second study showed slowed response time in the DID group compared to HC and MDD. Dissociative symptomatology was associated with reduced negative priming in the second study.
DPD	Guralnik et al., 2000	15 DPD, 15 HC	IQ, VM, VSM, EF, VS, Att	Positive	DPD patients performed worse on measures of VM, VSM, VS, and Att as compared to HCs. VS and VM functioning predicted membership in the DPD group.
	Guralnik et al., 2007	21 DPD, 17 HC	IQ, PS, VM, VSM, WM, Att	Positive	Dissociative symptoms in the DPD group were negatively correlated with IQ, PS, and WM scores. The DPD group performed worse on measures of PS, immediate VM and immediate VSM as compared to HCs
Dissociative Disorder	Elzinga et al., 2000	20 High Dissociator HC, 23 Low Dissociator HC,	VM	Negative	Patients and high dissociative controls completed more stem words with target words in a word completion memory test following a directed forgetting task compared to low

(Not Specified)	14 Dissociative Disorder patients	dissociative controls. High dissociative controls and patients showed less directed forgetting than low dissociative controls (i.e., an inability to purposefully forget target words), particularly for sex-related words.

HC = Healthy Controls; PTSD = Post-traumatic Stress Disorder; MDD = Major Depressive Disorder; BPD = Borderline Personality Disorder, DID = Dissociative Identity Disorder, DPD = Depersonalization Disorder, GAD = Generalized Anxiety Disorder

IQ = Intelligence

VM = Verbal Memory

WM = Working Memory

EM = Episodic Memory

AM = Autobiographical Memory

IM = Implicit Memory

VSM = Visuospatial Memory

VS = Visuospatial Functioning

EF = Executive Function; including response inhibition, perseveration, rule learning

PS = Processing Speed

Lang = Language

Att = Attention

DA = Divided Attention

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Chapter 3: Dissociative symptoms mediate the relation between PTSD symptoms and functional impairment in a sample of military members, veterans, and first responders with PTSD

Chapter Link

The work in the following chapter was published in March 2018 in *European Journal of Psychotraumatology*, *9*, 1463794, DOI: 10.1080/20008198.2018.1463794.

The previous chapter provided an overview of the relation between dissociative symptomatology and neuropsychological functioning among psychiatric conditions, including PTSD. Neuropsychological functioning is closely related to day-to-day functioning among individuals with PTSD. Thus, the following study was performed to evaluate the contribution of dissociative symptomatology to functional outcomes in PTSD, given it's relation to reduced cognitive functioning. Participants included an inpatient sample of military members, veterans, and first responders with probable PTSD (e.g., based on self-report symptoms).

Dissociative symptoms mediate the relation between PTSD symptoms and functional impairment in a sample of military members, veterans, and first responders with PTSD

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ABSTRACT

Background: Posttraumatic Stress Disorder (PTSD) is associated with significant functional impairment in important areas, including interpersonal relationships and occupational or educational roles. Preliminary evidence suggests that the dissociative subtype of PTSD (PTSD+DS), characterized by marked symptoms of depersonalization and derealisation, is associated with increased functional impairment and disease severity, including among military members and veterans diagnosed with PTSD. Similarly, first responders (e.g., police, fire, paramedics) have also been found to experience dissociative symptoms. Despite these findings, little work has investigated whether dissociative symptoms are related to heightened functional impairment among these populations.

Objective: We examined the relation between functional impairment and symptom level variables, including dissociative symptoms of depersonalization, derealisation, emotional constriction, disengagement, memory dissociation, and identity dissociation, among military members, veterans, and first responders with probable PTSD. We further investigated the hypothesis that dissociative symptoms mediate the relation between PTSD symptomatology and functional impairment.

Method: Eighty-one medical charts of inpatients at a residential PTSD treatment program were accessed via retrospective review. Sixty-two were included in the present analyses. Comparison of means on symptom measures between first responders and military members/veterans were conducted, followed by correlational and mediation analyses.

Results: Compared with first responders, military members and veterans showed higher levels of derealisation, functional impairment, alexithymia, anxiety and depression. Within the total sample, dissociative symptoms emerged as the strongest correlate of functional impairment and, among the dissociative symptom clusters, derealisation symptoms demonstrated the strongest relation with impairment. Mediation analyses revealed that total dissociative symptoms and derealisation symptoms significantly mediated the relation between PTSD symptoms and functional impairment.

Conclusions: These findings highlight the importance of assessing and treating dissociative symptoms, consistent with the dissociative subtype of PTSD, among military members, veterans, and first responders with PTSD. Successful recovery on a functional and symptomatic level may necessitate treatment of dissociative symptoms, particularly, derealisation.

Keywords: Functional impairment; dissociative subtype; derealisation; PTSD; military members; veterans; first responders

Highlights:

- Posttraumatic stress disorder (PTSD) is associated with reduced day-to-day functioning across multiple important life domains, including interpersonal relationships and occupational or educational roles
- This pattern is apparent among military members, veterans, and first responders with PTSD
- This study aimed to gain a better understanding of the symptoms associated with this reduced functioning

- The results of this study indicate that symptoms of dissociation, particularly derealization (feeling as though things around you are unreal or unfamiliar), accounts for the relation between PTSD symptoms and impairment in day-to-day functioning
- This work is important in improving both symptom and functional recovery among military members and first responders

1.0 Introduction

Posttraumatic stress disorder (PTSD) is associated with significant distress or impairment in day-to-day functioning in important areas such as family relationships, occupational roles, and educational settings (American Psychiatric Association, 2013). Indeed, PTSD is related to large reductions in work and mental health related quality of life (QOL) as compared to anxiety disorders (Olatunji, Cisler, & Tolin, 2007), significantly impaired workplace performance and productivity (Kessler, 2000) and the highest use of medical care services among DSM-IV anxiety disorders (Greenberg et al., 1999). In addition, recent work suggests that reduced QOL may persist following remission of PTSD symptoms. For example, Westphal et al. (2011) reported that individuals with a previous diagnosis of PTSD who did not currently meet criteria for the disorder experienced reduced QOL when compared to trauma-exposed controls. Despite these findings, limited research has sought to identify symptom level factors predictive of functional impairment among individuals with PTSD - knowledge that is central to tailoring treatment to promote both symptomatic and functional recovery.

The present study sought to identify trauma-related symptoms most strongly associated with functional impairment in a sample of military members, veterans, and first responders (e.g., police, fire, and paramedics) with probable PTSD.

1.1 Functional impairment among military members, veterans, and first responders with PTSD

The study of functional impairment may be particularly relevant among veteran samples, where individuals with PTSD experience poorer health functioning, increased

disability (Goldberg et al., 2014), greater functional impairment, and reduced QOL compared to veterans without PTSD (Shea, Vujanovic, Mansfield, Sevin, & Liu, 2010; Zatzick et al., 1997). Moreover, among trauma-exposed men, combat trauma has been related to greater incidence of PTSD, unresolved PTSD symptoms, and unemployment (Prigerson, Maciejewski, & Rosenheck, 2001). For example, men who identified combat trauma as their worst lifetime event were more likely to meet lifetime criteria for PTSD, have ongoing PTSD symptoms, and unemployment when compared to men who identified other traumatic experiences as their most disturbing life event (e.g., physical assault), with the exception of sexual assault or molestation (Prigerson et al., 2001). Similarly, first responders involved in rescue and recovery following disasters or terrorist attacks also experience significant functional impairment (North et al., 2002; Ruggero et al., 2013). To illustrate, firefighters who were diagnosed with PTSD following a shared traumatic experience (the Oklahoma City Bombing) reported greater interference in their daily activities, relationships, and decreased job satisfaction in comparison to firefighters who were exposed to the same traumatic event, but did not have PTSD (North et al., 2002).

In addition, reported levels of exposure to childhood abuse are significantly higher among military members and veterans when compared with the general population (Afifi et al., 2016; McCauley, Blosnich, & Dichter, 2015). Importantly, childhood abuse is associated with suicide and suicide attempts (Afifi et al., 2016), high utilization of mental health care services and perceived need for mental health care (Turner et al., 2017), and reduced health-related quality of life (Katon et al., 2015) among military

members. Although less research has been conducted among first responders, emerging work suggests that early physical abuse is related to worse mental health outcomes in these populations (Komarovskaya et al., 2014). These findings further highlight the importance of understanding functional impairment among military and first responder populations.

1.2 The link between functional impairment and PTSD symptomatology

Research investigating which PTSD symptom clusters are associated with the highest level of functional impairment has yielded mixed findings. Here, a small number of studies have found that among PTSD symptoms, emotional numbing/avoidance symptoms as per DSM-IV-TR PTSD diagnostic criteria (American Psychiatric Association, 2000) are most predictive of functional impairment among veterans and active duty military members (Rona et al., 2009; Shea et al., 2010) and among individuals exposed to terrorism (i.e., World Trade Center attacks) (Malta, Levitt, Martin, Davis, & Cloitre, 2009). By contrast, other work has identified hyperarousal symptoms as the most significant correlate of functional impairment among military personnel (Maguen, Stalnaker, McCaslin, & Litz, 2009) and natural disaster survivors (Heir, Piatigorsky, & Weisæth, 2010). In other studies, symptoms of emotion dysregulation (e.g., ability to regulate negative mood) and interpersonal difficulties, consistent with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013) conceptualization of PTSD, appear predictive of functional disability among victims of terrorism (Malta et al., 2009) and women with a history of childhood abuse (Cloitre, Miranda, Stovall-McClough, & Han, 2005). For example, Cloitre et al.

(2005) reported that measures of interpersonal functioning and emotion regulation were significant predictors of functional impairment in women with a history of childhood abuse, and made a contribution to functional impairment equal to that of PTSD symptoms.

1.3 PTSD, functional impairment, and dissociation: A probable link

Importantly, much of the work to date has investigated symptoms of PTSD as they were conceptualized in the DSM-IV-TR. DSM-5 brought about a new conceptualization of PTSD symptom clusters, including re-experiencing (e.g., intrusive thoughts, flashbacks), avoidance of trauma-related stimuli, negative alterations in mood and cognition (including emotion regulation difficulties), and alterations in arousal or reactivity (e.g., hypervigilance, increased startle response; American Psychiatric Association, 2013). DSM-5 also introduced the dissociative subtype of PTSD (PTSD+DS), reflecting approximately 15-30% of individuals with PTSD who experience significant dissociative symptoms of depersonalization (feeling as though one is separated from one's own body) and derealisation (feeling as though things around you are strange or unfamiliar) (Armour, Karstoft, & Richardson, 2014; Bennett, Modrowski, Kerig, & Chaplo, 2015; Blevins, Weathers, & Witte, 2014; Bremner & Brett, 1997; Bremner et al., 1992; Frewen, Brown, Steuwe, & Lanius, 2015; Hansen, Ross, & Armour, 2017; Lanius et al., 2010; Lanius, Brand, Vermetten, Frewen, & Spiegel, 2012; Spiegel et al., 2013; Steuwe, Lanius, & Frewen, 2012; Tsai, Armour, Southwick, & Pietrzak, 2015; Waelde, Silvern, & Fairbank, 2005; Wolf, Lunney, et al., 2012; Wolf, Miller, et al., 2012). Among military members and veterans, recent studies indicate that

8%-32% of veterans and active duty military personnel meet criteria for the dissociative subtype (Armour et al., 2014; Tsai et al., 2015; Waelde et al., 2005; Wolf, Lunney, et al., 2012; Wolf, Miller, et al., 2012). Critically, within military and veteran samples, as well as other trauma-exposed samples (e.g., incarcerated youth, individuals exposed to motor vehicle accidents, physical or sexual assault, and childhood abuse), PTSD+DS has been associated with greater PTSD symptom severity, depressive and alcohol abuse symptoms, and psychiatric comorbidity (Bennett et al., 2015; Blevins et al., 2014; Tsai et al., 2015; Waelde et al., 2005; Wolf, Lunney, et al., 2012; Wolf, Miller, et al., 2012) (but see Steuwe et al., (2012)). Although considerably less work has been done in first responder populations, early work has identified significantly greater levels of dissociative symptoms among police officers with PTSD as compared to those without PTSD (Carlier, Lamberts, Fouwels, & Gersons, 1996). In addition, recent work has identified the presence of peritraumatic dissociation in first responder samples, which has been associated with a greater likelihood of developing PTSD (Galatzer-levy, Madan, Neylan, Henn-haase, & Marmar, 2011; Maia et al., 2011; Marmar et al., 2006; van der Velden et al., 2006).

Dissociative symptoms have been related to functional indicators among additional trauma-exposed samples. For example, among a subgroup of men seeking treatment for alcohol dependence who had a lifetime diagnosis of PTSD, those with dissociative symptoms experienced greater interference in quality of life (Evren et al., 2011). Notably, in the total study sample, dissociation mediated the relation between childhood abuse and PTSD severity, and individuals with dissociative symptoms had

higher levels of childhood abuse. Further, childhood trauma was also related to worse quality of life, suggesting that experiences of childhood trauma and dissociative symptoms may interact to lead to reduced quality of life or functional impairment (Evren et al., 2011).

1.4 Dissociation is associated with poor cognitive functioning in PTSD

Dissociative symptoms are associated with worse cognitive functioning across domains of memory, attention, and executive functioning among individuals with PTSD (see McKinnon et al. (2016) for a review), including veterans (Morgan, Doran, Steffian, Hazlett, & Southwick, 2006; Roca, Hart, Kimbrell, & Freeman, 2006). Notably, cognitive impairment has been associated with reduced psychosocial functioning (Jaeger et al., 2006) and decreased ability to carry out instrumental activities of daily living (Vaughn McCall & Dunn, 2003) among individuals with depression, even after accounting for depressive symptoms (Jaeger et al., 2006). Similarly, within PTSD samples, reduced verbal memory performance and executive functioning difficulties have been associated with reduced psychosocial functioning (Ainamani, Elbert, Olema, & Hecker, 2017; Geuze et al., 2009; but see Twamley et al., 2009). Although no work to date has illustrated a three-way relation between dissociative symptoms, cognitive dysfunction, and functional impairment in individuals with PTSD, it is probable that the heightened level of cognitive dysfunction seen among individuals with dissociative symptoms and PTSD may be related to worse functional impairment compared to those without dissociative symptoms.

1.5 Objectives of the present study

Given that, among individuals with PTSD, dissociative symptoms are associated with heightened disease severity (Stein et al., 2013) and cognitive dysfunction (McKinnon et al., 2016) that together contribute to functional impairment in related disorders (e.g., depression (Gonda et al., 2015)), we hypothesized that when compared to classical symptoms of PTSD (e.g., re-experiencing, hyperarousal), dissociative symptoms will contribute most strongly to functional impairment in this population. Accordingly, the present study sought to examine whether dissociative symptoms were significantly associated with functional impairment among military personnel, veterans, and first responders with PTSD. We also investigated the relation between functional disability and classic PTSD symptom clusters, as well as with additional symptoms associated with PTSD. In order to test our main hypothesis, mediation analyses were used to determine whether dissociative symptoms mediate the relation between PTSD symptoms and functional impairment in this population. In order to determine if the first responder and military/veteran samples in our study experienced similar severity of symptomatology across clinical and functional measures and similar levels of exposure to adverse experiences in childhood, we compared symptom means and reported exposure to adverse childhood experiences between these two groups. Finally, due to the potential impact of childhood abuse exposure on functional outcomes, we conducted subsequent analyses including exposure to adverse childhood experiences as a covariate in these models.

2.0 Methods

2.1 Participants

This study was approved by the Homewood Health Centre Research Ethics Board. Eighty-one charts were accessed via retrospective chart review of patients seen at Homewood Health Centre's inpatient Program for Traumatic Stress Recovery between May 22, 2015 and June 30 2016. Participants were included if they had a score above the proposed cut-point for probable diagnosis of PTSD (score of 33 (Wortmann et al., 2016)) on the PTSD Checklist for DSM 5 (PCL-5) (n = 4 excluded) (Weathers et al., 2013). Participants were also excluded from the analyses based on missing or incomplete data (n = 12; missing data from any variable in the main analyses) or multiple admissions within the study period (n = 3), leaving a final sample of 62 patients. The patient sample was comprised of military members and veterans (n = 32), first responders (e.g., police, fire fighters, paramedics) (n = 27) and individuals who were/had previously been employed as both first responders and military members or veterans (n = 3) who were suffering from trauma-related psychological difficulties. Demographic characteristics are reported in Table 1. Secondary analyses investigating exposure to adverse childhood experiences (ACEs) were complete on a subset of the full sample (n = 59), as 3 respondents had missing data on a measure of ACEs.

Table 1. Demographic characteristics of the study sample

Characteristics	Combined Sample, *n* = 62	Military and Veteran, *n* = 32	First Responder, *n* = 27
Demographic Characteristics	Mean (SD)		
Sex (female:male)	10:52	7:25	2:25
Age	45.9 (9.5)	45.2(11.1)	47.3(7.3)
Education	% of Sample		
8th grade or less	1.6	3.1	0
Some high school	4.8	6.3	0
High school	16.1	21.9	11.1
Technical or trade school	12.9	18.9	7.4
Some college or university	25.8	28.1	25.9
Diploma or bachelor's degree	32.3	12.5	51.9
Graduate degree	6.5	9.4	3.7
Income	% of Sample		
Employed	59.7	40.6	77.8
Employment Insurance	8.1	3.1	14.8
Pension	19.4	31.3	3.7
Disability Insurance	25.8	28.1	25.9
Other (e.g., Investment, WSIB, Inheritance)	8.1	9.4	7.4
No Income	3.2	6.3	0
Characteristics	Combined Sample, *n* = 62	Military and Veteran, *n* = 32	First Responder, *n* = 27
Demographic Characteristics	Mean (SD)		
Sex (female:male)	10:52	7:25	2:25
Age	45.9 (9.5)	45.2(11.1)	47.3(7.3)
Education	% of Sample		
8th grade or less	1.6	3.1	0
Some high school	4.8	6.3	0
High school	16.1	21.9	11.1
Technical or trade school	12.9	18.9	7.4
Some college or university	25.8	28.1	25.9
Diploma or bachelor's degree	32.3	12.5	51.9
Graduate degree	6.5	9.4	3.7
Income	% of Sample		
Employed	59.7	40.6	77.8
Employment Insurance	8.1	3.1	14.8
Pension	19.4	31.3	3.7
Disability Insurance	25.8	28.1	25.9
Other (e.g., Investment, WSIB, Inheritance)	8.1	9.4	7.4
No Income	3.2	6.3	0

2.2 Materials

The World Health Organization Disability Assessment Schedule 2.0 (WHODAS; Ustün, 2010)

The WHODAS is a 36-item self-report inventory used to assess functional disability across six domains with high internal consistency; cognition (chronbach's alpha (α) = 0.94; understanding and communicating), mobility (α = 0.96), self-care (α = 0.95) (e.g., personal hygiene), getting along (α = 0.94) (interacting with others), life activities (α = 0.94) (e.g., work or home responsibilities), and participation in society (α = 0.95) (engaging in community, civil, and recreational activities). The WHODAS showed good test-retest reliability, and the WHODAS domain scores showed good convergence with comparable instruments that measure disability (Ustün, 2010).

The PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013)

The PCL-5 is a 20-item self-report questionnaire used to assess the severity of PTSD symptoms across the four symptom domains outlined in the DSM-5 with good to high internal consistency (Bovin et al., 2016). It contains items that assess intrusive symptoms (PCL Intrusions; α = 0.80-0.92), avoidance (PCL avoidance; α = 0.83-0.92), negative alterations in mood and cognition (PCL mood and cognition; α = 0.82-0.89), and alterations in arousal and reactivity (PCL arousal and reactivity; α = 0.75-0.84) (α for the total score = 0.91-0.95). The PCL-5 has also been found to have good test-retest reliability, convergent validity, and sensitivity (e.g., the ability to detect clinical levels of PTSD symptomatology) among civilian (Blevins, Weathers, Davis, Witte, & Domino, 2015), veteran (Bovin et al., 2016), and military populations (Wortmann et al., 2016).

The Multiscale Dissociation Inventory (MDI; Briere, 2002)

The MDI is a 30-item self-report inventory used to measure the frequency at which individuals experience six domains of dissociative symptoms over the past month with adequate-high internal consistency: disengagement (MDI disengagement; $\alpha = 0.83$), depersonalization (MDI depersonalization; $\alpha = 0.90$), derealisation (MDI derealisation; $\alpha = 0.91$), emotional constriction (MDI emotional constriction; $\alpha = 0.94$), memory disturbance (MDI memory disturbance; $\alpha = 74$), and identity dissociation (MDI identity dissociation; $\alpha = 75$). The MDI total score has an internal consistency of $\alpha = 0.96$.

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004)

The DERS assesses six dimensions of emotion regulation difficulties including, lack of awareness of emotional responses, lack of clarity of emotional responses, nonacceptance of emotional responses, limited emotion regulation strategies, difficulties controlling impulses when experiencing negative emotions, and difficulty completing goal-directed behaviours when experiencing negative emotions (Gratz & Roemer, 2004). The DERS has been found to have good internal consistency ($\alpha = 0.80$-0.89 for subscales), convergent validity with other measures of emotion regulation, and predictive validity for behavioural outcomes including self-harm (Gratz & Roemer, 2004).

The Toronto Alexithymia Scale (TAS; Bagby, Taylor, & Parker, 1994)

The TAS is a 20-item self-report measure assessing the construct of alexithymia, or difficulties recognizing and naming emotions. The TAS measures three dimensions of alexithymia: difficulty identifying feelings, difficulty describing feelings, and externally oriented thinking (i.e., the preference to focus on external details rather than internal

thought content related to emotions). The TAS has demonstrated good test-retest reliability and internal consistency (α = 0.81) (Bagby et al., 1994).

The Depression Anxiety and Stress Scale – 21-item version (DASS-21; Lovibond & Lovibond, 1995)

The 21-item version of the DASS was used to measure symptoms of depression (DASS depression) (low mood, motivation and self-esteem), anxiety (DASS anxiety) (physiological arousal, panic, and fear), and stress (DASS stress) (tension and irritability). The DASS-21 has demonstrated good internal consistency (α = 0.81-0.91 for subscales) and convergent validity (Lovibond & Lovibond, 1995).

The Adverse Childhood Experiences Questionnaire (ACE-Q) (Felitti et al., 1998; Merrick et al., 2017) was used to assess the presence or absence of 10 commonly experienced ACEs. Specifically, using dichotomous variables (0 = No, 1 = Yes), participants indicated whether they had been exposed to emotional, physical, or sexual abuse, emotional or physical neglect, domestic violence (physical abuse of mother), parental divorce or separation, substance abuse in the household, a mentally ill family member, or incarceration of a family member. A cumulative index combining individual ACE-Q items results in a total exposure score ranging from 0-10. ACE-Q scores are related to adverse mental health outcomes including drug use, alcohol use, depressed affect and attempted suicide, with increasing ACE scores being related to increased odds of experiencing adverse outcomes (Merrick et al., 2017).

2.3 Procedures and statistical analyses

All analyses were completed using SPSS version 24.0. Analysis of the

distribution of variables assessed in the current study revealed non-normality of several variables (Shapiro-Wilk >.05). Parametric analyses were reported for clarity and ease of interpretation. However, non-parametric tests (not reported) revealed consistent results across analyses.

Correlational analyses were conducted to examine the relation between PTSD symptomatology, dissociation, emotion regulation difficulties, alexithymia, depression, anxiety, and stress with functional impairment in the full sample (Pearson's r; two-tailed; alpha = 0.05). Correlational analysis was also conducted to examine the relation between exposure to ACEs and functional impairment for those respondents with complete ACE-Q data.

Comparisons of means on clinical measures and functional impairment were made between the military/veteran (n = 32) and first responder (n = 27) groups. Group differences were analyzed using a univariate analysis of variance (ANOVA), which treated military/veteran and first responder status as fixed variables and the clinical measures as dependent variables.

Comparison of mean number of ACEs reported was made between the military/veteran (n = 30) and first responder (n = 26) groups for those respondents with complete ACE-Q data. Pearson's chi-square tests were used to determine whether there was an association between military or first responder status and exposure to individual ACEs.

In order to test our hypothesis that dissociative symptoms (MDI total and derealisation score) mediate the relation between PTSD symptomatology (PCL-5 total

score) and functional impairment, we followed the tests proposed by (Hayes, 2013) as well as the bootstrapping procedure (5000 samples) recommended by Preacher and Hayes (Preacher & Hayes, 2004). Mediation analyses were carried out using the using the PROCESS macro, version 2.16, for SPSS (Hayes, 2013). In order to account for the possibility that exposure to ACEs may be associated with functional impairment and thus account for the relation between PTSD symptomatology and functional impairment, secondary analyses were completed, repeating the above mediation analyses with ACE-Q Total score included as a covariate in the models. Critically, as Lees & Neufeld (1994) describe, while statistical control (such as adding covariates) can lead to issues such as data residualization and deconstruction leading to compromised meaning of the covariate-adjusted value, this approach is often the only option in clinical research. However, if the inferences drawn from our initial data analysis (e.g., the mediating role of dissociative symptoms) remain stable in our secondary analyses (including the covariate), we can be confident in our conclusions.

3.0 Results

3.1 Relation between functional disability (WHODAS Total) and variables of interest

Table 2 reports the correlations between functional disability and clinical variables as well as cumulative ACE exposure. Correlations are reported as statistically significant after controlling for multiple comparisons. Among the variables of interest, symptoms of dissociation (MDI Total) were most strongly correlated with functional impairment as measured by the WHODAS Total score ($r = 0.59$, $p<.002$). In addition, in order of increasing strength of association, DERS Total ($r = 0.50$, $p<.002$), DASS depression ($r =$

0.47, $p<.002$), TAS Total ($r = 0.43$, $p<.002$), and DASS anxiety ($r = 0.40$, $p<.002$), were significantly related to functional impairment (WHODAS Total) (see table 2). PTSD symptoms and cumulative ACE exposure were not significantly correlated with WHODAS Total after correcting for multiple comparisons.

Among MDI subscales, MDI derealisation symptoms emerged as the most significant correlate with functional impairment ($r = 0.59$, $p<.002$). In addition, MDI disengagement ($r = 0.57$, p<.002), MDI emotional constriction ($r = 0.52$, $p<.002$), MDI memory dissociation ($r = 0.50$, $p<.002$), and MDI depersonalization ($r = 0.47$, $p<.002$) were significantly related to functional impairment.

Table 2. Correlations (Pearson's r) between functional impairment and PTSD and associated symptom dimensions, (N = 62 for all variables except for ACE-Q, N = 59)

	WHODAS Total
ACE-Q	0.27
PCL Total	0.30
PCL Intrusions	0.32
PCL Avoidance	0.16
PCL Cognition and Mood	0.23
PCL Arousal and Reactivity	0.30
MDI Total	0.59*
MDI Disengagement	0.57*
MDI Depersonalization	0.47*
MDI Derealization	0.59*
MDI Emotional Constriction	0.52*
MDI Memory Dissociation	0.50*
MDI Identity Dissociation	0.31
DASS-Depression	0.47*
DASS-Anxiety	0.40*
DASS-Stress	0.23
DERS Total	0.50*
TAS Total	0.43*

*Significant after controlling for multiple comparisons, $p<.002$;

ACE-Q, Adverse Childhood Experiences Questionnaire; PCL, PTSD Checklist For DSM-5; MDI, Multiscale Dissociation Inventory; DASS, Depression Anxiety Stress Scale; DERS, Difficulties in Emotion Regulation Scale; TAS, Toronto Alexithymia Scale

3.1 Group comparisons for results on clinical measures and exposure to ACEs

Table 3 reports the means, standard deviations, and group comparisons for clinical measures as well as percentage of the sample endorsing each ACE-Q and Pearson's chi-square test of association. Compared to first responders, the military/veteran group endorsed significantly higher scores on measures of functional impairment (F (1,58) = 15.15, p = .000), derealisation symptoms (F (1,58) = 4.17, p = .046), alexithymia (F (1,58) = 4.29, p = .043), depression (F (1,58) = 4.09, p = .048) and anxiety (F (1,58) = 4.16, p = .046). No other significant differences emerged.

No significant associations emerged between military/veteran or first responder status and exposure to individual ACEs. There was a trend-level association between military/veteran or first responder status and exposure to domestic violence (i.e., witnessing abuse of mother), $\chi^2(2) = 3.71$, p = 0.054, with 33.3% military/veterans compared with 11.5% of first responders endorsing exposure to domestic violence in childhood.

Table 3. Clinical characteristics of study sample and comparison of clinical measures and exposure to ACEs between military members/veterans and first responders

	Combined sample, $n = 62$	Military and veteran, $n = 32$	First Responder, $n = 27$	F (1,58)
Clinical Characteristics	Mean(SD)			
Functional Disability (WHODAS 2.0)	53.9(18.2)	62.3(14.2)	45.8(18.3)	15.15**
PTSD Symptoms (PCL-5)				
Total	59.5(10.3)	59.8(10.9)	59.8(9.8)	0.00
Intrusions	14.5(4.2)	14.8(4.6)	14.7(3.7)	0.00
Avoidance	6.1(1.8)	6.1(1.6)	6.3(2.0)	0.05
Cognition and Mood	21.5(3.8)	21.4(4.0)	21.2(3.5)	0.02
Arousal and Reactivity	17.1(3.4)	17.5(3.5)	21.2(3.5)	0.37
Dissociative Symptoms (MDI)				
Total	69.5(25.4)	75.4(27.9)	65.1(21.3)	2.48
Disengagement	16.3(4.9)	17.0(4.7)	16.1(5.2)	0.44
Depersonalization	8.9(4.9)	10.0(5.5)	8.1(4.1)	2.33
Derealisation	11.5(5.2)	12.9(5.4)	10.2(4.8)	4.17*
Emotional Constriction	14.0(6.0)	15.3(6.1)	13.3(5.5)	1.64
Memory Dissociation	12.2(5.6)	13.1(6.2)	11.6(4.8)	1.19
Identity Dissociation	6.5(3.1)	7.0(3.9)	5.8(1.7)	2.33
Emotion Dysregulation (DERS)	119.5(24.3)	123.8(27.9)	116.9(22.1)	1.18
Alexithymia (TAS)	63.4(12.3)	66.3(13.6)	59.7(9.9)	4.29*
DASS-Depression	27(10.4)	29.8(10.6)	24.4(9.6)	4.09*
DASS-Anxiety	23.4(10.1)	25.8(9.4)	20.6(10.2)	4.16*
DASS-Stress	27.5(8.5)	27.8(7.8)	27.5(9.5)	0.02
ACE-Q Total	3.36(2.73)	3.67(2.70)	3(2.79)	0.83
ACE-Q ($n = 59$; $n = 30$ Military/Veteran; $n = 26$ First Responder)	% of Sample Endorsing			$\chi^2(2)$
Emotional Abuse	57.6	60	53.8	0.22
Physical Abuse	50.8	53.3	50	0.06
Sexual Abuse	23.7	33.3	15.4	2.39
Emotional Neglect	38.9	36.7	42.3	0.19
Physical Neglect	18.6	23.3	15.4	0.56
Parental Separation/Divorce	40.7	43.3	34.6	0.44
Domestic Violence	23.7	33.3	11.5	3.71
Substance Abuse	39.0	40	38.5	0.01
Mental Illness	33.9	36.7	30.8	0.22
Incarceration of household member	6.8	6.7	7.7	0.02

*$P < .05$, ** $P <. 01$.

PCL, PTSD Checklist For DSM-5; MDI, Multiscale Dissociation Inventory; DASS, Depression Anxiety Stress Scale; DERS, Difficulties In Emotion Regulation Scale; TAS, Toronto Alexithymia Scale; ACE-Q, Adverse Childhood Experiences Questionnaire

F refers to *F* statistic for univariate analysis of variance; X^2 refers to the chi-square statistic for Pearson's chi-square test

3.3 Mediation of association between PTSD symptom severity and functional disability by dissociative symptoms

Given the strong correlation between MDI total and WHODAS total, as well as the theoretical rationale outlined above, we examined whether dissociative symptoms (MDI total) mediated the relation between PTSD severity (PCL Total) and functional impairment (WHODAS Total). In addition, we investigated whether dissociative symptoms of derealisation, in particular, were driving the relation between PTSD severity and functional disability, as among subscales of the MDI, the derealisation subscale emerged as the strongest correlate of functional impairment, and given that it represents an important symptom of PTSD+DS. Tests for mediation were carried out according to Hayes (2013). The proportion of variance accounted for by the mediation model is also provided. Although some of the data in the current study were not normally distributed (Shaprio-Wilk <.05), bootstrapping techniques as followed in the present analyses are robust to violations of the assumptions of normality and homoscedasticity (Erceg-Hurn & Mirosevich, 2008).

3.3.1 Mediation the of association between PTSD symptom severity and functional disability by MDI total

Table 4 reports the correlations between the variables in the mediation model.

Table 5

and figure 1 summarize the results of the mediation analysis. Results indicated that PTSD symptom severity was a significant predictor of dissociative symptoms, $b = 1.22$, SE = 0.28, $p = .000$, and that dissociative symptoms significantly predicted functional impairment, $b = 0.42$, SE = 0.09, $p = 000$. PTSD symptoms were no longer a significant predictor of functional impairment after controlling for dissociative symptoms, $b = 0.03$ SE = 0.21, $p = 0.902$. Approximately 35% of the variance in functional impairment was accounted for by the predictors ($R^2 = 0.35$). The indirect effect was estimated using a bootstrapping approach with 5000 samples. These results indicated the indirect coefficient was significant, $b = 0.51$, SE = 0.13, $p = 001$. For every 1-point increase in PTSD symptom severity, there was an approximately 0.51-point increase in functional impairment, as mediated by dissociative symptoms.

Inclusion of ACE-Q total as a covariate in a secondary mediation analysis completed on respondents with full ACE-Q data available ($n = 59$) revealed consistent results. Specifically, PTSD symptom severity was a significant predictor of dissociative symptoms after controlling for cumulative ACEs, $b = 1.26$, SE = 0.33, $p = .000$, and dissociative symptoms significantly predicted functional impairment after controlling for cumulative ACEs, $b = 0.36$, SE = 0.10, $p = .000$. PTSD symptoms were no longer a significant predictor of functional impairment after controlling for dissociative symptoms and cumulative ACEs, $b = 0.11$ (SE = 0.22), $p = 0.646$. Approximately 38% of the variance in functional impairment was accounted for by the predictors ($R^2 = 0.38$). The indirect effect was estimated using a bootstrapping approach with 5000 samples. These results indicated the indirect coefficient was significant, $b = 0.46$, SE = 0.18, $p = 008$.

Table 4. Correlation Matrix for Dissociation Symptom Severity (MDI Total), PTSD Symptom Severity (PCL Total), and Functional Disability (WHODAS Total), N = 62 (Pearson's r reported)

Variable	2	3
1. MDI Total	0.50***	0.59***
2. PCL Total		0.30*
3. WHODAS Total		

*p<.05; **p<.01 ***p<.001
PCL, PTSD Checklist For DSM-5; MDI, Multiscale Dissociation Inventory; WHODAS. World Health Organization Disability Assessment Schedule 2.0

Table 5. Mediation Effects of Dissociation Symptom Severity (MDI Total) on the Relationship between PTSD Symptom Severity (PCL Total) and Functional Disability (WHODAS Total), N = 62

Regression Paths	*b*	SE	*p*
Mediation *a* path (PCL Total on MDI Total)	1.22	0.28	<.001
Mediation *b* path (MDI Total on WHODAS Total)	0.42	0.09	<.001
Total effect, *c* path (PCL Total on WHODAS Total, No Mediator)	0.54	0.22	<.05
Direct effect *c'* (PCL Total on WHODAS Total including MDI Total as mediator)	0.03	0.21	0.902
Indirect effect bootstrapped (*c* – *c'*) with bootstrapped 95% CI	0.51 [0.27-0.79]		

Note. *b* = unstandardized coefficient; SE = standard error; CI = confidence interval. Fit for mediation model R^2= 0.35, F (2, 59) = 15.83, p<.001.
PCL, PTSD Checklist For DSM-5; MDI, Multiscale Dissociation Inventory; WHODAS, World Health Organization Disability Assessment Schedule 2.0

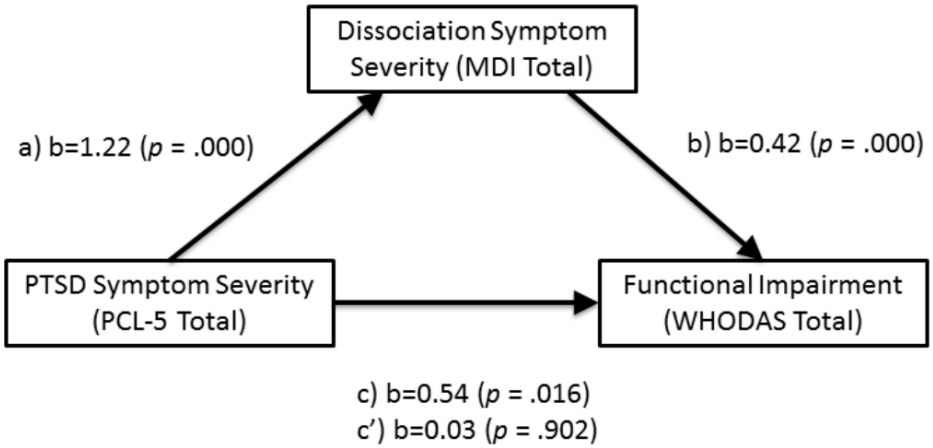

Figure 1: Depiction of the mediation model where dissociative symptoms (MDI total) mediate the relation between PTSD severity and functional impairment. The effect of PCL Total on change in WHODAS Total when MDI Total is introduced as a mediator (c') is nonsignificant.
b = unstandardized coefficient; a = effect of PCL total on change in MDI Total; b) effect of MDI Total on change in WHODAS Total; c = the total effect; c' = the direct effect; MDI multiscale dissociation inventory; PCL-5, PTSD checklist for DSM-5; WHODAS, World Health Organization disability assessment schedule 2.0.

3.3.2. Mediation of association between PTSD symptom severity and functional disability by MDI derealisation symptoms

Table 6 depicts the correlations between the variables in the mediation model. Table 7 and figure 2 summarize the results of the mediation analysis. Results indicated that PTSD symptom severity was a significant predictor of derealisation symptoms, b = 0.29, SE = 0.05, p = .000, and that derealisation symptoms significantly predicted functional impairment, b = 2.10, SE = 0.44, p = 000. PTSD symptoms were no longer a significant predictor of functional impairment after controlling for derealisation symptoms, b = -0.06, SE = 0.22, p = 0.785. Approximately 34% of the variance in functional impairment was accounted for by the predictors (R^2 = 0.34). The indirect effect

was estimated using a bootstrapping approach with 5000 samples. These results indicated the indirect coefficient was significant, $b = 0.60$, SE = 0.14, $p = 001$. For every 1-point increase in PTSD symptom severity, there was an approximately 0.60-point increase in functional impairment, as mediated by derealisation symptoms.

Inclusion of ACE-Q total as a covariate in a secondary mediation analysis completed on respondents with full ACE-Q data available ($n = 59$) revealed consistent results. Specifically, PTSD symptom severity was a significant predictor of dissociative symptoms after controlling for cumulative ACEs, $b = 1.26$, SE = 0.33, $p = .000$, and derealisation symptoms significantly predicted functional impairment after controlling for cumulative ACEs, $b = 1.85$, SE = 0.46, $p = .000$. PTSD symptoms were no longer a significant predictor of functional impairment after controlling for dissociative symptoms and cumulative ACEs, $b = 0.04$ (SE = 0.26), $p = 0.893$. Approximately 37% of the variance in functional impairment was accounted for by the predictors ($R^2 = 0.37$). The indirect effect was estimated using a bootstrapping approach with 5000 samples. These results indicated the indirect coefficient was significant, $b = 0.53$, SE = 0.14, $p = 003$.

Table 6. Correlation Matrix for Derealization Symptoms (MDI Derealization), PTSD Symptom Severity (PCL Total), and Functional Disability (WHODAS Total), N = 62 (Spearman's rho reported)

Variable	2	3
1. MDI Derealisation	0.56***	0.59***
2. PCL Total		0.30*
3. WHODAS Total		

*p<.05; **p<.01 ***p<.001

PCL, PTSD Checklist For DSM-5; MDI, Multiscale Dissociation Inventory; WHODAS, World Health Organization Disability Assessment Schedule 2.0

Table 7. Mediation Effects of Derealisation Symptoms (MDI Derealisation) on the Relationship between PTSD Symptom Severity (PCL Total) and Functional Disability (WHODAS Total), N = 62

Regression Paths	*b*	SE	*p*
Mediation *a* path (PCL Total on MDI Derealisation)	0.29	0.05	<.001
Mediation *b* path (MDI Derealisation on WHODAS Total)	2.10	0.44	<.001
Total effect, *c* path (PCL Total on WHODAS Total, No Mediator)	0.54	0.22	<.05
Direct effect *c'* (PCL Total on WHODAS Total including MDI Derealization as mediator)	-0.06	0.22	0.785
Indirect effect bootstrapped (*c – c'*) with bootstrapped 95% CI[b]	0.60 [0.33-0.89]		

Note. *b* = unstandardized coefficient; SE = standard error; CI = confidence interval. Fit for mediation model R^2= 0.34, F (2, 59) = 15.40, p<.001.
PCL, PTSD Checklist For DSM-5; MDI, Multiscale Dissociation Inventory; WHODAS, World Health Organization Disability Assessment Schedule 2.0

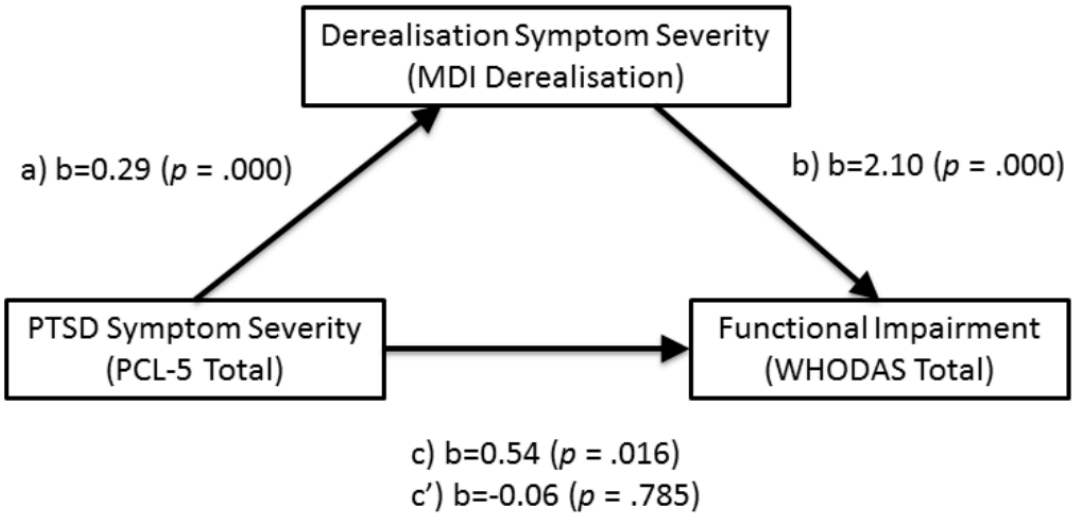

Figure 2: Depiction of the mediation model where derealization symptoms (MDI derealization) mediate the relation between PTSD severity and functional impairment. The effect of PCL Total on change in WHODAS Total when MDI Total is introduced as a mediator (c') is nonsignificant.
b = unstandardized coefficient; a = effect of PCL total on change in MDI Total; b) effect of MDI Total on change in WHODAS Total; c = the total effect; c' = the direct effect; MDI multiscale dissociation inventory; PCL-5, PTSD checklist for DSM-5; WHODAS, World Health Organization disability assessment schedule 2.0.

4.0 Discussion

This study is the first to explicitly examine the mediating role of dissociative symptoms in the relation between PTSD symptom severity and functional impairment. Here, we found that dissociative symptoms experienced over the past month, as measured by the MDI (Briere, 2002), significantly mediated the relation between PTSD symptom severity (as measured by the PCL-5) and functional impairment (as measured by the WHODAS 2.0) among a sample of military members, veterans, and first responders. Given that the highest correlation among MDI subscales and functional disability emerged for the derealisation subscale and the role of derealisation in PTSD+DS, we investigated whether derealisation symptoms mediated the relation between PTSD severity and functional disability and found a significant mediation effect. The emergence of derealisation symptoms as a significant mediator is interesting given previous findings that derealisation (but not depersonalisation) was associated with increased disease severity among individuals with trauma-related disorders (e.g., dissociative disorders and borderline personality disorder) (Sar, Alioğlu, & Akyuz, 2017), suggesting that derealisation and depersonalization symptoms represent distinct constructs with different properties. These results support previous literature highlighting increased disease severity and functional impairment among individuals with PTSD+DS (Evren et al., 2011; Stein et al., 2013), including military members and veterans (Tsai et al., 2015; Waelde et al., 2005; Wolf, Lunney, et al., 2012; Wolf, Miller, et al., 2012).

In the current sample, PTSD symptoms were not significantly correlated with functional impairment after controlling for multiple comparisons, despite being correlated

with other symptoms found to be significantly correlated with functional impairment (not reported), including dissociative symptoms, depression, emotion regulation difficulties, anxiety and alexithymia. Thus, it may be important for treatment to target these additional symptom domains in order to achieve functional recovery. These findings contrast with previous work identifying avoidance/numbing (Rona et al., 2009; Shea et al., 2010) and hyperarousal symptoms (Heir et al., 2010; Maguen et al., 2009) as being significantly related to functional impairment among individuals with PTSD. To our knowledge, this is the first study to investigate DSM-5 PTSD symptom dimensions in relation to functional impairment, which may account for these discrepant findings, given the differences in PTSD symptom domains between DSM-5 and DSM-IV-TR.

The current study is in keeping with findings of increased cognitive dysfunction among individuals with PTSD and dissociative symptoms (McKinnon et al., 2016), including veterans (Morgan et al., 2006; Roca et al., 2006). In particular, we hypothesize that symptoms of dissociation may lead to increased functional impairment at least partially via their relation with increased cognitive dysfunction. Here, given limited cognitive processing resources, it is probable that dissociative symptoms may reduce the amount of resource available to key cognitive domains, including attention and executive functioning, resulting in functional limitations (McKinnon et al., 2016). Indeed, among veterans with PTSD, reduced verbal memory performance has been associated with reduced social and occupational functioning (Geuze et al., 2009; but see Twamley et al., 2009). Future work will be necessary to confirm this hypothesis.

Notably, previous work has highlighted that among a subgroup of men seeking

treatment for alcohol abuse who had PTSD, the presence of dissociative symptoms was related to reduced quality of life. In addition, dissociative symptoms mediated the relation between childhood trauma and PTSD severity (Evren et al., 2011). Given these findings, and findings of high levels of childhood abuse among military members and veterans when compared with the general population (Afifi et al., 2016; Koola et al., 2013; Seifert, Polusny, & Murdoch, 2011), it is possible that dissociative symptoms may stem, in part, from childhood abuse rather than trauma experienced as part of a military or first responder service, thus leading to functional impairment. However, the results of the present study indicated the dissociative symptoms mediated the relation between PTSD symptoms and functional impairment after controlling for exposure to adverse childhood experiences (ACEs), suggesting that while ACEs may be associated with functional impairment, they do not account for the mediating role of dissociative symptoms.

Our findings support the critical importance of identifying dissociative symptoms when assessing and diagnosing PTSD. In particular, the present results suggest that treatment targeting dissociative symptoms, particularly derealisation symptoms, among military members and first responders may be imperative in allowing both symptomatic and functional recovery from PTSD. Given that recent studies have identified between 8% and 32% of veterans and military members with PTSD can be classified as a dissociative subtype (PTSD+DS) (Armour et al., 2014; Tsai et al., 2015; Waelde et al., 2005; Wolf, Lunney, et al., 2012; Wolf, Miller, et al., 2012), these findings hold particular importance for these populations. Critically, military members and veterans often struggle to shift from military or service life to other roles, a transition that is

potentially related to the high levels of functional impairment seen in the current sample. Moreover, some findings indicate that dissociative symptoms may impact negatively on treatment outcome with first-line treatments for PTSD such as, eye movement desensitization and reprocessing (EMDR) (Bae, Kim, & Park, 2016), cognitive processing therapy (CPT) (Resick, Suvak, Johnides, Mitchell, & Iverson, 2012), and early intervention using imaginal and in-vivo exposure techniques (Price, Kearns, Houry, & Rothbaum, 2014; Wolf, Lunney, & Schnurr, 2016). Although some authors questions the clinical significance of these findings (Resick et al., 2012; Wolf et al., 2016) and other studies have not found reduced treatment efficacy among individuals with PTSD demonstrating significant dissociative symptoms (Cloitre, Petkova, Wang, & Lu, 2012; Hagenaars, van Minnen, & Hoogduin, 2010; Speckens, Ehlers, Hackmann, & Clark, 2006; Wolf, et al., 2016), individuals with PTSD+DS may be vulnerable to ongoing symptoms and disrupted functioning following treatment. Accordingly, alternative or adjunctive treatment strategies targeting symptoms of dissociation may be necessary to achieve both full symptomatic and functional recovery. This is particularly relevant given work indicating that functional impairment may persist beyond symptom recovery in individuals with PTSD (Westphal et al., 2011). For example, mindfulness-based treatments have emerged recently as a promising alternative approach to treatment of PTSD symptomatology (Boyd, Lanius, & McKinnon, 2017; Hopwood & Schutte, 2017) and have been suggested to be an effective approach in the treatment of dissociative symptoms, whereby mindfulness based approaches foster increased connection and awareness to somatic experiences and awareness of the internal and external cues (Boyd

et al., 2017; Zerubavel & Messman-Moore, 2015).

The current sample included first responders, military members, and veterans with PTSD. Although PTSD+DS has been studied among military members and veterans, it remains understudied among first responders. Indeed, just one study to date has identified significant dissociative symptoms among first responders (Carlier et al., 1996). In the present study, military members and veterans demonstrated dissociative symptoms at or above clinically significant levels (Briere, 2002) across symptom clusters of disengagement, depersonalization, derealisation, emotional constriction, and memory dissociation, on average. In contrast, the first responder group demonstrated dissociative symptomatology at or above clinically significant levels (Briere, 2002) only on measures of disengagement, emotional constriction, and memory dissociation. Moreover, when comparisons were made between groups, the military and veteran group demonstrated significantly higher scores on the derealisation subscale of the MDI. With estimates between 8% and 22% of first responders meeting criteria for PTSD (Andrews, Joseph, Shevlin, & Troop, 2006; Bennett, Williams, Page, Hood, & Woollard, 2004; Clohessy & Ehlers, 1999; Jonsson, Segesten, & Mattsson, 2003; Pietrzak et al., 2014), it is important for future work to identify the extent to which first responders meet criteria for the dissociative subtype. The present findings indicate that while dissociative symptoms may be present among first responders, they may be at a lower level than those seen in military members or veterans. Importantly, the military and veteran group also reported significantly higher levels of functional impairment than the first responder group, suggesting that higher levels of derealisation symptoms in the military/veteran group may

lead to higher levels of functional impairment, when compared with the first responder group. Given the small sample size in the present study (n = 32 military members and veterans; n = 27 first responders), these findings will need to be replicated in future studies with larger samples. This is particularly important given the present findings of a strong relation between dissociative symptoms and functional disability in a sample including first responders.

Additional comparisons between the military member and veteran group and first responder group revealed that both groups exhibited similar levels of PTSD severity. In contrast, the military member and veteran group endorsed significantly greater depressive symptoms, anxiety symptoms, and alexithymia. These findings support previous literature indicating high comorbidity of depression and PTSD in veterans, which is associated with reduced quality of life and greater symptom severity (Ginzburg, Ein-Dor, & Solomon, 2010; Ikin, Creamer, Sim, & McKenzie, 2010), complementing findings of greater functional impairment in the military/veteran group than the first responder group in the current study. Moreover, the finding of greater alexithymia among the military member and veteran group converges with previous findings demonstrating higher levels of alexithymia in combat-related PTSD compared to other trauma types (Frewen, Dozois, Neufeld, & Lanius, 2008). Levels of exposure to ACEs were also compared between the military/veteran and first responder groups. Interestingly, in the current sample military members and veterans reported an average of 3.7 ACEs and first responders reported an average of 3, a difference that was not statistically significant. In addition, no significant associations were found between military/veteran or first responder status and exposure

to individual ACEs, although higher rates were reported among military members and veterans for experiencing sexual abuse (33.4% vs. 15.4%) and domestic violence (33.3% vs. 11.5%). Future work with larger sample sizes and utilizing community samples will be necessary to determine if there is a statistically significant difference in exposure rates.

Overall, the current study provides preliminary, but provocative evidence that dissociative symptoms mediate the relation between PTSD symptomatology and functional impairment among veterans, military members, and first responders with PTSD. It will be critical to investigate whether this mediating relation holds true for other populations with PTSD (e.g., childhood abuse survivors). Furthermore, the current study assessed PTSD symptoms over the past month, but did not assess chronic or persistent PTSD symptomatology. Previous work indicates that lower levels of psychosocial functioning is associated with maintenance of chronic PTSD (Zlotnick et al., 2004). Given the inpatient status of the current sample, it is likely that they have experienced a persistent and severe course of illness, consistent with a chronic presentation. Here, future work is required to evaluate the effect of course of illness (e.g., duration; severity) on the relation between chronicity of PTSD, dissociative symptoms and functional impairment and to determine if these findings will generalize to other groups (e.g., community samples, those seeking outpatient treatment). In addition, future work clarifying whether individuals with PTSD+DS exhibit greater functional impairment than those with PTSD will be important to determine whether differing mediating relations emerge among those with PTSD who meet criteria for the dissociative subtype and those who do not. In particular, prospective studies should identify which symptom domains

are most important in predicting functional impairment among those with PTSD+DS and PTSD.

There are several limitations to the present study that may be addressed in future research. The sample size of the current study is low and only self-report, retrospective questionnaires were used, along with best estimates of PTSD diagnosis based on self-report. Future work should utilize more rigorous psychodiagnostic measures to confirm a diagnosis of PTSD and to assess for the presence and severity of related symptoms, including dissociation. Furthermore, our study was limited to first responders, veterans, and military members, was largely composed of males, and may not generalize to other trauma-exposed populations or females with PTSD. In addition it was not possible to determine the traumatic experience from which participants in the current sample were experiencing the most distress (e.g., military or combat trauma or childhood abuse), thus although inclusion of ACEs as a covariate in our analyses did not affect the results, it is possible that subjects in this study were experiencing distress related to other traumatic experiences in addition to military/combat trauma or their work as first responders. Similarly, due to the potential overlap of symptoms due to different traumatic experiences (e.g., childhood abuse and combat trauma) it is possible that the mediating role of dissociation between PTSD and functional impairment is not accounted for solely by participant's combat or first responder experiences. We were also unable to account for a history physical injury, traumatic brain injury or other physical illnesses that may be associated with functional impairment and dissociative symptoms. This is particularly important given recent findings that physical injury may be associated with increased

dissociative symptoms among combat-exposed individuals with PTSD (Özdemir, Celik, & Oznur, 2015). Future studies should exclude individuals with these medical histories in order to ascertain a clearer picture of the relation between dissociation, PTSD symptoms, and functional impairment. The use of a cross-sectional design also limits the conclusions that can be drawn. Specifically, since all measures were collected at the same time, conclusions regarding causality are limited and it is difficult to determine if dissociative symptoms predict or mediate the relation between PTSD symptoms and functional impairment over time. The use of longitudinal designs in future research will be necessary to draw such conclusions. Moreover, given that PTSD symptoms and dissociative symptoms are highly correlated, and some models of dissociative symptoms in PTSD suggest that they both represent aspects of the same response to traumatic events (Dalenberg & Carlson, 2012), it is possible that removing the variance associated with dissociative symptoms in the mediation analysis will also remove variance associated with PTSD, thus erroneously reducing the significance of PTSD symptoms as predictors of functional outcomes.

Nonetheless, enhanced knowledge of the relation between PTSD and functional impairment and the mediating role of dissociative symptoms, particularly derealisation, is critical in assisting clinicians in understanding which symptoms must be targeted in order to achieve both functional and symptomatic recovery among individuals with PTSD.

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Chapter 4: Predictors of functional impairment in civilian inpatients with post-traumatic stress disorder

Chapter Link

The work in the following chapter was submitted in June 2019 to the *European Journal of Psychotraumatology*.

The previous study found that dissociative symptoms mediated the relation between PTSD symptoms and functional impairment among military members, veterans, and first responders with PTSD. In order to further understand impairments in functioning among individuals with PTSD, we explored the contribution of emotion regulation difficulties and dissociative symptoms to functional impairment among civilians with PTSD. In addition to hypothesizing that dissociative symptoms would contribute significantly to functioning, we hypothesized that emotion regulation difficulties would play a significant role in this sample, given the association between childhood abuse exposure and emotion dysregulation and the documented impact of emotion dysregulation on functioning.

Predictors of functional impairment in civilian inpatients with post-traumatic stress disorder

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Abstract

Background: Functional impairment among individuals with posttraumatic stress disorder (PTSD) represents a significant factor in recovery. Critically, functional impairment appears to persist following remission of PTSD symptoms. Moreover, higher levels of post-treatment functional impairment have been associated with heightened post-treatment symptom severity. To date, work investigating functional impairment among individuals with PTSD has focused on DSM-IV-TR PTSD symptom clusters, excluding other relevant symptoms, including emotion regulation difficulties and dissociative symptoms. Here, emerging work suggests that these symptoms may serve as important predictors of functional impairment among individuals with PTSD.

Objective: The present study investigated the predictive contributions of emotion dysregulation, dissociative symptoms, and individual PTSD symptom clusters to functional impairment among an inpatient civilian sample with probable PTSD and high rates of exposure to childhood abuse and neglect.

Results: Emotion regulation difficulties and dissociative symptoms contributed significantly to a model predicting functional impairment among individuals with probable PTSD. PTSD symptoms clusters did not predict significantly functional impairment after accounting for other predictors in the model. Differential patterns of predictors emerged for the various domains of functional impairment measured.

Conclusions: These findings add to a growing body of literature highlighting the importance of symptoms not traditionally associated with PTSD in predicting functional impairment among individuals with PTSD. In particular, emotion regulation difficulties

and dissociative symptoms appear to play a critical role in functional impairment in this disorder. Recovery to pre-morbid functional status in PTSD may require interventions that target directly emotion regulation difficulties and dissociative symptoms

1.0 Introduction

Functional impairment in posttraumatic stress disorder (PTSD) represents a significant challenge from both a public health and treatment perspective. PTSD is associated with high rates of functional impairment, including impaired workplace performance (Kessler, 2000), high use of medical care services (Amaya-Jackson et al., 1999; Greenberg et al., 1999), impaired psychosocial functioning, and reduced physical and mental-health related quality of life (Johansen, Wahl, Eilertsen, Weisaeth, & Hanestad, 2007; Olatunji, Cisler, & Tolin, 2007; Pagotto et al., 2015). Critically, these high levels of functional impairment may persist following treatment for PTSD or remission of PTSD symptoms (Murphy et al., 2016; Westphal et al., 2011). Although some treatment studies have reported a reduction in functional impairment, including improved social adjustment, housework completion, and family relationships (Monson et al., 2012) and increased physical health indicators (Galovski, Monson, Bruce, & Resick, 2009) following cognitive behavioural treatment approaches (e.g., cognitive processing therapy or prolonged exposure) for PTSD, other studies reveal a contradictory pattern of findings. Specifically, Murphy et al. (2016) found that among a sample of veterans receiving inpatient treatment for PTSD, higher post-treatment functional impairment was predictive of higher PTSD symptoms at 6 and 12 months post-treatment, with the authors concluding that increased supports may be necessary to adequately treat functional impairment in this population. Moreover, many individuals with a past diagnosis of PTSD continue to experience deficits in mental-health related quality of life, suggesting that reduced quality of life persists following remission of PTSD (Westphal et al., 2011).

Taken together, these findings highlight the critical importance of understanding contributors to functional impairment in PTSD, work that is particularly necessary to ongoing efforts to tailor treatments that effectively ameliorate functional difficulties in this condition. Accordingly, the current study sought to further our understanding of functional impairment in PTSD by exploring the impact of DSM-5 PTSD symptoms, as well as related symptoms of dysregulated emotion and of dissociation, on functioning among an inpatient sample of civilians with probable PTSD and high rates of exposure to childhood abuse and neglect.

To date, the majority of research investigating functional impairment among individuals with PTSD has focused on symptoms of PTSD as defined in the DSM-IV-TR (APA, 2000), yielding mixed results. Although the majority of these studies suggest that DSM-IV-TR avoidance/numbing symptoms are most strongly related to functional impairment in PTSD (Breslau, Reboussin, Anthony, & Storr, 2005; Malta, Levitt, Martin, Davis, & Cloitre, 2009; North et al., 1999; Rona et al., 2009; Shea, Vujanovic, Mansfield, Sevin, & Liu, 2010), others studies point towards re-experiencing (Norman, Stein, & Davidson, 2007) or hyperarousal (Heir, Piatigorsky, & Weisæth, 2010; Maguen, Stalnaker, McCaslin, & Litz, 2009) symptoms as being most strongly related to functional impairment in this disorder. Notably, DSM-IV-TR PTSD grouped avoidance and numbing symptoms together, where avoidance refers to avoidance of internal (e.g., memories, thoughts, feelings) and external (e.g., people, places, or situations) reminders of the traumatic event and numbing refers to symptoms that can be conceptualized as related to emotion regulation difficulties, such as restricted range of affect. Here, research

has demonstrated that avoidance and emotional numbing represent distinct symptom factors (Asmundson, Stapleton, & Taylor, 2004), a finding now reflected in the DSM-5 (APA, 2013). Interestingly, when investigated separately, emotional numbing but not avoidance symptoms have been found to be most strongly related to functional impairment (Breslau et al., 2005; Malta et al., 2009). It remains unknown, however, how other key symptoms of dysregulated emotion (e.g., difficulty accessing emotion regulation strategies, reduced awareness and understanding of emotions, acting impulsively in response to strong emotions) may contribute to functional impairment in PTSD. Critically, introduction of the DSM-5 saw not only the separation of avoidance and emotional numbing symptoms but also the inclusion of new symptoms reflective of emotion regulation difficulties, including persistent experience of negative emotions and inability to experience positive emotions (APA, 2013). Here, a recent study using network analysis, and investigating the relation between functional impairment and DSM 5 PTSD symptoms found that cluster D symptoms (negative alterations in mood and cognition), which include symptoms of emotion dysregulation, were most consistently related to functional impairment in PTSD (Ross, Murphy, & Armour, 2018). Here, impairments in close relationships were associated primarily with emotional numbing, restricted affect, and negative beliefs, impairments in leisure activities were related to anhedonia, physiological reactivity, restricted affect and sleep difficulties. By contrast, impairments in home management were associated with re-experiencing, anhedonia, and exaggerated startle and impairments in social leisure were related to anhedonia, flashbacks, and avoidance (Ross et al., 2018). These findings highlight not only the

importance of emotion regulation difficulties in contributing to dysfunction in key areas of functioning, including leisure and close relationships, but also the differential effect of various PTSD symptoms on the various domains of functioning assessed.

In keeping with this suggestion, another recent study reported that individual PTSD symptoms differentially predicted various domains of functioning among a sample of US military members (Kachadourian, Harpaz-Rotem, Tsai, Southwick, & Pietrzak, 2019). Specifically, whereas symptoms of anhedonia predicted physical functioning, mental functioning, cognitive functioning and quality of life, symptoms consistent with emotion regulation difficulties (e.g., difficulties experiencing positive affect and impulsive/self-destructive behaviours) significantly predicted levels of mental functioning, cognitive functioning, and quality of life among participants. Finally, additional symptoms including psychogenic amnesia, sleep difficulties, startle response, and concentration difficulties differentially predicted the various domains of functioning assessed (Kachadourian et al., 2019).

Previous work has highlighted further the role of emotion regulation difficulties in functional impairment. For example, Cloitre et al. (2005) found that negative mood regulation and interpersonal difficulties were strongly predictive of functional impairment after accounting for PTSD symptom severity among women with a history of childhood sexual or physical abuse. Emotion regulation difficulties also mediate the relation between insecure attachment and functional impairment among victims of childhood sexual and physical abuse (Cloitre, Stovall-McClough, Zorbas, & Charuvastra, 2008). Similarly, in addition to emotional numbing, Malta et al. (2009) found that beliefs about

the ability to regulate negative moods, social discomfort, and interpersonal sensitivity were predictive of socio-occupational impairment among World Trade Center attack survivors. Notably, however, the majority of studies pointing towards an effect of emotion dysregulation on functional impairment have done so via proxy measures of emotion regulation (e.g., symptoms of PTSD reflective of emotion dysregulation). Moreover, the majority of these studies have been conducted through outpatient or community samples or among individuals exposed to single-incident trauma (e.g., natural disaster) or work-related trauma (e.g., military or combat, first responders). These studies are therefore limited in their ability to identify predictors of functional impairment in more severely ill inpatient samples and in individuals exposed to high rates of childhood abuse and neglect. These populations are the subject of investigation in the current study.

In addition to increasing recognition of emotion regulation difficulties as symptoms of PTSD, DSM-5 also codified the dissociative subtype of PTSD, affecting 15-30% of individuals with PTSD (Armour, Karstoft, & Richardson, 2014; Bennett, Modrowski, Kerig, & Chaplo, 2015; Hansen, Ross, & Armour, 2017; Lanius, Brand, Vermetten, Frewen, & Spiegel, 2012; Wolf, Lunney, et al., 2012; Wolf, Miller, et al., 2012). Dissociative symptoms appear strongly related to functional impairment in psychiatric samples, including PTSD (Boyd et al., 2018; Evren et al., 2011; Stein et al., 2013; Tanner et al., 2019). For example, in a recent longitudinal study seeking to identify predictors of functional impairment in a diverse sample of patients with affective, substance use, anxiety, somatoform, dissociative and personality disorder symptoms, symptoms of dissociation were among the strongest predictors of functional impairment

(Tanner et al., 2019). Moreover, among individuals with PTSD included in the World Mental Health survey, dissociative symptoms were associated with more severe role impairment (Stein et al., 2013). Similarly, a recent study assessing functional status in veterans, military members, and first responders reported that dissociative symptoms mediated the relation between PTSD symptoms and functional impairment, pointing towards the central role of these symptoms in determining functional outcomes (Boyd et al., 2018). Finally, among a sample of men with alcohol dependence and a lifetime diagnosis of PTSD, dissociative symptoms were a significant predictor of interference in quality of life (Evren et al., 2011). Thus, dissociative symptoms appear to play a key role in determining functioning among individuals with PTSD, a role that may relate, in part, to the documented association between elevated dissociative symptoms and reduced cognitive functioning among individuals with PTSD (McKinnon et al., 2016).

Taken together, these findings point towards the urgent need to understand better the role of symptoms associated with PTSD previously excluded from analysis (e.g., emotion regulation; dissociation) in functional impairment in this disorder. This is particularly relevant given the chronic nature of functional impairment among individuals with PTSD, where functional impairment may persist following treatment or remission of symptoms (Murphy et al., 2016; Westphal et al., 2011). Accordingly, the aim of the present study was to investigate the relative roles of PTSD symptoms, symptoms of emotion regulation difficulties and dissociative symptoms in predicting functional impairment among a previously understudied population of severely ill inpatients with probable PTSD and high rates of childhood abuse. Consistent with previous literature, we

hypothesized that specific symptoms of dissociation and of emotion dysregulation, along with PTSD symptoms reflective of emotion dysregulation (e.g., emotional restriction), would emerge as the strongest predictors of functional impairment in this sample.

2.0 Methods

2.1 Participants

One-hundred and seventeen charts were accessed via retrospective chart review of patients seen at Homewood Health Centre's inpatient Program for Traumatic Stress Recovery between 22 May 2015 and 30 June 2016. Participants were included in the current analysis if they had a score above the proposed cut-point for a probable diagnosis of PTSD on the PTSD Checklist for DSM 5 (PCL-5) (Weathers et al., 2013) (score of 33; Wortmann et al., 2016) (n = 3 excluded). Participants were excluded from the analyses based on missing or incomplete data for any of the variables in our regression analyses (n = 39) or if they had multiple admissions within the study period (n = 8), leaving a final sample of 67 patients. Demographic variables are reported in Table 1. Eighty-nine percent of the sample reported exposure to at least one adverse childhood experience (ACE), with the average number of ACEs reported in the sample being 4.7 (SD = 2.7). 67.2% of the sample reported exposure to childhood sexual abuse and 53.7% of the sample reported exposure to childhood physical abuse. This study was approved by the Homewood Health Centre Research Ethics Board.

Table 1. *Demographic and clinical characteristics of the study sample*

Characteristics	*n* = 67
Demographic Characteristics	Mean (SD)
Sex (female:male)	50:17
Age	42.0 (9.9)
Education	% of Sample
Some high school	4.5
High school	13.4
Technical or trade school	3.0
Some college or university	25.4
Diploma or bachelor's degree	41.8
Graduate degree	11.9
Income	% of Sample
Employed	44.8
Employment Insurance	11.9
Pension	10.4
Social Assistance	1.5
Continuing Disability Insurance	40.3
Other (e.g., Investment, Inheritance)	16.4
No Income	7.5
Clinical Characteristics	Mean (SD)
Functional Disability (WHODAS)	
Total	51.0 (17.2)
Cognition	2.1 (0.8)
Mobility	1.5 (1.0)
Self-Care	1.1 (0.9)
Getting Along	2.0 (0.9)
Life Activities	2.4 (1.1)
Participation	2.4 (0.6)
PTSD Symptoms (PCL-5)	
Total	57.0 (10.6)
Intrusions	14.0 (3.9)
Avoidance	6.3 (1.3)
Cognition and Mood	20.8 (3.6)
Reactivity	15.8 (4.1)
Dissociative Symptoms (MDI)	71.6 (21.6)
Emotion Regulation Difficulties (DERS)	123.9 (22.0)
Childhood Trauma (ACE-Q) Total Number of Categories Endorsed	4.7 (2.7)
ACE-Q Types of Events	% of Sample Endorsing
Emotional Abuse	62.7
Physical Abuse	53.7
Sexual Abuse	67.2
Emotional Neglect	71.6
Physical Neglect	34.3

Parental Separation/Divorce	40.3
Domestic Violence	23.9
Substance Abuse	52.2
Mental Illness	56.7
Incarceration of Household Member	11.9

WHODAS, World Health Organization Disability Assessment Schedule 2.0; PCL-5, PTSD Checklist for DSM-5; MDI, Multiscale Dissociation Inventory; DERS, Difficulties in Emotion Regulation Scale; ACE-Q, Adverse Childhood Experiences Questionnaire

2.2 Materials

The World Health Organization Disability Assessment Schedule 2.0 (WHODAS; Üstün, 2010)

The WHODAS assesses six domains of functional disability using 36 self-report items. It yields a total impairment score as well as subscale scores, with higher scores representing greater levels of disability. The WHODAS subscales assess cognition (chronbach's alpha (α) = 0.94; understanding and communicating), mobility (α = 0.94), self-care (α = 0.95; e.g., personal hygiene), getting along (α = 0.94; interacting with others), life activities (α = 0.94; e.g., work or home responsibilities), and participation in society (α = 0.95; community, civil, and recreational engagement). The WHODAS also demonstrates good convergent validity with comparable instruments that measure disability (Üstün, 2010).

The PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013)

The PCL-5 assesses the severity of PTSD symptoms across 20 items representing the DSM-5 criteria for PTSD. The PCL-5 has demonstrated good to high internal consistency across subscales assessing intrusive symptoms, avoidance, negative alterations in mood and cognition, and alterations in arousal and reactivity (α = 0.75-0.95) (Bovin et al., 2016), as well as good test-retest reliability, convergent validity, and

sensitivity to detect clinical levels of PTSD symptomatology (Blevins, Weathers, Davis, Witte, Domino, 2015; Bovin et al., 2016; Wortmann et al., 2016).

The Multiscale Dissociation Inventory (MDI; Briere, Weathers, & Runtz, 2005)

The MDI assesses 6 domains of dissociative symptoms using 30 self-report items. It has demonstrated adequate to high internal consistency across the subscales assessing disengagement, depersonalization, derealization, emotional constriction, memory disturbance, and identity dissociation (α = 0.75-0.94), with the total score demonstrating an internal consistency of α = 0.96 (Briere, 2002).

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004)

The DERS is a 36-item self-report measure assessing six dimensions of emotion regulation difficulties, including lack of awareness of emotional responses, lack of clarity of emotional responses, nonacceptance of emotional responses, limited emotion regulation strategies, difficulties controlling impulses when experiencing negative emotions, and difficulty completing goal-directed activities when experiencing negative emotions. The DERS demonstrates good internal consistency (α = 0.80-0.89), convergent validity, and predictive validity for behaviours reflective of emotion regulation difficulties (e.g., self-harm) (Gratz & Roemer, 2004).

The Adverse Childhood Experiences Questionnaire (ACE-Q; Felitti et al., 1998; Merrick et al., 2017)

The ACE-Q assesses the presence or absence of 10 commonly experienced adverse childhood experiences (ACEs) using dichotomous variables (0 = No, 1 = Yes). Participants indicate the presence or absence of exposure to emotional, physical, or sexual

abuse, emotional or physical neglect, domestic violence (physical abuse of mother), parental divorce or separation, substance abuse in the household, a mentally ill family member, or incarceration of a family member. The ACE-Q yields a total exposure score ranging from 0-10. Higher ACE-Q total scores have been associated with drug and alcohol use, depressed affect, attempted suicide, and increased odds of experiencing adverse outcomes (Merrick et al., 2017).

2.3 Procedures and Statistical Analyses

All analyses were completed using SPSS version 25.0. Analysis of the distribution of variables assessed in the current study revealed non-normality of several variables (Shapiro-Wilk >.05). Parametric analyses were reported for ease of interpretation and clarity. However, non-parametric analyses (not reported) revealed consistent results.

Correlational analyses were conducted to examine the relation between PTSD symptomatology as measured by the PCL-5, dissociative symptoms as measured by the MDI, and emotion regulation difficulties as measured by the DERS with domains of functional impairment as measured by the WHODAS 2.0 (Pearson's r; two-tailed, alpha = 0.05).

Multiple regression analysis using the Enter method was used to determine whether PTSD symptom clusters, dissociative symptoms, and emotion regulation difficulties uniquely predicted functional impairment as measured by the WHODAS total score.

Given findings of the differential impact of symptoms depending on the functional domain assessed (Tanner et al., 2019), supplemental analyses were used to explore the

differential prediction of domains of functional impairment as per the WHODAS subscales by PTSD symptoms, dissociative symptoms, and emotion regulation difficulties.

3.0 Results

3.1 Main Analyses

Correlational analyses are reported as statistically significant after controlling for multiple comparisons ($p < .001$). WHODAS Total and WHODAS Cognitions were significantly correlated with the PCL Intrusions, PCL Mood and Cognition, PCL Arousal and Reactivity, MDI Total, and DERS Total scores. WHODAS self-care was significantly correlated with PCL Intrusions, PCL Mood and Cognition, MDI Total, and DERS Total. WHODAS Getting Along and WHODAS Life Activities were significant correlated with PCL Mood and Cognition, MDI Total, and DERS Total. WHODAS Participation was significantly correlated with PCL Intrusions, PCL Mood and Cognition, PCL Arousal and Reactivity, and MDI Total. The Mobility subscale was not significantly correlated with any of the PCL subscales, MDI Total, and DERS Total scores. The avoidance subscale of the PCL was not significantly correlated with any of the WHODAS total or subscale scores in this inpatient sample. Given the lack of significant correlations between these variables, these subscales were excluded from the regression analysis.

Routine inspection of the data revealed no violations of the assumptions of linear or multiple regression. Of note, the assumption of no multicollinearity was met as correlations among the predictor variables did not exceed 0.80 and the variance inflation factors were within an acceptable range (<10).

The multiple regression model for the WHODAS Total with PCL Cognition and Mood, PCL Arousal and Reactivity, PCL Intrusions, MDI Total, and DERS Total as predictors was significant, $F(5, 61) = 13.03$, $p = .000$, $R^2 = 0.52$, indicating that the model predicted 52% of the variance in WHODAS Total score. Only DERS Total ($p = .005$) and MDI Total ($p = .048$) added statistically significantly to the model when other variables in the model were controlled for.

Table 2. *Correlations (Pearson's r) between functional impairment and PTSD and associated symptom dimensions*

	WHODAS Total	WHODAS Cognition	WHODAS Mobility	WHODAS Self-Care	WHODAS Getting Along	WHODAS Life Activities	WHODAS Participation
PCL Intrusions	.43*	.44*	.14	.43*	.31	.26	.51*
PCL Avoidance	.14	.22	-.03	.15	.10	.08	.18
PCL Mood and Cognition	.59*	.59*	.27	.47*	.50*	.46*	.46*
PCL Arousal and Reactivity	.46*	.53*	.15	.34	.34	.36	.40*
MDI Total	.56*	.56*	.26	.50*	.40*	.45*	.45*
DERS Total	.63*	.60*	.35	.47*	.51*	.56*	.38

*Significant after controlling for multiple comparisons, $p<.001$;
WHODAS, World Health Organization Disability Assessment Scale 2.0; PCL, PTSD Checklist For DSM-5; MDI, Multiscale Dissociation Inventory; DERS, Difficulties In Emotion Regulation Scale

Table 3. *Multiple regression analysis predicting WHODAS total score (functional impairment)*

Predictor	*B*	*SE B*	β	*t*	R^2
Model (WHODAS Total)					.51***
PCL Intrusions	-.03	.55	-.01	-.05	
PCL Mood and Cognition	1.05	.65	.22	1.62	
PCL Arousal and Reactivity	.44	.49	.10	.88	
MDI Total	.18	.09	.23	2.02*	
DERS Total	.26	.09	.34	2.90**	

*$p < .05$; **$p < .01$; ***$p < .001$
B = unstandardized coefficient; *SE B* = standard error of the unstandardized coefficient; β = standardized coefficient
WHODAS, World Health Organization Disability Assessment Scale 2.0; PCL, PTSD Checklist For DSM-5; MDI, Multiscale Dissociation Inventory; DERS, Difficulties in Emotion Regulation Scale

Supplemental Analyses

All regression models for the WHODAS subscales were significant (see table 4). However, the extent to which each of the predictor variables contributed to the models differed by subscale. In particular, for the Cognition subscale, PCL Arousal and Reactivity (p = .047), MDI Total (p = .034) and DERS Total (p = .028) contributed statistically significantly to the model. For the Getting Along and Life Activities subscales only, DERS Total contributed statistically significantly to the model (p = .036; p = .008, respectively). For the Participation and Self-Care subscales, although the overall model was statistically significant, no individual predictors emerged as statistically significant predictors after controlling for the effects of the other predictors.

Table 4. *Supplemental multiple regression analysis predicting WHODAS subscales (functional impairment) that were significantly correlated with predictor variables*

Predictor	*B*	*SE B*	*β*	*t*	R^2
Model (Cognition)					.52***
PCL Intrusions	-.01	.03	-.04	-.33	
PCL Mood and Cognition	.05	.03	.20	1.51	
PCL Arousal and Reactivity	.05	.02	.24	2.02*	
MDI Total	.009	.004	.25	2.16*	
DERS Total	.01	.004	.26	2.25*	
Model (Getting Along)					.33***
PCL Intrusions	-.02	.03	-.07	-.48	
PCL Mood and Cognition	.08	.04	.30	1.91	
PCL Arousal and Reactivity	.01	.03	.05	.33	
MDI Total	.00	.01	.09	.69	
DERS Total	.01	.01	.29	2.15*	
Model (Life Activities)					.38***
PCL Intrusions	-.04	.04	-.15	-1.01	
PCL Mood and Cognition	.06	.05	.19	1.21	
PCL Arousal and Reactivity	.03	.04	.11	.86	
MDI Total	.01	.01	.19	1.44	
DERS Total	.02	.01	.36	2.74**	
Model (Participation)					.34***
PCL Intrusions	.05	.02	.29	1.96	
PCL Mood and Cognition	.01	.03	.07	.42	

PCL Arousal and Reactivity	.01	.02	.08	.58	
MDI Total	.01	.00	.21	1.55	
DERS Total	.00	.00	.08	.61	
Model (Self-Care)					.34***
PCL Total	.04	.03	.16	1.09	
PCL Mood and Cognition	.03	.04	.10	.62	
PCL Arousal and Reactivity	.00	.03	.01	.04	
MDI Total	.01	.01	.26	1.94	
DERS Total	.01	.01	.21	1.55	

*$p < .05$; **$p < .01$; ***$p < .001$
B = undstandardized coefficient; *SE B* = standard error of the unstandardized coefficient; β = standardized coefficient
WHODAS, World Health Organization Disability Assessment Scale 2.0; PCL, PTSD Checklist For DSM-5; MDI, Multiscale Dissociation Inventory; DERS, Difficulties in Emotion Regulation Scale

4.0 Discussion

This study adds to the growing literature exploring the impact of symptoms that extend beyond the traditional conceptualization of PTSD on functional impairment, including emotion regulation difficulties and dissociative symptoms (Boyd et al., 2018; Cloitre et al., 2008; Clotire, Miranda, Stovall-McClough, & Han, 2005; Evren et al., 2011; Malta et al., 2009). It also provides a critical examination of the contribution of these symptoms to key areas of functioning in a civilian sample of severely ill inpatients with high rates of exposure to childhood abuse and neglect, a previously understudied population. In the current study, we found that whereas emotion regulation difficulties and dissociative symptoms contributed statistically significantly to a model predicting overall functional impairment, PTSD symptom clusters did not, after accounting for the effects of other predictor variables (PTSD avoidance symptoms were excluded from the model due to a lack of significant correlations with functional impairment).

Consistent with previous findings of differential prediction of impairment depending on the domain of PTSD assessed (Ross et al., 2018), we found that the extent to which PTSD symptom clusters, emotion regulation difficulties, and dissociative symptoms predicted impairment differed by WHODAS subscale. In particular, whereas emotion regulation difficulties, dissociative symptoms, and PTSD arousal and reactivity symptoms significantly predicted impairment in the cognition domain (including items assessing concentration, remembering, understanding and communicating with others), only emotion regulation difficulties contributed significantly to the getting along (including items such as maintaining friendships, relative with strangers, and sexual relationships) and life activities (including items including household work, work or school functioning) domains, after controlling for the effects of the other predictors. By contrast, for the self-care and participation in society subscales of the WHODAS, although the overall model was significant, no single predictors emerged after accounting for the effects of other predictors.

Our finding that dissociative symptoms are particularly relevant to cognitive functioning is in keeping with previous findings of a strong relation between dissociative symptoms and cognitive impairment among individuals with PTSD and other psychiatric disorders (McKinnon et al., 2016). In particular, it is hypothesized that dissociative symptoms may reduce the ability to attend to information in the environment, resulting in downstream difficulties in cognitive domains such as attention, memory, and executive functioning. Moreover, our finding that emotion regulation difficulties serve as a key predictor of functional impairment across multiple domains, including getting along and

life activities, is in keeping with emerging work highlighting the importance of emotion regulation in adaptive functioning among individuals with PTSD (Cloitre et al., 2005; 2008; Kachadourian et al., 2019; Malta et al., 2009; Ross et al., 2018), particularly for domains associated with interpersonal functioning. These findings are also consistent with the established relation between emotion regulation and interpersonal functioning (Wei, Vogel, Ku, & Zakalik, 2005).

The finding that avoidance symptoms were not significantly correlated with the domains of functional impairment assessed is consistent with earlier findings that when avoidance and emotional numbing (or symptoms consistent with emotion regulation difficulties) are investigated separately, emotional numbing symptoms emerge as more consistently associated with functional impairment (Ross et al., 2018). Importantly, although avoidance may lead to significant impairment in overall functioning (e.g., by limiting the ability to engage with life activities), it may also temporarily decrease other, more impairing symptoms of PTSD, such as intrusive memories or emotion regulation difficulties that may be prompted by exposure to life stressors, possibly accounting for the lack of association between avoidance and functional impairment in the current study

Taken together, these findings point to the importance of assessing emotion regulation difficulties and dissociative symptoms among individuals with PTSD, particularly when considering functional recovery. Along with previous findings that functional impairment persists even among individuals with a past (but not current) diagnosis of PTSD (Westphal et al., 2011) and lower levels of psychosocial functioning are associated with the maintenance of chronic PTSD (Zlotnick et al., 2004), the current

results point strongly to the need to target emotion regulation difficulties and dissociative symptoms in order to achieve functional recovery. Although some existing work suggests that emotion regulation difficulties can improve with CBT-based treatments for PTSD (Hinton, Hofmann, Pollack, & Otto, 2009; Jerud, Zoellner, Pruitt, & Feeny, 2014), further work is needed to determine whether this finding is consistent across treatment modalities and whether these improvements translate to improvements in overall functioning. Moreover, previous work suggests dissociative symptoms are associated with reduced treatment effectiveness of evidence-based treatments for PTSD, including eye-movement desensitization and reprocessing (EMDR) (Bae, Kim, & Park, 2016) and prolonged exposure (Wolf, Lunney, & Schnurr, 2015); other studies, however, have failed to replicate these effects or have questioned whether these findings are clinically meaningful (Haagen, van Rijn, Knipscheer, van der Aa, & Kleber, 2018; Resick et al., 2012; Wolf, Lunney, & Schnurr, 2016), two studies suggesting that dissociative symptoms improve with CBT-based treatments for PTSD (Chard, 2005; Resick et al., 2012). Nonetheless, there is a need to determine whether dissociative symptoms can improve with current evidence-based treatments, and whether such improvements are associated with functional recovery. Alternatively, adjunctive treatment strategies may be necessary to target directly symptoms of dissociation and emotion regulation difficulties (e.g., dialectical behavioural therapy skills) in order to achieve full symptomatic and functional recovery in survivors of childhood abuse and neglect, as studied here.

The results of the present study should be interpreted in light of several limitations. Specifically, this study involved retrospective, self-report questionnaires and

did not include a clinician-administered assessment to confirm a probable diagnosis of PTSD. Rather, best estimates of PTSD diagnosis were based on self-report. In addition, we were unable to determine the index trauma associated with the symptoms reported by the current sample. Although the sample reported high rates of exposure to childhood abuse and neglect, not everyone in the sample endorsed this and thus the sample was likely composed of individuals with differing trauma etiology (e.g., childhood abuse, interpersonal violence in adulthood, single incident traumas). Finally, the current study utilized a cross-sectional design, limiting the conclusions that can be drawn. In particular, given that all measures were collected simultaneously, we cannot assume that emotion regulation difficulties, dissociative symptoms, or PTSD symptoms predict functional impairment over time, although such longitudinal associations have been previously documented (Johansen et al., 2007).

Despite these limitations, this study provides further support for the need to assess and treat symptoms associated with PTSD that may be overlooked in current first-line psychotherapies for PTSD. In particular, emotion regulation difficulties and dissociative symptoms may be necessary treatment targets in order to allow individuals with PTSD to achieve a full recovery, including amelioration of functional limitations.

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Chapter 5: An open-label feasibility trial examining the effectiveness of a cognitive training program, Goal Management Training, in individuals with posttraumatic stress disorder

Chapter Link

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Studies one to three identified the contributions of dissociative symptoms and emotion regulation difficulties to cognitive dysfunction and functional impairment in PTSD. In study four we explore an approach to cognitive remediation that may have impacts on symptoms associated with functional impairment, including emotion regulation difficulties, in a sample of inpatients with PTSD. This study is the first to explore the use of Goal Management Training, a well-established cognitive remediation program, for individuals with PTSD.

An open-label feasibility trial examining the effectiveness of a cognitive training program, Goal Management Training, in individuals with posttraumatic stress disorder

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ABSTRACT:

Background: Posttraumatic stress disorder (PTSD) is associated with dysfunction across multiple cognitive domains, including executive functioning, attention, and verbal memory. This dysfunction is associated with negative impacts on functional outcomes (e.g., work or social functioning) and reduced response to psychotherapy for PTSD. Despite this knowledge, little work has investigated the efficacy of cognitive remediation strategies (CRTs) in improving cognition and functional outcomes among individuals with PTSD. *Objective:* The current study investigated the efficacy of an established cognitive remediation program, Goal Management Training (GMT), in improving cognitive functioning in a pilot sample of individuals with PTSD in an inpatient treatment setting. *Method:* Thirty-four inpatients with PTSD symptoms participated in either GMT in addition to treatment as usual (consisting of psychiatric management, group and individual psychotherapy) (TAU+GMT; $n = 18$) or treatment as usual alone (TAU; $n = 16$). The TAU+GMT group received neuropsychological assessment at baseline and post-treatment, while both the TAU+GMT and TAU group received assessment with clinical self-report measures at baseline and post-treatment. *Results*: Paired-sample t-tests revealed significant improvements on measures of executive functioning (e.g., response inhibition, cognitive flexibility), processing speed, sustained attention, and verbal memory in the TAU+GMT group. Mixed-design ANOVAs revealed a trend toward an interaction effect indicating potentially greater improvements on a measure of the ability to engage in goal-directed behaviours while highly emotional in the TAU+GMT group as

compared to the TAU group. *Discussion:* The results of this small feasibility investigation of GMT in PTSD point towards the potential efficacy of GMT in ameliorating cognitive difficulties in individuals with PTSD.

Keywords: Cognitive dysfunction, cognitive remediation, emotion regulation, Goal Management Training, posttraumatic stress disorder

Introduction

Posttraumatic Stress Disorder (PTSD) is a debilitating mental health condition that affects a significant proportion of the population, with 8 to 9 percent of North Americans meeting criteria for this disorder in their lifetime.[1,2] PTSD is associated with significant functional impairment, including reductions in work and mental health related quality of life,[3] impaired workplace performance,[4] and high use of medical care services.[5] Importantly, impairments in quality of life may persist following remission of PTSD symptoms.[6] PTSD is also associated with cognitive impairments across a range of domains, with a meta-analytic study indicating that PTSD is associated with medium to large effect size impairments across measures of verbal learning (d = -.62), processing speed (d = -.59), attention and working memory (d = -.50), verbal memory (d = -.46), executive function (d = -.45), and language (d = -.43), and with small effect size impairments across visuospatial functioning (d = -.38), visual learning (d = -.32), and visual memory (d = -.29).[7] Similarly, a more recent meta-analysis identified mild to moderate executive functioning impairment among trauma-exposed individuals with PTSD as compared to trauma-exposed and healthy controls, regardless of the level of PTSD symptom severity, suggesting that cognitive dysfunction may be present even among individuals with milder levels of PTSD symptomatology.[8]

Cognitive dysfunction has been associated with poor functional outcomes among individuals with PTSD.[9,10] For example, among a sample of veterans with PTSD, impairments in verbal memory were associated with worse social and occupational outcomes.[9] Furthermore, the results of another study of veterans with PTSD indicated that

heightened executive dysfunction was associated with higher self-reported impairments in occupational functioning (e.g., absenteeism) and a poorer physical health-related quality of life.[10] Similarly, perceived cognitive impairment is a predictor of poor quality of life among military members and veterans with PTSD, after accounting for history of traumatic brain injury (TBI), PTSD symptoms, and depressive symptoms.[11]

Cognitive dysfunction has also been related to symptom severity. For example, inhibitory dysfunction (e.g., the ability to inhibit automatic responses, a component of executive function) has been related to re-experiencing and hyperarousal symptoms among individuals with PTSD, which has been thought of as impaired ability to regulate emotion responding.[12] Further, impaired cognitive functioning has been associated with reduced treatment response among individuals with PTSD.[13,14] Specifically, poor verbal memory performance predicted decreased response to cognitive behavioural therapy (CBT) for PTSD.[13] Moreover, among veterans with PTSD and co-morbid mild to moderate TBI, worse pre-treatment executive functioning was associated with increased drop-out and poorer response to treatment with cognitive processing therapy.[14] Cognitive dysfunction appears to be stable over time among individuals with PTSD, such that although clinical symptoms fluctuate over time, cognitive and functional impairments demonstrate relative stability.[15] However, one study reported improvements in executive functions following psychotherapy for PTSD in a small sample of 15 individuals.[16]

Taken together, these findings indicate that cognitive dysfunction in PTSD may interfere with functional recovery and poor treatment response, even after controlling for TBI. The mechanisms for this are not yet fully understood, however, it has been

hypothesized that executive dysfunction may be related to increased difficulty in coping with PTSD symptoms and thus increased emotional distress leading to reduced functioning in social and occupational roles.[10,14] Furthermore, difficulty encoding and recalling meaningful information (e.g., verbal memory deficits) may impact directly, response to psychotherapies such as CBT, where there is a significant component of encoding, recalling, and applying verbal information.[13] These findings indicate that treatment of cognitive dysfunction among individuals with PTSD who are experiencing cognitive difficulties is essential in achieving functional recovery from PTSD and in promoting symptomatic recovery by allowing these individuals to better respond to psychological interventions.

Despite findings of impaired cognitive functioning and associated functional impairment and reduced treatment response among individuals with PTSD, only a handful of studies to date have examined the impact of structured cognitive remediation interventions, aimed at improving cognitive functioning, among individuals with PTSD.[17-19] These studies suggest that cognitive dysfunction in PTSD may respond to treatment intervention. For example, a non-standardized intervention protocol aimed at improving cognitive functioning in PTSD found clinically effective (but not statistically significant) improvements on measures of cognitive functioning following implementation of a bottom-up executive training approach used in conjunction with transcranial direct current stimulation in a pilot sample of four patients.[17] Another recent study of individuals with PTSD examined the effectiveness of an 8-session computerized cognitive training program in reducing proactive interference, or the inability to inhibit

irrelevant or unwanted information from intruding into working memory.[18] Compared to patients enrolled in a control condition (involving training using low levels of proactive interference), participants who received the active treatment reported lower re-experiencing symptoms and performed better on a working memory task at post-treatment.[18] Finally, Fine et al.[19] plan to investigate a web-based program that will provide computerized cognitive training to recent trauma survivors with the aim of preventing the onset of PTSD symptoms by targeting executive functioning, emotion regulation and emotional reactivity.

Notably, these studies have employed "bottom-up", restitution- based approaches that begin with remediation of basic skills, such as attention (e.g., skill-drill exercises), advancing to more complex skills.[20] These approaches contrast with top-down approaches that begin with remediation of complex skills (e.g., executive functioning, problem solving) and have the overall aim of improving basic skills via downstream effects and generalization to real-world functioning.[20] Notably, a recent meta-analysis of computerized cognitive training (bottom-up approach) in the treatment of cognitive dysfunction in major depressive disorder (MDD) found no significant effects on executive functioning,[21] a key component of cognitive dysfunction among individuals with PTSD.[12]

Goal Management Training (GMT) is a cognitive remediation approach that employs "top-down" strategies taught in a staged manor, with the aim of reducing executive dysfunction and improving the ability to carry out goal-directed behaviours.[22] GMT provides patients with strategies that facilitate the resumption of supervisory

control of cognitive processes and allow individuals to improve monitoring and execution of daily functions. GMT has demonstrated efficacy as a stand-alone approach and when used in conjunction with psychotherapy among populations characterized by cognitive difficulties, including older adults,[23,24] traumatic brain injury,[22,25,26] attention deficit hyperactivity disorder (ADHD),[27] polysubstance abuse,[28] and spina bifida,[29] and was recently identified as an evidence-based strategy for the remediation of executive functioning difficulties for military members and veterans with TBI.[30] A recent meta-analysis of 21 treatment studies investigating GMT reported small-medium effect size improvements on measures of executive functioning, working memory, and long-term memory, as well as self- and other- (e.g., caregiver or therapist) reported executive difficulties, mental health status, and functional outcomes (e.g., instrumental activities of daily living).[31] The standard GMT protocol includes 9 sessions, GMT has been found to be effective at varying lengths (6-24 sessions), however, greater number of treatment hours is associated with greater reduction in executive dysfunction.[31] Critically, with the exception of improvements in self- and other-rated executive functioning, these results were maintained at follow-up.[31]

Given the previous success of this intervention in remediating cognitive dysfunction across a host of clinical populations, we hypothesize that GMT has the potential to remediate a similar pattern of cognitive dysfunction observed among individuals suffering from PTSD. Accordingly, the aim of the current open-label feasibility study was to evaluate the effectiveness of GMT in reducing cognitive dysfunction in PTSD. Specifically, our primary aim was to determine whether a 6-session

program of GMT would result in improvements in cognitive domains impaired in PTSD and previously shown to be targeted by GMT. In particular, as noted in a recent meta-analysis of GMT across various populations (e.g., traumatic brain injury, aging, polysubstance abuse), small-to-moderate effects across a wide range of executive function, working memory and long-term memory tasks have been found. Hence, it was these domains we expected to see the most improvement in. A secondary aim was to explore whether, relative to treatment as usual (TAU), augmentative participation in GMT, along with treatment as usual (TAU+GMT), would be associated with heightened functional improvement and greater reductions in clinical symptoms associated with executive dysfunction (e.g., emotion regulation).

Method

This study was approved by the Homewood Health Centre Research Ethics Board.

Participants

Sixty-five (n = 65) participants who met criteria for a probable diagnosis DSM-5 PTSD (e.g., assessed via structured interview of self-report assessment) were invited to participate in this study. Participants were included in the study if they: 1) were between the ages of 18 and 65 years; 2) had a diagnosis of PTSD based on clinical interview with the Clinician Administered PTSD Scale for DSM 5 (CAPS-5)[32] or scored above the proposed cut-point for a diagnosis of PTSD based on the PTSD Checklist for DSM 5 (PCL-5) (score of 33);[33] 3) were able to provide written, informed consent; 4) were able to read and write in English. Exclusion criteria were evaluated for participants in the TAU+GMT group and included: 1) treatment with anti-psychotic medications known to

adversely affect cognition; 2) electroconvulsive therapy within the past year; 3) history of a medical disorder known to adversely affect cognition in the past year (e.g., heart disease); 4) history of traumatic brain injury. Thirty-seven (n = 37) individuals elected to participate in TAU+GMT and n = 28 individuals elected to participate in TAU. Within the TAU+GMT group, n = 6 individuals dropped out from the GMT group but not from TAU and n = 3 individuals were discharged early our dropped out of the full treatment program. n = 2 individuals were discharged early or dropped out of the treatment program in the TAU condition. n = 5 individuals in the TAU+GMT group and n = 2 individuals in the TAU group did not complete follow-up assessment. n = 5 individuals in the TAU+GMT group and n = 8 individuals in the TAU group were excluded from the final analysis due to missing or incomplete neuropsychological, clinical, or demographic data, leaving a final sample of n = 18 TAU+GMT and n = 16 TAU participants. See figure one for a CONSORT diagram of dropout or loss to follow-up. Clinical and demographic characteristics of the study sample are provided in Table 1.

Experimental Design and Procedure

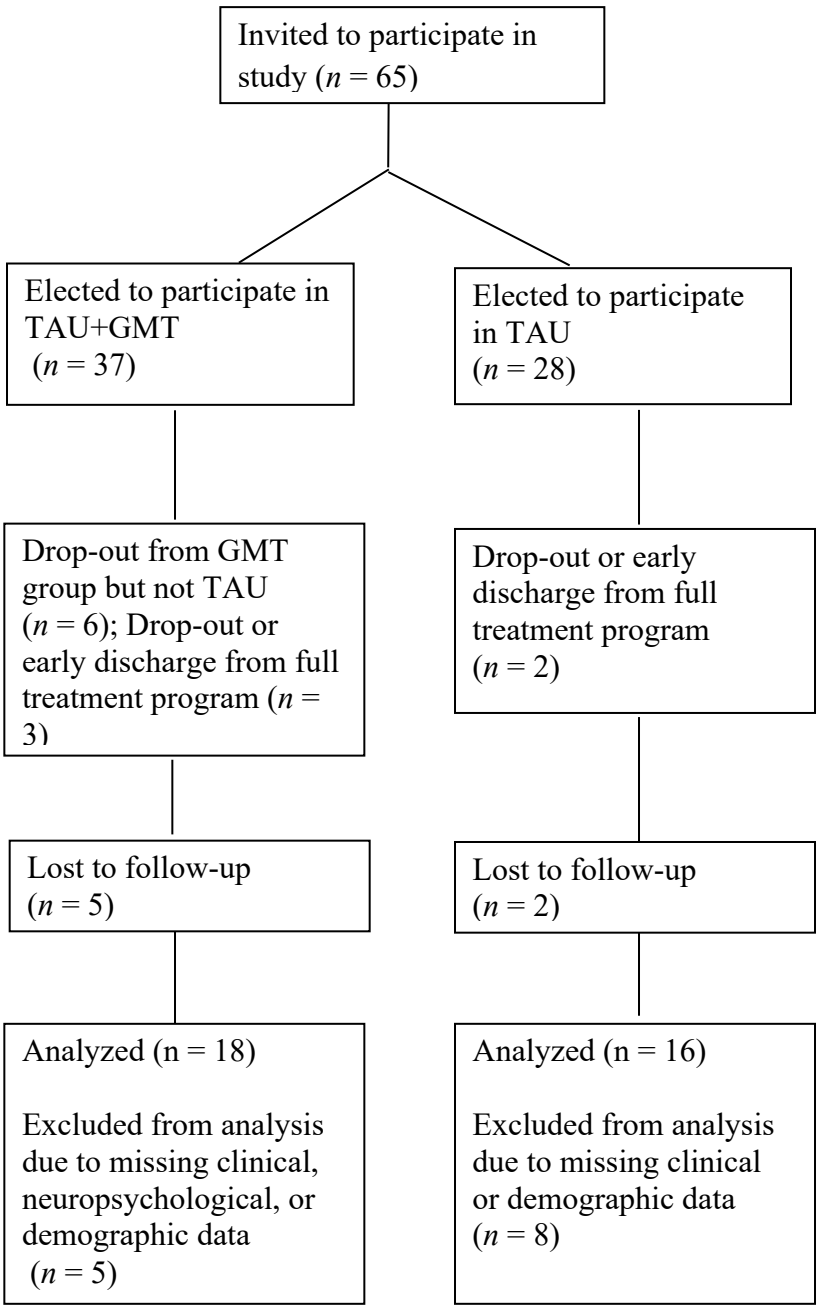
This study used an open-label feasibility trial design with the aims of: i) examining the feasibility of utilizing GMT among individuals with PTSD; and ii) determining whether a subsequent randomized controlled trial should be conducted (e.g., does GMT lead to significant improvements on measures of neuropsychological and psychological functioning and functional outcomes, thereby warranting further investigation of this approach?). Participants were not randomly assigned to treatment

groups but had the option to participate in TAU+GMT or TAU. Clinical assessors were aware of the treatment conditions in which participants were enrolled.

Participants were those receiving treatment on an inpatient psychological trauma treatment unit in Guelph, Ontario, Canada. All new patients admitted in the three weeks prior to the group commencing were invited to participate in the GMT program and research study. Patients who did not wish to participate in the GMT program, but who wanted to contribute to research, were asked to have their de-identified clinical data included in the study for comparison purposes. Participants elected to participate in either (a) a 6-session structured cognitive remediation program TAU+GMT group (n=18) or (b) TAU group (n=16). All participants were abstinent from alcohol or illicit drug use for the study period as per the policy of the inpatient treatment unit.

As part of routine clinical care, all participants (TAU+GMT and TAU) completed a self-report assessment battery on admission and discharge from the treatment unit. De-identified assessments from this battery (section 2.4) were included in this study. At baseline (within the three weeks prior to the GMT group commencing) participants in the TAU+GMT group underwent assessment with the Mini International Neuropsychiatric Interview for DSM 5 (M.I.N.I. 7.0) to determine additional DSM-5 diagnoses, and the CAPS-5 to confirm a diagnosis of PTSD.[32] They also received a battery of clinician-administered and self-report clinical, neuropsychological, and functional outcome measures at baseline and post-treatment (within two weeks after completion of GMT). Trained clinical researchers at the graduate level or higher administered all assessments.

Figure 1. Consort diagram depicting recruitment, drop-out, and follow-up of study participants



TAU = Treatment as usual; GMT = Goal Management Training

Table 1. Demographic and Clinical Characteristics of Study Sample

	GMT (*n* = 18)	TAU (*n* = 16)
Demographic Characteristics	**Mean (SD)**	
Sex (female:male)	5:13	9:7
Age	45.1 (8.0)	45.2(9.4)
Education	% of Sample	
Some high school	0	5.5
High school	31	11
Technical or trade school	0	5.5
Some college or university	12.5	27.8
Diploma or bachelor's degree	56.2	27.8
Graduate degree	0	22
Military or First Responder Status	% of Sample	
Military or Veteran	33.3	50
First Responder	18.9	25
Both	0	6.3
Clinical Characteristics	**Mean (SD)**	
PCL-5 Total Score (Baseline)	54.8(11.7)	62.9(10.1)
CAPS-5 Total Score (Baseline)	40.7(9.2)	n/a
Additional M.I.N.I. 7.0 Diagnoses	% of Sample	
Major Depressive Disorder	77.8	n/a
Panic Disorder	22.2	n/a
Agoraphobia	16.7	n/a
Social Anxiety Disorder	22.2	n/a
Generalized Anxiety Disorder	22.2	n/a
Obsessive Compulsive Disorder	0	n/a
Alcohol Use Disorder	5.6	n/a
Substance Used Disorder	5.6	n/a

Study Conditions

Goal Management Training (GMT)

GMT is a structured, short-term cognitive remediation program with an emphasis on practicing skills to regain executive and self-regulatory control.[22] A shortened version of GMT was administered over a three-week period with six 2-hour sessions. A six session version of GMT has been demonstrated to be effective[31] and was utilized due to logistical

reasons (e.g,. length of time on the inpatient unit, accommodation within other program elements). Over the course of the six sessions, participants were introduced to concepts including absentmindedness and automatic pilot errors and the usefulness of monitoring these errors in order to gain awareness of individual factors associated with executive functioning difficulties, including PTSD related symptoms (e.g., flashbacks, hypervigilance). See table 2 for details of information covered in each treatment session. GMT was administered by a registered occupational therapist highly experienced in the provision of GMT. Participants were provided with encouragement and support during and between sessions to encourage engagement with GMT.

Table 2. Description of GMT sessions

GMT Session	*Description*
Session 1: Absentminded slips	Introduce the concept of absentmindedness and absentminded slips, and discuss emotional and practical consequences.
Session 2: The Automatic Pilot	Describe "automatic pilot" as being a habitual mechanism which can lead to inappropriate responses or actions if not monitored.
Session 3: STOP the Automatic Pilot	Participants are introduced to the "STOP!" technique as a method of bringing one's attention to the present to monitor current behaviour.
Session 4: The Mental Blackboard	The construct of working memory as a "mental blackboard," which can be erased or over saturated with information, is explained. Participants are taught to check "the mental blackboard" to keep current goals at the in mind.
Session 5: State your Goal and Making Decisions	Describe how goals can become entangled when attempting to multi-task. Introduce the concept of stating one's goal as a way to aid encoding and recall of that goal.

	Introduce the concept of conflicting goals and detail strategies for how to make decisions.
Session 6: Check!	Review the material covered across previous sessions and underscore the importance of goal monitoring (the "STOP!" technique).

Treatment as usual (TAU)

TAU consisted of an 8-week inpatient treatment program for trauma-related psychological difficulties consisting of various components, including group treatment (e.g., emotion regulation skills training, mindfulness), individual treatment with a primary therapist using various approaches such as cognitive behavioural therapy, and medication management and consultation with an attending psychiatrist. No components of TAU focus specifically on cognitive functioning or remediation.

Measures and Materials

Symptom Measures

The PTSD Checklist for DSM-5 (PCL-5)[34] is a 20-item self-report questionnaire that assesses symptoms of PTSD as per DSM-5 criteria with good test-retest reliability, convergent validity, and sensitivity (e.g., ability to detect clinical levels of PTSD symptomatology).[33,35,36] The PCL-5 assesses intrusive symptoms (PCL Intrusions), avoidance (PCL avoidance), negative alterations in mood and cognition (PCL mood and cognition), and alterations in arousal and reactivity (PCL arousal and reactivity), with the total PCL-5 score demonstrating good-high internal consistency (Chronbach's alph (α) = 0.91-0.95).[36] A cut-off score of 33 has been found to be optimally efficient to detect PTSD cases according to DSM-5 criteria.[33]

The Difficulties in Emotion Regulation Scale (DERS)[37] assesses emotion regulation difficulties across six dimensions, including lack of awareness of emotional responses (awareness), lack of clarity of emotional responses (clarity), nonacceptance of emotional responses (nonacceptance), limited access to emotion regulation strategies (strategies), difficulties controlling impulsive behavior when experiencing negative emotions (impulsivity), and difficulty engaging in goal- directed behavior when experiencing negative emotions (goals).[37]

The Depression Anxiety and Stress Scale – 21-item version (DASS-21)[38] measures symptoms of depression (DASS depression) (low mood, motivation and self-esteem), anxiety (DASS anxiety) (physiological arousal, panic, and fear), and stress (DASS stress) (tension and irritability).[38]

Patient Health Questionnaire-9 (PHQ-9).[39] The TAU+GMT group only completed the PHQ-9, a self-report questionnaire measuring symptoms of depression over the past week, and the degree to which participant's symptoms of depression have impacted their day-to-day activities over the past two weeks.[39]

Subjective Cognition

The TAU+GMT and TAU group completed a brief self-report measure assessing subjective cognitive functioning, the Cognitive Failure Questionnaire (CFQ).[40] The CFQ assesses daily errors in distractibility, blunders, names, and memory with good internal consistency ($\alpha = 0.76\text{-}0.86$).[41]

The TAU+GMT group only completed the Dysexecutive Questionnaire-Self (DEX),[42] a self-report questionnaire found to assess four factors of executive functioning

difficulties in non-neurological populations: inhibition, intention, social regulation, and problem solving.[43]

Functional Outcomes

The TAU+GMT and TAU groups completed The World Health Organization Disability Assessment Schedule 2.0 (WHODAS),[44] 12-item version to assess functional disability.

Neuropsychological Assessment

A battery of standardized and experimental neuropsychological measures aimed at measuring executive functioning, attention, and memory was administered to the TAU+GMT group only. Current and premorbid intellectual functioning (administered at baseline only): (1) Wechsler Test of Adult Reading (WTAR):[45] estimate of premorbid IQ; (2) Wechsler Abbreviated Scale of Intelligence – II (WASI-II):[46] one subtest from the performance index (matrix reasoning) and one subtest from the verbal index (vocabulary) were administered to calculate current two-subtest full-scale IQ. Declarative memory: (1) California Verbal Learning Test-II (standard form administered pre-training and alternate form administered post-training) (CVLT-II):[47] word list learning task providing assessment of immediate and delayed memory, interference learning, and recognition. Executive Functioning: (1) Controlled Oral Word Association Task (COWAT):[48] a measure of verbal fluency, including phonemic (FAS) and semantic (animals) fluency; (2) Stroop Colour and Word Test:[48] a measure of processing speed and sensitivity to suppress habitual responses; (3) Trail Making Test Part A & B:[48] measure of attention, speed, and mental flexibility, including the ability to sequence two stimulus sets while alternating

between them; (4) DKEFS Tower Test:[49] requires participants to place disks on dowels to match increasingly complex models while following "rules" constraining the movement of these disks. DKEFS Tower Test measures planning, rule learning, response inhibition and perseveration. Attention: (1) Conners' Continuous Performance Test – Third Edition, a measure of sustained attention and response inhibition (CPT).[50]

Data Analysis

All analyses were completed using SPSS version 25.0. Analysis of the distribution of variables assessed in the current study revealed non-normality of several variables (Shapiro-Wilk >.05). Parametric analyses were reported for clarity and ease of interpretation; however, non-parametric tests (not reported) revealed consistent results across analyses.

Independent samples t-tests or Chi-square tests were used to analyze differences in demographic variables between the TAU+GMT and TAU groups at baseline. Repeated measures t-tests were used to analyze neuropsychological data within the TAU+GMT group in order to determine differences from baseline to post-treatment in performance on measures of neuropsychological functioning, with estimates of Cohen's d for effect size (interpreted conservatively as small = .20, medium = .50, and large = .80). Mixed-design 2x2 ANOVAs were used to determine differences from baseline to post-treatment on clinical variables between the TAU+GMT and TAU groups, with estimates of partial-eta squared for effect size (interpreted conservatively as small = .01, medium = .09, and large = .25).

In order to determine the extent to which individual participants improved across measures, we calculated the number of measures that each individual participant achieved an improvement of 1 standard deviation (SD) or higher, representing a rough estimate of clinically significant improvement as per the standard deviation method (although this approach has been criticized as potentially over-estimating level of clinically significant improvement)423. This was conducted for only those measures that demonstrated statistically significant improvement in the entire TAU+GMT sample. For each measure that demonstrated statistically significant improvement in the sample, we also calculated the number of individual participants who demonstrated slight worsening or no change (0 SD or less), a change of 0 to 0.5 SD, a change of 0.6 to 1.0 SD, a change of 1.1 to 1.5 SD, and a change of 1.6 SD or greater.

Results

No adverse effects of participation in TAU+GMT were reported.

No differences emerged between the TAU+GMT and TAU groups on any demographic variables at baseline.

Neuropsychological functioning in the TAU+GMT group

Significant improvements were found from baseline to post-treatment on the Stroop Word T Score ($t(17)=-2.73$, $p=.014$, d=-0.64) and Colour-Word T Score ($t(17)=-2.52$, $p=.022$, d=-0.59), the WAIS IV Coding Scaled Score ($t(17)=-3.69$, $p=0.002$, d=-0.87), the DKEFS Tower Time Per Move Scaled Score ($t(17)=-4.11$, $p=0.001$, d=-0.97) and Rule Violations ($t(17)=3.07$, $p=0.007$, d=0.72), the Short Delay Free Recall Z Score ($t(17)=-2.64$, $p=0.017$, d=-.62) and the Long Delay Cued Recall Z Score ($t(17)=-2.36$,

p=0.030, d=-.56) on the CVLT-II and on the CPT 3.0 Omissions T Score (*t*(17)=2.76, *p*=0.013, d=.65), Commissions T Score (*t*(17)=2.87, *p*=.011, d=.68), and the Detectability T Score (*t*(17)=3.04, *p*=0.007, d=.72). The results of paired-sample t-tests comparing pre- versus post-neuropsychological and psychological performance in the TAU+GMT group only are presented in Table 3.

72.2% of the sample improved by 1 SD or greater on at least one measure that demonstrated statistically significant improvement within the entire TAU+GMT sample. 5.6% of the sample improved on 1 measure, 38.9% of the sample improved on 2 measures, 5.6% of the sample improved on 3 measures, 5.6% of the sample improved on 4 measures, and 16.7% of the sample improved on 5 measures. 27.8% of the sample demonstrated no such improvement. The extent to which the sample improved on each statistically significant measure is reported in table 4.

Psychological functioning in the TAU+GMT group

Within the TAU+GMT group, significant improvements were found from pre- to post-treatment for the PHQ-9 depression (*t*(14)=3.19, *p*=.007, d=.82) and impairment scores (*t*(14)=5.13, *p*=.000, d=1.32). There was a trend towards a significant improvement on the DEX within the TAU+GMT group (*t*(15) = 2.94, *p*=.010, d=.76).

Comparison of psychological functioning in the TAU vs TAU+GMT groups

Main Effects of Time were found across all psychological measures and measure subscales administered (all $p < .05$; $\eta^2_p = .21\text{-}.71$), suggesting that the TAU+GMT group and the TAU group improved on total and subscale scores of the PCL-5, the DASS, the DERS, CFQ, and the WHODAS.

Main Effects of Group were found for PCL-5 total and subscale scores (all $p < .05$), with the exception of the Arousal and Reactivity subscale, where the TAU group demonstrated higher scores at pre- and post-testing in comparison to the TAU+GMT group, suggesting a higher level of PTSD symptom severity in the TAU group. A Main Effect of Group was found for the DERS Awareness subscale ($F(1,32) = 12.23$, $p = .001$, $\eta^2_p = .28$), such that the TAU+GMT group demonstrated higher scores at pre- and post-testing, in comparison to the TAU group, suggesting greater levels of difficulty in awareness of emotions in the TAU+GMT group.

No significant Group X Time interaction effects emerged. However, there was a trend towards a Group X Time interaction effect for the DERS Goals subscale ($F(1,32) = 2.92$, $p = .097$, $\eta^2_p = .08$) assessing the ability to engage in goal-directed behavior when experiencing negative emotions. Simple main effect analysis revealed a significant reduction on DERS goals in the TAU+GMT group ($F(1,32) = 19.29$, $p = .000$, $\eta^2_p = .38$). A smaller, non-significant reduction emerged on the DERS goals in the TAU group ($F(1,32) = 3.21$, $p = .083$, $\eta^2_p = .09$), suggesting greater improvement on this subscale in the TAU+GMT group. Results of the mixed-design ANOVAs comparing pre- and post-treatment outcomes in the TAU and TAU+GMT groups are presented in Table 5.

Table 3. Neuropsychological Outcomes of Patients who Received GMT+TAU (n = 18)

	Assessment Time		
Test	Baseline *M (SD)*	Post-Treatment *M (SD)*	Effect Size (Cohen's d)
Stroop Colour and Word Test			
Word T Score	40.67(14.62)	46.28 (13.68)*	-0.64
Colour T Score	41.50(11.34)	45.94(13.26)	-0.29
Colour-Word T Score	44.33(8.07)	49.00(8.25)*	-0.59
Interference T Score	47.39(8.20)	49.94(6.13)	-0.33
WAIS IV Coding Scaled Score	9.22(1.90)	10.56(2.28)**	-0.87
COWAT			
FAS T Score	48.61(10.15)	49.89(7.99)	-0.16
Animals T Score	49.06(11.66)	50.78(10.39)	-0.22
Trail Making Test			
Trails A T Score	54.17(12.99)	58.89(12.07)	-0.37
Trails B T Score	45.78(12.80)	50.22(14.43)	-0.36
DKEFS Tower Test			
Total Score Scaled Score	10.83(2.57)	10.94(2.21)	-0.04
First Move Time Scaled Score	11.06(1.89)	11.50(2.09)	-0.19
Time Per Move Scaled Score	11.00(1.03)	12.28(1.23)**	-0.97
Move Accuracy Scaled Score	9.06(2.62)	9.00(2.45)	0.03
Rule Violations	1.33(1.57)	0.39(0.61)**	0.72
CVLT-II			
Trial 1 Z Score	-0.53(1.09)	-0.72(0.94)	0.13
Trials 5 Z Score	0.00(0.75)	0.25(0.79)	-0.30
Trial 1-5 T Score	50.67(8.27)	52.39(6.90)	-0.21
Trial B Z Score	-0.28(1.05)	-0.89(0.76)	0.49
Short Delay Free Recall Z Score	0.06(0.77)	0.47(0.85)*	-0.62
Short Delay Cued Recall Z Score	0.08(0.77)	0.42(0.82)	-0.39
Long Delay Free Recall Z Score	-0.11(0.70)	0.11(0.81)	-0.36
Long Delay Cued Recall Z Score	-0.06(0.68)	0.33(0.64)*	-0.56
Repetitions Z Score	0.08(0.90)	-0.19(0.94)	0.26
Intrusions Z Score	0.86(1.04)	0.64(1.26)	0.16

Discriminability Z Score	0.06(0.78)	0.25(0.84)	-0.23
CPT 3.0			
Ommissions T Score	45.83(1.47)	44.94(0.64)*	0.65
Commissions T Score	48.83(7.37)	43.17(6.67)*	0.68
Detectability T Score	46.06(6.65)	39.72(8.10)**	0.72
Hit Rate T Score	45.06(8.05)	48.61(8.21)	-0.45
Variability T Score	47.11(6.32)	47.44(7.00)	-0.04
Perseveration T Score	47.28(4.07)	48.39(6.54)	-0.14

*$p < .05$; **$p < .01$

WAIS-IV, Wechsler Adult Intelligence Scale Fourth Edition; COWAT, Controlled Oral Word Association Task; DKEFS, Delis-Kaplan Executive Function System; CVLT, California Verbal Learning Test Second Edition; CPT, Conner's Continuous Performance Task 2.0

Table 4. Percent of sample achieving different levels of change for neuropsychological measures with statistically significant change in the TAU+GMT group

	Less than 0 SD	0-0.4 SD	0.5-0.9 SD	1.0-1.4 SD	1.5 SD or greater
Test	% of sample				
Stroop Colour and Word Test					
Word T Score	22.2	33.3	22.2	11.1	11.1
Colour-Word T Score	22.2	38.9	22.2	0	16.7
WAIS IV Coding Scaled Score	16.7	33.3	16.7	33.3	0
DKEFS Tower Test					
Time Per Move Scaled Score	5.6	50	27.8	16.7	0
Rule Violations	11.1	83.3	5.6	0	0
CVLT-II					
Short Delay Free Recall Z Score	16.7	27.8	27.8	11.1	16.7
Long Delay Cued Recall Z Score	16.7	27.8	22.2	22.2	11.1
CPT 3.0					
Ommissions T Score	11.1	88.9	0	0	0
Commissions T Score	22.2	27.8	22.2	11.1	16.7
Detectability T Score	22.2	22.2	22.2	16.7	16.7

SD, standard deviation; WAIS-IV, Wechsler Adult Intelligence Scale Fourth Edition; DKEFS, Delis-Kaplan Executive Function System; CVLT, California Verbal Learning Test Second Edition; CPT, Conner's Continuous Performance Task 3.0

Table 5. Clinical Outcome Data

Assessment	Group	Baseline *M* (SD)	Post-Treatment *M* (SD)	F, (df) Main effect of group	F, (df) Main effect of time	F, (df) Interaction effect
PTSD Checklist for DSM 5						
Total Score	GMT (*n*=18)	54.83(11.72)	34.06(16.01)	7.28(1,30)*	51.31(1,30)**	0.51(1,30)
	TAU (*n*=14)	62.71(9.21)	45.71(11.35)			
Intrusions	GMT	12.83(4.87)	8.67(4.93)	4.61(1,30)*	19.57(1,30)**	1.51(1,30)
	TAU	15.00(3.96)	12.64(3.93)			
Avoidance	GMT	5.83(1.92)	3.67(2.30)	10.43(1,30)*	22.39(1,30)**	0.01(1,30)
	TAU	7.36(1.15)	5.29(1.59)			
Cognitions and Mood	GMT	20.50(3.83)	11.28(5.24)	5.48(1,30)*	75.98(1,30)**	0.60(1,30)
	TAU	22.50(2.62)	14.79(4.74)			
Arousal and Reactivity	GMT	15.67(3.96)	10.44(5.32)	3.62(1,30)	27.50(1,30)**	0.36(1,30)
	TAU	17.86(4.29)	13.00(3.76)			
Depression Anxiety Stress Scale						
Depression	GMT (*n*=18)	22.89(10.12)	12.11(8.58)	1.14(1,32)	34.39(1,32)**	0.79(1,32)
	TAU (*n*=16)	27.75(10.04)	13.13(12.00)			
Anxiety	GMT	22.22(9.17)	13.89(9.37)	0.37(1,32)	22.04(1,32)**	0.29(1,32)
	TAU	23.12(10.50)	16.50(9.59)			

Stress	GMT	27.89(7.98)	15.35(7.73)	0.11(1,32)	31.66(1,32)**	0.36(1,32)
	TAU	27.38(9.46)	17.25(8.48)			
Multiscale Dissociation Inventory						
Total Score	GMT (*n*=18)	67.19(16.56)	51.78(10.47)	5.51(1,31)*	24.56(1,31)**	1.47(1,31)
	TAU (*n*=15)	82.33(23.60)	56.92(16.36)			
Disengagement	GMT	16.44(4.08)	13.06(3.28)	2.13(1,31)	17.26(1,31)**	0.47(1,31)
	TAU	18.47(4.10)	13.73(3.94)			
Depersonalization	GMT	8.78(3.66)	6.12(1.79)	8.30(1,31)*	18.77(1,31)**	1.16(1,31)
	TAU	12.67(5.79)	8.33(3.11)			
Derealization	GMT	10.00(4.10)	6.94(3.36)	7.86(1,31)**	17.46(1,31)**	0.14(1,31)
	TAU	13.47(5.29)	9.80(3.75)			
Emotional Constriction	GMT	14.83(5.17)	12.28(4.73)	0.01(1,31)	22.43(1,31)**	3.61(1,31)^{T}
	TAU	16.40(4.66)	10.42(4.00)			
Memory Dissociation	GMT	11.42(3.95)	8.33(3.22)	0.78(1,31)	23.93(1,31)**	1.94(1,31)
	TAU	13.60(5.00)	8.07(3.77)			
Identity Dissociation	GMT	5.72(1.78)	5.00(0.00)	7.01(1,31)*	3.89(1,31)^{T}	0.22(1,31)
	TAU	7.73(3.58)	6.57(2.87)			
Difficulties in Emotion Regulation Scale						
Total Score	GMT (*n*=18)	124.17(20.50)	95.21(24.22)	0.35(1,32)	29.62(1,32)**	0.06(1,32)
	TAU (*n*=16)	119.72(18.56)	93.22(23.09)			

Nonacceptance of Emotions	GMT	20.89(6.62)	15.83(6.44)	0.31(1,32)	15.19(1,32)**	0.21(1,32)
	TAU	21.44(7.09)	17.44(6.12)			
Goal Directed Behaviour	GMT	20.72(3.20)	16.28(4.42)	0.11(1,32)	18.62(1,32)**	2.92(1,32)^{T}
	TAU	19.05(4.45)	17.13(4.90)			
Impulsivity	GMT	16.56(4.80)	13.61(6.12)	0.19(1,32)	10.31(1,32)**	0.14(1,32)
	TAU	17.55(5.17)	13.84(3.88)			
Awareness	GMT	23.39(4.04)	20.00(4.28)	12.23(1,32)**	8.65(1,32)**	0.29(1,32)
	TAU	18.75(4.27)	16.41(5.12)			
Strategies	GMT	25.28(6.39)	19.99(7.41)	0.48(1,32)	12.27(1,32)**	0.01(1,32)
	TAU	26.75(7.23)	20.57(7.55)			
Cognitive Failures Questionnaire						
Total	GMT (*n*=15)	60.67(11.38)	40.53(19.65)	1.42(1,25)	33.75(1,25)**	0.57(1,25)
	TAU (*n*=12)	70.04(14.32)	44.00(22.58)			
World Health Organization Disability Assessment Schedule 2.0 – 12 Item Version						
Total	GMT (*n*=18)	43.06(18.91)	36.23(17.15)	0.21(1,31)	9.37(1,31)**	1.36(1,31)
	TAU (*n*=15)	44.72(18.71)	29.51(20.18)			

*$p < .05$; **$p < .01$

GMT, Goal Management Training group; TAU, treatment as usual group

Discussion

The results of this study point to the possibility that GMT may serve as an effective cognitive intervention for individuals with PTSD. In particular, our results demonstrate that it is possible to conduct GMT within an inpatient PTSD sample and that GMT is associated with improvements on measures of neuropsychological functioning. In addition, 72.2% of the sample demonstrated potentially clinically significant improvement on at least one measure where clinically significant improvements were found within the entire TAU+GMT sample. However, with respect to the exploratory analyses on clinical variables, while one trend-level interaction effect was found, it remains unclear the extent to which GMT may impact clinical symptoms relative to TAU.

The results of our analyses revealed significant, focused gains on tasks assessing cognitive domains commonly affected in PTSD, including executive processes, processing speed, response inhibition, sustained attention, and verbal short-term memory (on select measures only). Specifically, participation in GMT was associated with significant post-treatment improvements on an executive functioning measure, and on measures assessing processing speed, response, sustained attention, and verbal short-term memory.

These findings support the use of a "top-down" approach to cognitive remediation among individuals with PTSD, where higher-order cognitive processes (i.e., executive functioning) are targeted with the aim of achieving improvement in these areas and in downstream cognitive functions including attention and short-term memory. Critically, "bottom-up" approaches involving remediation of basic skills (e.g., processing speed and

attention) that aim to improve more complex skills (e.g., executive functioning) through repetitive "drill and practice" have been criticized for their limited generalizability to day-to-day functioning.[52] where, for example, approaches have limited effects on executive functioning among individuals with depression.[21] Critically, GMT aims specifically to instill skills that can be generalized to solve issues in daily functioning.[22,26,31] The present study is in keeping with previous meta-analytic findings of improvements on tasks tapping executive processes, including response inhibition, rule learning, and sustained attention, following treatment with GMT.

Although we did not a significant difference between the TAU+GMT and TAU groups on improvements on functional outcomes or in self-reported cognitive difficulties in the present study, these findings may stem, in part, from the limited opportunity for inpatients to experience functional improvements in day-to-day life. Further, both the TAU+GMT and the TAU groups reported a significant reduction in subjective cognitive and functional impairment following treatment. Here, the first several sessions of GMT focus on increasing awareness of cognitive and functional difficulties via monitoring absentmindedness or cognitive failures. This may have increased patients' awareness of cognitive difficulties and thus heightened reporting of daily functioning difficulties, leading to the absence of differences between groups.

No significant interaction effects were found between participants in the TAU+GMT and TAU groups from pre- and post-treatment. Notably, however, a trend-level interaction effect was found between the TAU+GMT and TAU group, such that participation in the TAU+GMT as opposed to TAU group was associated with a larger

improvement in patients' self-reported ability to engage in goal-directed behaviour when highly emotional, a behavioural indicator of executive control. This finding is in keeping with the objective reduction in executive dysfunction observed in the TAU+GMT group.

We did observe significant improvements in clinical symptoms across both the TAU+GMT and TAU groups (large effect sizes). In addition, there was a significant effect of group on several clinical measures, including the PCL-5 total and subscale scores (with the exception of the arousal and reactivity subscale). Given the non-randomized nature of the current study, it is possible that individuals with higher baseline symptom severity chose not to participate in the TAU+GMT group.

As stated above, GMT aims to reduce executive dysfunction and improving the ability to carry out goal-directed behaviours[22] by providing patients with strategies that facilitate the resumption of supervisory control of cognitive processes and allow individuals to improve monitoring and execution of daily functions. For example, as patients learn to attend to their environment and current behavior (e.g., via the STOP technique), they are better able to evaluate their behavior in order to determine if it is in-line with their current goals. The concept of monitoring current goals and behaviours is similar to strategies utilized in mindfulness based therapies, where such interventions have been associated with improvements in attention among individuals with PTSD[53]. General memory strategies such as stating and re-stating goals in order to enhance encoding into memory are also incorporated. The suggestion that GMT leads to improvements in executive control via increased monitoring and evaluation are supported by the current findings of improvements on measures of response inhibition (e.g., stroop

colour-word T score; DKEFS rule violations) and sustained attention (e.g., CPT 3.0 Omissions and Commissions) as well as trend level improvements on the ability to pursue goals despite high emotionality relative to the TAU group.

Although the current findings provide support for the use of GMT as a cognitive remediation intervention for PTSD, the results should be interpreted with caution. In the absence of control group with pre- and post- neuropsychological data, we cannot exclude the possibility that improvements in neuropsychological functioning observed in the TAU+GMT group occurred as a result of overall treatment (e.g., TAU), the passage of time, or practice effects, rather than a specific effect of participation in GMT. However, a study investigating practice effects for the CVLT found small, potentially negligible effects of practice, when alternate forms were employed, similar to the approach here.[54] The CPT 3.0 is also thought to be robust to the effects of practice.[50] Practice effects on the Stroop task are also small.[55] Limited research has examined the effect of practice on the Tower Test, however, tests measuring executive functioning may be particularly susceptible to practice due to learned strategies, thus, our findings of performance improvements on the DKEFS Tower Test time per move score and rule violations should be interpreted with caution.[49] Finally, one study reported an improvement on the WAIS-IV coding task similar to that observed here over a 3-6 month period.[56]

Participants in the present study had the option of participating in the TAU+GMT group or TAU and were not randomized, thus patients who chose to participate in TAU+GMT may have differed from those who chose to participate in TAU. To illustrate, we were unable to control for the fact that patients who opted not to participate in

TAU+GMT group had greater symptom severity (and potentially lower levels of treatment engagement). They may also have opted not to participate due to increased demands and anticipated stress such as being asked to participate in additional treatment and assessments. A randomized design would aid in eliminating these confounds. Further, only individuals who participated in the TAU+GMT group were assessed for specific exclusion criteria, which may have led to differences between groups. Similarly, only those in the TAU+GMT group received structured clinical interviews to confirm a diagnosis of PTSD, thus while participants in the TAU group reported symptoms above the proposed threshold for a diagnosis of PTSD on the PCL-5, a diagnosis of PTSD was not confirmed.

Future work should assess the durability of these effects. The current study did not include a follow-up assessment. Previous studies, however, suggest that GMT confers durable improvements in neuropsychological and functional outcomes.[22-24,26-28,57,58] It will be necessary for future studies to employ a randomized controlled design in order to account for the confounding factors associated with the current non-randomized design. Future studies may also investigate the impact of GMT or similar intervention on the hypothesized neurobiological mechanisms of cognitive dysfunction in PTSD, as has been previously suggested.[59] In the current study, we investigated GMT delivered simultaneously with treatment as usual. Given that cognitive dysfunction in PTSD has been found to negatively impact treatment outcome[13,14], it would be interesting to investigate the differential impact of GMT on treatment outcome if it was administered

prior to, as compared to being delivered in conjunction with, other psychological treatments for PTSD. Future research should aim to investigate this question.

The results of this study provide preliminary but promising evidence for the effectiveness of GMT as a cognitive remediation intervention for PTSD and is among the very few studies investigating interventions aimed at improving cognitive dysfunction in this population. These findings are particularly important given the critical impact of cognitive dysfunction on functioning and on treatment outcomes among individuals with PTSD.[6,9,10,13,14,59] On balance, remediation of cognitive dysfunction is expected to allow patients with PTSD to achieve greater benefit from cognitively demanding treatments (e.g., cognitive behavioural therapies),[13,14] to reduce deficits in day-to-day functioning that persist beyond PTSD symptom recovery,[6] and to reduce the overall economic and societal burden of this disorder.[9-11]

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Chapter 6: Conclusions

PTSD is a debilitating mental health condition associated with significant functional impairment (Amaya-Jackson et al., 1999; Greenberg et al., 1999; Johansen et al., 2007; Kessler, 2000; Olatunji et al., 2007; Pagotto et al., 2015) and reduced neuropsychological functioning (Scott et al., 2015; Woon et al., 2017) which may contribute further to impaired functioning (Ainamani, Elbert, Olema, & Hecker, 2017; Geuze, Vermetten, De Kloet, Hijman, & Westenberg, 2009; Wrocklage et al., 2016). Functional impairment and cognitive dysfunction appear to represent an aspect of PTSD that is resistant to treatment with current first-line treatment modalities (Crocker et al., 2018; Murphy et al., 2016; Westphal et al., 2011; Wild & Gur, 2008) (but see Galovski, Monson, Bruce, & Resick, 2009; Monson et al., 2012; Nijdam, Martens, Reitsma, Gersons, & Olff, 2018; Walter, Palmieri, & Gunstad, 2010). Thus, the aim of this thesis was to expand our knowledge of symptom level factors that contribute to reduced neuropsychological functioning and increased functional impairment among individuals with PTSD, as well as to investigate a novel approach to cognitive remediation in improving neuropsychological functioning and functional impairment in this population.

The central hypothesis that we tested was that previously understudied symptoms of emotion dysregulation and dissociation would contribute significantly to cognitive dysfunction and functional impairment in this population. Moreover, we hypothesized that a cognitive remediation program, GMT, aimed at promoting the resumption of self-regulation and control over automatic processes would be associated with improvements in cognitive functioning and in functional impairment. We also tested the hypothesis that

this approach would be associated with improvements in emotion regulation, given the association between emotion dysregulation and executive functioning (Diamond, 2013; Morillas-Romero, Tortella-Feliu, Balle, & Bornas, 2015).

6.0 Summary of Findings

Study one (Chapter two; *McKinnon, Boyd, et al., 2016) of this thesis provided a critical overview of the literature investigating associations between dissociative symptomatology and neuropsychological functioning transdiagnostically, including among individuals with PTSD. This literature review revealed a significant body of evidence documenting a relation between dissociative symptomatology and reduced neuropsychological functioning across domains of cognition including executive functioning, verbal and visuospatial memory, attention and working memory, episodic and autobiographical memory, processing speed, and social cognition. Moreover, this association was documented across various populations, including among healthy controls, trauma-exposed controls, individuals with PTSD, MDD, borderline personality disorder (BPD), dissociative identity disorder (DID), and depersonalization disorder. This review also proposed a neurobiological model linking dissociative symptomatology and reduced cognitive functioning, whereby dissociative experiences can be conceptualized as altered states of consciousness linked to defensive responding as in the defense cascade model of dissociation (Kozlowska, Walker, McLean, & Carrive, 2015; Schauer & Elbert, 2010). Here, dissociative responses are associated with reduced integration of sensory experiences (mediated by thalamic relay sites) and thus may lead to impaired encoding and responding to internal and external stimuli, leading to reduced cognitive functioning.

Finally, we reviewed associations between dissociative symptoms and functional connectivity of intrinsic networks consistently implicated in psychopathology and critically involved in cognitive functioning, the central executive network (CEN), the salience network (SN) and the default mode network (DMN) (Menon, 2011), which may also be related to reduced neuropsychological functioning.

Given the established association between dissociation and reduced cognitive functioning reviewed in study one, study two (chapter three; *Boyd et al., 2018) investigated the role of dissociative symptomatology, among other symptoms associated with PTSD, in functional impairment among military members, veterans, and first responders with PTSD. Here, we found that dissociative symptoms, particularly symptoms of derealization, mediated the relation between PTSD symptoms and functional impairment. Critically, in this study, PTSD symptoms were not significantly correlated with functional impairment, after controlling for multiple comparisons, suggesting that our understanding of functional impairment among military members, veterans, and first responders with PTSD would be significantly limited if symptoms beyond those captured by DSM 5 PTSD symptoms were not investigated.

Similar to study two, study three (chapter four; *Boyd et al., 2019b) investigated functional impairment among individuals with PTSD in a different study population. Here, study participants consisted of civilians with PTSD and high rates of exposure to childhood abuse or neglect. In this study, we aimed to determine the contribution of both symptoms of dissociation, and emotion regulation difficulties, given the association between emotion dysregulation and PTSD (Ehring & Quack, 2010), perhaps most notably

among individuals with PTSD resulting from childhood trauma (Burns, Jackson, & Harding, 2010; Goldsmith, Chesney, Heath, & Barlow, 2013; Stevens et al., 2013), and between emotion dysregulation and functional impairment (Cloitre, Miranda, Stovall-McClough, & Han, 2005; Malta, Levitt, Martin, Davis, & Cloitre, 2009). In this study, we found that emotion regulation difficulties and dissociative symptoms were significant predictors of functional impairment in a model including emotion regulation difficulties, dissociative symptoms, and PTSD symptom clusters. Here, PTSD symptom clusters did not emerge as statistically significant predictors after accounting for the effects of other predictors in the model. These findings again highlight the importance of assessing symptoms that extend beyond the scope of DSM 5 PTSD symptoms in order to fully understand functional impairment among individuals with PTSD.

Lastly, in study four (Chapter 5; *Boyd, O'Connor, Protopoescu, Lanius, & McKinnon, 2019a), we investigated the effectiveness and feasibility of GMT among an inpatient sample of individuals with PTSD. Here, GMT in addition to treatment as usual (TAU; consisting of psychological and psychiatric treatment) was delivered twice weekly for three weeks. Neuropsychological functioning was assessed pre- and post-treatment for individuals receiving GMT plus TAU (GMT+TAU). In addition, clinical measures were assessed both among those participating in GMT+TAU and among participants who elected not to participate in GMT (TAU group). We found improvements on measures of neuropsychological functioning, including measures of executive processes, processing speed, response inhibition, sustained attention, and verbal short-term memory. Further, we found a trend-level interaction effect for a measure of emotion regulation difficulties,

such that participation in the GMT group was associated with greater improvement in the ability to engage in goal-directed behaviours when highly emotional, than was participation in TAU alone. It was hypothesized that these improvements in neuropsychological functioning and emotion regulation would be associated with greater improvements on measures of functioning. However, we did not observe any significant differences between the TAU+GMT group and the TAU group on self-reported cognitive difficulties or on measures of daily functioning. This lack of expected findings may be due to the inpatient nature of the sample, whereby there would be limited opportunity to observe changes in functioning in daily life. Nonetheless, these findings add to the growing literature investigating cognitive remediation for individuals with PTSD. In comparison to previous studies, our findings suggest that non-computerized interventions may be more effective in ameliorating cognitive dysfunction in this population (Bomyea, Stein, & Lang, 2015; Clausen et al., 2019; Fonzo et al., 2019; Saunders et al., 2015).

Thus, consistent with the aim of this thesis to expand our understanding of cognitive dysfunction and functional impairment among individuals with PTSD and to investigate potential alternative treatments for cognitive dysfunction and functional impairment in PTSD, the studies included here expand our understanding of functioning in PTSD by evaluating oft over-looked symptom dimensions and a novel treatment approach.

6.2 Limitations

The results of the studies presented in this thesis should be interpreted with several limitations in mind. Perhaps the most significant limitation of studies two and

three is their cross-sectional design. This study design significantly limits the extent to which one can assume causality in our findings. In particular, within study two, we reported the results of a mediation analysis which assumes that the antecedent variable (e.g., PTSD symptoms) is related causally to the outcome variable (e.g., functional impairment) and that an intermediate variable (e.g., dissociative symptoms) accounts for, or mediates, this relation (Kraemer, Kiernan, Essex, & Kupfer, 2008; Mackinnon, Fairchild, & Fritz, 2007). Given that the data used in study two were collected simultaneously, we cannot assume that PTSD symptoms or dissociative symptoms preceded the emergence of functional impairment in this sample (although previous work has established longitudinal associations between PTSD symptomatology and functional impairment (Johansen et al., 2007)). Similarly, study four utilized a cross-sectional design to investigate whether emotion regulation symptoms and dissociative symptoms predicted functional impairment in individuals with PTSD. Again, multiple regression analysis assumes that predictor variables precede the onset of outcome variables (Tabachnick & Fidell, 2012). However, since all variables were collected at the same time, we cannot exclude the possibility that functional impairment preceded PTSD symptoms, emotion regulation difficulties and dissociative symptoms. Future work should employ longitudinal study designs in order to allow conclusions to be drawn about the causal relations between PTSD, dissociative symptoms, emotion regulation difficulties, and functional impairment. Further, in both studies three and four, we cannot assume that observed results are not accounted for by other unmeasured variables (Tabachnick & Fidell, 2012).

A second limitation of studies three and four is a lack of standardized clinician-administered clinical interview to establish a diagnosis of PTSD. Although participants were seeking treatment on an inpatient psychological trauma treatment unit, we were only able to establish a probable diagnosis of PTSD in these studies based on self-report questionnaires. Moreover, we were unable to establish the index trauma for which individuals in studies three and four were seeking help. Thus, it is possible that individuals in these studies may have been seeking treatment relating to traumas of differing etiology (e.g., childhood abuse, interpersonal violence, combat trauma, single incident trauma), creating heterogenous samples.

Study five also has several limitations. Most notably, this study was a feasibility trial and did not employ a randomized controlled study design. Individuals who participated in this study elected to participate either in the TAU+GMT condition or the TAU condition. Thus, we cannot exclude the possibility that those who chose to participate in TAU+GMT differed on any number of variables from those who chose to participate in TAU (e.g., symptom severity, experience of subjective cognitive complaints, functional impairment level, motivation). Indeed, higher PTSD symptoms were noted among those who opted not to participate for in TAU+GMT. A randomized design would aid in eliminating these confounds. Furthermore, control data were not available for neuropsychological assessments. Thus, it is not possible to determine if the improvements noted on measures of neuropsychological functioning were due to the effect of the intervention, practice effects, or the passage of time. A fully controlled study

design (i.e., including both clinical and neuropsychological measures in the control condition) would address this issue.

6.3 Implications and Future Directions

The studies presented in this thesis open the line of inquiry for several avenues of future research. In study one we reviewed the relation between dissociative symptomatology and neuropsychological functioning and presented neurobiological models that potentially underlie this relation. To date, the effect of dissociative symptomatology on recruitment and functioning of ICNs and subsequent effects on neuropsychological functioning has not been empirically established. Further, in this review we suggested a three-way relation between dissociative symptomatology, neuropsychological functioning, and functional impairment, such that we suggest that dissociative symptomatology among individuals with PTSD leads to reduced neuropsychological functioning and subsequent impairment in daily functioning. Future work will be necessary to confirm this proposed model. Nonetheless, this study has significant implications, namely, the suggestion that dissociative symptoms should be targeted within treatment protocols in order to ameliorate cognitive dysfunction among individuals with PTSD.

Studies three and four established that symptoms of dissociation and emotion dysregulation are strongly related to functional impairment among individuals with PTSD. Perhaps the most significant implication of this work is the suggestion that treatments targeting dissociative symptoms and emotion regulation difficulties may be necessary to effectively reduce functional impairment in this population. Although some

previous work has suggested that emotion regulation (Hinton, Hofmann, Pollack, & Otto, 2009; Jerud, Zoellner, Pruitt, & Feeny, 2014) and dissociative symptoms (Chard, 2005; Resick, Suvak, Johnides, Mitchell, & Iverson, 2012) can improve with current front-line treatments for PTSD, others have reported deleterious effects of these symptoms on treatment outcomes (Bae, Kim, & Park, 2016; Wolf, Lunney, & Schnurr, 2015). It remains unknown whether such improvements represent clinically significant changes that would be associated with reductions in functional impairment. Therefore, a critical avenue for further research is the investigation of the effects of first-line psychotherapies on emotion dysregulation and dissociative symptoms and resultant impacts on functioning as well as a comparison of the impact of other alternative or adjunctive approaches that more directly target these symptoms (e.g., dialectical behaviour therapy (DBT) or mindfulness-based interventions as suggested by Boyd, Lanius, & McKinnon, 2017 and Zerubavel & Messman-Moore, 2015).

Study five provided preliminary evidence for the effectiveness of GMT in reducing cognitive dysfunction and improving the ability to engage in goal directed behaviours when highly emotional. Importantly, it suggests that cognitive dysfunction among individuals with PTSD can be effectively targeted in a group-based treatment focused on learning skills transferable to daily functioning (as opposed to skill-drill computerized approaches). This works paves the way for future, more rigorous research studies to investigate this treatment. In particular, a randomized controlled study design with an active treatment comparison should be utilized to confirm that neuropsychological improvements observed in the GMT group in study five were not

merely a result of the passage of time or the non-specific effects of treatment (e.g., contact with a therapist and other group members). Moreover, we did not find a significant effect of GMT on functional outcomes which may be due to the inpatient nature of our study. Thus, GMT should be administered in an outpatient sample in order to determine if improvements in neuropsychological functioning translate to improvements in day-to-day functioning. Follow-up assessments should also be included in order to establish the durability of these effects.

6.4 General Conclusions

This thesis expanded our understanding of cognitive functioning and functional impairments associated with PTSD, both of which are under-studied in the context of treatment. New directions for the treatment of perhaps the most debilitating consequences of PTSD were provided through this work. This work highlights the importance of assessing and treating symptoms outside of the traditional conceptualization of PTSD, including emotion regulation difficulties and dissociative symptoms, in order to assist individuals with PTSD in regaining functional capacity.

Cognitive remediation utilizing a top-down approach appears to be one such avenue of treatment that is both effective and feasible among individuals with PTSD. This approach contrasts with other approaches that have been studied to date and that emphasize practice of specific tasks aimed to target aspects of cognition such as working memory or attention. Such approaches have been criticized for a lack of generalizability and have demonstrated limited utility among individuals with PTSD (Clausen et al., 2019; Fonzo et al., 2019; Saunders et al., 2015). GMT is distinct from such approaches in that it

teaches individuals skills that are directly transferable to daily functioning and the results presented in this thesis suggest that it can lead to improvements on measures of neuropsychological functioning, including executive functions, verbal memory, and processing speed.

Taken together, these findings extend our knowledge of and ability to treat cognitive and functional difficulties in PTSD, aspects of this illness that have significant debilitating effects at both a societal and individual level. It is my hope that these findings will lead to changes in assessment and treatment practices that will allow individuals with PTSD to live more functional and meaningful lives.

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