

COGNITIVE PROCESSES IN DEPRESSION

NEURAL AND CLINICAL CORRELATES OF COGNITIVE PROCESSES IN MAJOR
DEPRESSIVE DISORDER AND POSTTRAUMATIC STRESS DISORDER

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Lay Abstract

Major depressive disorder (MDD) and posttraumatic stress disorder (PTSD) negatively affect quality of life and day-to-day functioning. These populations show difficulties in domains related to cognitive processing, such as empathy, imagining future events, and neuropsychological functioning (e.g., memory and attention). This thesis focuses on examining variables that may be related to these difficulties. In particular, we study developmental variables, such as parental bonding, clinical symptoms, such as dissociation, and neuroimaging data. Our findings suggest that these variables are all related to impairments in different areas of cognitive processing. By understanding what may be contributing to these cognitive difficulties, we may be able to design treatment strategies that target the underlying causes of these difficulties.

Abstract

Major depressive disorder (MDD) and posttraumatic stress disorder (PTSD) are chronic, debilitating illnesses. Impairments in cognitive processes such as social cognition, episodic simulation, and neuropsychological performance have been documented separately in both disorders. Despite our increasing knowledge of these impairments, the potential underlying transdiagnostic mechanisms remain relatively unexplored. This thesis examines correlates of these processes in persons with a primary diagnosis of MDD with a history of trauma exposure, and in persons with PTSD. The first study examined the association between the social cognitive domain of empathy and parental bonding in women with PTSD associated with childhood abuse. Participants with PTSD reported altered levels of cognitive and affective empathy, compared to controls. Paternal care during childhood was the only predictor of cognitive empathy (i.e., perspective taking). The second study investigated the specificity of episodic simulation of future positive, negative, and neutral events in relation to parental bonding and neuropsychological functioning among participants with MDD. Optimal parental bonding and higher scores on measures of neuropsychological functioning were associated with increased specificity of episodic simulation. In the third study, we examined the relation between dissociative symptoms and neuropsychological functioning in participants with MDD. Patients with MDD report significantly higher levels of dissociation as compared to controls, and more severe dissociation was related to poorer neuropsychological performance among this patient group. Lastly, using independent component analysis of resting-state fMRI data, the fourth study examined the association between intrinsic connectivity networks and

neuropsychological performance among participants with MDD. Connectivity within the default mode, salience, and central executive networks was associated with neuropsychological and clinical (i.e., depression, dissociation, PTSD) variables. Overall, this thesis demonstrates that variables such as parental attachment, dissociation, and intrinsic connectivity networks may underlie some of the alterations in cognitive processes seen in MDD and trauma-related disorders.

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List of Abbreviations

ACC	anterior cingulate cortex
AI	Autobiographical Interview
AM	autobiographical memory
AMT-f	Autobiographical Memory Test - Future
ANOVA	univariate analysis of variance
BA	Brodmann Area
BDI	Beck Depression Inventory
BOLD	blood-oxygen-level dependent
BPD	borderline personality disorder
CAPS	Clinician-Administered PTSD Scale
CCN	cognitive control network
CEN	central executive network
CI	confidence interval
COWAT	Controlled Oral Word Association Test
CPT-II	Conners' Continuous Performance Test - II
CTQ	Childhood Trauma Questionnaire
CVLT-II	California Verbal Learning Test – II
dACC	dorsal anterior cingulate cortex
dIPFC	dorsolateral prefrontal cortex
DMN	default mode network
FDR	False Discovery Rate

fMRI	functional magnetic resonance imaging
FTT	Future Thinking Task
FWHM	full-width half-maximum
HAM-D	Hamilton Rating Scale for Depression
HC	healthy control
ICA	independent component analysis
IFC	intrinsic functional connectivity
IPL	inferior parietal lobe
IRI	Interpersonal Reactivity Index
ISI	interstimulus interval
LDFR	long-delay free recall
MCCB	Mindstreams Computerized Cognitive Battery
MDD	major depressive disorder
MDI	Multiscale Dissociation Inventory
MNI	Montreal Neurological Institute
mPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
PBI	Parental Bonding Instrument
PCC	posterior cingulate cortex
PIT	Prospective Imagery Task
PTSD	posttraumatic stress disorder
rACC	rostral anterior cingulate cortex

ROCF	Rey-Osterrieth Complex Figure Test
RT	reaction time
SCID-I	Structured Clinical Interview for DSM-IV-TR Axis I Disorders
SDFR	short-delay free recall
SN	salience network
STG	superior temporal gyrus
TE	echo time
TEQ	Toronto Empathy Questionnaire
ToM	theory of mind
TR	repetition time
vmPFC	ventromedial prefrontal cortex
WASI	Wechsler Abbreviated Scale of Intelligence
WCST	Wisconsin Card Sorting Test

Declaration of Academic Achievement

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

The study presented in Chapter 2 was conceived by Drs. Margaret McKinnon, Ruth Lanius, and Glenda MacQueen. Anthony Nazarov and Carolina Oremus completed data collection for Chapter 2. Participants with PTSD were recruited through London Health Sciences Centre, and healthy controls were recruited through St. Joseph's Healthcare Hamilton. I was responsible for data analysis and manuscript preparation, and Drs. McKinnon, Lanius, and Frewen provided critical revisions. This paper was submitted to *Brain and Behaviour* in November, 2013 and was published in 2014.

The research presented in Chapters 3 through 5 was supported by the Canadian Institutes for Health Research and the Ontario Mental Health Foundation. Dr. McKinnon was responsible for conception of the main research project and I assisted with the design of the following studies. I completed data collection and testing of all participants assessed for Chapters 3 through 5, under the supervision of Dr. McKinnon.

I conducted analysis and interpretation of the data for Chapter 3 under the guidance of Drs. McKinnon and Lanius. Alex Lee, Zeeshan Haqque, and Latisha Rhooms were involved in scoring, database management, and interpretation of the data. All authors critically read and revised the manuscript. The paper presented in Chapter 3 was submitted for review to *Clinical Psychological Science* in June, 2015.

I conducted analysis and interpretation of the data for Chapter 4 under the guidance of Drs. McKinnon and Lanius. Carolina Oremus and Dr. Paul Frewen were also involved in the design of the main study. All authors critically reviewed the manuscript. The paper presented in Chapter 4 was submitted for review to the *European Journal of Psychotraumatology* in July, 2015.

For Chapter 5, I conducted analysis and interpretation of the behavioural and neuroimaging data, under the supervision of Drs. Lanius and McKinnon, and under the guidance of Maria Densmore. Drs. Frewen and Hall were also involved in study design. The paper in Chapter 5 has been prepared for submission in July, 2015.

Chapter 1: General Introduction

This thesis examines the neural and clinical correlates of cognitive processes in trauma-exposed patients with major depressive disorder (MDD) and in patients with posttraumatic stress disorder (PTSD). These disorders are recognized as chronic, debilitating illnesses, with a lifetime prevalence of 16.6% and 6.8%, respectively (Kessler et al., 2005). Both disorders share overlapping cognitive processing dysfunction in areas such as neuropsychological performance (McDermott & Ebmeier, 2009; Polak, Witteveen, Reitsma, & Olf, 2012; Rock, Roiser, Riedel, & Blackwell, 2014; Vasterling et al., 2002), social cognition (Cusi, Nazarov, Holshausen, Macqueen, & McKinnon, 2012; Cusi, MacQueen, Spreng, & McKinnon, 2011; Cusi, Nazarov, MacQueen, & McKinnon, 2013; Nazarov et al., 2014), and in processes related to autobiographical memory (e.g., episodic simulation of future events) (Bjärehed, Sarkohi, & Andersson, 2010; A. D. Brown et al., 2013; King, MacDougall, Ferris, Herdman, & McKinnon, 2011; Kleim, Graham, Fihosy, Stott, & Ehlers, 2014; Kosnes, Whelan, O'Donovan, & McHugh, 2013; Morina, Deepro, Pusowski, Schmid, & Holmes, 2011). Critically, dysfunction in these domains leads to greater burden of illness (Pandina et al., 2009), poorer response to treatment (McLennan & Mathias, 2010), and decreased functioning (Jaeger, Berns, Uzelac, & Davis-conway, 2006; McCall & Dunn, 2003).

We have taken a transdiagnostic approach by examining mechanisms (e.g., dissociative symptoms, developmental variables, and resting-state connectivity networks) underlying dysfunction in social cognition, episodic simulation, and neuropsychological performance noted across these two psychiatric disorders. The central hypothesis of this

thesis is that less optimal levels of parental bonding, reduced levels of neuropsychological functioning, greater dissociative symptoms, and altered ICNs would be related to impairments in the aforementioned areas of cognitive processing.

The primary focus of this thesis is on patients with a primary diagnosis of recurrent MDD with a co-morbid history of trauma exposure. Thirty-to-forty percent of the risk of depression is due to genetic causes, but the remaining vulnerability is related to environmental risk factors (Sullivan, Neale, Ph, & Kendler, 2000). Trauma exposure represents a major risk factor for the onset of depression, and is indeed highly prevalent. Trauma history has a negative influence on many aspects of depression, such as cognitive functioning (Olf, Polak, Witteveen, & Denys, 2014) and response to treatment (Harkness, Bagby, & Kennedy, 2012; Lewis et al., 2010; Nanni, Uher, & Danese, 2012). Thus, trauma-exposed patients with MDD represent a critical population to study. Patients with a primary diagnosis of PTSD are the focus of the first of four empirical chapters, while the other three empirical chapters study trauma-exposed participants with a primary diagnosis of MDD.

The following overview is divided into four sections to provide a concise summary of the literature relevant to the four experimental studies included in this thesis. The first section provides a summary of social cognition in MDD and PTSD. Although social cognitive deficits are well-documented in patients with mood disorders, literature on social cognition in PTSD is relatively scarce. We aim to address this paucity of research in Chapter 2 with an experimental analysis that compares empathic responding between patients with PTSD and controls.

The second section of this chapter provides a summary of the topic of episodic simulation (i.e., future thinking). Episodic simulation is highly related to autobiographical memory (AM). Importantly, deficits in AM have been reliably reported in both patients with MDD (Williams et al., 2007) and PTSD (Moore & Zoellner, 2007). Episodic simulation has yet to be examined in trauma-exposed patients with MDD, and clinical correlates based on existing studies examining episodic simulation in MDD are not well-established. We aim to address this gap in the literature by studying the relation between episodic simulation, cognitive performance, and parental bonding in a trauma-exposed sample with recurrent MDD. This study is presented in Chapter 3.

The third section summarizes the literature on cognitive alterations in MDD and PTSD in order to provide a context for Chapters 4 and 5. These final two data chapters aim to contribute to our understanding of neuropsychological dysfunction in trauma-exposed patients with MDD, with a particular focus on the relation between cognition and clinical symptoms (i.e., dissociation) and neural processes (i.e., intrinsic network connectivity). The third section, therefore, describes cognitive impairment patterns in patients with MDD and trauma-exposure, followed by the role of dissociative symptoms in this context. The negative impact of dissociation on cognition has been shown in patients with PTSD, among other psychiatric disorders (Cromer, Stevens, DePrince, & Pears, 2006; Dorahy, Middleton, & Irwin, 2005; Haaland & Landrø, 2009; Roca, Hart, Kimbrell, & Freeman, 2006), but has yet to be examined in patients with MDD. The fourth section describes a summary of the findings in the literature related to neural dysfunction in our patient populations, providing context for our final data chapter which focuses on the

relation between resting state networks and cognition in trauma-exposed patients with MDD. The overall goal of this thesis is to provide information behind the transdiagnostic mechanisms (e.g., developmental, clinical, and neural) underlying dysfunctions in cognitive processing in order to understand homogeneity seen across disorders such as MDD and PTSD.

1.1. Social cognition

Social cognition involves understanding and responding to the thoughts and feelings of others and relies upon processes such as theory of mind (ToM), prosody, moral reasoning, and empathy. The neural correlates of social cognition are well-established in healthy controls (Adolphs, 2009; Frith, 2015; Lieberman, 2007) and include regions associated with both higher-order cognitive and affective processing, such as dorsolateral prefrontal cortex (DLPFC), ventromedial prefrontal cortex (vmPFC) anterior cingulate cortex (ACC), the amygdala, and the temporoparietal junction. Social cognition has received substantial attention in the fields of autism and schizophrenia as social cognitive deficits are considered a core feature of both disorders, with both disorders sharing overlapping alterations in regions associated with the neural network of social cognition (Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011). Structural and functional alterations of these same brain regions are also reliably reported in patients with mood disorders (Price & Drevets, 2010) and in patients with PTSD (Pitman et al., 2012). Moreover, fMRI paradigms of social cognitive tasks demonstrate alterations in these regions during task performance. A recent review has demonstrated that neuroimaging paradigms of social cognition reveal enhanced activation of emotion-related brain regions coupled with

reduced activation in structures related to higher-order cognitive processing in patients with mood disorders (Cusi et al., 2012). A recent study reported similar findings in patients with PTSD, where an fMRI eye contact paradigm resulted in reduced activation in the aforementioned brain regions, as compared to controls (Steuwe et al., 2014).

Our lab has conducted work on the behavioural alterations of social cognition in patients with both MDD and PTSD. Cusi et al. (2013) examined ToM performance and empathic responding (Cusi et al., 2011) among patients with a primary diagnosis of MDD and identified impairments in functioning across both domains of social cognition. In their study on ToM in MDD, the authors (Cusi et al., 2013) employed a social scenarios task (McKinnon & Moscovitch, 2007) that allows for assessment of both first-order (i.e., the ability to understand a person's thoughts/feelings) and second-order (i.e., the ability to infer what one person thinks about another person's thoughts) ToM. Compared to controls, patients with depression performed just as well on the first-order ToM portion of the task, but showed impairments on the second-order ToM questions.

Cusi et al.'s (2011) study on empathic functioning in MDD is of particular relevance, given that we examine the same social cognitive domain in patients with PTSD in Chapter 2. Using two well-validated self-report measures of empathic responding: i) the Interpersonal Reactivity Index (IRI; Davis, 1980) and ii) the Toronto Empathy Questionnaire (TEQ; Spreng, McKinnon, Mar, & Levine, 2009), Cusi et al. found that patients with MDD, as compared to controls, reported lower levels of empathic responding on the TEQ, and lower scores on the perspective taking and empathic concern subscales of the IRI. Notably, within this sample, a higher burden of illness was

associated with lower levels of perspective taking. Social cognitive impairments in patients with MDD have, however, been demonstrated even in the first episode of the illness. Ladgaard et al. (2014) found that compared to controls, patients in their first major depressive episode were impaired on tasks of ToM, social perception (including facial affect recognition) and metacognition. Critically, a recent review reported that while social cognitive functioning is inversely related with depressive symptoms, many of the social cognitive deficits reported in patients with depression (e.g., facial affect recognition and ToM) persist into the euthymic state (Weightman, Air, & Baune, 2014).

Additional work from our lab has identified alterations in social cognitive domains among patients with PTSD in the areas of ToM (Nazarov et al., 2014) and prosody (Nazarov et al., 2015). In addition to the empirical article presented in Chapter 2, two other studies have been published that have examined empathic responding in patients with PTSD. The first of the two studies examined empathy using behavioural measures (Nietlisbach, Maercker, Rössler, & Haker, 2010) and the second examined the neural correlates of cognitive and affective empathy (Mazza et al., 2015). Both studies identified alterations in empathic responding in patients with PTSD, particularly in emotional empathy. While there is emerging evidence that empathic responding is altered in patients with PTSD, the developmental mechanisms underlying this social cognitive domain remain poorly understood. No studies have examined the role of parental bonding in empathic responding in patients with PTSD. The study of attachment in traumatized populations is particularly relevant given that traumatic stress disrupts attachment systems (Wang, 1997) and critically, secure attachment is protective against trauma-

induced sequelae (Schoore, 2002). Attachment has been shown to be related to the development of cognition (De Ruiter & Van Ijzendoorn, 1993; West, Mathews, & Kerns, 2013), and more specifically, social cognition and interpersonal behaviours (Rom & Mikulincer, 2003; Vrtička & Vuilleumier, 2012) and represents a transdiagnostic feature of both MDD and PTSD, as studies repeatedly demonstrate a link between attachment disruptions and depression (Agid et al., 1999; Galynker et al., 2012; Levitan et al., 2009; Oakley-Browne, 1995). In Chapter 2, we therefore aimed to explore i) alterations in empathy in PTSD and ii) the association between empathy and attachment in this population.

1.2. Episodic simulation

Since Williams and Broadbent's seminal work on AM retrieval in suicide attempters (Williams & Broadbent, 1986) nearly three decades ago, a substantial body of work has aimed to examine AM retrieval in patients with MDD. These studies reliably demonstrate overgeneral AM recall among this population, where participants tend to recall primarily repeated or factual information, rather than details specific in time and place and reflecting vivid re-experiencing (for a review, see Williams et al., 2007). This deficit has important clinical implications given the proposed functions of AM, in particular its social functions and its role in establishing a sense of self (Bluck, 2003). Critically, overgeneral AM has been linked to worse prognosis in patients with MDD (Brittlebank, Scott, Williams, & Ferrier, 1993; Hermans et al., 2008). Overgeneral AM has also been reported in patients with PTSD (Moore & Zoellner, 2007). In fact, evidence suggests that among patients with MDD, a history of trauma is related to increased risk for overgeneral

AM and reduced specificity of AM retrieval (de Decker, Hermans, Raes, & Eelen, 2003; Hermans et al., 2004; Kuyken, Howell, & Dalgleish, 2006).

It is important to understand the themes noted in the literature on AM retrieval in patients with MDD, PTSD, and trauma-exposure, since one's ability to imagine future events relies on many of the same neural and cognitive processes as AM retrieval (Schacter, Addis, & Buckner, 2008). Episodic simulation describes the process of imagining the future. In order to imagine future events, we draw on our episodic memory system, that is, memories specific in time and place, and recombine or elaborate upon these memories in order to simulate or imagine a future event. Tulving's idea of "mental time travel" (e.g., Tulving, 2002) provides support for the idea of episodic simulation. He states that to remember the past and imagine the future, we must be able to detach from the present surroundings and draw on our episodic memory system and project ourselves into the past or the future. Much like AM retrieval, episodic simulation has important clinical implications. Engaging in episodic simulation is associated with emotion regulation and problem-solving behaviours (Brown, MacLeod, Tata, & Goddard, 2002; Taylor, Pham, Rivkin, & Armor, 1998; Taylor & Schneider, 1989). Participants who engaged in episodic simulation of ongoing real-life stressful events subsequently increased their coping behaviours, such as seeking social support, whereas participants who did not engage in episodic simulation did not (Taylor et al., 1998).

Given the shared neural and cognitive processes underlying AM retrieval and episodic simulation, it should not come as a surprise that in addition to their impairments in AM retrieval, patients with MDD and PTSD show dysfunction in episodic simulation. Studies

examining episodic simulation in patients with MDD are more common than those studying patients with PTSD. Briefly, patients with MDD tend to show impairments specifically in the generation of future positive events (Bjärehed et al., 2010; Kosnes et al., 2013; Morina et al., 2011). To date, only two studies have examined episodic simulation in patients with PTSD (Brown et al., 2013; Kleim et al., 2014). Here, the impact of emotional valence has been less clear, but the pattern of findings remains the same as patients with PTSD also show deficits in episodic simulation.

Cognitive performance variables (e.g., executive functioning, verbal fluency, working memory, verbal memory) (Dalgleish et al., 2007; Raes et al., 2005; Spinhoven et al., 2006) and attachment, specifically, maternal relationships (Fivush, Haden, & Reese, 2006; Harley & Reese, 1999; Nelson & Fivush, 2004) are associated with the retrieval and development of AM. The impact of these variables on episodic simulation is less clear, especially in clinical populations. This represents a critical gap in the literature given the link between AM retrieval and episodic simulation, and the well-established impairments of episodic simulation in patients with MDD and PTSD. Chapter 3 aims to address this gap by examining cognitive performance and parental bonding in relation to episodic simulation in a trauma-exposed sample with a primary diagnosis of *recurrent* MDD. Importantly, a meta-analysis examining predictors of hippocampal volume in patients with MDD found that changes in hippocampal volume were evident only in patients with multiple episodes of illness (McKinnon, Yucel, Nazarov, & MacQueen, 2009). Given the critical role of the hippocampus in both remembering the past and imagining the future (Addis, Pan, Vu, Laiser, & Schacter, 2009; Szpunar, Watson, &

McDermott, 2007) we chose to recruit patients with greater than three episodes of depression (i.e., recurrent depression), as they would likely show the greatest deficits in episodic simulation.

There are various assessments of episodic simulation, many of which have been used to study this process in clinical populations. Many of the studies that examine future thinking rely on tasks that assess the ability to generate mental imagery of future events. The Prospective Imagery Task (PIT; Stober, 2000) is a commonly used mental imagery task. In this task, participants are asked to form mental images in response to a set of scenarios and to rate these images in terms of vividness. This measure has been used in participants with low versus high dysphoria (Holmes, Lang, Moulds, & Steele, 2008) and also in patients with MDD and anxiety disorders (Morina et al., 2011). Another commonly used measure of future thinking is the Future Thinking Task (FTT; MacLeod, Rose, & Williams, 1993). FTT administration involves asking participants to name as many events as possible that they believe will happen during a specific time period in the future, within a specific time limit (e.g., 1 minute). This task has been implemented in a sample with MDD where patients were asked to imagine both positive and negative future events (Bjärehed et al., 2010). The majority of the research examining AM has used the Autobiographical Memory Test (AMT; Robinson, 1976; Williams & Broadbent, 1986). A future-thinking task has been derived from the AMT, the Autobiographical Memory Test Future (AMT-f) (for example, see Kleim et al., 2014). During this task, participants are shown a series of cue words and asked to generate and describe a specific personal future event related to each cue word and were given one minute per cue word.

Responses on this task are scored as specific if they reflect a personal event that would happen on one particular day. Another commonly used method of AM assessment is the Autobiographical Interview (AI; Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002). Our lab has reliably shown group differences in episodic simulation in patients with depression (King, MacDougall, et al., 2011) and bipolar disorder (King, Williams, et al., 2011) using a version of the AI adapted for episodic simulation, the Future-Oriented Autobiographical Memory. Here, participants are asked to imagine a day in the future and describe a personal event that could happen on that day in relation to nine cue words, three positive, three negative, and three neutral (i.e., *achievement, pleasure, friendly; afraid, broken, lie; hat, tree, quiet*) (see Chapter 3 for a full description of this task). The participant's response to each cue word is segmented into details, or information bits. Each detail is scored as episodic if it pertains specifically to their generated future event, or non-episodic if it is a semantic detail, a repeated detail, or unrelated to their future event. Notably, on the AMT-f, an event may be scored as specific but the scoring procedure does not allow for the quantification of the amount of non-episodic or non-specific details, which may reduce the ability of the task to capture overgeneralized episodic simulation (as reflected by greater number of non-episodic details). As mentioned, the Future-Oriented Autobiographical Interview has been used to dissociate episodic and non-episodic future-thinking performance in patients with mood disorders, but this measure had not yet been used to examine episodic simulation in trauma-exposed participants with MDD. Therefore, in Chapter 3, we used the Future-Oriented Autobiographical Interview to examine episodic simulation in this sample in relation to

key clinical, cognitive, and attachment-related variables.

1.3. Neuropsychological functioning in MDD and PTSD

In addition to its core affective components, MDD is characterized by deficits in neuropsychological functioning. Difficulties with concentration and decision making are a diagnostic criterion of a major depressive episode, as noted in the Diagnostic and Statistical Manual of Mental Disorders, Fourth and Fifth Editions (American Psychiatric Association, 2013; First, Spitzer, Gibbon, & Williams, 1997). This symptom likely impacts specific domains of cognition, such as attention, memory, executive functioning, and processing speed. In a study of over 200 patients with MDD, 71% reported cognitive functioning to be one of the most troubling symptoms of the disorder (Pandina et al., 2009). Cognitive impairments also impact negatively on functioning. Specifically, neurocognitive domains such as nonverbal functions, learning, and motor functions were predictive of disability in life functioning, as assessed by the Multidimensional Scale of Independent Functioning at a 6-month follow-up among patients with depression (Jaeger et al., 2006). Global cognition, as assessed by the Mini Mental State Exam, was also associated with instrumental activities of daily living in MDD (McCall & Dunn, 2003). Cognitive performance has also been shown to predict response to anti-depressant treatment, where verbal fluency and mental flexibility performance discriminated responders versus non-responder to antidepressant treatment (McLennan & Mathias, 2010). Cognitive dysfunction in depression is therefore not only a core feature of the disorder, but one that both subjectively and objectively impacts negatively on functioning. These findings emphasize the need for continuing to investigate treatment

efforts aimed at addressing cognitive dysfunction that will lead to improved functional outcome and a reduced illness burden.

A total of six review papers have been published focusing on neuropsychological functioning in patients with MDD (Hasselbalch, Knorr, & Kessing, 2011; Lee, Hermens, Porter, & Redoblado-hodge, 2012; McDermott & Ebmeier, 2009; McLennan & Mathias, 2010; Rock et al., 2014; Wagner, Doering, Lieb, & Tadic, 2012). The overall pattern of cognitive dysfunction noted in patients with MDD is characterized by alterations in frontal-temporally mediated domains of cognition, such as memory, attention, and executive functioning. Specifically, moderate cognitive deficits in these three domains were reported in Rock et al.'s meta-analysis (Rock et al., 2014). Further, pronounced deficits in domains of executive functioning (i.e., inhibition capacity and cognitive flexibility) were noted by Wagner et al. (2012). Importantly, even during a first episode of depression, small-to-medium effect size for cognitive deficits have been identified in the domains of psychomotor speed, attention, executive functioning, and visual learning and memory (Lee et al., 2012). While depression severity has been shown to be related to cognitive performance in areas of executive functioning, episodic memory, and processing speed (McDermott & Ebmeier, 2009), it is important to note that many of the cognitive alterations persist into euthymia (Hasselbalch et al., 2011; Rock et al., 2014) (but see Wagner et al., 2012 for conflicting results).

Notably, this frontal-temporal pattern of cognitive deficits reliably reported in patients with MDD is strikingly similar to the pattern of deficits in patients with PTSD (Cohen et al., 2013; Polak et al., 2012; Vasterling et al., 2002; Yehuda, Golier, Halligan, & Harvey,

2004). Many studies have examined neuropsychological functioning in patients with PTSD and patients with MDD, separately. Those which have examined co-morbid patient groups have found overall poorer neuropsychological performance in patients with depression and trauma (Burri, Maercker, Krammer, & Simmen-janevska, 2013; Olff et al., 2014). Given the highly overlapping patterns of neuropsychological dysfunction among these two patients groups and the findings suggesting a worsening of neuropsychological performance in co-morbid samples, it is critical to examine potential mechanisms, both clinical and neurobiological, that may underlie this pattern of impairment. Dissociative symptoms represent a clinical variable that has received increasing attention in patients with PTSD, and they have also been reported in patients with MDD (Žikić, Ćirić, & Mitković, 2009), especially those with a history of trauma (Molina-Serrano, Linotte, Amat, Souery, & Barreto, 2008). Importantly, dissociation is associated with worse neuropsychological functioning (Cromer et al., 2006; DePrince, Weinzierl, & Combs, 2008; Dorahy et al., 2005; Haaland & Landrø, 2009; a. Krause-Utz et al., 2012; Roca et al., 2006) but this relation has not yet been examined in patients with depression.

In Chapter 4, we take a transdiagnostic approach to examine the relation between both dissociative and depressive symptoms and neuropsychological functioning in trauma-exposed patients with a primary diagnosis of recurrent MDD. To our knowledge, this study is the first to examine dissociation as an underlying mechanism of neuropsychological dysfunction in patients with MDD.

1.4. Neural patterns associated with MDD and PTSD

Nearly two decades ago, Mayberg proposed a neural model of depression involving limbic-cortical dysregulation, where hypofunctioning of dorsal cortical regions is coupled with decreased inhibition of paralimbic regions (Mayberg, 1997). More recent structural and functional neuroimaging studies have provided evidence for this model. For example, a meta-analysis by Hamilton et al. (2012) showed that this pattern is noted particularly in response to negative stimuli, where analyses indicate that patients with MDD have heightened activation in the amygdala, dorsal ACC (dACC), and insula, yet reduced activation in the dlPFC, as compared to controls. Neuroimaging studies of patients with PTSD have also identified neural models of the disorder. PTSD is often viewed as a disorder of emotion dysregulation (Frewen & Lanius, 2006) and the neural activation patterns reflect this view. Emotion regulation in healthy populations recruits the dlPFC, the vmPFC, ACC and the orbitofrontal cortex, with subsequent deactivation of the amygdala (Ochsner, Bunge, Gross, & Gabrieli, 2002; Phan et al., 2005; Schaefer et al., 2003). Patients with the dissociative subtype of PTSD (American Psychiatric Association, 2013) show heightened activation in brain regions associated with emotion regulation, including the rostral ACC (rACC), dACC, and medial PFC, compared to control subjects (Lanius et al., 2002, 2005), reflecting emotion overmodulation. Participants of the reexperiencing/hyperarousal subtype show the opposite pattern, including reduced blood-oxygen-level-dependent (BOLD) signal in the medial prefrontal cortex (mPFC) and the ACC, relative to healthy control subjects (Lanius et al., 2002). The functional neuroimaging literature in patients with MDD and PTSD therefore suggests that these

disorders are characterized by alterations in the coupling between cognitive control regions with affective processing regions.

Despite the advancements in our knowledge of the brain regions affected in patients with MDD and trauma-related disorders, it is becoming increasingly accepted that focusing only on specific brain regions in isolation will not allow us to fully capture the complexity behind the neural underpinnings of these disorders and their clinical and cognitive profiles. Functional connectivity analyses have become increasingly utilized as a method of studying functional networks, that is, sets of consistently synchronous brain regions. Two predominant methods are used to study functional connectivity between brain regions: i) seed-based and ii) independent component analyses (ICA) (Joel, Caffo, Van Zijl, & Pekar, 2011). ICA is a data-driven alternative to seed-based analysis and it takes into account the relationship among all voxels (Calhoun, Kiehl, & Pearlson, 2008; Calhoun, Liu, & Adali, 2009). Seed-based analysis provides a single measure of connectivity for a pair of regions, whereas ICA can provide three measures of connectivity: i) total connectivity, ii) connectivity between networks, and iii) connectivity within networks (Joel et al., 2011). Intrinsic functional connectivity (IFC) represents task-independent connectivity (Fox, Snyder, Zacks, & Raichle, 2006), and is captured by functional connectivity measured during task-free resting state scans. Critically, altered IFCs are related to psychopathology (Menon, 2011). Menon's (2011) triple neural network model focuses on the default mode (DMN), salience (SN), and central executive networks (CEN) and their relation to psychopathology. The DMN is involved in self-related processes and shows reduced activation during cognitively demanding tasks (Fox,

Corbetta, Snyder, Vincent, & Raichle, 2006; Greicius, Krasnow, Reiss, & Menon, 2003). The SN plays a role in salience detection and is responsible for switching between the DMN and the CEN (Menon, 2011; Sridharan, Levitin, & Menon, 2008). Finally, the CEN is engaged during cognitively-demanding tasks and is involved in executive functioning (Fox, Corbetta, et al., 2006; Habas et al., 2009; Koechlin & Summerfield, 2007; Miller & Cohen, 2001; Seeley et al., 2007).

To date, no studies have examined the association between these three networks and clinical symptom presentation and neuropsychological dysfunction in trauma-exposed patients with a primary diagnosis of MDD. Trauma-related disorders and MDD both show alterations in ICNs, which are described at length in Chapter 5. Briefly, patients with MDD tend to show increased integration within the DMN (for a review, see Dutta, Mckie, & Deakin, 2014), whereas the opposite pattern is noted in patients with PTSD (for a review, see Patel, Spreng, Shin, & Girard, 2012). Further, increased integration of the SN with the DMN has been observed in patients with MDD (Greicius et al., 2003; Jacobs et al., 2014). Patients with PTSD also show increased connectivity between the DMN and SN (Sripada et al., 2012) in addition to increased integration within the SN (Patel et al., 2012). Both populations demonstrated reduced connectivity within the CEN (Diener et al., 2012; Patel et al., 2012). Critically, even without subsequent development of PTSD, trauma exposure has also been shown to lead to ICN alterations (Kennis, Rademaker, Rooij, Kahn, & Geuze, 2009; Wang et al., 2014).

The relation between ICN and cognitive functioning has begun to be assessed in other clinical populations, such as Parkinson's disease (Disbrow et al., 2014; Tessitore et al.,

2012), internet gambling disorder (Dong, Lin, & Potenza, 2015), and healthy controls (Seeley et al., 2007; Yakushev et al., 2013). A critical finding among all of these studies is that ICNs, as assessed during resting-state scans, do in fact relate to cognitive performance variables measured outside of the scanner. These studies are fundamental to our understanding of how alterations in brain networks relate to cognitive functioning, a variable which is so critical to functional outcome (Jaeger et al., 2006; McCall & Dunn, 2003; McLennan & Mathias, 2010) and illness burden (Pandina et al., 2009). No studies have examined the relation between ICN and symptom severity and cognitive performance in trauma-exposed patients with MDD. We aim to address this gap in the literature with the findings presented in Chapter 5. Here, we have used ICA to study this association. We have chosen to use ICA instead of seed-based analysis since the latter provides functional connectivity information of a given brain region, rather than information about the interactions within intrinsically connected networks, which is a benefit of using ICA.

The overlapping methodology in the following chapters, specifically regarding the participant samples, should be noted. We used the same participant groups (i.e., i) MDD and ii) controls) for Chapters 3 – 5. In Chapter 3, we assessed 21 patients and 20 controls. In Chapter 4, we assessed 23 patients and 20 controls, and in Chapter 5, we assessed 21 patients and 20 controls. The reason for the discrepant sample size between Chapters 3 – 5 is that some participants we tested were unable to complete the fMRI scan ($n = 2$), or they were unable to complete portions of the assessments due to time constraints (i.e., the future-thinking task) ($n = 2$). Therefore, the neuropsychological, clinical, and additional

behavioural data presented in Chapters 3 – 5 are overlapping. The participant sample in Chapter 2 does not overlap with the remaining chapters (i.e., patient group was recruited based on a primary diagnosis, and the control group was tested prior to participant recruitment for Chapters 3 – 5).

Taken together, the results of this thesis provide evidence of the transdiagnostic developmental, cognitive, clinical, and neural variables underlying alterations in cognitive processes in patients with depression and a history of trauma. The novel findings contribute to the growing body of literature aiming to explore mechanisms underlying symptom presentation and cognitive dysfunction in this population. Based on our findings, factors such as dissociative symptomatology and attachment history are critical in our understanding of this population and should be taken into account in the context of treatment planning, especially when considering treatments that are reliant on cognitive functioning. One of the most important conclusions that should be drawn from the following thesis is that there is an urgent need to further investigate the impact of trauma exposure in patients with depression, a variable that so often goes unaddressed.

Chapter 2: Alterations in empathic responding among women with post-traumatic stress disorder associated with childhood trauma

Chapter Link

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Studies have documented social cognitive deficits in persons with MDD and PTSD. Alterations in the domain of empathy in patients with PTSD, however, remain relatively unexplored and developmental variables relating to this domain have yet to be established. Therefore, the following study examined empathy in women with PTSD in relation to parental bonding. This study was done as part of a larger project in collaboration with Dr. Ruth Lanius to address social cognition in patients with PTSD.

Alterations in empathic responding among women with
post-traumatic stress disorder associated with childhood trauma

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ABSTRACT

Objective: Although studies increasingly point towards problems with social cognition among individuals with PTSD, few studies have assessed empathic responding. The aim of the current study was to investigate empathic responding in women with PTSD related to childhood trauma, and the contribution of parental bonding to empathic abilities in this sample.

Method: Participants with PTSD ($n = 29$) and sex- and age-matched healthy controls ($n = 20$) completed two self-report empathy measures, the Interpersonal Reactivity Index (IRI) and the Toronto Empathy Questionnaire (TEQ), and a self-report measure of attachment, the Parental Bonding Instrument (PBI).

Results: Women with PTSD, relative to controls, reported significantly lower levels of empathic concern ($r = .29$) and perspective taking ($r = .30$), yet significantly higher levels of personal distress ($r = .45$) on the IRI. Women with PTSD also reported elevated scores on the TEQ ($\eta^2 = 0.13$). Levels of paternal care on the PBI, rather than childhood trauma severity or PTSD symptom severity best predicted perspective taking scores on the IRI in the PTSD sample ($R^2 = 0.20$).

Conclusion: Women with PTSD associated with childhood trauma reported alterations among different domains of empathic functioning that may be related to low levels of paternal care.

Keywords: empathy; stress disorders, post-traumatic; adult survivors of child abuse

Significant Outcomes

- Depending on the specific domain of empathic function being assessed, women

with PTSD related to childhood trauma report either higher or lower levels of empathic functioning as compared to controls, suggesting that empathic abilities may not be globally disrupted in PTSD.

- Decreases in levels of perspective taking were predicted by decreases in levels of self-reported parental care during childhood.
- Severity of childhood trauma and current PTSD symptom severity were not predictive of empathic abilities.

Limitations

- Sample consisted entirely of female patients with PTSD associated with childhood trauma, limiting the generalizability of results to males.
- Empathy and parental bonding assessments were self-report measures which may have introduced a degree of bias. Future studies should include behavioural/non-self-report measures of empathy.

Introduction

Empathy is an essential part of social behavior. It allows us to understand others by inferring and sharing their feeling states in reference to ourselves (1) and is considered imperative to many forms of adaptive social interaction (2). Despite well-established evidence of impaired interpersonal functioning among individuals with post-traumatic stress disorder (PTSD) (3), to date little work has examined deficits in social cognitive functioning, including empathy, in this population (4-6). Here, we investigate empathic responding in a sample of women with PTSD following repeated childhood trauma (including neglect, physical and/or emotional and/or sexual abuse).

Predominant theoretical models of empathy propose that it is multidimensional and integrative in nature, consisting of both cognitive (i.e., inferring the thoughts and intentions of others using intellectual processes, often referred to as mentalizing) and emotional (i.e., feeling the affect and pain of others) components (7, 8). The neural network associated with empathic functioning supports this multidimensional model and includes cognitive (e.g., dorsolateral prefrontal cortex), memory (e.g., hippocampus; temporal poles; anterior and posterior cingulate) and affective systems (e.g., amygdala; orbitofrontal and medial frontal) (9-12). Individuals may show alterations in these neural networks following exposure to trauma, subsequently affecting the cognitive, memory, and affective processes requisite to empathic responding (13-20).

PTSD exerts negative effects on interpersonal functioning (3); these deficits may relate, in part, to the disruption of empathic responding, which is considered crucial to competent social interactions. For example, emotional numbing, a key symptom of

PTSD, is associated with the disruption of interpersonal functioning when assessed via self-report measures (21) and may also disrupt one's ability to empathize with others. Moreover, there are additional consequences of repeated childhood trauma that may enhance risk for alterations in empathic functioning. For example, childhood trauma is often associated with disorganized or insecure attachment, which is suspected to hinder the development of mentalizing (i.e., the process of making sense of one's own and other's mental states) (22) and the cerebral structures that support its development (23, 24). Secure attachment, on the other hand, is thought to foster the development of mentalizing (25). This is of importance as mentalizing is thought to comprise the cognitive component of empathy (26). Moreover, in one recent study children with recent histories of physical abuse, perpetrated by one or both parents, performed worse on a cognitive perspective-taking task (27) compared to children without histories of abuse (28). Further, a strong negative association exists between maternal care and alexithymia, suggesting that dysfunctional parent-infant relationships contribute to reduced awareness of one's own feelings. This is an important finding given that higher rates of alexithymia are associated with deficits in empathy (29) and that alexithymia contributes to dysfunction in interpersonal relationships (30).

To our knowledge, only one study has systematically examined the relation between empathic responding in adults with PTSD (4). Nietlisbach et al., 2010, found that, compared to healthy controls, participants with a history of PTSD reported significantly higher levels of personal distress as assessed by the Interpersonal Reactivity Index (IRI) (7, 31), a commonly used self-report measure of empathic responding. Nonetheless, this

was a highly-mixed sample, more than half of whom were sub-syndromal at the time of testing, and the types of traumatic events experienced were heterogeneous (i.e., 81% experienced a sexual assault whereas 19 % experienced an accidental trauma or natural disaster). Given that the psychiatric sequelae and physiological response associated with repeated developmental trauma and single-incident trauma are thought to differ (4, 32, 33), for the present study we only included individuals who met full diagnostic criteria for PTSD related to childhood trauma at the time of testing.

Empathic responding has also been studied in patients with a diagnosis of borderline personality disorder (BPD). These findings may be of particular relevance here as there is a high rate of co-occurrence of PTSD and BPD with significant overlap in both phenomenological aspects (e.g., affect dysregulation, dissociation) and the shared rates of exposure to adverse events (34). In one study, the IRI was used to assess empathic functioning in a sample of women with BPD; women with BPD exhibited higher levels of personal distress and higher levels of empathic concern, as compared to healthy controls (35).

Aims of the Study

We investigated empathic abilities in 29 women with PTSD associated with childhood trauma, as compared to 20 healthy women. In addition, due to role of parental bonding in social functioning and its disruption in individuals exposed to childhood trauma (36), we examined the predictive role that parental bonding may play in empathic abilities. Given the alterations in cognitive and affective processes seen in PTSD related to childhood

trauma, we hypothesized that our patient sample would show alterations in the cognitive and affective components of empathic responding, as compared to controls.

Materials and Methods

Subjects

Forty-nine women participated in this study. There were two groups of participants: 29 women who met DSM-IV diagnostic criteria for a primary diagnosis of current chronic PTSD due to a history of childhood trauma (PTSD group; mean age 42.5 [SD = 12.2] years), and 20 age- and sex-matched healthy controls (HC group; mean age 35.8 [SD = 13.2] years). Women with PTSD were recruited from London Health Sciences Centre (LHSC) in London, Ontario. Age-matched psychologically healthy women were recruited from St. Joseph's Healthcare Hamilton, in Hamilton, Ontario and LHSC.

Participants with a history of neurological disease, traumatic brain injury and/or head injury with loss of consciousness (lasting more than 60 s), substance abuse in the last six months, current or lifetime history of substance dependence, and/or current or prior history of untreated significant medical illness were excluded. In addition, women with PTSD were excluded if they had ever been diagnosed with bipolar disorder or a psychotic disorder and women in the psychologically healthy group were excluded if they had ever received psychotherapy. All participants provided written informed consent. The study was approved by the local Research Ethics Boards and was performed in accordance with the ethical standards laid down by the 1964 Declaration of Helsinki.

Clinical Assessments

PTSD diagnostic status and symptom severity was assessed using the Clinician-Administered PTSD Scale (CAPS) (37) and history of moderate-to-severe childhood trauma was confirmed for PTSD subjects by retrospective self-report using the Childhood Trauma Questionnaire (CTQ) (38). Depressive symptom severity was measured with the Beck Depression Inventory (BDI) (39). The CAPS and CTQ were also administered to the group of psychologically-healthy women to rule out the presence of any PTSD-related symptoms and lifetime trauma history. In addition, the Structured Clinical Interview for DSM IV-TR AXIS I Disorders (SCID-I) (40) was administered to identify co-morbid Axis I conditions in the sample with PTSD and to rule out the presence of any current or past Axis I conditions in the control group. Demographic and clinical characteristics of the study sample are reported in Table 1.

Table 1. Demographic and clinical characteristics of the study sample

	PTSD n = 29	Controls n = 20
Demographics		
Age, years, mean (SD)	42.5 (12.2)	35.8 (13.2)
Years of education, mean (SD)	13.71 (2.4)	16.20 (2.6)*
Caucasian	93%	65%
Married/Common-law/Engaged	28%	45%
Separated/Divorced	28%	20%
Single	34%	30%
Have children	45%	40%
Severity of PTSD Symptoms		
CAPS, mean (SD), range	79.9 (15.5), 55-118	0.5 (1.6), 0-7*
Parental Bonding Instrument		
Mean (SD)		
Paternal Care	11.22 (8.09)	30.93 (5.37)*
Paternal Overprotection	17.19 (9.13)	10.53 (6.46)*
Maternal Care	14.56 (8.82)	30.00 (6.92)*
Maternal Overprotection	16.63 (9.38)	9.93 (5.82)*
Childhood Trauma Questionnaire		
Mean (SD) ^a , %ile equivalent of mean ^b		
Total	76.55 (20.46)	29.68 (4.23)*
Emotional Abuse	18.9 (4.8), 90-95 th	6.2 (1.6)*, 40 th
Physical Abuse	12.6 (5.7), 90-95 th	5.5 (1.1)*, 50 th
Sexual Abuse	15.5 (7.3), 90-95 th	5.0 (0.0)*, 70 th
Emotional Neglect	18.0 (4.6), 90 th	7.0 (1.9)*, 30 th
Physical Neglect	11.7 (5.4), 95 th	6.0 (1.5)*, 70 th
	<u>Past</u>	<u>Current</u>
Comorbid Axis I Conditions in the PTSD Sample		
Alcohol Dependence	1	0
Substance Abuse	1	0
Major Depressive Disorder	16	11
Panic Disorder w/ wo Agoraphobia	8	3
Agoraphobia	4	5
Social Phobia	1	4
Specific Phobia	1	3
Obsessive Compulsive Disorder	0	2
Somatization Disorder	3	8
Dissociative Identity Disorder	1	4
Anorexia Nervosa	4	2
Bulimia Nervosa	2	1

Abbreviations: CAPS, Clinician-Administered PTSD Scale; SD, standard deviation.

Note: ^aMinimum score for each CTQ scale is 5, ^bPercentiles relative to the normative population of female health management organization members (N = 1187) described in Bernstein & Fink (1998, Table 4.5).

*Significant group effect ($P < 0.05$).

Assessments of empathic responding

The Interpersonal Reactivity Index (IRI) (7, 31) is a 28-item, self-report questionnaire based on the multidimensional models of empathy consisting of four, 7-item subscales, designed to tap different cognitive and emotional components of empathy. Specifically, the perspective taking and fantasy subscales measure the cognitive aspects of empathy whereas the empathic concern and personal distress subscales measure the emotional aspects of empathy. The perspective taking subscale assesses the ability to take on the psychological point of view of others, allowing one to anticipate the behavior and reactions of others (e.g., *I sometimes find it difficult to see things from the “other guy’s” point of view*). This subscale is associated with emotional sensitivity (41). The fantasy subscale assesses the tendency to imagine oneself experiencing the feelings and behaviors of fictitious characters in books, movies, and plays (e.g., *after seeing a play or movie, I have felt as though I were one of the characters*) and may be related to imagination (42), general verbal skills, and the ability to engage others in social interaction (41). The empathic concern subscale measures the tendency to experience feelings of sympathy and concern for unfortunate others (e.g., *I often have tender, concerned feelings for people less fortunate than me*). This subscale is also reflective of an ability to receive and understand verbal communication (41) and individuals scoring high in empathic concern tend to have good general knowledge regarding the norms of appropriate social behaviour

(43, 44). Finally, the personal distress subscale assesses personal anxiety and discomfort experienced in emotional social settings (e.g., *being in a tense emotional situation scares me*). This subscale is thought to measure self-control (42) and is positively related to neuroticism (45) and social sensitivity, and negatively related to emotional and social control (41). Items are rated on a scale ranging from 0 (does not describe me well) to 4 (describes me very well). The IRI has good test–retest reliability, good internal consistency (with indices ranging from 0.70 to 0.78), and adequate levels of convergence with other measures of empathy (7, 31, 37, 46).

The Toronto Empathy Questionnaire (TEQ) (47) is a 16-item self-report questionnaire that measures a broad range of empathic responses, emphasizing the emotional components of empathy. The items used in the TEQ appear to tap similar constructs as those represented by the empathic concern subscale of the IRI. Items are rated on a scale ranging from 0 (never) to 4 (always). A high score on the TEQ represents high self-reported levels of affective insight into the feeling states of others (47). The TEQ has shown good internal consistency (Chronback’s $\alpha = 0.85$), high test–retest reliability, and strong convergent validity (47).

Assessment of parental bonding during childhood

The Parental Bonding Instrument (PBI) (48) is a 25-item self-report questionnaire designed to assess parental bonding through two perceived parenting styles of the mother and father during the first 16 years of life: (1) care (e.g., *my mother/father was affectionate to me*) and (2) overprotection (e.g., *my mother/father tried to control everything I did*). High care and low overprotection are considered optimal, whereas low

care and high overprotection are considered least optimal. Each item is scored on a 4-point scale ranging from 1 (very like) to 4 (very unlike) and assessed separately for mother and father. Scores on the PBI demonstrate good concordance with sibling ratings (49) and do not merely reflect current depressed mood state (50). The PBI shows high test-retest reliability over months, and moderate consistency over extended periods of up to 10 years (49).

Statistical analyses

Due to non-normality of the IRI subscales (Shapiro-Wilk, $P < 0.05$), these scores were log transformed in order to perform a parametric analysis. The log transformation, however, did not result in a normal distribution of scores among all of the IRI subscales (Shapiro-Wilk, $P < 0.05$). Therefore, the group differences on these subscales were analyzed using the nonparametric Mann-Whitney U -test (using the non-log transformed scores). In order to examine group differences on the normally-distributed TEQ scores (Shapiro-Wilk, $P > 0.05$), these data were analyzed using a univariate analysis of variance (ANOVA), treating PTSD and control groups as fixed variables and the TEQ total score as the dependent variable. Estimated effect sizes were estimated by r for the Mann-Whitney U -test and by partial eta-square (η^2) for the ANOVA.

Follow-up multiple linear regression analyses using stepwise entry were conducted within the group with PTSD only, setting the empathy scores that differed significantly from controls as the dependent variable and including the following predictor variables: CTQ total scores, CAPS total scores (from previous month), PBI paternal care scores, PBI paternal overprotection scores, PBI maternal care scores, PBI maternal

overprotection scores, and years of education. Given the high prevalence of co-morbid MDD among our sample with PTSD (i.e., 11/29 current MDD; 16/29 past MDD), supplementary correlation analyses were conducted to determine if there is an association between scores on the BDI and empathy measures. Pearson's r or Spearman Rho (ρ) values were reported, depending on results from the Shapiro-Wilk test of normality. Alpha was set at 0.05 for all analyses.

Results

Group comparisons for responses on the empathy measures

Table 2 reports the means, standard deviations, and group comparisons for IRI and TEQ scores. Women with PTSD reported lower levels of perspective taking ($U = 187, z = -2.10, P = 0.035, r = 0.30$) and empathic concern ($U = 192, z = -2.00, P = 0.045, r = 0.29$), and higher levels of personal distress ($U = 137, z = -3.12, P = 0.002, r = 0.45$) on the IRI relative to controls. There were no significant group differences between mean scores on the fantasy subscale.

Relative to controls, the PTSD group also reported higher levels of empathic responding as assessed by the TEQ ($F(1,47) = 7.13, \eta^2 = 0.13$).

Table 2. Between group differences on empathy measures

	PTSD	Controls	Test Statistic	Effect Size
Interpersonal Reactivity Index				
Perspective Taking	16.8 (5.2)	20.3 (4.9)	*U = 187	0.30 ^r
Personal Distress	15.2 (5.8)	9.8 (4.5)	**U = 137	0.45 ^r
Fantasy	13.9 (5.3)	13.9 (5.6)	U = 282	0.02 ^r
Empathic Concern	20.3 (5.0)	23.1 (3.9)	*U = 192	0.29 ^r
Toronto Empathy Questionnaire	66.5 (13.1)	57.5 (8.8)	**F(1, 47) = 7.13	0.13 ^{η²}

Values are *n* or mean (standard deviation).

Values denoted by *r* indicate a Mann-Whitney *U* effect size estimate;

Values denoted by η^2 indicate an ANOVA effect size (partial eta-squared).

* $p < 0.05$, ** $p < 0.01$.

Parental bonding, current PTSD symptom severity, childhood trauma severity, and years of education as predictors of empathic responding

PBI paternal care was the best predictor of IRI perspective taking, accounting for 20% of the variance [$R^2 = 0.197$; adjusted $R^2 = 0.164$, $F(7, 25) = 5.893$, $P = 0.023$]. Only PBI Care significantly predicted perspective taking [$t(25) = 2.43$, $b = 0.293$; $P = 0.023$].

None of the independent variables entered into the regression models significantly predicted IRI personal distress, IRI empathic concern, or TEQ scores. Therefore, PTSD symptom severity, as assessed by the CAPS, did not predict scores on any of the empathy subscales. To explore if any specific criteria of PTSD symptomatology, rather than total symptom severity, was related to empathy, a correlation analysis was performed to determine if the scores from CAPS criterion A, B, C, or Associated Features (from previous month) were associated with empathy scores in the group with PTSD. The only

significant correlation that emerged was between criterion D (hyperarousal) and TEQ scores ($\rho = 0.41$, $P = 0.029$).

Supplementary Analyses

BDI scores indexing severity of potential co-morbid depressive symptoms were not significantly associated with IRI perspective taking ($\rho = 0.20$, $P = 0.309$), IRI empathic concern ($\rho = 0.33$, $P = 0.082$), IRI personal distress ($r = 0.18$, $P = 0.356$), or IRI fantasy ($r = 0.27$, $P = 0.158$), or TEQ total ($\rho = 0.22$, $P = 0.261$). Bivariate correlation analyses revealed no significant correlations between BDI scores and scores on the IRI subscales and the TEQ.

The distribution of empathy scores among the group with PTSD is of further interest as it may be expected that some individuals with PTSD have impaired empathy while others may have exaggerated empathy. The distribution of empathy scores among the sample with PTSD, as represented by the standard score of the skewness, was as follows: IRI fantasy: 0.77, IRI perspective taking: -1.64, IRI empathic concern: -2.00, IRI personal distress: 0.82, and TEQ: -2.35.

Discussion

To our knowledge this study is the first to reveal alterations in empathic responding among women with PTSD related to childhood trauma. Whereas women with PTSD reported a reduced ability to identify the social cognitive perspective of others (IRI perspective taking) and reduced feelings of care and concern in response to another's emotional experience (IRI empathic concern), their levels of personal distress in response to learning of others' negative experiences (IRI personal distress) were higher than those

reported by matched controls. Of the empathy subscales that differed significantly between groups, the only one that was predicted by clinical variables was IRI perspective taking. Specifically, higher levels of self-reported PBI parental care predicted higher levels of self-reported perspective taking ability among women with PTSD.

The finding of reduced perspective taking ability in the PTSD group is novel in the literature and suggests deficits in cognitive empathic abilities among women with PTSD associated with childhood trauma. Although previous studies, including work in our own laboratory (51), indicate that participants with MDD report reduced levels of perspective taking, this pattern did not emerge in Nietlisbach et al's 2010, study (4) where levels of perspective taking did not differ between participants with PTSD and controls. Critically, Nietlisbach et al. studied a group with PTSD that differed extensively from our group of participants with PTSD in terms of symptom severity, type of trauma exposure, and sex of participants, with half of the sample consisting of males. The present finding that women with a history of developmental trauma exposure showed reduced levels of perspective taking, an ability thought central to Theory of Mind (ToM), is in line with our earlier report that this sample shows alterations in mental state identification and in the perception of kinship interactions (6). Further work will be required to understand the relation between cognitive functioning (e.g., reduced working memory; poor executive functioning) and perspective taking in PTSD, since perspective taking is thought to rely on cognitive resources.

Although women with PTSD showed reduced cognitive empathy (i.e., IRI perspective taking), they scored higher than controls on the emotional IRI subscale of personal

distress. The personal distress subscale, which assesses anxiety and discomfort experienced in emotional social settings, is associated with social dysfunction, fearfulness, emotional vulnerability, shyness, uncertainty and anxiety (7). Heightened levels of personal distress in women with PTSD in the present sample are consistent with the results reported by Nietlisbach et al (2010). Notably, women with BPD also report higher levels of personal distress than controls (35). Moreover, complementary results were observed in the present study with the TEQ, also considered to be an emotionally-based measure of empathy.

Our results provide preliminary evidence that women with PTSD following a history of childhood trauma report less feelings of care and concern in response to other's emotional experiences, as assessed by the empathic concern subscale on the IRI. A reduction in empathic concern was also observed in individuals with MDD (51) and is thought to reflect a preoccupation with the self and negative ruminations (52, 53), rather than disinterest in another's well being. These results are in contrast with empathic responding in women with BPD who report increases in empathic concern (35), which may be reflective of the "especially empathic" pattern often noted in BPD. Interestingly, however, women did show preserved function on the fantasy subscale of the IRI, a cognitive facet of empathic responding, indicating that cognitive empathic abilities are not globally disrupted in PTSD and supporting the observation that individuals with PTSD are just as likely to help others as healthy controls (54). An important conclusion is therefore that empathic responding is *altered*, rather than *reduced or impaired*, in PTSD.

Our results support Davis' (1983) model of empathy as a multidimensional construct, consisting of both emotional and cognitive components.

An important characteristic of our patient sample is that the diagnosis of PTSD is associated with a history of repeated childhood trauma, rather than single-incident adult trauma. Among this sample, higher levels of paternal care on the PBI were predictive of higher scores on the perspective taking subscale of the IRI. In contrast, neither severity of childhood trauma, severity of current PTSD symptoms, nor years of education predicted empathic abilities, indicating that attachment during childhood, rather than trauma-related symptomatology or education history, may have the strongest impact on empathic functioning. Given that women with PTSD in our sample were repeatedly abused and/or neglected during childhood, it is possible that the perpetrator was the father in many of these cases, which may explain why levels of paternal care, but not maternal care, predicted empathic responding. Nonetheless, this finding highlights the need to focus on the role of the father, rather than only the more often-studied role of the mother, in the development of empathy and more broadly, social cognition. Frewen and colleagues (55) found that higher levels of paternal emotional availability but not maternal emotional availability (as assessed by the Childhood Attachment and Relational Trauma Screen (55)) were related to less trait negative affect in childhood in a sample of undergraduate students.

Other work also supports the notion that altered parental bonding contributes to aberrant development of empathy. For example, individuals who have experienced attachment trauma are more prone to hyperarousal (56) which typically reduces one's

ability to mentalize. Given that empathy is a component of mentalizing, this reduced capacity for mentalizing is likely reflected in the lowered levels of perspective taking ability seen in our sample, stemming from lower levels of perceived care offered by parents (as indicated in the PBI). When considering the experiences of a child growing up in a hostile environment where his or her caregiver is the perpetrator, it seems reasonable to suspect the development of the child's perspective-taking abilities would be hindered. Indeed, past research has suggested that low levels of empathy are associated with the presence of aggressive and bullying behaviours (57) . Thus, not only could potentially low levels of empathy among parents/ perpetrators be associated with the maltreatment of one's child, but this environment may provide poor modeling for the child, subsequently affecting development of empathy. Further, it is likely that for many children who are victims of maltreatment by their caregivers, it may simply be too frightening and aversive to take on the perspective of their parents, which may ultimately generalize to interpersonal situations with non-perpetrators. Critically, identification of mechanisms underlying the inter-generational transmission of the deleterious effects of trauma exposure (e.g., increased risk of subsequent abusive behaviour by offspring) will be central to intervention efforts (e.g., programs aimed at enhancing interpersonal sensitivity) aimed at reducing these effects.

There are several limitations to the present study that should be addressed in future research. First, our measures, while well-validated, consisted entirely of retrospective self-report questionnaires. Future studies should include behavioural/non-self-report measures of empathy and use prospective designs. In addition, because our sample

consisted of women with histories of complex trauma, the present results cannot be generalized to men or to individuals who have experienced traumatic events only in adulthood.

The current results suggest that empathy is not globally disrupted in PTSD stemming from childhood trauma, but that instead only select aspects (i.e., perspective taking, personal distress, empathic concern) are altered, while others (i.e., fantasy) remain spared. Furthermore, self-reported levels of parental care were more predictive of perspective taking abilities than were severity of childhood trauma or current PTSD symptom severity. Enhanced knowledge in the field of social cognitive functioning in PTSD may assist the development of strategies to improve social functioning with an aim of increasing the capacity to utilize social support. This is an important goal given that a lack of social support presents as the strongest risk for the maintenance of PTSD symptomatology (58).

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Chapter 3: Parental bonding and neuropsychological performance are associated with episodic simulation of future events in trauma-exposed patients with major depressive disorder

Chapter Link

The previous chapter demonstrated that self-reported levels of paternal bonding during development predicted cognitive empathic abilities in adulthood in persons with PTSD.

Parental bonding, more specifically maternal relationships, are related to autobiographical memory, a process that is known to share neural substrates with social cognition.

Episodic simulation of future events is a process that is heavily reliant on many of the same cognitive, psychological, and neural mechanisms as autobiographical memory.

Studies, however, have not examined the link between parental bonding and episodic simulation. The following study was performed to investigate the relation between parental bonding and episodic simulation and to further explore potential underlying mechanisms by also examining neuropsychological performance in relation to episodic simulation. Participants included a patient sample with a primary diagnosis of MDD with a history of trauma, a population that has reliably shown deficits in episodic simulation.

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Parental bonding and neuropsychological performance are associated with
episodic simulation of future events in trauma-exposed patients with major depressive
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Abstract

Major depressive disorder (MDD) and trauma-related disorders are associated with deficits in remembering the past and imagining the future (i.e., episodic simulation). We examined parental bonding and neuropsychological performance in relation to episodic simulation in trauma-exposed patients with recurrent MDD. Patients with MDD (n=21) and matched controls (n=20) completed a future-oriented Autobiographical Interview, the Parental Bonding Instrument and a standardized neuropsychological battery. MDD patients generated fewer episodic details for future neutral events compared to controls. Whereas higher reported levels of maternal care were associated with increased specificity of negative future events among the patient group, higher maternal overprotection was related to decreased specificity of negative and positive future events. Higher levels of performance on measures of intelligence, verbal memory, executive functioning, and sustained attention were associated with increased specificity of future events. Maternal relations during childhood continue to influence episodic simulation into adulthood.

Introduction

A substantial body of evidence suggests that patients with major depressive disorder (MDD) (King, MacDougall et al. 2010) and with post-traumatic stress disorder (PTSD) (Moore & Zoellner, 2007) are impaired in the retrieval of autobiographical memories (AM). In particular, these populations show a bias towards overgeneralized memory recall, where retrieval consists primarily of recollection of details related to repeated or long-standing events (non-episodic or semantic details), as opposed to the heightened recall of details specific in time and place (episodic details) seen in healthy populations. Episodic simulation is the construction of future events, achieved through drawing on episodic memories of past experiences and recombining and elaborating upon them, and is thought to require our awareness of subjective time (autonoetic awareness) (Schacter & Addis, 2007; Tulving, 2002). The ability to imagine future life events, or, episodic simulation, relies on many of the same cognitive, psychological, and neural processes known to be involved in AM (Hach, Tippet, & Addis, 2014; Schacter & Addis, 2007; Spreng & Levine, 2006). Although impairments in autobiographical memory and episodic simulation are well established in patients with depression and PTSD, factors contributing to the development of these deficits remain poorly understood. Here, we explore the relation between paternal attachment, thought central to the emergence of autobiographical memory in childhood (Fivush, Haden, & Reese, 2006; Harley & Reese, 1999; Nelson & Fivush, 2004), neuropsychological performance and the ability to imagine future happenings in patients with a history of recurrent MDD and trauma

exposure, primarily developmental in nature, and likely to have involved alterations in childhood attachments.

A number of studies reveal alterations in episodic simulation of future events in patients with MDD (Bjärehed, Sarkohi, & Andersson, 2010; Holmes, Lang, Moulds, & Steele, 2008; King, MacDougall, Ferris, Herdman, & McKinnon, 2011; Kosnes, Whelan, O'Donovan, & McHugh, 2013; MacLeod & Byrne, 1997; Morina, Deeprose, Pusowski, Schmid, & Holmes, 2011) and with PTSD (Brown et al., 2013; Kleim, Graham, Fihosy, Stott, & Ehlers, 2014) with some studies pointing towards a moderating influence of emotion on simulation. For example, Kleim et al. (2014) found that survivors with PTSD imagined fewer specific future events in response to positive cues, as compared to trauma-exposed participants without PTSD. Brown et al. (2013), however, found that combat veterans with PTSD were more likely to generate overgeneral future events in response to neutral cue words as compared to combat veterans without PTSD. In addition, patients with depression have repeatedly shown impairments in generation of future positive events (Bjärehed et al., 2010; Kosnes et al., 2013; Morina et al., 2011). Preliminary work indicates that clinical variables, including burden of illness and impaired social functioning, are associated with reduced generation of future episodic details among patients with mood disorders (King, MacDougall, et al., 2011; King, Williams, et al., 2011). The impact of parental bonding on episodic simulation has not yet been studied, despite knowledge that many patients with MDD suffer adverse childhood experiences likely to impact parental attachments. Indeed, in a sample of two thousand participants with anxiety and/or depressive disorders, only 8.8% *failed* to report

experiencing a potentially traumatic or bothersome life event (Spinhoven, Penninx, van Hemert, de Rooij, & Elzinga, 2014). These experiences are likely to impact significantly on autobiographical recall where for example, in one study, the left hippocampus, a region central to autobiographical memory, of patients with MDD and adverse experiences was 18% smaller in volume than that of MDD patients without adverse experiences, likely due to enhanced HPA-axis dysregulation among the trauma-exposed group (Joëls, 2011).

Indeed, attachment orientations have been associated with individual differences in autobiographical memory development and recollection (Fivush, Haden, & Reese, 2006; Harley & Reese, 1999; Nelson & Fivush, 2004). In one influential theory, mothers who are elaborative in discourse with their children, providing rich background details and asking open-ended questions, have children who showed more detailed autobiographical memories than did children of non-elaborative mothers (e.g., mothers who provide less background to the discussion and ask less open-ended and more repetitive questions) (Reese & Fivush, 1993), leading Nelson and Fivush (2004) to posit that the level of detail and richness in parental discourse influences strongly the development of autobiographical memory. This relation appears bi-directional, where the children of highly elaborative mothers also show more secure attachment (Fivush & Vasudeva, 2002). More recent work focuses on the role of attachment in the processing of negative emotions and memories and points towards attachment-related individual differences in how children encode, store, and recall negative memories (Chae et al., 2011). For example, in one study of undergraduate students, simply activating the mental

representation of an attachment figure following the retrieval of a distressing autobiographical memory leads to an enhanced regulation of negative affect in a sample of undergraduate students (Selcuk, Zayas, Günaydin, Hazan, & Kross, 2012), suggesting that, even in adulthood, attachment figures play a role in the processing of emotional autobiographical memories.

In addition to attachment orientations, cognitive functioning has also reliably been shown to relate to AM retrieval (for a review, see King et al., 2010). Deficits in working memory (Raes et al., 2005) verbal fluency (Dalgleish et al., 2007; Sumner et al., 2014), verbal memory (Spinhoven et al., 2006), and problem solving (Arie, Apter, Orbach, Yefet, & Zalzman, 2008) are correlated with reduced specificity of AM retrieval in this population. Further, executive control affects search processes and monitoring of retrieval output of AM (Conway & Pleydell-Pearce, 2000). Indeed, patients with PTSD have shown elevated production of non-episodic details during AM recall of both traumatic/negative and neutral events, which could reflect poor executive control and monitoring of extraneous information during event recall. (McKinnon et al., 2014). Research examining the impact of cognitive functioning on episodic simulation in this population is scarce. Trauma exposure and MDD have, individually, been linked to disruptions in a highly similar range of fronto-temporally mediated cognitive functions, including recollective memory (Talarowska et al., 2010; Yehuda, Golier, Halligan, & Harvey, 2004) working memory (Galecki et al., 2013; Vasterling et al., 2002), processing speed (Cohen et al., 2013; McDermott & Ebmeier, 2009), and cognitive flexibility (Polak, Witteveen, Reitsma, & Olff, 2012; Snyder, 2012). Given the impairments in cognitive

functioning among these populations and the overlapping cognitive processing resources required for AM retrieval and imagining future events (Schacter & Addis, 2007), it is important to assess the role of cognitive functioning in episodic simulation in this population.

The present study aimed to examine the role of both childhood attachments and neuropsychological performance in episodic simulation of future events among trauma-exposed patients with recurrent MDD. Participants in the present study were asked to imagine and describe future events in relation to positive, negative, and neutral cue words, allowing us to further examine the moderating role of emotional valence on episodic simulation. Details related to the imagined event were scored as internal (i.e., episodic and reflective of memory specificity), whereas details unrelated to the imagined event, or representing semantic knowledge or repeated events, were scored as external (i.e., non-episodic and reflecting poor memory specificity) (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002). We posited that parental attachments in childhood would continue to impact autobiographical episodic simulation in adulthood. Further, we predicted that poorer neuropsychological performance would be associated with reduced generation of episodic details in our patient group. In line with previous research, we also predicted that patients with MDD and co-morbid trauma exposure would show overgeneral episodic simulation as compared to controls. Finally, we examined latency to generate future events to determine if participants with MDD and trauma exposure were slower than controls at producing future events.

Method

Participants

This study was approved by the Hamilton Integrated Research Ethics Board of McMaster University and St. Joseph's Healthcare, Hamilton. Twenty-one right-handed patients (mean age: 41.3(14.5), 10 males, 11 females) who met DSM-IV diagnostic criteria for a primary diagnosis of recurrent (i.e., ≥ 3 episodes) MDD on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-1; First, Spitzer, Gibbon, & Williams, 1997) were recruited. All participants in the patient group had a history of trauma exposure, according to responses on the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995) and/or Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003). Among patients with MDD, 5 met criteria for moderate-to-severe childhood abuse on the CTQ only, 9 met criteria for lifetime PTSD or trauma exposure on the CAPS only, and 7 met criteria for childhood trauma exposure on the CTQ and a diagnosis of PTSD or trauma exposure on the CAPS. Among those participants who met criteria for PTSD or trauma exposure on the CAPS, 11 experienced interpersonal trauma (e.g., abuse by caregiver) and 5 experienced single-blow, accidental trauma (e.g., car accident). In total, 6 participants met criteria for current PTSD. A group of healthy controls (HC) consisted of 20 right-handed sex-, age- and education-matched participants with no history of psychiatric illness or trauma exposure (mean age: 36.5(13.4), 10 males, 10 females). Demographic and clinical characteristics of the study sample are summarized in Table 1.

Participants were recruited from St. Joseph's Healthcare Hamilton. Those with a past or current diagnosis of bipolar disorder, a psychotic disorder, neurological disease, traumatic brain injury and/or head injury with loss of consciousness (lasting more than 60

s), substance abuse in the last six months, current or lifetime history of substance dependence, and/or current or prior history of untreated significant medical illness were excluded. Participants were instructed not to use benzodiazepines within 12 hours prior to testing.

Measures

Future-Oriented Autobiographical Interview. A modified version of Crovitz's cue-word test was used (Addis, Sacchetti, Ally, Budson, & Schacter, 2009). Participants were presented with three positive, three negative, and three neutral randomly ordered cue words, one at a time. The cue words were chosen from the ANEW database (Bradley & Lang, 1999) and matched for concreteness, imagery, frequency and meaningfulness (Paivio, Yuille, & Madigan, 1968). After presentation of the cue word, participants were asked to orally describe in as much detail as possible a novel event related to that word, specific in time and place (i.e., autobiographical event) that could occur at some time in their future. Reaction time (RT) (i.e., latency to generate a future event in response to each cue word) was measured in seconds.

Following Addis et al. (Addis, Sacchetti, et al., 2009), if the participant could not think of an event in response to the cue word or if details were sparse, he or she was prompted no more than two times with cues from a standardized script that included phrases such as “What else may happen on that day?” or “Can you tell me a little bit more about that?”. Event descriptions were audio-recorded for transcription and scoring.

Participants' imagined events were placed separately in a common pool and scored at random by three experienced raters who had achieved high inter-rater reliability and who

were blind to group. The future event description for each word was segmented as either “internal” (i.e., episodic) or “external” (i.e., non-episodic or semantic information) details (Levine et al., 2002). These details were summed to form internal and external composites for positive, negative and neutral events.

Clinical Assessments. Severity of depressive symptoms over the past week was assessed using the 17-item Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960). Current (i.e., past month) and past PTSD diagnostic status, symptom severity, and history of trauma exposure were assessed with the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995). The Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003) was administered to assess for severity of childhood (1) emotional abuse, (2) physical abuse, (3) sexual abuse, (4) emotional neglect, (5) physical neglect. Participants also completed the Parental Bonding Instrument (PBI; Parker, Tupling, & Brown, 1979). The PBI is a 25-item self-report questionnaire designed to assess parental bonding through two perceived parenting styles of the mother and father during the first 16 years of life: (1) care (e.g., *my mother/father was affectionate to me*) and (2) overprotection (e.g., *my mother/father tried to control everything I did*). High care and low overprotection are considered optimal, whereas low care and high overprotection are considered least optimal. Each item is scored on a 4-point scale ranging from 1 (very like) to 4 (very unlike) and assessed separately for mother and father. Scores on the PBI do not simply reflect current depressed mood state (Parker et al., 1979) and show good concordance with sibling ratings (Duggan, Sham, Minne, Lee, & Murray, 1998; Gotlib, Mount, Cordy, & Whiffen, 1988).

Neuropsychological Test Battery. We administered an extensive battery of standardized neuropsychological measures aimed at measuring fronto-temporally mediated cognitive functioning. *Declarative memory:* i) California Verbal Learning Test II (standard form) (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000): word learning task that provides indices of immediate and delayed memory performance, and recognition. *Executive functioning:* i) Color Trail Making Test (Parts 1 and 2) (D’Elia, Satz, Uchiyama, & White, 1996): measures attention, speed, and mental flexibility, including the ability to sequence two stimulus sets while alternating between them; ii) Wisconsin Card sorting Test (128-item version) (WCST; Heaton, 2003): assesses the ability to form and shift concepts based on feedback. *Attention:* i) Conners’ Continuous Performance Test – Second Edition (CPT-II; Conners, 2000): a computerized task measuring sustained attention and response inhibition. *Current intellectual functioning:* i) Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999): one subtest of the performance index (i.e., matrix reasoning) and one subtest of the verbal index (i.e., vocabulary) were administered. Consistent with previous studies examining future thinking (Bjärehed et al., 2010; Kosnes et al., 2013), a verbal fluency task assessing phonemic fluency (stimuli: F, A, S), the Controlled Oral Word Association Test, was administered to assess for group differences in verbal fluency abilities (Gladsjo et al., 1999).

Statistical Analysis

To examine group differences on the demographic, clinical, and neuropsychological variables, independent samples t-tests or Mann-Whitney U tests were conducted,

depending on normality of data (assessed with the Shapiro-Wilk test). Associations between scores on the future-oriented autobiographical interview and clinical (i.e., HAM-D, CAPS, CTQ subscale scores, number of depressive episodes), parental bonding, and cognitive variables were calculated using Spearman's rho (two-tailed).

Due to non-normality of the scores on the future-oriented autobiographical interview (Shapiro-Wilk, $p < 0.05$), these scores were log transformed in order to perform a parametric mixed-design analysis of variance. The log transformation, however, did not result in a normal distribution among all of the scores (Shapiro-Wilk, $p < 0.05$). The scores on this measure were therefore analyzed using a mixed-effects model for non-parametric data (Noguchi, Gel, Brunner, & Konietzschke, 2012) (this method is robust for small sample sizes and outliers). Follow-up group comparisons of performance on the future-oriented autobiographical interview were conducted with non-parametric Mann-Whitney U-tests (using non-log transformed data). Group differences on the log-transformed reaction time data were analyzed using independent samples t-tests. Significance was set at $\alpha = 0.05$ for all analyses. Analyses were conducted with SPSS 21 (IBM, Armonk, NY, USA) and R 3.0 statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic and Clinical Characteristics

The patient group reported significantly higher symptom severity on all clinical measures (i.e., HAM-D, CAPS, CTQ) (see Table 1). Age, years of education, sex distribution, and verbal fluency performance did not differ significantly between the two groups.

Participants with depression and trauma exposure reported significantly lower levels of maternal and paternal care as compared to healthy controls ($U = 91.5, z = -2.93, p < .001, r = -.46$; $U = 81.5, z = -2.88, p < .001, r = -.47$, respectively). The reported levels of maternal and paternal overprotection did not differ between groups. Neuropsychological performance scores are reported in Table 2.

Table 1. Clinical and demographic characteristics of the study sample

Characteristic	MDD with Trauma (n = 21) Mean (SD)	Healthy Controls (n = 20) Mean (SD)
<i>Demographic characteristics</i>		
Age	41.3 (14.5)	36.5 (13.4)
Years of education	15.2 (3.9)	16.9 (2.6)
Sex (female:male)	11:10	10:10
Ethnicity (Caucasian) n (%)	19 (90%)	17 (85%)
Employment Status n (%)		
Employed	7 (33%)	17 (85%)
Unemployed	12 (57%)	0 (0%)
Student	2 (9%)	2 (10%)
Retired	0 (0%)	1 (5%)
<i>Clinical characteristics</i>		
HAM-D	*11.8 (6.1)	0.5 (0.9)
CAPS (month)	*29.2 (34.4)	0.0 (0.0)
Childhood Trauma Questionnaire		
Emotional abuse	*12.9 (6.4)	7.5 (3.9)
Physical abuse	7.0 (2.2)	5.9 (2.0)
Sexual abuse	*7.7 (5.6)	5.0 (0.0)
Emotional neglect	*13.7 (5.6)	8.5 (3.1)
Physical neglect	*9.3 (5.3)	5.9 (1.3)
Number of depressive episodes	14.1 (15.2)	NA
<i>Parental bonding characteristics</i>		
Parental Bonding Instrument		
Maternal Care	*20.7 (9.8)	29.5 (6.0)
Maternal Overprotection	14.6 (8.9)	12.6 (7.2)
Paternal Care	*19.0 (9.1)	27.3 (7.2)
Paternal Overprotection	9.7 (4.2)	10.4 (7.2)

Abbreviations: CAPS, Clinician-Administered PTSD Scale; HAM-D, Hamilton Depression Rating Scale; MDD, major depressive disorder.

* $p < 0.05$

Table 2. Raw scores on measures of neuropsychological performance

Cognitive Variable	MDD with Trauma (n = 21)	Healthy Controls (n = 20)
	Raw Score, Mean (SD)	Raw Score, Mean (SD)
CVLT-II		
Trials 1-5 total	51.9 (9.3)	56.5 (10.1)
Short-Delay Free Recall	11.1 (2.4)	12.9 (3.2)
Long-Delay Free Recall	*11.2 (2.6)	13.4 (2.7)
Color Trail Making Test		
Part 1 (seconds)	31.9 (13.3)	28.0 (8.7)
Part 2 (seconds)	*66.9 (21.1)	52.5 (14.1)
WCST		
Total Errors	23.8 (18.5)	19.9 (20.2)
Perseverative Errors	12.1 (11.8)	10.9 (10.8)
CPT-II		
Omissions	4.2 (12.7)	3.1 (7.9)
Commissions	14.7 (8.1)	11.8 (5.3)
WASI		
Matrix Reasoning	**26.2 (4.8)	30.1 (3.5)
Vocabulary	65.0 (9.1)	66.9 (7.4)
Two-subtest IQ	113.5 (13.2)	119.4 (12.7)
COWAT		
Phonemic Fluency	44.8 (12.3)	42.6 (13.1)

Abbreviations: CVLT-II, California Verbal Learning Test-II; CPT-II, Conners' Continuous Performance Test-II; COWAT, Controlled Oral Word Association Test; WASI, Wechsler Abbreviated Scale of Intelligence; WCST, Wisconsin Card Sorting Test.

* $p < 0.05$, ** $p < 0.01$

Correlations between Future-Thinking Scores and Clinical Variables

No correlations emerged between future-thinking scores and HAM-D, CAPS, the CTQ subscales, or number of depressive episodes.

Correlations Between Future-Thinking Scores and Parental Bonding Scores

Among the group with MDD, higher maternal care was associated with generation of fewer non-episodic (external) details for negative events ($r_s = -.45, p = .04, 95\% \text{ CI } [-.74, -.03]$), reflecting greater memory specificity (see Table 3). The opposite pattern was seen with the maternal overprotection subscale, where higher maternal overprotection was associated with an increased number of non-episodic details for negative events ($r_s = .52, p = .02, 95\% \text{ CI } [.11, .78]$), reflecting poorer memory specificity. Higher maternal overprotection was also associated with an increased number of non-episodic details for positive events ($r_s = .48, p = .03, 95\% \text{ CI } [.60, .78]$), again reflecting poorer memory specificity. Paternal care and overprotection were not correlated with future-thinking scores.

Correlations between Future-Thinking Scores and Cognitive Variables

Several cognitive correlates emerged in relation to future-thinking scores among the group with MDD, particularly in the domains of intelligence, verbal memory, executive functioning, and sustained attention (see Table 3). Better performance on the WASI Vocabulary subscale raw scores (a measure of crystallized intellectual functioning) was associated with generation of more internal (episodic) details for negative and neutral events ($r_s = .66, p < .01, 95\% \text{ CI } [.32, .85]; r_s = .52, p = .02, 95\% \text{ CI } [.11, .78]$, respectively), reflecting better memory specificity. Moreover, higher IQ based on the WASI two-subtest full-scale IQ was associated with generation of more episodic details for negative events ($r_s = .53, p = .02, 95\% \text{ CI } [.12, .78]$), reflecting better memory specificity. Better performance on an index measure of verbal memory, the CVLT-II

Total Raw scores subscale ($r_s = .47, p = .03, 95\% \text{ CI } [.05, .75]$) and the CVLT-II Short-Delay Free Recall subscale ($r_s = .45, p = .04, 95\% \text{ CI } [.05, .75]$) were related to increased production of episodic details for positive events, again reflecting better memory specificity. On a task of executive functioning, the WCST, number of total errors was associated with reduced generation of episodic details for both negative and neutral events ($r_s = -.56, p = .01, 95\% \text{ CI } [-.80, -.17]$; $r_s = -.53, p = 0.02, 95\% \text{ CI } [-.78, -.12]$, respectively), reflecting poorer memory specificity. More perseverative errors on the WCST were also associated with reduced generation of episodic details for positive, negative, and neutral events ($r_s = -.49, p = 0.03, 95\% \text{ CI } [-.76, -.10]$; $r_s = -.62, p < .01, 95\% \text{ CI } [-.83, -.25]$; $r_s = -.62, p < .01, 95\% \text{ CI } [-.83, -.26]$, respectively), reflecting reduced memory specificity. Finally, on a measure of sustained attention and impulsivity, the CPT-II, a greater number of omission errors, reflecting inattention, was associated with reduced production of episodic details for negative and neutral events ($r_s = -.53, p = .02, 95\% \text{ CI } [-.78, -.13]$; $r_s = -.52, p = .02, 95\% \text{ CI } [-.78, -.12]$, respectively), again reflecting reduced memory specificity. No significant correlations emerged between scores on the Color Trail Making Test or COWAT fluency scores and number of details generated on the future-oriented autobiographical interview.

Table 3. Correlates of future-thinking scores among trauma-exposed sample with MDD

	Positive Episodic	Positive Non- Episodic	Negative Episodic	Negative Non- Episodic	Neutral Episodic	Neutral Non- Episodic
Attachment Variable						
Parental Bonding						
Instrument						
Paternal Care	+.12	-.15	-.27	+.17	-.01	-.21
Maternal Care	+.01	-.43	+.09	*-.45	+.08	-.30
Paternal Overprotection	-.26	+.02	-.31	+.08	-.31	+.02
Maternal Overprotection	-.13	*+.48	-.14	*+.52	-.18	+.22
Cognitive Variable						
CVLT-II						
Trials 1-5 total	*+.47	-.07	+.41	+.28	+.30	+.30
Short-Delay Free Recall	*+.45	+.04	+.42	+.28	+.39	-.28
Long-Delay Free Recall	+.29	-.15	+.13	+.20	+.16	+.28
Color Trail Making Test						
Part 1 (seconds)	+.24	+.04	-.19	-.21	+.08	+.03
Part 2 (seconds)	+.03	+.11	-.14	-.01	-.01	+.13
WCST						
Total Errors	-.42	+.12	*-.56	-.06	*-.53	+.03
Perseverative Errors	*-.49	+.12	**-.62	-.10	**-.62	-.08
CPT-II						
Omissions	-.38	-.14	*-.53	-.11	*-.52	-.43
Commissions	+.22	+.34	+.12	+.33	+.08	+.35
WASI						
Matrix Reasoning	+.12	-.32	+.29	-.27	+.21	-.18
Vocabulary	+.35	+.08	**+.66	+.04	*+.52	+.11
Two-subtest IQ	+.17	-.04	*+.53	-.10	+.36	+.01
COWAT						
Phonemic Fluency	+.03	+.002	+.17	+.21	+.29	+.01

All correlation values are Spearman's correlation coefficients. * $p < 0.05$, ** $p < 0.01$

Abbreviations: CVLT-II, California Verbal Learning Test-II; CPT-II, Conners' Continuous Performance Test-II; COWAT, Controlled Oral Word Association Test; WASI, Wechsler Abbreviated Scale of Intelligence; WCST, Wisconsin Card Sorting Test.

Group Differences on Future-Thinking Task Performance

On the future-oriented autobiographical memory interview, there was a significant two-way interaction between detail type (i.e., episodic or non-episodic) and group (i.e., MDD vs. HC) ($F(1,39) = 4.0, p = 0.04$). Examining the mean number of episodic and non-episodic details produced (log-transformed), patients with MDD produced fewer episodic details than controls, however this finding did not reach significance ($t(37) = 1.5, p = .14, d = .48$) (HC mean = 117.1, SD = 53.4; MDD mean = 95.6, SD = 58.1). There was a trending effect of valence, where patients with MDD produced fewer episodic details in response to neutral cue words as compared to controls ($U = 138, z = -1.88, p = .056, r = -0.29$) (HC mean = 41.6, SD = 17.3; MDD mean = 33.1, SD = 20.3) (see Figure 1). Groups did not differ in their mean number of episodic details for positive cue words ($U = 167.5, z = -1.11, p > .05, r = -.17$) (HC mean = 36.2, SD = 19.1; MDD mean = 29.4, SD = 14.8) or negative cue words ($U = 148.5, z = -1.39, p > .05, r = -.22$) (HC mean = 39.3, SD = 23.9; MDD mean = 32.7, SD = 27.0). Groups also did not differ in the mean number of non-episodic details for positive ($U = 195.0, z = -.39, p > .05, r = -.06$) (HC mean = 11.7, SD = 15.6; MDD mean = 12.5, SD = 17.6), negative ($U = 174.5, z = -.69, p > .05, r = -.11$) (HC mean = 12.1, SD = 13.7; MDD mean = 14.8, SD = 14.9), or neutral details ($U = 168.0, z = -1.10, p > .05, r = -.17$) (HC mean = 9.5, SD = 15.7; MDD mean = 12.9, SD = 14.9).

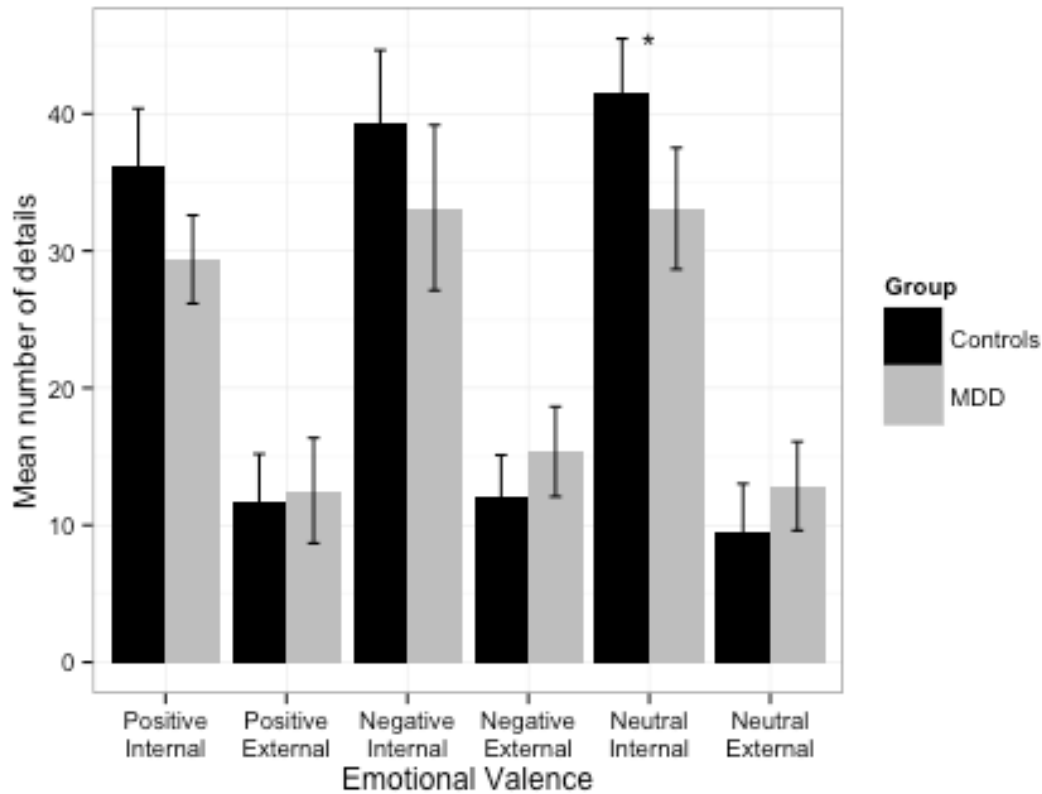


Figure 1. Mean number of internal (episodic) and external (non-episodic) details generated by comparison subjects and trauma-exposed patients with MDD on the future-oriented autobiographical interview. Error bars indicated standard error of the mean. * $p=0.056$.

Means for response latency to generate future events differed between groups for neutral cue words, where participants with MDD were significantly slower at generating a response compared to controls ($t(37) = -2.1, p = .04, d = -.67$) (HC mean = 35.2s, SD = 23.3; MDD mean = 71.0s, SD = 72.8). Groups did not differ in their latency in response to positive cue words ($t(37) = -1.47, p > .05, d = -.47$) (HC mean = 46.0s, SD = 34.8; MDD mean = 66.9s, SD = 57.3) or negative cue words ($t(37) = -.92, p > .05, d = -.30$) (HC mean = 67.7s, SD = 45.7; MDD mean = 91.8s, SD = 57.3).

Exploratory analyses were performed, excluding the six participants with MDD who also met current criteria for PTSD. With these participants excluded from the analyses, groups no longer differed in their latency in response to neutral cue words ($t(31) = -1.7, p = 0.08, d = -.58$), suggesting that the participants with co-morbid PTSD were driving the slower reaction time to neutral words. The remaining group comparison results remained consistent (i.e., non-significant).

Discussion

To our knowledge, this is the first study to examine the roles of parental bonding and neuropsychological performance in the specificity of episodic simulation in patients with a primary diagnosis of recurrent MDD and a history of trauma exposure, a population that reliably demonstrates deficits in autobiographical memory recall and episodic simulation. The main finding in this study was that higher levels of maternal care were associated with reduced generation of non-episodic details, reflecting increased specificity of episodic simulation in response to negative cue words and a greater ability to monitor retrieval output, whereas higher levels of maternal overprotection were related to increased production of extraneous details and poorer cognitive control operations in response to negative and positive cue words. In addition, higher levels of performance on neuropsychological measures of intelligence, verbal memory, executive functioning, and sustained attention were related to greater specificity of episodic simulation as indicated by a greater number of episodic details across positive, negative, and neutral memories. By contrast, levels of episodic simulation were unrelated to symptom severity, childhood trauma severity, and numbers of depressive episodes in this sample.

Higher levels of maternal care were associated with the generation of fewer non-episodic details for negative cue words, reflecting increased specificity, whereas high levels of maternal overprotection were related to an increased production of non-episodic details for negative and positive events, suggesting decreased specificity. These results suggest that attachment orientations, which are known to be involved in the development and retrieval of autobiographical memory even into adulthood, exert a protective effect on episodic simulation among individuals with depression that extends into adulthood (Harley & Reese, 1999; Nelson & Fivush, 2004; Selcuk et al., 2012). These results, in particular the correlations concerning details of negative future events, are in line with findings by Chae et al. (2011), who demonstrated that attachment plays a role in the development of emotional autobiographical memories, specifically for negative events. Experiencing higher levels of maternal care during childhood may contribute to the development of strategies that allow more effective processing and elaboration of negative events well into adulthood (Chae et al., 2011). Notably, maternal care (and overprotection) was only associated with the production of external, non-episodic details, suggesting that attachment plays a role in the increased (or decreased) production of details unrelated to the imagined event, rather than details specific in time and place concerning the future event. The reduced generation of extraneous details observed in association with maternal care likely reflects enhanced cognitive control and monitoring of mnemonic retrieval output, as impairments in cognitive control processes are related to elevated production of external/non-episodic details, which were associated with maternal overprotection in this sample (Levine et al., 2002; McKinnon et al., 2008). PTSD has

been associated with elevated production of non-episodic details during AM retrieval (McKinnon et al., 2014), likely related to reduced executive functioning. Indeed, future studies may examine whether the current finding that parental bonding is associated with production of non-episodic details is mediated by executive control. Increased rumination or functional avoidance during response generation could also lead the participant to focus on and generate details unrelated to the event in question (i.e., non-episodic details) as suggested by the CaR-FA-X model of overgeneral autobiographical memory that focuses on the impact of capture and rumination, functional avoidance, and impaired executive control in overgeneralized recall in participants with MDD (Williams et al., 2007)

Consistent with findings by King et al. (2011), our results suggest that patients show a deficit in generation of episodic details related to imagining future events, whereas the absolute level of non-episodic details generated did not differ between groups. Here, patients produced fewer internal details in response to neutral cue words than controls (results approached significance), and they were significantly slower than controls at generating responses for neutral events. A substantial literature indicates that negative and positive arousing events are better remembered than neutral events (Kensinger, 2009). Based on our findings, this bias towards more easily remembering emotional events may extend to imagining future events. Indeed, compared to controls, patients appeared to show a selective deficit for neutral events. These results, however, conflict with previous studies examining episodic simulation in patients with MDD, which have shown selective deficits in the generation of future positive events in particular (Bjärehed et al., 2010;

Holmes et al., 2008; Kosnes et al., 2013; MacLeod & Byrne, 1997; Morina et al., 2011). Methodological differences may account for these conflicting findings. Previous studies did not distinguish between episodic and non-episodic details generated during the simulation of future events, rather task scores were based on overall vividness of imagined events or the total number of separate events imagined. Further, our patient sample differed from those in previous studies, as no existing studies, to our knowledge, included only trauma-exposed participants with depression. Future studies will need to compare patients with and without trauma exposure to systematically assess if history of trauma may account for these conflicting findings.

A highly specific association was found between higher levels of neuropsychological performance and increased production of episodic details. Better performance on measures of intelligence (WASI vocabulary subtest and full-scale IQ scores), verbal memory (CVLT-II total scores), executive functioning (WCST total and perseverative errors), and sustained attention (CPT-II omissions) was associated with increased specificity of future events (i.e., greater number of internal details generated). Here, we have demonstrated that the association between neuropsychological performance and future thinking scores was specific to internal details, suggesting that neuropsychological functioning promotes enhanced episodic recall. Indeed, deficits in verbal memory (Talarowska et al., 2010; Yehuda et al., 2004), executive functioning (Polak et al., 2012; Snyder, 2012), and sustained attention (van der Meere, B rger, & van Os, 2007) are reported in patients with MDD and trauma-related disorders, and these processes are further thought to be involved in AM retrieval (Arie et al., 2008; Spinhoven et al., 2006), and by extension, episodic

simulation of future events. Verbal memory was only associated with positive future events, whereas intelligence and sustained attention scores were related to negative and neutral events, and executive functioning scores were related to all three emotional valences. A variable related to cognitive functioning that is worth considering for future studies is dissociation. Dissociative symptoms have been shown to be present in patients with MDD, and tend to be more severe in those with a history of childhood trauma (Molina-Serrano, Linotte, Amat, Souery, & Barreto, 2008; Žikić, Ćirić, & Mitković, 2009). Dissociation is related to poorer neuropsychological functioning in patients with PTSD (Roca, Hart, Kimbrell, & Freeman, 2006), borderline personality disorder (Haaland & Landrø, 2009; Krause-Utz et al., 2012) and also healthy controls (Brewin, Ma, & Colson, 2013; Brewin & Mersaditabari, 2013). Future studies should examine if dissociative symptoms may be mediating the relation between neuropsychological performance and episodic simulation in trauma-exposed patients with MDD.

There are several limitations to the present study that require consideration, such as the small sample size and retrospective nature of the parental bonding instrument. Notably, however, scores on the PBI have shown good concordance with sibling ratings (Duggan et al., 1998; Gotlib et al., 1988) and do not simply reflect a depressed mood state (Parker et al., 1979). Further, while the majority of our patient sample reported moderate-to-severe childhood trauma, the type of trauma exposure remained relatively heterogeneous, as a subset of participants reported experiencing only single-incident trauma. Future studies should systematically assess if specific subtypes of trauma differentially impact episodic simulation. Finally, the mechanisms underlying parental bonding and future thinking

remain unknown, and future studies should assess potential mediators of this association, such as increased rumination, functional avoidance, or emotion dysregulation during episodic simulation.

This study is the first to examine attachment and neuropsychological performance in relation to episodic simulation of future events, drawing on past theories proposing that maternal attachments and cognitive processes play crucial roles in the development and retrieval of autobiographical memory. The findings of the current study have important clinical implications. Interventions for trauma-related disorders and depression aim to decrease patients' negative biases towards the future and increase patients' positive biases. Difficulties in imagining and re-scripting future events may reduce one's ability to engage in this therapeutic process. Attachment with caregivers is an important developmental variable, as evoking stable attachment figures promotes emotion regulation during processing of negative personal memories (Selcuk et al., 2012) and is related to memory performance in adulthood. Attachment, together with neuropsychological dysfunction in patients with MDD and trauma-related disorders, should be taken into account during treatment planning as they may ultimately have an impact on one's ability to engage successfully in therapy.

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Chapter 4: Dissociative symptoms are associated with reduced neuropsychological functioning in patients with recurrent depression and a history of trauma exposure

Chapter Link

The preceding chapter demonstrated that optimal levels of maternal bonding and high levels of performance on neuropsychological tasks are related to greater specificity of episodic simulation of future events in patients with MDD. In order to better understand the mechanisms that may be underlying neuropsychological dysfunction in this sample, we examined this variable in the context of dissociative symptoms. This represents a relatively novel investigation in the area of dissociation given that dissociative symptoms have only recently begun to be examined in patients with depression. This chapter was submitted as a manuscript to the *European Journal of Psychotraumatology* in July, 2015.

Dissociative symptoms are associated with reduced neuropsychological functioning in
patients with recurrent depression and a history of trauma exposure

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ABSTRACT

Background: Although preliminary work suggests that dissociative symptoms may impact neuropsychological performance in trauma-exposed populations, the relation between dissociation and cognitive performance has not been explored in patients with depression.

Objective: The present study examined dissociative symptoms in relation to neuropsychological performance in participants with a primary diagnosis of recurrent major depressive disorder (MDD) and a history of trauma exposure.

Method: Twenty-three participants with MDD and 20 healthy controls who did not differ in age, sex distribution, education, or IQ were assessed. In addition to a standardized neuropsychological battery assessing fronto-temporally mediated cognitive processes, participants completed clinical measures assessing dissociative symptoms, illness severity, and past history of trauma exposure.

Results: Among participants with MDD, greater severity of derealization was associated with reduced performance on measures of delayed visuospatial recall and recognition on a task of verbal memory. In addition, more severe depersonalization was associated with slower processing speed and a response style lending itself towards better performance in a less active environment.

Conclusions: These findings point towards dissociative symptoms as a transdiagnostic factor associated with neuropsychological dysfunction in patients with depression and a history of trauma. Limitations and recommendations for future research are discussed.

Introduction

Cognitive dysfunction is widely reported among patients with major depressive disorder (MDD) (McDermott & Ebmeier, 2009; Rock, Roiser, Riedel, & Blackwell, 2014), contributing to impairments in multiple psychosocial domains (particularly employment) (McIntyre et al., 2013) and to disruptions in instrumental activities of daily living (Kiosses & Alexopoulos, 2005; McCall & Dunn, 2003). Critically, many persons with MDD have a co-morbid history of trauma exposure, where in a sample of two thousand participants with anxiety and/or depressive disorders, 91.2% reported experiencing a potentially traumatic or bothersome life event (Spinhoven, Penninx, van Hemert, de Rooij, & Elzinga, 2014). Trauma exposure and MDD have been linked to disruptions in a similar range of fronto-temporally mediated cognitive functions, including recollective memory (Talarowska et al., 2010; Yehuda, Golier, Halligan, & Harvey, 2004), working memory (Gałecki et al., 2013; Vasterling et al., 2002), processing speed (Cohen et al., 2013; McDermott & Ebmeier, 2009), and cognitive flexibility (Polak, Witteveen, Reitsma, & Olff, 2012; Snyder, 2012).

It is unclear, however, whether symptoms common to trauma exposure and to depression contribute to this shared pattern of cognitive dysfunction. For example, dissociative symptoms are present in MDD and in trauma-related disorders (e.g., posttraumatic stress disorder (PTSD)) with some studies revealing a link between dissociation and cognitive functioning (De Bellis, Woolley, & Hooper, 2013; Roca, Hart, Kimbrell, & Freeman, 2006). Dissociation is described as “disruption of and/or discontinuity in the normal subjective integration of one or more aspects of psychological

functioning, including – but not limited to – memory, identity, consciousness” (Spiegel et al., 2013). Etiologically, dissociation is thought to stem primarily from exposure to traumatic events or disruptions in attachment, serving to overmodulate affect and protect the individual from experiencing overwhelming distress during and/or after a traumatic event (Dalenberg et al., 2012; Lanius et al., 2010). Dissociative symptoms have been identified in persons with MDD, particularly among those with a history of trauma exposure. For example, in one study, compared to healthy controls, persons with MDD reported significantly higher levels of dissociative experiences (Molina-Serrano, Linotte, Amat, Souery, & Barreto, 2008). In the same study, those with a co-morbid history of childhood trauma also tended to report higher levels of dissociative symptoms than those without a childhood trauma history (though these results did not reach significance). Increased HPA-axis reactivity and psychosocial stressors have also been related to dissociative symptoms in depressed persons (Bob, Fedor-Freybergh, Jasova, Bizik, et al., 2008), where dissociation (specifically dissociative disengagement) is thought to act as a defense mechanism related to a passive coping style (Bob, Fedor-Freybergh, Jasova, Susta, et al., 2008). Dissociation may be particularly related to more severe forms of depression, as depressed persons who also experience depersonalization tend to report more severe depressive symptoms (Žikić, Ćirić, & Mitković, 2009).

As noted, persons with depression as well as persons with PTSD show impaired performance on measures of fronto-temporally mediated cognitive function, including executive functioning, verbal recollective memory (Johnsen & Asbjørnsen, 2009; Yehuda et al., 2004), attention (Vasterling, Brailey, Constans, & Sutker, 1998), and processing

speed (Cohen et al., 2013). Here, recent meta-analyses further reveal a small to medium effect size on measures of executive functioning in PTSD (Polak et al., 2012) and small to large effect sizes on these measures in MDD (Snyder, 2012). Importantly, the presence of executive dysfunction has been found to impact negatively on both pharmacological (Dunkin et al., 2000) and non-pharmacological treatments (Wild & Gur, 2008) for affective disorders, where the ability to engage in and successfully complete treatment relies heavily on such processes (Johnco, Wuthrich, & Rapee, 2013; Kalayam & Alexopoulos, 1999).

To our knowledge, no studies have directly examined the extent to which dissociation contributes to cognitive dysfunction in MDD. This association has, however, begun to be elucidated in trauma-related disorders, where the presence of cognitive dysfunction among patients with dissociative symptoms may contribute to poorer treatment outcomes (Mansfield et al., 2010; Price, Kearns, Houry, & Rothbaum, 2014; Spitzer, Barnow, Freyberger, & Grabe, 2007) (but see Hagenaars, van Minnen, & Hoogduin, 2010; Halvorsen, Stenmark, Neuner, & Nordahl, 2014; Jaycox, Foa, & Morral, 1998). In one study, veterans with a co-morbid dissociative disorder performed worse on measures of verbal recollective memory, attention, and executive functioning than veterans without a co-morbid dissociative disorder (Roca et al., 2006). Further, higher levels of non-pathological dissociation among healthy subjects were associated with increased interference on a Stroop task (DePrince, Weinzierl, & Combs, 2008) and inhibitory deficits (Cromer, Stevens, DePrince, & Pears, 2006); these findings have been replicated in dissociative identity disorder (Dorahy, Middleton, & Irwin, 2005). Similarly,

individuals with borderline personality disorder (BPD) who reported high levels of trait dissociation performed worse than healthy controls on tests of attention, executive functioning and long-term memory (Haaland & Landrø, 2009). Higher levels of dissociation in BPD were also associated with a dampened limbic activation during an affective processing task (Krause-Utz et al., 2012). Further, healthy controls demonstrated episodic impairment for events encoded during an experimentally-induced dissociative state (Bergouignan, Nyberg, & Ehrsson, 2014).

Here, we first compare self-reported levels of dissociation between patients with recurrent MDD and a history of trauma as compared to controls. We then examine the role of dissociation in cognitive functioning among patients with MDD as a potential transdiagnostic factor that could contribute to neuropsychological dysfunction observed across MDD and trauma-related disorders. We predicted that higher levels of depersonalization and derealization symptoms among persons with MDD and co-morbid trauma exposure would be associated with lower scores on objective measures of fronto-temporally mediated neurocognitive functions previously shown to be impacted in MDD.

Method

PARTICIPANTS

Twenty-three right-handed participants (mean age: 40.4 (14.2), 11 males, 12 females) who met DSM-IV diagnostic criteria for a primary diagnosis of recurrent (i.e., ≥ 3 episodes) MDD on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-1; First, Spitzer, Gibbon, & Williams, 1997) and who had a history of trauma exposure, according to responses on the Clinician-Administered PTSD Scale (CAPS;

Blake et al., 1995) and/or Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003) were recruited. A control group consisted of 20 right-handed participants with no history of psychiatric illness or trauma exposure (mean age: 35.3 (14.1), 10 males, 10 females) who did not differ from the patient group in terms of sex distribution, age, education or IQ. Among patients with MDD, 5 met criteria for moderate-to-severe childhood abuse on the CTQ only, 9 met criteria for lifetime PTSD or trauma exposure on the CAPS only, and 9 met criteria for childhood trauma exposure on the CTQ and a diagnosis of PTSD or trauma exposure on the CAPS. Among those participants who met criteria for PTSD or trauma exposure on the CAPS, 12 experienced interpersonal trauma (e.g., abuse by caregiver) and 6 experienced single-blow, accidental trauma (e.g., car accident).

Participants were recruited from St. Joseph's Healthcare Hamilton. Those with a past or current diagnosis of bipolar disorder, a psychotic disorder, neurological disease, traumatic brain injury and/or head injury with loss of consciousness (lasting more than 60 s), substance abuse in the last six months, current or lifetime history of substance dependence, and/or current or prior history of untreated significant medical illness were excluded. Participants were instructed not to use benzodiazepines within 12 hours prior to testing. The study was approved by the local Research Ethics Board and all participants provided written informed consent.

MEASURES

Clinical Assessments

The Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) was administered to assess the severity of depressive symptoms over the past week. We administered the

CAPS to assess for current (i.e., past month) and past PTSD diagnostic status and symptom severity to confirm history of trauma exposure. The CTQ was administered to confirm a history of moderate-to-severe childhood trauma. The CTQ is a 28-item self-report questionnaire that measures: (1) emotional abuse, (2) physical abuse, (3) sexual abuse, (4) emotional neglect, (5) physical neglect. The CTQ has good internal consistency and convergent reliability with therapist assessments of history of abuse is high (Bernstein et al., 2003). Lastly, participants completed the Multiscale Dissociation Inventory (MDI; Briere, 2002). The MDI is a 30-item self-report questionnaire that assesses dissociative responses. The current study focused on MDI depersonalization and derealization subscales, as these symptoms have been associated with increased depressive symptomatology (Žikić et al., 2009) and form the basis of the recently described dissociative subtype of PTSD (Spiegel et al., 2013).

Neuropsychological Test Battery

We administered an extensive battery of standardized neuropsychological measures aimed at measuring fronto-temporally mediated cognitive functioning. *Current intellectual functioning*: i) Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999): one subtest of the performance index (i.e., matrix reasoning) and one subtest of the verbal index (i.e., vocabulary) were administered to calculate two-subtest full-scale IQ. *Declarative memory*: i) California Verbal Learning Test II (standard form) (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000): word learning task that provides indices of immediate and delayed memory performance, and recognition; ii) the Brief Visuospatial Memory Test- Revised (BVM-T-R) (Form 1) (Benedict, 1997): a nonverbal test of

visuospatial memory under explicit encoding conditions. *Executive functioning*: i) Color Trail Making Test (Parts 1 and 2) (D’Elia, Satz, Uchiyama, & White, 1996) measures attention, speed, and mental flexibility, including the ability to sequence two stimulus sets while alternating between them; ii) Wisconsin Card sorting Test (128-item version) (WCST; Heaton, 2003): assesses the ability to form and shift concepts based on feedback. *Attention*: i) Conners’ Continuous Performance Test – Second Edition (CPT-II; Conners, 2000): a computerized task measuring sustained attention and response inhibition.

STATISTICAL ANALYSIS

To examine group differences on demographic, clinical, and neuropsychological scores, two-tailed independent samples t-tests or Mann-Whitney U tests were performed, depending on whether data were normally distributed (as assessed using the Shapiro-Wilk test of normality).

MDI subscales were not normally distributed and remained non-normal following log transformation. Associations between MDI subscale scores (depersonalization and derealization) and neuropsychological performance among the group with MDD and co-morbid trauma exposure were therefore calculated using Spearman’s rho (r_s , two-tailed). The relation between normally-distributed depressive symptoms (HAM-D scores) and neuropsychological performance was examined using Pearson correlation analyses. Significance was set at $\alpha = 0.05$ for all analyses. Analyses were conducted with SPSS 21 (IBM, Armonk, NY, USA).

Results

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Demographic and clinical data are displayed in Table 1. Age ($t(41) = -1.18, p = 0.24$), education ($t(41) = 1.71, p = 0.08$), IQ ($t(38) = 1.49, p = 0.15$), and sex distribution ($\chi(1) = 0.03, p = 0.85$) did not differ significantly between groups. As expected, the MDD group had significantly higher scores on all clinical variables, including dissociative symptoms (e.g., HAM-D, CAPS, CTQ, and all MDI subscales).

TABLE 1 Demographic and clinical characteristics of the study sample

Characteristic	MDD with Trauma (n = 23)	Healthy Controls (n = 20)
	Mean (SD)	Mean (SD)
<i>Demographic characteristics</i>		
Age	40.4 (14.2)	35.3 (14.1)
Sex (female:male)	12:11	10:10
IQ	114.0 (13.7)	120.2 (12.5)
Years of education	15.2 (3.7)	16.9 (2.4)
<i>Clinical characteristics</i>		
HAM-D	**11.7 (5.9)	0.5 (0.8)
CAPS (month)	**32.2 (33.2)	0.0 (0.0)
Childhood Trauma Questionnaire		
Emotional abuse	**13.3 (6.4)	6.5 (1.3)
Physical abuse	**7.5 (2.8)	5.5 (0.8)
Sexual abuse	**7.5 (5.4)	5.0 (0.0)
Emotional neglect	**13.7 (5.4)	8.1 (3.0)
Physical neglect	**9.1 (5.1)	5.6 (0.8)
MDI (total)	**51.1 (15.6)	33.8 (2.9)
Disengagement	**12.7 (3.9)	8.1 (2.1)
Depersonalization	**7.5 (2.6)	5.0 (0.3)
Derealization	**7.7 (3.6)	5.3 (0.6)
Emotional constriction	**9.4 (5.1)	5.2 (0.8)
Memory disturbance	**8.3 (4.1)	5.4 (0.7)
Identity dissociation	*5.6 (1.7)	5.0 (0.0)
Number of depressive episodes	13.2 (14.9)	NA
Age of MDD Onset	20.6 (10.1)	NA

Abbreviations: CAPS, Clinician-Administered PTSD Scale; HAM-D, Hamilton Depression Rating Scale; MDD, major depressive disorder; MDI, Multiscale Dissociation Inventory.

* $p < 0.05$, ** $p < 0.01$

NEUROPSYCHOLOGICAL PERFORMANCE

Group comparisons of performance on neuropsychological tests are displayed in Table 2. Participants with MDD and trauma exposure performed significantly worse than controls on several neuropsychological measures. Those with MDD recalled significantly fewer words on the CVLT-II long-delay free recall condition, based on both raw and z-scores ($U = 141, z = -2.19, p = .03, r = -.33$; $U = 145, z = -2.11, p = .035, r = -.32$, respectively). On the same measure, MDD participants made fewer hits on the recognition trial compared to controls, based on both raw and z-scores ($U = 140, z = -2.31, p = .021, r = -.35$; $U = 136, z = -2.37, p = .018, r = -.36$, respectively). Participants with depression also performed worse than controls on Color Trail Making Test Part 2 completion time (raw scores), a measure of mental flexibility and processing speed ($U = 100, z = -2.81, p = .005, r = -.44$).

TABLE 2 Raw and standardized scores on measures of neuropsychological performance

Cognitive Variable	MDD with Trauma (n = 23)		Healthy Controls (n = 20)	
	Raw Score, Mean (SD)	T-Score, Mean (SD)	Raw Score, Mean (SD)	T-Score, Mean (SD)
CVLT-II				
Trials 1-5 total	52.1 (9.0)	52.0 (9.9)	56.0 (9.8)	55.7 (10.3)
Short-Delay Free Recall (z)	11.4 (2.5)	0.17 (0.5)	12.5 (3.3)	0.50 (1.1)
Long-Delay Free Recall (z)	*11.4 (2.5)	*-0.08 (0.5)	*13.2 (2.8)	*0.50 (1.1)
Recognition Hits (z)	*14.6 (1.4)	*-0.48 (0.8)	*15.4 (0.9)	*0.05 (0.6)
False Positives (z)	0.9 (1.1)	0.15 (0.7)	0.7 (1.5)	0.18 (0.6)
BVMT-R				
Trials 1-3 total	25.9 (5.8)	50.5 (10.3)	27.0 (6.4)	51.1 (11.8)
Delayed Recall	10.7 (1.6)	55.8 (8.3)	10.4 (1.5)	52.1 (9.4)
Color Trail Making Test				
Part 1	31.8 (12.9)	54.6 (9.0)	26.8 (7.8)	54.8 (5.8)
Part 2	**66.5 (20.2)	56.4 (7.5)	**51.0 (13.9)	59.2 (5.2)
WCST				
Total Errors	22.9 (18.0)	48.7 (8.8)	19.9 (20.3)	49.5 (9.7)
Perseverative Errors	11.7 (11.4)	50.2 (9.8)	11.1 (11.1)	48.5 (10.1)
CPT-II				
Omissions	3.4 (12.1)	54.8 (40.5)	1.6 (3.0)	47.3 (8.9)
Commissions	14.1 (7.9)	52.5 (11.8)	11.7 (5.4)	50.2 (9.0)
Hit Reaction Time Block Change	-0.001 (0.02)	48.3 (7.8)	-0.006 (0.01)	47.1 (5.4)
Hit Reaction Time ISI	0.03 (0.03)	46.5 (12.1)	0.04 (0.02)	46.1 (6.9)

Abbreviations: BVMT-R, Brief Visuospatial Memory Test-Revised; CVLT-II, California Verbal Learning Test-II; CPT-II, Conners' Continuous Performance Test-II; WCST, Wisconsin Card Sorting Test.

Note: T-Score conversions used for neuropsychological test scores unless otherwise stated (e.g., "(z)" denotes z-scores).

* $p < 0.05$, ** $p < 0.01$

CORRELATIONS BETWEEN NEUROPSYCHOLOGICAL PERFORMANCE AND DISSOCIATIVE AND DEPRESSIVE SYMPTOMS

Results of correlation analyses conducted among the group with MDD and trauma exposure using standardized scores on the neuropsychological measures (e.g., t- and z-scores) are reported in Table 3. Significant correlations emerged between MDI

derealization symptoms and measures of verbal and visuospatial memory. Specifically, derealization symptoms were positively correlated with CVLT-II False Positive z-scores ($r_s = .43, p = .04$), where higher z-scores reflect a higher number of false positives. Derealization symptoms were also negatively associated with BVMT-R Delayed Recall t-scores ($r_s = -.57, p = .004$), where lower t-scores reflect worse performance on delayed recall. In addition, MDI depersonalization scores were correlated with measures of processing speed (and mental flexibility) and sustained attention. Specifically, Color Trail Making Test Part 2 t-scores were negatively correlated with depersonalization symptoms ($r_s = -.42, p = .047$), where lower t-scores indicate slower completion time. MDI Depersonalization was also associated with CPT-II Hit Reaction Time (RT) Interstimulus Interval (ISI) Change t-scores (vigilance measure) ($r_s = -.42, p = .05$) (where lower t-scores indicate sustained or increased response speed when stimuli are presented more slowly). In striking contrast, not a single significant correlation emerged between depressive symptom severity (HAM-D scores) and variability in neuropsychological performance.

TABLE 3 Correlations between dissociative symptoms, depressive symptoms, and standardized scores on neuropsychological measures

Cognitive Variable	ρ MDI Depers.	ρ MDI Dereal.	r HAM-D
CVLT-II			
Trials 1-5 total	+.11	-.27	-.23
Short-Delay Free Recall (z)	+.31	-.01	-.02
Long-Delay Free Recall (z)	+.31	+.23	+.05
Recognition Hits (z)	+.14	-.01	+.08
False Positives (z)	-.22	*+.43	-.11
BVMT-R			
Trials 1-3 total	-.05	-.40	-.19
Delayed Recall	-.22	**-.57	-.17
Color Trail Making Test			
Part 1	-.22	-.05	+.07
Part 2	*-.42	-.21	-.31
WCST			
Total Errors	+.01	-.11	-.18
Perseverative Errors	+.07	-.05	+.08
CPT-II			
Omissions	-.04	+.28	+.39
Commissions	-.12	+.06	-.38
Hit Reaction Time Block	+.28	+.22	+.07
Change			
Hit Reaction Time ISI	*-.42	-.36	+.26

Abbreviations: BVMT-R, Brief Visuospatial Memory Test-Revised; CVLT-II, California Verbal Learning Test-II; CPT-II, Conners' Continuous Performance Test-II; HAM-D, Hamilton Rating Scale for Depression; RT, reaction time; SE, standard error; WCST, Wisconsin Card Sorting Test.

Values denoted by ρ indicate Spearman's correlation coefficient.

Values denoted by r indicate Pearson's correlation coefficient.

Note: T-Score conversions used for neuropsychological test scores unless otherwise stated (e.g., "z"). Higher z-scores on CVLT-II False Positive scale indicate worse performance.

* $p < 0.05$, ** $p < 0.01$

Discussion

To our knowledge, this is the first study to examine the relation between dissociative symptoms and neuropsychological function in participants with a primary diagnosis of recurrent MDD. Despite a relatively small sample size and heterogeneity across persons with respect to history of trauma exposure, our findings indicate that persons with recurrent MDD and a history of trauma report significantly higher levels of dissociation compared to controls, an effect that was seen across each of the subscales of the MDI. Dissociative phenomena, therefore, should not be overlooked in depressed persons. Moreover, the main findings also point towards a detrimental association between dissociative symptoms and neuropsychological functioning in depressed persons, particularly in fronto-temporally mediated domains of cognition (i.e., memory and attention). The findings of the current study suggest that higher levels of dissociative symptoms (specifically derealization), rather than depression symptom severity, are related to worse performance on measures of verbal memory and visuospatial memory. Moreover, higher levels of depersonalization, but not depressive symptoms, were related to poorer processing speed, as well as a response style on a task of sustained attention indicative of faster reaction time when stimuli are presented more slowly. This finding suggests that greater dissociation is associated with higher vigilance in less active environments.

The link between dissociative symptoms and poor verbal declarative memory has been documented in healthy participants who were classified as high versus low dissociators (Amrhein, Hengmith, Maragkos, & Hennig-Fast, 2008), veterans with PTSD and

dissociative disorder (Roca et al., 2006), psychiatric inpatients (Prohl, Resch, Parzer, & Brunner, 2001), and patients with depersonalization disorder (Guralnik, Schmeidler, & Simeon, 2000). While there were no associations between dissociative symptoms and verbal learning or delayed recall scores on the CVLT-II in our MDD group, there was a significant correlation with scores on the recognition trial of this task. Specifically, higher levels of derealization were related to more false positive recognition errors. These results could be reflective of a negative impact of derealization on verbal learning and memory, but may also be related to increased suggestibility. Indeed, high levels of dissociation have been shown to predict a greater tendency to incorporate misleading information into memory (Eisen & Carlson, 1998). In our sample, it appears that being more prone to derealization is associated with an increased likelihood to think that a stimulus being presented for the first time has in fact already been presented.

Our finding that higher levels of derealization are associated with worse delayed visuospatial recall on the BVMT-R are in line with findings by Morgan et al. (2006) showing that in a group of special operations soldiers, higher levels of dissociation were associated with worse recall on the Rey-Osterrieth Complex Figure (ROCF). A similar relation has been demonstrated in healthy participants following experimentally-induced dissociation, who exhibited worse ROCF recall as compared to a control group (Brewin & Mersaditabari, 2013). Persons with depersonalization disorder also showed poorer performance on visuospatial tasks of the Wechsler Memory Scale (Guralnik et al., 2000). However, Haaland et al. (2009) failed to find an effect for dissociation in persons with BPD on a task of non-verbal memory.

Among the MDD group, there were also associations between dissociation and attention. Higher levels of depersonalization were related to slower completion time on the attention and processing speed task, Color Trail Making Test - Part 2. In comparison, no correlations emerged between Color Trail Making Test - Part 1 and dissociative symptoms. These results are consistent with findings by Roca et al. (2006) among a sample of veterans with PTSD and a dissociative disorder. In addition to measuring attention, Part 2 of the Color Trails Test also assesses mental flexibility, a domain of executive functioning. Other studies have examined the link between executive function and dissociation and have found that impairments in executive functioning, as measured by a random number generation task and by the Behavioural Assessment of Dysexecutive Syndrome, were related to dissociation (Horne, Evans, & Orne, 1982; Wilson, Alderman, Burgess, Emslie, & Evans, 1996) (but see Bruce, Ray, Bruce, Arnett, & Carlson, 2007 for conflicting results).

Depersonalization symptoms on the MDI were also related to the CPT-II RT ISI Change T-Score variable (a measure of vigilance), such that higher levels of depersonalization were related to better performance in a less active environment (where stimuli were presented less frequently). These results are in line with other studies that suggest that, depending on the attentional condition, dissociation may actually result in improved performance. For example, higher levels of dissociation are related to better interference control under divided attention conditions (e.g., on the Stroop Task) and worse interference control under selective attention conditions (DePrince et al., 2008). These results may be explained by the cognitive environments conceptualization of

dissociation (DePrince & Freyd, 1999), which suggests that dissociation may coincide with chronically fragmented attention, resulting in the ability to process multiple information streams simultaneously. Other studies, however, point towards attentional deficits caused by dissociation. Specifically, in children with a history of intrafamilial sexual abuse, dissociation mediates the relation between PTSD symptoms and attentional problems (Kaplow, Hall, Koenen, Dodge, & Amaya-Jackson, 2008). Similar evidence suggests that higher levels of dissociation among maltreated children are related to poorer performance on measures of attention (De Bellis et al., 2013).

The current findings point towards a number of important avenues for further investigation. For example, future studies may examine the role of dissociation in cognitive performance as a function of trauma exposure subtypes and/or disrupted attachment patterns and should compare neuropsychological performance in persons with MDD with and without a history of trauma exposure. Dissociative symptoms may be more severe in those with a history of sexual abuse, compared to those with a history physical abuse or combined physical and sexual abuse (Boysan, Goldsmith, Cavuş, Kayri, & Keskin, 2009). The role of attachment patterns was highlighted in a longitudinal study examining predictors of dissociation in an adult sample, which found that the quality of caregiving during childhood was the strongest predictor of dissociative symptoms, whereas extent of abuse was not predictive (Dutra, Bureau, Holmes, Lyubchik, & Lyons-Ruth, 2009). The findings of the present study could also have implications for clinicians and researchers working with depressed persons, and particularly those with a history of trauma exposure. Assessment of dissociative symptoms is rarely undertaken in those with

MDD. Our results are in line with previous findings which suggest that dissociation is related to specific and subtle impairments in neurocognition (Giesbrecht, Lynn, Lilienfeld, & Merckelbach, 2008). Given these findings, dissociative symptoms should ideally be assessed pre-treatment, as their effect on cognition may impact MDD treatment response. Given that a dissociative subtype of PTSD marked by increased depersonalization and derealization was included in the most recent version of the DSM-5 (APA, 2013), it may be reasonable to suspect that a dissociative subtype may be likewise present in a subset of persons with MDD. The findings of the present study point towards the urgent need to further investigate the impact of dissociation on neurocognition and other domains of functioning in participants with depression and a history of trauma exposure.

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Chapter 5: Relation between patterns of intrinsic network connectivity, cognitive functioning, and symptom presentation in trauma-exposed patients with major depressive disorder

Chapter Link

The preceding chapter demonstrated that among patients with MDD and a history of trauma, higher levels of dissociative symptoms are related to poorer neuropsychological functioning. In order to further explore the mechanisms underlying neuropsychological dysfunction, we used resting-state independent component analysis to examine the association between intrinsic functional connectivity networks (ICN) (i.e., default mode, salience, and central executive networks) and neuropsychological performance. This study is the first to examine this relation in this patient group and may contribute to future investigations aimed to develop treatments that will target disrupted ICNs in this population. This paper was prepared for publication for submission to *Neuropsychologia*.

Relation between patterns of intrinsic network connectivity, cognitive functioning, and symptom presentation in trauma-exposed patients with major depressive disorder

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Abstract

Trauma exposure is highly prevalent among patients with major depressive disorder (MDD), with trauma-related disorders and MDD sharing overlapping cognitive features (e.g., executive and memory dysfunction) and symptom presentation (e.g., dissociation). The present study investigates the association between resting connectivity of the salience (SN), default mode (DMN), and central executive (CEN) networks, cognitive functioning and severity of depressive, PTSD, and dissociative symptoms in trauma-exposed patients with MDD. Group independent component analysis was conducted on resting-state functional MRI data on patients ($n = 21$) compared to healthy controls ($n = 20$). The association between cognitive and clinical variables and ICNs was then analyzed among the patient group. Relative to controls, participants with MDD showed greater connectivity of the ventromedial prefrontal cortex within the DMN. Moreover, higher levels of performance on measures of verbal memory and executive functioning were related to increased connectivity within the DMN. Greater depression severity was related to reduced connectivity between the SN and the DMN, whereas higher dissociative symptoms were related to enhanced connectivity between these two networks. Higher symptoms of depersonalization were also associated with reduced integration of the DMN with the medial frontal gyrus. ICN patterns of the SN, DMN, and CEN are related to cognitive performance and symptom presentation among trauma-exposed patients with MDD.

Introduction

In addition to its core affective components, major depressive disorder (MDD) is characterized by dysfunction in frontal-temporally mediated cognitive domains, including executive functioning (Snyder, 2012), processing speed (McDermott & Ebmeier, 2009), working memory (Gałecki et al., 2013) and recollective memory (Talarowska et al., 2010). These deficits are of significant concern as they contribute to impairments in multiple psychosocial domains (McIntyre et al., 2013) and are related to disruptions in instrumental activities of daily living (McCall & Dunn, 2003). Notably, patients with trauma-related disorders, including PTSD, show deficits in a highly similar range of cognitive domains (Cohen et al., 2013; Polak, Witteveen, Reitsma, & Olff, 2012; Vasterling et al., 2002; Yehuda, Golier, Halligan, & Harvey, 2004), with structural and functional brain changes observed across MDD and trauma-related disorders in regions linked to recollective memory (e.g., hippocampus) (Campbell & MacQueen, 2004; McKinnon, Yucel, Nazarov, & MacQueen, 2009; Shin, Rauch, & Pitman, 2006), attention (e.g., anterior cingulate cortex) (Mayberg et al., 1997; Offringa et al., 2013; Yucel et al., 2008) and executive functioning (e.g., DLPFC) (Aupperle et al., 2012; Koenigs & Grafman, 2009). Critically, many patients with MDD have a co-morbid history of trauma exposure, where in a sample of two thousand participants with anxiety and/or depressive disorders, only 8.8% *failed* to report experiencing a potentially traumatic or bothersome life event (Spinhoven, Penninx, van Hemert, de Rooij, & Elzinga, 2014). Trauma exposure impacts negatively on cognitive functioning (Olff, Polak, Witteveen, & Denys, 2014) and treatment outcome (Harkness, Bagby, & Kennedy,

2012; Lewis et al., 2010; Nanni, Uher, & Danese, 2012) in patients with MDD and thus represents a critical variable to investigate in the context of depression. Here, we implement a transdiagnostic approach to examine the relation between patterns of intrinsic neural connectivity, cognitive functioning and symptom presentation (e.g., dissociation) among patients with a primary diagnosis of MDD and a history of trauma exposure.

Menon (2011) proposes a triple network model of psychopathology comprising three main intrinsic connectivity networks (ICNs) that together may underlie many of the neurocognitive and affective symptoms that characterize psychiatric disorders. This model includes the default mode network (DMN), the salience network (SN), and the central executive network (CEN). The DMN is defined most consistently by cortical midline structures (posterior cingulate: BA 23 and 31, ventromedial prefrontal cortex) (Buckner, Andrews-Hanna, & Schacter, 2008), and is involved in self-related processes, autobiographical memory, and social cognition (Amodio & Frith, 2006; Buckner et al., 2008; Greicius, Krasnow, Reiss, & Menon, 2003; Qin & Northoff, 2011; Spreng, Mar, & Kim, 2009). This network shows decreases in activation during the performance of cognitively demanding tasks (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Greicius et al., 2003). By contrast, the CEN, consisting of the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex, is instrumental in executive functioning and is engaged during cognitively-demanding tasks requiring attention (Fox et al., 2006; Habas et al., 2009; Koechlin & Hyafil, 2007; Koechlin & Summerfield, 2007; Miller & Cohen, 2001; Petrides, 2005; Seeley et al., 2007). Finally, the SN comprises the ventrolateral

prefrontal cortex, the anterior insula, and the dorsal anterior cingulate cortex (dACC) (Dosenbach et al., 2007; Lovero, Simmons, Aron, & Paulus, 2009; Seeley et al., 2007; Sridharan, Levitin, & Menon, 2008), playing a role in salience detection. The SN, in particular the anterior insula, is responsible for switching between the DMN and the CEN, thus facilitating the engagement of brain regions mediating higher-order cognitive processes (Menon, 2011; Sridharan et al., 2008). By examining the association between ICNs, cognitive dysfunction and symptom presentation in patients with MDD and a co-morbid history of trauma exposure, we hope to increase our understanding of the neural mechanisms underlying cognitive dysfunction and symptom presentation among a patient population that is often treatment resistant and presents with a heightened pattern of cognitive dysfunction (Harkness et al., 2012; Olff et al., 2014).

Resting-state fMRI studies in patients with depression have consistently identified abnormalities across ICNs, suggesting a reorganization of intrinsic functional connectivity that could contribute to symptoms of MDD (Manoliu et al., 2013). The majority of these studies have focused on the DMN, reporting that patients with MDD tend to show abnormal activation during goal-directed tasks, and increased functional connectivity during rest (for a review, see Broyd et al., 2009). Overall, it appears that patients with MDD have difficulty downregulating activity within the DMN, which may account for symptoms such as increased rumination (Hamilton et al., 2012; Nejad, Fossati, & Lemogne, 2013) and impaired attentional control (Marchetti, Koster, Sonuga-Barke, & De Raedt, 2012). Moreover, unmedicated adults with MDD show increased connectivity of the DMN with the SN (Greicius et al., 2003; Jacobs et al., 2014).

Additional studies however, found reduced integration of the anterior and posterior DMN in patients with depression (de Kwaasteniet et al., 2015; Sambataro, Wolf, Pennuto, Vasic, & Wolf, 2013). Aberrant connectivity of the CEN has also been observed during task performance (Fitzgerald et al., 2008) and at rest (Diener et al., 2012) in patients with MDD. Interestingly, increased activation of the anterior insula in response to negative stimuli has been shown in MDD (Strigo, 2010), and increased connectivity of the dorsal mid-insula cortex with limbic areas is positively correlated with depressive symptom severity (Avery et al., 2014) (but see Alexopoulos et al., 2012; Veer et al., 2010). Finally, the right fronto-insular cortical network, however, was found to be less active at rest in patients with MDD as compared to controls (Hamilton et al., 2012). In addition, remitted youth with MDD demonstrate hyperconnectivity of the DMN and SN with the cognitive control network (CCN), as compared to controls (Jacobs et al., 2014).

Aberrant connectivity of the ICNs comprising Menon's (2011) triple network model is also well-documented in patients with PTSD. Altered connectivity of the DMN has been reported among these patients, where strength of connectivity has been found to correlate with PTSD symptom severity (Birn, Patriat, Phillips, Germain, & Herringa, 2014; Cisler, Scott Steele, Smitherman, Lenow, & Kilts, 2013; Kennis, Rademaker, Rooij, Kahn, & Geuze, 2009; Lanius et al., 2010; Sripada et al., 2012). Interestingly, resting connectivity between the PCC (a node of the DMN) and the anterior insula predicts later development of PTSD (Qin et al., 2012) and PTSD symptom severity (Lanius et al., 2010; Zhou et al., 2012). In one additional study, patients with PTSD showed elevated connectivity between the DMN and the SN as well as greater connectivity within the SN as compared to

controls (Sripada et al., 2012). Finally, studies of CEN functioning in patients with PTSD reveal decreased connectivity within this network as compared to controls (Cisler et al., 2013), even during a working memory task (Daniels et al., 2010). Scores on the Dissociative Experiences Scale (indexing dissociative symptoms of PTSD including depersonalization and derealisation) positively correlated with DMN connectivity with the DLPFC (a node of the CEN) (Bluhm et al., 2009). Moreover, dissociative symptoms have been related to decreased integration of anterior and posterior DMN components (Tursich et al., 2015). Despite the high prevalence of trauma exposure in depression and its negative effects on cognitive functioning and treatment outcome, no studies have examined alterations in ICNs in relation to cognitive functioning and symptom presentation in this population. This effort may assist in better understanding the neural mechanisms underlying the reduced treatment and functional outcomes observed in this population. Critically, trauma exposure has been shown to lead to changes in ICNs, even without the development of PTSD (Kennis et al., 2009; Wang et al., 2014).

In this study, we investigate those core neural networks thought central to higher-order cognitive functioning to determine if alterations in the connectivity of ICNs is related to neuropsychological performance and symptom presentation among patients with MDD and co-morbid trauma exposure. Resting brain activity has been related to behavioural performance on cognitive tasks in various populations, where preliminary results suggest that elevated connectivity within the DMN and within the CEN is related to enhanced performance on cognitive tasks. For example, connectivity within the DMN is positively associated with verbal working memory (Yakushev et al., 2013) among healthy adults,

and with memory performance (using a memory composite score) among older adults (Ward et al., 2014). Healthy controls also demonstrated an association between CEN connectivity and superior performance on Trails B (Seeley et al., 2007). In related studies, patients with Parkinson's disease show elevated DMN connectivity in association with faster processing speed, better executive functioning (Disbrow et al., 2014), and higher memory and visuospatial task scores (Tessitore et al., 2012). Heightened functional connectivity of executive control networks during rest was also related to a reduced Stroop effect (i.e., better executive control) among participants with Internet gaming disorder and healthy controls (Dong, Lin, & Potenza, 2015). To our knowledge, there are the only two studies that examine the relation between cognitive functioning and ICNs in patients with MDD. Jacobs et al. (2014). studied youth with remitted MDD and found that hyperconnectivity of the DMN and SN with the CCN was positively correlated with sustained attention on a Go/No-Go task. In a sample of patients with late-life depression, low resting functional connectivity within the CCN prior to treatment was related to dysexecutive behaviour after treatment (Alexopoulos et al., 2012). To date, however, no studies have examined the relation between these core neural networks thought to be related to the psychopathology of affective disorders (Menon, 2011) and performance on standardized neuropsychological assessments tapping frontal-temporally mediated cognitive domains in patients with MDD and a history of trauma. Notably, few studies have investigated cognitive performance in relation to SN activity, as most studies focus on its association with the DMN and CEN. Addressing this topic from a transdiagnostic perspective will provide insight into overlapping characteristics of MDD and trauma-

related disorders, including altered frontal-temporally-mediated cognitive functioning and dissociative symptoms present across disorders.

Aims of the study

Here, we examine the association between connectivity of ICNs, cognitive performance, and symptom presentation in patients with MDD and a co-morbid history of trauma exposure. We begin by identifying patterns of intranetwork connectivity of the DMN, SN, and CEN in these patients relative to controls via independent components analysis (ICA). We also examined the association between scores on standardized neuropsychological assessments and intranetwork connectivity within the patient group, across all three ICNs. Our final aim was to evaluate the relation between clinical symptoms (e.g., dissociation) and ICNs. Our hypothesis concerning the preceding aims are non-directional.

Methods

Participants

This study was approved by the Hamilton Integrated Research Ethics Board of McMaster University and St. Joseph's Healthcare, Hamilton. Twenty-one right-handed patients (mean age: 40.2 (14.9), 10 males, 11 females) who met DSM-IV diagnostic criteria for a primary diagnosis of recurrent (i.e., ≥ 3 episodes) MDD on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-1; First, Spitzer, Gibbon, & Williams, 1997) and who had a history of trauma exposure, according to responses on the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995) and/or Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003) were recruited. Among patients with MDD, 5

met criteria for moderate-to-severe childhood abuse on the CTQ only, 9 met criteria for lifetime PTSD or trauma exposure on the CAPS only, and 7 met criteria for childhood trauma exposure on the CTQ and a diagnosis of PTSD or trauma exposure on the CAPS. Among those participants who met criteria for PTSD or trauma exposure on the CAPS, 11 experienced interpersonal trauma (e.g., abuse by caregiver) and 5 experienced single-blow, accidental trauma (e.g., car accident). Five participants met criteria for PTSD at time of testing. A control group consisted of 20 right-handed participants with no history of psychiatric illness or trauma exposure who did not differ from the patient group in age, sex, or education (mean age: 35.3 (14.1), 10 males, 10 females).

Exclusion criteria included past or current diagnosis of bipolar disorder, a psychotic disorder, neurological disease, electroconvulsive therapy or transcranial magnetic stimulation therapy in the last 12 months, traumatic brain injury and/or head injury with loss of consciousness (lasting more than 60 s), substance abuse in the last six months, current or lifetime history of substance dependence, and/or current or prior history of untreated significant medical illness were excluded. Participants were instructed not to use benzodiazepines within 12 hours prior to testing.

Measures

Clinical Assessments

In addition to the SCID-I, participants completed the 17-Item Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960). This interview assesses the severity of depressive symptoms over the past week. The CAPS (Blake et al., 1995) was also administered to assess current (i.e., past month) and past PTSD diagnostic status and symptom severity

and to confirm history of trauma exposure. Participants completed the CTQ which is a 28-item self-report questionnaire that measures: (1) emotional abuse, (2) physical abuse, (3) sexual abuse, (4) emotional neglect, (5) physical neglect. The CTQ has good internal consistency and convergent reliability with therapist assessments of history of abuse is high (Bernstein et al., 2003). Participants also completed the Multiscale Dissociation Inventory (MDI; Briere, 2002), a 30-item self-report questionnaire that assesses dissociative responses. The current study focused on MDI depersonalization and derealization subscales, as well as a composite score of the sum of these two subscales, as these symptoms have been associated with increased depressive symptomatology (Molina-Seranno et al, 2008; Žikić, Ćirić, & Mitković, 2009) and form the basis of the recently described dissociative subtype of PTSD (Lanius et al., 2012; Spiegel et al., 2013).

Neuropsychological Assessment Battery

We administered a battery of standardized neuropsychological measures to assess frontal-temporally mediated cognitive functioning. *Declarative memory*: i) California Verbal Learning Test II (standard form) (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000): word learning task that provides indices of immediate and delayed memory performance, and recognition. *Executive functioning*: i) Controlled Oral Word Association Test: taps phonemic (FAS) fluency (Gladsjo et al., 1999); ii) Colour Trail Making Test (Parts 1 and 2) (D'Elia, Satz, Uchiyama, & White, 1996): measures attention, speed, and mental flexibility, including the ability to sequence two stimulus sets while alternating between them; iii) Wisconsin Card Sorting Test (128-item version) (WCST; Heaton, 2003):

assesses the ability to form and shift concepts based on feedback. *Attention:* i) Conners' Continuous Performance Test – Second Edition (CPT-II; Conners, 2000): a computerized task measuring sustained attention and response inhibition.

Imaging Paradigm and Acquisition

Participants underwent a 4-minute resting-state scan during which they were shown a black fixation cross on a grey screen, following standard procedures (Ros et al., 2013). All images were obtained using a 3.0Tesla whole-body MRI scanner (General Electric) using an 8-channel parallel receiver birdcase head coil (General Electric, Milwaukee, WI.). For the resting state task, 34 axial slices (3mm thick, no skip) across the whole brain were imaged using a gradient echo pulse sequence [echo time (TE) = 35 ms; repetition time (TR) = 3000 ms; acquisition matrix = 64 x 64; FOV = 24 cm; flip angle = 90°] (note, due to technical error, a change was made setting TR = 2500 ms for the fMRI scans of eight participants).

Statistical Analyses

Demographics, Psychological, and Cognitive Characteristics. To assess group differences in demographic, clinical, and cognitive variables, data were first tested for normality ($p > 0.05$, Shapiro-wilk) and group comparisons were calculated using Independent Samples t-tests or Mann-Whitney U-test, depending on distribution of data. Group differences in gender and employment status were assessed with chi-square tests.

Image Preprocessing

Preprocessing of images (slice-timing correction, motion correction, spatial normalization, and smoothing) was performed using SPM8

(<http://www.fil.ion.ucl.ac.uk/spm/>) in MATLAB 8.3.0 (MathWorks Inc.) using standard procedures (Ros et al., 2013). Individual functional images were corrected for motion by realignment to the first volume of each session, resliced, and a mean functional volume created. The mean image was co-registered to the standard echo-planar imaging template in Montreal Neurological Institute (MNI) space supplied by SPM8, the deformation matrix was then created and applied to the functional volumes. All functional volumes were smoothed using a full-width half-maximum (FWHM) Gaussian filter of 8 mm.

Functional Connectivity Analysis

We performed ICA (Calhoun, Kiehl, & Pearlson, 2008; Calhoun, Liu, & Adali, 2009) of the resting-state functional data using the Group ICA of fMRI Toolbox (GROUPLICAT v3.0a/GIFT v2.0a; <http://mialab.mrn.org>) to identify ICNs for all 41 participants. We isolated 20 ICs using the Infomax algorithm in GIFT and repeated the estimation 20 times using the ICASSO method (Himberg, Hyvärinen, & Esposito, 2004) to enhance component reliability. Single subject spatial maps and time courses for each component were back-reconstructed for each participant and converted to z-scores to indicate the strength of each voxel's contribution to the component (Erhardt et al., 2011). The spatial sorting function in GIFT was used to identify the components whose spatial pattern showed the highest correlation (Pearson's r) with network templates (DMN and CEN available from http://findlab.stanford.edu/functional_ROIs.html; (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012)) and with network masks from our previous studies (SN; (Kluetsch et al., 2014; Ros et al., 2013)).

Statistical Comparison of Spatial Maps

Component z-score maps of interest were imported into SPM8 for group analysis.

Region-of-interest (ROI) analyses were carried out through the a priori defined standardized masks of the DMN (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012), CEN (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012) and SN (Kluetsch et al., 2014; Ros et al., 2013). Cluster-level significance will be denoted by pFDR_c, and voxel-level significance will be denoted by pFDR_v. Second-level multiple regression analyses were performed in SPM8 to determine the association between the components of interest and i) neuropsychological test scores (raw) and ii) clinical variables (i.e., MDI depersonalization, derealization, and composite scores, HAM-D total, and CAPS total) among the trauma-exposed group with MDD. ROI analyses were again carried out, thresholded at pFDR<0.05 using the a priori defined standardized masks (Kluetsch et al., 2014; Shirer et al., 2012; Ros et al., 2013).

Results

Participants

Groups did not differ in terms of age, years of education, sex distribution, or ethnicity.

The groups differed with respect to employment status, where the trauma-exposed MDD group had a significantly higher proportion of unemployed participants ($\chi^2_{(1,40)} = 4.19$, $p < 0.05$). The trauma-exposed MDD group scored significantly higher than the control group on all clinical subscales. See Table 1 for a description of the clinical and demographic characteristics of the study sample.

Table 1. Demographic and clinical characteristics of study sample

Characteristic	MDD (n = 21) Mean (SD)	Controls (n = 20) Mean (SD)
<i>Demographic characteristics</i>		
Age	40.2 (14.9)	35.3 (14.1)
Years of education	15.5 (3.7)	17.2 (2.7)
Sex (female:male)	11:10	10:10
Ethnicity (Caucasian) frequency	19	17
Employment status (employed/unemployed) frequency	8/13*	14/6
<i>Clinical characteristics</i>		
HAM-D	12.0 (5.8) **	0.5 (0.8)
CAPS (month)	29.1 (31.2) **	0.0 (0.0)
MDI		
Depersonalization	7.4 (2.6) **	5.1 (0.2)
Derealization	7.7 (3.6) **	5.3 (0.6)
Sum (depersonalization + derealization)	15.1 (5.6) **	10.4 (0.6)
CTQ		
Emotional abuse	12.3 (5.8) **	6.5 (1.3)
Physical abuse	7.5 (3.0) **	5.5 (0.8)
Sexual abuse	7.3 (5.4)	5.0 (0.0)
Emotional neglect	12.8 (4.7) **	8.1 (3.0)
Physical neglect	8.3 (4.7) **	5.6 (0.8)
Number of depressive episodes	13.2 (15.6)	NA
Age Onset Depression	19.8 (9.9)	NA

CAPS, Clinician-Administered PTSD Scale; CTQ, Childhood Trauma Questionnaire; HAM-D, Hamilton Depression Rating Scale; MDD, major depressive disorder; MDI, Multiscale Dissociation Inventory.

*significant group effect ($p < 0.05$)

**significant group effect ($p < 0.01$)

Neuropsychological performance

Compared to controls, participants with MDD and co-morbid trauma performed significantly worse on measures of verbal memory and executive functioning (i.e., mental flexibility, abstract reasoning, and forming concepts) (see Table 2). Specifically, patients retrieved significantly fewer words on the CVLT-II long-delay free recall subscale (LDFR) ($t(39) = 2.1, p < 0.05$) as compared to controls. On Color Trails 2, patients were significantly slower than controls ($U = 90.0, p < 0.01$). Patients also made more total errors on the WCST than controls, however, these results did not reach statistical significance ($U = 117.5, p = 0.07$). No group differences emerged on the COWAT phonemic fluency, CPT-II number of commissions or omissions, Color Trails 1, CVLT-II total and short-delay free recall, or WCST perseverative error raw scores.

Table 2. Neuropsychological performance comparing patients with MDD and trauma and healthy controls

Characteristic	MDD (n = 21) Mean (SD)	Controls (n = 20) Mean (SD)
<i>Measure</i>		
CVLT-II total raw	51.6 (9.2)	56.0 (9.8)
CVLT-II short-delay free recall raw	11.4 (2.6)	12.5 (3.3)
CVLT-II long-delay free recall raw	11.4 (2.5)*	13.2 (2.8)
COWAT phonemic (FAS)	46.3 (11.8)	42.8 (12.1)
Color Trails 1 raw (seconds)	31.4 (13.3)	26.8 (7.8)
Color Trails 2 raw (seconds)	67.1 (20.8)**	51.0 (13.9)
WCST total errors raw	23.5 (18.5) ^T	19.9 (20.2)
WCST perseverative errors raw	12.1 (11.8)	11.1 (11.1)
CPT-II omissions raw	4.2 (12.7)	1.6 (3.0)
CPT-II commissions raw	13.6 (7.5)	11.7 (5.4)

CVLT-II, California Verbal Learning Test-II; COWAT, Controlled-Oral Word Association Test; CPT-II, Conners' Continuous Performance Test; MDD, major depressive disorder; WCST, Wisconsin Card Sorting Test.

*significant group effect ($p < 0.05$), ** significant group effect ($p < 0.01$),

^T Trending group effect ($p = 0.07$)

Component identification

Four artifact-free components showed moderate-to-high spatial correlations with the predefined masks of the CEN (IC 8, $r = 0.46$), SN (IC 16, $r = 0.524$), and the DMN (IC 9, $r = 0.636$, and IC 18, $r = 0.38$) (see Figure 1). IC 8 (CEN) encompassed a large area of the right DLPFC (including the superior (BA 8) and inferior prefrontal cortex (BA 47)), extending to the bilateral inferior (BA 40) and superior (BA 7) parietal lobes, and left middle temporal gyrus (BA20, 21). IC 16 (SN) covered the bilateral insula (BA 13), extending to bilateral inferior frontal gyrus (BA 47), dorsal ACC and ventral ACC, as well as mPFC. IC 9 (DMN) consisted of the precuneus (BA 7) and ACC (BA 24, 32). IC 18 (DMN) encompassed the PCC, the right middle temporal gyrus (BA 39), medial prefrontal cortex (BA 9, 10), and the right inferior parietal lobe (BA 40). IC 8, IC 16, and IC 9/18 will be referred to as CEN, SN, and DMN, respectively.

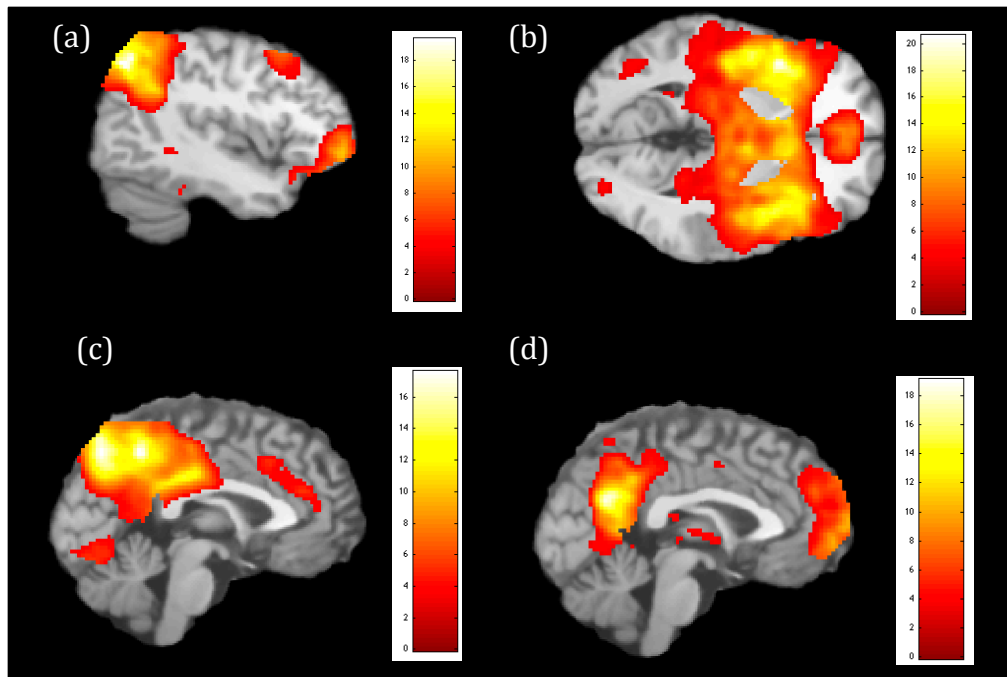


Figure 1. Independent components (IC) extracted for: (a) the central executive network (CEN), IC 8; (b) the salience network (SN), IC 16; (c) the default mode network (DMN), IC 9; (d) the default mode network (DMN), IC 18.

Statistical comparison of spatial maps

Compared to controls, participants with depression had increased functional integration of the left ventromedial PFC (vmPFC) within the DMN (IC9) (MNI coordinates: -18, 56, 8; $t = 4.93$, $p\text{FDRc} = 0.048$, BA10) (see Figure 2). No differential connectivity was found within the SN and CEN between the two groups.



Figure 2. Between group differences within the default mode network: Compared to healthy controls, patients with MDD showed a higher integration of the vmPFC ($p = 0.048$, FDR-corrected, $t = 4.93$) within IC 9.

Cognitive performance and spatial distribution

Second-level multiple regression analyses were performed among the group of trauma-exposed participants with MDD using their z-score spatial maps to examine the associations between cognitive performance variables and the CEN, SN, and DMN.

Within the salience network, better performance on the Colour Trail Making Test – Part 1 (i.e., faster completion time) was associated with increased connectivity of the left superior temporal gyrus (STG) (MNI coordinates: -36, -2, -20, $t = 5.20$, $p_{FDRv} = 0.049$, BA38). Within the default mode network (IC 18) there was a positive correlation between CVLT-II LDFR scores and the integration of the left inferior parietal lobe (IPL) (MNI coordinates: -50, -36, 36, $t = 10.95$, $p_{FDRv} < 0.001$, BA40) (see Figure 3a).

Further, increased connectivity of the right middle occipital gyrus within the DMN was related to worse performance on the COWAT FAS (MNI coordinates: 52, -58, -8, $t = 5.65$, $p_{FDRc} = 0.037$, BA19). Finally, increased integration of the precuneus within the DMN and was related to faster completion time on the Colour Trail Making Test – Part 2

(MNI coordinates: 14, -54, 28, $t = 5.72$, $p\text{FDRc} = 0.015$, BA31) (see Figure 3b). The CEN did not show any significant associations with cognitive test scores. Scores on the CPT-II and WCST were not significantly correlated with any of the components.

Clinical symptoms and spatial distribution

Higher HAM-D scores were associated with reduced connectivity of the PCC within the SN (MNI coordinates: -10, -50, 14, $t = 6.57$, $p\text{FDRc} = 0.006$, BA29) (Figure 3c).

Moreover, within the SN, increased integration of the right middle temporal gyrus (MTG) was related to higher scores on the MDI composite score (MNI coordinates: 52, -62, 8, $t = 7.17$, $p\text{FDRv} = 0.055$, BA39). Within the DMN, increased integration of the medial frontal gyrus was related to lower scores on the MDI depersonalization subscale (MNI coordinates: -14, 34, 36, $t = 7.29$, $p\text{FDRv} = 0.045$, BA9) (Figure 3d). Finally, CAPS (month) scores were positively correlated with connectivity of the left STG within the CEN (MNI coordinates: -50, -14, 4, $t = 5.98$, $p\text{FDRc} = 0.02$, BA22).

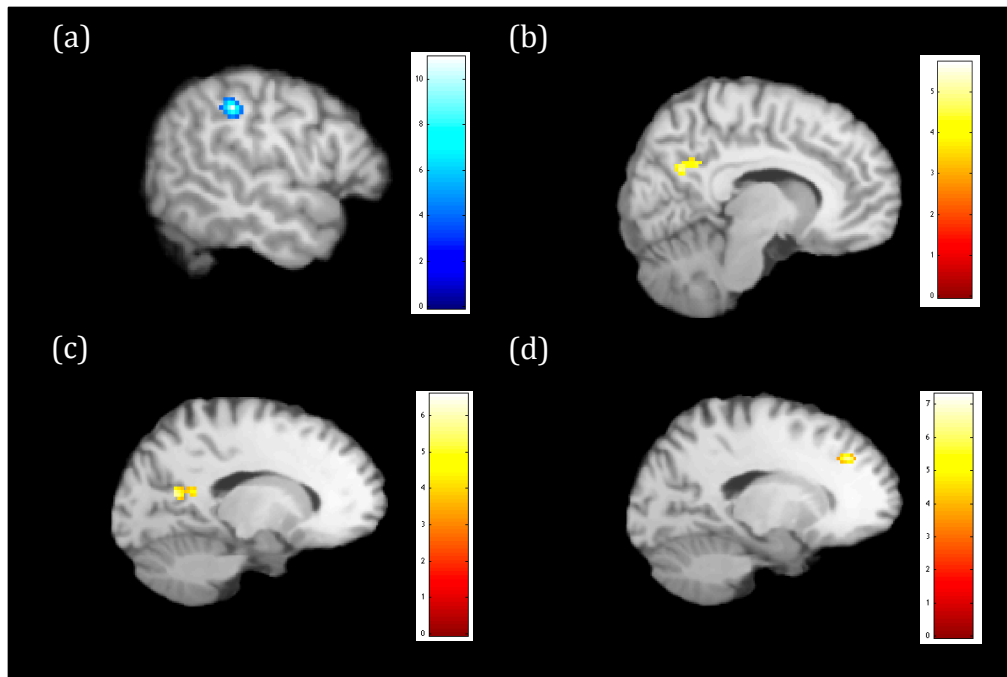


Figure 3. Regions (in blue) displaying positive correlations and regions (in yellow) displaying negative correlations with cognitive and clinical variables. a) correlation between CVLT-II LDFR and integration of the IPL within the DMN; b) correlation between completion time on Color Trail Making Test – Part 2 and integration of the precuneus within the DMN; c) correlation between HAM-D scores and connectivity of the PCC within the SN; d) correlation between MDI depersonalization scores and integration of the medial frontal gyrus within the DMN.

Abbreviations: CVLT-II LDFR, California Verbal Learning Test-II Long-Delay Free Recall; DMN, default mode network; HAM-D, Hamilton Rating Scale for Depression; IPL, inferior parietal lobe; MDI, Multiscale Dissociation Inventory; PCC, posterior cingulate cortex; SN, salience network.

Discussion

To our knowledge, this is the first study to examine the functional connectivity of the CEN, SN, and DMN in relation to cognitive performance and clinical symptoms in trauma-exposed patients with MDD. We found increased integration of the vmPFC within the DMN in patients compared to controls. Moreover, among the patient group, cognitive performance variables and symptoms of depression, PTSD, and dissociation were associated with distinct connectivity patterns within the three ICNs of interest.

Specifically, greater connectivity of the SN with the STG was associated with better performance on an attention task, whereas greater connectivity of the DMN with the inferior parietal lobe and precuneus was related to higher levels of performance on tasks of verbal memory and executive functioning, respectively. Greater severity of depressive symptoms was related to reduced connectivity of the PCC within the SN, whereas higher dissociation scores were associated with increased connectivity of the right MTG within the SN, and decreased integration of the medial frontal gyrus within the DMN. PTSD symptom severity was positively associated with connectivity of the STG within the CEN.

Comparing ICN activation patterns between patients with depression and controls, the only significant group difference that emerged was within the DMN, where patients demonstrated enhanced integration of the vmPFC within the DMN, as compared to controls. The vmPFC not only represents a core region of the DMN (Buckner et al., 2008), but it is also a critical region involved in self-referential processing (Lemogne, Delaveau, Freton, Guionnet, & Fossati, 2012; Northoff et al., 2006). This finding suggests

hyperconnectivity within the DMN in patients as compared to controls, consistent with previous studies in patients with depression (Alexopoulos et al., 2012; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Sheline, Price, Yan, & Mintun, 2010 but see de Kwaasteniet et al., 2015; Zhu et al., 2012 for conflicting findings). Among patients with PTSD, however, it is more common to observe disruptions in DMN integration (Bluhm et al., 2009; Rabellino et al., 2015; Sripada et al., 2012) where it has been proposed that early-life trauma disrupts the integration of the DMN (Daniels et al., 2010). Despite having a history of trauma exposure, the primary diagnosis among our patient sample was MDD, and the timing, type, and frequency of trauma were heterogenous among participants. These characteristics of our patient group may account for the increased connectivity observed within the DMN, compared to the pattern commonly observed in patients with PTSD. Future studies may compare patients with MDD with and without childhood trauma to explore if early-life trauma in this population results in reduced integration within the DMN. The finding that the vmPFC in particular showed enhanced connectivity in our patient group is particularly relevant given the role of the vmPFC in depressive self-referential focus (Lemogne et al., 2012). Clinically, this would likely manifest as increased rumination during the resting-state task in our patient group.

We found significant correlations between cognitive variables and connectivity within both the SN and DMN among the trauma-exposed participants with MDD. Better performance on the Colour Trail Making Test – Part 1, a measure of attention and processing speed, was related to greater connectivity of the left STG within the SN. The role of the STG in cognitive tasks has been demonstrated in patients with multiple

sclerosis (Achiron et al., 2012) and healthy controls (Bayless, Gaetz, Cheyne, & Taylor, 2006; Paulus, Feinstein, Leland, & Simmons, 2005). Specifically, the STG is activated during cognitive tasks requiring decision making (Bayless et al., 2006; Paulus et al., 2005) and thickness of the left STG correlates with information processing speed on the Mindstreams Computerized Cognitive Battery (MCCB) (Achiron et al., 2012). Given the role of the STG in cognitive processing, our results suggest that increased functional connectivity of the SN with this region may be a protective factor against deficits in attention and processing speed among patients with MDD. By contrast, decreased connectivity would be expected to result in cognitive processing deficits.

Within the DMN, increased connectivity with the left IPL was related to better performance on the CVLT-II LDFR condition, measuring delayed verbal memory. Notably, patients performed significantly worse than controls in the CVLT-II LDFR condition. The posterior parietal cortex is involved in attention and episodic memory retrieval, and is activated during verbal memory tasks (Hutchinson, Uncapher, & Wagner, 2009). Moreover, the IPL (BA 40) is considered to be a core component of the DMN (Buckner et al., 2008). As previously noted, patients with depression tend to show increased connectivity within the DMN as compared to controls, which is often viewed as reflecting increased self-referential focus and difficulty disengaging the task-negative state when needed. In our sample however, increased integration of the DMN with a core region of this network was related to better neuropsychological performance. Interestingly, studies in other populations, such as in patients with Parkinson's disease (Disbrow et al., 2014; Tessitore et al., 2012), healthy older adults (Ward et al., 2014), and

healthy controls (Yakushev et al., 2013) have reported that greater connectivity within the DMN is associated with better performance on different memory tasks. It is possible that among our sample of trauma-exposed patients with MDD, this hyperconnectivity noted within the DMN is an adaptive mechanism in that its recruitment of additional resources may help to maintain normal levels of cognitive performance. Similarly, our results indicate that increased connectivity of the precuneus (a core component of the DMN) within the DMN was related to better performance on Colour Trail Making Test – Part 2. This task measures processing speed, mental flexibility, and working memory, and compared to controls, the patient group was significantly slower at completing this task, reflecting poorer performance. Hence, consistent with our findings on the CVLT-II and DMN connectivity, we again see increased integration of the DMN associated with superior performance on a cognitive task. Importantly, the precuneus is involved in mental processes and self-operations (Cavanna & Trimble, 2006). Finally, within the DMN, increased integration of the middle occipital gyrus was related to worse performance on our measure of verbal fluency, the COWAT FAS subscale. The left middle occipital gyrus has been implicated in working memory processes in PTSD, where increased connectivity between this region and the mPFC was present during a working memory task (Daniels et al., 2010). Veer et al., found reduced connectivity of visual regions in patients with depression (Veer et al., 2010), but noted that this region is rarely implicated in depression and interpretations would therefore be speculative. Although our results suggest that increased connectivity of the DMN with this region is related to

poorer verbal fluency, further research will be required in order to interpret these findings.

Significant correlations also emerged between clinical variables (i.e., HAM-D, MDI, and CAPS scores) and each of the three ICNs. Within the SN, higher HAM-D scores were associated with reduced connectivity of the PCC, suggesting that greater depression severity is related to decreased integration of the SN within a node of the DMN. These results are contrary to earlier studies in patients with MDD, where it was reported that depression was associated with an increased integration of the SN with the DMN (Greicius et al., 2007; Jacobs et al., 2014). A possible factor accounting for the discrepancy in findings could be the history of trauma-exposure in our patient sample. For example, Wang et al. (2014). found that compared to patients with MDD without a history of trauma, those with trauma displayed a more widespread reduction in functional connectivity strength. Moreover, among patients with PTSD, aberrant resting-state connectivity between the DMN and SN has been observed (Bluhm et al., 2009; Lanius et al., 2010). As suggested by Daniels et al., (2011), early-life trauma may impact negatively on the integration of the DMN, and thus could also impact internetwork connectivity. Despite the heterogeneity among trauma subtype in our sample, the majority did report experiencing childhood trauma. Within the SN, increased integration of the right MTG, a component of the DMN (Laird et al., 2009), was related to higher scores on the MDI composite score (i.e., sum of depersonalization and derealization symptoms). The right MTG has been implicated in dissociative states, where patients with PTSD who dissociated during an fMRI traumatic script-driven imagery paradigm demonstrated

heightened levels of activation in this region, compared to controls (Lanius et al., 2002), supporting what has been termed the temporal lobe hypothesis of dissociation, based largely on epilepsy literature (Devinsky, Putnam, Grafman, Bromfield, & Theodore, 1989; Kenna & Sedman, 1965). On balance, these findings suggest that an enhanced connectivity of the right MTG within the SN, normally responsible for switching between the CEN and DMN, may underlie trait-like dissociative symptoms in depression.

Depersonalization symptoms of dissociation, as assessed by the MDI, correlated negatively with connectivity of the medial frontal gyrus within the DMN. This region has been linked to self-referential processing in depression (Lemogne et al., 2012). Interestingly, this finding suggests that higher levels of depersonalization (i.e., feeling as though one is disconnected from his/her body) are related to decreased connectivity of this core region associated with self-referential processing. Similar findings have been reported in patients with PTSD (Tursich et al., 2015). Depersonalization is an important feature of depression; related to a history of co-morbid trauma exposure and associated with greater illness severity (Molina-Serrano, Linotte, Amat, Souery, & Barreto, 2008; Žikić et al., 2009). These provocative findings suggesting that alterations in the SN and DMN underlie dissociative symptoms in MDD point towards the urgent need for future studies to address dissociative symptoms in patients with MDD to better understand underlying neural mechanisms and their impact on treatment outcome.

Lastly, increased severity of PTSD symptoms, as assessed by the CAPS, was associated with greater connectivity of the left STG within the CEN. As noted, the STG is involved in decision making (Bayless et al., 2006) and processing speed (Achiron et al.,

2012), and thus represents a cognitive processing region. These results are inconsistent with previous studies reporting decreased integration within the CEN in patients with PTSD (Cisler et al., 2013; Daniels et al., 2010), which has been shown to be associated with increasing CAPS scores (Rabellino et al., 2015). It is worth noting that a major difference between these studies and ours was the primary diagnosis of the patient sample, as our participants had a primary diagnosis of recurrent MDD. An interpretation of the current findings is that patients with greater PTSD symptom severity, in addition to their diagnosis of MDD, recruit additional neural resources which may help to maintain cognitive processing, as reflected through hyperconnectivity of the STG with the CEN.

The current study has several limitations. Most of the patients were taking psychotropic medications at time of testing (though they refrained from benzodiazepines for 12 hours prior to testing). Dutta et al. (2014). emphasize the lack of knowledge and often inconsistent results surrounding the impact of antidepressants on resting state activity in MDD. Future studies should carefully control for medication status. Further, we did not include a trauma-exposed control group, or a non-trauma exposed MDD group. The sample size is small, yet similar to other neuroimaging studies examining resting-state ICNs in psychiatric disorders. Finally, we assessed trait-like symptoms of depression, PTSD, and dissociation. Assessing state-like symptoms during scanning and neuropsychological testing would help to further elucidate the relation between these variables and ICNs.

To our knowledge, this is the first study to examine the association between neuropsychological performance and symptom presentation with resting-state ICNs in a

trauma-exposed sample with MDD. This study is an important first step towards better understanding the neurobiological mechanisms underlying transdiagnostic features, such as cognitive dysfunction and dissociation, characteristic of depression and trauma-related disorders. Importantly, our findings suggest that both cognitive performance and symptoms of depression, PTSD, and dissociation are related to DMN, SN, and CEN connectivity. Studies must continue to explore alterations in ICNs as a function of cognitive and clinical characteristics in this population with the goal of initiating treatment efforts that will target altered functioning in these ICNs. Lanius et al. (2015) have recently reviewed the literature on resting-state networks in PTSD and proposed neuroscientifically-informed treatment interventions to improve the functioning of the CEN, SN, and DMN in patients with PTSD. Here, the authors proposed interventions such as top-down cognitive remediation strategies, body scan meditations, and neurofeedback which may help to restore these neural networks and their related clinical and cognitive dysfunction. By increasing our understanding of the neural mechanisms underlying transdiagnostic variables characteristic of depression and trauma-related disorders, we will be able to move forward and propose treatment efforts aimed at restoring these core networks altered by psychiatric illness.

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Chapter 6: Conclusions

Summary of Findings

This thesis set out to examine developmental, behavioural, and neural correlates of cognitive processes in trauma-related disorders. Specifically, we investigated i) the relation between parental bonding and empathic responding in participants with PTSD, ii) episodic simulation and its association with parental bonding and neuropsychological performance in trauma-exposed persons with MDD, iii) the association between dissociative symptoms and neuropsychological performance in trauma-exposed persons with MDD and iv) intrinsic connectivity network (ICN) correlates of neuropsychological performance and clinical variables in trauma-exposed participants with MDD. The central hypothesis we tested was that less optimal levels of parental bonding, reduced levels of neuropsychological functioning, greater dissociative symptoms, and connectivity within the DMN, SN, and CEN would be related to impairments in the aforementioned areas of cognitive processing.

Study one (Chapter 2) demonstrated that women with PTSD related to childhood trauma showed altered empathic responding as compared to control participants. Specifically, women with PTSD reported significantly lower levels of perspective taking but higher levels of personal distress on the Interpersonal Reactivity Index. The patient group also reported higher levels of emotional empathic responding as assessed by the Toronto Empathy Questionnaire. I believe it is important to emphasize that our results do not suggest that women with PTSD are less empathetic than control participants; rather, they show greater emotional empathy coupled with reductions in cognitive empathy.

Comparing the effects of i) PTSD symptom severity, ii) childhood trauma severity, and iii) Parental Bonding Instrument (PBI) scores on empathic responding, we found that the Paternal Care subscale on the PBI was the only significant predictor of empathic responding. These findings provide evidence that the quality of parental relationships during development continue to impact social cognition, at least in the domain of empathy, in women with PTSD who experienced childhood trauma. Enhanced knowledge in the field of social cognition in patients with PTSD may assist in developing treatment strategies that improve interpersonal functioning and one's ability to utilize social support. These sorts of treatment targets are critical as social support represents the strongest protective factor against the maintenance of PTSD symptoms (Brewin, Andrews, & Valentine, 2000).

Study two (Chapter 3) showed that trauma-exposed participants with MDD produce fewer episodic details when imagining future events in response to neutral cue words, and are also slower at generating future neutral events, as compared to controls. These findings are in line with previous literature also reporting impairments in episodic simulation in patients with MDD (Bjärehed et al., 2010; Holmes et al., 2008; King, MacDougall, et al., 2011; Kosnes et al., 2013; A. MacLeod & Byrne, 1997; Morina et al., 2011) and with PTSD (Brown et al., 2013; Kleim et al., 2014). The majority of the studies that have looked at the moderating impact of emotional valence, however, have found deficits in imagining future positive events (Bjärehed et al., 2010; Kosnes et al., 2013; Morina et al., 2011). Methodological differences such as participant inclusion criteria (i.e., all participants with MDD in our study were required to have a history of trauma)

and differences in measurement of episodic simulation may partially account for the conflicting findings. Our findings do however extend on the work of Kensinger (2009) who posits that emotional events are more easily remembered than neutral events. Regarding developmental and neuropsychological variables, our research shows for the first time that optimal parental bonding, specifically maternal bonding, is a protective factor that promotes higher levels of episodic simulation. By contrast, reduced levels of neuropsychological functioning are a risk factor for impairments in episodic simulation. These findings draw on influential theories proposing the role of maternal relationships in the development of autobiographical memory (Fivush, Haden, & Reese, 2006; Harley & Reese, 1999; Nelson & Fivush, 2004), and on findings regarding the underlying neuropsychological mechanisms of autobiographical memory (Arie, Apter, Orbach, Yefet, & Zalzman, 2008; Conway & Pleydell-Pearce, 2000; Dalgleish et al., 2007; Raes et al., 2005; Sumner et al., 2014). These findings may lead to new advances in understanding and treating illness-related dysfunction in the area of imagining future events. Studies have focused on training programs for autobiographical memory and have also incorporated imagining positive future events into therapeutic interventions. If these methods are to be used as a clinical intervention for patients with MDD and trauma-related disorders, the underlying developmental and cognitive mechanisms that we have identified should be taken into account.

The third study (Chapter 4) first demonstrates that trauma-exposed persons with a primary diagnosis of recurrent MDD report significantly higher symptoms of dissociation across all subscales of the Multiscale Dissociation Inventory (i.e., disengagement,

depersonalization, derealization, emotional constriction, memory disturbance, and identity dissociation) as compared to controls. These findings are in line with reports by Molina-Serrano et al. (2008) and Zikic et al. (2009), which document that dissociative symptoms are in fact a feature of MDD. We then explored the association between depersonalization and derealization symptoms and neuropsychological performance on a battery of standardized measures aiming to examine fronto-temporally mediated cognitive domains. The main findings of this study also indicate a detrimental association between dissociative symptoms and performance across these neuropsychological domains, particularly in the areas of verbal and visuospatial memory, sustained attention, and processing speed. In striking contrast, no associations emerged between neuropsychological performance and severity of depressive symptoms and burden of illness (i.e., number of depressive episodes). These findings are consistent with previous studies that have demonstrated the negative impact of dissociation on neuropsychological performance in samples with trauma-related disorders (Cromer et al., 2006; DePrince et al., 2008; Dorahy et al., 2005; Haaland & Landrø, 2009; A. Krause-Utz et al., 2012; Roca et al., 2006). This study is the first to demonstrate this association in patients with a primary diagnosis of MDD. Clinically, assessing for dissociative symptoms in these patients will be important, given their relation to impairments in neurocognition and the impact that poor cognitive functioning can have on treatment response (McLennan & Mathias, 2010), functional outcome (Jaeger et al., 2006; McCall & Dunn, 2003), and burden of illness (Pandina et al., 2009).

Lastly, in study four (Chapter 5), we demonstrated that ICN (i.e., DMN, SN, and CEN) are related to neuropsychological performance and clinical variables. This study is the first to examine these associations in MDD. First, when comparing ICNs between controls and our patient group, we found increased integration of the vmPFC (a core region involved in self-referential processing (Lemogne, Delaveau, Freton, Guionnet, & Fossati, 2012; Northoff et al., 2006) within the DMN in patients. Moreover, among the patient group, greater connectivity of the SN with the STG was associated with better performance on an attention task, whereas greater connectivity of the DMN with the inferior parietal lobe and precuneus was related to higher levels of performance on tasks of verbal memory and executive functioning, respectively. Greater severity of depressive symptoms was related to reduced connectivity of the PCC within the SN. In addition, higher dissociation scores on the MDI depersonalization and derealization subscales were associated with increased connectivity of the right MTG within the SN, and decreased integration of the medial frontal gyrus within the DMN. PTSD symptom severity was positively associated with connectivity of the STG within the CEN. This study provides a foundation for future work studying the neurobiological mechanisms underlying transdiagnostic features of depression and trauma-related disorders, such as dissociation and neuropsychological dysfunction. Treatment efforts aimed at restoring the DMN, SN, and CEN, all of which are heavily implicated in psychopathology (Menon, 2011), may in turn lead to improvements in the neurocognitive domains and clinical symptoms which we have shown to be related to disruptions in these networks.

Overall, the aim of these studies was to contribute to the knowledge surrounding domains of impairment in the field of depression and trauma. We examined domains that are distinct, yet interrelated in that they have underlying cognitive processes. We expand on previous studies that have established dysfunction in these domains by studying if potentially transdiagnostic variables are related to these deficits. Specifically, we have examined the role of developmental variables, such as maternal and paternal care and overprotection. These variables are especially relevant in the populations we have studied. Attachment relationships are disrupted in these disorders our PTSD group and the majority of our depressed group experienced childhood trauma and it is possible that the caregivers were the perpetrators (Agid et al., 1999; Galynker et al., 2012; Levitan et al., 2009; Oakley-Browne, 1995; Schore, 2002). We also examined clinical variables with a focus on depersonalization and derealization symptoms. These symptoms are a core feature of PTSD and form the recently established dissociative subtype of the disorder (Spiegel et al., 2013). Critically, these features are also present in patients with depression and are related to a greater illness severity (Molina-Serrano et al., 2008; Zikic et al., 2009). In these patients, however, dissociative symptoms have received less attention. We also employed neuroimaging techniques that allow us to study three intrinsic connectivity networks that have been implicated in psychopathology (Menon, 2011) and more specifically been shown to be disrupted in MDD and PTSD. Using these techniques, we were able to examine if performance on neuropsychological tasks administered outside of the scanner was related to resting-state network connectivity (a relation which has been established in other disorders) (Disbrow et al., 2014; Dong et al., 2015; Seeley et al.,

2007; Yakushev et al., 2013). Overall, we have studied variables that are characteristic of persons with MDD and PTSD to see how they relate to areas of processing that we know are disrupted in these patient groups.

The results of these studies demonstrate that developmental, behavioural, and neural variables are related to distinct cognitive processes in PTSD and depression with a history of trauma. This work expands on our knowledge of the underlying mechanisms of social cognition, episodic simulation, and neuropsychological functioning among these populations. Specifically, we show that low levels of parental care during childhood may represent a risk factor for altered social cognition (i.e., empathy) and overgeneral episodic simulation of future events. Higher levels of performance on measures of neuropsychological functioning may be a protective factor promoting specificity of episodic simulation. Moreover, we have identified for the first time that dissociation may have debilitating effects on neuropsychological functioning in patients with depression. Lastly, we found that dysfunction in neuropsychological functioning is also related to connectivity within the DMN and SN.

Below, I discuss the limitations of the current studies followed by directions for future research in the field.

Limitations and Future Directions

The preceding studies have a number of limitations. First, the sample size in studies two and three was relatively modest for behavioural studies and may have limited the statistical power of the findings. Future studies should recruit larger samples sizes, which will help determine the reproducibility of our findings. Another limitation in regards to

our sample of patients with a primary diagnosis of MDD (studies 2-4) was the heterogeneity of trauma subtype. The majority of our sample ($> 75\%$) did report moderate-to-severe childhood trauma, but future studies with larger sample sizes should systematically compare patient groups according to trauma subtype (i.e., developmental versus single-incident). A strength of the first study (Chapter 2) was that all of the participants met criteria for PTSD resulting from childhood trauma, thus representing a relatively homogenous patient group. Future studies, however, will need to assess if the findings in this study extend to patients who developed PTSD following single-incident, rather than developmental trauma. Another limitation to consider regarding our patient group was that mood state was not homogenous; approximately half of the participants were currently depressed at time of testing, while the remaining were euthymic. Importantly, however, all participants had experienced >3 episodes of major depressive disorder, which is critical to our study as this illness profile demonstrates the greatest reduction in hippocampal volume (McKinnon et al., 2009), a region highly implicated in many of the cognitive processes assessed in the preceding studies. To account for the heterogeneity among mood state in our sample, we included a correlation analysis in each study to examine the relation between depression severity (i.e., HAM-D scores) and the variable of interest (e.g., episodic simulation scores, empathy scores, neuropsychological performance variables, ICN activation patterns).

Another limitation includes the use of self-report measures of empathy (i.e., IRI, TEQ) and parental bonding (i.e., PBI). A concern with the use of self-report measures of social cognition is the social desirability bias. Both scales, however, have strong convergent

validity with other measures of empathy (Davis, 1980, 1983; Spreng et al., 2009) and have been used in studies of other psychiatric populations, such as schizophrenia (Shamay-Tsoory, Shur, Harari, & Levkovitz, 2007) and mood disorders (O'Connor, Berry, Weiss, & Gilbert, 2002; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009; Wilbertz, Brakemeier, Zobel, Härter, & Schramm, 2010). Despite its retrospective nature, scores on the PBI show good concordance with sibling ratings (Duggan, Sham, Minne, Lee, & Murray, 1998; Gotlib, Mount, Cordy, & Whiffen, 1988). Further, they do not simply reflect current depressed mood state (Parker, Tupling, & Brown, 1979). Longitudinal studies that assess quality of parental care through observations in naturalistic settings (Dutra, Bureau, Holmes, Lyubchik, & Lyons-Ruth, 2009) would provide an optimal method of assessing parental relationships during development.

Overall, the current findings suggest that parental bonding, dissociation, and connectivity within ICNs are related to cognitive processes in trauma-exposed patients with MDD. In addition to demonstrating a link between dissociative symptoms and connectivity within both the DMN and SN, we have demonstrated that dissociation, rather than depression severity, is related to impairments in neuropsychological functioning. An important avenue for future research would be to investigate potential mechanisms subserving dissociative symptoms in patients with depression. We found that parental bonding impacts both social cognition in women with PTSD and also specificity of episodic simulation in patients with depression and a history of trauma. A link between parental bonding, and more specifically, insecure attachment, has been established in both disorders (Agid et al., 1999; Galynker et al., 2012; Levitan et al., 2009; Oakley-Browne,

1995; Schore, 2002; Wang, 1997). At a neural level, insecure attachment and depression have been shown to share overlapping neural networks (Galynker et al., 2012).

Dissociative symptoms have been studied in the context of attachment patterns, with remarkable results. Specifically, findings from Dutra et al.'s (2009) longitudinal study on predictors of dissociation found that the quality of caregiving, rather than the extent of abuse experienced, was the strongest predictor of dissociative symptoms in adulthood. Dissociative symptoms, which we have shown to be present in patients with MDD, should therefore be examined as a function of impaired attachment patterns in this population. Further, attachment is related to the development of cognition (De Ruiter & Van Ijzendoorn, 1993; West et al., 2013), and as we found that dissociative symptoms predict poorer cognitive functioning, it would be of interest to examine the interplay between attachment and dissociation in the context of cognitive processes.

Conclusions

The central aim of the thesis was to examine transdiagnostic variables related to cognitive processes in patients with MDD and a history of trauma. The findings of these studies could have implications for clinicians and researchers working with depressed persons, and particularly those with a history of trauma exposure. The majority of persons with depression will have experienced a distressing event in their lifetime (Spinhoven et al., 2014), and the assessment of transdiagnostic variables such as disrupted attachment patterns and dissociative symptoms should be undertaken. We have shown that these variables impact on social cognition, the ability to imagine future events, and neuropsychological functioning. These areas of functioning are critical to interpersonal

relationships, optimism, the ability to engage in therapeutic interventions, response to treatment, and daily functioning. Our finding that the default mode, salience, and central executive networks are related to both clinical and cognitive performance in this sample points towards the need to develop interventions that aim to restore the functioning of these ICNs with the goal of subsequently improving cognitive dysfunction and clinical symptoms. Taken together, my hope is that the findings of the preceding studies emphasize the need for assessing a history of trauma and its sequelae in patients with depression in both research and clinical settings.

References for General Introduction and Conclusions

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