

**Examining the neurophysiological impact of childhood sexual abuse in men: A series of
fMRI studies**

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Abstract

Childhood maltreatment can have detrimental consequences on individual well-being and cognitive functioning. One type of childhood maltreatment that remains stigmatized and under-researched among men is child sexual abuse (CSA). Research examining the neurophysiological consequences of CSA in males is limited even further. This dissertation presents three original research articles which provide preliminary evidence of the lasting neurophysiological impact of CSA in men. We recruited all male participants, of those who experienced CSA, some had PTSD (CSA+PTSD) others did not have PTSD (CSA-PTSD) allowing for the examination of differences in males with histories of CSA (but no PTSD) versus those who have CSA histories and PTSD. We also recruited control males with no CSA histories nor PTSD. Three functional MRI tasks and one resting state functional scan were obtained. The letter n-back, and an emotional picture n-back task were used in the first study as a measure of working memory and emotional processing. The first study highlights the lasting impact CSA can have on men, regarding brain activity during working memory, and working memory when negative emotional stimuli are involved. The second study examined how negative/traumatic memories are re-experienced. Results from the second study demonstrate that CSA impacts the neurophysiology of autobiographical memory for traumatic experiences. In the final study, resting state functional connectivity was examined within the default mode, salience and limbic networks, and differences in functional connectivity within the networks were observed. Together, these findings highlight the long-term neural impact of CSA and can validate the experience of men who have lived through CSA. They can also guide researchers and clinicians to potential avenues of support for the well-being of these men. These studies highlight the need for more research with men who have experienced CSA so we can fully understand their altered

neurophysiological responses, and how this knowledge can be used to support their mental health and continued wellness throughout their lives.

Statement of co-authorship

Three manuscripts are presented in this dissertation which were collaborative efforts. Jessie Moorman, Elisa Romano and Andra Smith assisted with each study from the study design, to providing critical feedback for the final manuscript edits. Jessie Moorman recruited participants, administered the clinical measures, obtained sociodemographic information, and attended the imaging sessions readily available to assist participants. Elisa Romano secured funding for these studies through a team grant and used her expertise to help conceptualise the studies. Andra Smith provided guidance and assistance with all aspects of the study, from the conceptualisation, to the neuroimaging analyses, and many, many, hours spent editing/providing feedback on early drafts. For the first manuscript “The influence of emotion on working memory: Exploratory fMRI findings among men with histories of childhood sexual abuse”, Michel Vezarov helped organize the large amount of neuroimaging results from the many examined contrasts, assisted with the search for other relevant research and assisted with early draft edits. Andrew Cameron created the emotional n-back task and performed the preliminary tests to ensure its efficacy. For the final manuscript “Altered resting state networks among men with histories of childhood sexual abuse: Exploratory findings”, Zhuo Fang was instrumental with the resting state functional connectivity analysis and manuscript preparation.

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List of Acronyms

ACC	Anterior cingulate cortex
AM	Autobiographical memory
ANOVA	Analysis of variance
BOLD	Blood-oxygen-level-dependent
CSA	Childhood sexual abuse
CTQ	Childhood Trauma Questionnaire
dACC	Dorsal anterior cingulate cortex
DMN	Default mode network
D-PTSD	Dissociative post-traumatic stress disorder
FC	Functional connectivity
fMRI	Functional magnetic resonance imaging
HPA	Hypothalamic pituitary adrenal
IAPS	International affective pictures system
MDD	Major depressive disorder
mPFC	Medial prefrontal cortex
PCC	Posterior cingulate cortex

PFC	Prefrontal cortex
PTSD	Post-traumatic stress disorder
rCBF	Regional cerebral blood flow
REB	Research ethics board
RSDI	Responses to script-driven imagery
RSFC	Resting state functional connectivity
RSN	Resting state network

Chapter 1

General Introduction

Childhood maltreatment can have lasting detrimental repercussions for the mental health of the abused/neglected child. Childhood sexual abuse (CSA), for example, is a form of childhood maltreatment that can contribute to such sequelae as post-traumatic stress disorder (PTSD) and depression in both sexes (Cicchetti & Toth, 1995; Kaufman & Charney, 2001; Romano & De Luca, 2001). CSA experienced by males can actually lead to a diverse range of outcomes from resilience (Ressel et al., 2018), to higher instances of suicidality (Martin et al., 2004; Molnar et al., 2001; Easton et al., 2013), psychological distress (Aosved et al., 2011), and frequent/severe substance use (Butt et al., 2011). Approximately 1 in 6 males experience sexual abuse during childhood (Dube et al., 2005; Finkelhor et al., 2014; Gartner, 1999; Romano & De Luca, 2001). Despite the prevalence of male CSA survivors and the severe consequences for their mental health, most research related to CSA has been conducted with females. Brain imaging has been one method used to investigate the impact of CSA on behaviour and well-being but little of this research has studied men specifically.

The neuroimaging research with samples of women who experienced CSA and mixed gendered samples with individuals who have experienced other forms of childhood maltreatment have provided empirical evidence of significant impacts on brain structure and function. The literature links these effects to playing a role in impairments in cognitive and emotional processing domains resulting from CSA (see below for details). The goal of this thesis was to use brain imaging techniques to ascertain the long-term effects of CSA on brain physiology, specifically in a sample of men. Childhood maltreatment is most frequently defined as emotional abuse, physical abuse, sexual abuse, emotional neglect and/or physical neglect before the age of 16. For the research summarized below this is the criteria for childhood maltreatment, unless

otherwise specified. CSA is commonly defined as an act of commission that can include a sexual act, abusive sexual contact, or noncontact sexual abuse (Leeb et al., 2008).

Sex Differences

Given that neuroimaging research with adult CSA survivors is mostly focused on women, it is important to consider the neurodevelopmental influence of biological sex. This is relevant to determine the neurological repercussions of CSA unique to men so they can be informed in a way that might better assist them in the pursuit of wellness.

Ritchie and associates (2018) used magnetic resonance imaging (MRI) to identify structural and functional connectivity differences in a large sample of males ($n=2466$) and females ($n=2750$) that were recruited from the UK Biobank—a biomedical population-based study with approximately 500 000 participants. Average whole brain volume, grey matter volume and white matter volume was significantly higher in males compared to females, with large effect sizes, when adjusting for age and ethnicity. Regarding subcortical measures, hippocampal volume differences between the sexes were attenuated when controlling for whole brain volume, however, amygdala volume remained significantly larger in males. Cortical structure volumes and surface areas were significantly greater in males, however cortical thickness was significantly greater throughout the whole brain in females, with few exceptions. Importantly, differences in cortical structures for decision making and emotion, such as the orbitofrontal cortex and insula, were found. Cortical thickness was significantly greater in males in the right insula. In the orbitofrontal cortex, cortical thickness was not significantly different between the sexes although the volume and surface area were greater in males. Regarding white matter connectivity, females exhibited greater default mode network (DMN) connectivity while males exhibited greater sensorimotor connectivity. This large sample study provided valuable insight into the innate differences in brain structure and functional connectivity that exist

between males and females, which in turn highlights the need for studies of both sexes when assessing the neurophysiological impact of CSA.

Childhood Sexual Abuse

The prevalence rates of CSA vary depending on the reporting source. In a large nationally representative study of Americans, Pérez-Fuentes et al., (2013) found 1 in 10 children (75% female, 25% male) experience sexual abuse before the age of 18. A meta-analysis by Barth and colleagues revealed 8-31% of girls and 3-17% of boys experienced CSA worldwide, with the lower end of the range corresponding to forced intercourse and the higher end of the range corresponding to non-contact forms of CSA (Barth et al., 2012). However, the rates of CSA in boys may be underreported. Romano and colleagues found that while almost 80% of males indicated disclosing sexual abuse, they waited approximately 15 years to reveal their experiences. Longer delays in disclosing abuse were associated with more externalizing behaviours (Romano et al., 2019). Following CSA, posttraumatic stress symptoms emerge with increased odds in those who experienced multiple types of childhood maltreatment (e.g. CSA and physical abuse) and those with less supportive social networks (Steine et al., 2017). The discrepancy of CSA prevalence rates between males and females could be falsely inflated by barriers that deter males from disclosing sexual abuse. Barriers that prevent males from disclosing CSA have been identified in sociopolitical (e.g. masculinity norms), personal (e.g. internal emotions) and interpersonal (e.g. abuser characteristics) domains (Easton et al., 2014). Given the differences in prevalence, it is understandable that most research related to CSA has been conducted with female participants. A conservative estimate would grant a population with approximately 7 females and 3 males per 10 (disclosed) CSA survivors.

Given these prevalence rates, the barriers for men to disclose and considering the differences in neurobiology between men and women, it is more than likely that the results from

imaging studies in women cannot be extrapolated to men. While most CSA research includes low numbers of males, or entirely female samples, there is more research including males when investigating other forms of childhood maltreatment, or early life stress in general. In order to determine if this research is transferrable to the population of males with CSA histories, it is important to determine if the neurological correlates of CSA are similar or different from other forms of childhood maltreatment, such as physical abuse or neglect.

Neurodevelopmental Perspective

Early research related to childhood maltreatment identified the prefrontal cortex (PFC), hippocampus, amygdala, and corpus callosum as key regions in the brain that are sensitive to early exposure to stress (Teicher et al., 1997). A recent review by Cross and colleagues (2017) indicated that the PFC, hippocampus and amygdala are especially sensitive to chronic, re-occurring interpersonal trauma during childhood, including, but not limited to, sexual abuse. This might be due to the cascading effects of repeated exposure to stressful/traumatic events in early life, along with genetic influences on stress responsivity. Adverse childhood experiences are thought to impact executive functions (i.e., working memory) and emotional regulation. This may occur by alterations of the functional connectivity of the PFC, hippocampus, and amygdala through neurochemical changes that occur as a result of repeated activation of the hypothalamic pituitary adrenal (HPA) axis during developmentally sensitive periods. This would consequently lead to increasing harm in individuals genetically predisposed to adverse stress reactivity. The neurological and stress reactivity changes that follow childhood trauma can induce psychopathologies such as PTSD and depression, however some individuals appear to be resilient to adverse stress reactivity (Cross et al., 2017). Understanding this variability in response to childhood trauma requires further investigation.

A review by Blanco et al., (2015) outlined structural and functional neurological changes associated with CSA and concluded that early intervention is necessary to improve the mental health of CSA survivors. The review provided support for a developmental approach to CSA research as some concerning cortical structural changes were related to age of onset of the abuse (Blanco et al., 2015). Following the trend of other CSA research, almost all of the neurological evidence provided for the review was based on female samples (Blanco et al., 2015). Results from human and animal studies have provided insight into the neurological processes involved with the stress response and emotional regulation. For example, damage to prelimbic medial prefrontal regions in adolescent (but not adult) rats lead to increased anxiety and helpless behaviours lasting into the adulthood, highlighting that adolescence is a critical stage for brain development (Uliana et al., 2020). A review by Teicher and Samson (2016) identified considerable support for a causal relationship between childhood maltreatment and changes in brain structure and function, evidenced by human and animal studies, neurobiological findings and the results from longitudinal studies. For humans, impacts on working memory, autobiographical memory and emotional processing were noted, among other considerations (e.g., depression; Teicher & Samson, 2016).

Previous Neuroimaging Literature

Structural imaging studies that examine CSA or other forms of childhood maltreatment have indicated that volumetric reductions in the corpus callosum, hippocampus, and the prefrontal cortex may occur as a result of this early life maltreatment. The corpus callosum is the main white matter tract that is centrally located, connects the cerebral hemispheres, and is important for coordination of neural activity between the hemispheres. The hippocampi and amygdalae are located in the medial temporal lobes. As important components of the limbic system, these structures are implicated in memory and emotion processing. The prefrontal cortex

is vital for executive functions, including working memory. Deviations from development in these regions, due to adverse childhood experiences, may result in significant cognitive impairments relative to the growth trajectories of a typically developed (or developing) brain.

Childhood maltreatment, including CSA, is associated with structural and volumetric brain changes. For example, an MRI study by Teicher et al., (1997) reported adolescents (average 12.9 years old) who experienced child abuse or neglect had a 17% reduction in the corpus callosum size compared with healthy controls. Their analysis included 15 children with documented or probable CSA, 10 girls and 5 boys, among other adolescents who experienced different types of childhood maltreatment such as physical abuse or neglect (Teicher et al., 1997). Another example by Andersen et al., (2008) used MRI scans of adult women CSA survivors ($n=26$) and found reduced hippocampal volumes in participants who experienced repeated CSA between the ages of 3-5 and 11-13. Women who were 9-10 at the age of onset had associated corpus callosum area reduction and had significantly more PTSD-like symptoms than the other age stages, while women who were 14-16 when the abuse began exhibited reduced grey matter volume in the frontal cortex (Andersen et al., 2008). In addition, using structural MRI, Bremner and colleagues (2003) found significantly reduced hippocampal volume in adult women with PTSD and CSA histories ($n=10$), compared to those with no PTSD ($n=12$) and those with neither PTSD nor CSA histories ($n=11$; Bremner et al., 2003). Considering these studies, the age and duration of abuse are important considerations, given that those factors may influence structural anomalies related to CSA.

Evidence from several studies has suggested that males with PTSD from childhood maltreatment may be more at risk for adverse neurodevelopment than females. For example, Rock et al., (2018) indicated that adolescent males with PTSD from childhood maltreatment had

more pronounced corpus callosum volume reduction than females with PTSD from childhood maltreatment and healthy controls (Rock et al., 2018). Additionally, a recent review found substantial evidence to support corpus callosum atrophy associated with PTSD from childhood maltreatment, specifically in the mid-body and posterior corpus callosum (Killion & Weyandt, 2018). Taken together, structural MRI scans of children and adults who experienced childhood maltreatment indicate anatomical vulnerability to the corpus callosum, hippocampus, and the prefrontal cortex. Structural alterations will inevitably lead to neurophysiological vulnerability. In fact, the prefrontal cortex and hippocampus are also often implicated in functional imaging studies related to childhood maltreatment.

Several dynamic imaging studies with adult women have identified cognitive and emotional processing differences that can be related to childhood maltreatment. One positron emission tomography (PET) study with a sample of adult women CSA survivors with ($n=10$) and without ($n=12$) PTSD reported women with PTSD from CSA had greater blood flow in the anterior PFC, posterior cingulate, and the motor cortex while listening to personalized CSA trauma scripts. The women with PTSD from CSA also exhibited decreased blood flow in the medial PFC and reported more fear and anxiety symptoms than the women without PTSD. These atypical patterns of activation could indicate difficulty with the emotional regulation of fear responses in CSA survivors with PTSD (Bremner et al., 1999). Another PET study found adult women with PTSD from CSA ($n=10$) had atypical activation in regions associated with memory and emotion while listening to emotionally charged words, but the activation was not significantly different for neutral word pairs. The women with PTSD from CSA had less blood flow in the medial PFC, orbitofrontal cortex, anterior cingulate, fusiform/inferior temporal gyri and the left hippocampus, but increased blood flow in the left middle frontal gyrus, posterior

cingulate and motor/visual association cortices, compared with women without PTSD/CSA histories ($n=11$; Bremner et al. 2003).

More recently, diminished activation in the medial prefrontal cortex during the recollection of stressful versus neutral events may be characteristic of PTSD (Dahlgren et al., 2018). Dahlgren and colleagues employed a functional MRI (fMRI) twin pair study with combat exposed male twins that had PTSD ($n=9$), and their identical twins that were not exposed to combat trauma and did not have PTSD ($n=9$). They also included combat exposed male twins that did not have PTSD ($n=12$), and their identical twins that were not exposed to combat trauma and did not have PTSD ($n=12$). They reported that the combat exposed twins with PTSD had reduced activation in the medial prefrontal cortex during a stressful versus neutral script-driven imagery task, compared with their identical twins, and the other two twin groups. The hypoactivation observed in the medial prefrontal cortex is consistent with other script-driven imagery tasks with trauma exposed women (Bremner et al., 1999; Bremner et al. 2003; Lanius et al., 2001; Shin et al., 1999)

While imagining an autobiographical trauma script one PET study indicated adult women with CSA and PTSD ($n=8$) have increased blood flow in the anterior temporal poles and orbitofrontal cortex. The CSA survivors without PTSD ($n=8$) also had this increase but to a lesser extent than CSA survivors with PTSD, which may indicate a heightened perception of surroundings in CSA survivors, particularly those with PTSD. The women with CSA histories but no PTSD had greater activity in the insular cortex and the anterior cingulate gyrus while the women with PTSD from CSA had decreased activity in the anterior frontal regions and inferior frontal gyrus. This suggested different patterns of brain activation among CSA survivors and CSA survivors with PTSD during a trauma recollection task (Shin et al., 1999).

Recently, Van Hoof and colleagues (2017) conducted a fMRI study with adolescents who had PTSD from CSA (n=17 females n=2 males), healthy control participants and participants with internalizing disorders. The adolescents with PTSD from CSA reacted slower to emotional faces than adolescents with internalizing disorders and reported higher levels of fear regarding neutral faces than adolescents with internalizing disorders and healthy controls. There were no significant regional brain differences noted between the three groups and no direct comparison between adolescents who experienced CSA and healthy controls was made. The authors proposed the slower reaction times and higher levels of fear reported were the result of a negative attentional bias which could interfere with daily social interactions and could even inhibit people who endure CSA from seeking treatment for the abuse (Van Hoof et al., 2017).

Resting state fMRI

Resting state fMRI measures blood-oxygen-level-dependent (BOLD) signal changes while participants are at rest (i.e., awake and not thinking about anything in particular). Changes in BOLD signal, inferred as functional connectivity, are strongly correlated between brain regions. At rest, compared to when individuals are engaged in goal directed behaviours, several networks become apparent through correlations (e.g., the salience and default mode network; Shulman et al., 1997; Raichle et al., 2001; Raichle 2015). Resting state fMRI studies can provide important insights into neurophysiology of specific populations with varying mental health and cognitive profiles. Components of the default mode network are important for emotional processing (ventromedial prefrontal cortex), self-referencing (dorsal medial prefrontal cortex) and remembering previous experiences (posterior regions; Raichle 2015), all important and potentially affected by CSA.

Several studies have examined lasting impacts of childhood maltreatment through resting-state functional connectivity (RSFC) methodologies, however no published studies have

examined RSFC in a group of adult males who experienced CSA. Both sexes were studied in van der Werff et al., (2013), who reported that childhood emotional maltreatment was associated with altered RSFC within the limbic system and the salience network, which could be indicative of the emotional and cognitive disturbances experienced by adults who experienced childhood maltreatment (van der Werff et al., 2013). Another study by van der Werff et al., (2013) found altered RSFC within the salience network in a group of adults who were exposed to childhood maltreatment compared to healthy controls ($n=11$). Individuals exposed to childhood maltreatment were further divided into those who were resilient ($n=11$), including those without a diagnosed axis-1 disorder from the DSM-IV, and those who were vulnerable ($n=11$), including those with an axis-1 disorder. The researchers found resilient individuals had increased negative RSFC between a seed region in the salience network, the left dorsal anterior cingulate cortex, and the fusiform/lingual gyri—which is an important functional region for declarative memory. Higher activity in the salience network, which is important for attending to internal and external stimuli, was negatively correlated with activity in brain regions important for declarative memory in individuals resilient to childhood maltreatment. This could indicate that when resilient individuals attend to information, they are less likely to draw upon traumatic memories (van der Werff et al., 2013).

The default mode network (DMN), important for both cognitive and emotional processes including self-referencing, is also impacted by the lasting effects of childhood maltreatment, and PTSD. In 2017 Lu and colleagues imaged adults with ($n=24$) and without ($n=24$) childhood maltreatment histories. Differences in interregional connectivity and intraregional connectivity within the DMN were identified. Previous studies reported aberrant DMN connectivity in individuals with PTSD, however this was the first to report differences in DMN connectivity

related to early stress exposure while excluding psychological disorders. In 2009, Bluhm et al., found aberrant DMN connectivity in adult women with PTSD from childhood maltreatment ($n=17$) who exhibited reduced connectivity from a seed region including the posterior cingulate cortex and the precuneus to the medial PFC, and from the same seed region to the right hippocampus, amygdala, and insula compared to healthy controls ($n=15$). More recently, Cisler (2017) reported adolescent girls with physical or sexual assault histories ($n=26$) had reduced functional connectivity between the amygdala and the medial PFC compared with healthy control girls ($n=30$). Weakened connections between the amygdala and medial PFC could explain greater negative affect and reduced emotional regulation as a function of weakened top-down processing from the medial PFC to the amygdala (Cisler, 2017).

Overall, resting-state studies with maltreated individuals have reported differences in functional connectivity in the DMN, salience and limbic networks. The impact of childhood maltreatment on these resting state networks may contribute to cognitive and emotional difficulties and thus is important to investigate in men who have experienced CSA specifically.

fMRI Tasks to Study CSA

In addition to resting state fMRI, task-based fMRI can be implemented to assess working memory and emotional processing to understand the impact of childhood maltreatment, including CSA. Individuals with PTSD experience intrusive thoughts from internal or external triggers which could diminish working memory accuracy in everyday tasks by detracting attention from the task at hand. When sentences include traumatic content, those with PTSD recalled fewer words than controls, compared to the word recall rate of sentences with neutral content (Schweizer & Dalgleish, 2011). In everyday life, emotion can interfere with working memory. In the context of PTSD, an emotional experience, such as a flashback, could result in forgetting to take, or taking too much medication, either of which would impact well-being.

The n-back task has been used extensively to study working memory processing in an fMRI environment. It is a test of information processing capacity whereby the participant must temporarily store and update incoming information, then manipulate this information in order to respond correctly (Owen et al., 2005). Philip and colleagues used the n-back paradigm and found increased temporal-parietal and prefrontal cortex activation in adult participants that were exposed to childhood maltreatment ($n=14$), but otherwise free of psychological and personality disorders, compared with healthy control participants ($n=13$). This aberrant activity was associated with significantly reduced accuracy in the working memory condition, which suggests diminished working memory capacity is associated with childhood maltreatment apart from psychological/personality disorders (Philip et al., 2016).

The n-back task can be modified to study emotional working memory by including affective and neutral stimuli. A recent meta-analysis by Schweizer and associates (2019) reported that emotional information influences working memory processing in the brain over and above the processing of neutral information. This was evidenced by greater ventrolateral PFC, amygdala, and temporal-occipital involvement for emotional compared to neutral stimuli, without significant differences in performance measures such as reaction time and accuracy. In some studies included in the meta-analysis, clinical populations responded less accurately than healthy controls when emotional stimuli were included in working memory tasks (Schweizer et al., 2019).

Although emotional working memory can give insight into how emotional context could interfere in everyday life, it does not allow researchers to investigate how people with and without PTSD process emotional memories of trauma based on their personal histories. A trauma-script driven imagery task can be used to investigate differences in emotional memory

processing as it relates to one's self. During this task, participants listen to audio scripts related to neutral and traumatic events from their past. Lanius and colleagues adapted a trauma-script driven imagery task for fMRI and reported that adult participants with PTSD from sexual assault or a motor vehicle accident ($n=9$) had reduced activation in the thalamus, anterior cingulate and medial frontal gyrus during traumatic memory recall compared with participants who experienced the same types of trauma but did not have PTSD ($n=9$). The authors suggest the reduced neural activation in the thalamus could be related to dissociative and flashback PTSD symptoms, since the thalamus is involved in transmitting sensory messages to other brain regions, including the prefrontal cortex (Lanius et al., 2001). Thus, it is important to consider that different symptoms experienced while participating in studies using the script-driven imagery paradigm can impact neurophysiological findings. The Responses to Script-Driven Imagery Scale (RSDI; Hopper et al., 2007) can assess reexperiencing, avoidance, and dissociative symptoms that might occur as a result of the traumatic memory recall during the trauma-script driven imagery task.

Although it may be more difficult to obtain a sample of male CSA survivors, it is imperative that we attempt to understand how CSA influences males. Again, despite the prevalence of male CSA survivors and the severe consequences that can impact their well-being, most neuroimaging research related to CSA has been conducted with female participants. The proposed research intends to address the lack of male CSA centered neuroimaging research. Valuable insights into the neural correlates of male-experienced CSA will be examined using resting-state functional connectivity of the salience network (important for attending to stimuli), the limbic network (important for emotion) and the DMN (important for cognition, self-regulation and emotion), and task-based fMRI of emotional processing, and working memory.

Due to the variety of sequelae from CSA in men and the significant impact that PTSD has on brain structure and function, it was also important to consider PTSD in the sample of men recruited for this study. Until the proposed study, the investigation into the neural correlates of CSA specifically in males with and without PTSD has not occurred. As such, identifying the neural correlates of CSA in a sample of adult males with and without PTSD is worthy of further investigation.

Presentation and Impact

The dissertation is presented in article format. The first article examines emotional working memory with the letter n-back and the emotional n-back tasks. The next article focusses on re-experiencing traumatic autobiographical memories. The final article examines the functional connectivity of the DMN, salience and limbic networks at rest.

Briefly, we recruited all male participants, of those who experienced CSA, some had PTSD (CSA+PTSD) others did not have PTSD (CSA-PTSD), This allowed for the examination of differences in males with histories of CSA (but no PTSD) compared with those who had CSA histories and PTSD. We also recruited males with no CSA histories nor PTSD. All the participants attended one neuroimaging session where structural brain images, and resting state activation was captured followed by three functional MRI tasks. The first task, the letter n-back is a reliable fMRI task that was used to measure working memory performance. The second task, an emotional pictures n-back task, featured images from the International Affective Picture System (IAPS; Lang et al., 2008), with responses required for 1-back and 2-back conditions. These pictures have well established norms for emotional valence ranging between negative, neutral, and positive. This task allowed us to examine differences in neural activation and response times for emotional working memory and information processing. Finally, the script-driven imagery task allowed for the investigation of differences in activation between those with

and without CSA histories while processing traumatic experiences from the past. These three articles foster a better understanding of how memory in males is influenced by their histories of abuse and current mental health symptoms. This, in turn, provides preliminary neurophysiological evidence of the impact CSA has on the male brain and thus behaviour. Armed with this information, an increased awareness of CSAs impact can be shared with the hopes of refining the ways in which both research and clinical practice is performed with this understudied, yet vulnerable, population to improve their mental health, well-being, and interpersonal relationships.

Hypotheses

Study 1. The influence of emotion on working memory: Exploratory fMRI findings among men with histories of childhood sexual abuse.

In the first study, working memory, and the potential influence of negative emotional stimuli on working memory, were examined. The objective was to provide preliminary insight into the neural basis of the impact of CSA in males during two working memory fMRI tasks, one with (emotional picture n-back) and one without (letter n-back) emotional content. It was first hypothesized that brain activity during working memory among CSA males would be different than in non-CSA males; specifically that CSA males would have higher PFC activation. The basis of this prediction being that more cognitive resources will be required to complete the working memory task for the men with CSA histories. Finally, it was hypothesized that the emotional content in the emotional picture n-back task would accentuate this difference in working memory activity particularly in participants with CSA and localized in more limbic areas (e.g., hippocampus, amygdala).

Study 2. Traumatic autobiographical memories: Preliminary fMRI findings among men with histories of childhood sexual abuse.

In the second study, we examined traumatic AM processing. The objective was to provide insight into how CSA affects the neural basis of traumatic AMs. It was hypothesized that differences in activation while experiencing traumatic/negative compared to neutral life events would be found between males with CSA histories and those without. In particular, it was expected that men without CSA histories would process the negative memory with more posterior cortices, related to perceptual (rather than emotional) information of their memory. Further, it was expected that there would be significant differences in activation within the CSA group, depending on the presence or absence of a PTSD diagnosis. As such, the CSA group was divided into those with (CSA+PTSD) and without PTSD (CSA-PTSD). For the final hypothesis, we expected, as previous studies have shown (Dahlgren et al., 2018; Driessen et al., 2004; Lanius et al., 2001, 2003; Shin et al., 2004) that trauma exposed participants without PTSD would re-experience their traumatic AM with more prefrontal activation compared to those with PTSD.

Study 3. Altered resting state networks among men with histories of childhood sexual abuse: Exploratory findings

The final study explored RSFC within the salience, limbic, and DMN in a sample of adult males who experienced CSA, with and without PTSD, compared with non-CSA males without PTSD. It was hypothesized that differences would be found between CSA and non-CSA participants in resting state functional connectivity patterns in networks commonly implicated in self-referencing, emotional processing, and memory, namely the default mode, limbic and salience networks. Although several studies have examined lasting impacts of childhood maltreatment through RSFC methodologies, no published studies have examined RSFC in a group of adult males who experienced CSA. As such, the resting state investigations are

exploratory. This research will provide valuable insight into the impact of their CSA experiences on the functional connectivity of these networks.

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Chapter 2

The influence of emotion on working memory: Exploratory fMRI findings among men with histories of childhood sexual abuse.

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Abstract

Background: Childhood maltreatment can have detrimental consequences on individual well-being and cognitive functioning. One type of childhood maltreatment that remains stigmatized and under-researched among men is child sexual abuse (CSA). Research examining the neurophysiological consequences of CSA in males is limited even further.

Objective: To provide preliminary insight into the neural basis of the impact of CSA during two working memory tasks.

Participants and Setting: Men with CSA histories, with and without post-traumatic stress disorder (PTSD; CSA+PTSD $n = 7$, mean age = 45; CSA-PTSD; $n = 9$, mean age = 41), and men without a CSA history nor PTSD ($n = 13$, mean age = 36) participated in the study at a local hospital.

Methods: Participants completed a letter n-back task and an emotional picture n-back task during fMRI to measure working memory and the influence of emotion on working memory. They also completed self-report measures to assess mental health and childhood abuse histories.

Results: In the letter n-back task, men with CSA+PTSD had less activation in the cerebellum and left fusiform gyrus compared to CSA-PTSD men. During the working memory task with negative emotional pictures the control group had greater frontal activation, while the CSA-PTSD group had greater limbic activation. Analyses were performed with independent-samples t-tests.

Conclusions: This study provides preliminary empirical evidence of the impact CSA can have on men regarding working memory when negative stimuli are involved. It highlights that CSA, even without a diagnosis of PTSD, can have a significant neurophysiological impact. It also provides clinicians with information to support well-being and help with potential day to day challenges.

Introduction

There can be lasting repercussions on the mental health of children who experience abuse or neglect. One form of childhood maltreatment that remains particularly stigmatized and under-researched among males is childhood sexual abuse (CSA). CSA among males can lead to a diverse range of outcomes, from pathogenic outcomes, such as post-traumatic stress disorder (PTSD; Tolin & Foa, 2006), depression, higher instances of suicidality (Easton et al., 2013; Martin et al., 2004; Molnar et al., 2001), and substance use difficulties (Butt et al., 2011), to salutogenic outcomes, such as resilience (Ressel et al., 2018).

CSA prevalence and impact on development

A well-accepted statistic is that 1 in 6 males has experienced sexual abuse during childhood (Dube et al., 2005; Finkelhor et al., 2014; Gartner, 1999; Romano & De Luca, 2001). Despite the prevalence of CSA among males and the range of potential CSA-related mental health consequences, research with this population remains limited. In the current study, we approached the topic of male CSA from a neurophysiological perspective. Although men with histories of CSA can experience diverse clinical outcomes, there are few published studies examining the neurophysiology of CSA, which may help explain how dysregulation of biological stress systems and adverse brain development are linked with the expression of certain CSA-related mental health difficulties (De Bellis et al., 2001).

The prefrontal cortex (PFC), and limbic regions such as the hippocampus and amygdala are sensitive to early exposure to stress; early interventions (e.g., social support) could provide the enriching environments that are required to establish resilience to early stress (Lupien et al., 2009). A review by Cross et al. (2017) indicated that the PFC, hippocampus, and amygdala are especially sensitive to chronic interpersonal trauma during childhood, including, but not limited to, sexual abuse. These findings may be explained by the cascading effects of repeated exposure

to stressful and traumatic events in early life, along with genetic influences on stress responsivity (Cross et al., 2017). In a study examining responses to novel compared to familiar faces, participants with childhood maltreatment histories and an inhibited (i.e. shy) temperament had greater activation in the fusiform gyrus and hippocampus compared to the uninhibited group of participants (Edmiston & Urbano Blackford, 2013). A review by Hart and Rubia (2012) noted cerebellar volume reductions are consistently documented in maltreated children and adolescents with PTSD (Hart & Rubia, 2012). The effects of childhood maltreatment are evident through structural and functional neurophysiological differences and are influenced by contextual factors such as temperament.

Adverse childhood experiences are thought to impact executive functions (e.g., working memory) and facets of emotion regulation (e.g., emotional identification and modulation). This may occur because of alterations of the functional connectivity of the PFC, hippocampus, and amygdala through neurochemical changes that occur as a result of repeated activation of the hypothalamic pituitary adrenal (HPA) axis during developmentally-sensitive periods (Cross et al., 2017). Consequently, such changes can lead to increasing harm (i.e., increased risk of psychiatric, emotional, and cognitive disturbances) in individuals who are genetically predisposed to adverse stress reactivity. In sum, the neurological and stress reactivity changes that follow childhood traumatic experiences (e.g., sexual abuse) can induce a range of mental health outcomes from resilience to such psychopathologies as PTSD and depression (Cross et al., 2017).

Blanco et al. (2015) outlined structural and functional neurological changes associated with CSA and concluded that early intervention is necessary to improve the mental health of CSA survivors. The review provided support for a developmental approach to CSA research as

some concerning cortical structural changes were related to age of onset of the abuse (Blanco et al., 2015). Results from human and animal studies have provided insight into the neurological processes involved with the stress response and emotional regulation. For example, damage to prelimbic medial prefrontal regions in adolescent (but not adult) rats lead to increased anxiety and helpless behaviours lasting into the adulthood, highlighting that adolescence is a critical stage for brain development (Uliana et al., 2020). A review by Teicher and Samson (2016) identified considerable support for a causal relationship between childhood maltreatment and changes in brain structure and function, impacts on working memory, and emotional processing were noted, among other considerations (Teicher & Samson, 2016).

Working Memory and the Influence of Emotion

Working memory is defined as an integrative cognitive process where existing knowledge is combined with temporarily stored new information in order to achieve a particular goal-oriented behaviour (Baddeley, 2000). As such, working memory requires maintained focus and attention, which is important for learning, problem solving, reasoning, and other important faculties required for successful daily functioning (Baddeley, 2003; Baddeley, 2010). Zelazny et al. (2019) noted that while childhood maltreatment was associated with an increase in suicidal behaviours, higher working memory and executive functioning scores were associated with a reduced risk of suicidal behaviour (Zelazny et al., 2019). A meta-analysis examining the lasting impact of child maltreatment on cognitive domains including working memory found working memory impairments observed in children occurred with large effect sizes and occurred with moderate effect sizes into adolescence (Masson et al., 2015). A meta-analysis of studies that examined the impact of PTSD on working memory in older adults and found older adults with PTSD had consistently lower test scores on all domains measured compared to older adults

without PTSD (Schuitevoerder et al., 2013). Taken together, childhood maltreatment and PTSD are associated with working memory impairments throughout the lifespan, and higher functioning working memory can reduce the risk of suicidal behaviours.

The influence of emotion on working memory has been explored for several decades, with increasing popularity in recent years due to its clinical relevance and influence on higher-order cognitive processes, such as emotion regulation (Mikels & Reuter-Lorenz, 2019). Different types of emotional stimuli have been used in research, such as facial expressions, auditory and picture stimuli (Tyng et al., 2017). These stimuli can be positive (e.g. a happy face, a good memory or a joyful picture) or negative (e.g. an angry face, a traumatic memory or a scary picture). A report by Schweizer et al. (2019) included a meta-analysis of functional magnetic resonance imaging (fMRI) research ($n = 33$) and a meta-analysis of behavioural studies ($n = 165$) on the influence of emotional information on working memory. Findings showed that emotion information influences working memory processing in the brain over and above the processing of neutral information, even when accuracy on working memory tasks is seemingly consistent between emotional and neutral content. These findings were demonstrated through greater ventrolateral PFC, amygdala, and temporal-occipital involvement during emotional stimuli compared to neutral stimuli in psychologically healthy populations, even though there were no significant differences in task accuracy. However, some research has shown that clinical populations responded less accurately than non-clinical controls when emotion eliciting stimuli were included in the working memory tasks (Schweizer et al., 2019).

The increased processing demand that occurs for emotional over neutral stimuli, without accompanying differences in accuracy (in non-clinical populations), implies that greater cognitive resources are required when emotional stimuli are present during working memory

performance. By introducing emotional stimuli to a working memory task, working memory capacity might become overwhelmed and lead to failures in achieving goal-directed behaviours (Figueira et al., 2017). This is especially problematic for certain clinical populations, such as those with PTSD or Major Depressive Disorder (MDD) since performance on working memory tasks is known to be impacted among these populations (Joorman et al., 2011; Schweizer & Dalgleish, 2011). Individuals with PTSD may experience intrusive thoughts from internal or external triggers which could diminish working memory accuracy in everyday tasks by detracting attention from the task at hand. For example, Schweizer and Dalgleish (2011) found that, when sentences included traumatic content, those with current PTSD from a traumatic incident (e.g., sexual assault, motor vehicle accident) recalled fewer words than controls with similar trauma history who never met criteria for a PTSD diagnosis, compared to the word recall rate of sentences with neutral content. These findings suggest that individuals with PTSD experience inhibition in their ability to use working memory when emotional content is present.

Emotional content might impede working memory but could also improve working memory capacity. Executive control, important for working memory, addresses the attention processes required to achieve goal-directed behaviours (McCabe et al., 2010). Pessoa (2009) proposed a dual-competition model of executive control whereby emotional information can either impede or benefit goal accomplishment depending on the relevance of the emotional stimulation to the goal. Highly intense emotional stimulation might impair information processing; however, less intense negative stimuli has been shown to enhance information processing (Sussman et al., 2013). Sussman and colleagues instructed participants to ignore content of emotional pictures with different arousal levels and report the colour of a dot. Results indicated that low arousal inducing negative distractor stimuli enhanced performance in an

attentional task with IAPS images whereas high arousal inducing negative distractor stimuli inhibited performance (Sussman et al., 2013). Mammarella and colleagues administered a working memory task with emotional words and found a negativity bias, where more negative words were remembered. Emotional stimuli might enhance working memory processing when additional context is provided through emotionally salient attention-grabbing content (Mammarella et al., 2013).

Various fMRI methodologies can be implemented in order to assess working memory and emotional processing. The n-back task (Kirchner, 1958) has been used extensively to study working memory processing in an fMRI environment (Owen et al., 2005). It is a test of information processing capacity whereby the participant must temporarily store and update incoming information, then manipulate this information in order to respond correctly (Owen et al., 2005). Philip et al. (2016) used the n-back paradigm and found increased temporal-parietal and PFC activation in adult participants that were at least moderately exposed to sexual, physical, emotional abuse or physical/emotional neglect but otherwise free of psychological and personality disorders ($n = 13$, 7 males), compared with healthy control participants ($n = 13$, 4 males). This activation was associated with significantly reduced accuracy in the working memory condition, which suggests that diminished working memory capacity is associated with childhood maltreatment even when participants are psychologically healthy (Philip et al., 2016).

Study Objectives

Childhood maltreatment, including sexual abuse, can lead to neurodevelopmental changes which can influence how working memory and emotional working memory are processed (Cross et al., 2017). A prominent and consistent gap is that most CSA-focused studies are not exclusively focused on male-specific outcomes. Given that many studies on CSA employ mixed-sex samples or targeted male populations (e.g., males with histories of abuse who are

offenders), the current study contributes to the CSA literature by focusing on a community-based sample of adult males and aims to understand how working memory is impacted by a history of CSA. There is a notable research gap where studies that examine lasting consequences of child abuse by including trauma-exposed participants with and without PTSD are lacking (Rausch, 2019). Further, given that CSA may trigger PTSD and that PTSD impacts working memory (Schuitevoerder et al., 2013), and working memory when emotion stimuli are involved (Schweizer et al., 2019; Schweizer & Dalglish, 2011), we wish to tease apart CSA and PTSD to better identify specific CSA-related impacts on working memory and emotional working memory.

In the current study, we examine working memory, and the potential influence of emotional stimuli, in a sample of adult males with CSA histories. The absence or presence of a formal PTSD diagnosis is taken into account for each participant. The objective is to provide preliminary insight into the neural basis of the impact of CSA in males during two working memory fMRI tasks, one with (emotional picture n-back) and one without (letter n-back) emotional content. It is hypothesized that brain activity during working memory among CSA males will be different than in non-CSA males; specifically that CSA males will have higher PFC activation. Further, it is expected that the emotional content in the emotional picture n-back task will accentuate this difference in working memory activity particularly in participants with CSA and localized in more limbic areas. As PTSD and childhood maltreatment are both associated with working memory impairments, the intention is to assess within group homogeneity and determine if it is suitable to report the CSA group as a whole or if it will need to be divided into two groups based on the diagnosis of PTSD.

Methods

Participants

This study was an exploratory research design and was part of a larger project examining psychological and adaptive functioning among adult males who experienced childhood sexual abuse (Moorman, 2020). The recruitment and neuroimaging protocols were approved by the University's Research Ethics Board (REB) and by the REB at a local mental health hospital where the neuroimaging tasks were completed. Participants were recruited through posters at local community centres (e.g., local YMCA) and through online advertising (e.g., Kijiji and Facebook).

A subset of CSA males from the larger sample ($n = 69$), and control males ($n = 40$) were selected based on their interest in the neuroimaging study and their fMRI compatibility. Potential participants were excluded from the neuroimaging study for moderate to severe substance use disorder from alcohol, cannabis, or opioid use; a recent concussion (i.e., within the past 6 months); post-concussion syndrome or attention deficit hyperactivity disorder; left-handedness; size/weight; and lack of interest. Additional factors, such as a glass eye, non-titanium metal implants, heart condition, or high blood pressure excluded several more potential participants. The final sample consisted of 29 participants, 16 of whom had CSA histories and 13 that served as control participants. Of the 16 participants with CSA histories, 7 met current criteria for PTSD, and had not had counselling for their CSA.

Demographics

A socio-demographic questionnaire obtained information on participant characteristics (e.g., age, education, and employment status). Information on the participants' physical health, criminal history, and intimate partner history was also collected through this questionnaire. On average, the control participants were 36.4 ($SD = 9.1$) years old and the participants with CSA histories were 42.6 ($SD = 10.8$) years old; the difference in age between the groups was not

statistically significant ($p = .113$). The distributions of race, education, and income were similar between the groups. Most of the participants were white (CSA 75.0%, control 76.9%), and college or university educated (CSA 81.2%, control 92.3%). About half of the participants in each group earned a yearly income less than \$60,000 in Canadian funds (CSA 62.5%, control 53.8). Fewer participants in the control group (23.1%) than the CSA group (56.2%) were married or in a common law relationship.

Measures

The Childhood Trauma Questionnaire.

The Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998), a sound measure of child abuse (e.g., Spinhoven, et al., 2014), was administered to retrospectively assess childhood physical/emotional abuse and physical/emotional neglect, each subscale contains 25 items scored from 0 (*never true*) to 5 (*very often true*). A score greater than 0 indicated childhood trauma was experienced. The CTQ was not used to assess sexual abuse as this was assessed with the Sexual Victimization Survey (SVS; Finkelhor, 1979).

The Sexual Victimization Survey.

The SVS was used to collect information on the age of onset of sexual abuse, the duration on a scale from 1 (*happened one day or a few days*) to 5 (*happened over a period of many years*), relationship to perpetrator (*extra-familiar* or *intra-familiar*) and emotional closeness to the perpetrator before the abuse began, on a scale from 1 (*very distant*) to 5 (*very close*). This study used a modified version of the SVS, that was shown to have good inter-rater reliability and test-retest reliability (Lyons & Romano, 2019).

The SCID for DSM-5.

The participants were assessed for a range of psychological disorders, including PTSD, with the Structured Clinical Interview for DSM-5 (SCID-5; First et al., 2015). The SCID is a common measure of psychological functioning administered in clinical settings (First et al., 2015).

Letter n-back.

The letter n-back task (e.g., Owen et al., 2005) was used to measure working memory processing. The task was presented as a block design. Stimuli for the letter n-back task were letters presented one at a time in the center of the screen. The conditions were ‘Press for X’, where the correct response was to press the button every time an ‘X’ was presented (baseline) and ‘Press for 2-back’, where the correct response was to press when the letter presented was the same as the letter that was presented two letters before (test). Stimuli were presented for 1 s and each block lasted 30 s. Four blocks of each condition were presented in a counterbalanced pattern and 21 s rest blocks were interspersed between with the word rest on the screen.

Emotional pictures n-back.

We adapted the n-back to include emotional pictures as the stimuli was used to assess emotional working memory. Emotional (negative and positive) and neutral images were selected from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008) and matched for valence, intensity, and dominance. After the images were selected from the IAPS, they were sorted into groups matched by emotional valence. No images were repeated between the blocks, and no images of adult males were included in the task. The final task images were visually inspected by a clinical psychologist in order to minimize the likelihood of triggering a CSA memory. A block design was used with 3 blocks of 16 images for each of the 6 conditions: 1-back and 2-back blocks for each of the emotional states (positive, negative and neutral). The 2-back condition increases the task difficulty by increasing the demands on working memory. The

IAPS images were presented for 2s each for a total of 33s blocks and a total task time of 11 minutes. In the 1-back condition, participants were asked to press a button on the response pad when the image was the same as the image displayed immediately preceding. In the 2-back condition, participants were asked to press a button on the response pad when the image presented was the same as the image displayed two images preceding.

Wechsler Adult Intelligence Scale.

The Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997) subtests were administered to assess working memory outside of the MRI environment. These included the forward and backward digit span, and the letter number sequencing subtests, scored according to the manual. Although outdated, the WAIS III forward and backward digit span as well as the letter number sequencing subtests, which were readily available at the university research laboratory, were used as a method to ensure participants had the basic working memory capacity required to complete the n-back task in the fMRI.

Procedure

Prior to the neuroimaging session, informed consent was provided, and a series of questionnaires was administered to gather information on socio-demographics, childhood maltreatment and mental health functioning. At a later date, participants attended one neuroimaging session and were compensated with \$30 for travel/parking expenses.

All imaging was performed on the 3T Siemens Biograph MRI-PET scanner at a local hospital using the 12-channel head coil. For the duration of the scanning session, participants lay supine on the MRI bed and looked at a mirror where the fMRI stimuli were projected. Participants were provided with noise reduction headphones which allowed the auditory communication to be heard while reducing noise from the scanner. They were given an emergency ball, which when squeezed would alert the technologist of any problems and they

were also equipped with a pulse oximeter which allowed for the detection of signs of physiological stress. The imaging followed the same order for each participant. These included a T1-weighted structural scan, followed by the two fMRI tasks. The pulse sequence for both fMRI scans was an echo planar imaging sequence with TR=3000 ms, TE=34 ms, 48 slices, 3 mm slice thickness, flip angle 90^0 , FOV 64x64.

Data Analyses

Descriptive statistics were used to present percentages for the demographic information, mental health profiles, and childhood trauma histories. To examine the influence of PTSD within the CSA group on working memory, the working memory tasks were examined across three groups, namely males with a CSA history without PTSD (CSA-PTSD), males with a CSA history and PTSD (CSA+PTSD), and the control males with neither a CSA history nor a PTSD diagnosis. One-way ANOVAS were performed across these groups to determine whether significant differences existed in working memory performance outside of the fMRI environment for the forward and backward digit span and letter number sequencing of the WAIS-III. One-way ANOVAS were also performed across these groups to determine whether significant differences existed in working memory performance parameters captured during the neuroimaging tasks (reaction times, errors of omission, errors of commission). The analyses described above were conducted with IBM SPSS, version 20.

Regarding the neuroimaging analyses, it is commonly reported that a sample size ≥ 12 is sufficient for 80% power to be achieved (Desmond & Glover, 2002). More recently, Geuter et al., (2018) noted that sample sizes with $N > 40$ are required to achieve 80% power, however some tasks with strong effects (e.g. working memory and emotion tasks) are able to detect effects with smaller sample sizes $N > 10$. It is less likely to obtain significant results with smaller sample sizes. As sample size increases, the sample variance decreases making it more likely for a

significant effect to be found, so the rate of false positives also increases. With a smaller sample size, when a significant result is found it has a higher chance of being a true effect (i.e. higher powered). In an effort to be conservative and avoid erroneously reporting a false positive, only clusters significant with a family-wise error correction ($p_{FWE-c} < .01$) are reported. Image post-processing was performed using SPM12 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, UK). Images were realigned to correct for motion and were spatially normalized to the Montreal Neurological Institute (MNI) template in SPM12. Spatial smoothing was performed to improve the signal to noise ratio with a 6 mm kernel.

Letter n-back.

Contrast images were produced to identify the neural activation related to working memory. This occurs through fixed-effects statistical analysis where the average activation during the control condition (Press for X - working memory is not required) for each participant is subtracted from their average activation during the working memory condition (Press for 2 back – working memory is required). The resulting activation can be attributed to working memory since the activation related to visual processing (seeing the letters) and physical movement (button presses) are the same between both conditions and are thus subtracted out leaving only the neural activity related to working memory.

These contrast images were then used for second level random-effects analyses which were conducted with two sample t-tests between groups of participants (CSA $n = 16$; control, $n = 13$); (CSA-PTSD, $n = 9$; CSA+PTSD, $n = 7$); (CSA-PTSD, $n = 9$; control, $n = 13$). Performance parameters; reaction times, errors of omission (no response when response required), and commission (pressed when no response was required) were captured during the scanning session. The performance parameters were analysed with ANOVAs in order to determine if there were between group differences in reaction times, errors of omission and errors of commission.

Emotional n-back.

Fixed-effects analyses were performed where three contrasts of interest were defined, in the same manner described above in the letter n-back working memory task. The resulting contrasts were; 2-back negative minus 1-back negative (negative working memory), 2-back positive minus 1-back positive (positive working memory), 2-back neutral minus 1-back neutral (neutral working memory). Second level, random-effects analyses were conducted with independent sample t-tests between the CSA and control participants. Performance parameters were analysed with ANOVAs to determine if there were between group differences in reaction times, errors of omission, and errors of commission.

Results

Trauma History and Mental Health

Information of the participants mental health and trauma history are presented in Table 1. Based on the CTQ results none of the participants experienced emotional neglect. A low proportion of participants in the CSA-PTSD group experienced physical neglect; no participants in either the control or the CSA+PTSD group experienced physical neglect. Of those who experienced emotional abuse, the range of scores was from 15-20 within the CSA-PTSD group and 12-20 in the CSA+PTSD group; the emotional abuse subscale is out of 25. Of those who experienced physical abuse, the range of scores was from 9-16 within the control group, 4-23 within the CSA-PTSD group and 5-15 in the CSA+PTSD group; the physical abuse subscale is out of 25. The age of sexual abuse onset was between five and thirteen years old for the CSA+PTSD participants and between five and twelve years old for the CSA-PTSD participants. In this sample, all CSA was perpetrated by males. On average, the participants first disclosed the abuse at 23.5 years of age.

Table 1. Trauma History and Mental Health

	Control ^a (n = 13)	CSA-PTSD ^b (n = 9)	CSA+PTSD ^c (n = 7)
CTQ			
<i>Experienced</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>
Emotional Abuse	0 *** ^b , * ^c	5 (55.6) *** ^a	3 (42.9) * ^a
Physical Abuse	3 (23.1) ** ^b	6 (66.7) *** ^a	4 (57.1)
SCID			
<i>Meets clinical criteria for</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>
Current MDD	4 (30.8)	0 * ^c	4 (57.1) * ^b
Past MDD	2 (15.4) * ^c	5 (55.6)	5 (71.4) * ^a
Social Anxiety	0	2 (22.2)	1 (14.3)
Current GAD	4 (30.8)	2 (22.2) * ^c	5 (71.4) * ^b
Past GAD	3 (23.1) * ^c	0 ** ^c	5 (71.4) * ^a , ** ^b
SVS			
<i>Duration</i>	-	<i>n (%)</i>	<i>n (%)</i>
One to a few days	-	2 (22.2)	3 (42.9)
Few weeks	-	1 (11.1)	0
Few months	-	1 (11.1)	2 (28.6)
Few years	-	4 (44.4)	2 (28.6)
Many years	-	1 (11.1)	0
<i>Relationship</i>	-	-	-
Extra-familiar	-	4 (44.4)	6 (85.7)
Intra-familiar	-	5 (55.6)	1 (14.3)
<i>Emotional closeness</i>	-	-	-
Very distant	-	2 (22.2)	3 (42.9)
Distant	-	1 (11.1)	1 (14.3)
Average	-	1 (11.1)	2 (28.6)
Close	-	2 (22.2)	1 (14.3)
Very close	-	3 (33.3)	0

Note. Participants who scored above 0 on the Childhood Trauma Questionnaire (CTQ) are considered to have experienced the abuse/neglect. Major depressive disorder (MDD), social anxiety and generalized anxiety disorder (GAD) were assessed with the DSM-5. Sexual Victimization Survey (SVS). ^{a, b, c} denotes a statistical significance assessed pairwise for the nominal variables with z-tests for two proportions. * for $p < .05$, ** for $p < .01$, *** for $p < .001$.

Working Memory Performance Parameters

For average reaction times, errors of omission, and errors of commission, one-way ANOVAs revealed no significant differences among CSA-PTSD, CSA+PTSD, and control participants for both the Press-for-X condition and the 2-back condition ($p > .05$). On average during the Press-for-X conditions, there were a small number of commission errors ($M = .41$, $SD = .73$, 95% CI [.14, .69]) and omission errors ($M = .31$, $SD = 1.04$, 95% CI [-.08, .71]). There

were slightly more commission errors on Press for 2-back trials ($M = 1.90$, $SD = 1.93$, 95% CI [1.16, 2.63]) as well as omission errors ($M = 2.17$, $SD = 2.70$, 95% CI [1.15, 3.20]). To ensure the task was working as anticipated, a repeated factor t-test between the average reaction times for Press for X and Press for 2-back conditions was performed and confirmed that the reaction times for the Press for 2-back condition were significantly slower than the Press for X control condition ($p < .001$). Turning to the WAIS results, one-way ANOVAs among control, CSA-PTSD, and CSA+PTSD participants determined that there were no significant differences in working memory capabilities, as measured by the digit span ($p = .311$) and letter number sequencing ($p = .461$) subtests.

Group Differences in Neural Activity during Working Memory

A preliminary analysis between participants with histories of CSA + PTSD ($n = 7$) and CSA-PTSD ($n = 9$) was performed and revealed a significant difference in brain activity during working memory. Specifically, the CSA+PTSD group had a cluster of 1672 voxels with significantly less activation in the cerebellum (bilateral; $p < .001$, $x\ y\ z = -12\ -46\ -22$, $T = 4.43$ and $x\ y\ z = 30\ -64\ -26$, $T = 3.99$) and the left fusiform gyrus ($p < .001$, $x\ y\ z = -36\ -52\ -18$, $T = 3.72$), compared to CSA-PTSD participants. As such, the variance in brain activation during working memory within the CSA group as a whole was not homogenous, therefore, additional analyses separated the CSA participants into those with and those without PTSD. Further, second level random-effects analyses were conducted between the CSA-PTSD ($n = 9$) and the control participants ($n = 13$). A two-sample t-test between these groups revealed no significant differences in activation during the 2back – Press for X contrast when correcting for multiple comparisons ($p = .01$) at the cluster level. The CSA+PTSD compared to controls contrast was not performed due to the small sample size.

Emotional Working Memory Performance Parameters

ANOVAs on the performance parameters for the emotional picture n-back revealed no significant differences among CSA-PTSD, CSA+PTSD, and control participants on the average reaction times, errors of omission, and errors of commission for both the press for 1-back and 2-back conditions across each of the negative, neutral, and positive blocks ($p > .05$). On average during the 1-back conditions, there were a small number of commission errors ($M = .18$, $SD = .39$, 95% CI [.03, .33]) and omission errors ($M = 1.61$, $SD = 2.22$, 95% CI [.75, 2.47]). There were few commission errors on 2-back trials ($M = .11$, $SD = .31$, 95% CI [-.01, .23]) but more omission errors ($M = 7.68$, $SD = 6.92$, 95% CI [4.99, 10.36]). To ensure the task was working as anticipated and was in fact more difficult for the 2-back condition than the 1-back condition, a repeated measures t-test confirmed the average reaction times for all the 2-back conditions combined were significantly slower than the average reaction times for all the 1-back conditions combined ($p < .001$; see Figure 1 for average reaction times for each group and each block).

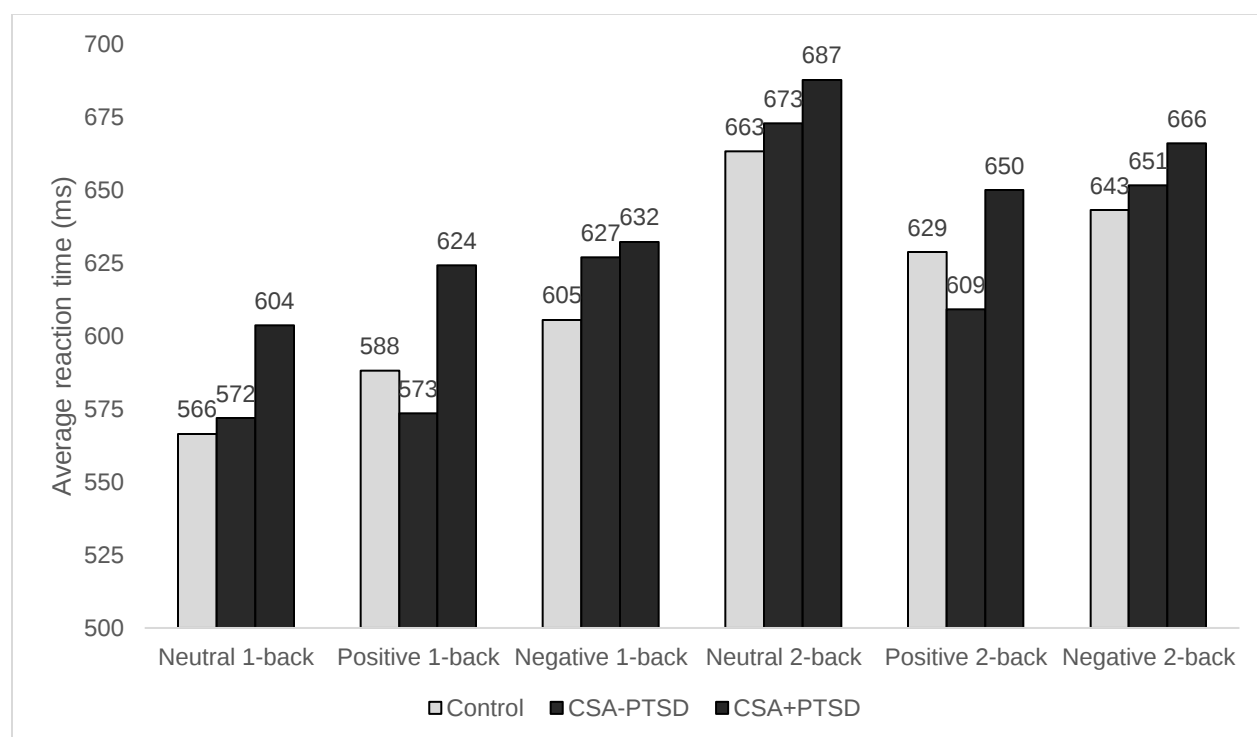


Figure 1. Average reaction times for each group across each block

Differences in Neural Activation during Emotional Working Memory

Neutral Working Memory: CSA-PTSD > Control.

Due to the clear working memory activation differences between the CSA+PTSD and CSA-PTSD groups, only the CSA-PTSD males were compared with the controls for this task. This allowed us to report significant clusters at the conservative $p = .01$ level and reduce the risk of erroneously reporting null results. Two significant clusters were found where the CSA-PTSD group had greater activation than the control participants for the 2 back neutral – 1 back neutral contrast (Table 2). The clusters included bilateral precentral and postcentral gyri, as well as bilateral superior parietal lobes.

Table 2. Emotional n-back second level random-effects analysis

Contrast	p(FWE-c)	cluster size	T	X, Y, Z	label
CSA-PTSD>control 2back neutral – 1 back neutral	<.001	1653	4.39	34, -30, 60	R postcentral gyrus
			4.32	18, -30, 68	R precentral gyrus
			3.62	24, -54, 70	R superior parietal lobe
CSA-PTSD>control 2back neutral – 1 back neutral	<.001	1065	4.29	-28, -38, 56	L postcentral gyrus
			3.75	-14, -76, 52	L superior parietal lobe
Control>CSA-PTSD 2back negative – 1 back negative	.01	863	4.61	26, -16, 66	R precentral gyrus
			4.44	14, -10, 50	R SMA
			3.66	30, -8, 58	R superior frontal gyrus (dorsolateral PFC)
Control> CSA-PTSD 2back negative – 1 back negative	<.001	1458	5.30	-8, -36, 58	L precuneus
			3.97	8, -20, 72	R SMA
			3.60	-20, -32, 60	L postcentral gyrus
			3.55	-16, -26, 74	L paracentral lobule
CSA-PTSD>control 2back negative – 1 back negative	<.001	1053	5.88	-26, -28, -20	L parahippocampal gyrus
			3.94	-24, -76, -12	L fusiform
			3.71	-40, -58, -28	L cerebellum
			3.66	-28, -62, -2	Left lingual gyrus
			3.53	-28, -76, 0	Left middle occipital gyrus

Note. p(FWE-c) is the p value with a family wise error correction applied. T is the obtained t value for the activation of the related voxel: X, Y, Z refers to the MNI coordinate for the

significant voxel; the labels were identified using the automated anatomical labeling (AAL) atlas; L, left; R, right.

Negative Working Memory: CSA-PTSD < Controls.

Two significant clusters were identified where the participants with CSA-PTSD histories had significantly less activation than the control participants for the 2 back negative – 1 back negative working memory condition. The first cluster spanned the right precentral gyrus, right supplementary motor area, and right superior frontal gyrus (dorsolateral PFC). The second cluster spanned the left precuneus, left postcentral gyrus, and paracentral lobule.

Negative Working Memory: CSA-PTSD > Controls.

A significant cluster was identified where the participants with CSA-PTSD histories had significantly greater activation than controls in the left parahippocampal gyrus (Figure 2), left fusiform gyrus, left cerebellum, left lingual gyrus, and the left middle occipital gyrus.

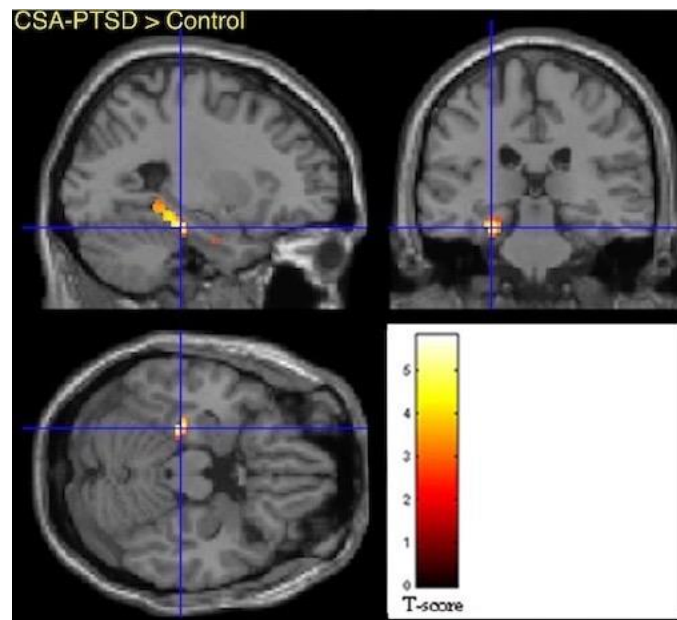


Figure 2. Region of the brain where participants with CSA-PTSD histories had significantly more activity than the control participants during negative emotional working memory. Blue crosshairs are located on the most significantly different voxel of the left parahippocampal gyrus (X, Y, Z = -26, -28, -20, $T = 5.88$, $p < .001$)

Discussion

This exploratory study focused on understanding the neurophysiological impact of CSA on males as they performed working memory tasks with and without emotional stimuli. There were no significant performance differences (reaction times or errors) between males with CSA-PTSD, CSA+PTSD, and those in the control group on either working memory task. There were, however, significant differences in brain activation patterns among groups on the emotional memory task. This finding provides preliminary empirical evidence to demonstrate that the experience of CSA has a long-term neurophysiological impact in males, that may explain a propensity for mental health consequences later in life (e.g., higher working memory and executive functioning scores are associated with a reduced risk of suicidal behaviour, Zelazny et al., 2019). Given the small sample of men obtained for the current study, future research should attempt to replicate and validate these findings.

Given the objective of isolating the neurophysiological influence of CSA on working memory in males, it was important to examine variability within the CSA group. Important differences were observed within the CSA group that made it clear it was not suitable to collapse all CSA participants into one homogeneous sample. For example, in the letter n-back task, there was a significant difference in brain activity in the cerebellum and fusiform gyrus, regions important for working memory and emotional processing (Guell, Gabrieli, & Schmahmann, 2018; Zhang et al., 2013), between CSA-PTSD and CSA+PTSD participants. This made it clear that further analyses should only include the CSA-PTSD group, as PTSD itself has its own impact on the brain and we were interested to see if CSA, on its own, would contribute to neurophysiological differences in males. This is also very important for further research as clearly childhood maltreatment, including CSA, can lead to PTSD, and this diagnosis impacts

brain functioning in a way that requires separate samples with and without PTSD, thus requiring a large enough sample size for sufficient power.

Interestingly, there were no significant differences between the nine males with CSA-PTSD and the controls when performing the letter n-back task. This suggests that working memory for letters was not affected by the CSA. Future studies could also include a 3-back letter working memory condition to increase the demands on working memory. Perhaps with this increase a group-difference would be observed between control participants and participants with CSA histories. There were, however, significant differences observed between these two groups for the emotional memory task.

CSA-PTSD participants had greater activation than control participants during the neutral 2-back minus neutral 1-back contrast which examined working memory with neutral pictures. Typically, increased activity suggests enhanced energy required to perform the task. This activity was observed in bilateral pre and postcentral gyri, as well as bilateral superior parietal lobules. These regions are required for successful working memory, attention, and visuospatial processing of IAPS images, rather than emotional processing (Bush, Privratsky, Gardner, Zielinski, & Kilts 2018; Koenigs, Barbey, Postle, & Grafman, 2009; Sack, 2009).

The emotional pictures revealed the most significant differences between the controls and the males with CSA histories (CSA-PTSD). More specifically, the negative 2-back minus negative 1-back images, assessing negative emotional working memory, revealed that controls used more traditional working memory areas, namely the right dorsolateral prefrontal cortex, while the participants with CSA histories had greater activation in the left parahippocampal gyrus. This finding in the parahippocampal gyrus was the most significant difference between the groups and is consistent with our hypothesis of greater limbic activation for emotional

working memory in the CSA participants. The parahippocampal gyrus has been shown to be overactive in individuals with childhood maltreatment histories while processing emotional face stimuli from a meta-analytic review that included 20 studies (Hein, & Monk, 2017). It is important to note that there were no significant differences between the groups for the positive 2-back minus positive 1-back working memory contrast.

Clinical Implications

The prevalence rates of CSA among males are likely underreported since barriers exist that prevent males from disclosing their abuse (Easton, Saltzman, & Willis, 2014). Delays in disclosing abuse are associated with more externalizing behaviours observed in male CSA survivors (Romano, Moorman, Ressel & Lyons, 2019). Early intervention can improve the mental health of those who experienced CSA (Blanco et al., 2015). Despite the prevalence of CSA in males, information related to specific consequences of CSA in male survivors is a notable research gap (Fisher, Goldsmith, Hurcombe, & Soares, 2017). Working memory is an important cognitive faculty for most work-related activities and for basic daily functioning. Knowing that negative emotional stimulation can influence working memory in male CSA survivors, evidenced by greater limbic activation, is an important piece of evidence that may help with understanding the potential long-term consequences of CSA in males.

Given that both CSA and PTSD are linked with working memory impairments (Masson et al., 2015; Schuitevoerder et al., 2013), and higher levels of working memory may be protective against maladaptive effects of childhood maltreatment (e.g., suicidal behaviours, Zelazny et al., 2019), there are important implications for clinicians to consider when working with males with CSA histories. Even without a diagnosis of PTSD, males who experienced childhood maltreatment are impacted when negative emotion stimuli are present during working memory. This information can give clinicians a potential avenue to approach their interventions

with men who experienced CSA but who do not have accompanying PTSD. Emotion stimulation occurs naturally throughout life, and working memory is an essential cognitive process for accomplishing goal-directed behaviours. Clinicians can help males with CSA histories learn to process negative emotions in a way that does not interfere with working memory processing, such as through mindfulness training. Mindfulness can improve emotional processing and has been linked with improvements in working memory (Mrazek, Franklin, Phillips, Baird, & Schooler, 2013; Wu et al., 2019).

Limitations

This study provides exploratory insight into the impact of CSA on the neurophysiological response during working memory, however the main limitation of this study is the small sample size. Over 100 males agreed to participate in the study, however most participants were excluded for various reasons, as described in the methods section. A large proportion of control participants and participants with CSA histories were excluded due to substance use issues. Although outside the scope of the current project, future studies could attempt to recruit enough control and CSA participants with and without substance use disorders (cannabis, alcohol or opioids) in order to examine differences in neurophysiological functioning related to substance use disorder. Due to low amounts of childhood maltreatment experienced by the control group we were unable to control for other types of childhood maltreatment experienced by the participants.

Importantly, given our small sample size, the study only had the statistical power to detect differences in activation with large effect sizes (Geuter et al., 2018). This leaves the possibility that significant differences in activation with small or medium effect sizes may have been erroneously reported as null. Regarding the neuroimaging results, pairwise analyses were conducted with CSA+PTSD ($n = 7$) and CSA-PTSD ($n = 9$) for the letter n-back task, as well as

between the CSA-PTSD ($n = 9$) and control participants ($n = 13$) for both the letter n-back and emotional working memory tasks. We addressed this limitation by using a conservative p value and not reporting null results with our smallest group (CSA+PTSD, $n = 7$). One important implication of the small sample size is that null results should be interpreted with caution, due to the possibility of a type two error. For example, it is possible that significant differences in working memory as measured by the WAIS and the performance parameters in the neuroimaging task would emerge in a larger sample, or if the demands placed on working memory were higher (e.g., by including a 3-back block). Finally, the males who participated in this study were required to disclose sensitive information about their histories. As such, the sample obtained does not represent males who are uncomfortable talking about and disclosing sensitive personal information.

Future Directions

Future studies should consider recruiting a large diverse sample. With a larger sample size, more complex statistical analyses could be performed that take into account the influence of potentially confounding variables. For example, when examining working memory, if significant differences in working memory outside of the scanner are found, working memory scores could be included as a covariate in the analysis. Future studies examining working memory with the letter n-back task could increase task difficulty to place higher demands on memory (e.g., include 3-back blocks). Further, a pre-post design separated by an intervention aimed to improve working memory could lead to valuable information. Indicators of well-being should be monitored continuously at several time points to see whether improving working memory, improves overall wellbeing, and if the impact lasts over time. Longitudinal research with a sizable and diverse sample would vastly contribute to efforts to map the neurophysiological impact of CSA into adulthood.

Conclusion

Working memory is of critical importance for daily functioning, and the influence of emotion on working memory is important to consider. There is a need to understand how vulnerable populations, such as males with CSA histories, are impacted during times of increased emotion, such as during times of personal stress. There is an increased awareness of the high prevalence rates of CSA among males, however, due to on-going social and masculinity norms, males still have lower incidences of speaking about their CSA experiences. Conventional, and perhaps toxic, masculinity norms therefore have the potential to generate self-blaming attributions that shape and influence how men respond to the experience of CSA. Understandably then, these norms and stereotypes contribute to the decreasing male disclosure of CSA, even across the lifespan (Gagnier & Colin-Vezina, 2016). The current study investigated the long-term neural impact of CSA on a component of executive function (i.e., working memory) and how emotional stimuli might augment this effect. These preliminary results suggested that males with CSA histories, even without a PTSD diagnosis, are impacted when working memory is influenced by negative emotion. The heightened limbic activation during working memory influenced by negative emotion can perhaps provide males with evidence to explain some of their previously misunderstood behaviour. Empirical evidence can assist in increasing awareness of CSA and its consequences for males, which may help reduce the stigma associated with this topic and provide clinicians with additional information necessary to help males with CSA histories. By reducing the stigma associated with male experienced CSA, more men can come forward earlier, and the benefits of early intervention can become more widespread.

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Chapter 3

Traumatic autobiographical memories: Preliminary fMRI findings among men with histories of childhood sexual abuse.

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Abstract

Childhood sexual abuse (CSA) is associated with autobiographical memory disturbances. Autobiographical memory is important for future thinking, sense of self, and coping with negative emotions. CSA is under-researched among men, with research examining long term neural correlates limited even further. This study explored the neural correlates of re-experiencing traumatic/negative memories to examine the influence of CSA on autobiographical memory into adulthood. 15 males who experienced CSA, with and without post-traumatic stress disorder (PTSD; CSA+PTSD $n = 6$, CSA-PTSD $n = 9$) and control males without CSA histories nor PTSD ($n = 11$) completed a script-driven imagery paradigm during functional magnetic resonance imaging (fMRI). Males with CSA histories, with and without PTSD, processed their negative autobiographical memories with less activation compared to control males. The CSA+PTSD group of males had less activation in the left superior occipital, left superior parietal and left parahippocampal gyri compared to control participants. The CSA-PTSD group had reduced activation in the same regions to a lesser extent. This study provides preliminary empirical evidence to suggest CSA impacts autobiographical memory for traumatic experiences, and the impact is notable even for men who experienced CSA but do not have PTSD. This study highlights the need for more research with men who have experienced CSA so we can fully understand the neural correlates of emotional memories, and better support the mental health and continued wellness of men who experienced CSA.

Keywords: Autobiographical memory, Maltreatment, Childhood sexual abuse, Male, fMRI

Introduction

Experiencing childhood adversity can predispose individuals to detrimental and potentially long-lasting consequences impacting cognitive functioning and well-being. Childhood sexual abuse (CSA) is one of several adverse childhood occurrences experienced by approximately 1 in 6 men (Dube et al., 2005; Finkelhor, Shattuck, Turner, & Hamby, 2014; Gartner, 1999; Romano & De Luca, 2001). Some men with histories of CSA will develop a range of difficulties later in life, such as substance use (Butt, Chou & Browne, 2011) or post-traumatic stress disorder (PTSD; Tolin & Foa, 2006); however, some men with CSA histories appear to experience resilient functioning (Ressel, Lyons, & Romano, 2018). Despite the prevalence of male experienced CSA and the potential consequences for the mental health of men with CSA histories, neuroimaging research related to CSA has been conducted mostly with female samples. Innate differences in brain structure and function exist between males and females, for example, in males compared to females, greater cortical thickness is observed in the orbitofrontal cortex and the insula, regions important for decision making and emotion (Ritchie et al., 2018). It is of interest to investigate why there is such diverse outcomes from CSA in men and the potential mechanisms which may contribute to varying mental health outcomes. In the current study, we examined the neural correlates of recalling early traumatic experiences to examine the influence of CSA on memory into adulthood. This research can guide clinicians and researchers to evidence informed practices which can positively influence the well-being of men who experienced CSA.

Autobiographical memory (AM) is an explicit form of memory for personally-relevant historical information, including details of traumatic experiences that occurred in childhood. Adverse childhood experiences, such as CSA, are associated with an increased prevalence of

childhood autobiographical memory disturbances (Brown et al., 2007). As such, understanding how AM is impacted in men with CSA histories, with and without a diagnosis of PTSD, can give insight into how men process their CSA memories. This is especially important since AM is important for future thinking, sense of self, and coping with negative emotions (D'Argembeau, 2012; Kross, Davidson, Weber & Ochsner, 2009; Prebble, Addis, Tippet & Hinshaw, 2013). An integrated model of AM explains how specific (i.e., episodic) and abstract (i.e., personal semantic) information about memories lead to the formation of a person's self-concept. Emotion, relevant for specific and abstract AMs, is a common theme which can provide insight into identity representation and self-continuity (Grilli & Ryan, 2020). Recently, a meta-analysis provided preliminary support for autobiographical episodic memory training, which aims to modify processing biases (e.g., overgeneralizations), as an effective and accessible treatment option for mood disorders such as depression (Hitchcock, Werner-Seidler, Blackwell & Dalgleish, 2017).

AM is achieved through a distributed brain network. The dorsal-medial subsystem (including prefrontal and temporal areas) underlies the processes of retrieval, such as abstract or oversimplified representations of cognitive information. The medial-temporal subsystem (e.g., the parahippocampal gyrus and retrosplenium) underlies the process of re-experiencing AM and is related to the perceptual imagery of AM (Thome, Terpou, McKinnon & Lanius, 2019). Thome and colleagues (2019) proposed that studies related to AM should distinguish between scanning during a traumatic imaging paradigm (likely related to retrieval) and after the traumatic exposure (likely related to re-experiencing), since the temporal order of events are related to different neural correlates as described above.

AM related to traumatic events can be studied with a script-driven imagery task. Lanius and colleagues (2001) adapted the trauma-script driven imagery task for functional magnetic resonance imaging (fMRI) and reported that participants with PTSD (from CSA or motor vehicle accident) had reduced activation in the thalamus, and medial prefrontal cortex (e.g., the anterior cingulate, and medial frontal gyrus) while re-experiencing their traumatic event, compared to participants who experienced similar trauma but did not have PTSD. This reduction in activity is thought to underlie disturbances in emotion regulation (Lanius et al., 2001, 2003). Commonly experienced symptoms of PTSD like re-experiencing, dissociation and avoidance are important to consider when performing fMRI studies with trauma script driven imagery tasks. For example, dissociative PTSD (D-PTSD) was associated with greater limbic and frontal activation during traumatic memory recall in women with D-PTSD from CSA (n=7) compared to control participants (n= 10; 1 male) who experienced similar trauma but did not have PTSD. Compared to participants with D-PTSD, control participants had significantly more activation in the left parahippocampal gyrus, right middle frontal lobe and left superior temporal gyrus (Lanius et al 2002).

Use of the Responses to Script Driven Imagery Scale (RSDI; Hopper, Frewen, Sack, Lanius & van der Kolk, 2007) can provide insight into the commonly experienced PTSD symptoms of re-experiencing, dissociation, and avoidance. Understanding the neural correlates of these symptoms during or following a script-driven imagery task is important. A study with participants who had PTSD (N = 27, 7 men) using the script-driven imagery paradigm found that re-experiencing was positively associated with right insula activity and negatively associated with right anterior cingulate cortex activity (Hopper et al., 2007). Commonly experienced

symptoms of re-experiencing, avoidance and dissociation are thus important considerations for the script-driven imagery paradigm.

Consistent with previous findings using script-driven imagery, Shin et al (2004) conducted a study using positron emission tomography (PET) and reported that combat veterans with PTSD (compared to combat veterans without PTSD) exhibited a regional cerebral blood flow (rCBF) decrease in medial frontal regions and an increase in rCBF in the amygdala, while re-experiencing a traumatic AM (compared to neutral AM) script. Driessen et al. (2004) studied traumatic compared to non-traumatic AM with fMRI in a sample (N = 12) of women diagnosed with borderline personality disorder, half with comorbid PTSD. The women without PTSD had more bilateral prefrontal cortex activation while the women with PTSD were more activated in temporolimbic areas (e.g., parahippocampal gyrus and amygdala), with more activation in the right hemisphere. Clinical disorders, such as major depressive disorder (MDD), can influence responses to script-driven imagery. Ludäscher et al (2010) used the script driven imagery task with women who had borderline personality disorder, some with comorbid presentations of PTSD. The scripts utilized by the study contained experiences that previously induced a dissociative state in the women and experiences that were emotionally neutral. The authors reported different activation patterns for the whole group of participants (n = 15) compared to a subgroup containing only the women with co-morbid PTSD (n = 10), for the analyses where the average activation during the neutral trials was subtracted from the average activation during the trials intended to induce a dissociative state (Dissociation > neutral). Also, Lanius and colleagues (2007) reported that participants with PTSD and major depressive disorder (MDD) had different patterns of neural activity during traumatic script imagery compared to participants with PTSD but no MDD and controls without PTSD nor MDD. Taken together, these studies provide

evidence to support the idea that populations with mental health disorders (e.g. MDD) have varied neural activation patterns during script-driven imagery tasks, and that co-morbid diagnoses need to be considered (Lanius et al., 2007; Ludäscher et al., 2010).

Another fMRI study imaged 6 participants ($n = 5$ males) within 3 months of a traumatic accident (e.g., motor vehicle) with the script driven imagery paradigm. This study utilized personal narrative scripts from the traumatic incident, personal narrative scripts related to a negative memory that was not related to the trauma (i.e., a non-traumatic negative memory) and a neutral memory. Results indicated that the traumatic and non-traumatic negative memory were processed similarly. Compared to the neutral memory, the memory of the traumatic accident was associated with increased activation bilaterally in the retrosplenial cortex, middle temporal gyri, and temporal poles, and other regions important for memory and emotion such as the left hippocampus and parahippocampal gyrus (Piefke et. al, 2008). More recently, a case-controlled twin study with 26 pairs of male twins (some with combat exposure, and some with associated PTSD) utilized the script driven imagery paradigm with stressful (trauma unrelated) events compared to neutral events. Males with PTSD from combat trauma exhibited diminished medial prefrontal cortex (e.g., the anterior cingulate cortex and the medial frontal gyrus) activation for stressful events compared to neutral events, when compared to males without PTSD (Dahlgren et al., 2018).

Notably, many studies have employed the script-driven imagery paradigm with participants with and without PTSD. Previous studies have shown that AM processing in participants with PTSD is different than that among non-PTSD participants. Moreover, potential symptoms of PTSD (e.g., dissociation) and other clinical disorders (e.g., MDD) can influence the

neural correlates of traumatic AMs. Although this literature has involved studies with participants who have experienced CSA, they have been predominantly conducted with females, or with mixed trauma groups (e.g., including participants with PTSD from CSA, and participants with PTSD from an accident). Understanding how AM for negative experiences is influenced in men, specifically, with CSA histories is important because it will increase understanding of how one's sense of self and coping with negative emotions may be impacted by CSA.

In the current study, we examined traumatic AM processing in a sample of adult males with CSA histories with and without a diagnosis of PTSD, and control participants with no CSA histories and no PTSD. The objective was to provide insight into how CSA affects the neural basis of traumatic AMs. It was hypothesized that differences in activation while experiencing traumatic/negative compared to neutral life events would be found between males with CSA histories and those without. In particular, it was expected that men without CSA histories would process the negative memory with more posterior cortices, related to perceptual information of their memory. Most studies that have used the script driven imagery paradigm have imaged participants with trauma histories and PTSD compared to participants with similar trauma histories without PTSD (controls). Our control group was different so the hypothesis related to our control group is exploratory. It was expected that there would be significant differences in activation within the CSA group, depending on the presence or absence of a PTSD diagnosis. The CSA group was divided into those with (CSA+PTSD) and without PTSD (CSA-PTSD). We expected, as previous studies have shown (Dahlgren et al., 2018; Driessen et al., 2004; Lanius et al., 2001, 2003; Shin et al., 2004) that trauma exposed participants without PTSD would re-experience their traumatic AM with more prefrontal activation compared to those with PTSD. Investigating these neural correlates of AM in a sample of only men with CSA is unique. This

imaging study may help characterize the impact of CSA on men and potentially provide empirical evidence of a neural consequence that demands more attention from clinicians and more support for these men.

Methods

Participants

This study was part of a larger project examining psychological and adaptive functioning among adult males who experienced CSA. The recruitment and neuroimaging protocols were approved by the University's Research Ethics Board (REB) and by the REB at a local mental health hospital where the neuroimaging tasks were completed. Participants were recruited through posters at local community centres (e.g., local YMCA) and through online advertising (e.g., Kijiji and Facebook).

A subset of CSA males from the larger sample ($n = 69$), and control males ($n = 40$) were selected based on their interest in the neuroimaging study and their fMRI compatibility. Potential participants were excluded from the neuroimaging study for moderate to severe substance use disorder from alcohol, cannabis, or opioid use (CSA $n = 27$; controls $n = 10$), a recent concussion (i.e., within the past 6 months), post-concussion syndrome or attention deficit hyperactivity disorder (CSA $n = 8$; controls $n = 3$), left-handedness (CSA, $n = 3$; controls, $n = 1$), size/weight (CSA $n = 6$; controls $n = 4$), and lack of interest (CSA $n = 5$; controls $n = 7$). A few participants could not complete the task due to technical difficulties (CSA $n = 1$; controls $n = 2$). Additional factors, such as a glass eye, non-titanium metal implants, heart condition, or high blood pressure excluded several more potential participants (CSA $n = 6$; controls $n = 2$). The final sample consisted of 26 participants, $n = 15$ CSA ($n = 9$ CSA-PTSD, $n = 6$ CSA+PTSD) and 11 control participants.

Measures

Questionnaires.

A socio-demographic questionnaire was administered to obtain information on the participant characteristics (e.g., age, education, and employment status). Information on the participants' physical health, criminal history, and intimate partner history was also collected through this questionnaire. The Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998) was administered to retrospectively assess physical/emotional abuse and physical/emotional neglect from their childhood. The CTQ was not used to assess sexual abuse as this was assessed with the Sexual Victimization Survey (Finkelhor, 1979). Participants were assessed for psychosis, mood symptoms, substance use, trauma and anxiety symptoms with the Structured Clinical Interview for DSM-5 (SCID-5; First, Williams, Karg, & Spitzer, 2015).

Script Driven Imagery Task.

The script-driven imagery task was unique to each participant. Days prior to the neuroimaging session, all participants were asked to record a brief neutral life event that was personally relevant. Participants with histories of CSA were asked to record a brief traumatic memory related to their abuse (e.g., recalling a particular CSA experience). Control participants were asked to record a negative/adverse memory from their childhood (e.g., death of a loved one). The memories were then turned into audio recordings with a neutral male voice, which was the same for each participant. During the task, a crosshair was visible on the screen and participants were instructed to keep their eyes open for the whole task. A 3s beep signaled the start of their life event audio, which lasted 33s and was then followed by 33s of quiet. The participants were asked to think about or remember the event as best as they could while listening to the audio, and during the 33s of rest that followed each presentation of the audio recordings. Three repetitions of the neutral memory condition (66s x3) were presented first, followed by three repetitions of

the negative/adverse memory condition (66s x3) (e.g., control males) or traumatic CSA memory (e.g., CSA+/- PTSD males).

Responses to Script Driven Imagery Scale.

Participants were assessed for symptoms that may have arisen during the traumatic script task using the Responses to Script-Driven Imagery (RSDI; Hopper et al., 2007) scale immediately following the neuroimaging session. The RSDI is an 11-item scale, with items measured on a scale from 0 -*not at all* to 6 - *a great deal*, intended to assess self-reported symptoms of re-experiencing, avoidance and dissociation that may occur during the script driven imagery task.

Procedure

Prior to the neuroimaging session, written consent was provided, and a series of questionnaires was administered to gather information on socio-demographics, childhood maltreatment, mental health functioning, and resilience, participants were compensated \$40 for the first session. At a later date, participants attended one neuroimaging session and were compensated with \$30 for travel/parking expenses. All imaging was performed on the 3T Siemens Biograph MRI-PET scanner at a local hospital using the 12-channel head coil. The imaging followed the same order for each participant. These included a T1-weighted structural scan, followed by the responses to script driven imagery task. The pulse sequence for the fMRI scans was an echo planar imaging sequence with TR=3000 ms, TE=34 ms, 48 slices, 3 mm slice thickness, 3mm3 voxel acquisition size, flip angle 900, FOV 64x64.

For the duration of the scanning session, participants lay supine on the MRI bed and looked at a mirror where the fMRI stimuli were projected. Participants were provided with noise reduction headphones which allowed the auditory communication to be heard while reducing noise from the scanner. They were given an emergency ball, which when squeezed would alert the technologist of any problems and they were also equipped with a pulse oximeter which

allowed for the detection of signs of physiological stress. During the script driven imagery fMRI task, participants were instructed to keep their eyes open for a crosshair on the screen. The participants were asked to think about or remember the event as best as they could while listening to the audio, and for a period of rest after each recording. The RSDI was administered immediately following the neuroimaging session. A clinical psychologist was available following neuroimaging sessions if participants were distressed. Similarly, phone numbers for help-lines and counselling services were available in the information forms presented to the participants at the start of the study.

Data Analyses

For the script-driven imagery task, images were post-processed with Statistical Parametric Mapping 12 (SPM12). This included realignment to correct for motion by employing the procedure outlined by Friston et al (1996). Images were spatially normalized to match the echo planar imaging template provided in SPM12. The 2x2x2 spatially normalized images were smoothed with a 8mm full-width at half-maximum Gaussian filter. Motion correction was applied using 6 regressors (x, y, z, pitch, roll, yaw) for all first level analyses, and the canonical hemodynamic response function (HRF) was estimated in the first level GLM. First level, fixed effects analyses were performed for each participant using these images, representing the different conditions of the task. Contrast images were produced to identify the neural activation related to re-experiencing AM by subtracting the average activation during the 3 baseline condition blocks (the 33s following the neutral memory script) from the average activation for the 33s following each of the 3 blocks of the traumatic memory condition. Data was analyzed using a general linear approach to identify voxels with activity that co-varied in time with the re-experiencing of traumatic/negative relative to neutral AMs. The resulting activation was attributed to re-experiencing traumatic AM.

Whole brain second level, random-effects analyses, with these contrast images, were then conducted with two sample t-tests between groups of participants (Control, $n = 11$; CSA-PTSD, $n = 9$); (Control, $n = 11$; CSA+PTSD, $n = 6$); (CSA-PTSD, $n = 9$; CSA+PTSD, $n = 6$). A set threshold of $p_{uncorr} = 0.05$, with a cluster-wise correction at $p_{FWE} = 0.05$ and a set cluster size larger than 100 voxels was used. Further analyses were conducted with the effect of age and childhood physical abuse was investigated by including these variables in the fMRI analyses as covariates. Each additional covariate added lowers power by one degree of freedom, and covariates of no interest should be distributed randomly and balanced across groups (Jenkinson et al., 2018). As such, emotional abuse was not included as a covariate in the analyses; the distribution of emotional abuse scores in the control group was not random. Childhood emotional and physical abuse scores were correlated ($r = .36$, $p = .053$).

Results

Participant Demographics

On average, the control participants were 35.3 ($SD = 8.9$) years old and the participants with CSA histories were 43.2 ($SD = 10.9$) years old; the difference in age between the groups was not statistically significant ($p = .06$). The distributions of race, education, and income were similar between the groups. Most of the participants were White (CSA 73.3%, control 72.7%), and college or university educated (CSA 80.0%, control 63.6%). About half of the participants in each group earned a yearly income less than \$60,000 in Canadian funds (CSA 62.5%, control 53.8). Fewer participants in the control group (27.3%) than the CSA group (60.0%) were married or in a common law relationship, but this difference was not statistically significant. Mental health status and significant childhood trauma history differences are denoted in Table 1.

Table 1. Trauma History, Mental Health and Results from the Responses to Script Driven Imagery Scale (RSDI)

	Control ^a (n = 11)	CSA-PTSD ^b (n = 9)	CSA+PTSD ^c (n = 6)
CTQ			
<i>Experienced</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>
Emotional Abuse	0 ^{**b, *c}	5 (55.6) ^{***a}	2 (33.3) ^{*a}
Physical Abuse	3 (27.3)	6 (66.7)	4 (66.7)
SCID			
<i>Meets clinical criteria for</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>
Current MDD	3 (27.3)	0 ^{**c}	4 (66.7) ^{**b}
Past MDD	2 (18.2) ^{**c}	5 (55.6)	5 (83.3) ^{***a}
Social Anxiety	0	2 (22.2)	1 (16.7)
Current GAD	3 (27.3)	2 (22.2)	4 (66.7)
Past GAD	2 (18.2) ^{*c}	0 ^{**c}	4 (66.7) ^{*a, **b}
SVS			
<i>Duration</i>	-	<i>n (%)</i>	<i>n (%)</i>
One to a few days	-	2 (22.2)	3 (50.0)
Few weeks	-	1 (11.1)	0
Few months	-	1 (11.1)	2 (33.3)
Few years	-	4 (44.1)	1 (11.1)
Many years	-	1 (11.1)	0
<i>Relationship</i>			
Extra-familial	-	4 (44.4)	5 (83.3)
Intra-familial	-	5 (55.6)	1 (16.7)
<i>Emotional closeness</i>			
Very distant	-	2 (22.2)	2 (33.3)
Distant	-	1 (11.1)	1 (16.7)
Average	-	1 (11.1)	2 (33.3)
Close	-	2 (22.2)	1 (16.7)
Very close	-	3 (33.3)	0
RSDI			
<i>Average dimension score</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
Re-experiencing	2.25 (1.82)	2.53 (1.73)	3.15 (1.56)
Avoidance	1.27 (1.57)	1.59 (1.52)	1.86 (1.71)
Dissociation	1.84 (1.53)	1.47 (1.42)	2 (1.42)

Note. Participants who scored above 0 on the Childhood Trauma Questionnaire (CTQ) are considered to have experienced the abuse/neglect. Major depressive disorder (MDD), social anxiety and generalized anxiety disorder (GAD) were assessed with the DSM-5. Sexual Victimization Survey (SVS). ^{a, b, c} denotes a statistical significance assessed pairwise for the nominal variables with z-tests for two proportions. * for $p < .05$, ** for $p < .01$. There were no significant differences on the SVS items reported. The Responses to Script Driven Imagery Scale (RSDI) dimensions were analysed with one-way ANOVAs, no significant differences were noted. For the RSDI dimensions, means (M) and standard deviations (SD) are presented.

Script-driven imagery fMRI task

CSA+PTSD participants had significantly less activity than control participants in the posterior cortices (Figure 1A) while re-experiencing their traumatic AM, as well as less bilateral dorsolateral prefrontal cortex activation (Figure 1B; Table 2). Similarly, CSA-PTSD participants had less activation in the posterior cortices while re-experiencing their traumatic AM compared to control participants (Figure 2). When compared to CSA+PTSD participants, the CSA-PTSD participants had more bilateral dorsolateral and right middle prefrontal cortex activation while re-experiencing traumatic AM (Figure 3). One-way ANOVAs of the RSDI subscales determined there were no significant differences in self-reported symptoms of re-experiencing (see Table 1 for mean scores and standard deviations from the RSDI dimensions by group). The overall patterns of activation for all analyses remained the same when age and childhood physical abuse were included as covariates.

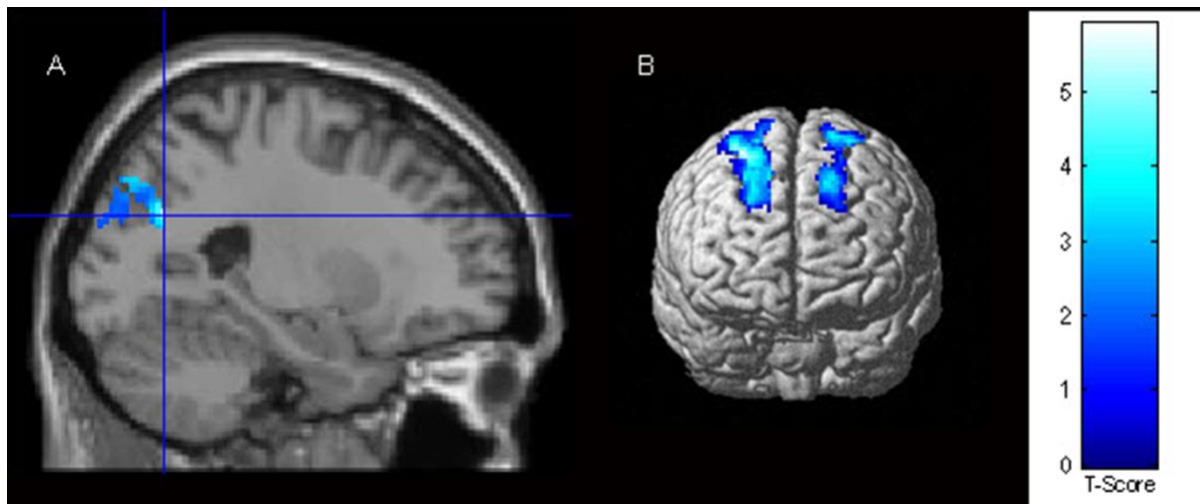


Figure 1: CSA+PTSD < controls - Regions of the brain where participants with CSA+PTSD histories had significantly less activity than the control participants during negative autobiographical re-experiencing, A) blue crosshairs are located on the left superior occipital gyrus and B) rendered image of bilateral prefrontal cortex.

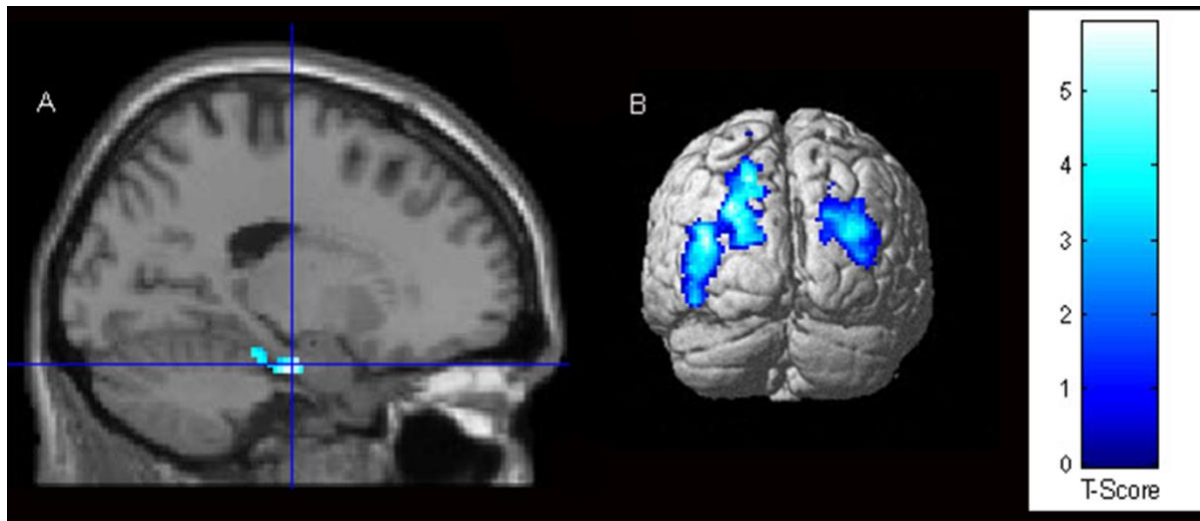


Figure 2: CSA-PTSD < controls - Regions of the brain where participants with CSA-PTSD histories had significantly less activity than the control participants during negative autobiographical re-experiencing A) blue crosshairs are located on the parahippocampal gyrus and B) rendered image of the superior, middle and inferior occipital gyri and left superior parietal lobule.

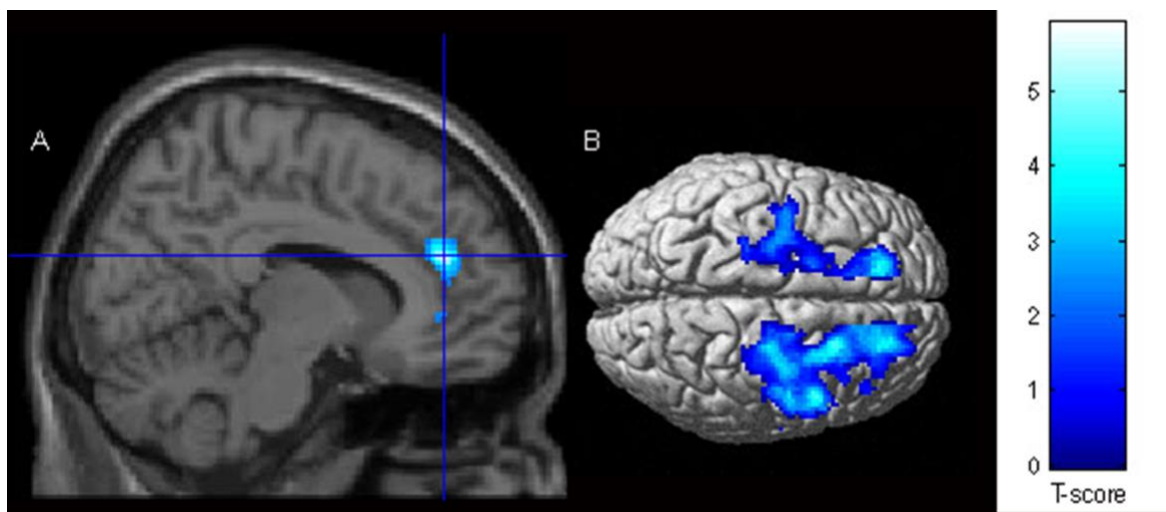


Figure 3: CSA+PTSD < CSA-PTSD - Regions of the brain where participants with CSA+PTSD histories had significantly less activity than the CSA-PTSD participants during negative autobiographical re-experiencing, A) blue crosshairs are located on the anterior cingulate and B) rendered image of bilateral prefrontal cortex activity differences.

Table 2. Significant Activation Differences for Re-experiencing Traumatic > Neutral

Contrast	p(FWE-c)	cluster size	T	X, Y, Z	label
CSA+PTSD < Controls	<.001	32729	6.56	52, 10, 46	R Precentral
			5.98	-24, -66, 28	L Superior Occipital
			5.54	-18, 6, 64	L Superior Frontal (dorsolateral)
			4.92	28, 14, 58	R Superior Frontal (dorsolateral)
			4.83	-8, -26, 64	L Paracentral Lobule
			4.80	-34, -16, 16	L Insula
			4.76	12, -16, 74	R SMA
			4.72	-16, -74, 48	L Superior Parietal
			4.65	-60, -4, 8	L Middle Temporal
			4.63	-16, -32, -10	L Parahippocampal
			4.62	56, -20, 12	R Superior Temporal
CSA-PTSD < Controls	<.002	6520	3.61	-42, -82, 16	L Middle Occipital
			3.43	-16, -18, -24	L Parahippocampal
			3.43	-46, -80, -12	L Inferior Occipital
			3.34	24, -48, -10	R Lingual
			3.20	-16, -92, 22	L Superior Occipital
			3.13	-26, -42, -14	L Fusiform
			3.11	-18, -68, 52	L Superior Parietal
			3.08	22, -82, 32	R Superior Occipital
			3.06	32, -82, 20	R Middle Occipital
CSA+PTSD < CSA-PTSD	<.001	20437	5.90	-14, 38, 38	L Superior Frontal (dorsolateral)
			5.82	50, 8, 44	R Precentral
			4.91	54, -16, 10	R Rolandic Operculum
			4.85	10, 44, 22	R Anterior Cingulate and Paracingulate
			4.63	30, 12, 60	R Middle Frontal
			4.55	34, -8, 58	R Superior Frontal (dorsolateral)
			4.14	8, 28, 52	R Superior Frontal, Medial
			4.07	-56, 8, 30	L Precentral

Note. X, Y, Z = Montreal Neurological Institute MNI coordinates. A set threshold of puncorr = 0.05, with a cluster-wise correction at pFWE = 0.05 and a set cluster size larger than 100 voxels was used. SMA = supplementary motor area.

Discussion

Most trauma literature for men has focused on combat related experiences. With the prevalence of CSA and the lack of research into its neural impact on men specifically, it was important to perform this investigation. Similarly, it was important to assess emotional memory re-experiencing as it may be impacted by the experience of CSA. Previous studies using the script-driven imagery paradigm have focused on the process of retrieval, re-experiencing, or both. This study focused on understanding the neural correlates of CSA in males while re-experiencing traumatic compared to neutral autobiographical memories. Men who experienced CSA with and without PTSD and control men without CSA histories completed the script-driven imagery paradigm, and provided subjective information about their experience during the task with the RSDI scale. Differences were found in activation between males with and without CSA histories. This finding provides preliminary empirical evidence to demonstrate that experiencing CSA has a long-term impact that may help explain a propensity for mental health consequences later in life. Given the small sample size included in this study it is important for future research to continue to investigate the impact of CSA on autobiographical memory in men who experienced CSA.

Participants with CSA histories, with and without PTSD, processed their negative AMs with less activation distributed widely across both hemispheres when compared to control males. In more posterior brain regions, the CSA+PTSD participants had less activation in the left superior occipital, left superior parietal and left parahippocampal gyri compared to control participants. The CSA-PTSD participants had reduced activation in the same regions, the left superior occipital, left superior parietal and left parahippocampal gyri, although to a lesser extent. Similarly, in a separate fMRI task (emotional working memory n-back), with the same group of participants, the males with CSA histories, even without a PTSD diagnosis, were

impacted when working memory was influenced by negative emotion. The study also reported differences in working memory processing between participants with CSA histories with and without PTSD (Chiasson et al., 2021).

The medial temporal lobe is important for several aspects relevant to memory. Anterior components of the parahippocampal gyrus are connected to occipital regions through dorsal streams important for object recognition. Posterior components of the parahippocampal gyrus are connected to the parietal cortex through ventral streams important for spatial recognition (Raslau et al., 2015). Reduced activation in these regions among males with CSA histories, with and without PTSD, demonstrates that non-CSA males are processing their negative memory in regions relevant to object and spatial details more so than both groups of participants with CSA histories. These neurological differences could underlie disruptive processing patterns (e.g., overgeneralizations) commonly experienced by individuals with mood and anxiety disorders.

Interestingly, all brain regions where there were significant differences between the CSA+PTSD and CSA-PTSD groups were localized to the frontal lobe. Specifically, while re-experiencing traumatic AM, CSA males without PTSD had greater activation bilaterally in the prefrontal cortex than those with PTSD. Previous studies have documented similar results with females. Lanius et al. (2002) showed that participants (n=10, 9 female) with similar trauma histories but no PTSD were more activated in the right middle frontal lobe compared to participants with PTSD while (n=7, female) re-experiencing traumatic more than neutral AM (Lanius et al 2002). Similarly, female participants with borderline personality disorder without PTSD were more activated bilaterally in the prefrontal cortex when compared to participants who also had borderline personality disorder and accompanying PTSD while re-experiencing traumatic more than neutral AM (Driessen et al., 2004). These similarities between results with

females and males suggest that although men's experiences of CSA, including their long-term consequences, may be different from females, their neural responses are somewhat similar. Similarly, males with PTSD from combat trauma exhibited diminished medial prefrontal cortex activation for stressful events compared to neutral events, when compared to males without PTSD (Dahlgren et al., 2018). As such, our finding during re-experiencing traumatic AM contributes to the literature by documenting reduced bilateral prefrontal activation for CSA males with PTSD compared to those without PTSD. Future studies should attempt to recruit a large, diverse sample of people who experienced CSA so further comparisons in terms of gender, mental health profiles and adverse childhood experiences can be conducted to strengthen our understanding of the impact of CSA on autobiographical memory.

The dorsolateral and ventromedial prefrontal cortices are important for emotion regulation and attention. The dorsolateral prefrontal cortex is important for cognitive processes (e.g., attention redirection) related to the valence of emotional stimuli, while the ventromedial prefrontal cortex is important for cognitive processes (e.g., extinction) related to emotional control (Nejati, Majdi, Salehinejad & Nitsche, 2021). Bilateral dorsolateral prefrontal cortex activation was reduced in the CSA+PTSD participants relative to both the controls and the CSA-PTSD participants. Further, there were no significant differences in dorsolateral prefrontal activation between the control participants and CSA-PTSD participants. Similarly, there were medial prefrontal cortex differences in the medial frontal gyrus between CSA+PTSD and CSA-PTSD participants, as well as differences in activation in the anterior cingulate cortex. The anterior cingulate cortex is an important brain region for emotion and cognition, as it is functionally connected to both limbic and prefrontal regions (Stevens, Hurley & Taber, 2011). Perhaps this prefrontal activation is what helps men with CSA histories avoid PTSD. Thus,

training the prefrontal cortex, by capitalizing on its neuroplasticity, through cognitive behaviour therapy, mindfulness or other lateral frontal attention network interventions may be of importance to investigate further for males with CSA histories. These interventions may harness protective factors including temperament, personality, basic attitudes toward one's self and the environment, as well as effective coping skills and use of social supports (Campbell-Sills, Cohan, & Stein, 2006; Guay, Billette, & Marchand, 2006; Yehuda & Flory, 2007; Yuan et al., 2011).

The subjective experience of negative/traumatic AMs during the script driven imagery task is an important consideration. The traumatic script of participants with and without PTSD from CSA was a memory of sexual abuse during childhood. The control group listened to an otherwise negative memory, unrelated to CSA as they did not experience CSA. However, other research has indicated that traumatic and non-traumatic negative memories are processed similarly (Piefke et. al, 2008; Dahlgren 2018). This study was one of the first to focus on AM with a sample of males who experienced CSA. Given the importance of AM for the formation of a person's self-concept and that emotional memories can provide insight into identity representation and self-continuity (Grilli & Ryan, 2020), studying traumatic AM in a sample of males with CSA histories should be a priority for researchers. Especially since autobiographical episodic memory training could be an effective and accessible treatment option for mood and anxiety disorders (Hitchcock et al., 2017).

Limitations

It is important to consider that each of the participants who experienced CSA would have experienced their trauma as individuals, and the amount of trauma experienced within the group varied. The variability in abuse experiences may have contributed to the results, for example there was a significant difference in the amount of physical and emotional abuse experienced

between the controls and the participants who experienced CSA. Although the participant's age and childhood physical abuse did not influence the results, the influence of childhood emotional abuse could not be examined due to a lack of distribution in the emotional abuse scores of the control group (i.e., all scores were null). The low number of participants in the study means there is a possibility that some significant activation differences were not captured (i.e., possibility of a type II error). Likewise, the lack of statistically significant differences in the RSDI subscales for symptoms related to re-experiencing, dissociation and avoidance could potentially be contributing to a type II error, given that a small sample size would only allow differences with large effect sizes to be captured as significant. Nonetheless, this study importantly provides preliminary evidence that suggests AM for traumatic events is impacted in men with CSA histories, with and without PTSD.

Conclusion

Autobiographical memory is important for future thinking, sense of self, and coping with negative emotions (D'Argembeau, 2012; Kross et al., 2009; Prebble et. al, 2013). This study provides preliminary empirical evidence to suggest CSA impacts AM for traumatic experiences, and the impact is notable even for men who experienced CSA but do not have PTSD. This evidence can provide men with validation of their lived experiences, be a step towards removing stigma related to CSA for men and may provide insight for clinicians to help men who have experienced CSA improve their cognitive functioning and overall well-being. Notably, due to the limited sample size included in this study, future research is needed with a large, diverse sample. Men who have experienced CSA could benefit from clinician support for processing their traumatic memories, for coping with distressing emotions and establishing a healthy sense of self. For clinicians, AM is an avenue that can be accessed in order to understand and provide

support to update a client's self-concept in order to establish a state of psychological well-being (Grilli & Ryan, 2020; Hitchcock et al 2017). This study highlights the need for more research with men who have experienced CSA so we can fully understand their altered response to emotional memories and support their mental health and continued wellness.

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Chapter 4

**Altered resting state networks among men with histories of childhood sexual abuse:
Exploratory findings**

Carley Chiasson, Jessie Moorman, Elisa Romano, Zhuo Fang, & Andra Smith

Abstract

There is a lack of research on childhood sexual abuse (CSA) experienced by men, with even less research examining long term neurophysiological repercussions. This study explored the neurophysiology of the brain at rest to examine the influence of CSA on resting state functional connectivity (RSFC) into adulthood. RSFC was examined with functional magnetic resonance imaging (fMRI) within the default mode, salience and limbic networks in men with CSA histories, with and without post-traumatic stress disorder (PTSD; CSA+PTSD $n = 7$, CSA-PTSD $n = 9$), and men without a CSA history nor PTSD ($n = 13$). CSA+PTSD participants had increased functional connectivity (FC) in the medial prefrontal cortex (mPFC) from the default mode network seed compared to participants with CSA-PTSD. Both CSA groups showed significantly less FC in the striatal-thalamic circuits of the salience network than the control group. Similarly, the robust FC between the bilateral amygdalae and the mPFC that was notable in control participants, was not exhibited in participants who experienced CSA with or without PTSD histories. These findings demonstrate that intrinsic neurophysiological differences in limbic, salience and default mode network connectivity are apparent even during a resting state between the groups of participants. This is preliminary evidence of long-term neurophysiological effects of CSA in men with PTSD, and even in those without. Importantly, these findings can validate the experience of men who have lived through CSA and guide researchers and clinicians to potential avenues to support their well-being.

Keywords: Childhood sexual abuse, Men, resting state functional connectivity, default mode network, salience network, limbic network

Introduction

Childhood sexual abuse (CSA) is one of several forms of maltreatment that can predispose individuals to various short-and long-term outcomes ranging from harmful consequences such as, substance use disorders (Butt, Chou & Browne, 2011) and post-traumatic stress disorder (PTSD; Tolin & Foa, 2006), to resiliency later in life (Ressel, Lyons, & Romano, 2018). Although the 1 in 6 statistic is widely accepted (Romano & De Luca, 2014), CSA experiences among adult men remain an understudied topic, and it is of interest to the current study to potentially begin to identify neurophysiological mechanisms for such diverse CSA-related outcomes. Among men with CSA histories, anxiety and acute stress disorders (e.g., PTSD) are most frequently diagnosed (Romano & De Luca, 2014; Spataro et al., 2004). Not all men who experience CSA are diagnosed with PTSD. Nevertheless, many experience impairments with emotional and social functioning (Dohrenwend, Yager, Wall, & Adams, 2013). Understanding long-term neurophysiological CSA-related impacts may provide insight into their contributions to the multiple outcomes among men. The current study made use of imaging techniques to study resting state networks among men who experienced CSA.

Resting state functional magnetic resonance imaging (fMRI) identifies blood-oxygen-level-dependent (BOLD) signal changes while participants are awake and not thinking about anything in particular. BOLD signal changes, caused by spontaneous neural activity, are strongly correlated between spatially distant brain regions. At rest, compared to when engaged in goal directed behaviours, several networks are apparent through these correlations, such as the salience and default mode network (Shulman et al., 1997; Raichle et al., 2001; Raichle 2015). Resting state studies can provide important insights into neurophysiology of specific populations with varying mental health and cognitive profiles. Components of the default mode network are important for emotional processing (ventromedial prefrontal cortex), self-referencing (dorsal

medial prefrontal cortex) and remembering previous experiences (posterior regions; Raichle 2015), all important and potentially affected by CSA. For example, studies investigating how trauma exposed individuals re-experience traumatic memories have shown that trauma exposed participants without PTSD re-experience their traumatic memories with more prefrontal activation compared to those with PTSD (Dahlgren et al., 2018; Driessen et al., 2004; Lanius et al., 2001, 2003; Shin et al., 2004).

The prefrontal cortex (PFC), hippocampus, and amygdala have been identified as key brain regions that are sensitive to early exposure to stress (Lupien et al., 2009). The PFC, hippocampus, and amygdala are sensitive to chronic interpersonal trauma during childhood (e.g., CSA). The cascading effects of repeated exposure to stressful and traumatic events in early life, along with genetic influences on stress responsivity, likely influence these findings. Alterations of the functional connectivity of the PFC, hippocampus, and amygdala through neurochemical changes can result from repeated activation of the hypothalamic pituitary adrenal (HPA) axis during developmentally sensitive periods. These changes can lead to increasing psychological, emotional, and cognitive disturbances in individuals who are genetically predisposed to adverse stress reactivity (Cross et al., 2017).

Childhood emotional maltreatment (i.e., emotional abuse/neglect) is associated with altered resting state functional connectivity (RSFC) within the limbic system and the salience network, indicative of the emotional and cognitive disturbances experienced by adults exposed to childhood emotional maltreatment (van der Werff et al., 2013a). Altered RSFC within the salience network was reported in a sample of adults who were exposed to childhood maltreatment (emotional abuse/neglect, physical abuse or sexual abuse) compared to adults without childhood maltreatment histories nor psychopathologies ($n = 11$; 3 males). Individuals

exposed to childhood maltreatment were further divided into those who exhibited resilience (defined as not having an axis-1 disorder from the DSM-IV; $n = 11$; 3 males), and those who had an axis-1 disorder ($n = 11$; 3 males). Individuals in the resilience group had increased negative RSFC between a seed region in the salience network, the left dorsal anterior cingulate cortex, and the fusiform/lingual gyri, which is an important functional region for declarative memory. Thus, higher activity in the salience network, which is important for attending to internal and external stimuli, was negatively correlated with activity in brain regions important for declarative memory in maltreatment-exposed individuals who displayed resilience. This finding could indicate that when resilient individuals attend to information, they are less likely to draw upon traumatic memories (van der Werff et al., 2013b).

In 2009, Bluhm et al., examined default mode network (DMN) RSFC in adult women with PTSD from childhood maltreatment (i.e., physical abuse/neglect, emotional abuse/neglect, or sexual abuse; $n=17$) who exhibited reduced connectivity from the posterior cingulate cortex to the medial PFC, as well as from the same seed region to the right hippocampus, amygdala, and insula compared to healthy control women ($n=15$). Additionally, a systematic review of seed-based functional connectivity reported a trend of decreased default mode functional connectivity and increased salience network functional connectivity in people with PTSD (Kosh et al., 2016). The DMN, important for both cognitive and emotional processes including self-referencing, is also impacted by the lasting effects of childhood maltreatment and PTSD. In 2017, Lu and colleagues imaged adults with ($n = 24$; 9 males) and without ($n = 24$; 9 males) childhood maltreatment histories (i.e., physical or emotional abuse/neglect). Differences in inter-and intraregional connectivity within the DMN were identified. Previous studies reported aberrant DMN connectivity in individuals with PTSD (e.g., Bluhm et al., 2009; Kosh et al., 2016),

however this was the first to report differences in DMN connectivity related to early stress exposure while excluding psychological disorders (Lu et al., 2017).

One study reported that adolescent girls with physical or sexual assault histories ($n=26$) had reduced functional connectivity between the amygdala and the medial PFC compared with girls without abuse experiences ($n=30$; Cisler, 2017). Weakened connections between the amygdala and medial PFC could explain greater negative affect and reduced emotion regulation as a function of weakened top-down processing from the medial PFC to the amygdala (Cisler, 2017). A longitudinal study with a community-based sample of adolescents ($N = 90$; 47 females) who experienced childhood maltreatment (i.e., physical abuse/neglect, emotional abuse/neglect, or sexual abuse) reported RSFC increases within the DMN of maltreated individuals (Rakesh et al., 2021). A sex-dependent effect was reported whereby RSFC increased within the limbic and salience networks for males (Rakesh et al., 2021).

Overall, resting-state fMRI studies with individuals who experienced childhood maltreatment have reported differences in functional connectivity in the DMN, salience and limbic networks which could contribute to cognitive and emotional difficulties. Several studies have examined lasting impacts of childhood maltreatment through RSFC methodologies; however, no published studies have examined RSFC in a group of adult males who experienced CSA. The current study will address this research gap by exploring RSFC within the salience, limbic, and DMN in a sample of adult males who experienced CSA, with and without PTSD, compared with non-CSA males without PTSD. This will provide valuable insight into the impact of their CSA experiences on the functional connectivity of these networks.

Methods

Participants

This study was part of a larger project examining psychological and adaptive functioning among adult males who experienced childhood sexual abuse (Moorman, 2020). The recruitment and neuroimaging protocols were approved by a University Research Ethics Board (REB) and by the REB at a local mental health hospital where the neuroimaging tasks were completed.

Participants were required to be between 25-60 years, fluent in English, reside in proximity of where the study was being conducted (i.e., within city limits so participants were largely from an urban city or small proximal townships), and have had a CSA experience before age 16 to be included in the CSA group. Participants in the control group had the same inclusion criteria, with the exception of the experience of CSA (although they could have experienced additional forms of maltreatment in childhood (e.g., physical/emotional abuse). Participants were recruited through posters at local community centers (e.g., local community centres) and through online advertising (e.g., Facebook). The final sample consisted of 29 participants, 16 of whom had CSA histories and 13 that served as control participants (see Chiasson et al., 2021a, for more details on the exclusion criteria).

Measures

As reported in Chiasson et al., (2021a,b) a socio-demographic questionnaire was administered to obtain information on the participant characteristics (e.g., age, education, racial identity, and employment status/income). Information on the participants' physical health, criminal history, and intimate partner history was also collected through this questionnaire. The Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998) was administered to retrospectively assess physical/emotional abuse and physical/emotional neglect from their childhood. The CTQ was not used to assess sexual abuse as this was assessed with the Sexual Victimization Survey (Finkelhor, 1979). Participants were assessed for psychosis, mood

symptoms, substance use, trauma, and anxiety symptoms with the Structured Clinical Interview for DSM-5 (SCID-5; First, Williams, Karg, & Spitzer, 2015).

Procedure

As stated in Chiasson et al., (2021a,b) men who met inclusion criteria for either the CSA or non-CSA group contacted the primary researcher via study email and following the receipt of informed consent, completed an in-person assessment consisting of a battery of self-report questionnaires and clinical interviews regarding their psychological functioning and maltreatment history. Initial questionnaires and clinical information were obtained prior to the neuroimaging session. Participants attended one neuroimaging session and were compensated for travel/parking expenses. Imaging was performed on the 3T Siemens Biograph MRI-PET scanner at a local hospital using the 12-channel head coil. Prior to the resting state scan participants were instructed to keep their eyes closed and think about nothing in particular. The scan was 5 minutes. The pulse sequence was an echo planar imaging sequence with TR = 3000 ms, TE = 34 ms, 48 slices, 3 mm slice thickness, flip angle 90°, FOV 64x64.

Functional Connectivity Analysis

According to the previous literature (e.g., van der Werff et al., 2013a), three resting-state networks (RSN) were investigated, including the DMN, the salience network, and the limbic network. A seed-based functional connectivity (FC) approach was applied using the CONN toolbox v18.0 (www.nitrc.org/projects/conn, RRID:SCR_009550). For each network, the most widely used hub region was selected as the seed. The posterior cingulate cortex (PCC), anterior cingulate cortex (ACC) and bilateral amygdalae were the seed regions for the DMN, salience network and limbic network, respectively. The seed regions were obtained from the network atlas provided by the CONN toolbox.

Functional image preprocessing was performed using the default pipeline in CONN toolbox, including realignment, co-registration, and smoothing (6mm FWHM kernel). The default denoising pipeline in the CONN toolbox was applied to remove nuisance signals. Specifically, the signals from white matter and cerebrospinal fluid were regressed out by estimating five potential noise components (Chai et al., 2012). The Friston 24-parameter model was utilized to regress out head motion effects from the realigned data. Scrubbing was performed using artifact detection tools with the threshold for global-signal above 5 (z-value) and for subject-motion above 0.9 mm. In addition, linear and quadratic trends were also included as regressors since the BOLD signal exhibits low-frequency drifts. Temporal filtering (0.008–0.09 Hz) was then performed on the time series. To control for the effects of head motion differences across groups, the head motion and scrubbing parameters were included in the first-level as covariates of no interests. Using the seed-to-voxel FC analysis approach, the correlation coefficients between the time series of these seed regions and all other voxels in the whole brain were calculated and converted to z scores using Fisher's r-to-z transformation.

For the group-level analysis, the FC of each RSN for each group (control, CSA without PTSD (CSA-PTSD), CSA with PTSD (CSA+PTSD)) was first explored. Next, we examined the group differences for each RSN. The following pairwise comparisons were conducted: control vs. CSA-PTSD; control vs. CSA+PTSD; and CSA-PTSD vs. CSA+PTSD. The significance threshold was set as uncorrected $p < 0.005$ at the whole brain level, and FDR-corrected $p < 0.05$ at the cluster level.

Results

Participant Demographics and Trauma History

The participant demographics and trauma history are summarized from Chiasson et al., (2021), the difference in age between the control participants ($M = 36.4$; $SD = 9.1$) and the

participants with CSA histories ($M = 42.6$; $SD = 10.8$) was not statistically significant ($p = .11$). Race, education, and income were similar between the groups. Mental health status based on DSM-5 criteria was not significantly different between controls and participants who experienced CSA for current major depressive disorder, social anxiety, as well as current or past general anxiety disorder. Participants with CSA histories were significantly more likely to have had major depressive disorder in the past. Based on CTQ results, none of the participants in either group reported experiencing emotional neglect. A low proportion of participants in the CSA group reported physical neglect, and no control participants reported physical neglect; the difference was not significant. A significant difference was found in emotional abuse histories; half of the participants with CSA histories reported emotional abuse compared to no control participants ($p < .01$). A significantly higher proportion of participants who experienced CSA (62.5%) also experienced physical abuse, compared to control participants (23.1%; $p < .05$).

Functional Connectivity Results

Default mode network

As shown in **Figure 1**, all three groups showed the classic DMN connectivity, including the PCC, bilateral parietal lobule, and medial prefrontal cortex (mPFC). However, there was a trend where the CSA-PTSD group showed less FC between the PCC and the mPFC compared to the other two groups. Between-group differences revealed that the controls showed greater FC between PCC and bilateral middle temporal gyrus (MTG) (left: -70, -32, -4; $t(20) = 5.37$, $p_{FDR} = 0.039$; right: 60, -42, 8; $t(20) = 4.51$, $p_{FDR} = 0.039$) than the CSA-PTSD group (**Figure 2A**). Additionally, the CSA+PTSD group showed increased FC in the left mPFC (-12, 56, -18; $t(14) = 6.35$, $p_{FDR} < 0.001$) compared to the CSA-PTSD group (**Figure 2B**).

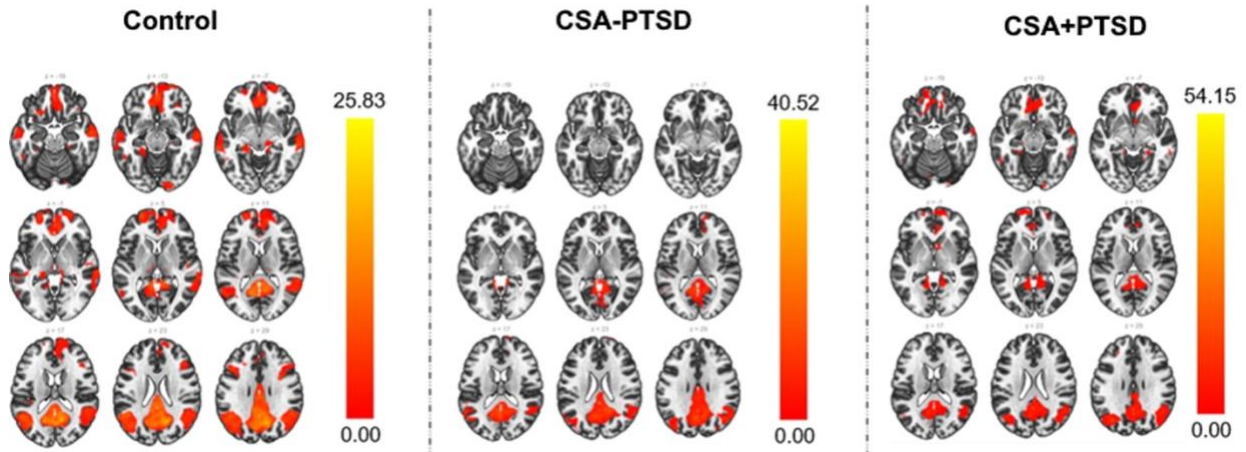


Figure 1. Single group results of the PCC-seed DMN FC.

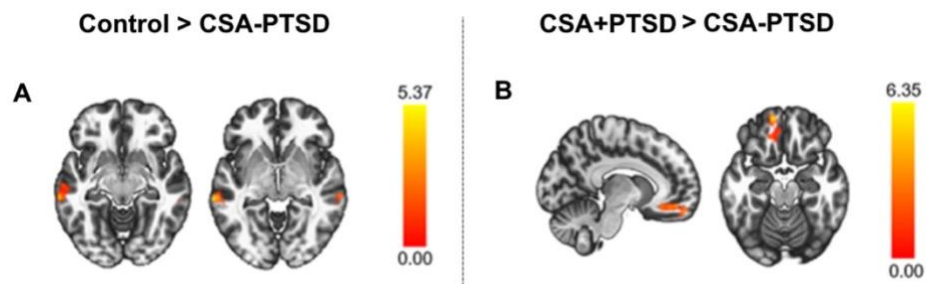


Figure 2. Group differences in PCC-seed DMN FC. (A) The control group showed greater FC between PCC and bilateral MTG than the CSA-PTSD group; (B) The CSA+PTSD showed greater FC between PCC and left mPFC than the CSA-PTSD group.

Salience network

The within group FC results of the ACC-seed for the salience network is shown in

Figure 3. All three groups showed robust FC in the main hubs of the salience network, including the dorsal anterior cingulate cortex (dACC) and the anterior insula. Additionally, the control group showed greater FC in the striatal-thalamic circuits, part of the salience network (Peters et al., 2016), compared to the other two groups.

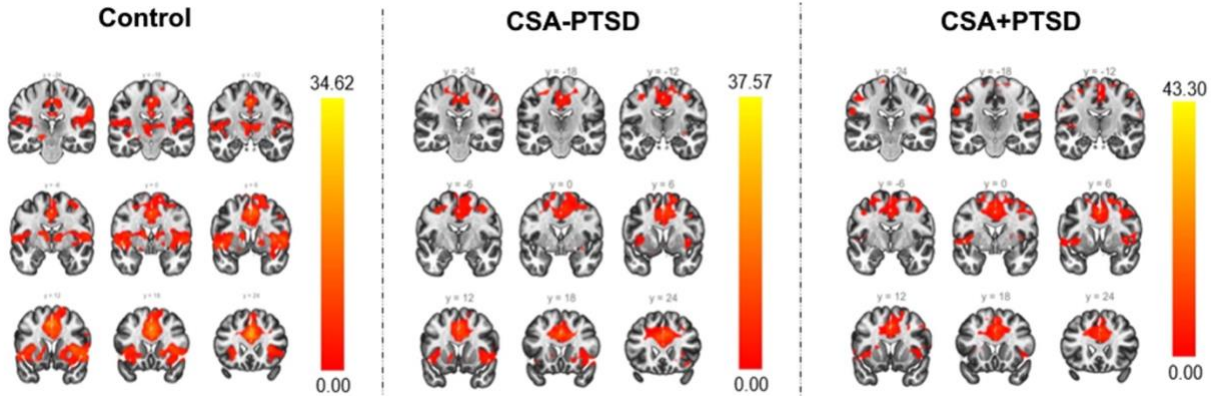


Figure 3. Single group results of ACC-seed Salience network FC

Between-group differences demonstrated that the control group showed greater FC in right caudate (10, -6, 4; $t(18) = 5.62$, $p_{FDR} = 0.04$) than the CSA+PTSD group (**Figure 4A**), and also showed greater FC in the calcarine area (-22, -74, 6; $t(20) = 7.38$, $p_{FDR} < 0.001$) than the CSA-PTSD group (**Figure 4B**). The differences between the two CSA groups showed that the CSA-PTSD group had greater FC in the left cerebellum (-34, -70, -44; $t(14) = 5.25$, $p_{FDR} = 0.018$) (**Figure 4D**) but less FC (**Figure 4E**) in the left postcentral gyrus (-56, -18, 26; $t(14) = -4.90$, $p_{FDR} = 0.048$) and cuneus (-16, -80, 28; $t(14) = -5.42$, $p_{FDR} = 0.048$) compared to the CSA+PTSD group.

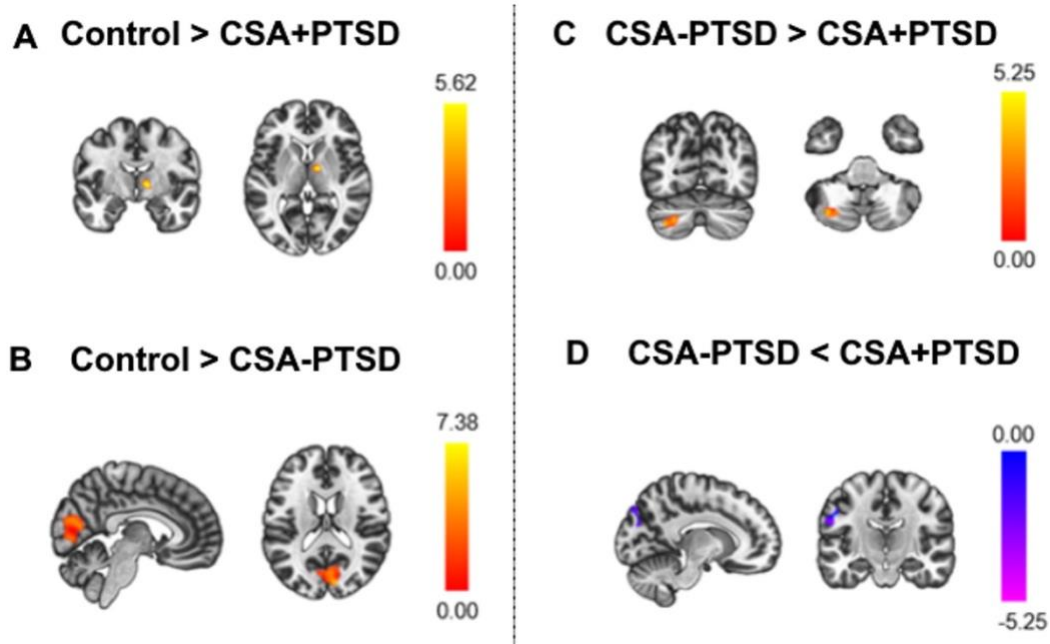


Figure 4. Group differences in ACC-seed Salience network FC. (A) Control group showed greater FC in right caudate than the CSA+PTSD group; (B) Control group showed greater FC in the calcarine area than the CSA-PTSD group; (C) CSA-PTSD group had greater FC in the left cerebellum than the CSA+PTSD group; (D) CSA-PTSD group had less FC in the left cerebellum than the CSA+PTSD group.

Limbic network

As shown in **Figure 5**, all three groups showed robust FC in the main hubs of the limbic network, including the amygdala and hippocampus. In addition, the control group also showed robust FC in the thalamus and cortical regions (i.e., Frontal and temporal lobe), including the mPFC.

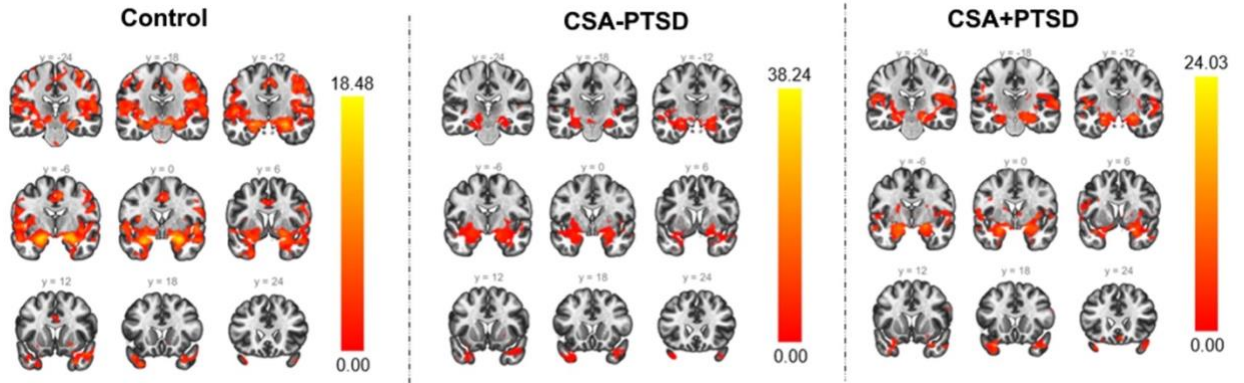


Figure 5. Single group results of amygdala-seed Limbic network FC

Between-group comparisons revealed that the control group showed greater FC in the left cerebellum (-18, -62, -40; $t(18) = 6.73$, $p_{FDR} < 0.001$) and right supramarginal gyrus (36, -40, 38; $t(18) = 5.70$, $p_{FDR} = 0.007$) than the CSA+PTSD group (**Figure 6**). No significant differences were found for the other contrasts.

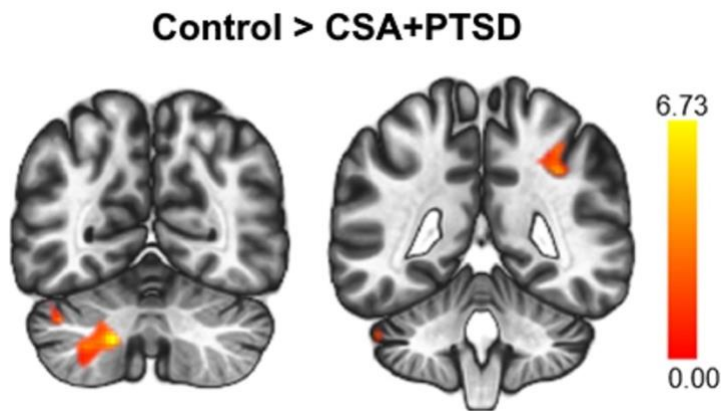


Figure 6. Group differences in amygdala-seed Limbic network FC. Control group showed greater FC in the left cerebellum and right supramarginal gyrus than the CSA+PTSD group.

Discussion

The present study examined RSFC in a sample of adult men with histories of CSA, with and without PTSD, compared to men without CSA histories. Differences were found in FC within the DMN, salience, and limbic networks. Understanding these networks can provide

insight into neurophysiological functioning important for mental health and efficient cognitive functioning.

In a previous study, we reported that men with CSA histories, even without a PTSD diagnosis, are impacted when working memory is influenced by negative emotion, and there are neurophysiological differences during working memory processing between these groups (Chiasson et al., 2021a). As such, it is important to investigate the implicated brain network, namely the salience and limbic networks at rest, to further investigate the neurophysiological functioning of men with CSA histories. Additionally, we previously reported that CSA impacts autobiographical memory for traumatic experiences, and the impact is notable even for men who experienced CSA but do not have PTSD. Given that autobiographical memory is an important component for self-concept, which is highly relevant for the DMN, it was also relevant to investigate DMN FC in this sample of men (Chiasson et al., 2021b).

In the present study, CSA+PTSD participants had increased FC in the mPFC from the PCC seed region compared to participants with CSA-PTSD. This contrasts the general finding of reduced DMN functional connectivity within participants with PTSD (Kosh et al., 2016) and highlights the importance of research with men who experienced maltreatment, such as CSA, since findings from studies with women, or mixed gendered studies with other types of trauma (e.g., combat trauma) are not generalizable. In our study, there was a trend where the CSA-PTSD group showed less FC in the mPFC compared to the other two groups. This could be indicative of higher negative and positive mood experienced by the participants with PTSD and controls, respectively. This is supported by findings from Ismaylova et al., (2018) where higher incidence of negative mood (reported by participants through daily diary of mood states) was associated

with increased FC between the PCC and the mPFC. Interestingly, higher positive mood was also associated with increased FC from the PCC to mPFC (Ismaylova et al., 2018).

Aberrant structure and function of salience network regions has been observed across various mental health disorders, whereby reduced grey matter and functional connectivity predicts lower performance on tasks requiring cognitive control (McTeague et al., 2016). In regard to our sample, the control group showed greater FC in the striatal-thalamic circuits than the CSA groups. The cortical striatal thalamic loop is implicated in various disorders and can be accessed with various methodologies. Brain stimulation techniques (e.g., deep brain stimulation) involving the striatal-thalamic circuits of the salience network are a potential avenue to improve cognitive control (Peters et al., 2016). Future longitudinal research should examine the salience network before and after brain stimulation of the striatal-thalamic circuits across various disorders, including PTSD from CSA, as we have shown that this network is implicated in men with CSA histories compared to controls.

Reduced medial prefrontal activation in participants with PTSD, compared to trauma exposed participants without PTSD, is a consistent finding in imaging studies with stress or emotion provoking tasks (Dahlgren et al., 2018; Koenigs & Grafman, 2009). This study reported robust FC between the bilateral amygdalae and the mPFC for control participants, and this FC was not exhibited in participants who experienced CSA with or without PTSD histories. This finding demonstrated that intrinsic neurophysiological differences in limbic network connectivity are apparent even during a resting state. Capitalizing on neuroplasticity by training the prefrontal cortex, through cognitive behaviour therapy, mindfulness or other lateral frontal attention network interventions is important to investigate further for males with CSA histories. Interventions could target protective factors (e.g., basic attitudes toward one's self and the environment), as well as

effective coping skills and use of social supports (Campbell-Sills, Cohan, & Stein, 2006; Guay, Billette, & Marchand, 2006; Yehuda & Flory, 2007; Yuan et al., 2011).

This was the first study to examine RSFC in men with CSA histories. However, the low number of participants in the study lends to the possibility of a type-II error (i.e., we could have missed some important differences in connectivity), and significant differences in other types of childhood maltreatment could influence the results. Although in this sample there was no significant difference for current major depressive disorder, social anxiety, as well as current or past general anxiety disorder, in the larger study there were significant differences between these groups on self-reported depressive/anxious scores, and those with CSA histories had higher rates of social anxiety (Moorman, 2020). Nonetheless, this study provides preliminary evidence of the long-term impact of experienced CSA in males and how it can have potentially profound effects on important resting state networks, even without a diagnosis of PTSD. There is reason to believe important differences exist in RSFC between males and females. Longitudinal research with a sizable and diverse (e.g. in terms of gender, ethnicity) sample would vastly contribute to efforts to map the neurophysiological impact of CSA into adulthood.

Conclusion

Intrinsic activation of the brain at rest can give insight into cognitive functions and emotional processing, which can direct both researchers and clinicians to specifically targeted treatment options that will promote well-being in vulnerable populations. The current study examined resting state networks in men who experienced CSA, with and without PTSD, compared to healthy control participants. We reported differences in functional connectivity within the salience, limbic and default mode networks between the groups of participants that are indicative of a long-term neurophysiological effect of CSA in men with PTSD, and those

without. These findings can validate the experience of men who have lived through CSA and guide clinicians to potential avenues to support the well-being of clients.

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Chapter 5**Discussion**

It is important to investigate how neurophysiology is impacted by CSA experienced by males, since this type of abuse can lead to salutogenic outcomes such as resilience (Ressel et al., 2018), but also to pathological outcomes such as higher instances of suicidality (Martin et al., 2004; Molnar et al., 2001; Easton et al., 2013), psychological distress (Aosved et al., 2011), and frequent/severe substance use (Butt et al., 2011). Despite the fact that males experience CSA, and there can be severe consequences for their mental health, most research related to CSA has been conducted with females. Further to this, innate differences in brain structure and function exist between males and females (Ritchie et al., 2018), which highlights the need for studies of both sexes when assessing the neurophysiological impact of CSA. In particular, research is needed to determine the neurological repercussions of CSA unique to men so they can be informed in a way that might better assist them in the pursuit of wellness. The research presented in this dissertation intended to address the lack of male experienced CSA neuroimaging research. Valuable insights into the neural correlates of male-experienced CSA were examined with fMRI, through resting-state functional connectivity analysis, analysis of neurophysiological activity for emotional processing (of negative information both related and unrelated to experienced trauma), and analysis of neurophysiological activity for working memory. Information obtained from this research provides empirical evidence for refinement to the ways in which this understudied, yet vulnerable, population is directed to improve their well-being and interpersonal relationships.

The lasting neurophysiological impact of CSA experienced by men (with and without PTSD) compared to healthy controls (with no CSA histories nor PTSD) was investigated through a series of studies specifically targeted to access domains that can influence well-being, namely working memory, emotional processing, autobiographical memory and several relevant resting state networks. This brief introduction to the overall discussion is followed by summaries of each

study, which are followed by a general limitation section and a section that discusses considerations for future studies. Then there is a section which integrates the results and discusses implications that arise from this dissertation before the overall conclusion is stated.

Study 1. The influence of emotion on working memory: Exploratory fMRI findings among men with histories of childhood sexual abuse.

Summary of results

Differences in activation while performing a letter n-back working memory task were found between males who experienced CSA, with and without PTSD, on a letter n-back task with baseline and two-back (working memory) blocks. Initially, we intended to examine the group who experienced CSA (with and without PTSD) compared to the controls (without CSA nor PTSD). However, after discovering significant differences in neurophysiological activity between the CSA+PTSD and CSA-PTSD for working memory, we noted that CSA+PTSD and CSA-PTSD participants should not be analyses within the same group due to the heterogeneous activation observed. On the same task, no significant differences were noted in neurophysiological working memory processing between control males (without PTSD nor CSA) and the CSA-PTSD group.

When emotional pictures were featured as the stimuli in a similarly designed n-back task, with 1-back (baseline) and two-back (working memory) blocks, we found differences in activation between control males and CSA-PTSD males contrasting the results stated above for working memory without emotional stimuli. In particular, while CSA-PTSD participants performed the working memory task with negative emotion eliciting images, they had greater limbic activation than control participants on the same task. In contrast, during the working memory task with negative emotion eliciting images control participants neural activity patterns reflected more traditional areas for working memory processing, such as the dorsolateral prefrontal cortex. In reflecting back, our hypotheses were partially supported. The first

hypothesis was not supported as we did not find differences between CSA and control participants on the letter n-back working memory. The final hypothesis of the first study was supported. Differences were identified in neurophysiological activation between CSA-PTSD and control participants for working memory involving negative stimuli. The CSA-PTSD group had increased limbic activation compared to the controls, as expected. This study contributes preliminary evidence of the lasting neural impact CSA can have into adulthood for men, even when the men do not have a PTSD diagnosis.

Study 2. Traumatic autobiographical memories: Preliminary fMRI findings among men with histories of childhood sexual abuse.

Summary of results

While re-experiencing traumatic/negative autobiographical memories during the script driven imagery paradigm, CSA+PTSD, and CSA-PTSD participants (to a lesser extent) had less activation in the left superior occipital lobe, left superior parietal lobe and the left parahippocampal gyrus than control participants. This finding, in support of the anticipated results, demonstrated that control males were processing negative autobiographical memories in regions relevant to object/spatial details (Raslau et al., 2015) more so than both groups of participants with CSA histories. These neurophysiological differences could underlie disruptive processing patterns, such as overgeneralizations, that are commonly experienced by individuals with mood and anxiety disorders. Further to this, and in support of the hypothesized results, CSA+PTSD participants had reduced bilateral prefrontal cortex activation compared to CSA-PTSD and control participants. Previous studies have documented similarly reduced activation in participants with PTSD compared to trauma exposed participants without PTSD (e.g. Dahlgren et al., 2018), providing further evidence that reduced prefrontal cortex activation during the

recollection of traumatic events can be attributed to PTSD, and supporting the final hypothesis for the second study.

Study 3. Altered resting state networks among men with histories of childhood sexual abuse: Exploratory findings

Summary of results

Functional connectivity of three resting state networks was assessed between participants with CSA histories with and without PTSD and healthy control participants without CSA nor PTSD histories. CSA-PTSD participants had reduced FC between the PCC and the mPFC compared to CSA+PTSD, and control participants. This reduced DMN FC could be indicative of lower and higher mood (Ismaylova et al., 2018) experienced by CSA+PTSD and control participants when compared to CSA-PTSD participants. Within the salience network, CSA-PTSD and CSA+PTSD participants had less FC within the striatal-thalamic circuits compared to control participants. The cortical striatal thalamic loop is implicated in various mental health disorders and is important for cognitive control (Peters et al. 2016). Intrinsic differences in FC within the limbic network were found between participants with CSA histories and controls. Within the limbic network, control participants had robust FC between bilateral amygdalae seeds and the mPFC, which was not apparent in either group of participants with CSA histories.

Limitations

All three studies in this dissertation were limited by the same, small sample size which can limit replication and generalizability of the results. There is a possibility, due to the low number of participants, that only differences in activation with large effect sizes were reported (Geuter et al., 2018). As such, there is a chance that significant differences in activation with small or medium effect sizes could have been erroneously reported as null.

It is important to note given our small sample size that over 100 males agreed to participate in the study, however most participants were excluded for various reasons. A subset of CSA males from the larger sample ($n = 69$), and control males ($n = 40$) were selected based on their interest in the neuroimaging study and their fMRI compatibility. Potential participants were excluded from the neuroimaging study for moderate to severe substance use disorder from alcohol, cannabis, or opioid use (CSA, $n = 27$; controls, $n = 10$), a recent concussion (i.e., within the past 6 months), post-concussion syndrome or attention deficit hyperactivity disorder (CSA, $n = 8$; controls $n = 3$), left-handedness (CSA, $n = 3$; controls, $n = 1$), size/weight (CSA, $n = 6$; controls, $n = 4$), and lack of interest (CSA, $n = 5$; controls, $n = 7$). Additional factors, such as a glass eye, non-titanium metal implants, heart condition, or high blood pressure excluded several more potential participants (CSA, $n = 4$; controls $n = 2$). The final sample consisted of 29 participants, 16 of whom had CSA histories (23.2% of the initial sample) and 13 that served as control participants (32.5% of the initial sample). Only 33% of the control participants and 23% of the participants with CSA histories were eligible for the neuroimaging portion of the study. A large proportion of control participants (25%) and participants with CSA histories (39%) were excluded due to substance use issues. This information gives future studies that are attempting to recruit men who experienced CSA an idea of recruitment challenges that should be anticipated.

For the first study in particular, we addressed the limitation of a small sample size for the neuroimaging data by using a conservative p value and by not reporting null results with our smallest group (CSA+PTSD, $n = 7$). Due to the low number of participants in the CSA+PTSD group we were unable to examine the neurophysiological response to the emotional working memory task in this group. Statistical analysis of data acquired outside of the scanner (i.e., the

performance parameters analyzed with ANOVAs) could have been erroneously reported as null and should be interpreted with caution.

Again, the second study was limited by the small sample size. The low number of participants in the study means there is a possibility that some significant activation differences were not captured (i.e., possibility of a type II error). Likewise, the lack of statistically significant differences in the RSDI subscales for symptoms related to re-experiencing, dissociation and avoidance could potentially be a type II error, given that a small sample size would only allow differences with large effect sizes to be captured as significant. The final study was also limited by the small sample size. For all three studies, there is a possibility that significant differences in other types of childhood maltreatment could influence the results of this study. We were unable to control for other types of childhood maltreatment due to the limited number of controls who experienced childhood maltreatment. Other important sources of variation such as the age and duration of abuse are important considerations, given that those factors could influence structural anomalies related to CSA.

Future Considerations

Future studies should consider recruiting a large diverse sample. With a larger sample size, more complex statistical analyses could be performed that take into account the influence of potentially influential variables. For example, when examining working memory, if significant differences in working memory outside of the scanner are found, this could be included as a covariate in the analysis. A larger sample would be beneficial when examining autobiographical memory with the script-driven imagery task. By increasing the number of participants, the variability observed in the symptoms experienced during the script-driven imagery paradigm would naturally increase, which would allow researchers to tease apart neurophysiological

response by symptomology for men who experienced CSA. Future studies should attempt to recruit large enough samples of control participants and participants with CSA histories that there is enough variability in the amount of childhood maltreatment experienced, so that non-CSA childhood maltreatment can be controlled for in analyses (e.g., as a covariate).

For future studies examining working memory with the letter n-back task, an additional block could be added to place higher demands on memory (e.g. include 3-back blocks). Ultimately, a pre-post design separated by an intervention aimed to improve working memory could lead to valuable information. Indicators of well-being should be monitored continuously at several time points to see whether improving working memory, improves overall wellbeing, and if the impact lasts over time. Further, by administering a pre-post design study with an intervention aimed at retraining neurophysiological reactions (e.g neurofeedback), we could begin to understand whether these types of interventions have practical applications. Recently, results from a randomized control trial provided evidence that neurofeedback training lead to a significant reduction in PTSD symptoms (Nicholson et al., 2020). As such, neurofeedback may allow men who experienced CSA to retrain neurophysiological responses, which could in turn reduce negative symptoms of posttraumatic stress.

Longitudinal research with a sizable and diverse sample would vastly contribute to efforts to map the neurophysiological impact of CSA into adulthood. Previous studies have demonstrated the potential for brain stimulation techniques to help improve cognitive control (Peters et al., 2016). Imaging FC of the salience network at rest, before and after brain stimulation of the cortical striatal thalamic loop could be a way to examine the efficacy of this treatment option. Examining FC of resting state networks before and after different interventions

aimed to retrain neurophysiological reactions could provide information on the efficacy of these treatment options.

Importantly, future studies attempting to recruit both men and women should make considerable effort to recruit men. As mentioned in the introduction, a conservative estimate would grant a population with approximately 7 females and 3 males per 10 (disclosed) CSA survivors. Future studies attempting to recruit males and females, will need to put considerable effort into recruiting men who experienced CSA in order to obtain a sufficient distribution of men in the sample.

Integration of Results and Implications

This dissertation provides preliminary insight into the impact of male experienced CSA on neurophysiological responses in domains that can influence well-being, namely, working memory, emotional processing, autobiographical memory and several relevant resting state networks. As evidenced by study 1, neurophysiological differences between CSA-PTSD males and healthy control males appear for working memory processing when negative emotional information is present. Further to this, CSA impacts autobiographical memory for traumatic experiences, and the impact is notable even for men who experienced CSA but do not have PTSD (study 2 results). In order to further investigate, and potentially integrate findings from studies 1 and 2, we investigated several resting state networks and reported important differences in networks important for working memory, processing emotional information and self-referencing.

Cognitive control is a top-down process that refers to the ability to maintain sustained attention in order to complete goal directed behaviours, and thus is imperative for both working memory and emotional processing (Tyng et al., 2017). Regions of the prefrontal cortex are

important for cognitive control, emotion processing/regulation and working memory (Tyng et al., 2017); for example, the dorsolateral prefrontal cortex is implicated in working memory and emotional regulation (Barbey et al., 2013; Opialla et al., 2015). Differences in activation in the prefrontal cortex were identified in all three studies presented in this dissertation. In study 1, controls exhibited more dorsolateral prefrontal cortex activation than CSA-PTSD participants for emotional working memory with negative pictures. In study 2, all brain regions where there were significant differences between the CSA+PTSD and CSA-PTSD groups were localized to the frontal lobe. Specifically, while re-experiencing traumatic AM, CSA males without PTSD had greater activation bilaterally in the prefrontal cortex than those with PTSD. In study 3, alterations in functional connectivity to prefrontal regions were found from seed regions within the DMN and limbic network. Robust FC was noted between the bilateral amygdalae and the mPFC for control participants, however this FC was not exhibited in participants who experienced CSA with or without PTSD histories. When combined, results from these studies suggest that differences in prefrontal activation are likely to contribute to emotional regulation difficulties experienced by men with CSA histories.

While the studies presented in this dissertation are all limited by the (same) small sample size, which reduces the generalizability of the results, there is a lack of research in men with CSA histories. This is, however, traditionally uncharacteristic of scientific research in general, where men historically represented most study participants. With knowledge of the benefits of diversity (e.g. gender diversity, cultural diversity, neurodiversity, etc.) and inclusion gaining considerable attention, future studies should attempt to examine the influence of CSA in diverse groups of people. Given that a large proportion of participants were excluded due to substance use disorders (cannabis, alcohol, or opioids), future studies may want to recruit subsamples

within the control and experimental groups of participants with substance use disorders (e.g. cannabis use), in order to examine the impact that substance use disorder has on neurophysiology within the population.

Due to recruiting challenges characteristic of the population of men with CSA histories (e.g., the low number of disclosed male CSA survivors that met the inclusion criteria), we obtained a small sample size. The small sample size is traditionally accepted for fMRI research, however the results may not be generalizable to the entire population of men who experienced CSA. Further, a larger sample size is required in order to have the power to detect subtle (but possibly significant) differences in performance measures (e.g. errors of omission and commission for the n-back tasks). Further to this, it is important to determine if the neurological correlates of CSA are similar or different from other forms of childhood maltreatment, such as physical abuse or neglect. While it was the intention of the current dissertation to unpack the unique contribution of male experienced CSA from other types of childhood maltreatment we were unable to accomplish this feat. Some of the participants who experienced CSA, also experienced other forms of childhood maltreatment. In order to control for this, the group of healthy controls would have required higher levels of childhood maltreatment (while excluding CSA), which would have naturally occurred with an increased sample size.

Some results from the research presented in this dissertation were consistent with other studies and some were not. For example, while re-experiencing traumatic AM, CSA males without PTSD had greater activation bilaterally in the prefrontal cortex than those with PTSD. Previous studies have documented similar results. Lanius et al. (2002) showed that participants (n=10, 9 female) with similar trauma histories but no PTSD were more activated in the right middle frontal lobe compared to participants with PTSD while (n=7, female) re-experiencing

traumatic more than neutral AM (Lanius et al 2002). Similarly, female participants with borderline personality disorder without PTSD were more activated bilaterally in the prefrontal cortex when compared to participants who also had borderline personality disorder and accompanying PTSD while re-experiencing traumatic more than neutral AM (Driessen et al., 2004). In the final study, CSA+PTSD participants had increased FC in the mPFC from the PCC seed region compared to participants with CSA-PTSD. This contrasts the general finding of reduced DMN functional connectivity within participants with PTSD (Kosh et al., 2016) and highlights the importance of research with men who experienced maltreatment, such as CSA, since findings from studies with women, or mixed gendered studies with other types of trauma (e.g., combat trauma) may not be generalizable.

Integrating the results from the studies presented in this dissertation gives rise to several potential interventions which could be examined in terms of their effectiveness for helping men who experienced CSA. For example, from study one we learned that negative emotional information can influence working memory processing in the brain. Mindfulness training could lead to improvements in working memory and emotional processing (Mrazek et al., 2013; Wu et al., 2019). As such, mindfulness training should be investigated as a potential treatment option for men who experienced CSA, as it could lead to improvements in emotional processing that could also benefit their working memory efficiency. Mindfulness could also be a valuable option to help men process traumatic autobiographical memories. Further to this, neurofeedback techniques have shown promise in reducing PTSD symptoms, and reorganizing FC of resting state networks (Nicholson et al., 2020). On a related note, deep brain stimulation techniques could help improve cognitive control through stimulation of the cortical striatal thalamic loop which is implicated in several mental health disorders (Peters et al., 2016).

People are diverse. Each person has their own unique histories, including their experience of trauma and abuse, and unique coping mechanisms which influence well-being. Biological sex is one important consideration but there are others. In order to assess potential protective factors, such as resilience, a diverse sample would be required in terms of gender, culture, adverse childhood experiences, protective factors (e.g., resilience), as well as childhood sexual abuse experiences (e.g. severity, duration, relationship to perpetrator). Given the diversity of people, as well as the diversity in their lived experiences, it makes sense that different treatment options would work for different people. As such, a variety of intervention options (e.g., mindfulness, neurofeedback, brain stimulation techniques) should be further investigated in regard to their efficacy to help men who experienced CSA. Through considering these divergent factors we can begin to further understand why CSA can lead to such diverse outcomes, from salutogenic to psychopathological outcomes.

Conclusion

In summary, results from the three studies presented in this dissertation provide insight into the neural basis of the impact of CSA in men specifically, including domains of working memory (letter n-back), emotional processing (trauma script and emotional picture n-back) and resting state activity. There are also important differences within the CSA group (CSA+PTSD compared to CSA-PTSD) in neurophysiological activity during working memory, while re-experiencing traumatic autobiographical memories, as well as differences in FC of the brain at rest. Recently, there has been an increased awareness of the high incidence of CSA in males, however, the stigma is still present, preventing many men from seeking help. Efforts to reduce the stigma associated with male experienced CSA may enable men to identify the abuse and seek help earlier. This would allow earlier interventions, and potentially less struggle could occur

throughout adulthood. This study provided preliminary evidence of the long-term neural impact CSA can have, even when the men who experienced CSA do not have a formal diagnosis of PTSD. It is the hope that this body of work can help highlight the need for more research and more support for men who experienced CSA.

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