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The Hijacked Self: Midbrain and Default Mode Network Functional Patterns in PTSD

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ABSTRACT

In post-traumatic stress disorder (PTSD), self-related processing disturbances are demonstrated commonly and have been linked to the default mode network (DMN), a large-scale, neural network altered significantly after trauma. However, emerging evidence suggests the midbrain may be underlying self-related processing disturbances as well, yet midbrain systems remain poorly characterized in PTSD. Here, we evaluated midbrain activity and functional connectivity during subliminal, trauma-related stimulus processing (Chapters 2–4), as well as during moral injury-related (MI) memory recall (Chapter 5) in participants with PTSD as compared to healthy controls. Initially, during subliminal, trauma-related stimulus processing, we revealed stronger midbrain periaqueductal gray (PAG) activity among participants with PTSD as compared to healthy controls (Chapter 2). Afterward, we evaluated the functional connectivity exhibited by the PAG, where we revealed stronger functional connectivity between the PAG and the medial prefrontal cortex (mPFC), as well as between the PAG and the precuneus (PCN) among participants with PTSD as compared to healthy controls (Chapter 3). Critically, the mPFC and the PCN are both DMN hubs, which we did not expect to covary functionally with the PAG. Next, we evaluated directionality, where we revealed stronger excitatory functional connectivity directed by the PAG toward the mPFC and toward the PCN among participants with PTSD as compared to healthy controls (Chapter 4). Lastly, during script-driven, MI-related memory recall, we revealed convergent evidence to the above using an independent component analysis (ICA) across participants with civilian-related PTSD, participants with military- or public safety-related PTSD, and MI-exposed, healthy controls. Here, we evaluated the functional network connectivity across the IC correlated most strongly to the DMN. In PTSD, we revealed stronger functional network connectivity exhibited by the PAG across the DMN IC as compared to MI-exposed, healthy controls (Chapter 5). Taken together, these findings suggest the midbrain may be related functionally to the DMN. In PTSD, critically, the DMN appears to be recruited during trauma- and MI-related memory processing, which assists to explain the clinical significance trauma has toward self-related processing and self-identity more generally. Lastly, these findings highlight the

importance the midbrain has toward large-scale, neural networks, a long-overlooked dynamic in psychopathology.

KEYWORDS

post-traumatic stress disorder, midbrain, periaqueductal gray, default mode network, self-related processing, neuroimaging, subcortical circuitry, activity, functional connectivity

SUMMARY FOR LAY AUDIENCE

Trauma may profoundly alter self-related thoughts and self-identity more generally. In post-traumatic stress disorder (PTSD), self-related thoughts tend to be very self-critical, and self-identity appears to shift to be more trauma-related, highlighting how tightly linked self- and trauma-related processing seem to be post-trauma. Self-related thoughts are mediated by a large-scale, neural network called the default mode network (DMN), which, critically, has been revealed to be altered in PTSD, especially while at rest. During task-based, trauma-related processing (e.g., trauma-related images, script-driven imagery), the DMN has been analyzed much less and limbic and extended brainstem and midbrain systems are analyzed more commonly, where they are revealed to be altered in PTSD as well. Since self- and trauma-related processing seem to be tightly linked in PTSD, limbic and extended brainstem and midbrain systems may serve a critical role underlying DMN-related processing. Here, we revealed a midbrain structure called the periaqueductal gray (PAG) to be more strongly active during subliminal (i.e., non-conscious), trauma-related stimulus processing in participants with PTSD as compared to healthy controls. Moreover, we revealed the PAG to be linked functionally to the DMN during subliminal, trauma-related stimulus processing, as well as during script-driven, trauma-related memory recall in PTSD. These findings support the link between self- and trauma-related processing during a trauma-related images paradigm (i.e., subliminal, trauma-related stimulus processing), as well as during a script-driven imagery paradigm. Critically, the PAG has been suggested to be involved in defense- and avoidance-related behaviour, which are demonstrated commonly in PTSD and vary based on arousal symptomatology. These findings assist to explain the clinical significance trauma seems to have toward self-related thoughts and self-identity more generally, as well as highlight the contribution midbrain systems have toward large-scale, neural networks, a long-overlooked dynamic in mental health research.

CO-AUTHORSHIP STATEMENT

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LIST OF ABBREVIATIONS

ACRONYM/ABBREVIATION	FULL FORM
AAN	ASCENDING AROUSAL NETWORK
AC-PC	ANTERIOR COMMISSURE – POSTERIOR COMMISURE
AMN	AUTOBIOGRAPHICAL MEMORY NETWORK
ANOVA	ANALYSIS OF VARIANCE
ANS	AUTONOMIC NERVOUS SYSTEM
APA	AMERICAN PSYCHIATRIC ASSOCIATION
ARAS	ASCENDING RETICULAR ACTIVATING SYSTEM
ART	ARTIFACT DETECTION TOOLS
BDI	BECK'S DEPRESSION INVENTORY
BMA	BAYESIAN MODEL AVERAGING
BMS	BAYESIAN MODEL SELECTION
BOLD	BLOOD-OXYGEN-LEVEL DEPENDENT
CADSS	CLINICIAN-ADMINISTERED DISSOCIATIVE STATES SCALE
CAF	CANADIAN ARMED FORCES
CAPS	CLINICIAN-ADMINISTERED PTSD SCALE
CEN	CENTRAL EXECUTIVE NETWORK
CTQ	CHILDHOOD TRAUMA QUESTIONNAIRE
dACC	DORSAL ANTERIOR CINGULATE CORTEX
DCM	DYNAMIC CAUSAL MODELING
dlPAG	DORSOLATERAL PERIAQUEDUCTAL GRAY
dmPFC	DORSOMEDIAL PREFRONTAL CORTEX
DMN	DEFAULT MODE NETWORK

DSM	DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS
FDR	FALSE DISCOVERY RATE
FF	FEARFUL FACE CONDITION
fMRI	FUNCTIONAL MAGNETIC RESONANCE IMAGING
FWE	FAMILY-WISE ERROR PROTECTION RATE
GIFT	GROUP ICA OF fMRI TOOLBOX
GLM	GENERAL LINEAR MODEL
HC	HEALTHY CONTROLS
IAS	INNATE ALARM SYSTEM
IC	INDEPENDENT COMPONENT
ICA	INDEPENDENT COMPONENT ANALYSIS
ICN	INTRINSIC CONNECTIVITY NETWORK
MDD	MAJOR DEPRESSIVE DISORDER
MDI	MULTISCALE DISSOCIATION INVENTORY
MI	MORAL INJURY
MIES	MORAL INJURY EVENTS SCALE
MNI	MONTREAL NEUROLOGICAL INSTITUTE STEREOTAXIC SPACE
mPFC	MEDIAL PREFRONTAL CORTEX
NF	NEUTRAL FACE CONDITION
NFB	NEUROFEEDBACK
NW	NEUTRAL WORD CONDITION
OCD	OBSESSIVE-COMPULSIVE DISORDER
PAG	PERIAQUEDUCTAL GRAY
PCC	POSTERIOR CINGULATE CORTEX
PCN	PRECUNEUS

PD	PANIC DISORDER
PPI	PSYCHO-PHYSIOLOGICAL INTERACTION
PTSD	POST-TRAUMATIC STRESS DISORDER
ROI	REGION OF INTEREST
RSDI	RESPONSES TO SCRIPT-DRIVEN IMAGERY SCALE
SCID	STRUCTURED CLINICAL INTERVIEW (DSM)
SN	SALIENCE NETWORK
SPM	STATISTICAL PARAMETRIC MAPPING
SSD	SOMATIC SYMPTOM DISORDER
STAI	STATE-TRAIT ANXIETY INVENTORY
SUIT	SPATIALLY-UNBIASED INFRATENTORIAL TEMPLATE TOOLBOX
TW	TRAUMA-RELATED WORD CONDITION
vlPAG	VENTROLATERAL PERIAQUEDUCTAL GRAY
WB	WHOLE-BRAIN SPACE

CHAPTER 1[1]

[1] Chapter 1 incorporates some material published previously by the author, featured in:

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1 INTRODUCTION

Trauma refers to a shocking and often dangerous event, which may provoke significant distress to an individual emotionally, cognitively, and self-referentially. Trauma may occur as a single event, such as often the case regarding a motor vehicle accident, an assault, or a natural disaster, or have a more prolonged exposure, such as often the case regarding childhood maltreatment and combat-related trauma(s). Generally, trauma(s) which are more prolonged and perpetrated by a family member or a close friend have worsened consequences (Herman, 1992; Wolf et al., 2012; Stein et al., 2013), such as a higher proclivity toward adult dissociation among childhood maltreatment victims (Bremner et al., 1998; Steuwe, Lanius, & Frewen, 2012; Terock et al., 2016).

Critically, trauma may alter the activity and the functional connectivity across large-scale, neural networks (McFarlane, Yehuda, & Clark, 2002; for a review, see Brown & Morey, 2012). In particular, lower-level, emotive systems and higher-level, cognitive systems have both been documented to be altered post-trauma, highlighting the distributed aftermath trauma may leave neurobiologically (Nicholson et al., 2017; for a review, see Terpou, Harricharan, McKinnon et al., 2019). In turn, altered large-scale, neural networks may provoke symptomatology (McFarlane, Yehuda, & Clark, 2002; Lanius et al., 2015; Zandvakili et al., 2020). Here, different symptoms are proposed to be mediated by different large-scale, neural networks. Whereas arousal symptoms are thought to be mediated more so by lower-level, emotive systems, cognitive symptoms are thought to be mediated more so by higher-level, cognitive systems (Zandvakili et al., 2020). Although symptoms developed post-trauma are very broad (and are distributed broadly across the brain as well), they tend to cluster and are co-expressed commonly, forming the basis toward a diagnostic profile capturing post-trauma psychopathology (APA, 2013).

1.1 POST-TRAUMATIC STRESS DISORDER

Post-traumatic stress disorder (PTSD) refers to a mental health disorder characterized by significant, trauma-related distress as defined in the diagnostic and statistical manual (APA, 2013). During the third and the fourth revisions, the diagnostic and statistical

manual of mental disorders (DSM) defined hyperarousal, reliving sensations, behavioural avoidance, and alterations in cognitions and mood as the hallmark symptoms related to PTSD (APA, 1994). More recently, the fifth revision (DSM-5) has acknowledged hypoarousal symptoms as another symptom cluster related to PTSD, captured diagnostically as the dissociative subtype (APA, 2013). With a prevalence around 13–30% in PTSD, the dissociative subtype is characterized by hypoarousal symptoms, including emotional detachment (i.e., numbing), as well as derealization and depersonalization symptoms (Lanius et al., 2012; Wolf et al., 2012; Cloitre et al., 2012; Hansen, Ross, & Armour, 2017). Moreover, the dissociative subtype tends to be related more so to prolonged trauma and trauma(s) perpetrated by a family member or a close friend (especially during childhood) (Stein et al., 2013; Lanius et al., 2012; Karam et al., 2014), which has led some to suggest the dissociative subtype emerges from a tendency to respond more passively to trauma, perhaps serving as a psychological escape when a physical escape may not be possible (Herman, 1992; Putnam, Helmers, & Trickett, 1993; Vermetten, Dorahy, & Spiegel, 2007; Cloitre et al., 2009). Here, hyperarousal and hypoarousal symptom patterns highlight the heterogeneity linked to trauma-related symptomatology in PTSD.

1.1.1 AROUSAL AND POST-TRAUMATIC STRESS DISORDER

Modulated largely by lower-level, emotive systems centered on the midbrain, arousal seems to serve a critical role in differentiating between PTSD and the dissociative subtype (Lanius et al., 2010; Nicholson et al., 2020; for a review, see Terpou, Harricharan, McKinnon et al., 2019). Here, Lanius and colleagues (2010, 2012) have proposed a model whereby hyperarousal and hypoarousal symptoms may be understood, in part, via under- and over-modulation by the medial prefrontal cortex (mPFC) toward the lower-level, emotive systems, respectively. Here, lower-level, emotive systems include the limbic system and the extended brainstem and midbrain, which show generally greater and weaker activity in PTSD and the dissociative subtype as compared to healthy controls, respectively (Lanius et al., 2002; 2006; Hopper et al., 2007; Felmingham et al., 2008). Although Lanius and colleagues (2010, 2012) have provided an early neurobiological framework to explain, in part, hyperarousal and hypoarousal

symptoms, they have presented a top-down, cognitive control framework primarily. Today – largely due to recent advancements in neuroimaging – we are better able to study the bottom-up, emotive systems and whether they show differential activity and functional connectivity in parallel to the top-down, cognitive systems. Studying lower-level (i.e., bottom-up), emotive systems and higher-level (i.e., top-down), cognitive systems and how they interact will be critical to expand the current neurobiological framework regarding PTSD. Related, since lower-level, emotive systems and higher-level, cognitive systems are thought to be underlying arousal symptoms and cognitive symptoms, respectively (Zandvakili et al., 2020), a more integrated approach to studying large-scale, neural networks may assist to elucidate whether these symptoms are inter-related. Take altered self-related processing as an example, a cognitive symptom common to PTSD and often co-expressed alongside shame, guilt, and remorse, yet rarely investigated in regard to lower-level, emotive systems.

1.2 SELF-RELATED PROCESSING IN PTSD

In PTSD, self-related processing disturbances highlight how profoundly trauma may alter self-identity and self-experience, where both cognitive and somatic disturbances to self-related processing are often reported clinically (Lanius et al., 2015; Lanius, Terpou, & McKinnon, 2020). Cognitively, self-related thoughts tend to be very self-critical and trauma-related in PTSD, which are captured eloquently by clinical statements like, “I have stained my soul permanently,” “I am ashamed I could not protect myself,” or “I do not remember who I was before my trauma” (Foa et al., 1999; Cox, Resnick, & Kilpatrick, 2014). Here, clinical statements often highlight shame, guilt, and remorse to be prominent themes, as well as a tendency to focus on unhealthy, self-criticism as opposed to healthy, self-reflection post-trauma (Dorahy, 2010; Lloyd et al., 2020; for a review, see Lanius, Paulsen, & Corrigan, 2014). Related, Sutherland and Bryant (2005) have revealed self- and trauma-related processing to be tightly linked clinically in PTSD. When asked to describe a self-defining memory, Sutherland and Bryant revealed participants with PTSD to be more likely to describe a trauma-related memory as compared to trauma-exposed, healthy controls, highlighting the centrality trauma seems to have toward self-identity in PTSD (Berntsen & Rubin, 2007). Somatically, self-related

perceptual disturbances are reported commonly as well, which are captured more so by clinical statements like, “I feel numb throughout my body” or “I feel like an object, not like a person” (Bernstein & Putnam, 1986; Foa et al., 1999; Briere & Runtz, 2002). Whereas cognitive disturbances to self-related processing have been proposed to be mediated by higher-level, cognitive systems, somatic disturbances to self-related processing have been proposed to be mediated by lower-level, emotive systems (for a review, see Lanius, Paulsen, & Corrigan, 2014). Taken together, clinical statements strongly underscore the vulnerability self-identity and self-experience have in regard to trauma, especially in participants who go on to develop PTSD.

1.2.1 NEURAL CORRELATES: THE DEFAULT MODE NETWORK

Distributed across the cortical mid-line, the default mode network (DMN) refers to a large-scale, neurocognitive network underlying self-related processing (for a review, see Raichle, 2015). The DMN has three functional connectivity hubs, namely the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC), and the precuneus (PCN) (Greicius et al., 2003; Spreng, Mar, & Kim, 2009; for a review, see Qin & Northoff, 2011). Recruited while at rest primarily, the DMN also shows recruitment during self-referential and social-cognitive processing, defined collectively as self-related processing (Greicius et al., 2003; Mars et al., 2012; for a review, see Raichle, 2015). Taken together, the DMN appears to be active during internally-directed, cognitive processing more generally, which includes autobiographical memory processing. Although the DMN supports internally-directed, cognitive processing, autobiographical memory processing draws on many supplementary neural cortices as well, namely the hippocampus and the parahippocampal gyrus, the lateral prefrontal cortices, the posterior parietal cortices, and the downstream visual cortices, which are defined together as the autobiographical memory network (AMN) (Svoboda, McKinnon, & Levine, 2006; Buckner & Carroll, 2007; Cabeza & St Jacques, 2007). Notably, self-related processing (mediated by the DMN) and autobiographical memory processing (mediated by the AMN) have been proposed to interact, whereby DMN-mediated, self-relevant knowledge and events are thought to converge and give way to self-identity and self-experience (Qin & Northoff,

2011; Fuentes-Claramonte et al., 2019; for a review, see Yeshurun, Nguyen, & Hasson, 2021).

In PTSD, critically, the DMN shows dramatically reduced functional connectivity while at rest as compared to healthy controls (Bluhm et al., 2009; Wu et al., 2011; Qin et al., 2012; King et al., 2016; for a review, see Wang et al., 2016; Koch et al., 2016), and reduced functional connectivity has been shown to predict stronger symptom severity among participants with PTSD (Bluhm et al., 2009; Lanius et al., 2015; Sripada et al., 2012; Miller et al., 2017). Reduced DMN functional connectivity may suggest a decreased network integrity in PTSD, which would help explain why many participants with PTSD report self-related processing disturbances, such as acute, self-perpetuated shame and guilt, as well as self-related perceptual disturbances, such as derealization and depersonalization symptoms (Cloitre, Scarvalone, & Difede, 1997; van der Kolk, 2005; Frewen, Brown, & Lanius, 2016; Lloyd et al., 2020; for a review, see Lanius, Terpou, & McKinnon, 2020).

1.3 TRAUMA-RELATED PROCESSING IN PTSD

Whereas the DMN has been analyzed more often during rest, threat- and trauma-related neural systems are analyzed more often during task-based paradigms. In PTSD, task-based paradigms are designed usually to evoke symptoms (i.e., symptom provocation), at least to a degree. Here, stimulus conditions that are trauma-related and personalized are used commonly, such as trauma-related images and script-driven imagery (Rauch et al, 1996; Bremner et al., 1999; Lanius et al., 2002; Hopper et al., 2007). Script-driven imagery involves presenting a short, verbal description related to a trauma memory, serving to facilitate trauma-related memory recall (or reliving) in PTSD. To date, trauma-related images and script-driven imagery have been implemented to great success, in particular when studying lower-level, emotive systems. Lower-level, emotive systems are very difficult to image hemodynamically during rest, but have been proposed by many to be where the vestiges caused by trauma(s) are represented most considerably (van der Kolk, 2002; Williamson et al., 2013; Lanius, Paulsen, & Corrigan, 2014), and should hence be investigated more extensively in PTSD.

1.3.1 NEURAL CORRELATES: THE INNATE ALARM SYSTEM

The innate alarm system (IAS), a subcortical network comprised by brainstem, midbrain, thalamic, and limbic structures, serves a key role underlying threat-related stimulus processing and has been demonstrated to be overactive in PTSD (Liddell et al., 2005; Tamietto & de Gelder, 2010; Lanius et al., 2017). Centered on the superior colliculus, the IAS serves to detect threat-related visual signals and transmit them toward arousal- and defense-related neural systems rapidly, offering an adaptive 'alarm' response to danger detected in the environment (Dean, Redgrave, & Westby, 1989; Liddell et al., 2005). Visual signals are transmitted initially by the retina to the midbrain superior colliculus, which has been demonstrated to be able to differentiate between threat-related and neutral visual signals, where only threat-related visual signals are supposed to be propagated throughout the IAS, at least theoretically (Liddell et al., 2005; Pessoa & Adolphs, 2010). From here, the superior colliculus relays the threat-related visual signals to the pulvinar, where they are redirected toward downstream visual processing systems (de Gelder et al., 1999; Vuilleumier et al., 2002). Critically, the IAS bypasses primary visual processing systems, which permits the rapid transmission, in part. The IAS may function subliminally as well, where visual signals presented at a very short latency (< 20 ms) may not be made aware consciously, but will nevertheless elicit activity throughout the IAS (Vuilleumier et al., 2002, 2003; Liddell et al., 2005).

In PTSD, emerging evidence suggests the IAS may be strongly overactive (for a review, see Lanius et al., 2017). In particular, several structures involved in the IAS have been demonstrated to be overactive in participants with PTSD as compared to healthy controls during subliminal, threat- and trauma-related stimulus processing, including the amygdala (Bryant et al., 2008; Kemp et al., 2009), the parahippocampal gyrus (Sakamoto et al., 2005; Zhang et al., 2011), the lower brainstem (Felmingham et al., 2008; Steuwe et al., 2014; Rabellino et al., 2016), and the periaqueductal gray (PAG) (Felmingham et al., 2008; Steuwe et al., 2014; Terpou, Densmore, Thome et al., 2019).

1.3.2 NEURAL CORRELATES: THE PERIAQUEDUCTAL GRAY

Located in the midbrain around the cerebral aqueduct, the PAG is innervated by the superior colliculus, the lower brainstem, the spinal cord, the amygdala, and the hypothalamus, which positions the gray matter optimally to be implicated in threat- and defense-related behaviour (Fanselow, 1994; De Oca et al., 1998; for a review, see Kozlowska et al., 2015). The PAG has two dissociable sub-units, namely the dorsolateral PAG (dlPAG) and the ventrolateral PAG (vlPAG) (Keay & Bandler, 2015), which have been revealed to be tightly linked to the autonomic nervous system. The autonomic nervous system has two subsystems, namely the sympathetic nervous system and the parasympathetic nervous system, which are mediated by the dlPAG and the vlPAG, respectively (De Oca et al., 1998; Brandão et al., 2008; Fenster et al., 2018; for a review, see Terpou, Densmore, Thome et al., 2019). When stimulated, the dlPAG and the vlPAG evoke active defense responses (e.g., fight, flight) and passive defense responses (e.g., freeze, tonic immobility) in rats, respectively (Dean, Redgrave, & Westby, 1989; Bandler et al., 2000; de Almeida et al., 2006). These defensive behaviours are observed across many mammals and are proposed to be evolutionarily conserved (Bandler & Depaulis, 1991; Carrive, 1993; De Oca et al., 1998; for a review, see Benarroch, 2012). Since the autonomic nervous system serves to connect the central nervous system to the viscera (e.g., heart, lungs, digestive system) (Bandler et al., 2000; Löw et al., 2015), active and passive defense responses are reflected throughout the body as well. In PTSD, hyperarousal and hypervigilance, as well as hypoarousal and dissociative symptoms appear to correspond well to active and passive defense responses, respectively (for a review, see Terpou, Densmore, Thome et al., 2019), which suggests the PAG may serve a critical role underlying post-trauma psychopathology.

Perry and colleagues (1995) have suggested hyperarousal and hypervigilance, as well as hypoarousal and dissociative symptoms to be related neurodevelopmentally to active and passive defense responses, respectively. Here, acute, active and passive defense responses are proposed to be engaged during the initial trauma(s) and are relived subsequently (while the trauma memory remains unprocessed), whereby the adaptive, defense-related response may become imprinted as a maladaptive and recurring, defense-related

symptom (i.e., state-to-trait). The work by Perry and colleagues has garnered strong support neurobiologically. In particular, Harricharan and colleagues (2016) have revealed altered functional connectivity exhibited by the PAG in participants with PTSD while at rest (i.e., resting-state). Here, Harricharan and colleagues revealed extensive functional connectivity between the dlPAG and the neural systems related to hyperarousal symptoms (e.g., dorsal anterior cingulate cortex, anterior insula) among participants with PTSD. Moreover, Harricharan and colleagues revealed stronger functional connectivity between the vlPAG and the neural systems related to hypoarousal symptoms (e.g., temporoparietal junction, rolandic operculum) among participants with PTSD who met the dissociative criteria as compared to healthy controls. Interestingly, Nicholson and colleagues (2017) have also revealed differences in functional connectivity exhibited by the PAG between participants with PTSD who do and do not meet the dissociative criteria. In particular, Nicholson and colleagues revealed stronger bottom-up, directed functional connectivity by the PAG toward the mPFC among participants with PTSD who did not meet the dissociative criteria (i.e., hyperarousal) as compared to participants with PTSD who did meet the dissociative criteria. Taken together, altered activity during subliminal, threat- and trauma-related stimulus processing, as well as altered functional connectivity and directed functional connectivity (i.e., effective connectivity) while at rest has been revealed in regard to the PAG in participants with PTSD. However, task-based (as opposed to resting-state) functional connectivity dynamics are much less understood in regard to the midbrain systems in PTSD.

1.4 OBJECTIVES

Here, we aimed to study the lower-level, emotive systems underlying threat- and trauma-related stimulus processing and arousal symptomatology more broadly in PTSD. In particular, we address an urgent need to expand the neurobiological framework to include lower-level, emotive systems into the predominant cortico-centric models. As we have outlined, early evidence suggests lower-level, emotive systems are altered profoundly in PTSD as well, but it remains unclear whether these differences are caused more so by alterations to higher-level, cognitive systems (e.g., under- vs over- modulation; Lanius et al., 2010), or whether alterations emerge across lower-level, emotive systems and are

propagated upward and toward large-scale, neurocognitive networks. To answer the above, we need to improve the resolution by which we image lower-level, emotive systems, as well as resolve the directionality problem, a pervasive concern in functional magnetic resonance imaging (fMRI). Here, we evaluated midbrain activity and functional connectivity during subliminal, trauma-related stimulus processing, as well as during script-driven, moral injury-related (MI) memory recall in participants with PTSD as compared to healthy controls.

In Chapter 2, midbrain, lower brainstem, and cerebellar activity differences were analyzed during subliminal, trauma-related stimulus processing in participants with PTSD as compared to healthy controls. In Chapter 3 and 4, midbrain functional connectivity and midbrain directed functional connectivity (i.e., effective connectivity) differences were analyzed during subliminal, trauma-related stimulus processing (same paradigm and same sample as characterized in Chapter 2) in participants with PTSD as compared to healthy controls. Lastly, in Chapter 5, midbrain functional network connectivity differences were analyzed during script-driven, MI-related memory recall in participants with civilian-related PTSD, participants with military- or public safety-related PTSD, and MI-exposed, healthy controls. Here, machine learning algorithms were used to determine whether we could replicate the previous findings, in part, using a data-driven approach. Ultimately, we believe these findings to be discussed are consistent with the clinical phenomenology related to self-identity and self-experience in PTSD.

1.5 REFERENCES

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CHAPTER 2[2]

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2 THE INNATE ALARM SYSTEM AND SUBLIMINAL THREAT PRESENTATION IN POST-TRAUMATIC STRESS DISORDER: NEUROIMAGING THE MIDBRAIN AND THE CEREBELLUM

2.1 ABSTRACT

Background: The Innate Alarm System (IAS), a network of inter-connected midbrain, lower brainstem, and thalamic structures, serves to rapidly detect stimuli in the environment prior to the onset of conscious awareness. This system is sensitive to threatening stimuli and has evolved to process these stimuli subliminally for hastened responding. Despite the conscious unawareness, the presentation of subliminal threat stimuli generates increased activation of limbic structures, including the amygdala and insula, as well as emotionally-evaluative structures, including the cerebellum and orbitofrontal cortex. Post-traumatic stress disorder (PTSD) is associated with an increased startle response and decreased extinction learning to conditioned threat. The role of the IAS in the clinical presentation of PTSD; however, remains poorly understood. **Methods:** Here, we compare midbrain, brainstem, and cerebellar activation in persons with PTSD (n = 26) and matched controls (n = 20) during subliminal threat presentation. Subjects were presented with masked trauma-related and neutral stimuli below conscious threshold. Contrasts of subliminal brain activation for the presentation of neutral stimuli were subtracted from trauma-related brain activation. Group differences in activation, as well as correlations between clinical scores and PTSD activation, were examined. Imaging data were preprocessed utilizing the spatially-unbiased infra-tentorial template (SUIT) toolbox within SPM12. **Results:** Analyses revealed increased midbrain activation in PTSD as compared to controls in the superior colliculus, periaqueductal gray, and midbrain reticular formation during subliminal threat as compared to neutral stimulus presentation. Controls showed increased activation in the right cerebellar lobule V during subliminal threat presentation as compared to PTSD. Finally, a negative correlation emerged between PTSD patient scores on the Multiscale Dissociation Inventory (MDI) for the depersonalization/derealization subscale and activation in the right lobule V of the

cerebellum during the presentation of subliminal threat as compared to neutral stimuli. **Conclusion:** We interpret these findings as evidence of IAS overactivation in PTSD and of the prominent role of the cerebellum in the under-modulation of emotion observed in PTSD.

2.2 INTRODUCTION

The Innate Alarm System (IAS) refers to a network of brain structures serving the rapid detection of evolutionarily-relevant and negatively-valenced stimuli in the environment, which may function during subliminal presentation (Liddell et al., 2005). Subliminal stimuli define information from the environment which are not perceived consciously. These stimuli are nonconscious since processing is predominantly restricted to a series of inter-connected midbrain, brainstem, and thalamic nuclei, which cannot support conscious processing due to reduced cortical engagement. These nuclei transmit sensory information that bypass primary cortices and directly innervate limbic and arousal brain circuitry (Liddell et al., 2005; Tamietto & de Gelder, 2010). Through bypassing the cortex, the stimuli can be processed more rapidly, thus conferring an evolutionary advantage when responding quickly to a threat in the environment (Pessoa & Adolphs, 2010). The IAS was identified via previous studies that presented fearful and neutral facial expressions to subjects very briefly such that they could not consciously discriminate between the expressions (Liddell et al., 2005). Despite participants' inability to discriminate these stimuli, subliminal fear presentation evoked an increase in brain activation at the level of the midbrain in the superior colliculus, lower brainstem in the locus coeruleus, and limbic circuitry in the amygdala (Liddell et al., 2005). In addition to faces, the IAS response has been reported for the subliminal presentation of body posture cues, eye contact, and trauma-related words (Steuwe et al., 2014; Rabellino et al., 2016).

Critically, post-traumatic stress disorder (PTSD) is associated with an overactive threat detection circuitry as a result of trauma exposure (Steuwe et al., 2014; Rabellino et al., 2016; for a review, see Lanius et al., 2017). In PTSD, traumatic experiences promote attentional biases towards threat stimuli by way of elevated fear responses coupled with reduced extinction (Fani, Tone, Phifer et al., 2012). Here, the threat bias in PTSD is

evidenced by increased startle responses and emotional dysregulation of limbic circuitry during the presentation of consciously perceived fearful or trauma-related stimuli (Fani, Tone, Phifer et al., 2012; Fani, Jovanovic, Ely et al., 2012). PTSD is further associated with difficulties in extinguishing prior learned fear, as indicated by increased amygdala activation and skin conductance during extinction phases of learning as compared to controls (Milad et al., 2008, 2009). Moreover, these neural and autonomic alterations are mirrored during the subliminal presentation of threat (Felmingham et al., 2008; Steuwe et al., 2014; Naim et al., 2015; Rabellino et al., 2016). Structures of the IAS showing increased activation in PTSD during the presentation of subliminal threat include the amygdala (Bryant et al., 2008; Kemp et al., 2009), parahippocampal gyrus (Sakamoto et al., 2005), lower brainstem (Felmingham et al., 2008; Kemp et al., 2009), and midbrain (Felmingham et al., 2008; Kemp et al., 2009). Importantly, hyperactive amygdala activation is not a consistent finding for research that employs affect-related stimuli more generally in persons with PTSD as compared to controls (Sakamoto et al., 2005; Steuwe et al., 2014; Patel et al., 2012). Here, hyperactive amygdala findings within the PTSD literature may be contingent upon the data analysis approach (i.e., whole-brain versus region-of-interest), as well as the comparison subjects employed (i.e., healthy controls versus trauma-exposed controls) (Hayes et al., 2011). However, studies employing subliminal and supraliminal stimuli routinely elicit greater amygdala activation in PTSD as compared to control subjects (for a review, see Wager & Etkin, 2007; Hayes, Hayes, & Mikedis, 2012; Sartory et al., 2013). Taken together, these findings support the notion of a hyperactive IAS in PTSD towards threat (for a review, see Lanius et al., 2017). However, it remains unknown the contribution that specific low-level structures, contained within the midbrain, lower brainstem, and cerebellum, have towards the physiological signatures displayed in PTSD. Greater specificity of threat detection circuitry could improve our clinical understanding of the disorder.

The physiological signatures that indicate a threat response are coordinated by low-level brain structures that alter activation of opposing nervous systems. The autonomic nervous system (ANS) is the central system for responding to threat in the environment. The ANS is a division of nerve fibers that supply muscles and glands to regulate bodily functions without the need for conscious control. The sympathetic and parasympathetic branches of

the ANS enact active (e.g., fight, flight) and passive (e.g., faint, tonic immobility) defensive responses, respectively (Bandler et al., 2000; Pole, 2007). These responses are characterized by dissociable changes in physiology, with active and passive defenses exemplifying sympathoexcitation (e.g., hypertension, tachycardia) and sympathoinhibition patterns (e.g., hypotension, bradycardia), respectively (Löw, Weymar, & Hamm, 2015).

The periaqueductal gray is a midbrain structure that coordinates the defensive responses via activation of its opposing subunits – the dorsolateral periaqueductal gray (active defenses) and ventrolateral periaqueductal gray (passive defenses) (De Oca et al., 1998; for a review, see Kozlowska et al., 2015). The periaqueductal gray is heavily connected with the IAS, as it receives projections from limbic and subcortical structures which evaluate the emotional valence of stimuli. Moreover, the periaqueductal gray shares connectivity with the insula, a cortical region involved in the regulation of the ANS (Oppenheimer et al., 1992; for a review, see Wager & Etkin, 2007). Critically, both the periaqueductal gray and the insula show increased activation in PTSD during symptom provocation (Phan et al., 2002; Felmingham et al., 2008). In addition, the periaqueductal gray exhibits increased resting-state functional connectivity with areas underlying emotional reactivity in PTSD as compared to controls (Harricharan et al., 2016). These reports converge with a study by Felmingham and colleagues (2008), where persons with PTSD displayed increased periaqueductal gray activation as compared to controls during subliminal threat presentation. Taken together, these findings suggest that overactive threat detection circuitry may promote periaqueductal gray-mediated physiological changes, which can present as symptoms of hypervigilance, or, in severe cases, defensive responses in PTSD (e.g., fight, flight, tonic immobility), depending on the level of threat perceived.

The midbrain reticular formation is another midbrain area associated with threat stimuli. The midbrain reticular formation is a combination of nuclei that occupy a large portion of the midbrain tegmentum (Goetz et al., 2016). The initial functional characterization of the midbrain reticular formation associated it with transitions in brain states, for example, transitioning from a sleeping to a waking state (Moruzzi & Magoun, 1949). These

transitions are guided by ascending and descending cholinergic projections from the midbrain reticular formation throughout the ascending reticular activating system (ARAS) (Mesulam et al., 1984; Roš et al., 2010). The ARAS refers to a network of connected brainstem, midbrain, and thalamic nuclei that drive cholinergic and glutamatergic projections to the cortex (Chen & May, 2000; Edlow et al., 2012). These projections assist in the generation and the maintenance of arousal states reflected in the limbic and prefrontal cortices (Garcia-Rill, 1991; Kinomura et al., 1996; Goetz et al., 2016). Moreover, the midbrain reticular formation receives crudely processed sensory information from the superior colliculus – the central structure of the IAS (Grofová et al., 1978; Liddell et al., 2005). In concert with the superior colliculus, the midbrain reticular formation can produce involuntary changes in gaze direction when stimulated in primates (Cohen et al., 1985; Wang et al., 2013). Together, the evidence suggests that cholinergic projections from the midbrain reticular formation engage arousal and limbic circuitry following the detection of a threat (Grofová et al., 1978; Wang et al., 2013; Brudzynski, 2007, 2013, 2014). Moreover, this system appears capable of initiating strong aversive emotional states during threat display in rats (Decsi & Karmos-Várszegi, 1969; Brudzynski, 1994; Panksepp, 2010). Despite the known role of the midbrain reticular formation in the generation of arousal states, to our knowledge, it remains unclear how this region contributes to symptom expression in PTSD.

The cerebellum is a hindbrain region involved in the regulation of emotional states that may function in concert with the IAS (Schutter & van Honk, 2009; Ferrucci et al., 2012). The cerebellum shares connectivity with midbrain and limbic circuitry and elicits activation in the presence of threat (Moulton et al., 2011). Moreover, stimulation of the cerebellum can induce activation in mesolimbic circuitry and cerebellar lesions are associated with symptoms of emotion dysregulation (Parvizi, 2001; Turner et al., 2007). The right cerebellar lobule V is a cerebellar region with a preference for aversive stimuli, as indicated by increased activation to fearful as compared to neutral facial expressions in healthy participants (Moulton et al., 2011; Baumann & Mattingley, 2012). The pattern of activation in the right cerebellar lobule V mirrors that of the amygdala, lending support to their co-involvement during evoked aversive states (Eippert et al., 2007; Baumann & Mattingley, 2012). Whereas amygdala activation maintains an aversive state, cerebellar

activation may attenuate the emotional response (Schmahmann & Sherman, 1998; Schutter & van Honk, 2009). The latter finding is supported by studies employing slow repetitive transcranial magnetic stimulation to inhibit cerebellar function during emotion generation (Schutter & van Honk, 2009). During inhibition of the cerebellum, participants report heightened aversive states and greater amygdala activation. In PTSD, the right cerebellar lobule V demonstrates a resting-state decoupling with multisensory cortices, including the temporoparietal junction and the parietal operculum (Rabellino et al., 2018). Moreover, PTSD is associated with a general decrease in right cerebellar activation during symptom provocation (for a review, see Hayes, Hayes, & Mikedis, 2012). To the extent that the cerebellum regulates aversive states, reductions in its function may promote IAS overactivation in PTSD.

The IAS is a network of low-level structures that process subliminal stimuli and may demonstrate altered activation in PTSD (Liddell et al., 2005; for a review, see Lanius et al., 2017). The contribution of specific midbrain, brainstem, and cerebellar structures to the exaggerated threat response observed in PTSD is not well understood. Accordingly, our aim was to investigate neural activation in PTSD during subliminal threat presentation using improved normalization of the functional magnetic resonance imaging data (fMRI) generated from these low-level structures. We hypothesized that individuals with PTSD would show increased activation during the presentation of subliminal threat stimuli within the midbrain by way of the over-recruitment of the IAS (for a review, see Lanius et al., 2017). For non-trauma exposed controls, we hypothesized they would demonstrate increased right cerebellar activation as compared to PTSD as a reflection of their enhanced capacity to regulate affect (Schutter & van Honk, 2009; Baumann & Mattingley, 2012).

2.3 METHODS

2.3.1 PARTICIPANTS

This study was approved by the Health Sciences Research Ethics Board of Western University and adhered to the standards set forth by the Tri-Council Policy. In total, forty-six, English-fluent participants were recruited for the study, twenty-six met the

criteria for a primary diagnosis of PTSD and twenty were included as healthy, non-trauma-exposed controls. Participants were recruited by the London Health Services Centre via referrals from physicians, community clinics, mental health professionals, and advertisements in the community. Data generated on this sample and paradigm have been analyzed separately and reported in previous work (Rabellino et al., 2015, 2016, 2017). All participants provided written and informed consent for their involvement.

Exclusion criteria for the study included incompatibility with scanning requirements, previous neurologic and developmental illness, pregnancy, comorbid schizophrenia or bipolar disorder, alcohol or drug abuse within six months prior to scanning, or a history of head trauma. Diagnoses for PTSD were ascertained using the Clinician Administered PTSD Scale (CAPS) [CAPS-IV cut-off score > 50 for PTSD diagnosis], as well as a Structured Clinical Interview for DSM-IV Axis-I disorders (SCID-I) (Blake et al., 1995; First, 2015). In terms of the type of trauma experienced, 23 of the 26 persons with PTSD experienced childhood interpersonal trauma while the remaining 3 of the 26 persons experienced a personal threat of life or witnessed a violent death. Control subjects did not meet any current or lifetime criteria for psychiatric disorders. In addition, the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003), Multiscale Dissociative Inventory (MDI) (Briere, Weathers, & Runtz, 2005), and Beck's Depression Inventory (BDI) were administered (Beck et al., 1997). Following scanning, participants completed the State-Trait Anxiety Inventory (STAI; Spielberger, 1989) and the Responses to Script Driven Imagery (RSDI; Hopper et al., 2007) questionnaire to assess any perceptible fluctuations in state and trait anxiety and PTSD symptoms related to the paradigm, respectively. Lastly, the Clinician Administered Dissociative States Scale (CADSS; Bremner et al., 1998) was administered to determine whether persons experienced a dissociative episode during functional magnetic resonance imaging (fMRI).

2.3.2 EXPERIMENTAL TASK

The fMRI procedure and psychophysical thresholds were based on previously published methods for the presentation of subliminal and supraliminal stimuli (Williams et al., 2006; Felmingham et al., 2008; Rabellino et al., 2015). All stimuli had a subliminal and a supraliminal presentation over two consecutive sessions, which were counterbalanced

across subjects and involved a two-minute rest period between sessions. Cues represented both threat-related (fearful facial expressions and personalized trauma words) and neutral (neutral facial expressions and words) stimuli presented in a pseudo-randomized block design. Word cues were subject-specific, with trauma words generated with respect to a patient's individualized trauma experience or, in the case of controls, an aversive experience. Neutral words were selected if they had not elicited a strong positive or a strong negative reaction during pre-scan exposure to the word. All words were matched for syllable and letter length. Each block (neutral words, trauma words, neutral faces, fearful faces) was repeated five times in a fixed order to the participant. Face stimuli were three-dimensional and selected from a standardized database (Gur et al., 2002). Each block consisted of eight repetitions of the stimulus as either subliminal or supraliminal. Subliminal stimuli were presented for 16 ms and separated by a jittered inter-stimulus interval that varied in duration from 823 to 1823 ms. Subliminal presentation of stimuli was masked (mask duration: 161 ms) to ensure preconscious processing (Liddell et al., 2005). Supraliminal stimuli were presented for 500 ms and separated by a jittered inter-stimulus interval of 500 to 1500 ms. A button press task was implemented between stimulus presentation blocks to ensure sustained attention throughout the scanning session (letter recognition; 4500 ms). Lastly, each run was preceded by a 30-second rest period, which was used as an implicit baseline for comparisons in subsequent analyses (stimuli: fixation cross).

2.3.3 fMRI DATA ACQUISITION

Functional images were collected on a 3.0 T whole-body MRI scanner (Siemens Biograph mMR, Siemens Medical Solutions, Erlangen, Germany) using a 32-channel phased array head coil. T1-weighted anatomical images were collected with 1 mm isotropic resolution (MP-RAGE, TR/TE/TI = 2300 ms/2.98 ms/900 ms, FA 9º, FOV = 256 mm x 240 mm x 192 mm, acceleration factor = 4, total acquisition time = 192 s). Sixty-four whole-brain, 2 mm thick imaging planes for blood-oxygen-level dependent (BOLD) fMRI were generated parallel to the AC-PC. Functional data was acquired using the manufacturer's standard gradient-echo EPI pulse sequence (single-shot, blipped EPI) with interleaved slice acquisition order and tridimensional prospective correction and an

isotropic resolution of 2 mm [(FOV=192 mm x 192 mm x 128 mm (94 x 94 matrix, 64 slices), TR/TE = 3000ms/20 ms, FA = 90º (FOV = Field of View, TR = Time Resolution, TE = Echo Time, FA = Flip Angle)].

2.3.4 fMRI ANALYSIS USING SUIT TOOLBOX

To improve the normalization procedure and receive a clearer depiction of midbrain, brainstem, and cerebellar activation, data were normalized to the spatially unbiased infra-tentorial template (SUIT) toolbox (Diedrichsen, 2006; Diedrichsen et al., 2009). The SUIT toolbox offers a high-resolution atlas template of the cerebellum and the brainstem with improved voxel-by-voxel normalization of fMRI. The SUIT toolbox functions on Statistical Parametric Mapping (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK: http://www.fil.ion.ucl.ac.uk/spm) within MATLAB 9.2 (R2017a, MathWorks Inc., MA) and contains several preprocessing steps. Firstly, anatomical images were reoriented in SPM, where the horizontal plane was defined approximately according to the AC-PC line. Secondly, functional images were reoriented to correspond to the reoriented anatomical image. Thirdly, subject-specific functional volumes were realigned to the first volume of each session to correct for movement in the scanner and then resliced to a voxel size of 2 x 2 x 2 mm^3. At this time, six realignment parameters for changes in motion across the different planes and an ART regressor for global movement correction were saved. Fourthly, subject-specific brainstem and cerebellum were isolated and cropped from the T1-weighted anatomical images in order to focus on the infra-tentorial structures of interest. Fifthly, individual cropped anatomical images of the brainstem and cerebellum were normalized into the SUIT atlas template. During this step, a subject-specific transformation matrix was generated for the linear part of the normalization that deforms each cerebellum to provide optimal correspondence to the SUIT template (Ashburner, 2007). Sixthly, functional volumes were resliced into SUIT-space in order to align functional images with the SUIT-normalized anatomical images by applying the subject-specific transformation matrix. Lastly, a three-dimensional, isotropic, 4 mm full-width at half-maximum Gaussian kernel was applied to each set of SUIT-resliced functional data to smooth the data in accordance with previous methods using SUIT preprocessing (Köhler, Bär, & Wager, 2016; Mehnert et al., 2017).

2.3.5 STATISTICAL ANALYSES

In the first-level analyses, a fixed-effects model was generated in which the time-series of the eight conditions (Subliminal: Trauma Words (TW), Neutral Words (NW), Fearful Faces (FF), and Neutral Faces (NF) and Supraliminal: TW, NW, FF, and NF) were convolved to the default canonical hemodynamic response function. The button task and realignment parameters were included as regressors of no interest. An ART regressor, which accounts for effects of movement and global signal correction (version 2015-10; Gabrieli Lab, McGovern Institute for Brain Research, Cambridge, MA), was added as a within-subject covariate of no interest as well. Software default thresholds for ART regressor outliers were selected (global signal threshold = 9.0 mm, absolute subject motion threshold = 2.0 mm, rotational threshold = .05 mm, scan-to-scan subject motion = 2.0 mm, and scan-to-scan subject rotation = .02 mm). At this time, contrast images were created for the subliminal presentation of trauma-related words minus the subliminal presentation of neutral words (Subliminal: TW > NW), as well as the subliminal presentation of fearful faces minus the subliminal presentation of neutral faces (Subliminal: FF > NF) for each subject. As well, contrasts for the supraliminal presentation of trauma minus neutral words (Supraliminal TW > NW) and fearful minus neutral faces (Supraliminal: FF > NF) were also conducted. These contrasts were carried forward to the second-level for random-effects group comparisons.

In the second-level, a full factorial analysis of variance (ANOVA) was conducted on the data to examine the 2 x 2 x 2 interaction between group (PTSD, controls), conscious level (subliminal, supraliminal), and stimulus contrast condition (TW > NW, FF > NF). These comparisons were analyzed using random-field theory as implemented by SPM12. Variances were set to unequal to account for differences in group sizes. While exploring random-effects group comparisons across SUIT-space, an initial significance threshold was set to p-uncorrected < .005, $k \geq 5$. An initial liberal threshold was employed due to the analyses being novel and to allow for the overall trends of the data to be observed using a less-conservative threshold.

Subsequent region-of-interest (ROI) analyses were conducted to restrict the voxels of examination to regions involved in the IAS and associated with PTSD. No subject-

specific coordinates were employed. All results for the ROI analyses were thresholded at p-FWE < .05, $k \geq 5$. Identification of brain regions were obtained by using the cerebellar probabilistic atlas template for SUIT, as well as the ascending arousal network (AAN) atlas, which details the position of many brainstem nuclei in MNI space (Diedrichsen, 2006; Edlow et al., 2012). The ROI used for the analyses was a single mask generated by combining midbrain and cerebellar structures. From the midbrain, the bilateral superior colliculus, periaqueductal gray, and midbrain reticular formation were selected. Masks for the periaqueductal gray and midbrain reticular formation were adopted from the AAN atlas due to its strong structural and functional validation and free access (Edlow et al., 2012). The superior colliculus mask was generated using PickAtlas software (WFU PickAtlas, version 2.5.2; Maldjian et al., 2003) and followed the anatomical description provided by Martin (1989). From the cerebellum, the particular coordinates for the right cerebellar lobule V were adopted from the SUIT template (Diedrichsen, 2006). Lastly, the four regions were merged into a single mask using the IMCalc toolbox provided in SPM12 [http://tools.robjellisnet] and verified using MRIcron (Rorden & Brett, 2000).

A multiple regression was conducted within the PTSD group to determine whether clinical scores correlated with brain activation within the conditions of interest. In this case, we were interested in the contrasts of the subliminal presentation of TW > NW and FF > NF. Activation within the PTSD group was correlated with symptom scores of re-experiencing (CAPS criterion B), avoidance (CAPS criterion C), negative alterations in cognition and mood (CAPS criterion D), and dissociation (MDI depersonalization and derealization subscales). For the CAPS scores, each criteria were analyzed separately, as well as the sum of frequency and intensity scores for B, C, and D (Blake et al., 1995). Moreover, correlations of PTSD activation were conducted with trauma history (CTQ) and state symptom scores (STAI, RSDI, CADSS). The analysis was thresholded initially at p-uncorrected < .005 with follow-up ROIs using p-FWE < .05, $k \geq 5$.

2.4 RESULTS

2.4.1 DEMOGRAPHICS AND CLINICAL MEASURES

Independent sample t-tests did not reveal any significant differences between PTSD and the control group with respect to demographic measures. As predicted, persons with PTSD scored significantly higher on total scores for the CAPS, MDI, and CTQ (see Table 2.1).

TABLE 2.1: *CLINICAL AND DEMOGRAPHIC INFORMATION*

Measure	**PTSD (N = 26)**	**HC (N = 20)**	χ^2	**T-Test**
	M ± SD	M ± SD	*p*	*p*
Years of Age	38.8 ± 12.2	32.5 ± 11.6	.088	-
Sex (n)	Male = 11, Female = 15	Male = 10, Female = 10	.604	-
Employment Status (n)	Employed = 18, Unemployed = 7	Employed = 17, Unemployed = 3	.297	-
CAPS Total	70.6 ± 11.9	.94 ± 2.9	-	< .001
CTQ – Emotional Abuse	14.5 ± 6.1	6.8 ± 3.1	-	< .001
Moderate Cut-Off Met (n)	5	-	-	-
Severe Cut-Off Met (n)	11	-	-	-
CTQ – Physical Abuse	10.1 ± 6.4	5.7 ± 1.6	-	.004
Moderate Cut-Off Met (n)	0	-	-	-
Severe Cut-Off Met (n)	9	-	-	-
CTQ – Sexual Abuse	13.4 ± 7.8	5.3 ± 1.1	-	< .001
Moderate Cut-Off Met (n)	1	-	-	-
Severe Cut-Off Met (n)	14	-	-	-
CTQ – Emotional Neglect	13.5 ± 5.9	8.8 ± 4.2	-	.004
Moderate Cut-Off Met (n)	2	-	-	-

Measure	PTSD (N = 26)	HC (N = 20)	χ^2	T-Test
	M ± SD	M ± SD	*p*	*p*
Severe Cut-Off Met (n)	10	-	-	-
CTQ – Physical Neglect	10.2 ± 4.7	6.8 ± 2.7	-	.006
Moderate Cut-Off Met (n)	5	-	-	-
Severe Cut-Off Met (n)	6	-	-	-
MDI Total	58.8 ± 21.6	33.7 ± 3.8	-	< .001
MDI Depersonalization	7.8 ± 4.1	-	-	-
MDI Derealization	9.5 ± 4.5	-	-	-
MDI Dep./Der.	8.7 ± 4.1	-	-	-
Axis-I Comorbidities (current [past]) frequency	Major Depressive Disorder (8[9])			
	Dysthymic Disorder (0[3])			
	PD w/ Agoraphobia (0[1])			
	PD w/o Agoraphobia (1[1])			
	Agoraphobia w/o PD (3)			
	Social Phobia (4)			
	Specific Phobia (2)			
	OCD (1[1])			
	Eating Disorders (1[1])			
	Somatoform Disorder (6)			

Measure	PTSD (N = 26)	HC (N = 20)	χ^2	T-Test
	M ± SD	M ± SD	*p*	*p*
	Lifetime Alcohol Abuse or Dependence [16]			
	Lifetime Substance Abuse or Dependence [7]			

Abbreviations: Clinician Administered PTSD Scale (CAPS); Childhood Trauma Questionnaire (CTQ); Multiscale Dissociation Inventory [(MDI): Dep: Depersonalization Subscale, Der: Derealization Subscale, Dep/Der: Depersonalization and Derealization

2.4.2 IMAGING RESULTS

Within-Group Comparisons

No significant differences in neural activation were revealed for within-group, between-group, or clinical correlations for the contrast condition of the subliminal presentation of FF > NF, as well as any supraliminal presentation contrasts. As a result, the results and discussion will focus specifically on the subliminal presentation of TW > NW.

All results were restricted to the SUIT-space offered by the toolbox. For controls, no significant voxels were detected at the significance of p-FWE < .05, $k \geq 5$. For the PTSD group, a significant cluster emerged with a peak-coordinate centered on the periaqueductal gray [(x: 0, y: -32, z: -11), k = 53, p-FWE = .013] during subliminal trauma-related words as compared to neutral stimulus presentation (see Table 2.2). This cluster also covered areas of the superior colliculus and midbrain reticular formation.

TABLE 2.2: *WITHIN-GROUP DIFFERENCES IN SUIT-SPACE*

Contrast	Region	*k*	*p*(FWE)	*z*	MNI Coordinates		
					x	*y*	*z*
Subliminal TW > NW							
Control	None						
PTSD	Periaqueductal Gray	53	.013	4.39	0	-32	-11

Within-Group BOLD activation restricted to SUIT-space without ROI corrections for subliminal threat presentation. Reported results are at a significance of p-FWE < .05, $k \geq 5$.

Between-Group Comparisons

Applying the ROI mask of the bilateral superior colliculus, periaqueductal gray, midbrain reticular formation, and right cerebellar lobule V to the partial-brain space yielded significant between-group results at p-FWE < .05, $k \geq 5$. For the subliminal presentation of the contrast condition of TW > NW, control subjects demonstrated significantly greater activation as compared to the PTSD group at a peak-coordinate centered on the right cerebellar lobule V [(x: 18, y: -48, z: -23), k = 5, p-FWE = .019] (see Table 2.3). Conversely, the same contrast yielded greater activation in the PTSD group at a peak-coordinate centered on the periaqueductal gray, midbrain reticular formation, and superior colliculus [(x: -2, y: -28, z: -7), k = 13, p-FWE = .019] (Figure 2.1).

TABLE 2.3*: BETWEEN-GROUP DIFFERENCES IN SUIT-SPACE (ROI)*

Contrast	Region	*k*	*p*(FWE-cor)	*z*	MNI Coordinates		
					x	*y*	*z*
Subliminal TW > NW							
Control > PTSD	Cerebellar Lobule V	5	.019	3.87	18	-48	-23
PTSD > Control	Periaqueductal Gray / Midbrain Reticular Formation / Superior Colliculus	13	.019	3.87	-2	-28	-7

Group differences in BOLD activation between PTSD and controls within the subliminal task from the ROI analysis. All reported results for the ROI analysis are at a significance of p-FWE < .05, $k \geq 5$.

Clinical Correlations

The whole SUIT-space analysis did not reveal any significant correlations between clinical scores and BOLD activation in the PTSD group during the multiple regression analysis. The follow-up ROI analysis yielded significant results at p-FWE < .05, $k \geq 5$ for the subliminal contrast of TW > NW. The significant correlation was negative and emerged between scores on the MDI depersonalization/derealization subscales and BOLD activation in the right cerebellar lobule V [(x: 12, y: -56, z: -23), k = 11, p-FWE = .032] in the PTSD group (see Table 2.4).

TABLE 2.4: *CLINICAL CORRELATIONS*

Clinical Measure	**Region**	***k***	***p*(FWE-cor)**	***z***	**MNI Coordinates**		
(Direction of Effect)					***x***	***y***	***z***
Subliminal TW > NW							
MDI Dep./Der. (Negative)	Cerebellar Lobule V	11	.032	3.77	12	-56	-23

Correlations of clinical scores with BOLD activation in the PTSD group within the region-of-interest. All reported results for SUIT-space are at a significance of p-FWE < .05, $k \geq 5$.

2.5 DISCUSSION

2.5.1 OVERVIEW

To date, the PTSD neuroimaging literature has focused predominantly on the divergence of cortical networks in the pathological brain when compared to healthy controls. Here, theories have emerged that attempt to explain how PTSD symptoms arise as a result of dysfunction in top-down, cortical networks. These theories, however, often neglect to incorporate midbrain, brainstem, and cerebellar involvement despite the reliance of the cortex on these structures. In the present study, we implemented a more precise analysis protocol with improved normalization of the midbrain, brainstem, and cerebellum to image persons with PTSD and healthy controls during the presentation of a subliminal

threat as compared to a neutral stimulus. As predicted, midbrain regions associated with the IAS showed increases in activation during the viewing of trauma-related words in persons with PTSD as compared to controls. In controls, elevated activation in the subliminal threat condition was detected in the right cerebellar lobule V as compared to PTSD. Moreover, the right cerebellar lobule V was found to correlate negatively with MDI symptom scores of depersonalization/derealization in persons with PTSD. These different neural responses to subliminal threat provide novel evidence towards the alterations of low-level structures in PTSD, which, when considered together, may contribute to a more integrated understanding of this disorder.

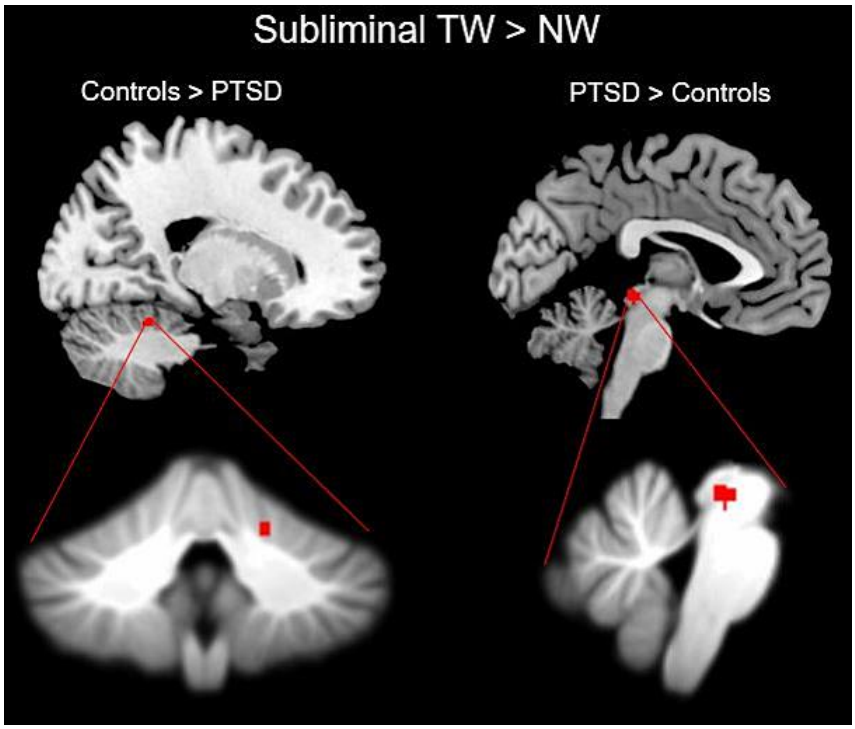

FIGURE 2.1: *SIGNIFICANT BETWEEN-GROUP DIFFERENCES IN SUIT-SPACE*

Figure details the exported clusters that reached significance for the contrasts of Controls > PTSD and PTSD > Controls during the subliminal presentation of trauma-words as compared to neutral words. Above are the clusters as they appear on the SUIT template.

2.5.2 BETWEEN-GROUP COMPARISONS

Our analyses revealed increased response of the superior colliculus, periaqueductal gray, and midbrain reticular formation for the ROI analysis of the subliminal presentation of trauma-related words in PTSD as compared to controls. These results converge with studies involving participants with PTSD that revealed increased activation to threat when presented at (Liberzon et al., 1999; Phan et al., 2002; Simmons et al., 2008), or below conscious threshold (Rauch, Whalen, & Shin, 2000; Felmingham et al., 2008; Bryant et al., 2008; Steuwe et al., 2014). In particular, our findings resemble those of Felmingham and colleagues (2008) who reported increased activation in the superior colliculus and periaqueductal gray of women with PTSD as compared to a control group during the presentation of a subliminal threat. We argue that these results provide evidence for the overactivation of threat detection circuitries towards a pathological extreme in PTSD (for a review, see Lanius et al., 2017).

The superior colliculus refers to a set of paired midbrain nuclei that are central to the function of the IAS. This structure transmits crude visual information to the pulvinar nuclei of the thalamus to form an alternative visual pathway that supports the act of saccadic eye movements (Liddell et al., 2005). Moreover, this pathway is proposed to assist in detecting novel and evolutionarily-relevant stimuli for rapid processing (Morris, 2001; Vuilleumier et al., 2005). Stimulation of the superior colliculus in rodents and in non-human primates can elicit approach or defensive responses in the form of orienting/pursuit eye movements (i.e., approach) or fight/flight responses (i.e., defense), respectively (Dean, Redgrave, & Westby, 1989; DesJardin et al., 2013). These responses are subserved by distinct output projections from the superior colliculus (Comoli et al., 2012). Interestingly, stimulation of the deep layers of the superior colliculus and the periaqueductal gray evoke a similar response of anxiety-like behaviours in rats, such as freezing or flight (de Almeida et al., 2006). Alternatively, stimulation at a more rostral location of the superior colliculus elicits a response of orienting and approach in rats, similar to the pattern of response observed through stimulation of the midbrain reticular formation (Groves, Wilson, & Boyle, 1974; Sahibzada, Dean, & Redgrave, 1986). Taken together, these complementary findings provide evidence of the co-engagement of the

superior colliculus with the periaqueductal gray and midbrain reticular formation for the generation of defensive and orienting responses, respectively.

We interpret the increase in midbrain activation in the PTSD group observed in the present study as reflecting an overactivation of the IAS towards subliminal threat. Here, the superior colliculus may initiate a response following detection of the trauma-related words and transmit relevant information to the nearby midbrain (Liddell et al., 2005). In turn, cholinergic projections may be sent from the midbrain reticular formation throughout the ascending reticular activating system towards limbic and prefrontal cortices to engage arousal circuitry to better orient to the threat present (Grofová et al., 1978; Mesulam et al., 1984; Brudzynski, 2007). Simultaneously, information relayed to the periaqueductal gray may prompt a defensive cascade, where subunits project to brainstem nuclei to initiate physiological changes coordinated through the ANS (Oppenheimer et al., 1992; Pole, 2007; for a review, see Kozlowska et al., 2015). Here, the periaqueductal gray would coordinate the appropriate defensive response by evaluating certain characteristics of the threat, as well as the situation in which it occurs. Additionally, individual differences in trauma experience also effect the proclivity by which one defensive response is favoured over another (Kozlowska et al., 2015). In summary, this interpretation centered on the midbrain can account for many experimental characteristics of PTSD, including increased startle responses to threat (Felmingham et al., 2008; Fani, Tone, Phifer et al., 2012; Elsesser et al., 2004), neutral cues (Grillon & Morgan, 1999), blunted (Rocha-Rego et al., 2009; Lanius et al., 2010; D'Andrea et al., 2013), or exaggerated autonomic reactivity (Pavic, 2003; Ehring & Quack, 2010), as well as the inability to achieve a restful state (Cohen et al., 2000; Hughes, Dennis, & Beckham, 2007; Harricharan et al., 2016; Rabellino et al., 2018).

In addition, our analyses revealed significantly greater cerebellar activation in controls as compared to PTSD during the presentation of a subliminal threat. In particular, the increased response was generated in the right cerebellar lobule V, a lobule involved in the expression and regulation of aversive states (Eippert et al., 2007; Baumann & Mattingley, 2012). Within individuals with PTSD, activation of the right lobule V was found to correlate negatively with scores on the MDI for the depersonalization/derealization

subscales. As dissociative symptom scores increased in the PTSD group, the activation of the right lobule V decreased. This finding converges with a resting-state study that showed reduced functional connectivity of the anterior cerebellum with cortical regions involved in multisensory integration and bodily self-consciousness in persons with PTSD who met the criteria for the dissociative subtype as compared to controls (2018). Whereas we show that during threat display, persons with greater dissociative scores – and, hence, higher detachment from their emotions – have the lowest engagement of the right cerebellum, Rabellino and colleagues (2018) reveal that the dissociative subtype demonstrates reduced connectivity of the cerebellum, a region involved in emotion processing, with cortical areas that may ground emotions within the body. Furthermore, our results corroborate earlier studies that revealed a positive association between hyperarousal symptoms in PTSD and regional cerebral blood flow to the right lobule V (Osuch et al., 2001). Whereas hyperarousal symptoms characterize a state of emotional under-modulation, dissociative symptoms reflect a state of emotional over-modulation (Lanius et al., 2010). To the extent that the right cerebellum acts to regulate emotions, one would expect to observe opposing patterns of associated neural activation with dissociative and hyperarousal symptom measures. Taken together, studies distinguishing between PTSD with and without the dissociative subtype may examine patterns of correlation between cerebellar lobule V and hyperarousal and dissociation symptom scores in order to identify more precisely the role of this region in emotion regulation in PTSD.

The role of the cerebellum has been expanded recently to reflect its modulatory influence on the maintenance of a homeostatic baseline between low-level brainstem and midbrain activation and high-level limbic and cortical processing (Schmahmann, 2000, 2004). Here, the cerebellum is thought to integrate information across these levels to smooth transitions between different emotional states (Schmahmann, 2004). Evidence for this theory arises from the low- and high-level networks that the cerebellum is involved in (Snider & Maiti, 1976; Stoodley & Schmahmann, 2010), lesion studies demonstrating emotional impairments following cerebellar damage (Parvizi, 2001; Schmahmann, Weilburg, & Sherman, 2007), and the effect that cerebellar inhibition has on limbic dysregulation (Schutter & van Honk, 2009). The right lobule V showed a significant

decrease in activation in our PTSD sample as compared to controls during the presentation of subliminal threat (Baumann & Mattingley, 2012). This effect likely contributes to symptoms of emotional impairment in PTSD and is further supported by studies that report reduced cerebellar volumes in PTSD (Carrion et al., 2009; De Bellis et al., 2015). Whether reduced volumes occur as a result of trauma or are a predisposing characteristic to PTSD remains to be elucidated.

2.5.3 LIMITATIONS

There are several limitations to the present study. To begin, the results reported here rely on a small sample size. Replication with a larger sample size may reveal additional between-group differences in neural activation. In particular, we predict that the insignificant findings for the negatively-valanced facial expressions in the PTSD group are the result of reduced power, as well as the stimuli not representing learned associations to trauma unlike the trauma-related words. Moreover, an increased patient sample could allow researchers to differentiate between persons with PTSD with and without the dissociative subtype. The subtype is distinguishable in both neural and clinical characteristics, which may be reflected in differential midbrain, brainstem, and cerebellar activation (Felmingham et al., 2008; Lanius et al., 2010). In addition, the control group included in the present study represents a healthy control sample as opposed to a trauma-exposed control. As such, any discrepancies in activation cannot be definitively attributed to the PTSD diagnosis as they may arise as a product of trauma exposure and not the subsequent development of PTSD. Notably, however, trauma-exposed controls are not a perfect comparison group as early life trauma prior to PTSD onset and the type of trauma experienced are rarely controlled for in these samples (Brewin et al., 2000). Furthermore, the present study matched trauma-related and neutral words for syllable and letter length, but not for frequency of occurrence in the English language. As a result, the personalized trauma words may have had unanticipated effects of novelty that could promote greater activation. Lastly, trauma-related words were used as our stimuli of focus due to the high limbic activation that is reported during their presentation (Felmingham et al., 2008; Ashley et al., 2013; Rabellino et al., 2016). However, words may not be considered a “natural” source of threat. Hence, it remains

unclear whether these responses reflect the detection of a current threat in the environment or rather a reminder of a past threat. Here, different interpretations of the responses may be proposed depending upon this.

As a point of caution, the authors urge readers to not conceptualize the IAS as entirely separate from supraliminal circuits of threat detection. It is only through experimental procedures that employ brief durations of presentation and backward masks that stimuli may be presented as subliminal. Generally, the IAS should be conceptualized as a "head-start" pathway that rapidly processes salient and threatening stimuli in the environment prior to the onset of more conscious systems. Here, future research is urged to study the activation of the IAS over longer durations of time to determine whether its activation reduces when conscious systems are online or whether the IAS remains an active pathway that is perpetually a few steps ahead of conscious processes.

2.6 CONCLUSION

Despite these limitations, our results further highlight the involvement of the IAS in the psychopathology of PTSD. Using improved normalization methods, we demonstrated a significant increase in midbrain activation for persons with PTSD as compared to healthy controls during the subliminal presentation of threat. These midbrain structures are known to detect threat in the environment as well as to orient towards the threat and prime defensive responses. Crucially, overactivation of these systems may lead to emotional dysregulation in PTSD – as perception is biased towards perceiving threat. In turn, the cerebellum, a region thought to attenuate emotional responses, demonstrates reduced activation during the subliminal presentation of threat in PTSD as compared to controls. In summary, this heightened inclination to perceive the world through a threatening lens, coupled with a reduced ability to regulate threat detection circuitry, may have profound implications for treatment of PTSD.

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CHAPTER 3[3]

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3 THE THREATFUL SELF: MIDBRAIN FUNCTIONAL CONNECTIVITY TO CORTICAL MID-LINE AND PARIETAL REGIONS DURING SUBLIMINAL, TRAUMA-RELATED PROCESSING IN PTSD

3.1 ABSTRACT

Background: The Innate Alarm System (IAS) refers to a subcortical network of inter-connected midbrain, lower brainstem, and thalamic nuclei, which together mediate the detection of evolutionarily-relevant stimuli. The periaqueductal gray (PAG) is a midbrain structure innervated by the IAS, which coordinates the expression of defensive states following threat detection. In participants with post-traumatic stress disorder (PTSD), the PAG displays overactivation during the subliminal presentation of trauma-related stimuli, as well as altered resting-state functional connectivity. Aberrant functional connectivity is also reported in PTSD for the Default Mode Network (DMN), a large-scale, neural network recruited during self-referential processing and autobiographical memory. Here, research lacks investigation on the extent to which functional interactions are displayed between the midbrain and the large-scale, neural networks in PTSD. **Methods:** Using a subliminal threat presentation paradigm, we investigated psycho-physiological interactions during functional neuroimaging in participants with PTSD (n = 26) and healthy control subjects (n = 20). Functional connectivity of the PAG was investigated across the whole-brain of each participant during subliminal exposure to trauma-related and neutral word stimuli. **Results:** As compared to controls during subliminal threat presentation, the PTSD group showed significantly greater PAG functional connectivity with regions of the DMN (i.e., angular gyrus, precuneus, superior frontal gyrus). Moreover, multiple regression analyses revealed that the functional connectivity between the PAG and the regions of the DMN correlated positively to symptoms of avoidance and state dissociation in PTSD. **Conclusion:** Given that the PAG engages the expression of defensive states, stronger midbrain functional coupling with the DMN may have clinical implications to self-referential and trauma-related processing in participants with PTSD.

3.2 INTRODUCTION

The Innate Alarm System (IAS) refers to a subcortical network of inter-connected midbrain, lower brainstem, and thalamic nuclei, which together mediate the detection of evolutionarily-relevant stimuli in the environment (Liddell et al., 2005). The IAS is centralized on the superior colliculus, a midbrain structure that processes and transmits multisensory information. For visual stimuli, projections from the retina are relayed through the superior colliculus and the pulvinar of the thalamus and directed towards frontolimbic neural circuits (Tamietto & de Gelder, 2010). Given its rapid transmission and bypass of primary sensory cortices, visual information processed by the IAS are represented crudely (Liddell et al., 2005). This hastened transmission of threat stimuli, however, confers an evolutionary advantage to the individual, with the IAS postulated to function during subliminal exposure (Pessoa & Adolphs, 2010). Subliminal exposure refers to sensory information that are not perceived consciously but may nonetheless generate an increase in activation of threat detection circuits and, as a corollary, neural systems underlying defensive responses (Liddell et al., 2005; Dean, Redgrave, & Westby, 1989).

The periaqueductal gray (PAG) is a midbrain structure innervated by the superior colliculus, in addition to other brainstem nuclei, the spinal cord, the amygdala, the hypothalamus, and the cortex, and is thus well-positioned to coordinate defensive responses to a perceived threat (Grofová et al., 1978; De Oca et al., 1998; Keay & Bandler, 2015). Defensive responses refer to a set of behavioural states that are engaged through the excitation or the inhibition of the sympathetic nervous system, as well as through the expression of opioid- or endocannabinoid-mediated analgesia (Kozlowska et al., 2015; Lanius et al., 2018). Behaviourally, defensive responses may take the form of an active (e.g., fight, flight) or a passive state (e.g., tonic immobility, shutdown) and their expression is dependent on the context and the level of threat perceived (Fanselow, 1994). In rodents, electrical stimulation of the PAG induces elevated levels of fighting and/or fleeing that are coincident with increases in heart rate, core body temperature, and blood pressure (de Almeida et al., 2006; Comoli et al., 2012). These rodent findings corroborate human studies employing functional magnetic resonance imaging (fMRI)

during threat anticipation paradigms to model brain activation as a function of the imminence of a threat encounter (Mobbs et al., 2009, 2010). In these studies, Mobbs and colleagues (2009) have shown that as the distance between an individual and a perceived threat decreases, there is a concordant shift in brain activation from a pattern of top-down, or ventromedial prefrontal-mediated, to a pattern of bottom-up processing. Specifically, as the imminence of danger increases, a pattern of bottom-up processing involving increased activation of the locus coeruleus, the PAG, and the amygdala is observed. These increases in activation have been interpreted as evidence for the predominance of evolutionarily-conserved, subcortical systems of response during experiences of imminent threat, that contrast sharply with the more cognitive, top-down systems of response observed when threat is perceived at a distance (Mobbs et al., 2010). Critically, the degree to which the PAG is activated in response to threat stimuli may increase as a function of prior lifetime experiences and, in particular, of trauma exposure (Corrigan, Fisher, & Nutt, 2011).

Post-traumatic stress disorder (PTSD) is a mental disorder characterized by hypervigilance, hyperarousal, and, at times, dissociative symptoms following exposure to a traumatic experience (APA, 2013). Often, exposure to a traumatic event can promote an attentional threat bias, or threat sensitization, whereby negatively-valenced stimuli are processed preferentially, leading to exaggerated PTSD symptoms (Bryant & Harvey, 1997; Cisler & Koster, 2010; Fani et al., 2012). This attentional bias is thought to be the product of the overactivation of threat detection circuitry and, in particular, the IAS (Lanius et al., 2017). Notably, several structures associated with the IAS display overactivation during the presentation of fear- or trauma-related material in PTSD, including the amygdala (Protopopescu et al., 2005; Bryant et al., 2008; Kemp et al., 2009), the parahippocampal gyrus (Sakamoto et al., 2005; Zhang et al., 2011), the lower brainstem (Felmingham et al., 2008; Rabellino et al., 2016), and the PAG (Bremner et al., 1999; Felmingham et al., 2008; Terpou et al., 2019). Critically, this pattern of neural response emerges under conditions of subliminal and of supraliminal presentation (Felmingham et al., 2008; Kemp et al., 2009; Rabellino et al., 2016). In particular, a recent study by Terpou and colleagues (2019) revealed a cluster of significantly greater activation of the PAG, as compared to controls, in participants with PTSD during the

subliminal presentation of trauma-related word stimuli – to which the present report builds on these findings.

In addition to increased activation during threat detection, the PAG demonstrates aberrant functional characteristics in individuals with PTSD during rest, where PTSD symptoms are present not only during threat- or trauma-related processing, but also during baseline conditions (O'Donnell, Creamer, & Pattison, 2004; Grupe et al., 2016; Van Wyk et al., 2016). Here, the PAG exhibits increased resting-state functional connectivity with cortical regions associated with environmental monitoring and autonomic nervous system regulation in individuals with PTSD as compared to healthy controls (Harricharan et al., 2016). These findings suggest a strong association between subcortical systems involved in defensive responding and higher-order, cognitive networks of the brain in PTSD (Lanius et al., 2017). To ascertain the directionality of these subcortical-cortical interactions, Nicholson and colleagues (2017) employed dynamic causal modelling of resting-state fMRI in a group of participants with and without PTSD. The results of this study revealed that, as compared to controls, the PTSD group had a stronger pattern of directed connectivity extending from the PAG towards the amygdala and the ventromedial prefrontal cortices. Taken together, these findings provide evidence for a bottom-up, or PAG-mediated pattern of neuronal connectivity in PTSD.

The increased functional connectivity directed from the PAG towards the cortex in PTSD may interfere significantly with the function of large-scale, Intrinsic Connectivity Networks (ICNs). An ICN is a neurocognitive network of brain regions that displays high functional connectivity between network nodes (Menon, 2011). The Default Mode Network (DMN) refers to a task-negative ICN active during self-referential processing, internal cognition, and episodic memory retrieval (Menon & Uddin, 2010). The DMN contains a series of functional hubs that extend along the mid-line of the brain and include the medial prefrontal, posterior cingulate, and posterior parietal cortices (Menon, 2011; Andrews-Hanna et al., 2014). Critically, individuals with PTSD show reduced resting-state functional connectivity between anterior prefrontal (e.g., ventromedial prefrontal, anterior cingulate) and posterior parietal nodes (e.g., precuneus, posterior cingulate) as compared to controls, and these reductions correlate with symptom severity

(Bluhm et al., 2009; Sripada et al., 2012; Qin et al., 2012; Tursich et al., 2015). Here, aberrant DMN connectivity is thought to contribute to clinical disturbances in self-related processing among individuals with PTSD, which may include altered self-perceptions of body state, and of emotional and perceptual experiences (Cloitre, Scarvalone, & Difede, 1997; van der Kolk et al., 2005; Frewen et al., 2008). Disturbances in self-related processing are associated more strongly with the dissociative subtype of PTSD, which is identified by greater illness severity and the presence of supplementary dissociative symptoms (e.g., depersonalization, derealization) during threat- or trauma-related stimulus exposure (Steuwe, Lanius, & Frewen, 2012; Wolf et al., 2012; Stein et al., 2013).

The research summarized above highlights the importance of threat detection systems and features the influential role the PAG serves in responding to threat. Additionally, we discussed the function of the DMN and the atypical characteristics that are displayed within this network in PTSD. Despite a preponderance of evidence suggesting a strong influence of bottom-up processes, research rarely investigates functional connectivity patterns between the midbrain and large-scale, cortical networks. Accordingly, our aim was to investigate the functional connectivity displayed by the PAG in participants with PTSD and control subjects during subliminal threat processing. The present report extends on a previous study that revealed greater activation of the PAG in PTSD as compared to controls during subliminal, trauma-related word exposure (Terpou et al., 2019). Psycho-physiological interactions are conducted here to analyze group-level differences in the functional connectivity exhibited by the PAG seed that is reported in the previous study during subliminal presentation. We predicted that the PTSD group will show increased PAG functional connectivity with the DMN during subliminal threat exposure as a result of co-activation of self-referential and threat processing systems. The DMN is activated during self-referential processing; we hypothesize that the onset of trauma-related cues to participants with PTSD will stimulate the DMN, as well as the PAG to mediate the fear-inducing effects. The co-engagement of these systems is thought to produce a strong functional relatedness to be determined in the present study.

3.3 METHODS

3.3.1 PARTICIPANTS

The study was approved by the Health Sciences Research Ethics Board of Western University and adhered to the standards set forth by the Tri-Council Policy. The study included forty-six, English-speaking participants recruited by the London Health Services Centre via referrals from physicians, community clinics, mental health professionals, and advertisements. In total, twenty-six participants met the criteria for a primary diagnosis of PTSD, and the remaining twenty participants were included as healthy, non-trauma-exposed controls. Written and informed consent was provided by all participants. The analyses discussed in the present paper are novel; however, the data generated on this sample are analyzed in our other published works (Rabellino et al., 2015, 2016; Terpou et al., 2019; for a review, see Lanius et al., 2017).

The exclusion criteria for participation in the study included incompatibilities with the scanning requirements, previous neurologic and development illness, comorbid schizophrenia or bipolar disorder, alcohol or substance abuse within six months prior to scanning, a history of head trauma, or pregnancy during the time of the scan. Diagnoses were determined using the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995) and confirmed by a Structured Clinical Interview for DSM-IV Axis-I disorders (SCID-I; First, 2015). Control subjects were permitted if they did not meet any current or lifetime criteria for a psychiatric disorder, and participants with PTSD were medication free for at least six weeks prior to scanning. In addition to the diagnostic inventories, participants completed a battery of questionnaires prior to scanning, which included the Beck's Depression Inventory (BDI; Beck et al., 1997), the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003), and the Multiscale Dissociation Inventory (MDI; Briere, Weathers, & Runtz, 2005). Whereas twenty-three of the twenty-six participants diagnosed with PTSD had experienced childhood interpersonal trauma as their trauma origin, the remaining three of the twenty-six participants had experienced a personal threat of life or had witnessed a violent death. None of the participants in the current sample were diagnosed with PTSD related to military trauma. After fMRI

scanning was complete, participants were administered state-related inventories, including the State-Trait Anxiety Inventory (STAI; Spielberger, 1989), the Responses to Script Driven Imagery Questionnaire (RSDI; Hopper et al., 2007), and the Clinician Administered Dissociative States Scale (CADSS; Bremner et al., 1998).

***TABLE 3.1**: CLINICAL AND DEMOGRAPHIC INFORMATION*

Measure	**PTSD (*N* = 26)**	**HC (*N* = 20)**	χ^2	**T-Test**
	M ± SD	M ± SD	*p*	*p*
Years of Age	38.8 ± 12.2	32.5 ± 11.6	.088	-
Sex (n)	Male = 11, Female = 15	Male = 10, Female = 10	.604	-
Employment Status (n)	Employed = 18, Unemployed = 7	Employed = 17, Unemployed = 3	.297	-
CAPS Total	70.6 ± 11.9	.94 ± 2.9	-	< .001
CTQ – Emotional Abuse	14.5 ± 6.1	6.8 ± 3.1	-	< .001
CTQ – Physical Abuse	10.1 ± 6.4	5.7 ± 1.6	-	.004
CTQ – Sexual Abuse	13.4 ± 7.8	5.3 ± 1.1	-	< .001
CTQ – Emotional Neglect	13.5 ± 5.9	8.8 ± 4.2	-	.004
CTQ – Physical Neglect	10.2 ± 4.7	6.8 ± 2.7	-	.006
MDI Total	58.8 ± 21.6	33.7 ± 3.8	-	< .001
MDI – Depersonalization	7.8 ± 4.1	-	-	-
MDI – Derealization	9.5 ± 4.5	-	-	-
MDI – Dep./Der.	8.7 ± 4.1	-	-	-
CADSS Total	4.3 ± 2.6	-	-	-
STAI Total	6.2 ± 2.5	-	-	-
RSDI Total	4.1 ± 1.8	-	-	-
RSDI – Distress	2.2 ± 0.9	1.0 ± 0.0	-	< .001
RSDI – Reliving	2.0 ± 1.0	1.0 ± 0.0	-	.001

Measure	PTSD (*N* = 26)	HC (*N* = 20)	χ^2	T-Test
	M ± SD	M ± SD	*p*	*p*
RSDI – Avoidance Thoughts	1.9 ± 0.8	1.1 ± 0.3	-	.001
Axis-I Comorbidities (current [past]) frequency	Major Depressive Disorder (8[9])			
	Dysthymic Disorder (0[3])			
	Agoraphobia w/o PD (3)			
	Social Phobia (4)			
	Specific Phobia (2)			
	OCD (1[1])			
	Eating Disorders (1[1])			
	Somatoform Disorder (6)			
	Lifetime Alcohol Abuse or Dependence [16]			
	Lifetime Substance Abuse or Dependence [7]			

Age, sex, trait scores (CAPS Total, CTQ, MDI (Total, Dep, Der, Dep/Der), CADSS, STAI, RSDI (Total, Distress, Reliving, Avoidance Thoughts), and comorbidities for PTSD and control groups as mean values plus/minus standard deviations.

Abbreviations: CAPS: Clinician Administered PTSD Scale; CTQ: Childhood Trauma Questionnaire; MDI: Multiscale Dissociation Inventory [Dep: Depersonalization Subscale; Der: Derealization Subscale; Dep/Der: Depersonalization and Derealization Subscales Averaged]; CADSS: Clinician Administered Dissociative States Scale; STAI: State-Trait Anxiety Inventory; RSDI: Responses to Script Driven Imagery; PD: Panic Disorder; OCD: Obsessive-Compulsive Disorder

3.3.2 EXPERIMENTAL TASK

The paradigm and psychophysical thresholds used were based on previously published methods (Williams et al., 2006; Felmingham et al., 2008; Rabellino et al., 2016). Stimuli had a subliminal and a supraliminal display session over two consecutive sessions that were counterbalanced across subjects and involved a two-minute rest period between. Stimuli represented both threat (fearful faces (FF) and individualized trauma-related words (TW)) and neutral (neutral faces (NF) and neutral words (NW)) cues, presented in a pseudo-randomized block design. Word-related stimuli were subject-specific, with trauma-related words generated in reference to a traumatic memory or, in the case of controls, an aversive experience. Neutral words were selected had they not elicited a strong positive or negative reaction during pre-scan exposure to the word. Trauma-related and neutral words were matched for syllable and for letter length. For a more detailed description of the subliminal-supraliminal threat protocol, please refer to Figure 3.1.

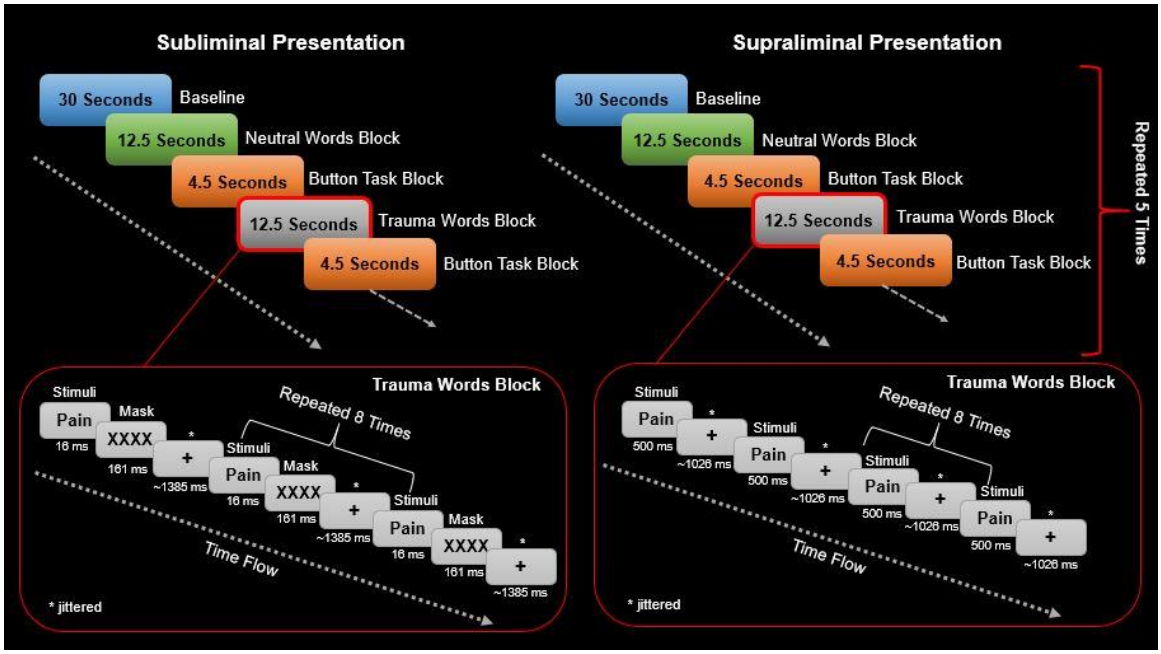

FIGURE 3.1: *SUBLIMINAL-SUPRALIMINAL THREAT PRESENTATION PARADIGM*

An illustration of the subliminal-supraliminal threat presentation paradigm. Stimuli had one subliminal and one supraliminal presentation session over two consecutive sessions that were counterbalanced across subjects and involved a two-minute rest period between the sessions. Stimuli represented both threat as well as neutral cues, presented in a pseudo-randomized block design (i.e., pseudo-randomized since neutral

words were not to follow trauma-related or fearful stimuli). Each presentation block was repeated five times in a fixed order to the participant. Blocks consisted of eight repetitions of stimuli with either a subliminal or a supraliminal display. Subliminal stimuli were presented for 16 ms and separated by a jittered inter-stimulus interval that varied in duration from 823 to 1823 ms and were followed by a mask. Supraliminal stimuli were presented for 500 ms and separated by a jittered inter-stimulus interval of 500 to 1500 ms. A button press task was implemented between presentation blocks to ensure sustained attention throughout the fMRI scanning session. Finally, each run was preceded by a 30-second rest period that was used as an implicit baseline for subsequent statistical analyses.

3.3.3 fMRI DATA ACQUISITION

Functional images were collected using a 3.0 T whole-body MRI scanner (Siemens Biograph mMR, Siemens Medical Solutions, Erlangen, Germany) with a 32-channel phased-array head coil. T1-weighted anatomical images were collected with 1 mm isotropic resolution (MP-RAGE, TR/TE/TI = 2300 ms/2.98 ms/900 ms, FA 9º, FOV = 256 mm x 240 mm x 192 mm, acceleration factor = 4, total acquisition time = 192 s). For blood-oxygen-level dependent (BOLD) fMRI, transverse imaging slices covering the whole-brain were prescribed parallel to the anterior commissure-posterior commissure (AC-PC) line. Functional data were acquired using a gradient echo planar imaging (EPI) sequence (single-shot, blipped) with an interleaved slice acquisition order and tridimensional prospective acquisition correction (3D PACE) and an isotropic resolution of 2 mm [(FOV=192 mm x 192 mm x 128 mm (94 x 94 matrix, 64 slices), TR/TE = 3000ms/20 ms, FA = 90º (FOV = Field of View, TR = Repetition Time, TE = Echo Time, FA = Flip Angle)].

Data were analyzed using Statistical Parametric Mapping (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK: http://www.fil.ion.ucl.ac.uk/sp) within MATLAB 9.2 (R2017a, MathWorks Inc., MA). A breakdown of the preprocessing steps for whole-brain and the spatially-unbiased infratentorial template (SUIT; Diedrichsen, 2006; Diedrichsen et al., 2009) toolbox are provided in the Supplemental Information.

3.3.4 STATISTICAL ANALYSES

3.3.4.1 WITHIN: PSYCHOLOGICAL REGRESSOR

Within the first-level analyses, a fixed-effects general linear model was created for each subject with three main factors, each with two experimental levels (Factor 1: Group: PTSD, Control; Factor 2: Conscious Level: Subliminal, Supraliminal; Factor 3: Stimuli: Faces (FF, NF), Words (TW, NW)). The signals derived from the stimulus onsets were modelled as the convolution of the stimulus function to the default hemodynamic response function. The button press task, realignment parameters, and artifact detection regressor were included as regressors of no interest. The experimental conditions were used to generate contrasts between threat and neutral conditions for both subliminal and supraliminal presentation sessions (i.e., FF > NF, TW > NW). These contrasts were carried into the second-level for between-group analyses. The results from these subtraction analyses have been published by Terpou and colleagues (2019) and are restricted to the partial-brain space as offered by the SUIT toolbox. The SUIT toolbox improves the normalization procedure of the midbrain, lower brainstem, and cerebellum to offer greater resolution of these subcortical structures than can be afforded by whole-brain standards (Diedrichsen, 2006; Diedrichsen et al., 2009). In the previous study, significant results were generated only for the subliminal contrast of trauma-related minus neutral word exposure (Subliminal: TW > NW) (Terpou et al., 2019). As a result, the psycho-physiological interactions (PPIs) conducted here will focus on this experimental contrast as our psychological regressor of interest.

3.3.4.2 WITHIN: PHYSIOLOGICAL REGRESSOR

The physiological regressor for the present study used the time course of the PAG that was informed by Terpou and colleagues (2019). The previous study was conducted on the same participant sample and paradigm and revealed greater PAG activation ([*x*: 0, *y*: -32, *z*: -11], *k* = 53, *p*-FWE = .013) in PTSD as compared to controls during the contrast of Subliminal: TW > NW. The present study extracted the eigenvariate from the PAG by creating a spherical volume-of-interest of 6 mm centered on these coordinates to gather the seed time course of the PAG across all participants.

3.3.4.3 BETWEEN: PSYCHO-PHYSIOLOGICAL INTERACTION

The PPI interaction terms were obtained by deconvolving the BOLD signal of the PAG by the hemodynamic response function and then multiplying the deconvolved time series by the psychological variable (Subliminal: TW > NW). This generated a series of estimated interaction term parameters that were then re-convolved with the default hemodynamic response function. These interaction parameters were carried into the second-level for within- and between-group analyses. One- and two-sample t-tests were evaluated and reported at a significance threshold of p-FWE < .05, k > 10. A region-of-interest (ROI) analysis was also conducted using a DMN mask adopted from the Functional Imaging in Neuropsychiatric Disorders Lab database that contained regions of the medial prefrontal, posterior cingulate, and posterior parietal cortices (Shirer et al., 2012).

3.3.4.4 CLINICAL CORRELATIONS

Multiple regression analyses were conducted within the PTSD group to determine whether clinical scores correlated with PAG functional connectivity. Interaction term parameters were correlated with symptom scores of re-experiencing (CAPS criterion B), avoidance (CAPS criterion C), negative alterations in cognition and mood (CAPS criterion D), dissociation (MDI), childhood trauma (CTQ), depressive symptomatology (BDI), as well as to state-related scores as measured by the STAI, RSDI, and CADSS.

3.4 RESULTS

3.4.1 DEMOGRAPHIC AND CLINICAL MEASURES

As noted, these PPI analyses were guided by a previous study revealing group differences in activation of the PAG during Subliminal: TW > NW in participants with PTSD as compared to controls (2019). However, the previous report failed to yield significant activation of the PAG for either group during supraliminal contrast conditions or the subliminal contrast of FF > NF. To this end, our analyses will focus on the subliminal display of trauma-related and neutral words, specifically. All reported results for PPI analyses surpassed a significance threshold of p-FWE < .05, k > 10.

Independent t-tests conducted on demographic measures between the PTSD and the control group did not reveal significant differences. As expected for clinical measures, as compared to controls, participants with PTSD scored significantly higher on total scores for the CAPS, MDI, CTQ, and RSDI (Table 3.1).

3.4.2 PSYCHO-PHYSIOLOGICAL INTERACTION RESULTS

3.4.2.1 WITHIN-GROUP

The PPI analyses did not reveal significant results for the PAG within the control group for whole-brain or ROI analyses. The PTSD group, however, demonstrated significant whole-brain PAG functional connectivity with the medial segment of the superior frontal gyrus ([*x*: -2 *y*: 60 *z*: 12], *k* = 871, *p*-FWE = .003) as well as the right angular gyrus ([*x*: 54 *y*: -58 *z*: 34], *k* = 172, *p*-FWE = .021). Moreover, ROI analyses for the DMN mask yielded significant PAG connectivity with the medial segment of the superior frontal gyrus ([*x*: -2 *y*: 60 *z*: 12], *k* = 689, *p*-FWE = .001) as well as the precuneus ([*x*: 2 *y*: -52 *z*: 32], *k* = 420, *p*-FWE = .017) in the PTSD group (Table 3.2).

3.4.2.2 BETWEEN-GROUP

Between-group findings did not yield significant results for greater PAG functional connectivity in the control group as compared to the PTSD group in whole-brain or ROI analyses. By contrast, results from the DMN ROI yielded significantly stronger PAG functional connectivity with the medial segment of the superior frontal gyrus ([*x*: 0 *y*: 60 *z*: -2], *k* = 372, *p*-FWE = .003), the right precuneus ([*x*: 6 *y*: -52 *z*: 30], *k* = 192, *p*-FWE = .025), and the anterior cingulate cortex ([*x*: 0 *y*: 46 *z*: 20], *k* = 69, *p*-FWE = .029) in the PTSD group as compared to the control group (Table 3.2).

Table 3.2: *WITHIN- AND BETWEEN-GROUP DIFFERENCES*

Contrast	Region	*k*	*p*(FWE-cor)	*z*	MNI Coordinates		
					x	*y*	*z*
Subliminal TW > NW (Whole-Brain)							
Control	None						
PTSD	Superior Frontal Gyrus	871	.003	5.46	-2	60	12
	Angular Gyrus	172	.021	5.05	54	-58	34
Control > PTSD	None						
PTSD > Control	None						
Subliminal TW > NW (DMN ROI)							
Control	None						
PTSD	Superior Frontal Gyrus	689	.001	5.46	-2	60	12
	Medial Segment of SFG	Of 689	.001	5.04	0	60	-2
	Precuneus	420	.017	4.38	2	-52	32
Control > PTSD	None						
PTSD > Control	Superior Frontal Gyrus	372	.003	4.75	0	60	-2
	Medial Segment of SFG	Of 372	.007	4.55	-2	60	12
	Precuneus	192	.025	4.21	6	-52	30
	Anterior Cingulate Gyrus	69	.029	4.18	0	46	20

Within- and between-group differences in BOLD functional connectivity between PTSD and controls within the subliminal threat presentation task. Reported results for whole-brain and ROI analyses are at a significance threshold of p-FWE < .05, k > 10. The contrast column lists the specific comparison of the experimental conditions. The hemisphere of the region (L/R), region, cluster size (k), significance (p(FWE)-cor), z-score (z), and MNI coordinates (x, y, z) of the peak coordinates are included as columns.

Abbreviations: PAG: Periaqueductal Gray; TW: Trauma-Related Word Stimulus; NW: Neutral Word Stimulus; WB: Whole-Brain; DMN: Default Mode Network; ROI: Region-of-Interest; SFG: Superior Frontal Gyrus

3.4.2.3 CLINICAL CORRELATIONS

Multiple regression analyses conducted between PTSD clinical scores and PAG functional connectivity yielded several significant results. A positive correlation was detected between state dissociation scores (CADSS) and functional connectivity exhibited between the PAG and the right middle frontal gyrus ([*x*: 34 *y*: 22 *z*: 46], *k* = 168, *p*-FWE = .037) in the PTSD group. Moreover, frequency/intensity scores of CAPS criterion B (re-experiencing) revealed a positive correlation with the functional connectivity between the PAG and the right posterior orbital gyrus ([*x*: 28 *y*: 28 *z*: -20], *k* = 45, *p*-FWE = .019). Finally, a positive association was revealed between CAPS criterion C (avoidance) symptom scores and PAG functional connectivity with the left middle temporal gyrus ([*x*: -60 *y*: -38 *z*: 2], *k* = 143, *p*-FWE = .044) in the PTSD group (Table 3.3). No significant results were generated for the multiple regression analysis for symptom measures of the CAPS criterion D subscale, MDI, CTQ, BDI, and the RSDI.

TABLE 3.3: *CLINICAL CORRELATIONS*

Clinical Measure	Direction	Region	*k*	*p*(FWE)	*z*	MNI Coordinates		
						x	*y*	*z*
Subliminal TW > NW (WB)								
CADSS	+	Middle Frontal Gyrus	168	.037	5.01	34	22	46
CAPS Criterion B Symptoms	+	Posterior Orbital Gyrus	45	.019	5.15	28	28	-20
CAPS Criterion C Subtotal	+	Middle Temporal Gyrus	143	.044	4.95	-60	-38	2

Clinical correlations from the multiple regression analysis between clinical scores in the PTSD group and functional connectivity extending from the periaqueductal gray during subliminal trauma-related word exposure greater than neutral word exposure. Reported results for whole-brain findings are at a significance threshold of p-FWE < .05, k > 10. The contrast column lists the specific inventory or questionnaire administered. The direction (+/-), hemisphere of the region (L/R), region, cluster size (k), significance (p(FWE)-cor), z-score (z), and MNI coordinates (x, y, z) of the peak are included as columns.

Abbreviations: CADSS: Clinician Administered Dissociative States Scale; CAPS: Clinician Administered PTSD Scale; PAG: periaqueductal gray; WB: whole-brain

3.5 DISCUSSION

3.5.1 OVERVIEW

Threat detection is a crucial function of the human brain with its underlying circuitry expressed across midbrain as well as cortical systems. These systems are often studied in isolation, revealing overactivation and altered functional connectivity in PTSD. To further our understanding of the effects of PTSD on threat detection and defensive response circuitry, it is critical to analyze responses to trauma-related stimuli within and across different levels of neural organization. The present study revealed significant group differences in the functional connectivity of the PAG during the subliminal presentation of trauma-related stimuli. As compared to controls, individuals with PTSD

displayed increased PAG functional connectivity with a range of cortical structures involved in the DMN (e.g., superior frontal gyrus, angular gyrus, precuneus) (Figure 3.2). Here, the DMN is recruited generally in the absence of externally-directed attention, where internal cognition predominates. Despite our employment of an external and subliminal stimulus, the DMN showed strong functional coupling with the PAG in the PTSD group, a novel finding of critical interest.

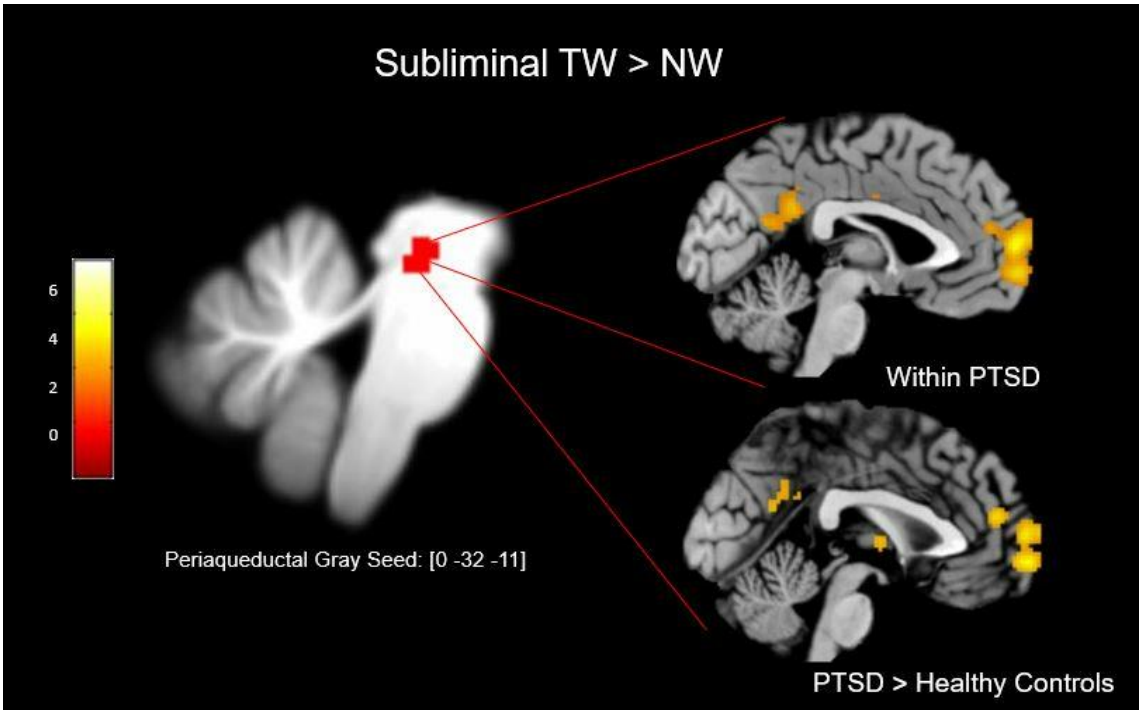

FIGURE 3.2: *PSYCHO-PHYSIOLOGICAL INTERACTION SUMMARY GRAPHIC*

Illustration above demonstrates the coordinates of significant activation as reported by Terpou and colleagues within SUIT-space (left) (Terpou et al., 2019).Within-subject eigenvariates were derived from the coordinates and psycho-physiological interactions were conducted at the between-group level (right). As compared to controls, the PTSD group displayed significantly greater PAG functional connectivity with multiple regions associated with the DMN (e.g., superior frontal gyrus, precuneus, angular gyrus, anterior cingulate gyrus).

The DMN is a neurocognitive network engaged during processes of internally-directed thought, such as mind-wandering, self-referential processing, and autobiographical memory retrieval (Menon & Uddin, 2010). It is now well documented that a series of mid-line brain regions underlie the DMN, showing strong resting-state functional

connectivity, as well as robust structural connections (Greicius et al., 2009; for a review, see Raichle, 2015). Healthy participants display increased activation and functional connectivity of the DMN in the absence of externally-directed attention (Menon & Uddin, 2010). By contrast, as compared to controls, individuals with PTSD exhibit reliably reduced resting-state functional connectivity of the DMN (Bluhm et al., 2009; Sripada et al., 2012; Qin et al., 2012; Shang et al., 2014; DiGangi et al., 2016; Miller et al., 2016). In turn, aberrant DMN functional connectivity is thought to promote clinical disturbances to self-related processing in PTSD, which may include alterations to self-perception of the body, or emotional and perceptual experiences (Cloitre, Scarvalone, & Difede, 1997; van der Kolk et al., 2005; Frewen et al., 2008). In contrast to the reduced connectivity demonstrated at rest, the DMN has been shown to display increased functional connectivity during trauma-related processing in PTSD (Tursich et al., 2015; Nicholson et al., 2016). For example, Nicholson and colleagues (2016) employed a thirty-minute session of neurofeedback (NFB) during fMRI that targeted the attenuation of amygdala activity. These results demonstrated that NFB successfully shifted amygdala connectivity from a pattern of bottom-up (pre-NFB) to a pattern of top-down connectivity (post-NFB) in participants with PTSD. In this study, bottom-up connectivity emerged in relation to functional coupling of the superficial amygdala and the PAG during the contrast of pre-NFB > post-NFB. By contrast, top-down connectivity was in relation to greater coupling between the central nucleus of the amygdala and the medial prefrontal cortex for the contrast of post-NFB > pre-NFB. Interestingly, Nicholson and colleagues (2018) analyzed the activation of the ICNs over the NFB paradigm and found an increase in DMN recruitment in individuals with PTSD during conditions of trauma-related stimulus exposure as compared to rest for both pre-/post-NFB. These findings corroborate our findings in that the DMN is recruited in PTSD to a greater extent during trauma-related stimulus exposure.

These results diverge markedly from the characteristics displayed by control subjects and require careful consideration. Here, it is possible that exposure to trauma-related material used in our paradigm cued the autobiographical retrieval of traumatic memories in participants with PTSD. To this end, traumatic memories are thought to be distinct in form from the aversive memories cued within the control group. For instance, some

traumatic memories remain in an unprocessed state, where the cognitive, affective, and sensory components of the memory are fragmented, or dissociated (van der Kolk & Fisler, 1995; Berntsen, Willert, & Rubin, 2003; St. Jacques, Kragel, & Rubin, 2013; Brewin et al., 2014; McKinnon et al., 2017). This fragmentation of traumatic memories may result from the overwhelming affect that occurs during original encoding, thus interfering with the consolidation of the memory to long-term storage (Pitman, 1989; Corrigan, 2002; Lanius et al., 2004; Harper et al., 2009; Carletto et al., 2017). In turn, the traumatic memory may remain in a state-dependent, emotionally-charged form that exhibits strong perceptual priming to trauma-related cues (van der Kolk & Fisler, 1995; Arntz, De Groot, & Kindt, 2005; Michael, Ehlers, & Halligan, 2005; Ehlers et al., 2006; Kleim, Ehring, & Ehlers, 2012; Brewin, 2014). As a result, trauma-related word exposure may have triggered greater re-experiencing symptoms in individuals with PTSD as compared to controls, as evidenced, in part, by the increased state reliving scores measured by the RSDI. Whereas the precuneus and the posteromedial cortices are thought to underlie the self-referential and the visual imagery aspects of the DMN (Cavanna & Trimble, 2006; Fransson & Marrelec, 2008), the medial prefrontal cortices are thought to contribute strongly to its role in autobiographical memory (Shallice et al., 1994; Simons & Spiers, 2003). Importantly, both the precuneus and the superior frontal gyrus displayed greater PAG functional connectivity in the PTSD group as compared to controls. Given that the DMN displays reduced connectivity at rest in PTSD, it is possible that individuals with PTSD experience greater self-related processing in the presence of trauma-related stimuli, thus explaining the strong coupling revealed between the PAG and the DMN. In turn, this may decrease an individual's likelihood to engage in self-related processing, promoting dissociative symptomatology. The latter supposition is supported by the clinical correlation analysis, where individuals with increased state dissociation (CADSS) and avoidance scores (CAPS Criterion C) showed greater PAG functional connectivity with the middle frontal and middle temporal gyri, respectively. Taken together, these findings suggest a strong interaction between midbrain, threat-related processing systems with higher-order, self-related processing systems during trauma-related stimulus processing in PTSD.

3.5.2 LIMITATIONS

There are several limitations to the study. To begin, a relatively small sample was recruited, which did not permit investigation of the differences between individuals who met or did not meet the criteria for the dissociative subtype of PTSD. The subtype is distinguishable in both clinical and functional characteristics from the non-subtype of PTSD, which introduces heterogeneity to our sample (Hopper et al., 2007; Steuwe, Lanius, & Frewen, 2012; Wolf et al., 2012). Moreover, our study follows the previous reports of group-level differences in PAG activation during subliminal threat presentation (Terpou et al., 2019). However, the previous study did not yield significant activation of the PAG for the PTSD or control group during the subliminal display of fearful and neutral facial expressions. This did not permit the extraction of the eigenvariate for the PAG for the experimental contrast of Subliminal: FF > NF. In turn, we cannot discern whether the PAG–DMN coupling displayed in the PTSD group results from trauma-related stimulus exposure specifically or extends to fearful stimuli more generally. Finally, trauma-related and neutral words were not matched for frequency of exposure. In the event that the trauma-related words were less common in language as compared to the neutral words, this may have introduced novelty effects that could increase the signal generated that are unrelated to the emotional nature of the word stimuli.

3.6 CONCLUSION

These findings contribute to our understanding of self-related processing systems in PTSD. The PAG is involved in subliminal threat detection and the coordination of defensive responses and exhibits overactivation in PTSD. During the subliminal presentation of trauma-related stimuli, we extracted the seed time course of the PAG in participants with PTSD and controls to measure the functional connectivity of the structure. Strikingly, the PTSD group showed significantly greater PAG connectivity with the DMN as compared to controls. These results provide evidence for a midbrain structure exhibiting functional relatedness, and potentially involvement, within large-scale, cortical networks during subliminal, trauma-related processing in PTSD. Given the role of the DMN in self-referential processing and of the evolutionarily-conserved

function of the PAG during the execution of defensive states, functional coupling of these regions has strong clinical implications to self-referential processing systems in the presence of traumatic reminders in PTSD.

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CHAPTER 4[4]

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4 THE HIJACKED SELF: DISRUPTED FUNCTIONAL CONNECTIVITY BETWEEN THE PERIAQUEDUCTAL GRAY AND THE DEFAULT MODE NETWORK IN POST-TRAUMATIC STRESS DISORDER USING DYNAMIC CAUSAL MODELING

4.1 ABSTRACT

Self-related processes describe various self-relevant and social-cognitive functions that allow us to gather insight and to draw inferences related to our own mental experiences. Self-related processes are mediated by the Default Mode Network (DMN), which, critically, shows altered functionality in participants with post-traumatic stress disorder (PTSD). In PTSD, the midbrain periaqueductal gray (PAG) demonstrates stronger functional connectivity with the DMN [i.e., precuneus (PCN), medial prefrontal cortex (mPFC)] as compared to healthy individuals during subliminal, trauma-related stimulus processing. Directed functional connectivity, or, effective connectivity, between the PAG and the PCN, as well as between the PAG and the mPFC were analyzed here, where we modeled these network dynamics during both subliminal, neutral and subliminal, trauma-related stimulus conditions in individuals with PTSD (n = 26) and healthy controls (n = 20). Models were proposed, which varied in regard to context-dependent modulatory directions (i.e., bi-directional, bottom-up, top-down). Evidence for the models were compared across groups, where the optimal models were identified by Bayesian model selection group-specifically. Following, we compared the strength for every model parameter across the models and between our groups with Bayesian model averaging. Bi-directional models were found to be favoured across both groups. In PTSD, we revealed the PAG to show stronger excitatory effective connectivity to the PCN, as well as to the mPFC as compared to controls. In PTSD, we showed further that the PAG-directed effective connectivity to the PCN, as well as to the mPFC were modulated more strongly during subliminal, trauma-related stimulus conditions as compared to controls. Clinical disturbances towards self-related processes are reported widely by participants with

PTSD during trauma-related stimulus processing, where altered functional connectivity directed by the PAG to the DMN may assist to explain the intrinsic links between self- and trauma-related processing in traumatized individuals.

4.2 INTRODUCTION

Trauma may have a severe affect on the sense of self, where traumatized individuals remain often tortured by thoughts that reflect strongly negative core beliefs about themselves and may experience somatically-based alterations to self-identity. Clinical disturbances towards self-related processes are evidenced by statements, like, “I do not know myself anymore,” “I will never be able to feel normal emotions again,” or, “I feel as though my body does not belong to me” (Foa et al., 1999; Bernstein & Putnam, 1986; Dell, 2006). Statements such as these are recited often by individuals with post-traumatic stress disorder (PTSD), which underscores the vulnerability the sense of self has in regard to trauma (for a review, see Frewen et al., 2020). In PTSD, traumatized individuals who report the greatest symptom severity are more likely to reveal an apparent link between self- and trauma-related processing (Berntsen & Rubin, 2007). Related, when participants with PTSD are asked to characterize a self-defining memory, they state more often a trauma-related memory as compared to trauma-exposed individuals (Sutherland & Bryant, 2005). Clinical disturbances in self-related processes have been described robustly in participants with PTSD (for a review, see Frewen & Lanius, 2006; Lanius, Bluhm, & Frewen, 2011), where these disturbances are thought to arise from intrinsic brain networks (Conway & Pleydell-Pearce, 2000; Qin & Northoff, 2011).

Self-related processes are mediated predominantly by the Default Mode Network (DMN), which refers to a large-scale, intrinsic brain network distributed across the cortical mid-line and comprised primarily by the posterior cingulate cortex, the precuneus (PCN), as well as the medial prefrontal cortex (mPFC) (Greicius et al., 2003; Spreng et al., 2009; Qin & Northoff, 2011; for a review, see Raichle, 2015). The DMN is recruited during rest principally, but also shows activity during internally-guided cognition, which includes autobiographical memory and self-referential processes (Greicius & Menon, 2004; Fransson, 2005). Self-referential processes describe various self-relevant and social-

cognitive functions that allow us to gather insight and to draw inferences about the mental and the physical states of ourselves and others (Greicius et al., 2003). In PTSD as compared to healthy individuals, both the PCN and the mPFC demonstrate reduced functional connectivity with the DMN during rest (Bluhm et al., 2009; DiGangi et al., 2016; Reuveni et al., 2016; Wu et al., 2011). Furthermore, reductions in DMN functional connectivity are found to be related to greater symptom severity in participants with PTSD (Bluhm et al., 2009; Sripada et al., 2012; Qin et al., 2012). Traumatized individuals who display the strongest symptom severity are more likely to show the clinical disturbances in self-related processes that were mentioned prior (Cloitre et al., 1997; Frewen et al., 2017; Qin et al., 2012; Nicholson et al., 2020; for a review, see van der Kolk et al., 2005; Frewen et al., 2008). In PTSD, clinical disturbances towards self-related processes are seen both during rest, as well as during trauma-related stimulus conditions (Lanius et al., 2011; Sutherland & Bryant, 2005), where the latter may be mediated by the DMN as well.

In PTSD, traumatized individuals report clinically a link between self- and trauma-related processing (Berntsen & Rubin, 2007), where these links may be mediated by aberrant functional connectivity across distributed systems. Here, Terpou et al. (2019a) have described an interaction between the midbrain periaqueductal gray (PAG) and the DMN in participants with PTSD during subliminal, trauma-related stimulus conditions. The PAG refers to the gray matter located around the cerebral aqueduct of the midbrain, which, when activated, can elicit evolutionarily conserved defense responses that function to quell or to escape an impending threat (e.g., fight, flight, faint; De Oca et al., 1998; Brandão et al., 2008; Fenster et al., 2018; for a review, see Keay & Bandler, 2014). Interestingly, the PAG reveals stronger activity in participants with PTSD as compared to controls during subliminal, trauma-related stimulus conditions (Terpou et al., 2019b; Rabellino et al., 2016; Felmingham et al., 2008), where the PAG is thought to mediate, in part, threat-evoked physiological changes (for a review, see Kozlowska et al., 2015; Terpou et al., 2019c). In PTSD, Terpou et al. (2019a) have revealed increased functional connectivity between the PAG and the PCN, as well as between the PAG and the mPFC during subliminal, trauma-related stimulus conditions as compared to controls. Trauma-related stimulus conditions were contrasted to neutral stimulus conditions, where

conditions were presented subliminally to prevent participants from exercising avoidance to reduce neurophysiological responses. Stronger functional connectivity between the PAG and the DMN were interpreted as evidence linking both self- and trauma-related processing in participants with PTSD (Terpou et al., 2019a), which we sought to define more explicitly here.

These findings by Terpou et al. (2019a) are intriguing both in regard to the unanticipated functional connectivity revealed between the PAG and the DMN, as well as the context by which the findings were generated, namely – subliminal, trauma-related stimulus conditions. However, we have yet to study the effective connectivity dynamics between the PAG and the DMN across the corresponding sample, where effective connectivity has the advantage to measure the directed functional connectivity between two regions. Hence, we implemented dynamic causal modeling (DCM) to estimate the directionality across network interactions between the PAG and the PCN, as well as between the PAG and the mPFC in participants with PTSD and healthy controls during subliminal, neutral and subliminal, trauma-related stimulus conditions. Specifically, we sought to determine whether these stimulus conditions modulate functional connectivity between the PAG and the DMN predominantly via bi-directional, bottom-up, or top-down effective connectivity. Nicholson et al. (2017) have documented previously greater bottom-up, PAG-mediated effective connectivity to the mPFC in participants with PTSD who displayed a typical symptom pattern as compared to participants with PTSD who displayed a dissociative symptom pattern principally. Accordingly, we hypothesized that the participants with PTSD in the current sample would show stronger condition-dependent modulations in effective connectivity in the bottom-up direction, a pattern that would suggest the PAG is driving the aberrant functional connectivity observed with the DMN. By contrast, we hypothesized that the healthy participants would reveal greater condition-dependent modulations in effective connectivity bi-directionally; however, we caution that the healthy individuals did not show strong functional connectivity between the PAG and the DMN in Terpou et al. (2019a), and thus were not the primary focus to characterize in the present study. Additionally, we sought to determine the group-specific strengths in effective connectivity between the PAG and the PCN, as well as between the PAG and the mPFC. Identification of the effective connectivity strengths, as well as the

excitatory and the inhibitory characteristics of the network interactions, would afford a stronger understanding of the functional dynamics that may mediate the intrinsic link between self- and trauma-related processing in participants with PTSD.

4.3 METHODS

4.3.1 PARTICIPANTS

Our study was reviewed by the Health Sciences Research Ethics Board of Western University and adhered to the standards set out by Canada's Tri-Council Policy in accordance with the Code of Ethics of the World Medical Association (i.e., Declaration of Helsinki). The study sample included 46 participants recruited by the London Health Services Centre via referrals from family physicians, community clinics, mental health professionals, and local advertisements. Twenty-six participants met criteria for a primary PTSD diagnosis and the remaining twenty participants were included as healthy control subjects. Written and informed consent was provided by all participants. Analyses discussed in the present paper are novel; however, data generated on the present sample have been analyzed in previous publications (Rabellino et al., 2015, 2016, 2017; Terpou et al., 2019a, 2019b). Scanning began on March 29, 2011 and concluded on November 12, 2013 for the present study.

Exclusion criteria included incompatibilities with scanning conditions, previous neurologic and development illness, comorbid schizophrenia or bipolar disorder, alcohol or substance abuse, a history of head trauma, or pregnancy during scan. Diagnoses were determined using a Clinician Administered PTSD Scale (CAPS-IV (cut-off score > 50 for PTSD diagnosis); Blake et al., 1995), as well as a Structured Clinical Interview for DSM-IV Axis-I disorders (SCID-I; First, 2015). Healthy controls were permitted if they did not meet any current or lifetime criteria for an Axis-I psychiatric disorder. Participants with PTSD were medication free for at least six weeks prior to scanning. The Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003) and the Multiscale Dissociation Inventory (MDI; Briere et al., 2005) were administered as well to characterize our clinical sample. The State-Trait Anxiety Inventory (STAI; Spielberger, 2010), the Responses to Script Driven Imagery Questionnaire (RSDI; Hopper et al., 2007), and the Clinician

Administered Dissociative States Scale (CADSS; Bremner et al., 1998) were administered after each scanning session to provide information on subject symptom states for individuals with PTSD and controls.

***TABLE 4.1**: CLINICAL AND DEMOGRAPHIC INFORMATION*

Measure	**PTSD (N = 26)**	**HC (N = 20)**	χ^2	***t*-Test**
	M ± SD	M ± SD	*p*	*p*
Years of Age	38.8 ± 12.2	32.5 ± 11.6	-	.088
Sex (n)	Male = 11, Female = 15	Male = 10, Female = 10	.604	-
Employment Status (n)	Employed = 18, Unemployed = 7	Employed = 17, Unemployed = 3	.297	-
CAPS Total	70.6 ± 11.9	.94 ± 2.9	-	< .001
CTQ – Emotional Abuse	14.5 ± 6.1	6.8 ± 3.1	-	< .001
CTQ – Physical Abuse	10.1 ± 6.4	5.7 ± 1.6	-	.004
CTQ – Sexual Abuse	13.4 ± 7.8	5.3 ± 1.1	-	< .001
CTQ – Emotional Neglect	13.5 ± 5.9	8.8 ± 4.2	-	.004
CTQ – Physical Neglect	10.2 ± 4.7	6.8 ± 2.7	-	.006
MDI Total	58.8 ± 21.6	33.7 ± 3.8	-	< .001
MDI – Depersonalization	7.8 ± 4.1	-	-	-
MDI – Derealization	9.5 ± 4.5	-	-	-
MDI – Dep./Der.	8.7 ± 4.1	-	-	-
BDI	24.0 ± 6.7	-	-	-
CADSS Total	4.3 ± 2.6	-	-	-
STAI Total	6.2 ± 2.5	-	-	-
RSDI Total	4.1 ± 1.8	-	-	-
RSDI – Distress	2.2 ± 0.9	1.0 ± 0.0	-	< .001
RSDI – Reliving	2.0 ± 1.0	1.0 ± 0.0	-	.001

Measure	PTSD (N = 26)	HC (N = 20)	χ^2	*t*-Test
	M ± SD	M ± SD	*p*	*p*
RSDI – Avoidance Thoughts	1.9 ± 0.8	1.1 ± 0.3	-	.001
Axis-I Comorbidities (current [past]) frequency	Major Depressive Disorder (8[9])			
	Dysthymic Disorder (0[3])			
	Agoraphobia w/o PD (3)			
	Social Phobia (4)			
	Specific Phobia (2)			
	OCD (1[1])			
	Eating Disorders (1[1])			
	Somatoform Disorder (6)			
	Lifetime Alcohol Abuse or Dependence [16]			

Age, sex, trait scores (CAPS Total, CTQ, MDI (Total, Dep, Der, Dep/Der), BDI, CADSS, STAI, RSDI (Total, Distress, Reliving, Avoidance Thoughts), and comorbidities for participants with PTSD and healthy individuals as mean values plus/minus standard deviations.

Abbreviations: CAPS: Clinician Administered PTSD Scale; CTQ: Childhood Trauma Questionnaire; MDI: Multiscale Dissociation Inventory [Dep: Depersonalization Subscale; Der: Derealization Subscale; Dep/Der: Depersonalization and Derealization Subscales Averaged]; BDI: Beck's Depression Inventory; CADSS: Clinician Administered Dissociative States Scale; STAI: State-Trait Anxiety Inventory; RSDI: Responses to Script Driven Imagery; PD: Panic Disorder; OCD: Obsessive-Compulsive

4.3.2 EXPERIMENTAL TASK

Paradigm and stimulus presentation durations were based on other previously published methods (Williams et al., 2006; Felmingham et al., 2008; Rabellino et al., 2016). Stimuli had a subliminal and a supraliminal display over two consecutive sessions that were separated by a two-minute rest period and were counterbalanced across subjects. Whereas

subliminal stimuli were presented for 16 ms and followed by a backward mask, supraliminal stimuli were presented for 500 ms. Stimuli consisted of both threat (i.e., fearful faces and trauma-related words) and neutral (i.e., neutral faces and neutral words) material, presented in a pseudo-randomized block design. Word stimuli were subject-specific, with trauma-related words generated in reference to a trauma memory, or, in the case of controls, an aversive memory. Neutral words were selected on the basis that they had not elicited a strong positive or a strong negative reaction during a pre-scan exposure to the words. Trauma-related and neutral words were matched for syllable and for letter length. For a detailed description of the subliminal-supraliminal threat paradigm, please see Supplemental Information.

4.3.3 fMRI DATA ACQUISITION

Functional magnetic resonance imaging (fMRI) was conducted using a 3.0 T whole-body MRI scanner (Siemens Biograph mMR, Siemens Medical Solutions, Erlangen, Germany) with a 32-channel phased-array head coil. T1-weighted anatomical images were collected with 1 mm isotropic resolution (MP-RAGE, TR/TE/TI = 2300 ms/2.98 ms/900 ms, FA 9º, FOV = 256 mm x 240 mm x 192 mm, acceleration factor = 4, total acquisition time = 192 s). For blood-oxygen-level dependent fMRI, transverse imaging slices covering the whole-brain were prescribed parallel to the anterior commissure-posterior commissure (AC-PC) line. Data were acquired using a gradient echo planar imaging (EPI) sequence (single-shot, blipped) with an interleaved slice acquisition order and tridimensional prospective acquisition correction (3D PACE) and an isotropic resolution of 2 mm [(FOV=192 mm x 192 mm x 128 mm (94 x 94 matrix, 64 slices), TR/TE = 3000 ms/20 ms, FA = 90º (FOV = Field of View, TR = Repetition Time, TE = Echo Time, FA = Flip Angle)].

Preprocessing and statistical analyses were conducted on Statistical Parametric Mapping (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK: http://www.fil.ion.ucl.ac.uk/sp) within MATLAB 9.2 software (R2017a, MathWorks Inc., MA). Preprocessing protocols for both whole-brain as well as the partial-brain space as provided by the spatially-unbiased infratentorial template toolbox (SUIT; Diedrichsen, 2006) are detailed further in the Supplemental Information.

4.3.4 DYNAMIC CAUSAL MODELING

DCM estimates the directionality of the functional dependencies that exist across an underlying dynamical system (for a review, see Friston et al., 2003). DCM allows for inferences to be made about the architecture of distributed brain networks in terms of the effective connectivity shown by the network, as well as the network's condition-dependent modulations (Kiebel et al., 2007). DCM is a model-driven Bayesian approach, where network architectures of plausible models are specified *a priori* and are then evaluated on their ability to explain observed neural responses with Bayesian model selection (BMS) (Stephan et al., 2009). DCM also offers an ability to compare the strength of model connectivity parameters using Bayesian model averaging (BMA) (Friston et al., 2007; Stephan et al., 2010). Although group comparisons can be conducted within either conventional statistical or Bayesian frameworks, we implemented conventional statistics in the present study.

4.3.5 FIRST-LEVEL: TIME-SERIES EXTRACTION

Coordinate locations of three brain regions that we have revealed formerly to demonstrate group differences in functional connectivity between participants with PTSD and healthy controls during subliminal, trauma-related (as compared to neutral) stimulus conditions were selected (Terpou et al., 2019a): the PAG, the PCN, and the mPFC. Notably, it is well-established there are structural connections to facilitate, in part, inter-nodal network dynamics between the PAG, the PCN, and the mPFC (Linnman et al., 2012; Menant et al., 2016; Ezra et al., 2015). Whereas time series of the PAG were extracted from subject-specific general linear models (GLMs) computed in SUIT- space, time series of the PCN and the mPFC were extracted from subject-specific GLMs created in whole-brain space. Here, SUIT-space refers to the partial-brain space implemented in the SUIT toolbox, which, through improved normalization procedures, afforded a greater signal resolution and hence signal extraction of the PAG across the included participants (Diedrichsen et al., 2009).

First-level GLMs modeled the stimulus condition onsets and included an artifact detection regressor and realignment parameters as multiple regressors. Time series were

extracted from a contrast that modeled both subliminal, neutral and subliminal, trauma-related stimulus conditions. Coordinates and sizes of the spheres for the time series were as follows: PAG ([*x*: 0; *y*: -32; *z*: -11 (mm)]; sphere size: 6 mm), PCN ([*x*: 6; *y*: -52; *z:* 30 (mm)]; sphere size: 8 mm), and mPFC ([*x*: 0; *y*: 60; *z*: -2 (mm)]; sphere size: 8 mm). Extracted time series were permitted to vary slightly from these coordinates and were inspected visually to assure that the relocated volumes-of-interest remained in the proper anatomical location. Whereas a ± 2 mm variation in each coordinate plane was allowed for the PAG, a ± 3 mm variation in each coordinate plane was allowed for the PCN and the mPFC. Smaller sphere sizes and variations were used for the PAG to account for the size of the structure and to limit the potential signal interference of neighbouring midbrain structures. Each eigenvariate extracted for the PAG were examined to confirm that the signal variation was explained mainly by the set volume-of-interest (> 75% explained; see Supplemental Information).

4.3.6 FIRST-LEVEL: NEURAL MODEL SPECIFICATIONS

Modeling Specifications

Subliminal, neutral and subliminal, trauma-related stimulus onsets were imported from the GLMs into the DCM framework. In line with relevant scanning parameters, slice timing was set to 2 s. Bilinear, one-state model terms were selected, where the models did not include stochastic effects or mean centre-input. Each DCM modeled fMRI in the time domain, where we assessed condition-specific, time-varying fluctuations in effective connectivity due to our experimental context. Three models were specified varying in regard to the direction of the condition-dependent modulations in effective connectivity across participants (i.e., bi-directional, bottom-up, top-down) (Figure 4.1).

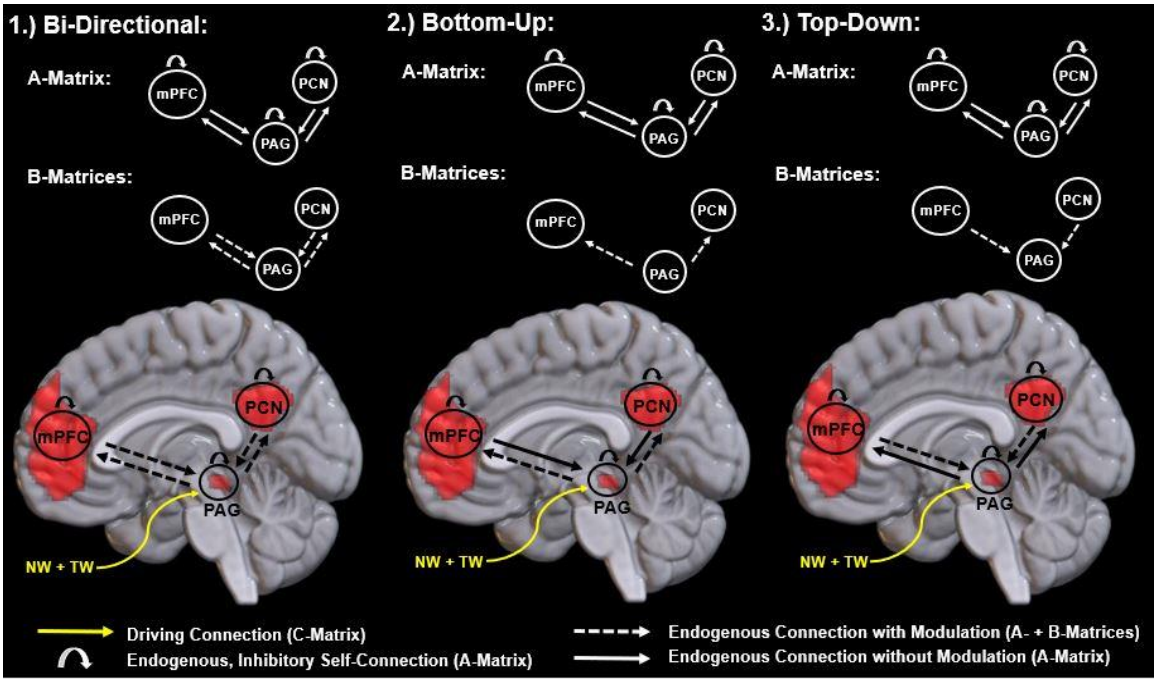

***FIGURE 4.1**: DCM ENDOGENOUS, MODULATORY, AND DIRECT CONNECTIONS*

The above illustration details the three specified models. On the top, we illustrate the endogenous and the modulatory model connectivity parameters as specified in the A-matrix and the B-matrix, respectively. On the bottom, we superimpose these model connectivity parameters (as well as the C-matrix) onto template masks that give a relative indication of the coordinate locations that correspond to the various network nodes. Note that neither template masks nor circles represent actual coordinate locations or sizes of the spheres used for signal extraction and are intended for graphic illustration only. On the very bottom, we provide a legend for these model connectivity parameters.

Abbreviations: PAG: periaqueductal gray; PCN: precuneus; mPFC: medial prefrontal cortex; NW: neutral condition; TW: trauma-related condition

Direct Connections (C-Matrix)

C-matrices specify the direct connections and were held constant across our models, where each stimulus condition had a direct input into the network at the PAG. The selection was based on the relationship between the PAG and the superior colliculus, where the superior colliculus receives visual information from the retina (Liddell et al., 2005; Tamietto & de Gelder, 2010), discriminates between threat and non-threat stimuli (Liddell et al., 2005), and innervates the PAG subsequently (Grofová et al., 1978; Keay & Bandler, 2014). Taken together, stimulus conditions are likely to have onset into the network at the PAG and not at the level of the mid-line cortices of the DMN.

Endogenous Connections (A-Matrix)

Endogenous connections were specified in the A-matrix and did not differ across the models or across the stimulus conditions. Whereas endogenous connections between the PAG and the PCN, as well as between the PAG and the mPFC were modeled, endogenous connections between the PCN and the mPFC were not modeled. We restricted the model space to address specifically the key question (Stephan et al., 2010), which was whether the PAG or the DMN nodes (e.g., PCN, mPFC) guided functional connectivity between these neural systems, where the research question was a direct follow-up to the findings reported by Terpou et al. (2019a). The PCN and the mPFC were included in the present study by virtue of the functional connectivity each node shared with the PAG. Hence, we did not model the endogenous connection between the PCN and the mPFC to provide the most parsimonious model space. Moreover, Rabellino et al. (2015) have revealed that the PCN displays reduced functional connectivity with the DMN during subliminal, threat-related stimulus processing in the same participant sample and paradigm analyzed here. In turn, we omitted the endogenous connection between the PCN and the mPFC to focus on the network interactions yet to be characterized. Additionally, endogenous, inhibitory self-connections were modeled for the PAG, the PCN, and the mPFC across the models. Each model had the same seven endogenous connections, which included three inhibitory self-connections and two bi-directional connections between the PAG and the PCN, and the PAG and the mPFC.

Modulatory Connections (B-Matrix)

Modulatory connections were specified in the B-matrix and were the only model parameters that were varied across the three models (Figure 4.1). Modulatory connections exert their influence over endogenous connections, where different B-matrices can be specified for each stimulus condition across a given model. Each model included endogenous connections that were modulated to have the same condition-dependent modulations across the stimulus conditions. Bi-directional models were specified to have both the neutral and the trauma-related stimulus conditions modulate the endogenous connections between the PAG and the PCN, as well as between the PAG and the mPFC

in both directions. Bottom-up models were specified to have both the stimulus conditions modulate the endogenous connections from the PAG to the PCN, as well as from the PAG to the mPFC, whereas top-down models were specified to have both the stimulus conditions modulate the endogenous connections from the PCN to the PAG, as well as from the mPFC to the PAG.

4.3.7 SECOND-LEVEL: GROUP COMPARISONS

Bayesian Model Selection (BMS)

Following the specification and the estimation of the three models across participants, a random-effects BMS was conducted in SPM12. BMS evaluates the evidence for each model and identifies the model that best accounts for the data, where winning models are identified when they exhibit relatively high exceedance probabilities. Exceedance probability is a measure of how likely it is that a given model is more frequent than the other models at explaining the data in the comparison test (Stephan et al., 2009). Exceedance probabilities quantify the properties of a good model to allow for comparisons between competing models (Stephen et al., 2010). In BMS, each model is evaluated with respect to its accuracy (i.e., how well the model parameters predicted the observed data) and its complexity (i.e., how much divergence the model parameters exerted from the model priors) (Friston et al., 2007; Stephan et al., 2009). Highly accurate and minimally complex models have strong model evidence and are hence more likely to be generalizable (Stephan et al., 2010).

Bayesian Model Averaging (BMA)

BMA was also conducted across the models within each group, where BMA reflects the weighted average of each model parameter across the group and weights are given based on model evidence. Means and standard deviations of BMA parameter estimates were recorded for every parameter, where these values can be interpreted as the evidence for the connection strength of a parameter. Means and standard deviations were used to conduct independent *t*-tests. Seventeen *t*-tests were conducted, where we corrected for multiple comparisons and adjusted significance thresholds to $p_{(FWE)} \leq .0029$.

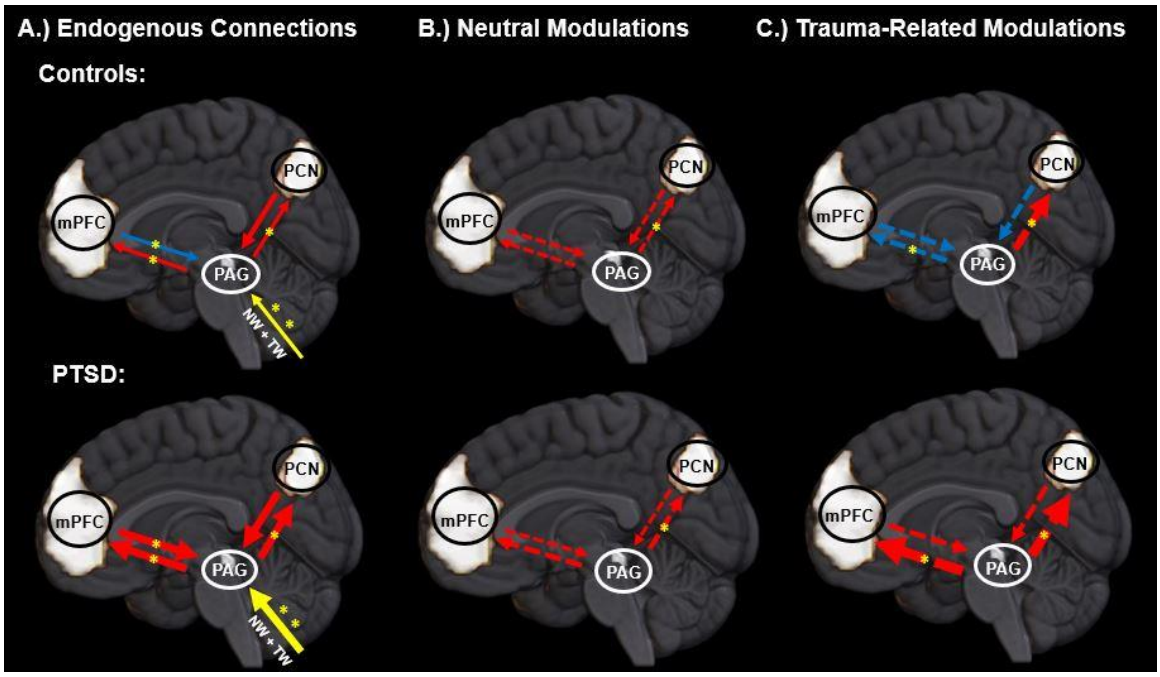

***FIGURE 4.2**: GROUP-SPECIFIC BMA EFFECTIVE CONNECTIVITY DYNAMICS*

Top and bottom images illustrate the group-specific effective connectivity dynamics for control and PTSD groups, respectively. Asterisks denote the parameter surpassed significance in group comparisons. Network nodes are included in the circles and lines represent the connections between nodes. Solid and dashed lines indicate an endogenous or a modulatory connection, respectively. Yellow, blue, or red lines indicate a direct, an inhibitory (or decrease), or an excitatory (or increase) connection, respectively. Sizes of the lines gives a relative indication of the strength of the underlying model connectivity parameter.

Abbreviations: PAG: periaqueductal gray; PCN: precuneus; mPFC: medial prefrontal cortex; NW: neutral stimulus condition; TW: trauma-related stimulus condition; PTSD: post-traumatic stress disorder

4.4 RESULTS

4.4.1 DEMOGRAPHIC AND CLINICAL MEASURES

Independent *t*-tests conducted across the demographic measures did not reveal significant group differences. As expected for clinical measures, participants with PTSD scored significantly higher on total scores for the CAPS, MDI, CTQ, and RSDI as compared to healthy controls (see Table 4.1).

4.4.2 BAYESIAN MODEL SELECTION

Output for BMS favoured bi-directional models for both groups. Exceedance probabilities for the bi-directional models of the control and the PTSD group were .935 and .969, respectively. These are well above the common thresholds to report model superiority (> .85 – .90; Stephan et al., 2009) and suggest bi-directional modulations to be favoured across our current experimental conditions.

4.4.3 BAYESIAN MODEL AVERAGING

Direct Connections (C-Matrix)

Subliminal, neutral and trauma-related stimulus conditions showed greater parameter estimates for driving inputs to the PAG in PTSD as compared to controls (see Table 4.2).

Endogenous Connections (A-Matrix)

In PTSD, stronger excitatory effective connectivity from the PAG to the PCN, as well as from the PAG to the mPFC were demonstrated as compared to controls (see Table 4.2). In PTSD, stronger excitatory effective connectivity from the mPFC to the PAG were also revealed as compared to controls, where controls featured a weak inhibitory connection for the parameter. No differences were shown across endogenous, inhibitory self-connections for the PAG, the PCN, or the mPFC.

Modulatory Connections (B-Matrix)

In PTSD as compared to the control group, stronger modulations to the subliminal, neutral stimulus conditions were revealed, where neutral stimulus conditions prompted greater increases in the rate of change in effective connectivity from the PAG to the PCN. In PTSD as compared to controls, stronger modulations to the subliminal, trauma-related stimulus conditions were revealed as well, where trauma-related stimulus conditions led to greater increases in the rate of change in effective connectivity from the PAG to the PCN, and from the PAG to the mPFC (see Table 4.2). In controls, trauma-related stimulus conditions led to increases as well as decreases in the rate of change in effective connectivity from the PAG to the PCN, and from the PAG to the mPFC, respectively.

TABLE 4.2: *MEAN AND STANDARD DEVIATION BMA MODEL PARAMETER ESTIMATES*

Matrices (Condition)	Model Parameters	Mean		Standard Deviation		Effect Size	*t*-Tests (*df* = 44)	
		HC	PTSD	HC	PTSD	Cohen's *d*	*t*-stat	*p*-value
C(NW)	**PAG**	**-0.1371**	**-0.2863**	0.0469	0.0472	**3.1732**	**113.612**	**< 0.001**
C(TW)	**PAG**	**-0.2433**	**-0.3223**	0.0490	0.0493	**1.6134**	**30.729**	**< 0.001**
A	**PAG -> PAG**	-0.0362	-0.0377	0.0275	0.0240	0.0582	0.0389	0.844
	PCN -> PCN	-0.0155	-0.0119	0.0281	0.0242	-0.1376	0.2175	0.643
	mPFC -> mPFC	-0.0223	-0.0104	0.0278	0.0248	-0.4524	2.3432	0.133
	PAG -> PCN	**0.0016**	**0.0362**	0.0222	0.0211	**-1.5981**	**29.055**	**< 0.001**
	PAG -> mPFC	**0.0116**	**0.0352**	0.0251	0.0225	**-0.9916**	**44.237**	**< 0.001**
	PCN -> PAG	0.0261	0.0422	0.0261	0.0228	-0.6585	5.0324	0.031
	mPFC -> PAG	**-0.0004**	**0.0251**	0.0256	0.0227	**-1.0547**	**13.131**	**0.002**
B(NW)	**PAG -> PCN**	**0.2135**	**0.4256**	0.1768	0.1641	**-1.2447**	**17.670**	**< 0.001**
	PAG -> mPFC	0.1435	0.2297	0.1944	0.1788	-0.4619	2.4358	0.126
	PCN -> PAG	0.1204	0.1789	0.2124	0.1863	-0.2934	0.9869	0.326
	mPFC -> PAG	0.1021	0.1335	0.2096	0.1831	-0.1599	0.2951	0.589
B(TW)	**PAG -> PCN**	**0.3287**	**0.5069**	0.1774	0.1591	**-1.0591**	**12.833**	**< 0.001**
	PAG -> mPFC	**-0.0236**	**0.1841**	0.1941	0.1756	**-1.1236**	**14.419**	**< 0.001**
	PCN -> PAG	-0.0361	0.1381	0.2101	0.1862	-0.8791	8.8502	0.005
	mPFC -> PAG	-0.0402	0.0623	0.2112	0.1824	-0.5208	3.1119	0.085

Means and standard deviation values for BMA model parameters are represented for each group. For endogenous connections, whereas positive parameter values indicate that an increase in activity in the one region results in an increase in the rate of change in the activity of the connected region, negative parameter values indicate that an increase in activity of the one region results in a decrease in the rate of change in activity of the connected region. Bold font represents significance at $p_{(FWE)} \leq .0029$.

Abbreviations: C(NW): Neutral Stimulus Condition Direct Connections; C(TW): Trauma-Related Stimulus Condition Direct Connections; A: Endogenous Connections; B(NW): Neutral Stimulus Condition Modulatory Connections; B(TW): Trauma-Related Stimulus Condition Modulatory Connections; PAG: Periaqueductal Gray; PCN: Precuneus; mPFC: Medial Prefrontal Cortex

4.5 DISCUSSION

4.5.1 OVERVIEW

We sought to characterize the effective connectivity dynamics between the PAG and the PCN, as well as between the PAG and the mPFC during both subliminal, neutral and subliminal, trauma-related stimulus conditions in participants with PTSD as compared to healthy controls. Critically, we uncovered stronger excitatory effective connectivity between the PAG and the mPFC in both directions, as well as from the PAG to the PCN in participants with PTSD as compared to healthy controls (Figure 4.2A). Additionally, we also revealed that the effective connectivity from the PAG to the PCN, as well as from the PAG to the mPFC were modulated more strongly in participants with PTSD as compared to controls during subliminal, trauma-related stimulus conditions (Figure 4.2C). Accordingly, bottom-up, or PAG-mediated functional connectivity to the DMN contributed more to group differences, where subliminal, trauma-related stimulus conditions were revealed to lead to stronger increases in the rate of change in the effective connectivity. These findings may assist to explain the links between self- and trauma-related processing in traumatized individuals.

4.5.2 SECOND-LEVEL: ENDOGENOUS CONNECTIVITY

Endogenous connectivity from the PAG to the PCN, from the PAG to the mPFC, as well as from the mPFC to the PAG showed greater excitatory effective connectivity in participants with PTSD as compared to controls, which we interpret here as the PAG-mediated recruitment of the DMN.

Nicholson et al. (2018) reported similarly an increase in DMN recruitment in participants with PTSD during trauma-related stimulus conditions across a real-time neurofeedback protocol. In particular, the DMN revealed stronger recruitment during instructions to view a trauma-related stimulus as compared to during rest in participants with PTSD. Related, Nicholson et al. revealed also the PAG to be incorporated functionally within the salience network during the data-driven identification of the intrinsic connectivity networks. Switching between the intrinsic connectivity networks is mediated by the

salience network and thought to be modulated by the anterior insula (Menon & Uddin, 2010; Seeley et al., 2007; Sridharan et al., 2008). In PTSD, Harricharan et al. (2016) have reported greater resting-state functional connectivity between the anterior insula and the PAG as compared to healthy individuals. Furthermore, Daniels et al. (2010) revealed that the intrinsic connectivity networks feature a dysregulated equilibrium in PTSD, where individuals do not inhibit appropriately the DMN during a working memory task. Accordingly, the PAG may be contributing to the aberrant recruitment of the DMN in traumatized individuals. Here, we found that the PAG demonstrates greater bottom-up, excitatory effective connectivity during subliminal, trauma-related stimulus conditions in participants with PTSD as compared to healthy individuals. These findings are in keeping with Nicholson et al. (2017), where stronger bottom-up, excitatory effective connectivity from the PAG to the mPFC were displayed during rest in participants with PTSD who presented with typical symptom patterns as compared to participants with PTSD who presented with more dissociative symptom patterns. These dynamics provide an early signal that PAG-mediated recruitment of the DMN – shown here during subliminal, trauma-related stimulus conditions – may support, in part, the apparent link between self- and trauma-related processing.

4.5.3 SECOND-LEVEL: MODULATORY CONNECTIVITY

Subliminal, Trauma-Related Stimulus Conditions

Subliminal, trauma-related stimulus conditions modulated effective connectivity more strongly in participants with PTSD as compared to controls, where greater increases in effective connectivity from the PAG to the PCN, as well as from the PAG to the mPFC were revealed. Trauma-related stimulus conditions are used often to re-establish certain elements of a trauma memory (Elsesser et al., 2005; Liberzon et al., 1999; Halligen et al., 2006), where the PCN and the mPFC are thought to contribute to self-related (as well as visual imagery) processes and memory-related construction, respectively (for a review, see Cabeza & St. Jacques, 2007; Svoboda et al., 2006). In PTSD as compared to controls, the PCN and the mPFC display stronger and lesser activity during trauma-related stimulus conditions, respectively (for a review, see Sartory et al., 2013; Thome et al., 2019). Enhanced activity in the PCN (as well as the posterior parietal cortices more

generally) support reliving experiences during trauma-related stimulus processing in participants with PTSD (for a review, see Brewin, 2015). Reliving experiences are thought to re-establish the physiological, or the visceral conditions encountered by the traumatized individual during trauma-related encoding (Rubin et al., 2004). Physiological changes are coordinated, in part, by the PAG (Brandão et al., 2008), where these changes may be provoked during trauma-related stimulus conditions in PTSD.

Subliminal stimulus conditions are used principally to evoke responses across subcortical systems, which may help explain why the PAG showed stronger excitatory effective connectivity to the PCN, as well as to the mPFC in participants with PTSD. Moreover, effective connectivity from the PAG to the PCN, as well as from the PAG to the mPFC were modulated more strongly in PTSD as compared to controls during trauma-related stimulus conditions. Subliminal, trauma-related stimulus conditions may then lead to PAG-mediated functional connectivity to the DMN in participants with PTSD. Indeed, Nicholson et al. (2017) have demonstrated similarly stronger bottom-up, or PAG-mediated effective connectivity to the mPFC in participants with PTSD who presented with typical symptom patterns as compared to participants with PTSD who presented with more dissociative symptom patterns; however, these results were shown during rest, where individuals with PTSD demonstrate reduced DMN functional connectivity. Here, trauma-related stimulus conditions appeared to drive greater bottom-up, excitatory effective connectivity, where these patterns may serve to re-establish the physiological experiences related to trauma, which, in turn, may bring online trauma-related reliving through a self-related frame of reference in PTSD.

Subliminal, Neutral Stimulus Conditions

Subliminal, neutral stimulus conditions also modulated the effective connectivity from the PAG to the PCN more strongly in participants with PTSD as compared to controls. Stronger condition-dependent modulations to the neutral stimulus conditions may support an attention threat bias in participants with PTSD. Traumatized individuals generally exhibit stronger startle responses and emotion dysregulation during trauma-related stimulus conditions (Fani, Tone, Phifer et al., 2012; Fani, Jovanovic, Ely et al., 2012;

Naim et al., 2015), but these responses are documented as well under neutral stimulus conditions (Felmingham et al., 2003; Pineles et al., 2009; Litz et al., 2000; for a review, see Weber 2008). Attention threat biases are often indexed indirectly via autonomic responses (e.g., heart rate, blood pressure, skin conductance), which are mediated, in part, by the PAG (for a review, see Terpou et al., 2019c). Moreover, subliminal stimulus conditions are used to elicit activity across evolutionarily conserved, fast-responding midbrain systems (Liddell et al., 2005). In PTSD, neutral stimulus conditions may have then been misidentified to be threatening, which can assist to explain the stronger modulations to neutral stimulus conditions revealed here.

4.5.4 LIMITATIONS AND FUTURE DIRECTIONS

Current sample sizes were relatively small, thus precluding authors to investigate the differences between participants with PTSD who meet or do not meet criteria for the dissociative subtype of the disorder. In PTSD, the dissociative subtype differs from the typical symptom pattern in both its clinical and neural characteristics (Lanius et al., 2010; Steuwe et al., 2012; Wolf et al., 2012), where the mPFC is involved considerably in differentiating between these diagnoses (Nicholson et al., 2019). Secondly, neutral and trauma-related words were not matched on English language frequency, which could include novelty effects on the trauma-related words in the event that the words were less common as compared to the neutral words. Thirdly, we did not remove effects related to cardiac or to respiratory activity by adjusting our data to a contrast during eigenvariate extraction. Hence, DCMs may have been required to explain noise or confounds in the data via task-related processes, which would have reduced the accuracy of the model parameter estimates. Fourthly, subliminal stimulus durations were in keeping with standard procedure (Felmingham et al., 2008; Williams et al., 2006; Rabellino et al., 2016); however, we did not verify whether every individual perceived each stimulus subliminally. Lastly, we remind readers that present findings were generated from the same sample and the paradigm as investigated by Terpou et al. (2019a). Consequentially, we urge caution during the generalization of these findings to other samples and paradigms. We encourage future researchers to examine the network interactions across the DMN, where fully-connected models may uncover different effective connectivity

dynamics during rest, as well as during similar threat- or trauma-related stimulus conditions in participants with PTSD.

4.6 CONCLUSION

Here, we explored the effective connectivity dynamics between the PAG and the PCN, as well as between the PAG and the mPFC during subliminal, neutral, as well as subliminal, trauma-related stimulus conditions in participants with PTSD as compared to healthy individuals. In PTSD, we revealed the PAG to display stronger bottom-up, excitatory effective connectivity to the PCN and to the mPFC, where effective connectivity between these model parameters were also modulated more strongly during subliminal, trauma-related stimulus conditions as compared to the controls. It remains unclear whether these effective connectivity dynamics occur during other experimental contexts; however, we present evidence to understand further the phenomenological disturbances to self-related processing as reported in participants with PTSD during trauma-related processing. Future research evaluating the effective connectivity between the PAG and the DMN during rest are warranted critically. We discuss these findings in regard to the different elements expressed during trauma-related reliving, where the PAG and the DMN are thought to mediate physiological sensations related to trauma and self-related perspectives, respectively. We find evidence that the former drives the latter, which does beg intrigue into whether other network-related alterations in traumatized individuals are driven by subcortical systems that remain poorly described in PTSD.

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CHAPTER 5[5]

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5 MORAL WOUNDS RUN DEEP: ENHANCED MIDBRAIN FUNCTIONAL NETWORK CONNECTIVITY ACROSS THE DEFAULT MODE NETWORK IN POST-TRAUMATIC STRESS DISORDER (PTSD)

5.1 ABSTRACT

Background: Moral injury (MI) has begun to garner strong clinical and research interest, although the neural correlates differentiating MI and post-traumatic stress disorder (PTSD) remain poorly characterized. MIs and PTSD often co-occur, where a MI refers more so to the biopsychosocial injury that results from moral and ethical violations transgressed by the self or by a trusted leader, peer, or institution. Intrinsic connectivity networks (ICNs) and the default mode network (DMN) in particular have been revealed to be altered in participants with PTSD who have endured MIs. However, brainstem, midbrain, and cerebellar systems are rarely integrated into the ICNs, a critical oversight since these systems display marked differences in PTSD and are thought to be underlying moral emotions (e.g., shame, guilt, betrayal) and cognitions, at least in part. **Methods:** Here, we conducted an independent component analysis (ICA) on data generated during script-driven, MI-related memory recall in participants with military- and law enforcement-related PTSD (N = 28), participants with civilian-related PTSD (N = 28), and MI-exposed, healthy controls (N = 28). All independent components were correlated spatially to a DMN mask and the component most similar to the DMN was selected. Group-level functional network connectivity differences were compared across the DMN component, with a particular focus on brainstem, midbrain, and cerebellar systems. **Results:** Critically, we revealed stronger midbrain and cerebellar functional network connectivity across the DMN in participants with civilian-related PTSD as compared to MI-exposed, healthy controls, as well as a trend toward stronger midbrain functional network connectivity in participants with military- and law enforcement-related PTSD as compared to MI-exposed, healthy controls. In particular, midbrain and cerebellar functional network connectivity was centered on the periaqueductal gray (PAG) and the cerebellar lobule IX, respectively. These results corroborate previous work revealing

stronger PAG functional connectivity across the DMN in PTSD. **Conclusion:** In PTSD, we provide evidence that the DMN may be biased toward lower-level, midbrain systems, which may be driving toxic shame and related moral emotions observed commonly in PTSD, highlighting the depth at which MIs are represented.

5.2 INTRODUCTION

Moral injury (MI) has garnered strong clinical and research interest recently, especially as the construct relates to military members, first responders, and frontline health care workers who are exposed to morally adverse events regularly. MIs refer to the biopsychosocial injury that results from perpetrating morally violating behaviour, or from witnessing or learning about an event wherein a trusted leader, peer, or institution betrayed deeply held moral beliefs and expectations (Litz et al., 2009). MIs may be conceptualized as a form of prolonged moral suffering, which results from acute and evolving emotional responses (e.g., shame, guilt, betrayal) prompted by a morally adverse event(s) which, in turn, overwhelms the capacity to cope (Farnsworth et al., 2014). Difficulty regulating the intense, albeit normal emotional responses that follow moral and ethical violations have been related to many adverse mental health outcomes, including post-traumatic stress disorder (PTSD) symptom development (Protopopescu et al., 2021) and suicidality (Bryan et al., 2018; Koenig et al., 2018), to name only a few.

Related, shame seems to be a strong emotional response expressed commonly after a MI and has been suggested to be a hallmark feature underlying MIs (Jinkerson, 2016; Lloyd et al., 2021). Indeed, interpersonal trauma(s) are thought to be related more so to shame rather than fear (Saraiya & Lopez-Castro, 2016), and shame has emerged repeatedly as a vulnerability factor motivating PTSD symptom development in military members (Litz et al., 2009; Nazarov et al., 2015; Crocker et al., 2016; Cunningham et al., 2018; for a review, see Herman, 2011; Gaudet et al., 2016), law enforcement officers (Ricciardelli et al., 2018; Papazoglou et al., 2020), and civilian frontline health care workers (Haller et al., 2020), as well as a risk factor motivating greater suicidal ideation and attempts (Cunningham et al., 2019), highlighting the significant burden MIs may have when punctuated by shame.

Preliminary research has begun to disentangle the neural correlates underlying MI and PTSD (Barnes et al., 2019). Here, dissociable neural activity has been revealed during resting-state (Sun et al., 2019), as well as during script-driven, MI-related memory recall in U.S. veterans and Canadian Armed Forces (CAF) members (Lloyd et al., 2021), respectively. In particular, Lloyd and colleagues (2021) have revealed altered activity patterns across brain regions underlying MI event-related emotions and cognitions in participants with PTSD as compared to MI-exposed, healthy controls. During script-driven, MI-related memory recall, participants with PTSD revealed stronger activity in regions underlying defensive responding (e.g., postcentral gyrus, innate alarm system (IAS; Liddell et al., 2005)), viscerosensory responding (e.g., posterior insula, dorsal anterior cingulate cortex), as well as concomitant reduced activity in regions underlying top-down, modulatory control (e.g., dorsomedial prefrontal cortex (dmPFC)) as compared to MI-exposed, healthy controls. Additionally, the authors revealed shame scores to be anticorrelated to superior frontal gyrus activity, a region located in the dmPFC and thought to be involved in self-reflection. Here, Lloyd and colleagues suggested that the anticorrelated pattern may speak to the tendency to engage in unhealthy, self-criticism as opposed to healthy, self-reflection, a pattern that likely perpetrates the MI further (Cloitre et al., 2006). Collectively, the above research revealed altered activity patterns across brain regions involved in social cognition, moral reasoning, and emotion regulation, highlighting the distributed aftermath MIs may leave, especially when co-occurring alongside PTSD (Bryan et al., 2018).

Critically, brain regions reported by Lloyd and colleagues (2021) overlap considerably with critical hubs involved in the intrinsic connectivity networks (ICNs), which have been revealed to display altered activity and functional connectivity patterns in PTSD as well (Rabellino et al., 2015; Tursich et al., 2015; for a review, see Lanius et al., 2015). Although marked differences emerge in regard to activity and functional connectivity patterns across the ICNs in PTSD, these differences provide a cortico-centric perspective and generally fail to incorporate brainstem, midbrain, and cerebellar systems into the larger picture. Midbrain systems and the PAG more particularly have been revealed to display overactivity and altered functional connectivity with the default mode network (DMN) in PTSD (Terpou et al., 2019a, 2019b), yet these systems are rarely discussed in

tandem with the ICNs (i.e., DMN, salience network (SN), and central executive network (CEN)), a critical oversight in mental health research more generally.

The PAG surrounds the cerebral aqueduct and has been demonstrated able to modulate the autonomic nervous system (ANS) (De Oca et al., 1998), which, critically, suggests the midbrain structure has a central role in primary affective emotions (e.g., fear, rage, panic, care, lust, play, and seeking; Panksepp, 2000, 2011), as well as innately conserved, defense responses (e.g., fight, flight, faint, tonic immobility) (Coimbra et al., 2006; Brãndao et al., 2008). Here, PAG-mediated neural systems underlying the urge to cringe, hide, or withdraw have been proposed to be co-opted functionally in PTSD and serve as the substrate underlying, in part, avoidance-related symptomatology (Panksepp, 2011; for a review, see Tangney & Dearing, 2002). In PTSD, the PAG has been revealed to display altered activity and functional connectivity patterns with the ICNs during resting-state (Harricharan et al., 2016; Nicholson et al., 2017; Webb et al., 2020), as well as during subliminal, trauma-related stimulus processing (Felmingham et al., 2010; Steuwe et al., 2014; Terpou et al., 2019a, 2019b, 2020). Here, Terpou and colleagues recently demonstrated activity and functional connectivity differences in regard to the PAG in PTSD as compared to healthy controls. In particular, stronger activity (Terpou et al., 2019b), stronger functional connectivity with the mPFC and the PCN (DMN hubs) (Terpou et al., 2019a), as well as stronger PAG-directed functional connectivity toward the DMN (Terpou et al., 2020) were all revealed in PTSD. Taken together, these results suggest the PAG and the midbrain systems more broadly may be implicated in the ICNs after all. In fact, integrating the midbrain systems into the ICNs may help to understand complex emotions such as shame, which evokes a strong response viscerally, but also has an inherent social-cognitive and self-reflective component to it (Lanius, Paulsen, & Corrigan, 2014). Whereas the ruminative, self-reflective (or self-critical) component underlying shame would be thought to be mediated by the DMN, the visceral component, including the urge to cringe, hide, or withdraw, would be thought to be mediated by the midbrain and the PAG more particularly (Dorahy, 2010; Qin & Northoff, 2011; for a review, see Lanius, Paulsen, & Corrigan, 2014).

Here, we sought to study ICN-related functional network connectivity in MI-exposed samples with and without PTSD, with a particular focus on brainstem, midbrain, and cerebellar systems and whether they are recruited differently across the ICNs in PTSD. We employed a script-driven, MI-related memory recall task (Lloyd et al., 2021) – a DMN-mediated task largely – to address these study aims. In addition, we used a data-driven, computational technique (i.e., independent component analysis (ICA)) to identify the ICNs, since the functional connectivity patterns across the dataset employed had yet to be characterized and hence a more exploratory approach was favoured. In line with Terpou and colleagues (2019a, 2019b, 2020), we hypothesized that the midbrain and the PAG in particular would be recruited more strongly across the DMN in participants with PTSD. Enhanced midbrain functional network connectivity across the DMN would assist to explain why many participants with PTSD report persistent viscerosensory hyperactivity, especially when engaged in autobiographical memory and self-related processing, functions mediated by the DMN largely (Raichle, 2015). Finally, given the significant role shame has toward MI, we correlated clinical scores related to shame to DMN-related functional network connectivity. More broadly, the proposed study serves to highlight the significant (yet under-investigated) role brainstem, midbrain, and cerebellar systems have toward ICNs and PTSD symptomatology.

5.3 METHODS

5.3.1 PARTICIPANTS

The study sample included (N = 74) fifty-six participants with a primary PTSD diagnosis (N = 56) and eighteen MI-exposed, healthy controls (N = 18). Two groups with co-occurring MI and PTSD were compared, namely a group comprised by twenty-eight CAF members and law enforcement officers with occupational-related MI and PTSD (N = 28), and a group comprised by twenty-eight civilian participants with occupational-related MI and PTSD (e.g., paramedics, fire fighters, frontline health care workers, interpersonal violence victims) (N = 28). Group demographics and clinical characteristics are provided in Table 5.1. Please refer to Lloyd and colleagues (2021) regarding recruitment procedures. Study procedures were approved by Health Sciences Research Ethics Board

at Western University and McMaster University, as well as the Internal Research Ethics Review Board at Homewood Research Institute.

All participants provided written and informed consent before study involvement and were compensated financially. Exclusion criteria included past or present bipolar disorder, psychotic disorder, or a present substance use disorder. Full remission for past substance use disorder was required for a minimum three months prior to study involvement. Any lifetime psychiatric illness or psychotropic medication served as an exclusion criteria for MI-exposed, healthy controls. Lastly, non-compliance with 3 Tesla fMRI safety standards, significant untreated medical illness, pregnancy, a neurobiological or developmental disorder, and a significant head injury involving loss of consciousness were served as exclusion criteria for all participants.

TABLE 5.1: *GROUP DEMOGRAPHIC AND CLINICAL CHARACTERISTICS*

	Military and Law Enforcement PTSD Group	***Civilian-Related PTSD Group***	***Control Group***
N	28	28	18
Sex	25 males, 3 females	9 males, 19 females	7 males, 11 females
Age	48.5 ± 8.3	49.1 ± 7.5	33.1 ± 10.9
CAPS–Total	40.89 ± 7.94 *	41.7 ± 6.6 *	0 ± 0
CAPS–D	15.39 ± 3.53 *	15.4 ± 3.2 *	0 ± 0
CTQ–Total	50.4 ± 22.6 *	58.4 ± 15.6 *	30.3 ± 8.4
MDI–Total	60.3 ± 16.3 *	55.1 ± 8.4 *	35.6 ± 5.2
MDD Recurrent	Current = 9, Past =0	Current = 21, Past = 0	Current = 0, Past = 0
MDD Single Episode	Current = 1, Past =1	Current = 0, Past = 0	Current = 0, Past = 0

Psychotropic Medication	23	10	0

Asterisks indicate significantly higher clinical symptom values, relative to the MI-exposed control group.

Abbreviations: PTSD: Post-Traumatic Stress Disorder; CAPS: Clinician-Administered PTSD Scale for DSM-5; CTQ: Childhood Trauma Questionnaire; MDI: Multiscale Dissociation Inventory; MDD: Major Depressive Disorder

5.3.2 CLINICAL AND SELF-REPORT MEASURES

5.3.2.1 CLINICAL INTERVIEWS AND MEMORY SCRIPTS

Participants attended 1–2 clinical interviews; wherein diagnostic testing was completed. Additionally, participants were asked to describe a neutral event as well as a MI event. Each event-related memory was delivered according to procedures outlined in past autobiographical memory investigations in the trauma literature (McKinnon et al., 2015; Palombo et al., 2016). During script-driven, MI-related memory recall, participants were asked to actively recall the neutral event (presented audio-visually and in chronological order), followed by the MI event, while undergoing an fMRI scan (see Lloyd and colleagues (2021) for scanning parameters).

5.3.2.2 MORAL INJURY-RELATED STATE SHAME RATINGS

Immediately following each script, participants were asked to rate their state shame in relation to the event recalled (1 = not at all; 4 = very much so).

5.3.2.3 STRUCTURED CLINICAL INTERVIEW FOR DSM-IV (SCID-I)

The Structured Clinical Interview for DSM-IV Axis-I Disorders – Research Version (SCID-I; First, 2015) was administered to ascertain psychiatric illness history, to determine comorbid illnesses, and served to inform study inclusion and exclusion.

5.3.2.4 CLINICIAN-ADMINISTERED PTSD SCALE FOR DSM-5 (CAPS-5) AND LIFE EVENTS CHECKLIST

The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Blake et al., 1995) was used to assess total PTSD symptom severity as well as Criterion D symptom severity, pertaining to alterations in cognitions and mood (i.e., the inability to recall event details, exaggerated negative beliefs and expectations, distorted cognitions leading to blame, persistent negative state, apathy, interpersonal detachment, and diminished positive emotion).

5.3.2.5 OTHER SELF-REPORT MEASURES

The Moral Injury Events Scale (MIES; Nash et al., 2013) was used to confirm exposure and distress related to a MI-related event (with items 8–9 omitted with respect to non-military participants). Additionally, the Multiscale Dissociation Inventory (MDI; Briere et al., 2005) and the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003) were used to assess group differences in dissociative symptomatology and childhood maltreatment and neglect, respectively.

5.3.3 STATISTICAL ANALYSES

Group-level, functional network connectivity was compared across the independent component (IC) correlated to the DMN in the present study, with a particular focus on brainstem, midbrain, and cerebellar systems and how they contribute to the ICNs. Results from the other ICNs will be reported elsewhere and at a later date.

5.3.3.1 INDEPENDENT COMPONENT ANALYSIS

An independent component analysis (ICA) refers to a data-driven, computational technique used to determine whole-brain, voxel-wise functional connectivity patterns (for a review, see Calhoun et al., 2009). To analyze the functional network connectivity across the DMN, we performed a single spatial group ICA, using the Group ICA of the fMRI Toolbox (GIFT; Calhoun et al., 2001). We included functional images across all participants (N = 74) and task-related conditions into the ICA, to analyze inter-subject as

well as inter-group differences toward IC spatial extent and amplitudes (Allen et al., 2012; Ros et al., 2013). We then selected the INFOMAX algorithm and calculated twenty ICs (following minimum description length criteria), which were estimated twenty times through ICASSO to ensure the ICs reliability (Allen et al., 2012). Afterward, the averaged group ICs were back-reconstructed using a principal component analysis into single-subject spatial maps and time courses (for a review, see Calhoun & Adali, 2012). Finally, single-subject spatial maps and time courses were converted into z-scores (Calhoun & Adali, 2012). Here, a z-score represents the voxel-wise, functional network connectivity across any derived IC.

All twenty ICs were inspected visually to confirm artifacts (e.g., ventricles, white matter, edges) were not present. Subsequently, the twenty ICs were correlated spatially to the DMN mask produced by the Functional Imaging in Neuropsychiatric Disorders Lab (FIND; Shirer et al., 2012). We selected the IC correlated most strongly to the DMN (DMN IC), and single-subject spatial maps and time courses from the DMN IC were compared between groups in Statistical Parametric Mapping (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK: http://www.fil.ion.ucl.ac.uk/spm) in MATLAB R2019a software (MathWorks Inc., MA).

5.3.3.2 GROUP DIFFERENCES

In SPM12, single-subject spatial maps and time courses from the DMN IC were sorted based on group and added to a one-way ANOVA to analyze differences between participants with military- or law enforcement-related PTSD, participants with civilian-related PTSD, and MI-exposed, healthy controls (variance set to unequal). After we estimated the one-way ANOVA, we computed contrast images to compare the functional network connectivity underlying the DMN IC group-wise. We observed the results at an uncorrected threshold set at $p < .001$, $k \geq 10$ and assessed significance at a threshold set at $p\text{FDR} < .05$, $k \geq 10$ (peak-corrected).

In addition to the whole-brain analysis, we conducted a region of interest (ROI) analysis to elucidate brainstem, midbrain, and cerebellar systems more closely. In particular, we selected the spatially-unbiased infratentorial template toolbox (SUIT; Diedrichsen, 2006)

mask as the ROI. The SUIT template mask includes an MNI-normalized, cropped cerebellum and brainstem and affords greater subcortical resolution as compared to whole-brain outputs. We observed the ROI results at an uncorrected threshold set at $p < .001$, $k \geq 10$ and assessed significance at a threshold set at pFDR $< .05$, $k \geq 10$ (peak-corrected), similar to the whole-brain analysis above-mentioned.

5.4 RESULTS

5.4.1 DEMOGRAPHICS AND CLINICAL MEASURES

Group demographics and clinical characteristics are described in Table 5.1. Significant differences were found between groups for age; however, closer examination of the influence of age on the BOLD signal was found to reveal non-significant differences across conditions. While the PTSD groups reported higher scores on the CTQ, the entire sample endorsed exposure to childhood maltreatment or neglect (as measured by any subscale > 5, or minimization scale > 0). As expected, the PTSD groups reported significantly higher dissociation scores on the MDI as well.

5.4.2 COMPONENT SELECTION

In GIFT, IC 3 ($r = 0.379$) and IC 9 ($r = 0.371$) were revealed to be correlated more strongly to the DMN mask than any other ICs. Whereas IC 3 contained anterior (e.g., medial prefrontal cortex) and posterior (e.g., posterior cingulate cortex, precuneus) DMN hubs, IC 9 contained anterior DMN hubs only. Afterward, IC 3 and IC 9 were correlated to the MI and neutral event-related task onsets, since memory recall has long been regarded as a DMN-mediated faculty. Here, IC 3 ($r = 0.177$) and IC 9 ($r = 0.167$) correlated similarly, but ultimately IC 3 was selected as the DMN IC, since IC 3 revealed the strongest correlations (spatially and temporally) and had the greatest DMN overlap visually.

5.4.3 GROUP DIFFERENCES

Participants with civilian-related PTSD revealed stronger precuneus (MNI = [14, -46, 54], t = 5.67, Z = 5.38, pFDR (peak-corrected) = 0.009, k = 43) functional network connectivity across the DMN IC as compared to participants with military- or law enforcement-related PTSD (Table 5.2). In the ROI output, we revealed stronger PAG (MNI = [0, -32, -8], t = 4.95, Z = 4.75, pFDR (peak-corrected) = 0.028, k = 39) and cerebellar lobule IX (MNI = [10, -66, -40], t = 4.44, Z = 4.29, pFDR (peak-corrected) = 0.046, k = 49) functional network connectivity among participants with civilian-related PTSD as compared to MI-exposed, healthy controls. Finally, we revealed a trend toward stronger PAG (MNI = [4, -30, -2], t = 4.22, Z = 4.09, pFDR (peak-corrected) = 0.076, k = 60) functional network connectivity among participants with military- or law enforcement-related PTSD as compared to MI-exposed, healthy controls.

TABLE 5.2: *GROUP DIFFERENCES – FUNCTIONAL NETWORK CONNECTIVITY*

Independent Component	Contrast	Brain Region	Cluster (*k*)	MNI Coordinates			*t* Statistic	*Z* Score	*p*FDR (Peak)
				x	*y*	*z*			
IC 3: DMN (WB)	CIVILIAN > MILITARY	Precuneus	43	14	-46	54	5.67	5.38	0.009
IC 3: DMN (ROI)	CIVILIAN > CONTROL	PAG	39	0	-32	-8	4.95	4.75	0.028
		Cerebellar Lobule IX	49	10	-66	-40	4.44	4.29	0.046
	MILITARY > CONTROL	PAG	60	-4	-30	-2	4.22	4.09	0.076†

Group differences in functional network connectivity contained within the DMN IC across whole-brain (WB) and suit-space (ROI). T-contrasts are evaluated at a significance threshold set at pFDR < .05, k > 10 (peak-corrected).

Abbreviations: H: Hemisphere; FDR: False Discovery Rate; DMN: Default Mode Network; WB: Whole-Brain; ROI: Region-of-Interest; PAG: Periaqueductal Gray

5.4.4 CLINICAL CORRELATIONS

In participants with military- and law enforcement-related PTSD, we revealed a significant negative correlation between precentral gyrus functional network connectivity and MI-related state shame scores (MNI = [-36, -28, 40], t = 8.29, Z = 5.18, pFDR (peak-corrected) = 0.049, k = 24). In the ROI, we revealed a significant positive correlation between cerebellar lobule IX functional network connectivity and MI-related state shame scores among participants with military- and law enforcement-related PTSD (MNI = [2, -56, -24], t = 8.10, Z = 5.12, pFDR (peak-corrected) = 0.006, k = 24). Lastly, we revealed a significant positive correlation and a significant negative correlation between cerebellar lobule VII functional network connectivity (MNI = [42, -60, -34], t = 5.10, Z = 4.48, pFDR (peak-corrected) = 0.041, k = 28) and brainstem functional network connectivity (MNI = [14, -16, -18], t = 4.96, Z = 4.48, pFDR (peak-corrected) = 0.049, k = 19) and CAPS total score among participants with PTSD more generally (N = 56), respectively.

TABLE 5.3: *CLINICAL CORRELATIONS – FUNCTIONAL NETWORK CONNECTIVITY*

Independent Component	Group	Clinical Score (Direction)	Brain Region	MNI Coordinates			*t* Statistic	*Z* Score	*p*FDR (Peak)
				x	*y*	*z*			
IC 3: DMN (WB)	MILITARY	State: Shame (-)	Postcentral Gyrus	-36	-28	40	8.29	5.18	0.049
IC 3: DMN (ROI)	MILITARY	State: Shame (+)	Cerebellar Lobule IX	2	-56	-24	8.10	5.12	0.006
	PTSD	CAPS Total (+)	Cerebellar Lobule VII	42	-60	-34	5.10	4.48	0.041
		CAPS Total (-)	Brainstem	14	-16	-18	4.96	4.48	0.049

Clinical correlations between functional network connectivity contained within the DMN IC and state-and trait-related clinical scores are displayed across whole-brain (WB) and suit-space (ROI). Clinical correlations are evaluated at a significance threshold set at pFDR < .05, k > 10 (peak-corrected).

Abbreviations: H: Hemisphere; FDR: False Discovery Rate; DMN: Default Mode Network; WB: Whole-Brain; ROI: Region-of-Interest; CAPS: Clinician-Administered PTSD Scale

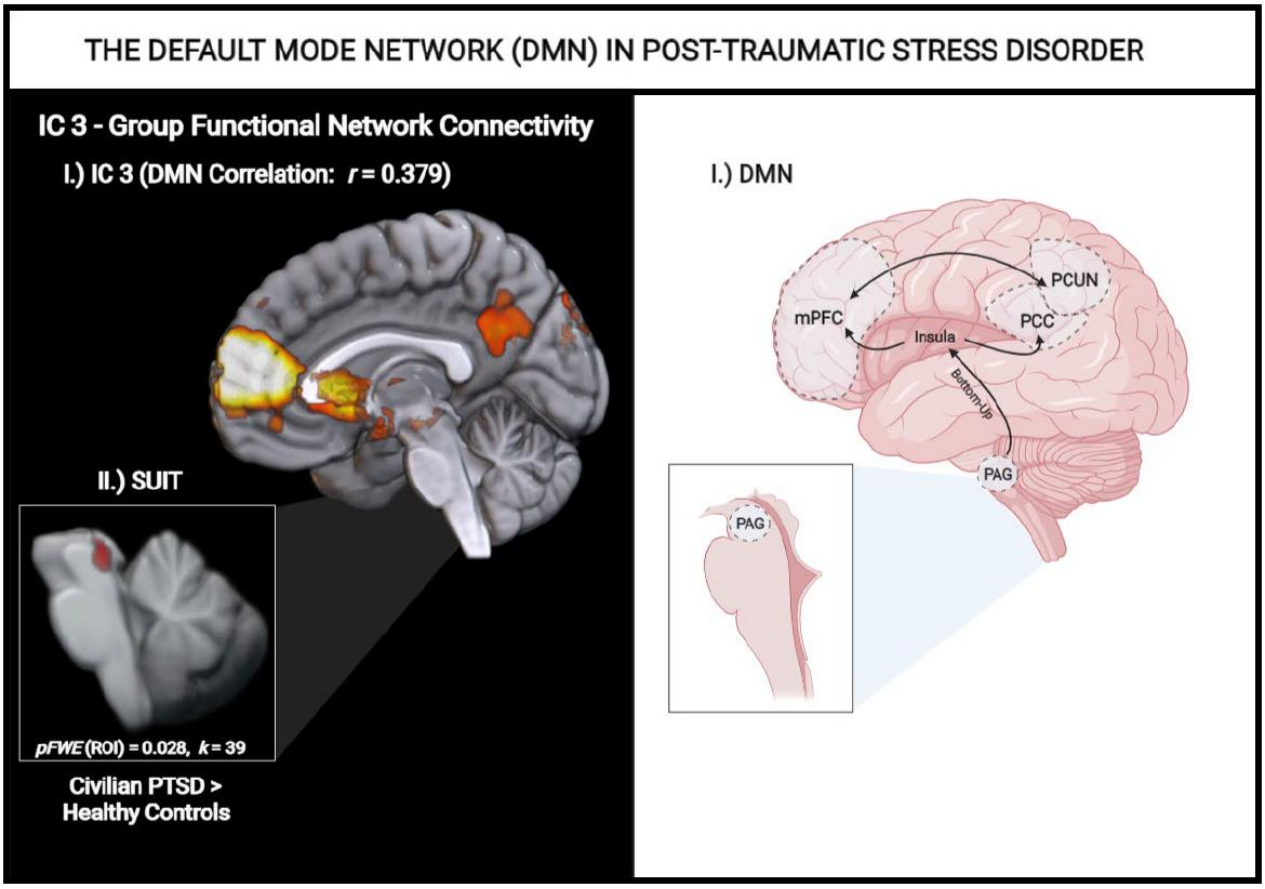

FIGURE 5.1: *DEFAULT MODE NETWORK FUNCTIONAL NETWORK CONNECTIVITY*

Left Panel: On the top, Independent Component 3 (IC 3) as revealed by the ICA and the associated spatial correlation value is shown. In addition, the box shows the significant cluster of functional network connectivity differences between participants with civilian-related PTSD as compared to MI-exposed, healthy controls.

Right Panel: Here, we offer an illustration outlining the functional connectivity between the PAG and the DMN, based on work presented here and by Terpou and colleagues (2019a, 2019b, 2020).

5.5 DISCUSSION

In the present study, we sought to identify the neural correlates underlying MI with and without PTSD, with a particular focus on brainstem, midbrain, and cerebellar systems. We conducted an ICA during script-driven, MI-related memory recall and revealed stronger midbrain and cerebellar functional network connectivity across the DMN in participants with civilian-related PTSD as compared to MI-exposed, healthy controls, as well as a trend toward stronger midbrain functional network connectivity across the

DMN in participants with military- and law enforcement-related PTSD as compared to MI-exposed, healthy controls. In particular, midbrain and cerebellar functional network connectivity differences were centered on the PAG and the cerebellar lobule IX, respectively. In PTSD, critically, we produced very strong evidence that the DMN – a network dominated by higher-level, cortical systems and underlying autobiographical memory and self-related processing – appears to be influenced by lower-level, midbrain systems more profoundly, similar to the results demonstrated by Terpou and colleagues (2019a, 2019b). How exactly midbrain systems alter DMN-mediated processing remains to be seen, but we suspect the effects underpin, at least in part, how MIs are represented in the brain. We discuss and elaborate on these results clinically to follow.

The DMN refers to an ICN underlying autobiographical memory, social cognition, self-related processing, and emotion regulation (Raichle, 2015). Centered on the cortical mid-line, the DMN has three hubs, namely the medial prefrontal cortex, the posterior cingulate cortex, and the precuneus (Qin & Northoff, 2011; Mars et al., 2012; Utevsky et al., 2014). During script-driven, MI-related memory recall, we revealed the DMN to be represented differentially in participants with PTSD as compared to MI-exposed, healthy controls. In particular, functional network connectivity across the DMN appears to be biased toward innately conserved, defensive responding when these morally adverse events are recalled in participants with PTSD. Like any life-threat, MIs tell the body a threat has occurred (moral violation), which may motivate defense responses to mitigate any harm caused by the threat. Failure to defend the self against moral and ethical violations may result in shame and sympathetic shut-down responses, since sympathetic activity would not serve well against a threat represented internally (Harenski & Hamann, 2006). Sympathetic and parasympathetic activity are mediated by the dorsolateral and the ventrolateral PAG, respectively (Carrive, 1993), with the latter thought to be related more so to shut-down responses (Kozlowska et al., 2015; Terpou, Harricharan, & McKinnon, 2019). Taken together, stronger midbrain functional network connectivity across the DMN in PTSD may be driving a tendency to engage in shut-down responses (as opposed to approach, e.g., fight, flight) in response to moral and ethical violations, which may assist to explain, in part, dissociative symptomatology (e.g., derealization,

depersonalization) – an escape inward so as to not have to endure the pain and confront the violation outwardly (van der Kolk & Fisler, 1995; Ogawa et al., 1997).

Midbrain functional network connectivity across the DMN may be critically important to shame and other strong moral emotions (e.g., guilt, betrayal) that often accompany a MI. Shame and other strong moral emotions are underpinned, in part, by the PAG, which has been proposed to communicate with the DMN to supplement the social-cognitive and the self-referential features critical to the emotion (Lanius, Paulsen, & Corrigan, 2014). In PTSD, persistent shame and related moral emotions are reported commonly (Cloitre et al., 2006), which may suggest the self as a moral agent may carry the moral wounds brought on by a MI, leading potentially to affective flooding. Here, shame has been referred to metaphorically as a psychological friction blister that interferes with the normal cicatrization required to heal. We surmise that the enhanced midbrain functional connectivity across the DMN may underpin persistent and toxic shame in the present context in participants with PTSD.

Somewhat unexpectedly, we revealed stronger cerebellar lobule IX functional network connectivity across the DMN in participants with civilian-related PTSD as compared to MI-exposed, healthy controls. In addition, in participants with military- and law enforcement-related PTSD, we revealed a positive correlation between cerebellar lobule IX functional network connectivity and MI-related, state shame scores. Although the DMN has been thought to be represented more so cortically (Greicius et al., 2003), Habas and colleagues (2009) have revealed the DMN and the ICNs more broadly to have distinct correlates in the cerebellum. In a healthy sample, Habas and colleagues conducted a resting-state ICA and revealed the cerebellar lobule IX to be sorted functionally within the DMN, similar to the results generated here. Habas and colleagues referenced the work by Addis and colleagues (2007) in the discussion, where Addis and colleagues had revealed the cerebellar lobule IX to show activity during past- and future-related event recall in parallel to the precuneus and the retrosplenial cortex, suggesting that cerebellar lobule IX functional connectivity to the DMN may extend well beyond resting-state.

Notably, altered cerebellar lobule IX functional connectivity across the DMN has been demonstrated in schizophrenia and somatic symptom disorder (SSD) as well. Here, Guo and colleagues (2015) and Wang and colleagues (2016) have revealed stronger cerebellar lobule IX functional connectivity across the DMN in first-episode, drug-naïve participants with schizophrenia and drug-naïve participants with SSD as compared to healthy controls, respectively. In common, PTSD, schizophrenia, and SSD all feature exaggerated bottom-up processing and related perceptual symptoms, such as hypervigilance in PTSD, hallucinations in schizophrenia, and physical pain and fatigue in SSD (Wigman et al., 2015). Although these symptoms present very differently, they are all thought to be mediated by overactive bottom-up, autonomic and sensory systems, as well as concomitant underactive top-down, modulatory systems (Lanius et al., 2010; Dima et al., 2010; Wigman et al., 2015). Across these disorders, the cerebellar lobule IX serves a more profound role in the DMN, however the exact role served has yet to be understood fully.

5.6 LIMITATIONS AND FUTURE DIRECTIONS

The proposed study has several limitations. Firstly, although fMRI affords high spatial resolution, the resolution procedures are largely based on grey and white matter distributions at the cortical level, which have a more easily discernable delineation. Subcortically, grey and white matter overlap a lot more, which limits the spatial accuracy a bit. However, since the midbrain clusters we reported were very large, we have confidence that the midbrain structures discussed herein were in fact included in the clusters reported significant. In addition, we did not identify participants with PTSD who met the dissociative criteria. Dissociative symptomatology has distinct activity and functional connectivity patterns as compared to PTSD more generally (Lanius et al., 2010; Wolf et al., 2012), which may have added some heterogeneity at the group-level. Based on the different results between participants with military- and law enforcement-related PTSD and participants with civilian-related PTSD, we encourage future research to study occupational differences in moral codes and how these differences relate to MIs. Since a moral code must be violated to lead to a MI (at least presumably), research needs to unpack occupational factors (e.g., workplace norms, demand characteristics)

underlying moral codes so as to better understand how to address MIs when they emerge in the workplace, especially in high-stress workplaces like the military, police force, and frontline health care settings.

5.7 CONCLUSION

Collectively, these results make the case that midbrain systems are not only involved in the DMN, but are the systems where differences between participants with PTSD and MI-exposed, healthy controls are expressed most profoundly. Given the role the DMN serves toward self-related processing, these results assist to explain, in part, self-related processing disturbances reported commonly in PTSD, including the urge to cringe, hide, or withdraw and engage in ruminative, self-critical thoughts (Lanius, Paulsen, & Corrigan, 2014; Terpou et al., 2019b; Lloyd et al., 2021). More generally, these results highlight the need to expand on the current cortico-centric models that predominate mental health research to include brainstem, midbrain, and cerebellar systems – systems altered considerably in PTSD yet under-investigated by comparison. Lastly, these results suggest bottom-up psychotherapy approaches should be considered strongly as an adjunct to top-down psychotherapy. Yoga (Libby et al., 2012; Nolan, 2016), sensory-motor therapy (Fraser et al., 2017; Warner et al., 2013), deep brain reorienting (Corrigan & Christie-Sands, 2020), expressive arts (Lusebrink & Hinz, 2020), and neurofeedback (Nicholson et al., 2016) have been implemented to great success in PTSD and – when conducted in parallel to top-down psychotherapy – provide an embodied cognitive approach that may benefit the client therapeutically.

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CHAPTER 6

6 INTEGRATED DISCUSSION AND CONCLUSIONS

6.1 OVERVIEW

Here, we set out to study the lower-level, emotive systems centered on the midbrain during subliminal, trauma-related stimulus processing and script-driven, MI-related memory recall in PTSD. To date, midbrain systems remain poorly characterized in the current cortico-centric models that predominate mental health research. Yet, many researchers and clinicians suggest midbrain systems may be where the vestiges caused by trauma are represented most significantly (van der Kolk, 1994; Panksepp, Fuchs, & Iacobucci, 2011; Williamson et al., 2013; Corrigan & Grand, 2013). Altogether, we provided strong evidence to support the above, where we revealed altered activity, functional connectivity, and directed functional connectivity by the midbrain during subliminal, trauma-related stimulus processing, as well as altered functional network connectivity during script-driven, MI-related memory recall in PTSD. These results tell a simple story, that we have to integrate the lower-level, emotive systems into the current cortico-centric models. We discuss these results more comprehensively to follow.

6.2 PERIAQUEDUCTAL GRAY ACTIVITY IN PTSD

In Chapter 2, we sought to analyze the brainstem, the midbrain, and the cerebellum during subliminal, trauma-related stimulus processing, a task that has been revealed to provoke activity throughout the IAS (Liddell et al., 2005). Notably, subcortical structures are generally more difficult to image than cortical structures, so we used a high-resolution atlas template developed by Diedrichsen and colleagues (2006) to image these structures more accurately. Strikingly, we revealed stronger midbrain activity during subliminal, trauma-related stimulus processing among participants with PTSD as compared to healthy controls. In particular, we revealed stronger activity across a large cluster centered on the PAG and covering the superior colliculus in part (Terpou et al., 2019b), which we took to support the claim that the IAS may be overactive in PTSD (Lanius et al., 2017). Although midbrain activity has been revealed during subliminal, threat- and trauma-related stimulus processing elsewhere (Felmingham et al., 2008; Steuwe et al.,

2014; Rabellino et al., 2016), we revealed midbrain activity in much higher resolution, which allowed us to pinpoint activity to the PAG more assuredly.

Not only do these results suggest an IAS overactivity in PTSD (Lanius et al., 2017), but they speak to the altered physiological changes reported commonly as well. In PTSD, chronic physiological hyperarousal (e.g., elevated heart rate, blood pressure, skin conductance) has been observed during rest (Cohen et al., 2000; Kendall-Tackett, 2000; Taft et al., 2007), as well as during symptom provocation (Cohen et al., 1998; O'Donnell et al., 2004; Yehuda & Ledoux, 2007; Grupe et al., 2016). As discussed, hypoarousal and dissociative symptoms are reported commonly in PTSD and are thought to be related more so to early childhood maltreatment and trauma(s) that have a more prolonged exposure (Stein et al., 2013; Lanius et al., 2012; Karam et al., 2014). Here, altered physiological changes related more so to passive defenses have been demonstrated in PTSD as well. For example, Volchan and colleagues (2011) have revealed reduced body sway and heart rate variability in participants who had a childhood maltreatment history during script-driven, trauma-related memory recall. These changes were proposed to reflect a tonic immobility state and were confirmed via self-report. Hyperarousal and hypoarousal physiological changes are communicated through the ANS and coordinated by the PAG (Bandler et al., 2000; Löw et al., 2015). Taken together, midbrain hyperactivity may be underlying symptomatology expressed more viscerally in PTSD, which we revealed here using subliminal stimulus conditions.

The fact that subliminal (and not supraliminal), trauma-related stimulus processing revealed these differences cannot be overstated and has many implications clinically. Recently, it has become more and more evident that the vestiges caused by trauma stretch to the lower-level, emotive systems, systems which cannot support conscious processing. Although top-down psychotherapy approaches may be used to regulate these systems indirectly (by bringing online higher-level, cognitive systems), therapy that focuses on reacquainting the client to the body should be considered strongly as an adjunct. Yoga (Libby et al., 2012; Nolan, 2016), sensory-motor therapy (Fraser et al., 2017; Warner et al., 2013), deep brain reorienting (Corrigan & Christie-Sands, 2020), and expressive arts

(Lusebrink & Hinz, 2020) have been implemented to great success in PTSD and reflect a more bottom-up approach to psychotherapy.

6.3 PERIAQUEDUCTAL GRAY FUNCTIONAL CONNECTIVITY IN PTSD

Activity does not tell the full story and in Chapter 3 we sought to analyze the midbrain functional connectivity during subliminal, trauma-related stimulus processing. Using the high-resolution midbrain cluster revealed to be overactive in PTSD (Terpou et al., 2019b), we conducted a psycho-physiological interaction to compare the functional connectivity of the PAG observed during subliminal, trauma-related stimulus processing in PTSD as compared to healthy controls (Terpou et al., 2019a). In PTSD, we expected to identify downstream IAS structures (e.g., amygdala, anterior cingulate cortex) to be correlated to the PAG during the task. However, we actually revealed stronger functional connectivity between the PAG and the mPFC, as well as between the PAG and the PCN in participants with PTSD as compared to healthy controls. As a quick aside, in Chapter 3, we refer to the mPFC as the medial superior frontal gyrus. Whereas the mPFC refers to this area as defined through functional means, the medial superior frontal gyrus refers to this same area but as defined through structural means, i.e., situated above the superior frontal sulcus. In any regard, they are analogous and based on the same coordinate definitions. Henceforth, we refer to these coordinates as the mPFC. The mPFC and the PCN are critical hubs involved in the DMN (Greicius et al., 2003), a network recruited more commonly during self-related and autobiographical memory processing (Raichle, 2015). In PTSD, whereas the mPFC and the PCN have been revealed to show reduced functional connectivity during rest (Bluhm et al., 2009; Wu et al., 2011; Qin et al., 2012; King et al., 2016), we revealed these DMN hubs to be more connected functionally to the midbrain during subliminal, trauma-related stimulus processing as compared to healthy controls (Terpou et al., 2019a).

Since these results were very novel and had not yet been corroborated, we discussed them in the context in which they emerged and withheld any broader interpretations. Here, we suggested that the subliminal, trauma-related images may have cued reliving sensations

more strongly in PTSD as compared to healthy controls (Terpou et al., 2019a), which was supported by the greater self-reported, state reliving scores as measured by the RSDI (Hopper et al., 2007). Reliving sensations are commonly referred to as flashbacks and are a hallmark symptom related to PTSD (APA, 2013). Reliving sensations are thought to be related to the fragmented way by which trauma-related memory components are encoded and retrieved subsequently. Here, Ehlers and Clark (2000) have proposed a model whereby fragmented, trauma-related memory components and idiosyncratic, negative appraisals related to the self (e.g., 'I am inadequate') are suggested to be critical factors driving symptomatology post-trauma. According to the model, lower-level, sensory and affect-related memory components may be retrieved independently, detached from the larger context necessary to ground the memory in the past so to not relive the memory in the present. Not only are these lower-level, sensory and affect-related memory components detached from the larger context, but they are cued more easily in PTSD as well (Michael et al., 2005). Hence, enhanced perceptual priming toward the subliminal, trauma-related images may have provoked reliving sensations in participants with PTSD, where the affect-related memory component would be subserved by the midbrain, at least in theory.

Although we did not assess whole-brain activity in the paper by Terpou and colleagues (2019b), Rabellino and colleagues (2016) assessed whole-brain activity during subliminal, trauma-related stimulus processing across the same sample and revealed greater activity in the PCC and the PCN in participants with PTSD as compared to healthy controls. Interestingly, whereas the posterior parietal systems (e.g., PCC, PCN) involved in the DMN are thought to be related more so to visual imagery and self-related processing, the prefrontal systems are thought to be related more so to retrieval monitoring (Svoboda et al., 2006; St Jacques et al., 2011), a process altered more significantly in PTSD (Thome et al., 2019). Taken together, activity results by Terpou and colleagues (2019b) and Rabellino and colleagues (2016) point to enhanced reliving sensations mediated by midbrain and posterior parietal systems in PTSD, respectively. Although the mPFC did not show stronger activity, insofar that the mPFC (in addition to the PCC and the PCN) is recruited alongside the PAG during reliving more generally, we would expect the PAG to be connected functionally to the DMN. Here, the former and

the latter would be thought to mediate the affect-related, or terror-inducing and the idiosyncratic, or self-related components related to a trauma-related memory, respectively.

6.4 PERIAQUEDUCTAL GRAY DIRECTED FUNCTIONAL CONNECTIVITY IN PTSD

In Chapter 4, we sought to resolve the directionality problem related to the functional connectivity between the PAG and the mPFC, as well as between the PAG and the PCN during subliminal, trauma-related stimulus processing. Perhaps unsurprisingly, when we analyzed the directed functional connectivity (i.e., effective connectivity) between the PAG and the mPFC, as well as between the PAG and the PCN, we revealed stronger bottom-up, or PAG-mediated excitatory effective connectivity toward the mPFC and the PCN in participants with PTSD as compared to healthy controls (Terpou et al., 2020). These results were also discussed with respect to reliving sensations, which, in the present context, are revealed to be directed by the lower-level, emotive systems toward the higher-level, cognitive systems. Here, we discuss these results more so in relation to the broader functional connectivity literature, and less so in relation to how these functional connectivity patterns translate to clinical phenomenology in PTSD.

To date, only three other papers have analyzed functional connectivity related to the PAG in PTSD, and all three were conducted during rest. Firstly, Harricharan and colleagues (2016) revealed extensive functional connectivity between the dlPAG and the dorsal anterior cingulate cortex and the anterior insula in PTSD, as well as stronger functional connectivity between the vlPAG and the temporoparietal junction and the rolandic operculum in participants with PTSD who met the dissociative criteria as compared to healthy controls. Harricharan and colleagues suggested that these altered functional connectivity patterns may contribute, in part, to the proclivity toward active defenses (i.e., hyperarousal, e.g., fight, flight) and passive defenses (i.e., dissociation, e.g., freeze, tonic immobility), respectively. In PTSD, Webb and colleagues (2020) analyzed functional connectivity related to the PAG and sought to determine whether any acute, functional connectivity patterns (two weeks post-trauma) predicted symptomatology at a later time.

Critically, Webb and colleagues revealed stronger functional connectivity between the PAG and the frontal pole, as well as between the PAG and the PCC to be related positively to symptom severity six months post-trauma. Although they are not the exact same brain areas, it is interesting to note that Webb and colleagues also revealed stronger functional connectivity between the PAG and the frontal cortex, as well as between the PAG and the parietal cortex, similar to Terpou and colleagues (2019a). Lastly, Nicholson and colleagues (2017) revealed stronger bottom-up, or PAG-mediated excitatory effective connectivity toward the mPFC in participants with PTSD who were characterized primarily by hyperarousal symptomatology (as compared to dissociative symptomatology). Taken together, these results highlight the midbrain and the PAG in particular to be densely connected functionally to the cortex and to be driving these altered functional connectivity patterns during rest (Nicholson et al., 2017), as well as during subliminal, trauma-related stimulus processing in PTSD (Terpou et al., 2020). Yet, midbrain systems are rarely discussed alongside the higher-level, cognitive systems, especially the large-scale, neurocognitive networks, which are altered significantly in PTSD.

6.5 PERIAQUEDUCTAL GRAY FUNCTIONAL NETWORK CONNECTIVITY IN PTSD

In Chapter 5, we explored a different paradigm, namely script-driven, MI-related memory recall. The paradigm had yet to be characterized with respect to functional connectivity, and had only been featured once in the literature (Lloyd et al., 2020). Consequently, we used a more data-driven approach to analyze the differences between participants with civilian-related PTSD, participants with military- or public safety-related PTSD, and MI-exposed, healthy controls. In particular, we conducted an ICA and evaluated the functional network connectivity across the IC correlated most significantly to the DMN. In PTSD, critically, we revealed stronger functional network connectivity exhibited by the PAG across the DMN IC as compared to MI-exposed, healthy controls. These coordinates were remarkably similar to those reported by Terpou and colleagues (2019b) and strongly punctuate the common thread linking these papers, in particular that the

lower-level, emotive systems are not only involved in the large-scale, neurocognitive networks, but are the systems where the differences between participants with PTSD and healthy controls are represented most profoundly.

A MI does not refer to a mental disorder per se, but rather a strong response to a morally adverse event (Griffin et al., 2019). MIs occur commonly post-trauma and speak more so to the psychological, behavioural, and social aftermath from having had deeply held moral beliefs and expectations violated (i.e., moral dissonance) (Litz et al., 2009; Thompson, 2015). Shame is a prominent emotion reported after a MI (Nazarov et al., 2015; Lloyd et al., 2020), and persistent shame and self-criticism are more commonly expressed among participants with PTSD as compared to MI-exposed, healthy controls (Litz & Kerig, 2019; Zalta & Held, 2020). Some researchers have gone so far to suggest that PTSD may be best characterized as a shame disorder (Herman, 2011), or that shame serves a central role in maintaining symptomatology (Lee, Scragg, & Turner, 2001; Leskela et al., 2002; La Bash & Papa, 2014). Notably, shame has been proposed to be represented across lower-level, emotive systems as well as higher-level, cognitive systems, which interact together to create the complex emotion. Whereas lower-level, emotive systems centered on the midbrain are thought to be underlying the fast, visceral response felt during a shame-eliciting state, higher-level, cognitive systems and the DMN more namely are thought to be underlying the ruminative, self-critical thoughts that so often follow (Lanius, Paulsen, & Corrigan, 2014). We revealed very strong results to support the above (Terpou et al., in press), namely that, in PTSD, the midbrain and the PAG in particular are more strongly connected to the DMN than in MI-exposed, healthy controls, providing a neurobiological basis to explain persistent shame and avoidance-related symptomatology (mediated by the PAG) in PTSD. More broadly, these results also punctuate the common thread further, i.e., the DMN is altered significantly in PTSD and midbrain functional connectivity to the DMN seems to be a main contributor underlying these alterations (Figure 6.1). Lastly, that these results were generated using a data-driven, exploratory approach only serves to bolster their relevance. Since these results emerged without any strong *a priori* assumptions, we are confident that further inquiry will support the presented findings.

6.6 LIMITATIONS AND FUTURE DIRECTIONS

Before we conclude, we have flagged a few general limitations to consider. Firstly, although we have demonstrated elevated functional connectivity and directed functional connectivity between the PAG and the DMN, these patterns have been revealed using fMRI only, which records brain activity indirectly by reference to a hemodynamic response function. Hence, we cannot speak to how the interplay arises between these networks, only to general directionality. If we were to speculate, we would suspect glutamatergic, serotonergic, cholinergic and noradrenergic modulatory neurotransmission directed by the PAG toward the cortex may be underlying these patterns. Glutamate aside, these neurotransmitters are modulatory in nature and are represented densely across the PAG, with neurotransmission directed diffusely across the cortex and especially toward the mPFC (Silva & McNaughton, 2019). Secondly, we remind readers that these patterns were elicited during subliminal, trauma-related stimulus processing and script-driven, MI-related memory recall, i.e., not during rest. In PTSD, reduced functional connectivity across the DMN has been revealed extensively during rest. We wanted to discuss these results in regard to the context by which they emerged. However, these results may speak to the reduced functional connectivity across the DMN while at rest in PTSD more generally, albeit indirectly. Many researchers have suggested the PAG to be involved in the ascending reticular activating system (ARAS), a network comprised by brainstem and midbrain structures which drive cholinergic and noradrenergic neurotransmission toward the cortex (Magoun, 1952; Yeo et al., 2013). Here, the ARAS has been suggested to up-regulate arousal, which generally leads to an increase and a decrease in activity across the salience network and the DMN, respectively. Given the interplay between the ARAS and the salience network, overactivity across the PAG would be thought to suppress the DMN in a protracted manner, perhaps leading to a breakdown in the equilibrium between the intrinsic connectivity networks more broadly, which has been revealed in PTSD previously (Daniels et al., 2010; Sripada et al., 2012). Thirdly, comorbid disorders are often present in PTSD. In the samples we included, depression and past alcohol abuse scores were generally higher in the PTSD groups than the healthy controls, which added variability to the PTSD groups. Past alcohol abuse may

be a concern particularly, since alcohol-related neurotoxicity has been related to reduced functional connectivity (Hertling et al., 2011; Wang et al., 2016). However, we wanted the PTSD groups to represent the PTSD population at large. Hence, comorbid disorders were permitted (and added as a covariate wherever possible). Fifthly, subliminal fearful and neutral faces were not assessed in the functional connectivity or directed functional connectivity analyses. Since these stimulus conditions did not elicit any significant group differences in activity, we did not include them in follow-up analyses. However, we acknowledge fear-related stimulus processing – similar to trauma-related – do reveal differences in activity across the IAS in PTSD and hence may warrant future inquiry. Lastly, we used the default hemodynamic response function invariably. Given the challenges when imaging brainstem and midbrain structures, we encourage future research to try varying hemodynamic response functions.

In addition to addressing the above limitations, we encourage future research to assess functional connectivity patterns between the midbrain systems and the DMN related to the dissociative subtype. We did not have a large enough sample size to permit such investigation, but recent research has demonstrated altered structural connectivity patterns in participants with PTSD who meet the dissociative subtype criteria as compared to participants with PTSD who do not meet the dissociative subtype criteria (Sierk et al., 2021). In particular, whereas participants with PTSD who met the dissociative subtype criteria revealed stronger structural connectivity (i.e., fractional anisotropy) between the ventral diencephalon with the pallidum and the putamen, participants with PTSD who did not meet the dissociative subtype criteria revealed stronger functional connectivity across fear and memory-related structures, including the amygdala, the hippocampus and the thalamus. These results may explain, in part, why participants who meet dissociative subtype criteria do not have strong re-living symptoms. Rather, dissociative symptomatology may be largely represented across brainstem and midbrain systems, where Sierk and colleagues suggest altered structural connectivity across these low-level, motor-related structures may be underlying passive defense responses expressed more commonly during dissociation, such as tonic immobility. In rodent work, we encourage future research to leverage optogenetic technology to reveal which PAG-mediated modulatory neurotransmitters directed toward

the mPFC are most implicated in PTSD-homologous symptomatology, like chronic avoidance and depression. Optogenetics may be used to selectively activate or inhibit PAG-mediated glutamatergic, serotonergic, cholinergic and noradrenergic neurotransmission toward the mPFC during paradigms thought to precipitate symptoms related to PTSD, such as an inescapable foot-shock paradigm, which reliably generates learned helplessness in rodents, a behavioural phenotype commonly associated with depression (Silva & McNaughton, 2019). These endeavors may be critical to reveal how PAG-mediated neurotransmission drives various symptoms, as well as the pathophysiology underlying PTSD more generally.

6.7 CONCLUSIONS

In the introduction, we made the claim that the current cortico-centric models that predominate mental health research need to be updated to include lower-level, emotive systems. Here, we have made a strong case that the midbrain and the PAG are not only involved in the DMN in PTSD, but are the systems where differences are revealed most strongly as compared to healthy controls. These results strongly support clinical research related to self-related processing in PTSD and grant a neurobiological basis to interpret the intrinsic links between self- and trauma-related processing observed often post-trauma(s). These results are relevant therapeutically as well, where we recommend a more integrated approach to psychotherapy, combining top-down and bottom-up (e.g., yoga, sensory-motor therapy, deep brain reorienting, expressive arts) approaches. Effectively, top-down and bottom-up approaches may prepare the client to be more aware of the process by which thoughts emerge and distort cognition while also reacquainting the client to the body and the visceral signals underlying symptoms, respectively. Over time, a more integrated approach to psychotherapy may reduce the influence the midbrain has on the DMN, which may reinstate a healthy, self-identity in the aftermath of trauma.

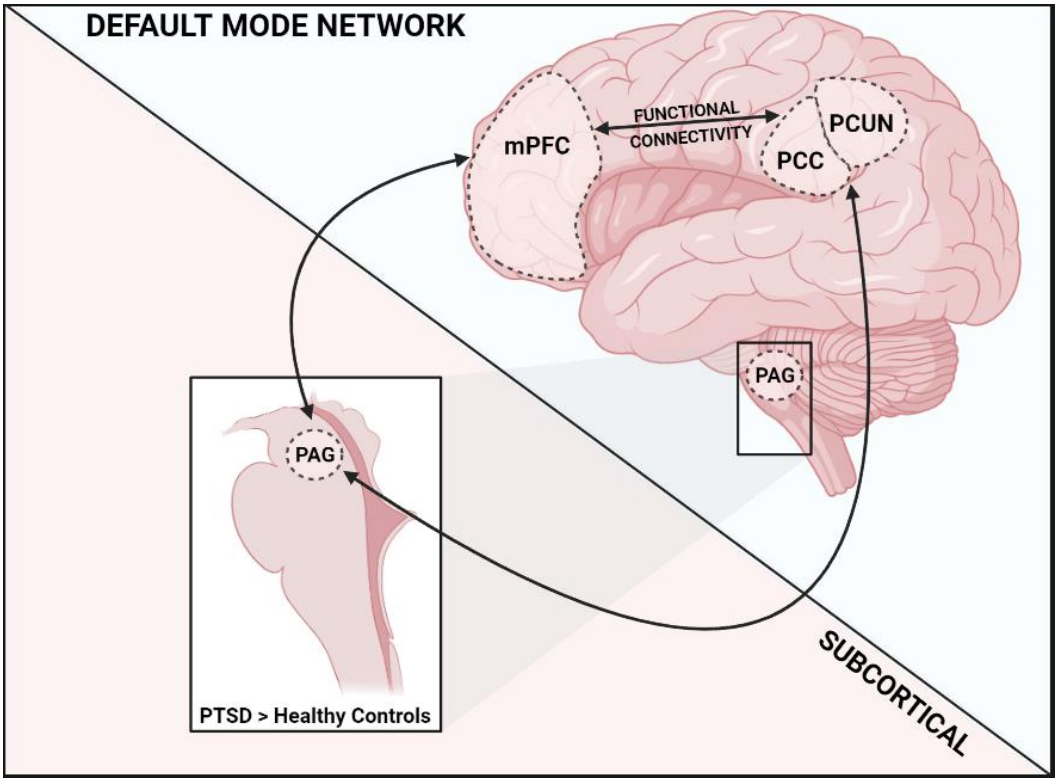

FIGURE 6.1: *SUMMARY FIGURE*

In PTSD, the midbrain and the PAG are connected functionally to the DMN, a network underlying self-related processing and autobiographical memory processing. These altered functional connectivity patterns map well onto the clinical symptomatology observed commonly in PTSD.

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APPENDICES

APPENDIX A: SUPPLEMENTARY MATERIAL (CHAPTER 3)

Whole-Brain Functional Data Preprocessing

All images were analyzed using Statistical Parametric Mapping (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK: http://www.fil.ion.ucl.ac.uk/sp) within MATLAB 9.2 (R2017a, MathWorks Inc., MA). Firstly, functional images for each participant were realigned to the first volume of the session to correct for movement during scanning. During realignment, a mean functional image was created for each subject, which was used to co-register the T1-weighted anatomical image so to align subject-specific BOLD signals within their anatomical space. All volumes were spatially normalized (2 x 2 x 2 mm^3) to an EPI in MNI space through the application of a deformation matrix. At this time, an ART regressor, which accounts for effects of movement and global signal correction (version 2015-10; Gabrieli Lab, McGovern Institute for Brain Research, Cambridge, MA), was generated for subliminal and supraliminal presentation sessions. Default thresholds for the outlier detection in the ART regressor were selected (global signal threshold = 9.0 mm, absolute subject motion threshold = 2.0 mm, rotational threshold = .05 mm, scan-to-scan subject motion = 2.0 mm, and scan-to-scan subject rotation = .02 mm). Finally, functional images were then smoothed via a three-dimensional isotropic 8 mm full-width at half-maximum Gaussian kernel and a high-pass filter was applied to reduce data low-frequency noise.

SUIT-Space Functional Data Preprocessing

To improve the normalization procedure and receive a clearer depiction of midbrain, lower brainstem, and cerebellar activation, data were also normalized to the spatially unbiased infra-tentorial template (SUIT). The SUIT toolbox offers a high-resolution atlas template of the cerebellum and brainstem with improved voxel-by-voxel normalization of fMRI. The SUIT toolbox functions on SPM12 within MATLAB 9.2 and contains several preprocessing steps. Firstly, anatomical images were reoriented in SPM where the horizontal plane was defined approximately according to the AC-PC line. Secondly,

functional images were reoriented to correspond to the reoriented anatomical image. Thirdly, subject-specific functional volumes were realigned to the first volume of each session to correct for movement in the scanner and then resliced to a voxel size of 2 x 2 x 2 mm^3. At this time, six realignment parameters for changes in motion across the different planes and an ART regressor for global movement correction were saved for each participant. Fourthly, subject-specific brainstem and cerebellum were isolated and cropped from the T1-weighted anatomical images in order to focus on the infra-tentorial structures of interest. Fifthly, individual cropped anatomical images of the brainstem and cerebellum were normalized into the SUIT atlas template. During this step, a subject-specific transformation matrix was generated for the linear part of the normalization that deforms each cerebellum to provide optimal correspondence to the SUIT template. Sixthly, functional volumes were resliced into SUIT-space in order to align functional images with the SUIT-normalized anatomical images by applying the subject-specific transformation matrix. Lastly, a three-dimensional isotropic 4 mm full-width at half-maximum Gaussian kernel was applied to each set of SUIT-resliced functional data to smooth the data in accordance with previous methods using SUIT preprocessing measures.

APPENDIX B: SUPPLEMENTARY MATERIAL (CHAPTER 4)

Figure S4.1

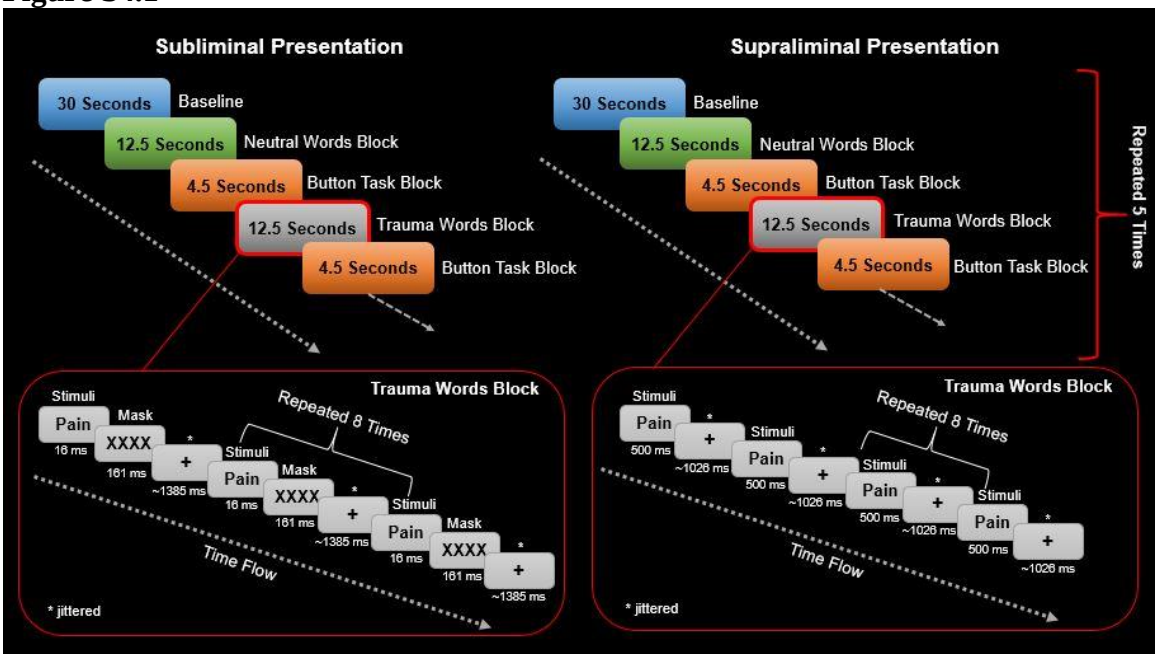

Figure S4.1: The above figure illustrates the subliminal-supraliminal threat presentation paradigm. Stimuli have a subliminal and a supraliminal display over two consecutive sessions that are separated by a two-minute rest period and are counterbalanced across subjects. Stimuli include both threat and neutral cues presented in a pseudo-randomized block design (i.e., pseudo-randomized since neutral words do not follow trauma-related or fearful stimuli). Each presentation block is repeated five times in a fixed order. Blocks consist of eight repetitions of stimuli with either a subliminal or a supraliminal display. Subliminal stimuli are presented for 16 ms and are separated by a jittered inter-stimulus interval varying in duration from 823 to 1823 ms and are followed by a backward mask. Supraliminal stimuli are presented for 500 ms and separated by a jittered inter-stimulus interval of 500 to 1500 ms. A button press task is implemented between blocks to ensure sustained attention throughout the fMRI scanning session. Finally, each run is preceded by a 30-second rest period that is used as an implicit baseline for subsequent statistical analyses.

Whole-Brain Functional Data Preprocessing

All images were analyzed using Statistical Parametric Mapping (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK: http://www.fil.ion.ucl.ac.uk/sp) in MATLAB 9.2 systems (R2017a, MathWorks Inc., MA). Firstly, functional images for each participant were realigned to the first volume of the session to correct for movement during scan. During realignment, a mean functional image was created for the subject, which was then used to co-register the T1-weighted anatomical image so to align subject-specific BOLD

signals within their proper anatomical space. Volumes were then spatially normalized (2 x 2 x 2 mm^3) to an EPI in MNI space via application of a deformation matrix. At this time, an ART regressor, which accounts for effects of movement as well as global signal correction (version 2015-10; Gabrieli Lab, McGovern Institute for Brain Research, Cambridge, MA), were generated for both the subliminal and the supraliminal stimulus conditions. Default thresholds for the outlier detection in the ART regressor were selected (global signal threshold = 9.0 mm, absolute subject motion threshold = 2.0 mm, rotational threshold = .05 mm, scan-to-scan subject motion = 2.0 mm, and scan-to-scan subject rotation = .02 mm). Finally, functional images were then smoothed via a three-dimensional isotropic 8 mm full-width at half-maximum Gaussian kernel and a high-pass filter was applied to reduce data low-frequency noise.

SUIT-Space Functional Data Preprocessing

To receive a clearer depiction of brainstem, midbrain, and cerebellar activation, data were normalized to the spatially unbiased infra-tentorial template (SUIT). The SUIT toolbox offers a high-resolution atlas template of the cerebellum and the brainstem with improved voxel-by-voxel normalization of fMRI. The SUIT toolbox is used within SPM12 in MATLAB 9.2 and contains several preprocessing procedures. Firstly, anatomical images were reoriented in SPM, where the horizontal plane is defined according approximately to the AC-PC line. Secondly, the functional images were reoriented to correspond to reoriented anatomical images. Subject-specific functional volumes were then realigned to the first volume of each session to correct for movement in the scanner and were then resliced to a voxel size of 2 x 2 x 2 mm^3. Six realignment parameters were generated to account for changes in motion across the different planes and an ART regressor for global movement correction was saved for each subject. Next, subject-specific brainstem and cerebellums were isolated and then cropped from the T1-weighted anatomical images in order to focus on the infra-tentorial structures of interest. Individual cropped anatomical images of the brainstem and the cerebellums were then normalized to the SUIT atlas template. Subject-specific transformation matrices were generated for the linear part of the normalization that deforms each cerebellum to provide optimal correspondence to the SUIT template. Lastly, functional volumes were resliced into

SUIT-space so to align functional images with the SUIT-normalized anatomical images by applying subject-specific transformation matrices. A three-dimensional isotropic 4 mm full-width at half-maximum Gaussian kernel was applied to then smooth SUIT functional images.

Proportion of Censored Volumes

Using the outlier detection of the ART regressor, the number of censored volumes for each participant were tallied with respect to the study group (see Table S4.2).

Table S1: PROPORTION OF CENSORED VOLUMES

Controls		PTSD	
Subject	Censored Volumes ART Regressors	Subject	Censored Volumes ART Regressors
8003	0	8001	0
8005	3	8002	0
8010	0	8004	0
8012	17	8006	3
8015	0	8007	0
8016	15	8008	0
8017	0	8009	0
8020	0	8011	0
8021	0	8013	0
8026	0	8014	0
8028	0	8018	0
8038	0	8019	0
8039	0	8023	0

8040	0	8024	0
8042	11	8025	6
8046	15	8027	0
8047	0	8029	17
8048	0	8030	0
8050	0	8032	24
8052	0	8033	0
		8034	2
		8035	0
		8041	11
		8044	16
		8049	0
		8051	0
Total	**61**	**Total**	**79**

Eigenvariate Extraction Specifications

Eigenvariates were extracted using the SPM GUI from the bulleted coordinates at a cluster-level extent threshold of $k > 5$ and a significance threshold of $p(\text{uncorrected}) < .05$:

- PAG ([x: 0; y: -32; z: -11 (mm)]; sphere size: 6 mm)
- PCN ([x: 6; y: -52; z: 30 (mm)]; sphere size: 8 mm)
- mPFC ([x: 0; y: 60; z: -2 (mm)]; sphere size: 8 mm)

Extracted time series were permitted to vary from these coordinates and were inspected individually to assure that relocated volumes-of-interest (VOIs) remained in the proper anatomical location. Whereas a ± 2 mm variation in each coordinate plane was

allowed for the PAG, a ± 3 mm variation in each coordinate plane was allowed for the PCN and the mPFC. Smaller sphere sizes and variations were used for the PAG to account for the size of the structure and to limit the potential signal interference of neighbouring midbrain structures. We wanted to obtain the raw values of the segmented functional data for each participant. Finally, extracted time series were inspected individually to assure that the % variance explained by all the eigenvariates surpassed 75% variance explained and each VOI had greater than 15 voxels contributing to the time series.

Psycho-Physiological Interaction General Linear Model (GLM) Output

Eigenvariate locations and coordinates were identified with reference to a previous study conducted by Terpou et al. (2019a) on the same participant sample and paradigm. Here, Terpou et al. conducted a psycho-physiological interaction on the time series of the PAG to reveal brain regions that demonstrated functional connectivity with the PAG. Group differences in functional connectivity were compared between participants with PTSD and controls, where, in PTSD, the PAG was revealed to display significantly stronger functional connectivity with the PCN and the mPFC as compared to controls. These group differences were displayed with respect to a stimulus contrast that subtracted signal of subliminal, neutral stimulus conditions from subliminal, trauma-related stimulus conditions. Output for this particular contrast from the GLM can be found below:

TABLE S4.2: Psycho-Physiological Interactions of the Periaqueductal Gray

Contrast	Region	*k*	*p*(FWE-cor)	*z*	MNI Coordinates		
					x	*y*	*z*
Subliminal TW > NW (WB)							
Control	None						
PTSD	Superior Frontal Gyrus	871	.003	5.46	-2	60	12
	Angular Gyrus	172	.021	5.05	54	-58	34
Control > PTSD	None						
PTSD > Control	None						

Subliminal TW > NW (DMN ROI)							
Control	None						
PTSD	Superior Frontal Gyrus	689	.001	5.46	-2	60	12
	Medial Prefrontal Cortex	Of 689	.001	5.04	0	60	-2
	Precuneus	420	.017	4.38	2	-52	32
Control > PTSD	None						
PTSD > Control	Superior Frontal Gyrus	372	.003	4.75	0	60	-2
	Medial Prefrontal Cortex	Of 372	.007	4.55	-2	60	12
	Precuneus	192	.025	4.21	6	-52	30
	Anterior Cingulate Gyrus	69	.029	4.18	0	46	20

Parametric Empirical Bayes: Bayesian Model Reduction

Parametric empirical Bayes (PEB) were utilized to assess group-level model connectivity within a Bayesian framework. In PEB, the random-effects are the parameters included in a given model as opposed to the models themselves, where subjects are assumed to have the same model architectures across participants. We selected the bi-directional model and conducted a Bayesian model reduction (BMR) analysis to search over nested models. Objectives of BMR are to 'prune' away model parameters that do not contribute to model evidence via an iterative search referred to as a greedy search. BMR evaluates thousands of nested models quickly and efficiently and stops when discarding model parameters further decreases the model evidence. Hence, BMR evaluates each parameter's individual probability by comparing the evidence for all the models that had the parameter included versus all the models that did not have the parameter included after the search.

Moreover, PEB requires the specification of a design matrix to be regressed across model parameters that are included in our bi-directional model. In BMR, whereas columns that designate group membership were mean-centered in our design matrix, the columns that

represent subject-specific clinical and behavioural scores were not mean-centered in the analyses.

Results

Two parameters contributed to between-group differences in effective connectivity from the BMR analysis. Whereas our model parameter for the endogenous connection from the PAG to the mPFC had greater than 95% chance of being present following the final iteration of the BMR, the model parameter from the modulatory connectivity from the PAG to the mPFC during the subliminal, trauma-related stimulus conditions had greater than 99% of being present after BMR.

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