REM Sleep is Associated with Neuromelanin-Sensitive MRI Signal in the Locus Coeruleus in Veterans with a History of Post-Traumatic Stress Disorder

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Abstract

Post-traumatic stress disorder (PTSD) is a psychiatric condition caused by exposure to a traumatic event. Veterans are at especially high risk of PTSD. In Canada, in a survey conducted in 2016, 16% of Regular Force Veterans released during 1998-2015 reported having PTSD, which is at least two times higher than the estimated prevalence rate in the general population. Individuals with PTSD experience a range of debilitating symptoms, such as the intrusion of unwanted and distressing memories, persistent flashbacks, hypervigilance and nightmares. The neuropathophysiological mechanisms underlying symptoms of PTSD are not well understood, which remains a significant barrier to developing effective treatments. Hallmark PTSD symptoms such as hyperarousal and sleep disturbances may be related to dysregulation of noradrenaline (NA), a neurotransmitter produced in the locus coeruleus (LC) known to modulate cognition, arousal and sleep. This thesis examines the possible associations between dysregulation in rapid-eye-movement (REM) sleep and dysfunction in NA-containing neurons in the LC among veterans with PTSD. Twenty-two operationally deployed veterans with a history of PTSD were recruited through the Royal Ottawa Mental Health Centre in Ontario, Canada. A novel, non-invasive neuroimaging method, neuromelanin-sensitive magnetic resonance imaging (NM-MRI), was used to detect a by-product of NA called neuromelanin (NM) in the LC of each participant. Then a contrast-to-noise ratio (CNR) was calculated to obtain a marker of the NA function. The LC was segmented into three subdivisions to assess whether the association between NM and REM sleep may differ across regions of the LC. As hypothesized, we observed different associations between NM and REM sleep across regions of the LC. After controlling for antidepressant usage, there was (i) a moderate, negative, significant correlation between the

percentage of REM sleep and rostral LC_{CNR}, $r(19) = -.476$, $p = .029$, (ii) a weak positive non-significant correlation between the percentage of REM sleep and caudal LC_{CNR}, $r(19) = .33$, $p = .145$, and (iii) no significant correlation between REM sleep percentage and LC_{CNR} in the middle LC, $r(19) = -.04$, $p = .876$. This thesis is the first study to show that NM and REM sleep may be related in veterans with PTSD and that this relationship may vary across subdivisions of the LC. These results improve understanding of REM sleep among individuals with PTSD. The results may stimulate the investigation of novel pharmacotherapy focused on sleep disturbances in PTSD, the development of personalized treatments for PTSD, and the search for clinical biomarkers of PTSD based on brain function. The current study also made methodological contributions that may be applicable beyond the research on PTSD to the field of REM sleep and the NA system. Specifically, the current study showed the suitability of the NM-MRI method for examining the connections between NM and REM sleep, and it showed that segmenting the LC can lead to a more nuanced understanding of its role in the human body.

Keywords: Post-traumatic stress disorder, rapid-eye-movement sleep, noradrenaline, neuromelanin, neuromelanin-sensitive magnetic resonance imaging, locus coeruleus, caudal locus coeruleus, middle locus coeruleus, rostral locus coeruleus

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"Everything is, in reality, good, or in itself good, or good in respect of its results."

Said Nursi (*The Letters*, p.437)

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List of Abbreviations

NREM – Non-Rapid Eye Movement

REM – Rapid Eye Movement

EEG – Electroencephalogram

PSG – Polysomnography

LC – Locus Coeruleus

SubC – Locus Subcoeruleus

NA – Noradrenaline

NE – Norepinephrine

NM – Neuromelanin

NM-MRI – Neuromelanin-sensitive Magnetic Resonance Imaging

CNR – Contrast-to-Noise Ratio

Chapter 1: Introduction

Post-traumatic stress disorder (PTSD) is a psychiatric condition caused by exposure to a traumatic event, such as war. Individuals with PTSD experience a range of debilitating symptoms, such as the intrusion of unwanted and distressing memories, persistent flashbacks, hypervigilance, and nightmares. Increased irritability, trouble concentrating, and disturbed sleep commonly occur in PTSD. Additionally, individuals with PTSD have a higher risk of experiencing comorbid conditions, such as depression and anxiety, and an increased risk of suicide (Fox et al., 2021; Stevens et al., 2013). Military members and veterans are at increased risk for developing PTSD. This is because members of the armed forces risk exposure to life-threatening stressors, such as combat, injury, and witnessing suffering and death (Inoue et al., 2021; Xue et al., 2015). It has been reported that 3–17% of members of the armed forces develop PTSD in the first year after deployment (Engelhard et al., 2007; Richardson et al., 2010). In Canada, according to a survey conducted in 2013, 13% of Regular Force Veterans who retired between 1998 and 2012 had PTSD, which was significantly higher than the prevalence of PTSD in the general population (1.3%), even after controlling for demographic differences between military and non-military members (Thompson et al., 2016). In a recent survey conducted in 2016, the prevalence of PTSD among Regular Force Veterans who retired between 1998 and 2015 was even higher, at 16.4% (VanTil et al., 2017). Despite these studies showing an increase in the prevalence rate of PTSD among veterans over time, the neuropathophysiological mechanisms underlying symptoms of PTSD are not well understood. Since noradrenaline (NA[1]) mediates rapid-eye-movement (REM) sleep (Ranjan et al., 2010) and is involved in REM sleep

[1] Noradrenaline is also known as norepinephrine.

regulation (Gottesmann, 2008), REM sleep and NA are relevant candidates for investigating neuropathological mechanisms of PTSD (Nollet et al., 2020; Sherin & Nemeroff, 2011). This thesis investigates the possible associations between dysregulation in REM sleep, dysfunction in NA-containing neurons in the LC, and dysfunction in neurons in the subcoeruleus (SubC) among veterans with PTSD. More specifically, this thesis examines the potential involvement of neuromelanin (NM)—a by-product of NA—in REM sleep among veterans with PTSD using NM-sensitive Magnetic Resonance Imaging (NM-MRI), which is a marker of NA function (O'Callaghan et al., 2021).

The remainder of this introduction is organized as follows. First, the main diagnostic criteria and primary features of PTSD are described. Second, an overview of the sleep profile of PTSD is provided, with an emphasis on REM sleep abnormalities. Third, the involvement of NA in symptoms of PTSD is described. Fourth, the relationship between REM sleep and NA-containing neurons in the LC is reviewed. Fifth, it is proposed that NM may be involved in the relationship between REM sleep and LC functions among veterans with PTSD. Finally, NM-MRI is presented as an effective method for detecting dysfunction in the LC-NA system to better understand some of the common pathophysiology underlying PTSD and REM abnormalities.

Diagnostic Criteria and Symptomatic Profile of PTSD

The sections below present the diagnostic criteria and symptomatic profile of PTSD, focusing on the symptoms that relate most closely to the current thesis.

Diagnostic Criteria of PTSD

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM–5), individuals six years and over must meet the following eight criteria for a diagnosis of PTSD (American Psychiatric Association, 2013). Below is a slightly shortened version of the requirements for a diagnosis of PTSD in the DSM-5. Appendix A contains further details on each of these criteria.

A. Exposure to actual or threatened death, serious injury, or sexual violence.
B. Presence of intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred.
C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred.
D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred.
E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred.
F. Duration of the disturbance (Criteria B, C, D and E) is more than one month.
G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
H. The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.

Symptomatic Profile of PTSD

PTSD is a complex disorder influenced by multiple interacting factors. It stems from an abnormal response to a traumatic event(s), which triggers a cascade of physiological, cognitive, and psychological dysfunctions.

A key feature of PTSD is the dysregulation of the stress system leading to increased autonomic activation and hyperarousal. Autonomic activation refers to an increase in the activity of the autonomic nervous system, which is the system that is responsible for regulating bodily functions and the body's fight-or-flight response. Hyperarousal refers to a heightened physiological and psychological arousal (Weston, 2014). Individuals who experience hyperarousal describe feeling like they are constantly "on guard," which interferes with daily functioning. Even when the threats of their traumatic events are no longer present, individuals with PTSD continue to experience bodily responses as if the threats were still there.

Abnormal cortisol levels notably reflect increased autonomic activation and hyperarousal, elevated blood pressure and heart rate, reduced heart rate variability, faster breathing rate, increased skin conductance and abnormal temperature regulation (Bremner et al., 2003; Bryant et al., 2008; Cohen et al., 1997; Rissling et al., 2016; Yehuda et al., 1996). In addition, autonomic activation and hyperarousal may also interfere with one's ability to fall asleep and stay asleep and with the phenomenology of bad dreams and nightmares, which are common features of PTSD. In turn, sleep disturbances, bad dreams, and nightmares may worsen autonomic system dysfunctions and hyperarousal in PTSD (Oliver et al., 2019; Richards et al., 2020; Tanev et al., 2017) and may thus modulate the physiological and psychological profile linked to PTSD.

Cognitively, PTSD may result from overactive memories surrounding the traumatic event (Rubin et al., 2008). Difficulties with forming new memories, processing speed, attention and

higher mental skills, such as executive functions, have also been noted in PTSD (Jelinek et al., 2006; Polak et al., 2012; Twamley et al., 2009; Uddo et al., 1993). These disabling cognitive difficulties may result partly from several abnormalities in brain functions observed using electroencephalography (EEG) and MRI.

Indeed, evidence from MRI studies suggests that people with PTSD may exhibit structural and functional alterations, notably in some brain regions implicated in fear memory expression and consolidation, such as the amygdala, medial prefrontal cortex and hippocampus (Karl et al., 2006; Kitayama et al., 2005; Nardo et al., 2013; Rauch et al., 2003; Shin et al., 2006; Smith, 2005; Tomoda et al., 2009; Van Harmelen et al., 2010; Woon et al., 2010). A post-mortem study also unveiled reduced volumes of neuromelanin-containing cells in the locus coeruleus in people with PTSD (Bracha et al., 2005). The LC is the region where noradrenergic cell bodies are located. NA is a critical neurotransmitter in learning and stress responses (Aston-Jones et al., 1994; Naegeli et al., 2018). Recent techniques now enable the quantification of neuromelanin in-vivo (Cassidy et al., 2019; Chen et al., 2014; Sasaki et al., 2006; Shibata et al., 2007; Sulzer et al., 2018), but this needs to be further investigated in PTSD.

Furthermore, neurochemical abnormalities, such as increased glutamate in the hippocampus and prefrontal cortex (Popoli et al., 2012; Reul & Nutt, 2008), may also relate to REM sleep abnormalities in PTSD. For instance, it has been suggested that reduced prefrontal activation in PTSD may lead to maladaptive REM-dependent processing of traumatic memories (Murkar & De Koninck, 2018).

At the psychological level, PTSD often co-occurs with other mental disorders, especially major depression, characterized by a consistently low mood and a loss of interest in daily activities, among other symptoms (Price et al., 2019; Young et al., 2014). Approximately 50% of

individuals with PTSD also experience clinical depression (Rytwinski et al., 2013). Individuals with PTSD are also more at risk of anxiety disorders, substance use disorders, and other health-related conditions (Brady et al., 2000). From this perspective, it is essential to adjust for comorbid depression in analyses focused on PTSD.

Sleep and PTSD

Poor sleep quality and disturbances have long been considered hallmarks of PTSD (Germain et al., 2004, 2008; Lamarche & De Koninck, 2007). Individuals with PTSD report experiencing difficulties falling asleep, difficulties staying asleep (e.g., frequent and/or early morning awakenings), regular and persistent nightmares, and other parasomnias (Ohayon & Shapiro, 2000). They also experience anxiety, hyperarousal, and more body movements during sleep (Inman et al., 1990). Such sleep disturbances are core features of PTSD, regardless of patient-related characteristics such as gender or age, other disorder-related characteristics such as type of trauma or severity of PTSD, and psychiatric comorbidity (Germain et al., 2004). Nightmares, a phenomenon occurring most commonly during REM sleep, are often linked to intrusions of traumatic flashbacks in the oneiric content and are closely related to physiological arousal, as reflected notably by increased heart rate, disrupted respiration and sweating (Phelps et al., 2018). From this perspective, their involvement in PTSD symptomatology is not that surprising.

Sleep disturbances are often resistant to first-line treatments of PTSD, such as selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioural approaches such as exposure-based and cognitive therapy (Ballenger et al., 2000; Germain et al., 2008; “The Expert Consensus Guideline Series. Treatment of Posttraumatic Stress Disorder. The Expert Consensus Panels for PTSD.,” 1999). Sleep disturbances significantly impair daily functioning and diminish

the quality of life (Baglioni et al., 2016; Evren et al., 2011; Warshaw et al., 1993). In addition, they cause an accumulation of sleep debt over time, which further harm physical and mental health and overall well-being. Even among healthy individuals, sleep loss increases irritability and neurophysiological responses to emotional stimuli (Boivin et al., 1997; Walker, 2009). Among individuals with PTSD, even after controlling for the presence of other psychiatric disorders, sleep quality explains a significant portion of the variance of PTSD symptom severity and mental health (Belleville, Guay, & Marchand, 2009). These findings indicate that the poorer sleep quality an individual has, the more symptoms of PTSD and mental health issues they experience.

During sleep, individuals cycle through four distinct stages. Three of these stages are referred to as non-rapid eye movement (NREM) sleep, increasing in depth from stage N1 to stage N3. Another stage is referred to as REM sleep. REM sleep is defined by the presence of desynchronized (low-voltage, mixed-frequency) electroencephalographic activity, muscle atonia, and bursts of rapid eye movements (Carskadon & Dement, 2005). It is characterized by more structured and vivid dreams, and is involved in memory consolidation (for a review of sleep and memory consolidation, see (Frazer et al., 2021), especially in emotional memory (Diekelmann et al., 2009; Stickgold & Walker, 2007). It also has significant implications that could lead to life-threatening situations. For example, compared with non-suicidal individuals, suicidal individuals averaged a shorter REM sleep latency and a higher REM percentage (Agargun & Cartwright, 2003).

Even though individuals with PTSD report experiencing significant sleep disturbances, the results of polysomnographic (PSG) studies have been mixed. In a recent meta-analysis of 31 studies, Zhang and colleagues (Zhang et al., 2019) observed that individuals with PTSD exhibit

PSG abnormalities. Specifically, compared to healthy controls, individuals with PTSD experience decreased total sleep time, slow-wave sleep and sleep efficiency, and increased wake time after sleep onset. They also found that reduced sleep efficiency and slow-wave sleep percentage are associated with the severity of PTSD as measured by the Clinician-Administered PTSD Scale (CAPS).

Results regarding the duration and percentage of REM sleep have been mixed. Some studies have reported longer REM sleep time among individuals with PTSD than those without PTSD (Nielsen et al., 2005) and a higher percentage of REM sleep among combat veterans with PTSD than combat veterans without PTSD (Engdahl et al., 2000; Germain, 2013). However, other studies have reported lower percentages of REM sleep among individuals with PTSD than healthy controls or no significant group differences. In a meta-analysis, Zhang et al. (2019) found that differences in REM sleep percentage between people with PTSD and healthy controls were significantly associated with the mean age of participants with PTSD. They found that individuals with PTSD have significantly decreased REM sleep percentage compared to healthy controls in studies of participants with mean age under 30 years. They found no between-group difference in studies of participants with a mean age above 30 years. Zhang et al. (2019) did not find between-study differences in the relationship between REM sleep percentage, REM sleep density, or REM sleep latency and PTSD based on the sex distribution of study participants. In addition to differences in duration and percentage of REM sleep, individuals with PTSD also often experience other indices of increased REM sleep pressure, such as increased REM density, compared to individuals without PTSD (Baglioni, Nanovska, et al., 2016; Kobayashi et al., 2007; Lanius et al., 2017; Nielsen et al., 2005). Such patterns have also been observed among combat veterans (Thompson et al., 2016). Compared to combat veterans without PTSD, combat veterans

with PTSD have lower perceived sleep quality, including awakenings and restless sleep, and a higher percentage of REM sleep (Engdahl et al., 2000; Germain, 2013). Therefore, it is essential to study REM sleep and the underlying factors affecting it and PTSD symptomatology.

NA and PTSD

It has been suggested that PTSD symptomatology may be related to the dysregulation of NA. NA is a neurotransmitter supplied by a small, bilateral nucleus in the brainstem called the LC; the LC also regulates the amount of NA in the forebrain. NA is important for modulating some cognitive processes, arousal, and sleep (Berridge et al., 2012; Berridge & Waterhouse, 2003b; Matosevich & Nir, 2021). Thus, some distinguishing characteristics of PTSD, such as cognitive difficulties and increased hyperarousal, with related sleep disturbances and REM abnormalities, such as nightmares, might be influenced by the dysregulation of NA. Indeed, while the literature in this area is still emerging, there are indications that NA is involved in PTSD symptomatology (Betts et al., 2019; Geracioti et al., 2001; Hendrickson & Raskind, 2016, 2018; Strawn et al., 2004; Strawn & Geracioti, 2008). For example, individuals with PTSD have higher levels of NA in their cerebrospinal fluid (compared to individuals without PTSD), and their levels of NA are strongly correlated with the severity of their hyperarousal and sleep symptoms (D. G. Baker et al., 2001; Geracioti et al., 2001). In animal studies using EEG recordings, pharmacologically decreasing LC activity has been found to lower arousal and pharmacologically increasing LC activity has been found to increase arousal (Berridge et al., 1996; Berridge & Foote, 1991).

Furthermore, there is evidence that Prazosin, an NA α1 receptor antagonist, reduces nightmares, increases total sleep time, and increases REM sleep in veterans and civilians with

PTSD (for a review, see (Reist et al., 2020). However, some studies on Prazosin did not find significant benefits for individuals with PTSD, so the American Academy of Sleep Medicine (AASM) downgraded the use of Prazosin in a position paper (Morgenthaler et al., 2018). This might be because individuals with PTSD experience a range of symptoms, and Prazosin might be beneficial only for alleviating symptoms relating to hyperarousal and sleep-wake cycle dysregulation. As such, in a meta-analysis of eight studies, patients with PTSD taking Prazosin showed statistically significant relief from nightmare symptoms compared to the placebo group but not for the overall PTSD symptoms (Zhang et al., 2020). More generally, some researchers have theorized that the LC-NA system might be especially essential for PTSD symptomatology characterized by hyperarousal and sleep-wake cycle dysregulation rather than all clusters of PTSD symptoms (Germain et al., 2012; Hendrickson et al., 2021; Raskind et al., 2018).

LC neurons affect daily functioning since they are crucial in arousal, stress, and cognitive processes. For example, LC neurons modulate individuals' arousal and alertness in response to threats and stressors (Morris et al., 2020); regulate sleep-wake functions (Grimm et al., 2004); help to maintain focus during tasks (Aston-Jones & Cohen, 2005); and promote long-term potentiation (Poe et al., 2020), which is the building block of memory. The "innate alarm system" (IAS), a subcortical brain network (including the brainstem and amygdala), is thought to be involved in detecting subconscious and conscious threats to facilitate rapid threat response (Lanius et al., 2017). Dysfunctions in the IAS are believed to contribute to hyperarousal symptoms (Lanius et al., 2017). Historically, it was thought that the amygdala controls threat responses (fight-or-flight) in individuals with PTSD. However, more recent research has moved toward studying the IAS. This line of research has argued that understanding threat reactivity among individuals with PTSD will require looking beyond the amygdala to regions such as

brainstem and midbrain structures and cerebellum. In fact, all these brain regions (e.g., LC, amygdala, superior colliculus, and prefrontal cortex) exhibit functional connectivity and increased neural activity in individuals with PTSD, both during subconscious threat processing and at rest (Lanius et al., 2017).

As per the DSM-5 (APA, 2013), a heightened startle response is among the hyperarousal symptoms of PTSD. Naegeli et al. (2018) compared the startle responses of individuals with PTSD to the startle responses of trauma-exposed individuals without PTSD to loud sounds. Individuals with PTSD had heightened startle responses, such as increased eye blinking, heart rate, and skin conductance, which positively correlated with increased LC activity. In another study, Morey and colleagues (2015) administered a fear-conditioning task to veterans with PTSD and trauma-exposed veterans without PTSD. The stimuli were photos of a human face that varied between a neutral to a very fearful look, and the participants' brain activity was measured using fMRI. Compared to trauma-exposed veterans without PTSD, veterans with PTSD had increased regional activation in the LC in response to the fear stimulus.

In summary, the studies reviewed in this section provide evidence for the hypothesis that PTSD symptomatology is related to dysregulation of the LC-NA system, especially symptoms of hyperarousal and sleep disturbances.

REM Sleep and NA-Containing Neurons in the LC

Connections Between REM Sleep and the LC

Many neurotransmitters are involved in regulating REM sleep, and their dysregulation can result in significant sleep disturbances (for a review, Roguski et al., 2020). The key transmitters involved in REM sleep include Acetylcholine, Glutamate, Histamine, Orexin,

GABA, and NA (Roguski et al., 2020). The current thesis focuses on NA and its involvement in the LC and SubC during REM sleep. Neurons that must be active for the onset and maintenance of REM sleep are called REM-on neurons, and neurons that must cease activity for the beginning and maintenance of REM sleep are called REM-off neurons (Pal & Mallick, 2007). There is not much literature on the connections between REM sleep and LC among humans. Still, as seen in the following section, there are reasons to believe that REM sleep and LC activity are interconnected.

First, in addition to being involved in the regulation of arousal levels during sleep (Mellman et al., 1995), NA is involved in REM sleep (for a review, see (Gottesmann, 2008). NA is located predominantly in the neurons of the LC. It has long been known that these neurons fire at their highest rate during wakefulness and less during sleep. Historically, it was thought that NA-containing neurons in the LC must be silent for the onset and maintenance of REM sleep (Aston-Jones & Bloom, 1981; Berridge & Waterhouse, 2003a) and that increased levels of NA cause REM sleep deprivation (Mallick et al., 2002; Samuels & Szabadi, 2008). More recently, studies have concluded that a critical low but non-zero amount of NA is required for the onset of REM sleep; the reason for this is unknown (for a review, see Gottesmann, 2008; Ouyang et al., 2004). It is possible that for the onset and maintenance of REM sleep, some section(s) of the LC must be active while other(s) must be silent. For example, the locus subcoeruleus, which is situated caudal to the LC, has been classified as a region of REM-on neurons (Fraigne et al., 2015). NA neurons in the LC are well-known to be REM-off, which suggests a negative correlation between NM and REM sleep in the LC globally. However, if the caudal part of LC contains REM-on neurons, the relationship between NM and REM sleep is less clear and warrants section-specific investigation.

Additionally, studies indicate excitatory interactions of activity and silence in the LC that might play essential roles in sleep-dependent memory consolidation (Frazer et al., 2021; Poe, 2017; Sara, 2017; Swift et al., 2018). These connections between LC and REM sleep have been identified primarily in animal studies that use methods such as microdialysis and intracerebroventricular injection; these methods are invasive and cause side effects, such as prolonged wakefulness and marked behavioral depression, so they are rarely used with human subjects (Cordeau et al., 1971; Feldberg & Sherwood, 1954; Haley & McCormick, 1957; Matsuda, 1968; Park, 2002; Shouse et al., 2000). In this thesis, as explained in the following sections, a non-invasive method is employed to examine the connections between LC and REM sleep among veterans with PTSD.

Second, studies on REM sleep behaviour disorder (RBD) have reported differences in the pons (in which the LC is located) between participants with and without RBD. According to MRI studies, the white and grey matter in the pons appears significantly different in humans with RBD compared to healthy controls (Boucetta et al., 2016; Rahayel et al., 2019). Other studies using diffusion tensor imaging have observed differences in the midbrain tegmentum[2] and the rostral pons in patients with idiopathic RBD compared to healthy controls (Scherfler et al., 2011; Unger et al., 2010). However, conventional MRI studies do not offer the level of precision that NM-MRI can achieve. For example, the NM-MRI signal in the LC was found to be significantly lower in people with Parkinson's Disease and RBD compared to those Parkinson's Disease alone (García-Lorenzo et al., 2013) and in people with RBD compared to healthy controls (Ehrminger

[2] The substantia nigra (SN), which has NM derived from dopamine, is located in the midbrain tegmentum. The LC has NM derived from NA. The majority of NM is located in these two nuclei.

et al., 2016). Moreover, there is a significant relationship between altered NM-MRI signal in the LC and abnormal muscle tone during REM sleep (García-Lorenzo et al., 2013).

Possible Connections Between REM Sleep and the LC Among Veterans With PTSD

Animal studies indicate that the abnormal activity in the LC may play a key role in forming symptoms of PTSD via sleep dysregulation and the suppression of hippocampal bidirectional plasticity (for a review, see (Vanderheyden et al., 2014). Yet, little is known about the relationship between NA and REM sleep in humans with PTSD. However, Germain et al. (2013) conducted a closely related study. Specifically, they used PSG and positron emission tomography (PET) to examine sleep-wake regulation among combat-exposed veterans with and without PTSD. Compared to veterans without PTSD, veterans with PTSD had elevated activity in brain regions involved in arousal regulation, fear responses, and reward processing during wakefulness and REM sleep. During wakefulness, veterans with PTSD had elevated activity in both the left and right LC compared to veterans without PTSD. During REM sleep, veterans with PTSD had elevated activity in the right LC compared to veterans without PTSD. Studies need to investigate the neural mechanisms underlying potential causal relationships between sleep and arousal regulation in individuals with PTSD. While the current thesis does not explicitly study arousal regulation, it studies a brain region (i.e., LC) and neurons involved in arousal regulation and sleep.

LC and SubC Complex

The LC plays a critical role in learning and memory formation, especially for threat-related learning. The LC is a small nucleus in the brainstem, approximately 15 mm in the rostral-caudal axis (Naidich et al., 2009; Naidich & Duvernoy, 2009), though the length may vary

between individuals and by age. A closely situated entity is the SubC, a nucleus mainly involved in controlling atonia during REM sleep (Boeve et al., 2007; Lu et al., 2006), which is caudal to the LC. Due to the small sizes and nearness of the LC and SubC, some studies have not distinguished between them. Even when studies aim to measure only the LC, they likely include a portion of the top of the SubC. Furthermore, there is no uniform method to separate the LC and SubC. Some studies separate the LC and SubC by dividing the complex in half; for example, Ehrminger et al. (2016) divided it by 7 mm length each. Other studies have used other divisions.

Further, even the LC itself can be subdivided by region; studies have found that different regions of the LC are differently vulnerable to degeneration (Cassidy et al., 2022), and even in normal functioning, different regions of the LC play distinct roles in LC circuitry (Poe et al., 2020). For example, in previous research, degeneration in the caudal LC has not been found in individuals with Alzheimer's disease but has been found in individuals with Parkinson's disease (Betts et al., 2019; German et al., 1988). While many studies have examined the LC as a structure, animal and post-mortem studies with humans examined the LC in subdivisions.

For example, Vijayashankar and Brody (1979) conducted a post-mortem study and examined the brains of 24 human males aged 14 to 87 years who did not have neurological diseases during their lifetime. They counted all cells containing NM in the LC and SubC and measured the total combined length of the nuclei, which ranged between 8.8mm and 15.0mm across subjects. This variation between subjects was explained by age: the cell counts and lengths of the nuclei began to decrease at age 60 (Vijayashankar & Brody, 1979). In a similar study, German et al. (1998) did a computer reconstruction of the cellular distribution of the LC in the brains of 5 human subjects, which spanned 13mm to 17mm in length. The authors divided the LC into six sections from the rostral to caudal ends, each 2.4mm in length. They detected

NM in the SubC: Specifically, the computer reconstructions showed NM-containing cells in the sixth section (last 2.4mm) of the LC, ventrolateral to the caudal LC. The authors concluded that the visibility of NM pigment is a marker of NA neurons.

In a post-mortem study, Baker et al. (1989) measured the entire human LC to be ~12 mm long and the SubC to be ~5-6 mm long. It is revealed that these two nuclei contain NA, and the cells are pigmented due to NM (K. G. Baker et al., 1989; Olson & Fuxe, 1972). German et al. (1988) and Baker et al. (1989) revealed that researchers studying the SubC inadvertently included the caudal LC in their tissue analyses, either partially or in whole. Thus, the researchers investigating LC/SubC complex likely captured the caudal LC in their cell counts. The existing literature about the SubC may be the caudal LC or at least part of it. The main difference between cell bodies in LC and SubC is that SubC cells are larger and more oval than LC cells (Olson & Fuxe, 1972). Baker et al. (1989) conducted a post-mortem tissue analysis on human LC (~12 mm) and SubC (~5-6 mm) and used computer reconstruction to produce the cellular distribution of the human LC/SubC complex. With this computer reconstruction figure, they highlighted that the LC cells appear more clustered together, whereas the SubC cells are scattered; the SubC is positioned very close, adjacent to the caudal LC, both of which are very small (Baker et al., 1989). As the SubC needs to be active in order to initiate and maintain muscle atonia during REM sleep (Fraigne et al., 2015; Ouyang et al., 2004; Roguski et al., 2020), the researchers were likely capturing the caudal LC in their cell-counts.

LC/SubC complex parcellation has evolved since its first discovery. Manger and Eschenko (2021) reviewed the mammalian LC/SubC complex. They showed differences and similarities published in previous studies regarding the nuclei containing NA neurons in the rostral hindbrain of a mammal. The consistencies and variations of these nuclei in different

studies were also illustrated with the parcellation of NA neurons to describe the LC/SubC complex across mammalian species (Manger & Eschenko, 2021). Some studies considered the LC (A4 nucleus) and part of SubC as a whole, while others separated them. However, the area marked as the A4 nucleus is consistent across the studies, which probably corresponds to the LC or, rather, rostral LC in humans. The SubC, marked as the A6 nucleus, in the rat brain atlases of Paxinos and Watson (2004) and the mouse brain (Robertson et al., 2013) was subdivided into three parts, the SubC alpha (SubCA/SubCα); SubC dorsal (SubCD); and SubC ventral (SubCV). Since many studies in this area were conducted with animals such as rodents, it is essential to understand how much of these findings can be translated to humans.

Possible Connections Between REM Sleep and SubC

There are some reasons to believe that the SubC, which is caudal to the LC, plays a role in muscle atonia during REM sleep. Anatomically, the SubC in humans is comparable to the sublaterodorsal (SLD) nucleus in rats (Boissard et al., 2003; Lu et al., 2006), and the SLD is known to play a role in REM sleep in cats and rats. For example, in rats, SLD plays a role in muscle atonia during REM sleep. Specifically, the SLD in rats contains glutamatergic neurons that activate the GABA/glycinergic neurons, which then block the spinal lower motor neurons, thereby generating muscle atonia during REM sleep (Luppi, 2010; Luppi et al., 2011). Since the SLD in rats is considered anatomically equivalent to the SubC in humans, the SubC may play a similar role in initiating muscle atonia during REM sleep in humans. There is also some indirect evidence that orexin might promote REM sleep by activating REM-on neurons in the SLD (M. C. Xi et al., 2002, 2003). Orexins are neuropeptide modulators of the sleep-wakefulness cycle (Arrigoni et al., 2016). Some animal studies have reported that orexin injections into the SLD prolong waking if injected during wakefulness and prolong REM sleep if injected during slow-

wave sleep (Xi & Chase, 2010). However, other studies report that orexin neurons fire only occasionally during REM sleep and that there is no direct evidence for orexin release in the pons during REM sleep (Arrigoni et al., 2016). Thus, while the evidence on orexin remains inconclusive, it still points to the possibility that the SubC in humans may also be related to REM sleep. However, current literature has not examined these possible connections between SubC and REM sleep.

NM and its Potential Role in PTSD

NM is a dark, pigmented granule found in various neurons of the human central nervous system, predominantly in the substantia nigra (SN) and LC. For a long time, NM was regarded as an inert waste product. Only recently has NM been found to play an active function in the brain. In the LC, NM is created from the oxidation of NA, where it accumulates with age (Wakamatsu et al., 2015; Zecca et al., 2004, 2008). NM plays a role in regulating arousal, focused attention, autonomic function, and sleep (Betts et al., 2019; Grimm et al., 2004; Osorio-Forero et al., 2021). However, the link between NM in the LC and REM sleep among individuals with PTSD has yet to be studied. This thesis studies NM in the LC, which can provide new insights into understanding PTSD symptomatology and promote REM sleep quality.

Standard methods to acquire and measure NM in the LC are labour-intensive and invasive, such as post-mortem studies (Sulzer et al., 2018). More generally, non-invasive, in vivo assessments of the LC in humans are notoriously difficult, given the nucleus' small size and location deep in the brainstem. So, until about fifteen years ago, studying NM was restricted to material obtained post-mortem at autopsy. More recently, researchers have discovered that, since

NM binds with iron, MRI is a valuable imaging tool to measure NM via the detection of paramagnetic NM-iron complexes. In addition, NM-MRI is non-invasive and easy to administer.

Using NM-MRI, it has already been found that NM is implicated in neurodegenerative and neuropsychiatric disorders (e.g., Betts et al., 2019; Shibata et al., 2007; Sulzer et al., 2018). Neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases, involve the degeneration of dopaminergic and noradrenergic neurons in the substantia nigra and LC. NM is always packaged in healthy cells and is harmful if released from this packaging. Thus, the role of NM in neurodegeneration is likely due to its triggering spread of damage when it is released from a damaged cell.

The use of NM-MRI in the study of PTSD is in its infancy and very promising (Cassidy et al., 2022; McCall, 2022). So far, NM-MRI has been used primarily in studying Parkinson's and Alzheimer's diseases to measure NM content and detect degeneration of dopaminergic and noradrenergic neurons in the SN and LC. NM-MRI signal in the LC can reflect not only integrity but also function. There is evidence that the NM-MRI signal in the SN may be a measure of dopamine system function (Cassidy et al., 2019), so the signal in the LC may be similarly a measure of NA system function, although more work is still needed to confirm this. This is important for the study of PTSD because, unlike individuals with Parkinson's and Alzheimer's diseases, individuals with PTSD exhibit dysfunction, rather than degeneration, in the LC. In emerging research using NM-MRI, NM in the caudal LC has been positively correlated to hyperarousal symptoms among operationally deployed veterans with a history of PTSD (Cassidy et al., 2022; McCall, 2022). Cassidy and colleagues (2022) also found a very large group difference in that PTSD patients have higher NM-MRI signals in middle and caudal LC compared to healthy controls.

NM-MRI has yet to be used in the study of sleep. Studies investigating the role of the LC in REM sleep have thus far focused on LC activity (i.e., firing or ceasing of NA-ergic neurons). NM-MRI instead measures signal intensity in the LC based on accumulated content rather than current activity alone. Furthermore, emerging research has indicated that LC activity and LC signal intensity, as measured by NM-MRI, are significantly correlated (Liu et al., 2017). Thus, NM-MRI may be an effective method for capturing the role of the LC in REM sleep. Using NM-MRI, this thesis measures NM to detect dysfunction in the LC and its relationship with REM sleep among individuals with PTSD.

Chapter 2: Current Study

One of the most prominent sleep features of PTSD relates to dysregulation in REM sleep, including lower REM sleep time, which may notably result from dysfunction in NA-containing neurons in the LC (Aston-Jones et al., 2007; Poe et al., 2020). As mentioned before, the oxidation of NA creates NM, which can be measured using MRI imaging techniques. Using NM-MRI is a novel means of studying the association between REM sleep and NM-MRI signal in the LC among operationally deployed veterans with PTSD.

Objectives

The present study sought to investigate the association between REM sleep and NM in different subsections of the LC using NM-MRI among operationally deployed veterans with PTSD. More specifically, we examined the LC in three sub-sections: rostral, middle, and caudal. We hypothesize that these LC sub-sections may differ in association with REM sleep. However, these differences are not so surprising because different sub-sections of the LC fire to different brain regions. Specifically, neurons in the rostral LC project to structures of the forebrain, such as the hippocampus, which is important for memory consolidation, and neurons in the middle and caudal LC project to the basal ganglia, cerebellum, and spinal cord (Loughlin et al., 1986; Mason & Fibiger, 1979; Pickel et al., 1974; Satoh et al., 1977).

Our first hypothesis is that the associations between REM sleep percentage and NM-MRI signal may differ for the LC subsections. Our exploratory hypothesis is that the correlation between NM and REM sleep is negative in the rostral LC and positive in the caudal LC of Veterans with PTSD. Due to the mixed approaches of dividing the LC/SubC complex, our

hypothesis about middle LC is more like the rostral LC since, in most studies, middle LC was defined as LC, not SubC or part of SubC.

Chapter 3: Methods

Participants

Twenty-two operationally deployed veterans with a history of PTSD (7 females and 15 males; M_{age} = 47.4 (±8.6) years; ranging from 33 to 60 years) were recruited through the Operational Stress Injury clinic at the Royal Ottawa Mental Health Centre, Ontario, Canada. Exclusion criteria were: current or past diagnosis of psychotic and/or bipolar disorder, current substance abuse disorder (within <6 months), current major medical illness (e.g., HIV, cancer) or medical condition that is not sufficiently stabilized according to the clinician, current neurological condition (e.g., epilepsy, Alzheimer's Disease, Parkinson's disease), head injury with loss of consciousness >5 minutes, MRI contraindications (e.g., non-MR compatible metal implants, claustrophobia, pregnancy), taking a benzodiazepine, hypnotic, or stimulant medication regularly, recent trans-meridian travel (wait three days for each jet lag hour before entering the study) or shift work within the last two months, enrolled in an interventional study, unable to withhold caffeine or nicotine products for about 16 hours in a row (i.e., overnight), and unable to withhold recreational drug use (except cannabis) for about three weeks (from two weeks before the study until the end of the study). All participants provided informed consent.

Procedure

Participants underwent a psychiatric interview and completed validated questionnaires. Two nights of PSG were recorded, the first to help participants adapt to sleeping in a laboratory environment with PSG equipment, and the second was used for final analysis. On the evening of the second recording, all participants underwent an MRI scanning session. Participants were compensated for their time in this study.

Clinical and Cognitive Measures

PTSD diagnosis was confirmed using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), which, together with the PTSD Checklist for DSM-5 (PCL-5), was also used to determine symptom severity. Depression and anxiety symptoms were assessed with the Beck Depression Inventory (BDI-II) and Beck Anxiety Inventory (BAI).

Sleep Recordings

On the nights of PSG, participants were asked to sleep and wake up at their mean sleep schedule monitored in the previous week. PSG was collected using a 27-channel (night 1) and 128-channel (night 2) EEG caps with 2 EOG channels, 2 EMG channels, an ECG channel, and mastoid references with BrainAmp amplifiers (Brain Products GmbH, Gilching, Germany) at a 500 Hz sampling rate. Signals were acquired using BrainVision software. The PSG data were visually scored by a registered sleep technologist using AASM criteria (Iber et al., 2007). While the primary analyses focused on REM sleep, global polysomnography variables were computed for descriptive purposes: total sleep time, sleep onset latency, REM sleep latency, wake after sleep onset (WASO), and percentage of time spent in Stage 1 (N1) sleep, Stage 2 (N2), slow wave sleep (N3), and REM sleep. Total sleep time was calculated as the time spent asleep between “lights off” and “lights on” tags. WASO was defined as epochs following sleep onset that was scored as wake. Sleep stage percentages were calculated as the time between “light off” and “lights on” scored as N1, N2, N3, and REM divided by TST.

MRI Acquisition and Preprocessing

MRI was acquired using a 3T MR-PET Siemens Biograph scanner. Scanning sequences included a T1-weighted anatomical scan and an NM-MRI scan in the same scanning session. A 12-channel head coil was used for all scans. The NM-MRI scan was a 2D-GRE scan with magnetization transfer contrast (similar to (Chen et al., 2014) with the parameters shown in Table 1. Whole-brain, high-resolution structural MRI scans were acquired for preprocessing of the NM-MRI data: a T1-weighted MPRAGE sequence shown in Table 2 was applied. The quality of NM-MRI images was visually inspected for artifacts immediately upon acquisition, and scans were repeated when necessary.

Table 1

Imaging Parameters for NM-MRI Scan

NM-MRI Image Parameters	**Parameter Value**
Repetition Time (TR)	337 ms
Echo Time (TE)	3.97 ms
Flip Angle	50°
In-plane resolution	0.39×0.39 mm^2
FoV (partial coverage of midbrain)	165 × 220
Matrix	416 × 512
Number of Slices	10
Slice Thickness	3 mm
Slice Gap	0 mm
Magnetization Transfer Frequency Offset	1200 Hz
Number of Excitations (NEX)	6
Acquisition Time	7.25 minutes

Table 2

Imaging Parameters for T1-Weighted Scan

T1-Weighted Image Parameters	**Parameter Value**
Repetition Time (TR)	2500 ms
Echo Time (TE)	1.69 ms
Flip Angle	7°
Inversion Time	1050 ms
FoV (whole brain coverage)	162 x 192
Matrix	192 x 256
Number of Slices	256
Isotropic Voxel Size	1 mm
Acquisition Time	5.47 minutes

Measuring NM-MRI Signal in the LC

To measure the NM-MRI signal in the LC, we used an automated pipeline (see Figure 1) that was developed by our research group (Cassidy et al., 2022) using MATLAB (MathWorks, R2019b) and SPM 12. This automated pipeline (see figures 2-9 for the steps) preprocessed the NM-MRI images, divided the LC into three subsections, and calculated the NM-MRI signal in each subsection. The Contrast-to-Noise Ratio (CNR), which is calculated by the change in NM-MRI signal intensity (*I)* relative to a reference region (RR) containing minimal NM, was determined for every voxel (*v*) in each slice using this formula:

$$\mathrm{CNR}_v = (I_v - \mathrm{mode}(I_{RR})) / \mathrm{mode}(I_{RR})$$

The reference region was defined as a white matter tract in the center of the pontine tegmentum. The overinclusive mask was used as a landmark to define the location of the reference region. The mode of the signal intensity for all voxels within the reference region was determined as in our previous method (Cassidy et al., 2019). This procedure was repeated for all slices with the overinclusive LC mask. LC locations were retrieved within an overinclusive mask of the LC traced from an average of all subjects' NM-MRI scans. The LC overinclusive mask was divided in standardized space into slice-specific masks (see Figure 10). These slice-specific masks were deformed to each individual's native space using the same method as the LC overinclusive mask. This allowed the LC to be divided into three rostrocaudal sub-sections with anatomical demarcations linked to the z-coordinate of standardized MNI space. The LC signal peak intensity (CNR) was calculated by taking the brightest voxel within each subsection (i.e., rostral $\mathrm{LC}_{\mathrm{CNR}}$, middle $\mathrm{LC}_{\mathrm{CNR}}$, and caudal $\mathrm{LC}_{\mathrm{CNR}}$).

Figure 1

The Flow of the Automated Pipeline

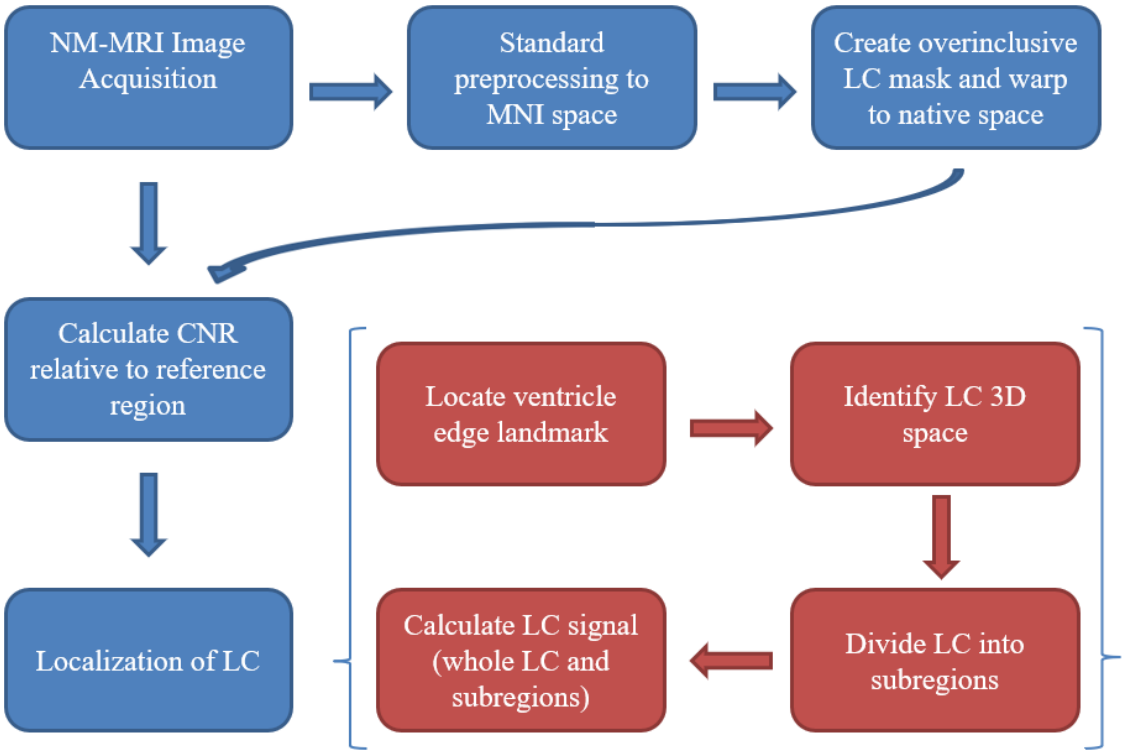
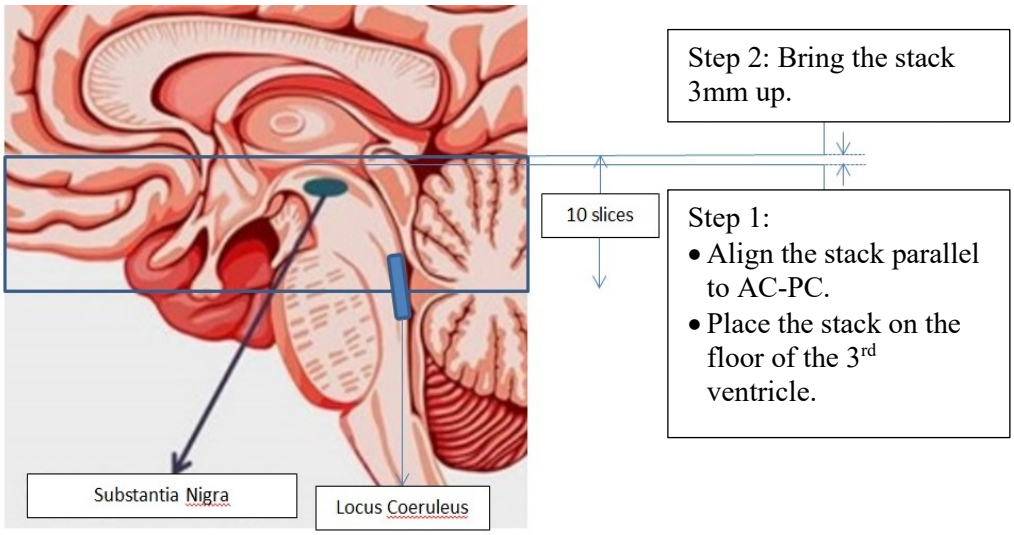


Figure 2

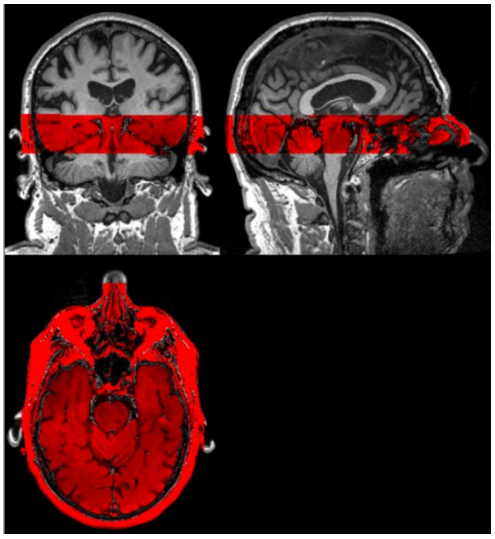
NM-MRI Stack Placement



Note. After acquiring the anatomical scan, a stack of 10 slices aligned by AC-PC was placed on the surface of the cerebral peduncle to cover SN and LC for the NM-MRI scan.

Figure 3

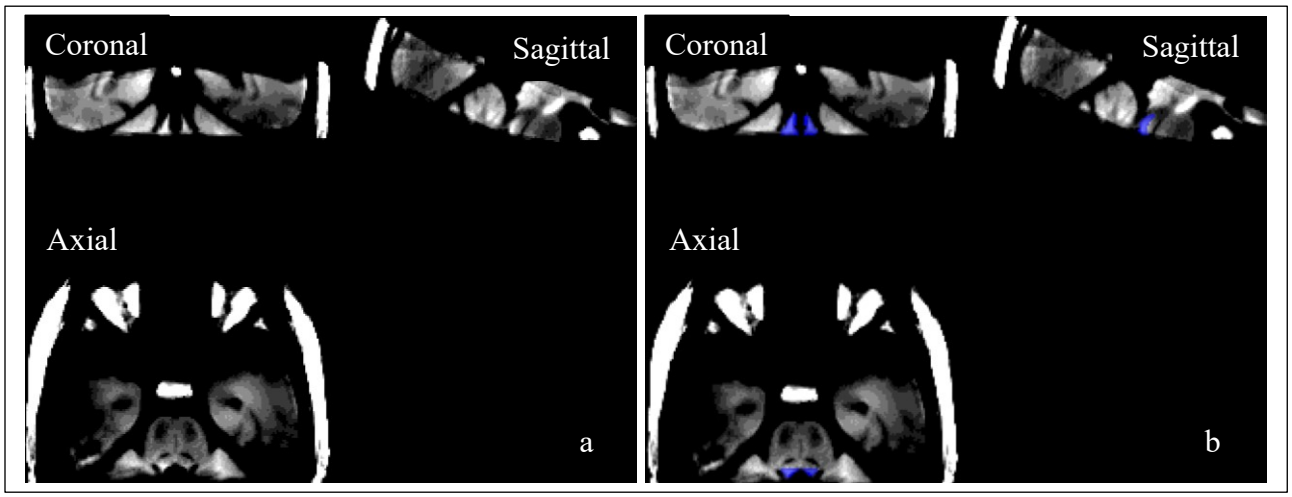
Co-Registered NM-MRI Scan to T1-Weighted Anatomical Scan of a Participant



Note. NM-MRI scans (in red) covering the midbrain could then be normalized to MNI space following the guidelines determined from the normalization of the T1-weighted anatomical scans.

Figure 4a-b

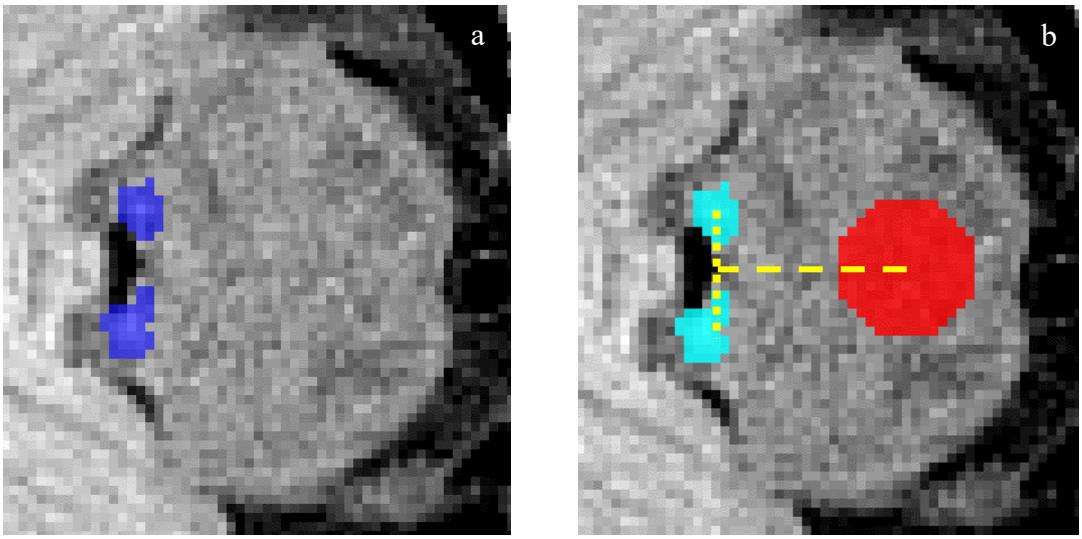
NM-MRI Visualization Template and LC Overinclusive Mask in MNI Space



Note. The NM-MRI visualization template was constructed from the average of the normalized images from all participants (4a). LC overinclusive mask (in blue) was created by manually tracing LC and surrounding voxels on the average image of NM-MRI scans (4b).

Figure 5a-b

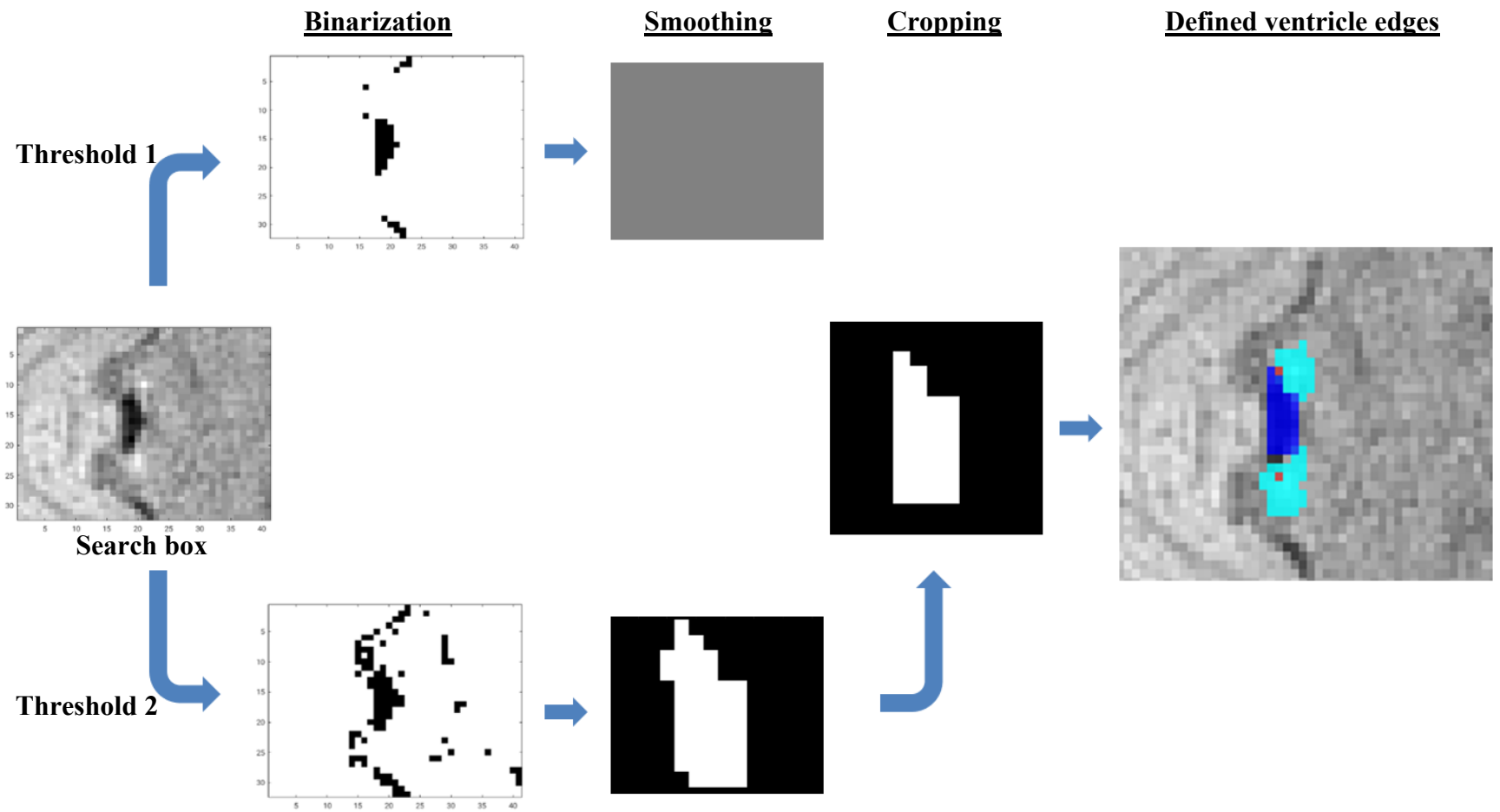
Axial View of LC Overinclusive Mask and Reference Region



Note. An axial view of one slice of LC overinclusive mask warped to the native space of a participant is shown in 5a. The reference region of 5a is shown in 5b. A reference region with ~6 mm diameter in the pons (in red) was defined as a circle whose center was ~14 mm anterior from the midpoint of a line (broken yellow line on figure) between the center of the right and left LC overinclusive masks (in cyan).

Figure 6

The Process to Define Forth Ventricle and Ventricle Edges

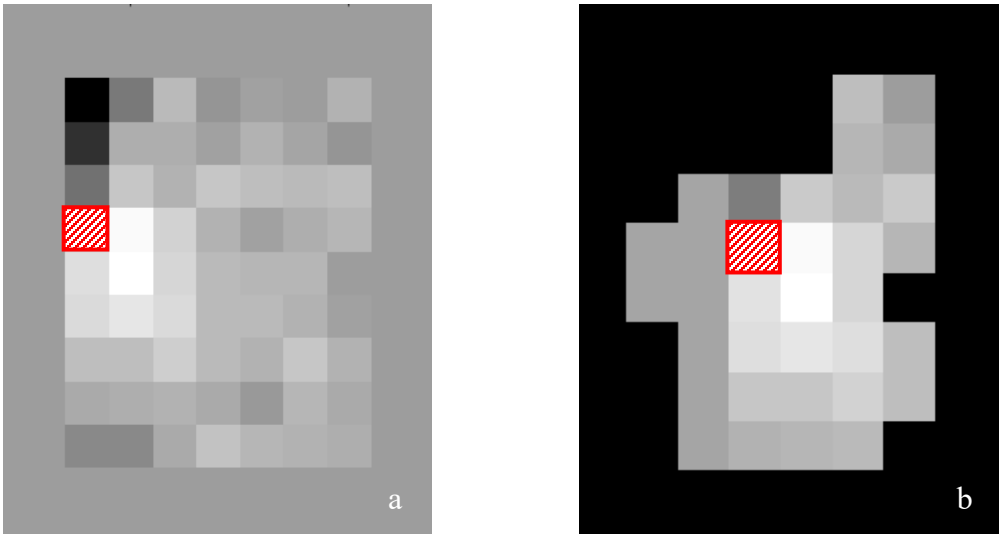


Note. A search box was defined to surround the fourth ventricle using the location of the LC overinclusive mask as a landmark. The image was binarized to separate dark voxels (including the ventricle) from bright voxels (likely to be tissue) to locate the ventricle

within this box. The binarized image was smoothed to eliminate small clusters of low signals, unlikely to contain the ventricle (the appearance of the ventricle switches from black to white by inverting the binarization to facilitate subsequent steps). Then, this smoothed image was cropped to remove the dorsal portion of the ventricle (in some cases, the dorsal portion extended laterally, causing errors). This left an estimated ventricle shape; the edges of the ventricle (displayed as red voxels in the image at far right) were determined based on the lateral edges of this ventricle shape and the position of the overinclusive mask. Due to the variable contrast between the ventricle and the tissue in different subjects and slices, the binarization of the image was performed at two thresholds. A more lenient threshold was selected (threshold 2) if the strict threshold failed to find a sufficiently sized ventricle (as was the case here for the topmost path).

Figure 7a-b

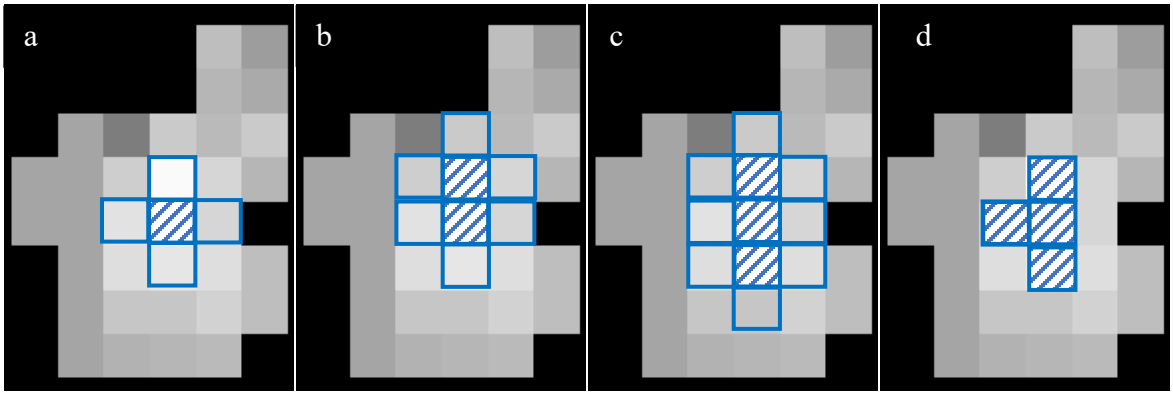
Right LC Search Box in Conjunction with the Right LC Overinclusive Mask



Note. Right LC Search Box (7a) in Conjunction with the Right LC Overinclusive Mask (7b). Voxels outside the overinclusive mask are shown in black. Voxels within the overinclusive mask but outside the LC search box (defined by proximity to the ventricle edge, tinted in red) are shown as a uniform shade of gray. Voxels shown as varying shades of grey represent the conjunction of the overinclusive mask and the LC search box, wherein a search for the true LC will be performed. This procedure was repeated for the left LC as well.

Figure 8

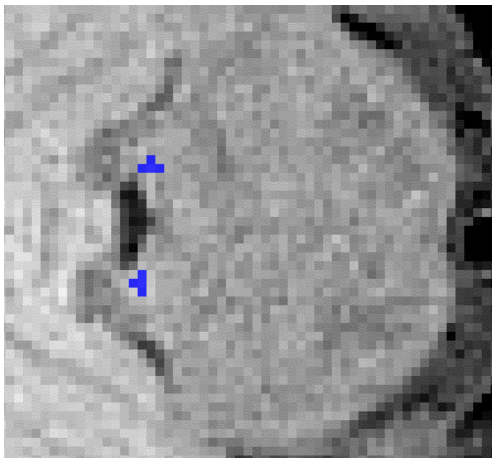
Cluster Forming Algorithm to Find the Right LC on A Single Slice



Note. Cluster Forming Algorithm to Find the True Location of the Right LC on A Single Slice. Starting from the brightest voxel (circled in blue with a pattern filled in 8a) within the search space, a search proceeds for the next brightest voxel amongst the adjacent voxel (unfilled blue boxes). This process continued until four voxels were identified (as illustrated in 8b-d).

Figure 9

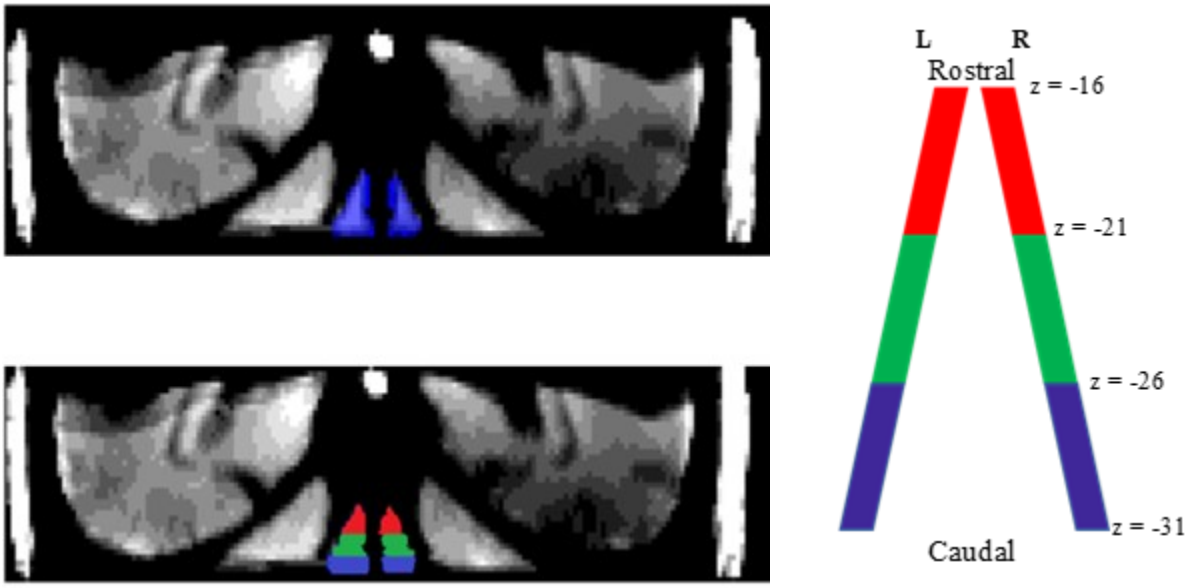
Bilateral LC Mask on One Slice



Note. The bilateral LC mask, defined by the landmark of ventricle edges, and the LC overinclusive mask are shown in blue.

Figure 10

Subdivided Rostrocaudal LC



Note. The bilateral LC overinclusive mask (top-left) was divided into subsections (colour-coded, in bottom-left). The schematic representation of LC showing the z-coordinates of section boundaries in MNI space is illustrated on the right.

Statistical Analysis

Pearson's correlational analyses were used to explore the relationships between the main variables of interest (i.e., REM sleep (the number of minutes and percentage) and LC_{CNR}) and the descriptive variables. An independent-samples t-test was also run to compare rostral, middle, and caudal LC_{CNR} in the subgroup using antidepressant medication to the subgroup not using antidepressant medication. All potential confounders significantly correlated with the primary outcome variables were included as covariates in partial correlations assessing the relationships between REM sleep and the rostral, middle, and caudal LC_{CNR}.

Chapter 4: Results

Sample Characteristics and Influence of Potential Confounders

Sixty-eight percent of the participants were males, and 73% were taking psychotropic medication. Average scores on the PCL-5 and the CAPS-5 ranged between 24-65 and 25-63, respectively (i.e., mild to severe PTSD symptoms). In terms of other psychiatric symptoms, 95.5% of the participants had a BDI-II ≥14 (i.e., at least mild depression symptoms) and a BAI ≥8 (i.e., at least mild anxiety symptoms). Based on the CAPS-5, 19 participants still met the criteria for a current diagnosis of PTSD. Table 1 provides further descriptive details on the participants and their sleep architecture.

Table 3

Sample Characteristics and Sleep Architecture Information

	Mean ± SD
Demographic and clinical characteristics	
Age (years)	47.41 ± 8.59
Males (%)	68.2
CAPS-5 Total Severity	41.95 ± 11.91
Intrusion/Re-experiencing	8.64 ± 4.24
Avoidance	5.05 ± 2.13
Negative alterations in cognition and mood	15.18 ± 5.28
Alterations in arousal and reactivity	13.09 ± 4.58
PCL-5 Total Score	42.59 ± 12.14
Criterion B (Re-experiencing)	8.68 ± 4.20
Criterion C (Avoidance)	5.00 ± 2.20
Criterion D (Negative alterations in cognition and mood)	15.32 ± 5.03
Criterion E (Hyperarousal)	13.59 ± 3.35

BDI-II Score	27.23 ± 9.72
BAI Score	22.59 ± 9.57
Medications	
Any Psychotropic Medication[a] [*n* (%)]	17 (77.3)
Antidepressants [*n* (%)]	14 (63.6)
Sleep Architecture	
Total Sleep Time [TST (min)]	428.44 ± 59.71
Sleep Onset (min)	9.08 ± 7.07
Wake After Sleep Onset (min)	42.23 ± 25.63
REM Latency from Sleep Onset (min)	138.59 ± 72.77
Sleep Efficiency (%)	89.32 ± 5.48
Number of Awakenings	21.50 ± 8.51
N1 (min)	48.83 ± 9.72
N2 (min)	267.70 ± 52.62
N3 (min)	19.82 ± 21.76
REM (min)	92.09 ± 37.51
N1 (% of TST)	11.81 ± 7.26
N2 (% of TST)	62.34 ± 7.46
N3 (% of TST)	4.61 ± 4.88
REM (% of TST)	21.24 ± 7.58

Note. Sample characteristics (n=22); BDI-II Beck Depression Inventory, *BAI* Beck Anxiety Inventory, *CAPS-5* Clinician-Administered PTSD Scale for DSM-5, *PCL-5* PTSD Checklist for DSM-5, *REM* Rapid eye movement, *N1* Non-REM 1, *N2* Non-REM 2, *N3* Non-REM 3. On the CAPS-5 and PCL-5, total symptom severity scores range from 0 to 80, with higher scores indicating worse PTSD symptom intensity.

[a] If participants reported using any of the following psychotropic medications, they were included here.

Potential Confounders

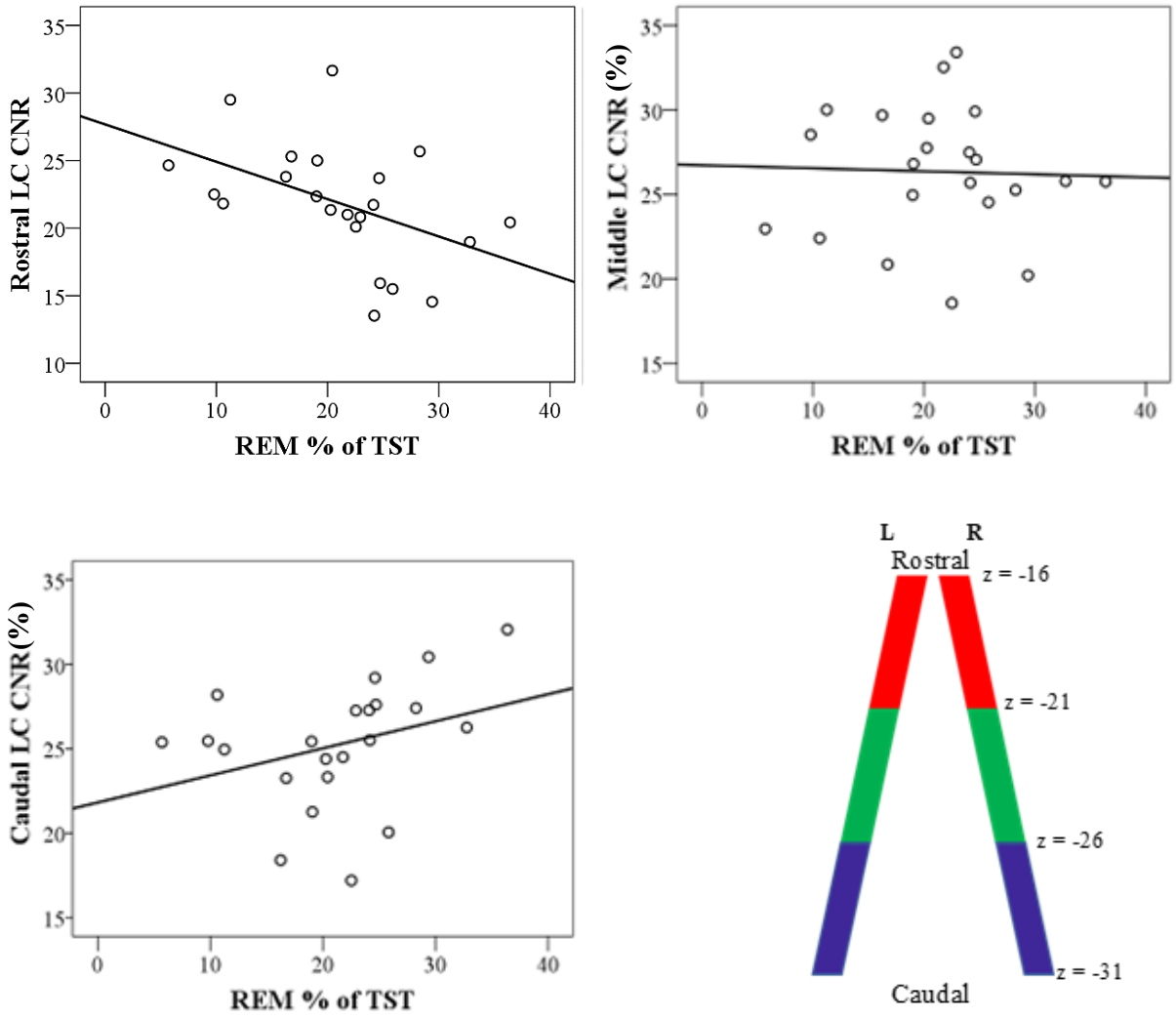
There was no significant correlation between age or BDI-II and any of the NM or sleep variables (all $p > .10$). The middle LC_{CNR} was significantly lower in the subgroup of participants who were using antidepressant medications ($M \pm SD = 24.63 \pm 3.27$) than in those who were not, $t\,(20) = -3.39$, $p = .003$.

Association between REM Sleep and LC Signal

Figure 11 shows the relationship between the percentage of REM sleep and NM-MRI CNR across the LC's rostral, middle, and caudal portions. After controlling for antidepressant usage, there was a moderate, negative partial correlation between the percentage of REM sleep and rostral $LC_{CNR,}$ which was statistically significant, $r(19) = -.476$, $p = .029$. In other terms, after adjusting for antidepressant medication use, higher proportions of REM sleep were associated with lower LC_{CNR} in the rostral LC. The reverse pattern, with a higher percentage of REM sleep linked to higher LC_{CNR}, seemed to occur in the caudal section of the LC, but this was not statistically significant, $r(19) = .33$, $p = .145$). There was also no significant correlation between REM sleep and LC_{CNR} in the middle LC, $r(19) = -.04$, $p = .876$).

Figure 11a-d

The Relationship Between LC_{CNR} and REM Percentage of Total Sleep Time



Note. This figure shows the correlations between the sections (seen in d) of the brightest LC_{CNR} and REM sleep percentage of Total Sleep Time (TST). In (a), the association between Rostral LC_{CNR} and REM percentage of TST is shown. In (b), the association between middle LC_{CNR} and REM percentage of TST is shown. In (c), the association between Caudal LC_{CNR} and REM percentage of TST is shown.

Chapter 5: Discussion

This thesis investigated some pathophysiological correlates of PSTD that are linked to sleep and markers of noradrenergic functions. This is the first study to report an association between LC_{CNR} and REM sleep. This association differed across portions of the LC, with a significant negative association in the rostral portion of the LC and a non-significant positive association in the caudal portion of the LC. While further work in larger samples should be conducted to better understand how psychotropic medications commonly used by Veterans with PTSD may influence this phenomenon, these associations persisted after controlling for any antidepressant intake.

Different Associations between LCCNR and REM Sleep Percentage Across Portions of the LC

There were no previous human studies on the relationship between NM and REM sleep in PTSD, let alone on the relationship between NM and REM sleep in subdivisions of the LC. Hence, our initial hypotheses for the rostral LC and the middle LC were based on studies on arousal regulation and sleep in individuals with PTSD because both the LC and NA neurons are involved in arousal regulation and sleep. For example, Germain et al. (2013) explored metabolic changes in the limbic system during wakefulness and REM sleep in combat-exposed military veterans. They found that, during REM sleep, veterans with PTSD had increased activity in the right LC compared to veterans without PTSD. Since the researchers used positron emission tomography (PET), activation was observed in the entire LC region (right or left) rather than in subdivisions of the LC. The LC is too small of a structure to study its subdivisions with standard neuroimaging techniques such as functional MRI or PET. Thus, when researchers study the LC,

they usually study it as an entire region or identify the first 8–12mm (e.g., Baker et al., 1989) as the LC, which corresponds to the rostral and middle LC in this thesis. Though this is speculative, NA projection/release may differ within the sub-sections of the LC. It was therefore deemed relevant to use a finer-grained approach, dividing what is typically studied as the LC into the rostral and middle LC.

Rostral LC

The negative association between the percentage of REM sleep and rostral LC_{CNR} is consistent with our initial hypothesis. Since this was a correlational analysis, it cannot determine causal pathways. Some of the causal pathways could be speculated upon.

Recall that NM is a by-product of NA. Thus, the negative association between the percentage of REM sleep and rostral LC_{CNR} would be consistent with the theory that NA affects REM sleep (Gottesmann, 2008). Specifically, higher levels of NM indicate more NA release, which has detrimental effects on REM sleep if the level of NA passes a bare minimum amount required for REM sleep to be initiated and maintained. These theories were developed based on indirect studies, and there was no previous empirical evidence to support them prior to the current study. Individuals with PTSD have altered arousal, fear, and sleep functions, and their traumas likely cause increased NA activity and increased accumulation of NM (McCall et al., 2021). It was not known whether variations in NA would still be associated with REM sleep in individuals with PTSD, who already potentially have elevated NA/NM. Moreover, the literature on NA and sleep had not used MRI techniques. Instead of capturing natural levels of NA in participants, the researchers would administer NA injections, medications with NA, or medications with NA inhibitors to participants and then monitor REM sleep reactions on PSG (Osorio-Forero et al., 2021). However, participant reactions to these exogenous interventions

may differ from reactions to non-experimental NA release. The results of this thesis on the rostral LC would be consistent with the possibility that even among veterans with PTSD, altered/differentiated NA could affect REM sleep patterns.

Other causal pathways could be theorized. For example, it may be possible that trauma causes REM sleep disturbances among individuals with PTSD, that the amount of disturbance differs based on individual characteristics that are not captured in this thesis, and that a lower REM sleep percentage (more sleep disturbances) leads to elevated NA activity. Future research would need to conduct causal analyses to delineate the causal pathways at play.

Middle LC

As described earlier in this chapter, we had mixed hypotheses about the middle LC. The lack of an association between the percentage of REM sleep and middle LC_{CNR} is inconsistent with our hypothesis that the middle LC would be similar to the rostral LC in terms of the (negative) association between REM sleep percentage and NM. However, it is consistent with our hypothesis that the (negative) association observed between REM sleep percentage and NM may not be true of all regions of the LC.

Caudal LC

There was a positive association between caudal LC_{CNR} and REM percentage, but the association was not statistically significant. The positive association was consistent with our hypothesis above, though we expected the association to be stronger and statistically significant. This is somewhat aligned with the positive relationship between REM sleep and the SubC that is reported in the existing literature (Arrigoni et al., 2016; Ehrminger et al., 2016; García-Lorenzo

et al., 2013; Gottesmann, 2011) and may relate to the need for the SubC to be active in order to initiate and maintain muscle atonia during REM sleep (Fraigne et al., 2015; Ouyang et al., 2004; Roguski et al., 2020).

First, the weak positive association may be due to the inadvertent inclusion of a part of the SubC in our caudal LC scans. Since the SubC is positioned very close, adjacent to the caudal LC, both of which are very small (post-mortem work measured the entire human LC to be ~12 mm long and the SubC to be ~5-6 mm long (Baker et al. (1989)), these regions could get confounded. The current study may have blurred any association between the caudal LC and REM sleep percentage. In other words, since it is difficult to separate the SubC from the caudal LC, the caudal LC_{CNR} values in this thesis likely include at least a part of the SubC as well. German et al. (1988) and Baker et al. (1989) revealed that researchers studying the SubC inadvertently included the caudal LC in their tissue analyses, either partially or in whole. Thus, it may be the case that the results in the literature about the SubC may be actual of the caudal LC since the researchers were likely capturing the caudal LC in their cell counts. Furthermore, it remains unclear whether NA neurons are genuinely in the SubC. However, in a post-mortem study, German et al. (1988) divided the LC into six sections which helped better distinguish the SubC from the caudal LC, and they detected NM in the SubC. As the authors concluded, the detected NM pigment is a marker of NA neurons since no other neurons clearly show this type of pigmentation.

Ideally, we would have liked to capture the caudal LC and SubC separately so that we could first test whether the association between SubC and REM sleep that is reported in the animal literature is observed in the sample of veteran participants in this study as well. And then, we could test whether an association between caudal LC and REM sleep is also observed.

However, the 3-Tesla MRI machine and the NM-MRI sequence used to collect the data for this thesis did not have the resolution to divide the LC into more than three subdivisions. Furthermore, even if the resolution was higher, differentiating the SubC from the LC may be challenging, but perhaps not impossible, with deep learning techniques, due to the scattered nature of the cells of the SubC with the current methods (i.e., NM-MRI). Additionally, accurately calculating the CNR in this region is not easy. Therefore, false-positive results are likely, such as higher CNR values due to noise rather than due to NM-containing cells in the area of interest.

Second, it is possible that there is indeed a positive association between the caudal LC and REM sleep percentage but that the inadvertent inclusion of a part of the middle LC in the caudal LC weakened the measured association in this thesis. German et al. (1998) did a computer reconstruction of the cellular distribution of the LC of the brains of five human subjects, which spanned 13mm to 17mm in length. The authors divided the LC into six sections from the rostral to caudal ends, each 2.4mm in length. In this thesis, the LC is measured as ~15 mm and was divided into three subsections, with the last section, namely the caudal LC (5 mm), potentially containing part of the SubC and/or part of the middle LC.

Finally, it is also possible that the true association between the caudal LC and REM sleep percentage is a weak positive relationship and that the sample size of 19 participants did not yield sufficient statistical power to detect an association of this magnitude. The possible association between the caudal LC and REM percentage warrants more investigation in larger cohorts of people with PTSD.

Significance and Contributions of the Current Study

The results of this thesis provide new evidence that the NA system is involved in PTSD pathophysiology. While previous research also points to the NA system's involvement in PTSD pathophysiology, this thesis provides the first line of evidence that REM sleep may be a key mechanism by which the NA system is involved. This raises the question of whether there may be benefits in incorporating assessments of NA function in clinical assessments of individuals with PTSD. For example, in clinical settings, drugs targeting the NA system (e.g., Prazosin) by blocking excessive responsiveness to NA stimulation are prescribed to individuals with PTSD to alleviate nightmare symptoms and hyperarousal (Reist et al., 2020; Zhang et al., 2020). Prazosin does not help with all symptoms of PTSD but significantly reduces nightmares and hyperarousal symptoms. A common challenge in the clinical assessment of PTSD is that clinicians must often rely on patients' self-reports of symptoms and symptom severity, and self-reports often either overestimate or underestimate the patient's situation (Matto et al., 2019). Thus, clinicians may prescribe medications such as Prazosin to patients who will not benefit from them and not be prescribing them to patients who would benefit from them. The NM-MRI method used in this thesis can be adopted in clinical settings to objectively and reliably measure the amount of NM and the integrity of the LC in patients with PTSD.

Further research could be done to investigate whether NM-MRI may help predict treatment response to drugs acting on the NA system, which may facilitate the development of individualized treatment plans for people with PTSD. With more data and future studies replicating our method, thresholds or benchmarks could be determined to be used in the clinical setting so that clinicians can quickly interpret whether a patient's LC_{CNR} is higher or lower than average. Since nightmares are related to NA overstimulation and less REM sleep (Hendrickson

et al., 2018), it is likely that individuals with more LC_{CNR} (especially rostral) as detected by the NM-MRI would have more nightmares and hyperarousal symptoms compared to individuals with less LC_{CNR} and would likely be better candidates for medications targeting the NA system. This remains to be investigated.

The current study also illustrates the suitability of the NM-MRI method for examining the connections between NM and REM sleep. The insight gained from segmenting the LC (which revealed that the association between NM and REM sleep might vary across regions of the LC) may be widely applicable beyond the literature on PTSD to the literature on REM sleep and the NA system. The results also provide starting points for improving how to divide the LC in ways that may have functional relevance, including the number of subdivisions, which can be pursued in future research.

Overall, these results improve understanding of some neurophysiological correlates of REM sleep abnormalities among individuals with PTSD. This may inform the development of new studies investigating novel pharmacotherapy approaches for sleep disturbances in individuals with PTSD, the development of personalized treatments for PTSD, and the search for clinical biomarkers of PTSD that are based on brain function.

Limitations of the Current Study

Like every study, this thesis also has limitations. The results of the current study do not speak to causality or directionality. While we hypothesized that dysregulation in REM sleep might result from dysfunction in NA-containing neurons in the LC and dysfunction in neurons in the SubC, the current study cannot establish the causal directions of these relationships. These

connections may also work in the opposite direction; dysfunction in the LC and SubC may result from dysregulation in REM sleep, or this may be a bi-directional phenomenon.

Many participants in this study had both PTSD and major depressive disorder (MDD), which some may argue could have influenced the outcomes. However, previous research (e.g., (Leskin et al., 2002; Woodward et al., 1996) did not find a significant effect of MDD comorbidity on REM sleep or sleep disturbances in people with PTSD. Leskin and colleagues (2002) compared the sleep disturbances of participants with PTSD who had different comorbid disorders. One comparison group consisted of participants with PTSD and a current comorbid panic disorder (henceforth PTSD-PD), and a second comparison group consisted of participants with PTSD and MDD (henceforth PTSD-MDD) while controlling for additional comorbid diagnoses (generalized anxiety disorder, alcohol abuse). The authors found that participants in the PTSD-PD group reported significantly more nightmare complaints (96%) and insomnia (100%) than other comorbid groups. In contrast, in the PTSD-MDD group, 78% of participants endorsed nightmare complaints, and 78% reported insomnia, which did not differ statistically significantly from the other groups. However, the scope of these findings is limited because this study was based on epidemiological self-reported data (Leskin et al., 2002). Therefore, further research is needed to examine the role of psychiatric comorbidity in sleep disturbances linked to PTSD.

Furthermore, most participants in the current studies were taking psychotropic medications that could have influenced sleep and NM profiles. Notably, past studies on people with MDD have suggested that individuals who use certain antidepressants (i.e., SNRIs) have lower LC_{CNR} compared to healthy controls (Guinea-Izquierdo et al., 2021; Shibata et al., 2007). Nevertheless, we controlled for antidepressant usage in the analyses of the current study.

Some results in this thesis (notably the positive association between caudal LC_{CNR} and REM percentage) did not reach statistical significance. This may be due to challenges related to the small sample size and/or other methodological aspects of this study. Although the sample size of 19 is not too small relative to other studies in this field (Szucs & Ioannidis, 2020), we believe it is worth investigating this positive but nonsignificant association in the caudal LC with a bigger sample size. Additionally, while the data collection and analysis of the LC/SubC complex with a 3-T MRI machine in this study is a significant contribution to the field, this method is still relatively new and limited some of the details that could be captured in the analysis. For example, due to the available resolution and the location of the region, we were not able to better separate the SubC from the LC, and there was much noise towards the caudal part of the LC, where some voxels that were potentially capturing the SubC had to be played down. Finally, the in-plane resolution of the NM-MRI scans was high, but the slices were thick (3 mm). A newer version was recently developed with thinner slices (1.5 mm), sacrificing a bit of in-plane resolution. This works much better for dividing the LC into rostrocaudal divisions since the borders are imprecise with the thick slices (as slices are cut in the rostrocaudal axis). Future research may use this new approach to investigate the relationship between NM and REM sleep across subdivisions of the LC.

Future Research

First, future research can improve NM-MRI methods so that the LC can be divided into more than three sections. In contrast, this study divided the LC into three sections; previous post-mortem studies have found that dividing the LC into six sections allowed better separation of the caudal LC from the SubC. In our recent paper (Cassidy et al., 2022) conducted with participants with Alzheimer's Disease, we divided the LC into five sections. However, the study did not

include a sleep portion as this thesis does, so we did not investigate the SubC, which has a crucial role in muscle atonia during REM sleep. Future research can investigate the optimal way to subdivide the LC, including the counts and lengths of subdivisions.

Second, future research should further inspect the possible association between caudal LC and REM sleep percentage. When doing so, researchers may wish to use a larger sample size than the current study to ensure that they have sufficient statistical power to detect moderate associations.

Third, the current study is correlational. Future studies can undertake causal analyses to identify the precise causal pathways that might underlie the relationship between NM and REM sleep percentage among individuals with PTSD. Also, since many people with PTSD battle with other psychiatric comorbidities, it would seem essential to examine how these comorbidities may influence the relationship between NM and sleep disturbances linked to PTSD. For example, the methods of this thesis could be applied to military personnel pre- and post-deployment to then assess potential changes in those who may develop PTSD upon their return.

Fourth, future research may examine potential links between REM sleep, PTSD, memory, and LC. In a way, PTSD can be seen as a memory-processing failure (Samuelson, 2011; van Marle, 2015). Both REM sleep and healthy LC activity play an integral role in memory consolidation. Recent animal research has shown that abnormal activity in the LC can alter memory consolidation during sleep and impair certain types of memory (Kim & Payne, 2020; Swift et al., 2018). If individuals with PTSD have impaired REM sleep and impaired LC activity, then interacting REM and LC alterations stemming from PTSD may modulate sleep-related memory consolidation. To start addressing this argument, future studies could ask individuals with PTSD to complete novel memory tasks and compare their performance

improvements following selective REM vs NREM sleep deprivation to the performance improvements of healthy controls.

Fifth, future research could consider whether the relationship between NM and REM sleep might be different for different subtypes of PTSD. For example, the disassociation subtype of PTSD may be associated with elevated NM in the LC, and disassociation may modify some of the cognitive functions in which the LC is involved (Amrhein et al., 2008; Brewin et al., 2013; Bruce et al., 2007; DePrince & Freyd, 1999; Krystal et al., 1995; McKinnon et al., 2016; Roca et al., 2006). Unfortunately, the current study did not have a large enough sample with sufficient variations in PTSD subtypes to assess whether the relationship between NA and REM sleep might differ across subtypes.

Chapter 6: Conclusion

This thesis generated new insights into some neurophysiological correlates of sleep disturbances in humans with PTSD. Specifically, it was the first study to show that NM and REM sleep may be related in veterans with PTSD and that this relationship may vary across subdivisions of the LC. This may stimulate further research on novel multi-systemic biomarkers, the pharmacotherapy of PTSD, and new avenues for personalized treatments.

The current study also made methodological contributions that may be applicable beyond the research on PTSD to the field of REM sleep and the NA system in various clinical and non-clinical populations. In fact, REM sleep deprivation has not only been associated with neurodegeneration memory loss but is also believed to cause day-to-day dysfunction, including reduced cognitive performance that can lead to fatal errors in human performance, such as car crashes. All individuals rely on adequate REM sleep for various areas of cognitive and emotional functioning, making it an area of research with widespread implications. The current study leveraged new ways by which the NA system can be studied, highlighting the great potential to tackle research questions that remained unanswered to date. First, the current study showed the suitability of the NM-MRI method for examining the connections between NM and REM sleep. This novel neuroimaging method detected changes in NM signal in the LC, which may potentially communicate information regarding changes in LC function and activity of the LC-NA system. Second, the current study showed that segmenting the LC can lead to a more nuanced understanding of its potential role in sleep physiology. Finally, the results provided starting points for developing a common understanding of how precisely to divide the LC, including the number of subdivisions, which can be pursued in future research. Ultimately, the

current study has led to further advancement of PTSD research which may inspire further work to investigate targeted treatment for this complex condition.

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Appendix A: DSM-5 Diagnostic Criteria for PTSD

Note: The following criteria apply to adults, adolescents, and children older than 6 years. For children 6 years and younger, see the DSM-5 section titled "Post-traumatic stress disorder for Children 6 Years and Younger" (APA, 2013a).

A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
    a. Directly experiencing the traumatic event(s).
    b. Witnessing, in person, the event(s) as it occurred to others.
    c. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
    d. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse). **Note:** Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.

B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
    e. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). **Note:** In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.
    f. Recurrent distressing dreams in which the content and/or effect of the dream are related to the traumatic event(s). **Note:** In children, there may be frightening dreams without recognizable content.
    g. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) **Note:** In children, trauma-specific re-enactment may occur in play.

h. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
i. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
j. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
k. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
l. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia, and not to other factors such as head injury, alcohol, or drugs).
m. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
n. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
o. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
p. Markedly diminished interest or participation in significant activities.
q. Feelings of detachment or estrangement from others.
r. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

s. Irritable behavior and angry outbursts (with little or no provocation), typically expressed as verbal or physical aggression toward people or objects.
t. Reckless or self-destructive behavior.
u. Hypervigilance.
v. Exaggerated startle response.
w. Problems with concentration.
x. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

F. Duration of the disturbance (Criteria B, C, D and E) is more than 1 month.
G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
H. The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.

Specify whether:

With dissociative symptoms: The individual's symptoms meet the criteria for post-traumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

1. **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
2. **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted). **Note**: To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify whether:

With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate).

Source: (American Psychiatric Association, 2013), pp. 271–272.