HIPPOCAMPAL ROLES IN TRAUMA RECALL FOR PTSD AND SUBTYPE

DIFFERENTIAL ROLES OF THE ANTERIOR AND POSTERIOR HIPPOCAMPUS DURING TRAUMA MEMORY RECALL IN POST-TRAUMATIC STRESS DISORDER AND ITS DISSOCIATIVE SUBTYPE

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TITLE: Differential Roles of the Anterior and Posterior Hippocampus During Trauma Memory Recall in Post-Traumatic Stress Disorder and Its Dissociative Subtype

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Lay Abstract

One of the most debilitating effects of post-traumatic stress disorder (PTSD) is the recall of trauma memories. These distressing experiences involve extremely vivid images of the traumatic event, making the individual feel as if the trauma is happening again. The hippocampus, a critical part of the brain for episodic memory, often shows abnormalities in PTSD. In this thesis, we focused on two different parts of the hippocampus during trauma memory recall: the anterior portion (involved in emotional processing) and the posterior portion (involved in spatial and contextual processing). We also investigated a subtype of PTSD called the dissociative subtype (PTSD+DS), which includes emotional numbness and dissociative symptoms, such as recalling trauma memories from an out-of-body perspective. Our findings showed that the anterior hippocampus is more active during trauma memory recall in classic PTSD, while the posterior hippocampus is more involved in PTSD+DS.

Abstract

Post-traumatic stress disorder (PTSD) is a psychiatric condition that may occur after exposure to a traumatic event such as sexual assault. One of its most noticeable adverse effects is abnormality in recalling traumatic memories, leading to severe distress and the sensation that the trauma is unfolding in the present moment. The dissociative subtype of PTSD (PTSD+DS) is a distinct form of PTSD with rather different symptoms, including emotional numbing and dissociative symptoms of depersonalization and derealization. Individuals with PTSD+DS tend to recall trauma memories from an out-of-body or third-person perspective, presumably as a maladaptive mechanism to distance themselves from the trauma. Many brain areas involved in episodic memory exhibit structural and functional abnormalities in PTSD, including the hippocampus, a core component of the episodic memory system. However, findings regarding the hippocampal role in the neurocircuitry of PTSD are rather inconsistent. These inconsistencies may stem from the often overlooked different functions of the anterior (aHipp) and posterior hippocampus (pHipp). The aHipp is primarily involved in processing the emotional aspects of episodic memories, while the pHipp is more involved in spatial and contextual processing. We therefore hypothesized that the aHipp would be more dominant during trauma memory recall in classic PTSD compared to the pHipp. In PTSD+DS, we expected the dominance of the aHipp to diminish. Our findings mainly supported our predictions. Graph-theoretic analyses revealed

the aHipp to be a dominant hub in the brain in classic PTSD during both resting state and trauma memory recall. In PTSD+DS, however, the aHipp did not emerge as a hub, and instead, the pHipp assumed a more pronounced role. Our findings advance the current understanding of the hippocampal roles in PTSD and PTSD+DS and may guide future therapeutic efforts.

In memory of the 176 souls who lost their precious lives in the downing of Flight PS752

by the Islamic Republic regime on January 8, 2020

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List of Abbreviations

ACC	Anterior cingulate cortex
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
aHipp	Anterior hippocampus
aIC	Anterior insula
AM	Autobiographical memory
BDI	Beck Depression Inventory
CAPS	Clinician-Administered PTSD Scale
CEN	Central executive network
CTQ	Childhood Trauma Questionnaire
C-rep	Contextualized representation
dACC	Dorsal anterior cingulate cortex
DCM	Dynamic Causal Modelling

DG	Dentate gyrus
dHipp	Dorsal Hippocampus
dlPFC	Dorsolateral prefrontal cortex
DMN	Default-mode network
dmPFC	Dorsomedial prefrontal cortex
DRT	Dual Representation Theory
EC	Entorhinal cortex
EPM	Elevated plus maze
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FN	Fastigial nucleus
GLM	General linear model
GR	Glucocorticoid receptor
IAS	Innate alarm system
ICC	Intracalcarine cortex
ICN	Intrinsic connectivity network
ITG	Inferior temporal gyrus
LEA	Lateral entorhinal area

LOC	Lateral occipital cortex
MCC	Midcingulate cortex
MCI	Mild cognitive impairment
MDI	Multiscale Dissociation Inventory
MEA	Medial entorhinal area
MI	Moral injury
MIES	MI events scale
mPFC	Medial prefrontal cortex
MTG	Middle temporal gyrus
MTL	Medial temporal lobe
MVGC	Multivariate Granger causality
OFC	Orbitofrontal cortex
OFusG	Occipital fusiform gyrus
PAG	Periaqueductal gray
PaHipp	Parahippocampal gyrus
Para	Parasubiculum
PCC	Posterior cingulate cortex
PET	Positron emission tomography

PHC	Parahippocampal cortex
pHipp	Posterior hippocampus
pIC	Posterior Insula
PL	Prelimbic cortex
PRC	Perirhinal cortex
Pre	Presubiculum
PTSD	Post-traumatic Stress Disorder
PTSD+DS	Dissociative subtype of PTSD
rCBF	Regional cerebral blood flow
ROI	Region of interest
RSC	Retrosplenial Cortex
RSDI	Responses to Script-Driven Imagery
SAM	Situationally accessible memo
SC	Superior colliculus
SCID	Structured Clinical Interview for DSM-IV
SCR	Skin conductance response
SMA	Supplementary motor area
SMG	Supramarginal gyrus

SMN	Somatosensory-motor network
SN	Salience Network
S-rep	Sensory representation
STG	Superior temporal gyrus
Sub	Subiculum
SUDS	Subjective units of distress scale
TOFusC	Temporal occipital fusiform cortex
TP	Temporal pole
TPJ	Temporoparietal junction
TTX	Tetrodotoxin
VAM	Verbally accessible memo
vHipp	Ventral Hippocampus
vmPFC	Ventromedial prefrontal cortex
VN	Vestibular nuclei

Declaration of Academic Achievement

This thesis is structured into five chapters. Chapter 1 provides a general background, highlights gaps in the literature, and outlines the structure of the thesis. Chapters 2, 3, and 4 consist of empirical papers that are either published or in the process of being prepared for publication. The final chapter presents the conclusions, limitations, and future directions.

The research described in Chapter 2 was supported by the MacData Institute. Data for this chapter was obtained from the publicly available Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. M. Chaposhloo curated the data, conducted the analyses, and drafted the original manuscript under the supervision of Dr. Becker and the co-supervision of Dr. Shaw. Research questions were formulated jointly by M. Chaposhloo and Dr. Becker, with the research being conceptualized by them and Dr. Shaw. Dr. Becker, Dr. Shaw, Dr. Nicholson, and Dr. Lanius contributed to the data interpretation and manuscript revisions. Chapter 2, in its entirety, was published in the journal *NeuroImage: Clinical* in April 2023.

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Dr. Becker provided the main supervision throughout all stages of this thesis.

Chapter 1

Introduction

"I think this man is suffering from memories."

Sigmund Freud about trauma (1895; as paraphrased in van der Kolk, 2015, p. 15).

Introduction

Post-traumatic Stress Disorder (PTSD) is a psychological disorder that arises after an individual experiences or witnesses a traumatic event, such as a plane crash, sexual assault, or exposure to an explosion (American Psychiatric Association, 2013). Normally, such fear should trigger transient physiological changes—the "fight-or-flight" response—in the body to defend against or avoid danger, and most individuals naturally recover from these acute changes. However, should these alterations persist for a month or more, the individual may be diagnosed with PTSD. Symptoms of PTSD include hyperarousal, hypervigilance, avoidance of trauma-related reminders, negative mood, insomnia, and—most relevant to the topic of this thesis—"flashbacks," during which the person vividly *relives* the traumatic event, experiencing intense sensory load as if the event were unfolding right there and then (Yehuda et al., 2015). This lack of contextualization in trauma memories in PTSD is a key feature distinguishing them from "normal" memories. Specifically, individuals with PTSD struggle to establish a sense of safety when recalling trauma memories in a *safe* environment. Later on, we shall also delve into another quality of trauma memories: their fragmentary nature.

The lifetime prevalence of exposure to traumatic events varies significantly across nations due to historical, cultural and political factors. While this rate is reported at 73.8% in South Africa, in Europe and Japan it ranges between 54-64% (Atwoli et al., 2015). This percentage also differs among age groups, with 60% of adolescents (McLaughlin et al., 2013) and 79% of adults (Roberts

et al., 2011) in the US reporting experiences of trauma. Of those exposed, around 8% may eventually develop PTSD (Kessler et al., 1995). Indeed, a substantial portion of the population is likely to suffer from PTSD at some point during their lives. In the United States, the lifetime prevalence among civilians ranges from 3.4% to 26.9% (Schein et al., 2021). Despite its high prevalence, current interventions for PTSD are, at best, moderately effective (Bryant, 2019; Levi et al., 2022), underscoring the critical need for more efficacious therapeutic strategies. A more comprehensive understanding of the neural underpinnings of PTSD could provide valuable insights that inform and refine therapeutic approaches, potentially improving outcomes. By identifying specific neural circuits involved in trauma processing and symptom maintenance, future interventions may become more targeted, offering possibilities for novel treatments, such as neurofeedback or personalized brain stimulation techniques.

Most predominant theories of PTSD have implicated three core brain regions as the epicentres of dysfunction within the neurocircuitry of PTSD (figure 1): the amygdala, the medial prefrontal cortex (mPFC) and the hippocampus (Shin et al., 2006). However, more recent studies suggest that other brain areas, such as the cerebellum, brain stem, and insula, may also play significant roles, particularly through their interaction with the aforementioned core areas (e.g., Harricharan et al., 2016, 2017, 2020; Rabellino et al., 2018). This thesis will primarily concentrate on the hippocampus while also examining its abnormal connectivity with the rest of the brain. To justify the focus on the hippocampus, a detailed examination of the neural and behavioural abnormalities in PTSD, especially those related to trauma memories, is warranted.

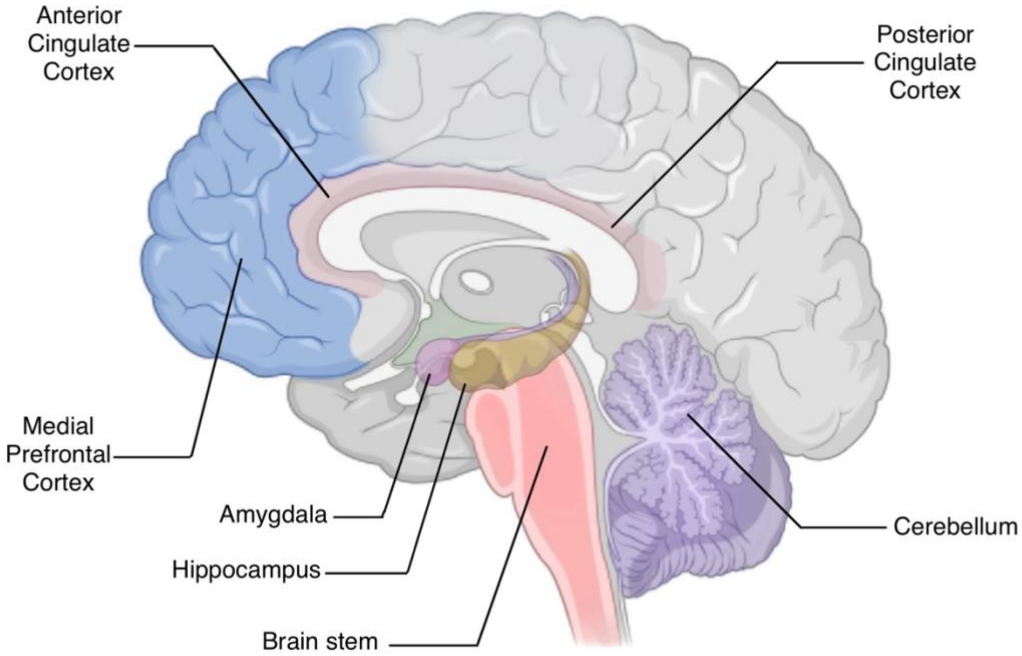

Figure 1: Brain regions implicated in the neurocircuitry of PTSD.

PTSD, Its Dissociative Subtype, and Moral Injury

In the preceding sections, we briefly discussed PTSD and its symptomatology. However, PTSD is not a monolithic disorder, as individuals show wide variations in symptom manifestation. Importantly, research over the past decade has identified a distinct subtype of PTSD characterized by unique symptoms and neural signatures (Lanius et al., 2012). This subtype is defined by dissociative symptoms, involving a sense of detachment from one's body, thoughts, feelings, memories, surroundings, and identity. Consequently, this subtype is termed the dissociative subtype of PTSD (PTSD+DS). PTSD+DS is marked by two core dissociative symptoms: depersonalization and derealization. Depersonalization is characterized by a persistent sense of

detachment from oneself, akin to "out-of-body" experiences. Similarly, derealization involves perceiving oneself or one's surroundings as "dream-like" or unreal. Approximately 15-30% of those with PTSD are estimated to belong to the dissociative subtype (Schiavone et al., 2018). In addition to its distinct behavioural signature, recent neuroimaging studies have revealed distinct neural patterns differentiating PTSD from PTSD+DS, the details of which we shall further explore in subsequent sections of this thesis.

One of the hallmark symptoms of PTSD is the dysfunctional recall of trauma memories, to the extent that some scholars consider PTSD as a disorder of memory. Trauma memories often lack appropriate context, leading to their retrieval accompanied by a misperception of the present context—which is actually secure—as identical to the context of the traumatic event. Consequently, stimuli reminiscent of the trauma (for instance, a veteran encountering a trash can in a peaceful city) become associated with threat and provoke intense fear and emotional reactions. In this example, the veteran may perceive the innocuous trash can as analogous to one observed in a war-afflicted city where it concealed an explosive device, thereby failing to distinguish between the past perilous context and the current safe one.

Another reported aspect of trauma memories in PTSD is that their voluntary recall is difficult, "fragmented," "disorganized," and lacking coherence (Bisby et al., 2020; Brewin, 2014; Halligan et al., 2003; Harvey & Bryant, 1999; Jelinek et al., 2009; Jones et al., 2007). This phenomenon aligns with the notion that trauma memories lack context, as context serves as the cohesive element within an episodic memory, binding together its various components. Consequently, the episodic recall of trauma memories appears fragmented and disorganized due to the absence of a robust contextual representation that integrates its disparate elements, resulting in memories that are merely fragmented sensory and motor representations (Brewin et al., 1996; van der Kolk & Fisler,

1995). This concept forms the crux of a prominent theory of PTSD known as the Dual Representation Theory (Brewin et al., 2010), which will be explored in greater depth later. Another similar perspective suggests that the excessive emotional intensity present during the encoding of traumatic memories interferes with attention and memory processes, resulting in truncated, overly simplistic and "poorly articulated" recollections of the traumatic event (Foa & Rothbaum, 1998). However, it is worthwhile to note that the characterization of trauma memories in PTSD as fragmented is not universally accepted, with some scholars contesting this viewpoint (Berntsen et al., 2003; Rubin et al., 2008).

Moral Injury (MI) is a condition closely associated with PTSD, arising from situations in which an individual participates in, fails to prevent, or merely witnesses actions that fundamentally violate their core moral and ethical values (Litz et al., 2009). MI is particularly prevalent among military personnel and public safety workers, eliciting extreme feelings of guilt, shame, disgust, anger, or even suicidality. For instance, during the COVID-19 pandemic, healthcare professionals faced the harrowing decision of allocating scarce medical resources, which involved determining which patients would receive care—an illustration of such moral dilemmas. MI and PTSD share considerable overlap in their etiology and symptomatology (Koenig et al., 2020). Furthermore, individuals with comorbid PTSD and MI often experience exacerbated PTSD symptoms and subsequent functional impairments (Bryan et al., 2018). Therefore, it is reasonable to treat MI-related experiences as traumatic events, and throughout this thesis, they will be regarded as such.

The Hippocampus as the Hub in the Episodic Memory System

Now that we are acquainted with memory-related impairments in PTSD, it is important to examine a brain region critical for episodic memory processes. For several decades, it has been established

that the hippocampus, in particular, and the medial temporal lobe (MTL), more broadly, are key contributors to episodic memory (Scoville & Milner, 1957; Squire, 1986). The Medial Temporal Lobe (MTL) encompasses the hippocampus as well as the surrounding entorhinal cortex (EC), perirhinal cortex (PRC), and parahippocampal cortex (PHC), which collectively play a crucial role in declarative memories, spatial navigation and contextual processing. Seminal evidence of the hippocampus's critical involvement in episodic memory emerged from the case of patient H.M. (Scoville & Milner, 1957), now known as Henry Molaison (1926-2008). At the age of 27, he underwent a surgical procedure intended to mitigate his incapacitating seizures, which involved the resection of the anterior two-thirds of his bilateral MTL. An unforeseen consequence of this surgery was the development of severe anterograde amnesia in H.M., characterized by an inability to form new memories and rapid forgetting of events almost as they occurred, although his working memory and procedural memory remained intact. Additionally, he experienced moderate temporally graded retrograde amnesia, losing most memories from one to two years before the surgery, with some memories affected as far back as 11 years. Since H.M. had shown no memory impairments before the surgery, the removal of his MTL was deemed the sole cause of his profound deficits in encoding and recalling episodic memories. The knowledge gleaned from H.M.'s condition provided the foundation for subsequent research that revolutionized our understanding of human memory. In the following, we will briefly introduce the circuitry of MTL structures (for a review of the MTL and its role in episodic memory, see Dickerson & Eichenbaum, 2010).

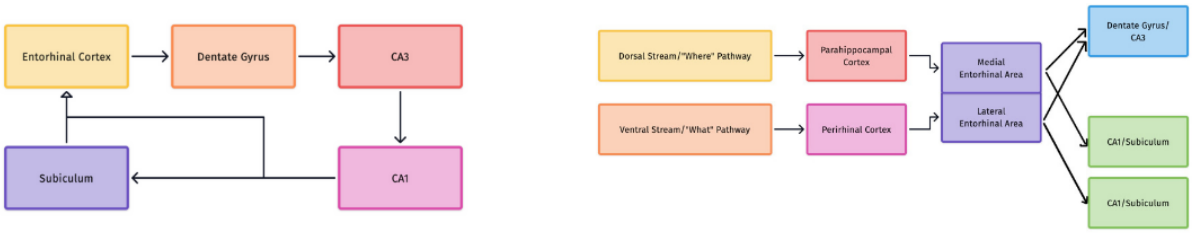

Figure 2: ***Left:*** *simplified circuitry of hippocampal subfields.* ***Right:*** *dorsal and ventral streams within the MTL.*

The hippocampus is a banana-shaped structure with its long axis oriented along the dorsoventral axis in rodents, and this alignment is transposed to a posterior-anterior axis in primates. A cross-section of the hippocampus, perpendicular to its long axis, would reveal its sub-fields: the dentate gyrus (DG), the hippocampus proper (comprising CA3, CA2, and CA1), the presubiculum (Pre), the parasubiculum (Para), and the subiculum (Sub). The classical understanding of the hippocampal circuitry centres around the so-called "trisynaptic circuit." In this model, the EC provides input to the DG via the perforant path (synapse 1). The DG, in turn, projects to CA3 through mossy fibres (synapse 2), and CA3 subsequently propagates signals to CA2 and CA1 via the Schaffer collaterals (synapse 3). However, it is worth noting that the trisynaptic circuit is only partially accurate. It is now known that the CA1 projects to the Sub, which, along with the CA1, reciprocally sends output back to the EC (figure 2; left). Beyond the confines of the hippocampus, the flow of information follows a specific trajectory. Generally, sensory information is initially processed by unimodal sensory cortices before being transmitted to multimodal cortical areas. This information is then channeled to the EC, which acts as a conduit to the hippocampus. After processing in the hippocampus, the information is relayed back to the deep layers of the EC and then projected to both multimodal and unimodal cortices. This flow of information mirrors the well-known dorsal and ventral visual streams, also referred to as "where"/"how to" and "what" pathways, respectively. Specifically, the PRC predominantly receives information from the ventral

visual stream, which is responsible for processing nonspatial information related to stimulus identity. In contrast, the PHC obtains information from areas along the dorsal visual stream, which primarily handles spatial information. This segregation of information is preserved within the EC, as the PRC preferentially projects to the lateral entorhinal area (LEA), while the PHC targets the medial entorhinal area (MEA). LEA and MEA then separately project to the hippocampus, where information integration occurs in a rather interesting way. Specifically, projections from LEA and MEA terminate on the same neurons in the DG and CA3, while they target different populations of neurons in CA1 and the Sub (figure 2; right). This distinctive pattern of EC projections to the hippocampus is hypothesized to underly the hippocampus' ability to simultaneously associate and discriminate events and their corresponding contexts. The opposite route from the hippocampus to the EC, parahippocampal and neocortical areas also reflects a "what" versus "where" segregation, which is hypothesized to support the phenomenological experience of episodic recall. In particular, back projections from LEA/PRC to neocortical areas along the ventral visual stream may bring about a sense of familiarity and memory of items during episodic retrieval. Conversely, back projections from the hippocampus to MEA/PHC and subsequently from MEA/PHC to neocortical areas along the dorsal visual stream may facilitate the recollection of contextual information and context-item association.

The hippocampus is also essential for spatial navigation, with early evidence coming over half a century ago from electrophysiological recordings in rodents' hippocampus, revealing the existence of "place cells" (O'Keefe, 1976). These neurons exhibit "view-invariance" and are sensitive solely to the animal's location, regardless of its orientation. Collectively, place cells are thought to form the foundation of an allocentric "cognitive map" of the animal's surrounding environment (O'Keefe & Nadel, 1978). Moreover, hippocampal damage (particularly to the right hippocampus)

impairs allocentric representation of memory, such as remembering a location from different perspectives (Abrahams et al., 1997; Hartley et al., 2007; Holdstock et al., 2000; King et al., 2002) and spatial navigation (Bohbot et al., 1998; Jarrard, 1993; Morris et al., 1982; Spiers et al., 2001). However, it is worth noting that contemporary neuroscientific consensus suggests that the roles of the hippocampus in episodic memory formation and spatial navigation are not separate processes but are intricately interwoven.

Hippocampus Shows Abnormal Activity and Functional Connectivity in PTSD

We have established that PTSD is associated with impaired memory recall and that the hippocampus plays an essential role in the episodic memory system. Consequently, it is logical to investigate whether the hippocampus exhibits any abnormalities in PTSD. Structural neuroimaging studies consistently report a reduction in hippocampal volume among individuals with PTSD (Bremner et al., 1995; Bromis et al., 2018; Karl et al., 2006; Logue et al., 2018; O'Doherty et al., 2015; Woon & Hedges, 2008). However, findings related to hippocampal activation are more nuanced and task-dependent. An early PET study found a positive correlation between script-induced flashback intensity in individuals with PTSD and regional cerebral blood flow (rCBF) in the left hippocampus, alongside other regions such as the brainstem, insula, somatosensory, and cerebellar regions (Osuch et al., 2001). Another study using a word stem completion task showed increased rCBF in the bilateral hippocampus and the left amygdala in the PTSD group compared to the control group, with no differences in accuracy scores (Shin et al., 2004). The same study reported that within the PTSD group, hippocampal rCBF positively correlated with symptom severity. Moreover, in a virtual Morris Water task, individuals with

PTSD showed reduced hippocampal BOLD response compared to controls, and the degree of reduction correlated with PTSD severity, even though behavioural performance did not differ between groups, suggesting that individuals with PTSD utilized non-hippocampal regions to complete the task (Astur et al., 2006).

Regarding semantic and episodic memory tasks, the hippocampus typically exhibits attenuated activation in those with PTSD during memory retrieval (Carrión et al., 2010; Geuze et al., 2008; Hayes et al., 2011), coupled with inferior task performance compared to control groups. Interestingly, studies reporting equal hippocampal activation in those with PTSD relative to controls during encoding also observed weaker task performance during retrieval in the PTSD cohort (Carrión et al., 2010; Geuze et al., 2008). In cases where the hippocampal activity was elevated in PTSD, task performance was comparable to control (Brohawn et al., 2010; Thomaes et al., 2009; Werner et al., 2009). Brohawn et al. (2010) reported elevated BOLD response in the amygdala and hippocampus during successful encoding of negative images compared to neutral ones in PTSD groups, with a positive correlation between the amygdala and hippocampus activity and PTSD symptom severity (Brohawn et al., 2010). In contrast, another PTSD group exhibited reduced BOLD response in these regions during the encoding of trauma-related pictures, with reduced left hippocampal activity linked to heightened arousal symptoms (Hayes et al., 2011). This study also reported higher false alarm rates for novel lures in the PTSD group, suggesting an over-reliance on gist-based representations. Together, these findings from Brohawn et al. (2010) and Hayes et al. (2011) suggest that the hippocampus and amygdala in PTSD may exhibit hyperactivity in response to novel aversive stimuli but hypoactivity to trauma-related stimuli. In another study involving the retrieval of intense autobiographical memories (AM), the PTSD group exhibited increased hippocampal activation during the construction phase of negative versus positive

emotionally intense AMs, compared to controls (St. Jacques et al., 2011). The study also reported a greater sense of reliving for negative versus positive AMs and more recalled stressful events in the PTSD group, potentially linked to heightened hippocampal activation. In summary, these findings hint at a compensatory mechanism in PTSD involving the hippocampus, where increased hippocampal activation appears necessary to achieve task performance in those with PTSD comparable to control groups.

In the domain of fear-associated learning tasks (fear acquisition, extinction, extinction recall, and fear renewal), the prevailing view is that the amygdala is generally involved in aversive conditioning, while the hippocampus plays an additional role in contextual conditioning, aligning with its crucial role in spatial representations. Indeed, hippocampal spatial representations influence fear generalization, where conditioned fear is expressed in a safe context. For example, an fMRI study using a cue-context conditioning paradigm in a healthy population found that individuals with weaker hippocampal spatial representations exhibited heightened fear generalization, as indicated by higher differential skin conductance response (SCR) in the safe context compared to those with stronger representations (de Voogd et al., 2020). Interestingly, in the threat context, those with weaker representations showed a diminished differential SCR, indicating reduced discrimination between threat and safe cues.

It seems that hippocampal activation in individuals with PTSD depends on the context and specific phases of experimental procedures. For example, in an ABC conditioning procedure—where participants underwent fear conditioning in context A, fear extinction in context B, and fear renewal in a novel context C—the hippocampus showed increased activation in response to the CS+ in context C, along with elevated SCR in those with PTSD compared to controls (Wicking et al., 2016). Conversely, in an ABB paradigm (encompassing fear conditioning, extinction, and

extinction recall), the hippocampus and the ventromedial prefrontal cortex (vmPFC) showed decreased activation during extinction recall in those with PTSD, alongside deficits in extinction recall (Milad et al., 2009).

Similarly, in an ABBA conditioning procedure—where fear renewal occurred in the same threat context during the fourth stage—the hippocampus showed decreased activation in those with PTSD during fear renewal (Garfinkel et al., 2014). Moreover, those with PTSD showed deficits in recalling extinction within the extinction context and in fear renewal in the conditioning context, as evidenced by decreased SCR in response to the extinguished CS+ in the conditioning context (Garfinkel et al., 2014). This suggests that those with PTSD were unable to use safety and danger contexts to inhibit and enhance extinguished fear memory, respectively, resulting in abnormally high fear levels in the safety context and abnormally low fear levels in the danger context. This may be due to either unavailable contextual information within the hippocampus or difficulties in utilizing this information to disambiguate threats from safe cues and regulate fear. In contrast, the control group behaved normally, retaining the extinction memory in the safe environment and experiencing a return of fear in the dangerous context (Garfinkel et al., 2014). Additionally, the study found that individuals with PTSD did not show any deficits in fear and extinction learning, indicating these processes remain unchanged in PTSD. This suggests abnormalities lie in either extinction recall or the use of contextual information, with impairment in fear renewal supporting the latter. Reduced hippocampal activity during fear renewal in response to CS+ in individuals with PTSD, compared to controls, further supports deficiencies in contextual processing (Garfinkel et al., 2014).

In another study, during both fear acquisition and extinction phases, hippocampal activity positively correlated with greater avoidance symptoms within the PTSD cohort (Sripada et al.,

2013), raising the possibility that increased hippocampal activation facilitates over-consolidation of fear during both fear acquisition and recall, or overgeneralization of fear into a neutral context. Finally, in a recent study (van Rooij et al., 2021), participants were scanned two months after exposure to a traumatic event while undergoing a contextual fear acquisition and extinction task. In response to threat cues during acquisition, there was a positive correlation between hippocampal activation and a measure of resilience. Additionally, hippocampal activation during the extinction task was negatively correlated with PTSD symptoms three months post-trauma. These findings suggest that the extent to which the hippocampus is recruited during and after a traumatic event may play an important role in regulating fear response and may even prevent the development of PTSD.

Mixed results also extend to studies of hippocampal functional connectivity. Some research has found increased connectivity between the hippocampal and regions associated with emotional processing, such as the anterior insula (Sripada, King, Welsh, et al., 2012). In contrast, decreased connectivity with the amygdala, another emotional processing region, has been observed in PTSD (Sripada, King, Garfinkel, et al., 2012). However, other studies have found no such effects (Brown et al., 2014; Nicholson et al., 2015; Rabinak et al., 2011), highlighting the variability in findings.

Functional differentiation along the long axis of the hippocampus

These aforementioned mixed results regarding the hippocampal abnormalities in PTSD might, in part, come from those studies not taking into consideration the fact that the hippocampus exhibits functional differences along its long axis (Fanselow & Dong, 2010; Grady, 2020; O'Leary & Cryan, 2014; Poppenk et al., 2013; Strange et al., 2014; Zeidman & Maguire, 2016). Generally, the anterior (ventral in rodents) hippocampus (aHipp) plays a more prominent role in emotional

and anxiety-related behaviour, while the posterior (dorsal in rodents) hippocampus (pHipp) is more involved in spatial cognition and detailed spatio-temporal contextual representations. This functional differentiation may result from differences in anatomical connectivity along the long axis of the hippocampus noted previously. For instance, the dorsal CA1 and subicular areas project to the retrosplenial cortex (Cembrowski et al., 2018; Kitanishi et al., 2021; Van Groen & Wyss, 2003), which is an important region for visuospatial memory. Conversely, the vHipp connects to areas important for stress and anxiety, such as the amygdala and the insula (Arszovszki et al., 2014; Cenquizca & Swanson, 2007). However, ongoing debates persist regarding the distinct roles of the aHipp versus the pHipp. In the following, we will explore some of the evidence for these differential roles, focusing primarily on rodent studies due to the abundance of data. Thus, when mentioning vHipp and dHipp, we refer to rodent studies. In contrast, aHipp and pHipp will refer to primate studies (both human and non-human).

The dHipp has consistently been implicated in spatial cognition and memory. In rodents, lesions to the dHipp, but not the vHipp, result in deficits in spatial memory (Bannerman et al., 2002; E. Moser et al., 1993; M.-B. Moser et al., 1995; Pothuizen et al., 2004). Additionally, place fields in the dHipp have a higher density and sharper tuning curves than those in the vHipp (Jung et al., 1994). In monkeys, the pHipp showed more active neurons than the aHipp following a spatial learning task (Colombo et al., 1998). Furthermore, London taxi drivers, known for their superior spatial navigation skills, had an increased volume in their pHipp relative to controls (Maguire et al., 2000). The dHipp also plays a critical role in contextual processing and encoding contextual fear memories. Antagonizing NMDA receptors in the dHipp impaired the encoding of the context memory (Matus-Amat et al., 2007). Similarly, antagonizing NMDA receptors in the dHipp disrupted the encoding of contextual fear conditioning, as well as both the encoding and retrieval

of trace fear memories (Quinn et al., 2005). Moreover, optogenetic manipulation of dHipp (but not vHipp) activity led to deficits in the contextual encoding of footshocks (Kheirbek et al., 2013), and adult-born neurons in the dDG were shown to be necessary for the acquisition of contexts in a contextual fear discrimination task (Wu & Hen, 2014). Reports also indicate the involvement of the dHipp in fear extinction. For instance, stimulating the dHipp at low frequency can result in extinction deficits (Garcia et al., 2008).

On the other hand, the vHipp is more involved in anxiety-related behaviours compared to the dHipp. In rats, lesions in the vHipp—but not dHipp—led to reduced innate anxiety behaviours (Bannerman et al., 2004; Pentkowski et al., 2006) and reduced freezing in response to both context and conditioned stimuli (CS) (Trivedi, 2004). These lesions also decrease freezing behaviour following unsignaled footshocks (Bannerman et al., 2003). Moreover, muscimol (an $GABA_A$ agonist that enhances neuronal inhibition through $GABA_A$ receptors) injections into the vHipp—but not the dHipp—weakened the auditory CS-US association when administered before fear conditioning (Maren & Holt, 2004). Similarly, Tetrodotoxin (TTX) infusion—which abolishes neuronal activity—into the vHipp before the training session blocked fear responses to both the CS and context (Bast et al., 2001). Administering this agent after extinction, however, did not alter context-US associations but impaired context-dependent fear renewal (Hobin et al., 2006). Furthermore, disrupting pathways from the vHipp to the amygdala or the prelimbic cortex (PL)—the rodent analogue to the human dACC—impaired fear renewal (Orsini et al., 2011). Additionally, inactivation of the vHipp an hour before fear conditioning impaired fear acquisition (Chen et al., 2016). Also, administering a glucocorticoid receptor (GR) antagonist into the amygdala and vHipp—but not the dHipp—before contextual fear conditioning reduced freezing behaviour a day after training, though not immediately after (Donley et al., 2005). These findings

suggest that the vHipp and its projections to the amygdala and PL might be necessary for fear renewal and that GR activation within the vHipp (and not the dHipp) is important for forming long-term memory for contextual fear conditioning. Moreover, in an elevated plus maze (EPM) paradigm, rats with vHipp—but not dHipp—lesions spent more time in the open arm, indicating reduced unconditioned fear responses (Kjelstrup et al., 2002). Finally, muscimol in the vHipp reduced anxiety-like behaviours in the EPM, whereas its administration in the dHipp increased such behaviours (Zhang et al., 2014). Overall, these results underscore the vHipp's role in anxiety-like behaviours, while the dHipp might play a role in mitigating anxiety.

In summary, the findings reviewed above indicate that the dHipp in rodents is primarily involved in spatial and contextual processing, while the vHipp is more involved with anxiety-related behaviours. While translating these findings from rodents to primates, including humans, is not straightforward, more recent human studies suggest that the aHipp and pHipp indeed generally align with the corresponding roles of the vHipp and dHipp in rodents in anxiety and spatial processing, respectively. For example, in a study involving contextual fear conditioning among healthy populations (Lang et al., 2009), the pHipp showed activity during the early phase of contextual fear conditioning in which an unsignaled US was associated with a visual context. On the other hand, the more anterior region of the hippocampus demonstrated activity during the later phase of acquisition. This pattern of activation suggests that the aHipp is more involved in the expression of contextual fear, while the pHipp is more involved in encoding contextual fear (Maren et al., 2013). Moreover, in rhesus macaques, elevated metabolism in the aHipp has been associated with anxiety (Shackman et al., 2013), and in humans, state anxiety has been linked to aHipp activity (Satpute et al., 2012). In contrast, the pHipp showed greater activation during spatial memory tasks that require precise spatial representations, while the aHipp showed more

involvement in the non-spatial tasks and those requiring less detailed spatial information (Brunec et al., 2018; Evensmoen et al., 2013, 2015; Nadel et al., 2013; Ryan et al., 2010).

The Dual Representation Theory

This thesis aims to enhance our understanding of hippocampal involvement during trauma memory recall in PTSD. The Dual Representation Theory of PTSD (Brewin, 2014; Brewin et al., 2010), which is among the most influential frameworks for understanding the neural circuitry of PTSD, makes some assertions regarding the hippocampal role in PTSD. In this thesis, we will argue that some modifications to this theory are necessary. Therefore, here, we will review the dual representation theory to provide the reader with a basic understanding of the theory.

The theory begins by proposing a memory system dedicated to long-term representations of perceptual information, such as visual, spatial, auditory, and olfactory data, which operates independently of their autobiographical significance. This system is distinct from the memory system for verbal materials and appears to encode information automatically. For example, in the case of visual information, even a brief fixation is sufficient to encode data into a long-lasting representation. While this is more than just a "gist" of the scene, it is not as complete and detailed as the original perceptual experience. Instead, it is a "higher-level abstraction of the original input that preserves many perceptual features." The contents of this perceptual system are accessible only involuntarily, and their retrieval evokes a sense of "reliving" or "newness."

PTSD impacts perceptual and episodic memories of traumatic events in contrasting ways. Firstly, individuals with PTSD frequently experience involuntary and intense recall of traumatic scenes, known as flashbacks. During a flashback, patients encounter vivid and detailed images related to the traumatic event. While these images are primarily visual, they may include other sensory

modalities accompanying the trauma. The dissociative aspect of this symptom is that patients feel or act as though the traumatic event is occurring in the present. The intensity of this experience varies with PTSD severity. In mild cases, there is a transient sense of the trauma occurring in the present. In severe cases, the connection to their "current autobiographical self and present surroundings" is significantly diminished during a flashback.

Conversely, when PTSD patients attempt to recall traumatic events voluntarily, they often experience partial failure. These memories are typically reported as difficult to recall, "fragmented," and "disorganized." Repetitions, unfinished thoughts, and speech fillers characterize fragmentation. Similarly, disorganization involves utterances suggesting "confusion or disjointed thinking," contrasting with statements indicating "realization, decision-making, or planning, which are coded as organized thoughts" (Brewin, 2016; Foa et al., 1995). In other words, there are "gaps" or "discontinuities" in their traumatic memories. Additionally, PTSD patients' accounts of their traumatic memories are described as "incoherent," meaning the narrative elements are not "meaningfully related to one another" (Brewin, 2016). Thus, it appears that while perceptual memories are enhanced, episodic memories of traumatic events are weakened (Brewin, 2014).

Based on the distinction between perceptual memory and verbal narrative memory, Brewin and colleagues proposed the Dual Representation Theory of PTSD (Brewin et al., 2010). According to its original version (Brewin et al., 1996), there are two types of accessible memory systems: situationally accessible memory (SAM) and verbally accessible memory (VAM). The SAM system holds detailed sensory and perceptual images, encoding a substantial amount of sensory information relevant to survival, while conscious attention focuses on the source of danger. Flashbacks, within this framework, are perceptual SAMs encoded rapidly during traumatic events

without conscious attention, accessible only automatically. Importantly, the SAM system is maintained by subcortical and perceptual brain areas rather than the hippocampus and areas involved in higher-order cognitive control. Therefore, SAMs lack context and are perceived as if occurring in the present. SAMs coexist with VAMs, which are memories encoded with the participation of the hippocampus and prefrontal areas (Brewin, 2001), using more conscious attention. As a result, VAMs are contextualized, verbally and voluntarily accessible, and can be processed like other information in the autobiographical memory system.

In this framework, flashbacks are considered part of a "recovery process" where the automatic recall of these SAMs facilitates conscious attention in accessing their contents. This process allows the memories to be "re-encoded" into the episodic memory system, making them verbally accessible and providing them with a "temporal and spatial context." As conscious attention aids in this re-encoding, the ability of sensory cues to signal the presence of a threat diminishes, leading to a reduction in both the frequency and intensity of flashbacks. In those with PTSD, this process is disrupted. Either the SAM system encodes events in an uninhibited or exaggerated manner, or the VAM system becomes deficient in encoding or re-encoding events. Consequently, flashbacks remain intense and frequent.

In the revised Dual Representation Theory (Brewin et al., 2010), SAM and VAM are replaced with S-rep (sensory representation) and C-rep (contextualized representation), respectively. C-reps are abstract, verbally accessible allocentric representations, and supported by medial temporal lobe (MTL) structures, including the hippocampus and parahippocampus. Notably, episodic memories and verbal narratives of traumatic or other events are facilitated by C-reps. In contrast, S-reps are depictive, situationally accessible egocentric representations and accessed only involuntarily.

In the encoding of an ordinary event into the episodic memory system, lower-level sensory information is transformed into higher-level information within the parietal areas and MTL. During voluntary recall, the allocentric MTL representation is converted into egocentric imagery through the transformation mechanism proposed by Byrne et al. (2007). Typically, these S-reps rapidly fade and become inaccessible. However, in the case of distressing or emotionally significant events, S-reps become more durable. This durability is possibly due to the involvement of the insula, which encodes emotions such as fear or disgust (A. D. Craig, 2002; Critchley et al., 2004) and associates them with the low-level sensory attributes of the event, with assistance from the amygdala (LeDoux, 1998). S-reps are restored in two ways: either through sensory input resembling the original event in a bottom-up manner or through reconstructed egocentric representation in the precuneus that shares similar viewpoints and characteristics with the original event. Despite this, healthy individuals manage distressing events effectively because each S-rep is linked to its corresponding C-rep in the MTL. This association serves two functions: first, it contextualizes the event, providing it with appropriate semantic and autobiographical meaning, preventing the individual from re-experiencing it as if it were occurring in the present. Second, due to its connection with the MTL, the prefrontal cortex can exert top-down control over the memory, enabling the individual to suppress the recall of the event (Anderson et al., 2004) or to disambiguate events with similar contexts (King et al., 2005). The revised dual representation model suggests that during a traumatic event in PTSD, S-reps are encoded more strongly than usual, while the encoding of C-reps and the normal association between an S-rep and its analogous C-rep are weakened. This may occur because excessive stress negatively impacts the hippocampus while hyperactivating the amygdala (Elzinga & Bremner, 2002; Metcalfe & Jacobs, 1998; Payne et al., 2006; Vyas et al., 2002).

In healthy individuals, retrieval involves the activation of egocentric visual imagery through C-reps, which in turn reactivates weaker sensory representations (S-reps). In contrast, in PTSD patients, the absence of robust C-reps leads to egocentric visual imagery that is driven primarily by strong S-reps and remains unaffected by C-reps. Consequently, the resulting flashback is experienced more as perception than as recall, lacking the contextual and autobiographical meaning typically provided by C-reps. It is important to note that the diminished strength of C-reps does not imply that PTSD patients are incapable of voluntarily retrieving the traumatic event because C-reps are rarely entirely absent. However, the voluntary recall of traumatic events tends to be fragmented and disorganized.

In summary, the dual representation theory posits that the whole hippocampus is relatively "offline" during trauma memory recall in PTSD. However, we contend that this assertion requires modification in two key aspects. First, the hippocampus exhibits functional differentiation along its long axis; thus, while one part may be "offline," another part could become "online" during trauma memory recall in PTSD. Second, trauma recall in individuals with PTSD+DS presents unique phenomenological features that differ from those observed in classic PTSD. Therefore, the dual representation theory should be revised to account for these differences in PTSD+DS. As will be demonstrated in the subsequent chapters, the data support the need for this modification.

Other brain regions involved in the neurocircuitry of PTSD

The abnormalities in hippocampal connectivity with other brain regions in PTSD are a primary focus of this thesis. Therefore, we hypothesize that many of these areas will overlap with brain regions previously implicated in PTSD. In the following sections, we will briefly highlight a few of these brain regions and their associated abnormalities in PTSD. Subsequent chapters will

expand on additional brain regions with abnormal connectivity to the hippocampus and discuss the significance of these abnormalities.

The first set of regions introduced here belongs to the innate alarm system (IAS). Recent research has implicated IAS regions in both PTSD and PTSD+DS (Lanius et al., 2017). The IAS, which includes structures such as the periaqueductal gray (PAG), superior colliculus, and pulvinar, is involved in the rapid, cortex-independent processing of sensory information for subliminal threat detection (Lanius et al., 2017). The superior colliculus, a midbrain structure, plays a role in threat detection and defensive responses (Almeida et al., 2015; Carello & Krauzlis, 2004; Comoli et al., 2012; Gitelman et al., 2002; Krebs et al., 2010; Maior et al., 2012). In PTSD+DS, compared to PTSD, there was a decrease in the functional connectivity of the superior colliculus with the dorsolateral prefrontal cortex (dlPFC), which is involved in emotional modulation. Conversely, there was increased connectivity between the superior colliculus and the temporoparietal junction, which is important for bodily self-consciousness (Olivé et al., 2018). The PAG, another midbrain structure connected to the superior colliculus, is crucial for the acquisition and expression of defensive responses (De Oca et al., 1998). In PTSD+DS, evidence suggests that the PAG undergoes excessive inhibition by the prefrontal cortex, a mechanism thought to underlie emotional detachment, depersonalization, and derealization (Lanius et al., 2010; Nicholson et al., 2017). In contrast, in PTSD, the PAG showed heightened effective connectivity with the medial prefrontal cortex (mPFC) and the precuneus (Terpou et al., 2020). The pulvinar, another IAS region, is a thalamic nucleus that facilitates cortical communication (Saalmann et al., 2012), and is involved in fear saliency and threat anticipation detection (Hakamata et al., 2016; Koizumi et al., 2019). In PTSD and PTSD+DS, the pulvinar exhibited reduced connectivity with the pre/postcentral gyrus, superior and inferior parietal lobules, and the precuneus compared to

controls (Terpou et al., 2018). This reduction may reflect impairments in episodic memory and self-related processing.

Finally, the insula is a brain structure located beneath the lateral sulcus, which separates the temporal lobe from the parietal and frontal lobes. Its name, derived from the Latin word for "island," reflects its concealed position beneath the brain's surface. The insula is involved in various functions, including interoceptive awareness, emotional processing, salience detection, and viscerosensory processing (Couto et al., 2013; A. D. B. Craig, 2011; Critchley et al., 2004; Menon & Uddin, 2010; Uddin et al., 2017). It processes raw sensory information from the brainstem, leading to the identification of emotional states and contributing to sensory-emotional awareness. Additionally, it translates sensory information for the prefrontal cortex, which is involved in cognitive and emotional control, as well as multisensory integration (Harricharan, 2021). In PTSD, the insula exhibits hyperactivation in response to trauma-related stimuli, whereas in PTSD+DS, it shows hypoactivation (Etkin & Wager, 2007; Hopper et al., 2007). Furthermore, insular activity positively correlates with PTSD symptoms (Carrion et al., 2008; Hopper et al., 2007; Mickleborough et al., 2011; Sripada et al., 2013), suggesting heightened arousal in PTSD. The insula also demonstrates increased connectivity with the amygdala (Nicholson et al., 2016) and decreased connectivity with somatomotor areas such as the pre- and post-central gyri, as well as executive areas like the dorsolateral prefrontal cortex (dlPFC), in both PTSD and PTSD+DS (Harricharan et al., 2020). This decreased connectivity indicates a reduced ability in these individuals to perform contextual interoceptive inference, regulate emotions, and integrate multisensory information by relaying sensory input to the prefrontal cortex (Harricharan et al., 2021). Conversely, the insula shows increased connectivity with the occipital cortex in PTSD+DS

and with limbic and brainstem areas in PTSD (Harricharan et al., 2020), potentially reflecting a state of hypervigilance.

The current thesis

In this thesis, we address the question of the differential contributions of the aHipp and pHipp to the neurocircuitry of PTSD and PTSD+DS, particularly during the recall of trauma memories. While several influential theories have been proposed regarding the role of the hippocampus in trauma memory recall, the most prominent being the dual representation theory of PTSD (Brewin et al., 2010), none have specifically differentiated between the aHipp and pHipp, nor did they theorize the hippocampal role in PTSD+DS. This thesis aims to address this gap in the literature.

The following chapter (Chapter Two) examined the differential involvement of the aHipp and pHipp in PTSD during the resting state (Chaposhloo et al., 2023). Utilizing the publicly available Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset (Weiner et al., 2014), which includes fMRI scans from elderly Vietnam War veterans with and without PTSD, we aimed to explore this distinction. Given the aHipp's preferential role in the emotional processing of episodic memory, we hypothesized that it would become over-connected in individuals with PTSD, in contrast to the pHipp, which we expected to be under-connected. This hypothesis represents a refinement of the dual representation theory, which posits that the entire hippocampus is "offline" in PTSD. Our data supported this proposed refinement of the dual representation theory: the aHipp exhibited a hub-like function in PTSD, showing numerous augmented connections with affective brain regions, such as the insula, when compared to controls. Conversely, the pHipp demonstrated far fewer abnormal connections.

Chapter Three explored two additional aspects. First, it examined how the functional connectivity of the aHipp and pHipp with other brain regions differs *during the recall of trauma memories* compared to neutral memories. Second, it investigated how these functional connectivities vary between individuals with PTSD and PTSD+DS. To address these questions, we utilized a previously collected fMRI dataset from individuals with PTSD, PTSD+DS, and healthy controls while they recalled a morally injurious trauma memory. Building on the findings from Chapter Two (Chaposhloo et al., 2023), we anticipated that the aHipp would exhibit increased activity and enhanced connectivity with affective brain areas in PTSD during trauma memory recall. In contrast, we expected the pHipp to demonstrate decreased activity in PTSD under the same conditions. For individuals with PTSD+DS, we hypothesized a reduction in aHipp activation during trauma memory recall. Additionally, given that PTSD+DS individuals recall trauma memories from a third-person perspective and considering the pHipp's greater involvement in spatial processing, we expected increased activity in the pHipp and its connectivity with the visual areas of the occipital cortex during trauma memory recall. The data partially supported our predictions. Specifically, while the aHipp did not exhibit significant differences between groups and conditions, the left pHipp—associated with context-dependent and verbal episodic memory—showed reduced activation during trauma versus neutral memory recall in PTSD+DS. Conversely, the right pHipp—linked to spatial memory—displayed the opposite pattern. Moreover, the pHipp showed increased connectivity with the occipital cortex during trauma memory recall.

Chapters Two and Three, while informative in their own right, remain agnostic about one critical question: the effective (i.e., directed) connectivity between the hippocampus and other brain areas during trauma memory recall, which can enable us to assess causality of the functional connectivity between two brain regions. To fill this gap, we aimed to investigate the connectivity of the

hippocampus with subcortical areas, such as regions within the brainstem, during trauma memory recall in PTSD—an area often overlooked in the literature. Accordingly, Chapter Four is dedicated to exploring these questions. We utilized the same dataset employed in Chapter Three but narrowed our focus to a set of pre-defined regions of interest (ROIs), including the anterior and posterior hippocampus, brainstem, pulvinar, prefrontal and posterior parietal cortex, and cerebellum. We employed Multivariate Granger Causality (Barnett & Seth, 2014) to infer the effective connectivity of the hippocampal ROIs with the rest of the ROIs. Consistent with our previous findings, we again expected the aHipp to take on a more hub-like role, driven by bottom-up influences from the IAS in the PTSD-only group during the trauma memory recall. In contrast, we anticipated a more top-down modulation of the IAS by the hippocampus in those with PTSD+DS, with the pHipp exhibiting greater connectivity with circuitry involved in perspective switching. Our data largely supported these predictions: the aHipp functioned as a hub in the PTSD-only group during trauma memory recall. Moreover, the PAG showed increased effective connectivity to the pHipp in the PTSD-only group, while showing decreased effective connectivity with the pHipp in PTSD+DS. Also, the retrosplenial cortex showed increased connectivity with the pHipp in PTSD+DS compared to PTSD-only group.

Chapter 2

Altered Resting-State functional connectivity in the anterior and posterior hippocampus in Post-traumatic stress disorder: The central role of the anterior hippocampus

Introductory note: The work presented in the following chapter was published in April 2023 in the academic journal *NeuroImage: Clinical* (DOI: 110.1016/j.nicl.2023.103417).

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M. Chaposhloo curated the data, conducted the analyses, and drafted the original manuscript under the supervision of Dr. Becker and the co-supervision of Dr. Shaw. Research questions were formulated jointly by M. Chaposhloo and Dr. Becker, with the research being conceptualized by them and Dr. Shaw. Dr. Becker, Dr. Shaw, Dr. Nicholson, and Dr. Lanius contributed to the data interpretation and manuscript revisions.

This chapter investigates the differential resting-state functional connectivity patterns of the anterior hippocampus (aHipp) and posterior hippocampus (pHipp) in a sample of elderly male Vietnam War veterans with and without PTSD. Previous research examining the hippocampus as a whole in PTSD has yielded inconclusive results. The few studies that have considered the aHipp and pHipp in PTSD have done so with significant methodological limitations, such as not employing a whole-brain approach, the absence of a control group, or small sample sizes. By addressing these limitations, the results of this chapter allowed us to test our hypothesis regarding the more pronounced role of the aHipp in PTSD compared to the pHipp.

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Altered Resting-State functional connectivity in the anterior and posterior hippocampus in Post-traumatic stress disorder: The central role of the anterior hippocampus

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ABSTRACT

Background: Post-traumatic stress disorder can be viewed as a memory disorder, with trauma-related flashbacks being a core symptom. Given the central role of the hippocampus in autobiographical memory, surprisingly, there is mixed evidence concerning altered hippocampal functional connectivity in PTSD. We shed light on this discrepancy by considering the distinct roles of the anterior versus posterior hippocampus and examine how this distinction may map onto whole-brain resting-state functional connectivity patterns among those with and without PTSD.

Methods: We first assessed whole-brain between-group differences in the functional connectivity profiles of the anterior and posterior hippocampus within a publicly available data set of resting-state fMRI data from 31 male Vietnam war veterans diagnosed with PTSD (mean age = 67.6 years, sd = 2.3) and 29 age-matched combat-exposed male controls (age = 69.1 years, sd = 3.5). Next, the connectivity patterns of each subject within the PTSD group were correlated with their PTSD symptom scores. Finally, the between-group differences in whole-brain functional connectivity profiles discovered for the anterior and posterior hippocampal seeds were used to prescribe post-hoc ROIs, which were then used to perform ROI-to-ROI functional connectivity and graph-theoretic analyses.

Results: The PTSD group showed increased functional connectivity of the anterior hippocampus with affective brain regions (anterior/posterior insula, orbitofrontal cortex, temporal pole) and decreased functional connectivity of the anterior/posterior hippocampus with regions involved in processing bodily self-consciousness (supramarginal gyrus). Notably, decreased anterior hippocampus connectivity with the posterior cingulate cortex/precuneus was associated with increased PTSD symptom severity. The left anterior hippocampus also emerged as a central locus of abnormal functional connectivity, with graph-theoretic measures suggestive of a more central hub-like role for this region in those with PTSD compared to trauma-exposed controls.

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Conclusions: Our results highlight that the anterior hippocampus plays a critical role in the neurocircuitry underlying PTSD and underscore the importance of the differential roles of hippocampal sub-regions in serving as biomarkers of PTSD. Future studies should investigate whether the differential patterns of functional connectivity stemming from hippocampal sub-regions is observed in PTSD populations other than older war veterans.

1. Introduction

Post-traumatic Stress Disorder (PTSD) is a psychiatric condition resulting from exposure to one or more traumatic events (Yehuda et al., 2015). It affects a considerable portion of the population; as of 2008, it was estimated that 9.2% of Canadians had been diagnosed with PTSD at some point during their lives (Van Ameringen et al., 2008). PTSD leads to involuntary, intrusive, and vivid re-experiencing of traumatic memories (i.e., "*flashbacks*") (Brewin, 2014), intense anxiety, hypervigilance even when no apparent threat is present, and chronic unfavourable changes in cognition and mood (American Psychiatric Association, 2013; Harricharan et al., 2021). Individuals with PTSD may also experience more general memory deficits, including impaired voluntary recall of "ordinary" episodic memories of the trauma (Brewin, 2014), deficiencies in verbal declarative (Bremner et al., 2004) and working memory (Vasterling et al., 2002), over-generalization of fear responses (Brown et al., 2013), and failure to employ contextual information to identify real threats (Garfinkel et al., 2014).

One core component of the episodic memory system is the hippocampus (Scoville & Milner, 1957; Squire, 1986), which is involved in autobiographical memory and episodic future thinking (Okuda et al., 1998; Szpunar et al., 2007), spatial memory, planning and navigation (for a review, see Burgess et al., 2001a), emotional memory (Kim & Fanselow, 1992), emotion regulation (Herman et al., 1989), and encoding of context during fear conditioning (Rudy & Matus-Amat, 2005). Incontrovertibly, the hippocampus has a unique role in forming coherent memories of complex events, by associating multiple elements of an event (such as multisensory information, location, emotion and time) and binding them together (Horner & Burgess, 2013). Therefore, it is unsurprising that the hippocampus has been implicated in the neuropathology of PTSD (Rauch et al., 2006; Shin et al., 2006).

1.1. The case for hippocampal dysfunction in PTSD

Hippocampal-related abnormalities are linked to some PTSD symptoms, such as intrusive trauma memories, impaired retrieval of trauma-related details and over-generalization of fear responses (Brewin, 2014; Kheirbek et al., 2012). Specifically, hippocampal inactivity may underlie the overgeneralization of conditioned fear in PTSD (Kaczkurkin et al., 2017). Moreover, hippocampal volume reductions have been observed in PTSD (Bremner et al., 1995; Gurvits et al., 1996), and smaller hippocampal volume may be a risk factor for developing PTSD following a traumatic event (Gilbertson et al., 2002).

Yet another indication of altered hippocampal function in PTSD is the evidence of PTSD-linked changes in large-scale intrinsic brain networks. Three major intrinsic brain networks have been identified within the widely influential *triple network model* (Menon, 2011): the default mode network (DMN), salience network (SN), and central executive network (CEN; also known as the frontoparietal network (FPN)). These networks play a significant role in behaviour and cognition through interactions among them, and abnormalities within and between these networks could be attributed to various psychopathologies (Menon, 2018). The DMN primarily consists of the hippocampus, medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC) and precuneus, and in healthy individuals, it is predominantly active during wakeful rest (Greicius et al., 2003; Raichle et al., 2001), autobiographical memory (AM) retrieval (for a *meta*-analysis, see Svoboda et al., 2006 and future thinking (Addis et al., 2007); moreover, the DMN couples with the SN during AM retrieval (Shaw et al., 2021). The DMN is also involved in self-related mentation, such as mind-wandering, personal introspection, spatial planning and navigation (Burgess et al., 2001b; Spreng et al., 2009; Spreng & Grady, 2010). Importantly, the DMN appears highly dysregulated in PTSD (Koch et al., 2016), as evidenced by decreased within-DMN functional connectivity (Patel et al., 2012; Sripada et al., 2012b), which may underlie PTSD symptoms such as intrusive memories, avoidance (Akiki et al., 2017), deficient autobiographical memory (Menon, 2011), and the loss of a sense of self, exemplified by statements such as I am not me anymore'' following trauma (Foa et al., 1999). These changes in DMN connectivity may be partly explained by an underlying alteration in hippocampal functional connectivity, given its central role in episodic memory (Joshi et al., 2020). Notably, in those with PTSD, the DMN is more strongly coupled with the SN (Akiki et al., 2017; Joshi et al., 2020; Sripada et al., 2012b), comprised of the amygdala, anterior insula, dorsal anterior cingulate cortex (dACC), and temporal pole (TP). Abnormal connectivity has also been observed between other SN regions and brain regions within the innate alarm system (IAS) (Lanius et al., 2017), potentially impacting the functional roles of the SN in detecting salient external stimuli and internal events (Menon, 2011), switching between the DMN and CEN according to task demands (Shaw et al., 2021), and integrating multisensory information with affect and emotions to facilitate an embodied sense of self (Harricharan et al., 2021; Lanius et al., 2020; Nicholson et al., 2020).

One striking aspect of PTSD trauma memories is their firm grounding in sensory-motor representations (Van der Kolk & Fisler, 1995), such as flashbacks accompanied by re-experiencing of pain (for a report of one such individual, see Whalley et al., 2007). One study found that the somatosensory-motor network (SMN), comprised of the pre- and post-central gyri (primary motor cortex and somatosensory cortex, respectively), the primary sensory cortices, and the supplementary motor area (SMA), undergoes a within-network decrease in functional connectivity in those with PTSD, especially in the somatosensory cortex (Shang et al., 2014), which is consistent with catastrophic, fearful orientation to somatic signals in PTSD (Tsur et al., 2018). Conversely, hyperconnectivity between the posterior DMN and SMN in PTSD is consistent with symptoms such as involuntary re-experiencing of, vivid sensory-motor imprints of the original traumatic memory (Kearney et al., 2023). Based on these findings, it is reasonable to hypothesize that PTSD may involve abnormal connectivity between the hippocampus and SMN.

Those with PTSD commonly manifest impaired suppression of flashbacks, which has been at least partially attributed to decreased prefrontal activity. The prefrontal cortex is involved in emotion regulation, decision making, fear extinction and retention of extinction (for reviews of prefrontal involvement in the neurocircuitry of PTSD, see Harricharan et al., 2021; Shin et al., 2006). Prefrontal hypoactivation leads to an inability to exert top-down inhibition on limbic (e.g., amygdala) and brainstem (e.g., periaqueductal gray) regions (Nicholson et al., 2017), potentially leaving those brain areas over-activated in response to emotional cues, irrespective of their trauma relevance (Admon et al., 2013a). Consequently, in the absence of adequate top-down prefrontal control, bottom-up subcortical processes prevail, with *"raw"* affective internal sensations and external stimuli dominating them (Harricharan et al., 2021). However, studies have produced inconsistent findings on amygdala hyperactivation in PTSD, which could be due to task-related differences and the inclusion (or lack thereof) of individuals with the dissociative subtype (Lee et al., 2021; Sartory et al., 2013; Schulze et al., 2019; Stark et al., 2015; Suarez-Jimenez et al., 2020; Thome et al., 2019)(we further consider the dissociative sub-type

in the Discussion). The insula and orbitofrontal cortex (OFC) are other brain areas of relevance in PTSD. Children with PTSD who had self-injurious behaviours exhibited elevated insula and OFC activation levels, and their symptom severity correlated positively with insula activation (Carrion et al., 2008). The above evidence raises the question of whether altered hippocampal functional connectivity with structures including the prefrontal cortex, insula and OFC may arise in PTSD.

1.2. Distinct functional roles of the anterior and posterior hippocampus

Considering the evidence reviewed so far, it is reasonable to predict that the hippocampus might exhibit altered functional connectivity with other brain areas in those with PTSD. However, findings regarding such alterations are mixed. For example, hippocampal-prefrontal functional connectivity has repeatedly been shown to be decreased in PTSD relative to controls (Heyn et al., 2019; Jin et al., 2014) and relative to exposure therapy recipients (Zhu et al., 2018), and some studies reported decreased functional connectivity between the hippocampus and the amygdala (Sripada et al., 2012a). However, several others reported no functional connectivity differences in the hippocampus in PTSD vs. controls (Brown et al., 2014; Nicholson et al., 2015; Rabinak et al., 2011).

The discrepant reports of altered hippocampal connectivity in PTSD may result from seed-based fMRI studies treating the hippocampus as a single structure (e.g., Carrion et al., 2010, and ignoring potentially crucial functional differences along its longitudinal axis. Though ongoing debate persists regarding precise functional roles of the anterior versus posterior hippocampi (for reviews, see, e.g., Fanselow & Dong, 2010; Poppenk et al., 2013; Strange et al., 2014), human imaging research has increasingly focused on investigating this important question. In healthy humans, evidence indicates greater posterior than anterior hippocampal functional connectivity with the PCC, precuneus (Chen & Etkin, 2013; Poppenk & Moscovitch, 2011), and parahippocampal cortex (Dalton et al., 2019; Libby et al., 2012), while the anterior portion is more functionally connected to perirhinal cortex (Dalton et al., 2019; Libby et al., 2012). Consistent with this evidence from resting-state functional connectivity studies, task-based fMRI studies indicate that the posterior hippocampus has greater activation in spatial tasks requiring precise spatial representations, while the anterior portion is more involved in tasks requiring less detailed contextual information (Brunec et al., 2018; Evensmoen et al., 2013; 2015; Nadel et al., 2013). Accordingly, the predominant view amongst cognitive neuroscientists is that the anterior portion is more heavily involved in gist-like, schematic, or coarse-scaled contextual representations while the posterior portion is more heavily involved in finely detailed spatial representations (Poppenk et al., 2013; Zeidman & Maguire, 2016) (although for a different view, see Dandolo & Schwabe, 2018), where memory recall among those with PTSD has been associated more heavily with the former form of memory (Hayes et al., 2011).

While the above view of the anterior hippocampus as being crucial for schematic representations has considerable empirical support, this view ignores the wealth of convergent evidence from both human and non-human animal studies for a broader role for this region in emotional and stress-related functions. For example, in humans, the anterior subiculum is more heavily functionally connected to the ventral striatum, midbrain, and amygdala (Chase et al., 2015; Kahn & Shohamy, 2013); similarly, in non-human primates, the anterior hippocampus is more connected to emotional and stress-related neural circuitry, including the amygdala (Aggleton, 1986; Wang & Barbas, 2018), the insula (Pribram & Maclean, 1953), and the limbic prefrontal circuitry (Barbas & Blatt, 1995; Carmichael & Price, 1995). Similarly, task-based fMRI studies in humans reveal that the anterior is more activated than the posterior hippocampus in emotional memory tasks (Murty et al., 2011), high state anxiety (Satpute et al., 2012) and goal-directed spatial decision making (Viard et al., 2011). Moreover, in humans with epilepsy, direct recordings in the amygdala and the anterior hippocampus revealed synchronized Beta-frequency activity between these areas during fear memory retrieval (Wang et al., 2020) and greater low-frequency coupling of these areas during processing of fearful faces vs. neutral landscape stimuli (Zheng et al., 2017).

Corresponding to these differences in anatomical and functional connectivity, cellular recording studies in rodents lend more specific evidence as to the type of information encoded along the longitudinal axis of the hippocampus, where in rodents, the long axis is in the dorsal–ventral direction, corresponding to the posterior-anterior direction in primates. In rodents, granule cells in the ventral dentate gyrus suppress intrinsic anxiety without impacting contextual learning (Kheirbek et al., 2013). Moreover, the dorsal CA1 is highly populated by place cells, while the ventral CA1 is dominated by "anxiety cells", triggered by being in anxiogenic environments and involved in avoidance behaviour (Jimenez et al., 2018). Furthermore, synapses in dorsal CA1 are particularly vulnerable to short and concurrent stress compared to ventral CA1 (Maras et al., 2014), suggesting its sensitivity to psychopathologies such as PTSD, which could render the animal overly reliant upon the ventral hippocampus for memory functions. Interestingly, the posterior hippocampus shows reduced volume in PTSD (Bonne et al., 2008). Thus, when one considers all the evidence across species, it is apparent that the differences between anterior and posterior hippocampal functions in humans go beyond different spatial scales of information representation. Instead, the anterior portion may be more specialized to support detailed memories for the emotional component of events.

Considering the evidence discussed above, we hypothesize that in humans with PTSD, there may be differential abnormal functional connectivity between the anterior versus posterior hippocampus and areas implicated in the neurocircuitry of PTSD, including prefrontal, parietal, and insular cortices. Moreover, investigating the functional connectivity patterns of the anterior and posterior hippocampus separately could have implications for a prominent view of PTSD, the *Dual Representation Theory of PTSD* (Brewin, 2014; Brewin et al., 2010), which proposes that the hippocampus is not appropriately involved in encoding and retrieval of trauma memories, a topic we return to in the discussion.

To the best of our knowledge, only four prior studies have examined the differential resting-state functional connectivity profiles of the anterior and posterior hippocampus in PTSD. Of those four, two studies (Lazarov et al., 2017; Malivoire et al., 2018) employed ROI-to-ROI analyses within narrow pre-defined subsets of regions rather than whole-brain functional connectivity analyses. Lazarov et al., (2017) found that in PTSD, the posterior hippocampus shows increased functional connectivity (reported as decreased negative connectivity) with the precuneus, as well as different functional connectivity patterns for the anterior versus posterior hippocampus among controls but not among those with PTSD (Lazarov et al., 2017). Additionally, increased functional connectivity was found between the posterior hippocampus and PCC in the PTSD group (Malivoire et al., 2018). However, given the aforementioned evidence of widespread brain areas pathologically affected by PTSD that extend well beyond the nodes prescribed by the triple network model, directly assessing functional connectivity via ROI-to-ROI analysis in a restricted set of ROIs may hinder detection of critical changes. Two studies that we are aware of analyzed whole-brain functional connectivity with the anterior vs posterior hippocampus. One such study obtained results in the opposite direction to those of Lazarov et al. and Malivoire et al., i.e., decreased posterior hippocampus functional connectivity with the precuneus and PCC (Chen & Etkin, 2013). Unfortunately, this study was limited by the relatively small sample size of the PTSD group (17 participants). Finally, the fourth study did not include a control group (Jung & Kim, 2020), limiting its ability to detect PTSD-linked functional connectivity changes relative to healthy controls. To resolve the above discrepant findings in the literature, a follow-up study is warranted, incorporating a control group and a much larger sample size, utilizing a data-driven approach to assess whole-brain

differences in anterior vs. posterior hippocampal functional connectivity in those with PTSD. Moreover, while previous research has applied graph-theoretical analyses to whole-brain connectivity in PTSD (Suo et al., 2015; Zhu et al., 2019), to our knowledge, no studies have investigated hippocampal connectivity specifically.

Accordingly, in the present study, we performed a seed-based whole-brain functional connectivity analysis, separately seeding the anterior versus posterior hippocampi, followed by post-hoc ROI-to-ROI connectivity analysis on the discovered clusters. This data-driven approach does not limit the functional connectivity analysis to previously defined brain regions, providing the best chance of discovering altered patterns of hippocampal functional connectivity in those with PTSD in an unbiased manner. Based on our current understanding of the unique connectivity profiles of the anterior and posterior hippocampus and considering the previous research reviewed above, we predicted the following:

1. Given the SN's role in assessing potential threats and identifying salient stimuli, and with hypervigilance and hyperarousal being core symptoms of PTSD, we predicted a functional connectivity increase between the anterior hippocampus and SN nodes. Additionally, considering the greater relevance of the anterior hippocampus to emotion and stress-related functions, we expected it to play a greater role in PTSD, potentially exhibiting stronger rather than weaker functional connectivity with stress-related circuits compared to the posterior hippocampus.
2. We hypothesized that the functional connectivity between the posterior hippocampus and DMN would be diminished in PTSD on the grounds that individuals with PTSD demonstrate impaired episodic memory and internal mentation.
3. Given that those with PTSD exhibit alterations in their sense of body and self, and many therapeutic efforts are geared towards targeting somatic and motor pathways, we expected to observe altered functional connectivity between both the anterior and posterior hippocampus and somatosensory and motor areas.

The present study was undertaken to test the above predictions in a freely available set of resting state fMRI data previously collected from a sample of individuals with PTSD.

2. Material and methods

2.1. Participants

We utilized a previously collected, open-source set of resting-state fMRI data acquired from male Vietnam War veterans, obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI was to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see https://www.adni-info.org. The ethics boards of all collaborating sites within ADNI approved the collection of this data set, and all participants provided written informed consent. While the primary focus of ADNI is on AD, a sizeable subset of participants was diagnosed with PTSD without exhibiting symptoms of mild cognitive impairment (MCI) or AD. For the analyses reported here, 60 male, combat-exposed subjects (mean age = 68.3 years, sd = 3.0) were selected, excluding those with MCI, traumatic brain injury or AD. Of those 60, 31 (mean age = 67.6 years, sd = 2.3) were included in the PTSD group, with the inclusion criterion of Clinician-Administered PTSD Scale IV (CAPS-IV, assessed decades after their war exposure) $\geq$ 50 (average CAPS-IV within the PTSD group = 64.7, sd = 13.3). This inclusion criterion (CAPS $>$ 50) has been extensively used previously to define PTSD groups in neuroimaging analyses (e.g., Harricharan et al., 2020; Rabellino et al., 2015; Terpou et al., 2018). The remaining 29 participants (mean age = 69.1 years, sd = 3.5) were included in the control group (average CAPS-IV = 1.5, sd = 2.9). A Welch's *t*-test to assess differences in the mean age of the two groups revealed that they were not significantly different (t(48.7351) = −1.9610, p = 0.0556).

2.2. Neuroimaging data acquisition and pre-processing

We downloaded all T1-weighted anatomical scans along with corresponding resting-state fMRI scans from the ADNI website, where the details of data acquisition and preliminary pre-processing steps can also be found (https://adni.loni.usc.edu/methods/mri-tool/mri-analysis/). All MRI data were acquired using GE 3T MRI scanners (General Electric Healthcare, Milwaukee, WI). In brief, a T1-weighted anatomical scan was acquired for each participant using IR prepped sagittal 3D SPGR sequence (TI/TR/TE = 400/7.34/3.04 ms, 11 flip angle, 1.2 mm-thick slices of size 256 × 256) along with resting-state fMRI scans with 160 time points (Scanning Sequence: EP/GR, TR = 2.9 ~ 3.52 s, TE = 30 ms, 3.3 mm-thick slices of size 64 × 64, 48 slices per time point).

fMRI data were pre-processed using SPM12 (Wellcome Centre for Human Neuroimaging, London, UK) and the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) within MATLAB version R2020a (The MathWorks, Inc., Natick, MA, USA). We used the default pre-processing and denoising pipelines within CONN, including realignment and unwarping of the fMRI scans, followed by motion correction using estimates of motion along 12 degrees-of-freedom (3 translation, 3 rotation, 3 first-derivatives of translation, 3 first-derivatives of rotation) as nuisance regressors in a denoising general linear model (GLM). Next, frequency-domain based phase shift slice timing correction (STC) was applied, along with scrubbing of outlier scans detected using ART. A unified segmentation and normalization procedure (Ashburner and Friston, 2005) was then used to normalize the scans to the MNI152 atlas and segment skull, white matter, grey matter and cerebro-spinal fluid (CSF). Potential physiological confounds were minimized by including the average signal from white matter and CSF as nuisance regressors. Finally, spatial smoothing was applied with an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel, followed by temporal band-pass filtering (0.008–0.09 Hz).

2.3. Functional connectivity analysis

Resting-state functional connectivity analyses were performed using the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). The first analysis performed was a seed-to-voxel connectivity analysis while seeding the entire hippocampus, and then the anterior and posterior hippocampus. To perform this analysis, the seed regions of interest (ROIs) for the left and right anterior and posterior hippocampus were acquired from the Brainnetome atlas (Fan et al., 2016). Next, the mean BOLD signal intensity time course was extracted for each seed and for each subject. Then, a whole-brain functional connectivity analysis was performed, where for each subject and each hippocampal ROI, the Fischer-transformed correlation coefficient between the time course of the seed ROI and the time course of every other voxel in the brain was calculated, resulting in a whole-brain map of functional connectivity for each seed ROI and every subject (Bijsterbosch et al., 2017). These maps were then used in a second-level group analysis where we compared the PTSD group against the control group using the PTSD $>$ Control contrast. In addition, we correlated the whole-brain functional connectivity of each seed ROI (used for the seed-to-voxel analysis described above) with the CAPS-IV scores for subjects within the PTSD. These results were corrected for multiple comparisons at the cluster level (Worsley et al., 1996), excluding clusters that did not meet a voxel-discovery threshold of p-uncorrected $<$ 0.001 and a cluster-level p-FDR $<$ 0.05.

To further investigate group differences between hippocampal subregions and other parts of the brain, we then performed a post-hoc ROI-to-ROI analysis, where we estimated the functional connectivity between hippocampal seed ROIs and target ROIs, defined using the clusters discovered in the previous seed-to-voxel analysis. In this way, we could investigate the functional connectivity of those brain areas that did not survive correction for multiple tests but showed a trend nevertheless. Target ROIs were defined in a data-driven manner. To do so, we identified clusters of differences in functional connectivity values for each brain region. These clusters may or may not survive multiple comparison corrections. Next, a spherical ROI with a radius of 5 mm was placed in the centre of each cluster using the MarsBaR toolbox (Brett et al., 2002). The post-hoc analysis was designed to further investigate connectivity patterns over restricted brain regions, similar to the network-restricted approach followed by Akiki et al., 2018, and care was taken to minimize Type-1 error (Brooks et al., 2017; Kriegeskorte et al., 2009) by including a wider set of brain regions based on prior PTSD literature. This was performed in lieu of orthogonal contrasts (Kriegeskorte et al., 2009) recommended for reproducibility due to the limited number of experimental conditions available from the publicly available data set used in this study. Furthermore, the risk of limited reproducibility was also mitigated by the use of this publicly available data set that can be independently downloaded and assessed.

2.4. Graph-theoretic analysis

Finally, to better understand the global properties of the observed ROI-to-ROI connectivity, we analyzed group differences in graph-theoretic measures. While ROI-to-ROI analyses identify differences in functional connectivity between ROI pairs, graph-theoretic analyses assess the global role of a node (ROI) within the larger group of ROIs, providing a global overview of each node's functional connectivity profile. For instance (and much to our interest), it can reveal which nodes act as hubs that are heavily (and centrally) connected with many other nodes and can efficiently transfer information between them (Bullmore & Sporns, 2009). "Hubness", or the hub-like behaviour of a node, is often assessed by measures of centrality (e.g., degree, cost, betweenness centrality; described below), and efficiency (path length and clustering coefficient; for a review of hubness in the context of brain science, see van den Heuvel & Sporns, 2013). To perform the graph-theoretic analyses, we first defined a graph for each participant using the ROIs studied as the nodes, and the ROI-to-ROI connectivity between every pair of nodes as the edges. To allow sensitive between-network comparisons, the graphs were thresholded to only include the top 15% of connections based on their cost (described below). These graphs were then used to estimate several node-based graph theoretic measures; namely,

1. *degree* - an estimate of how connected the current node is, as determined by the number of neighbouring nodes,
2. *cost* (also known as *strength*) - is the weighted form of the degree and gives an estimate of the net connectivity strength. It is determined as the sum of all neighbouring weights, accounting for both the number of edges and their strength,
3. *path length* - quantifies the distance that information has to travel to reach other nodes from the current node. It is determined by the number of edges that constitute the shortest path between two nodes,
4. *node-wise global efficiency* - is an estimate of the efficiency of information transfer from the current node to all other nodes, determined by the average of inverse path lengths leading to a node across the entire graph,
5. *node-wise local efficiency* - is an estimate of the efficiency of information transfer from the current node to nodes it is directly connected to, determined by as the average global efficiency across the sub-graph consisting of only the neighbours of the given node.
6. *clustering coefficient* - is an estimate of how well the neighbours of a node are connected to each other and form a cluster (defined as the number of existing edges between neighbours of a node divided by the total number of possible edges between those same nodes), and
7. *betweenness centrality* - an estimate of how central the node is in the network (defined as the fraction of all shortest paths that a node participates in).

Finally, group differences in the above node-wise graph-theoretic metrics were assessed after FDR-based corrections for multiple comparisons were applied. All analyses were performed using the CONN toolbox 20.b (Whitfield-Gabrieli & Nieto-Castanon, 2012).

3. Results

3.1. Whole-brain functional connectivity analysis

We started by seeding the entire hippocampus to investigate whether the functional connectivity of the hippocampus with any brain regions differs between the two groups. No significant group differences were found when the seed ROI was the entire hippocampus. We then separately seeded the anterior and posterior hippocampi to examine the group differences along the long axis of the hippocampus. The bilateral posterior hippocampus (pHipp) and right anterior hippocampus (aHipp) exhibited no significant group differences. However, when the seed ROI was the left aHipp, it showed significantly more functional connectivity with the left anterior insula (aIC), right posterior insula (pIC), and right temporal pole (TP) in PTSD compared to the control group (Table 1 and Fig. 1). These previously unreported and novel findings provide the first insight into seed-based whole-brain functional connectivity differences stemming from the aHipp, suggesting a dysfunction in emotion processing circuitry (aHipp) along with affective brain regions (a/pIC and TP).

The next question we sought to answer was to what degree the functional connectivity of hippocampal subregions correlated with symptom severity in PTSD. Here, the CAPS-IV score provided a suitable and general measure of symptom severity in PTSD. Again, only the aHipp yielded significant results. Unexpectedly, within the PTSD group, the functional connectivity of the right aHipp with PCC and precuneus was negatively correlated with CAPS scores (cluster size = 346, T(29) = -5.07, p-FDR = 0.0009, MNI coordinates (mm) = −6–48 24; Fig. 2). This finding seems to be at odds with our second hypothesis that the pHipp rather than aHipp would show diminished functional connectivity with DMN nodes in those with PTSD. We return to this point later on.

3.2. ROI-to-ROI functional connectivity analysis

Based on the whole-brain functional connectivity analysis, 21 target ROIs were manually defined that had differential functional connectivity in PTSD compared to controls. MNI coordinates of these ROIs are listed below (Table 2). Next, we conducted an ROI-to-ROI analysis on these 21 ROIs (see Table 3).

This approach allowed us to more carefully examine functional connectivity differences between the brain regions that were observed to differ in the seed-based functional connectivity analysis in PTSD,

Table 1
Significant clusters that showed increased functional connectivity with the left anterior hippocampus for the PTSD > Controls contrast in the whole-brain seed-based functional connectivity analysis. TP: Temporal pole; pIC: Posterior insula; aIC: Anterior insula.

Brain Region	Cluster size	T-statistics	p(FDR)	MNI Coordinates (mm)
R. TP/R. pIC	472	T(58) = 5.11	0.001454	+36–2 −8
L. aIC	281	T(58) = 5.55	0.011783	−38 + 8–8

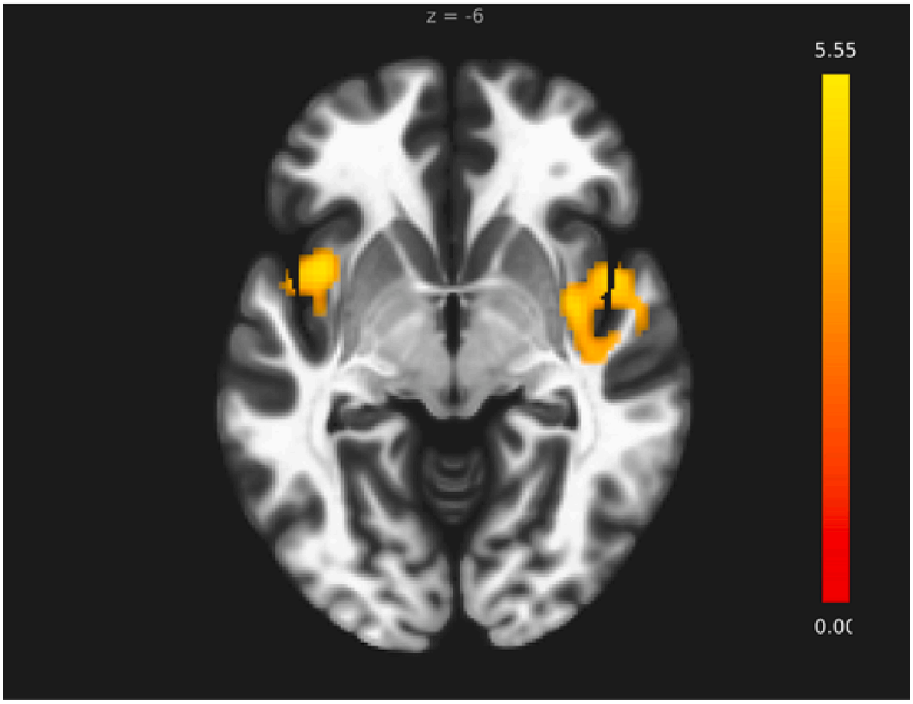

Fig. 1. Areas of increased functional connectivity with the left anterior hippocampus. Whole-brain functional connectivity analysis revealed that in the PTSD group, the left anterior hippocampus was significantly more connected to the left anterior insula, right posterior insula, and right temporal pole (areas shown in yellow) as compared to the control group (the colour bar represents T-values). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

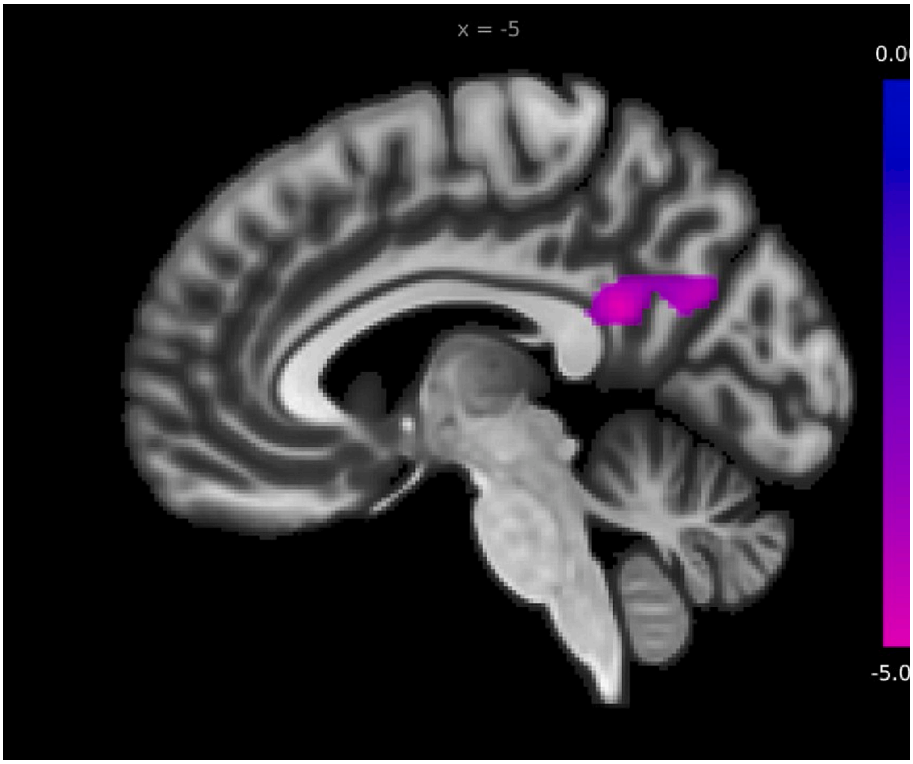

Fig. 2. Medial sagittal view of the left hemisphere showing that within the PTSD group, symptoms severity as represented by CAPS scores was negatively correlated with the functional connectivity between the right anterior hippocampus and PCC/precuneus (areas shown in magenta; the colour bar represents T-values). PCC: Posterior cingulate cortex; CAPS: Clinician-Administered PTSD Scale. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

increasing statistical power while correcting for multiple comparisons (Poldrack, 2007). In addition to these 21 ROIs, an ROI for the amygdala was added from the Harvard-Oxford atlas provided with the CONN toolbox. Here, it is important to note that although we did not observe any group differences in hippocampus-amygdala functional connectivity in the whole-brain seed-based analysis, the extensive literature surrounding abnormal functional connectivity of these two regions in PTSD (especially between them) (Heyn et al., 2021; McIntosh et al., 2022; Sripada et al., 2012a; Zhang et al., 2016; Zhu et al., 2018) justifies the inclusion of the amygdala in our analysis. Likewise, while we did not observe any group differences in functional connectivity between the ventromedial prefrontal cortex (vmPFC) and the hippocampus, many theories of PTSD regard vmPFC as a key region involved in the symptomatology of PTSD (Shin et al., 2006), motivating the inclusion of the vmPFC in our analysis. The ROI for vmPFC was acquired from a recent study carried out in our lab (Shaw et al., 2021). In the following

Table 2
MNI coordinates of the 21 target ROIs used with the hippocampal ROIs (source ROIs) for the ROI-to-ROI functional connectivity analysis.

MNI coordinates of target ROIs	
Brain Region	Coordinates (mm)
left anterior insula (aIC)	[–39 7 –8]
right anterior insula (aIC)	[37 13 –13]
left posterior insula (pIC)	[–39 –6 –6]
right posterior insula (pIC)	[39 –6 –6]
left temporal pole (TP)	[–47 14 –14]
right temporal pole (TP)	[49 5 –6]
left lateral orbitofrontal cortex (lOFC)	[–29 21 –19]
right lateral orbitofrontal cortex (lOFC)	[35 22 –17]
left periaqueductal gray (PAG)	[–5 –26 –12]
right periaqueductal gray (PAG)	[5 –29 –14]
right anterior superior temporal gyrus (aSTG)	[59 –8 –5]
right posterior superior temporal gyrus (pSTG)	[61 –32 10]
left posterior superior temporal gyrus (pSTG)	[–60 –34 14]
right posterior middle temporal gyrus (pMTG)	[61 –33 –10]
left posterior middle temporal gyrus (pMTG)	[–60 –48 7]
left posterior inferior temporal gyrus (pITG)	[–54 –48 –15]
right angular gyrus	[51 –48 22]
left postcentral gyrus	[–43 –24 60]
left supramarginal gyrus (SMG)	[–55 –24 50]
left precuneus, A7m, medial area 7(PEp)	[–6 –68 49]
right precuneus, A7m, medial area 7(PEp)	[6 –62 46]
ventromedial prefrontal cortex (vmPFC)	[–3 40 0]

paragraphs, we summarize the results of functional connectivity analyses between these ROIs and the hippocampal ROIs acquired from the Brainnetome atlas (Fan et al., 2016).

3.3. Anterior hippocampus

Bilateral aHipp was more connected to bilateral anterior insula (aIC) and bilateral temporal pole (TP) in the PTSD group relative to controls. Additionally, the left aHipp was more connected to bilateral pIC and bilateral lOFC and the right aHipp was more connected to the right lOFC in the PTSD group relative to controls. It is noteworthy that these are all considered to be affective brain regions. Other brain areas that exhibited greater functional connectivity with the aHipp in PTSD included the posterior portions of the superior, medial and inferior temporal gyrus (pSTG, pMTG and pITG, respectively), areas that support unisensory and multisensory processing. Specifically, we observed increased functional connectivity between the bilateral aHipp and bilateral pSTG and left pMTG. Additionally, the right aHipp was more connected to the left pITG in PTSD relative to controls. We also observed greater bilateral aHipp functional connectivity with bilateral precuneus, a key DMN node important for mental imagery, among other functions (Byrne et al., 2007; Cavanna & Trimble, 2006). The greater functional connectivity of aHipp with these areas critical for visual and auditory perception and mental imagery is consistent with the symptomatology of flashbacks, which may also include auditory components (Hackmann et al., 2004). In contrast to these findings of greater functional connectivity, the left supramarginal gyrus (SMG) was less connected to bilateral aHipp in PTSD relative to the control group. Interestingly, the SMG is implicated in bodily self-consciousness (Blanke et al., 2015), and in PTSD, there have been reports of altered bodily representation in *peri*-personal space (Rabellino et al., 2020) and sense of body ownership (Rabellino et al., 2018a). In summary, the aHipp exhibited elevated functional connectivity with many brain regions involved in affective, visual, auditory and multi-sensory processing and mental imagery, whereas it showed less functional connectivity with areas involved in bodily self-consciousness (Figs. 3 and 4).

Table 3
The results of the post-hoc ROI-to-ROI functional connectivity analysis between the seed hippocampal ROIs and target ROIs. All the connections were FDR corrected at the cluster level. aHipp: Anterior hippocampus; pHipp: Posterior hippocampus; aIC: Anterior insula; pIC: Posterior insula; TP: Temporal pole; lOFC: Lateral orbitofrontal cortex. pSTG: Posterior superior temporal gyrus. pMTG: Posterior middle temporal gyrus; SMG: Supramarginal gyrus; pITG: Posterior inferior temporal gyrus; vmPFC: Ventromedial prefrontal cortex.

Seed ROI	Target ROI	T-statistics	p(FDR)
Left aHipp	Left aIC	$T(58) = 4.69$	p-FDR = 0.0004
	Right aIC	$T(58) = 2.47$	p-FDR = 0.0396
	Right pIC	$T(58) = 2.99$	p-FDR = 0.0135
	Left pIC	$T(58) = 2.82$	p-FDR = 0.0189
	Right TP	$T(58) = 3.96$	p-FDR = 0.0027
	Left TP	$T(58) = 2.46$	p-FDR = 0.0396
	Right lOFC	$T(58) = 3.03$	p-FDR = 0.0135
	Left lOFC	$T(58) = 2.01$	p-FDR = 0.0900
	Right pSTG	$T(58) = 3.49$	p-FDR = 0.0082
	Left pSTG	$T(58) = 3.17$	p-FDR = 0.0125
	Left pMTG	$T(58) = 2.41$	p-FDR = 0.0418
	Right precuneus	$T(58) = 3.26$	p-FDR = 0.0121
	Left precuneus	$T(58) = 2.28$	p-FDR = 0.0522
	Left SMG	$T(58) = -2.99$	p-FDR = 0.0135
Right aHipp	Right aIC	$T(58) = 2.70$	p-FDR = 0.0391
	Left aIC	$T(58) = 2.00$	p-FDR = 0.1080
	Left TP	$T(58) = 2.97$	p-FDR = 0.0246
	Right TP	$T(58) = 2.36$	p-FDR = 0.0581
	Right lOFC	$T(58) = 2.39$	p-FDR = 0.0581
	Left pSTG	$T(58) = 2.94$	p-FDR = 0.0246
	Right pSTG	$T(58) = 2.49$	p-FDR = 0.0581
	Left pMTG	$T(58) = 3.49$	p-FDR = 0.0242
	Left pITG	$T(58) = 3.19$	p-FDR = 0.0246
	Right precuneus	$T(58) = 2.35$	p-FDR = 0.0581
	Left precuneus	$T(58) = 2.21$	p-FDR = 0.0728
	Left SMG	$T(58) = -2.97$	p-FDR = 0.0246
Left pHipp	Right lOFC	$T(58) = 2.72$	p-FDR = 0.0742
	Right precuneus	$T(58) = 2.78$	p-FDR = 0.0742
	Right pSTG	$T(58) = 3.18$	p-FDR = 0.0615
	Left pMTG	$T(58) = 2.49$	p-FDR = 0.0845
	Right angular gyrus	$T(58) = 2.48$	p-FDR = 0.0845
	vmPFC	$T(58) = -2.18$	p-FDR = 0.1428
Right pHipp	Right lOFC	$T(58) = 2.19$	p-FDR = 0.1421
	Right precuneus	$T(58) = 2.96$	p-FDR = 0.0562
	Right pSTG	$T(58) = 2.62$	p-FDR = 0.0725
	Right angular gyrus	$T(58) = 2.82$	p-FDR = 0.0562
	Left postcentral gyrus	$T(58) = -2.37$	p-FDR = 0.1086
	Left SMG	$T(58) = -2.88$	p-FDR = 0.0562

3.4. Posterior hippocampus

The ROIs showing increased functional connectivity with bilateral pHipp in PTSD, compared to controls, were the right lOFC, right precuneus, right pSTG, and right angular gyrus. Furthermore, the left pHipp had elevated functional connectivity with left pMTG in PTSD, relative to controls. On the other hand, the left pHipp was less connected to vmPFC, while the right pHipp was less connected to the left postcentral gyrus and the left SMG in PTSD relative to controls. The decreased functional connectivity between the right pHipp and the left postcentral gyrus is quite interesting since the latter is the loci of the primary somatosensory cortex, and as noted earlier, bodily representation in PTSD is often compromised (Figs. 5 and 6).

Taken together, the above findings indicate that the pHipp exhibits significantly fewer abnormal connections with affective ROIs (insula, TP, and lOFC), as compared to the aHipp. The pHipp also showed decreased functional connectivity with areas involved in somatosensation. Surprisingly, neither the anterior nor posterior hippocampus showed any group difference in functional connectivity with the amygdala, in contrast to previous findings in the literature (Sripada et al., 2012a; Zhu et al., 2018). The increased functional connectivity

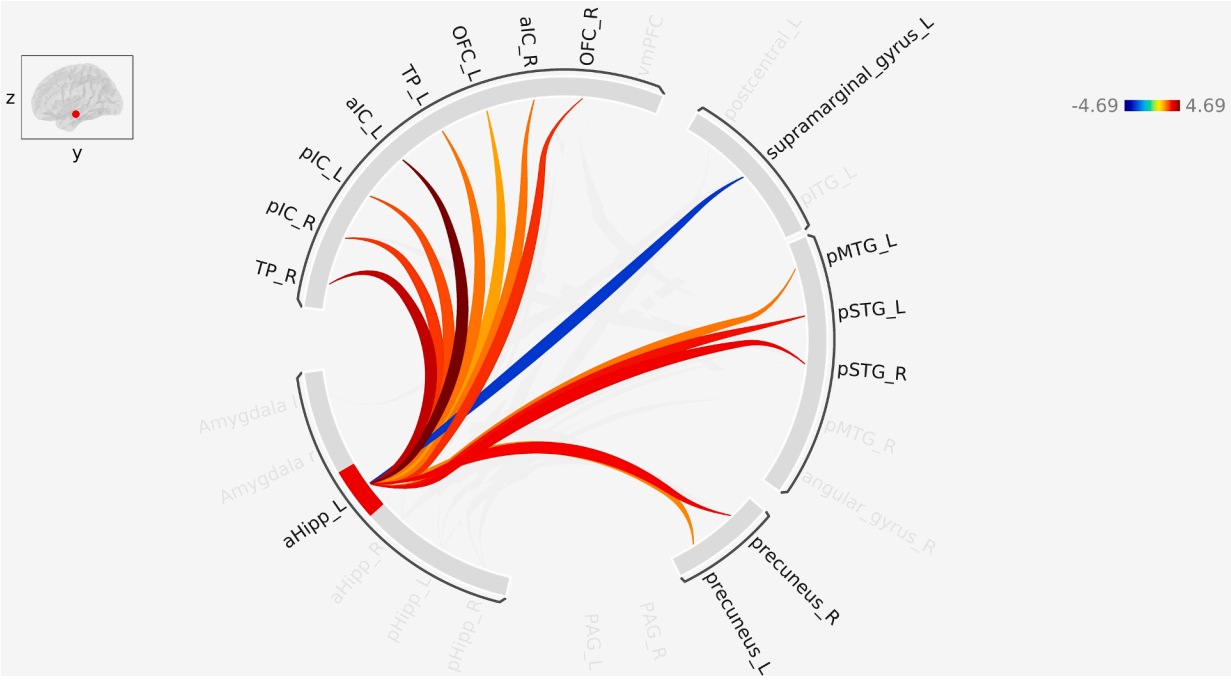

Fig. 3. Pathways identified in ROI-to-ROI functional connectivity analysis of the left anterior hippocampus. Red lines represent increased functional connectivity, and blue lines indicate decreased functional connectivity in PTSD compared to control. aHipp: Anterior hippocampus; aIC: Anterior insula; pIC: Posterior insula; TP: Temporal pole; OFC: orbitofrontal cortex; pSTG: Posterior superior temporal gyrus; pMTG: Posterior middle temporal gyrus. The color bar represents T-values. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

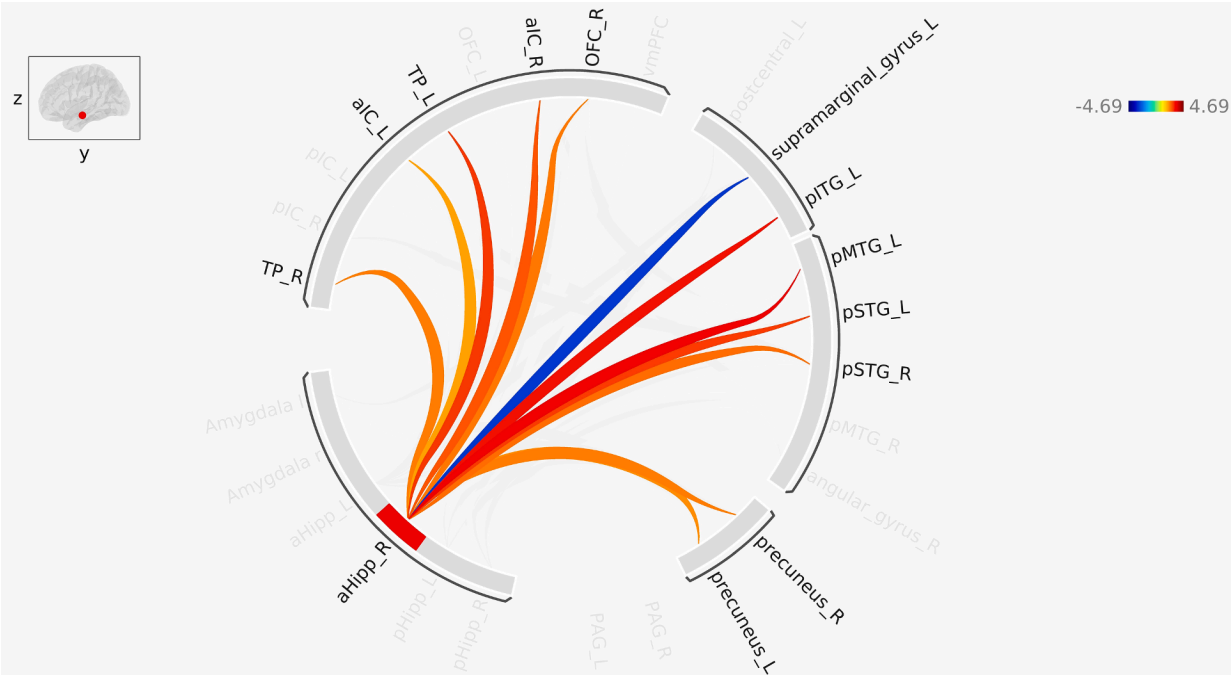

Fig. 4. Pathways identified in ROI-to-ROI functional connectivity analysis of the right anterior hippocampus. Red lines represent increased functional connectivity, and blue lines indicate decreased functional connectivity in PTSD compared to control. aHipp: Anterior hippocampus; aIC: Anterior insula; TP: Temporal pole; OFC: orbitofrontal cortex. pSTG: Posterior superior temporal gyrus; pMTG: Posterior middle temporal gyrus; pITG: Posterior inferior temporal gyrus. The color bar represents T-values. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

with the precuneus and various regions of the temporal gyri is a recurring theme for both the anterior and posterior hippocampus, consistent with the multisensory imagery of flashbacks (Hackmann et al., 2004; Van der Kolk & Fisler, 1995).

3.5. Graph-theoretic analysis

As the final step in our analyses, we examined our set of ROIs and the functional connectivity between them for node-wise group differences from a graph-theoretic perspective (Rubinov & Sporns, 2010) in order to

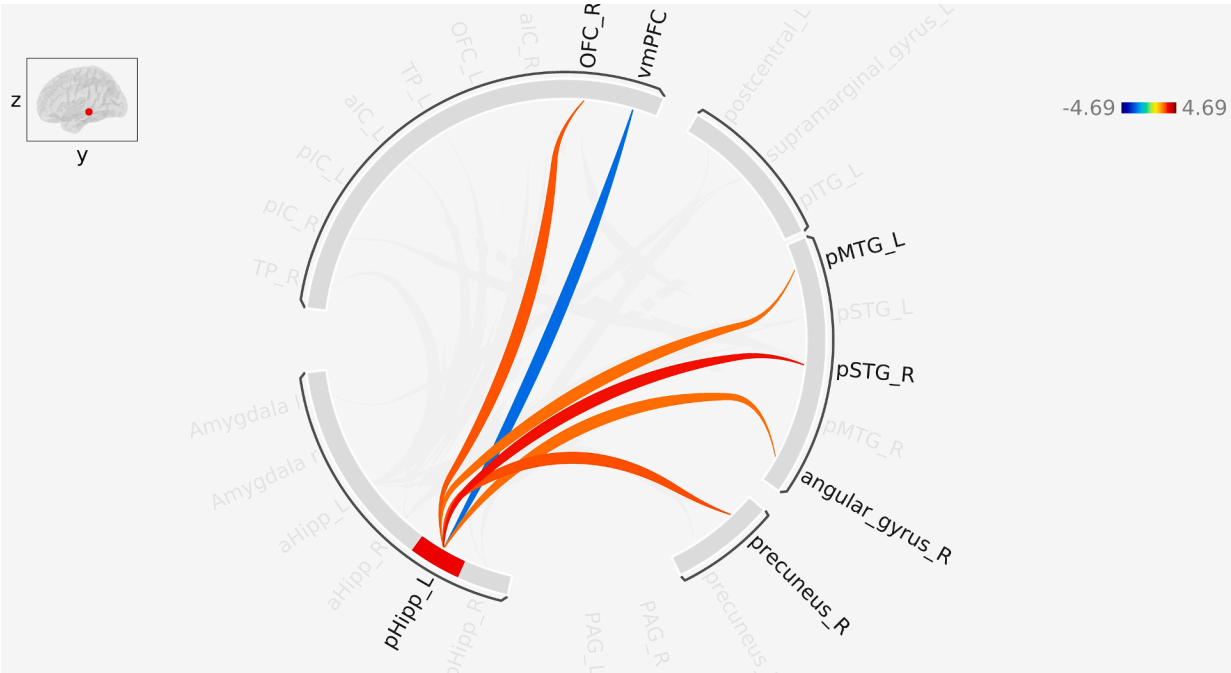

Fig. 5. Pathways identified in ROI-to-ROI functional connectivity analysis of the left posterior hippocampus. Red lines represent increased functional connectivity, and blue lines indicate decreased functional connectivity in PTSD compared to control. pHipp: Posterior hippocampus; OFC: Orbitofrontal cortex; pSTG: Posterior superior temporal gyrus; pMTG: Posterior middle temporal gyrus; vmPFC: Ventromedial prefrontal cortex. The color bar represents T-values. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

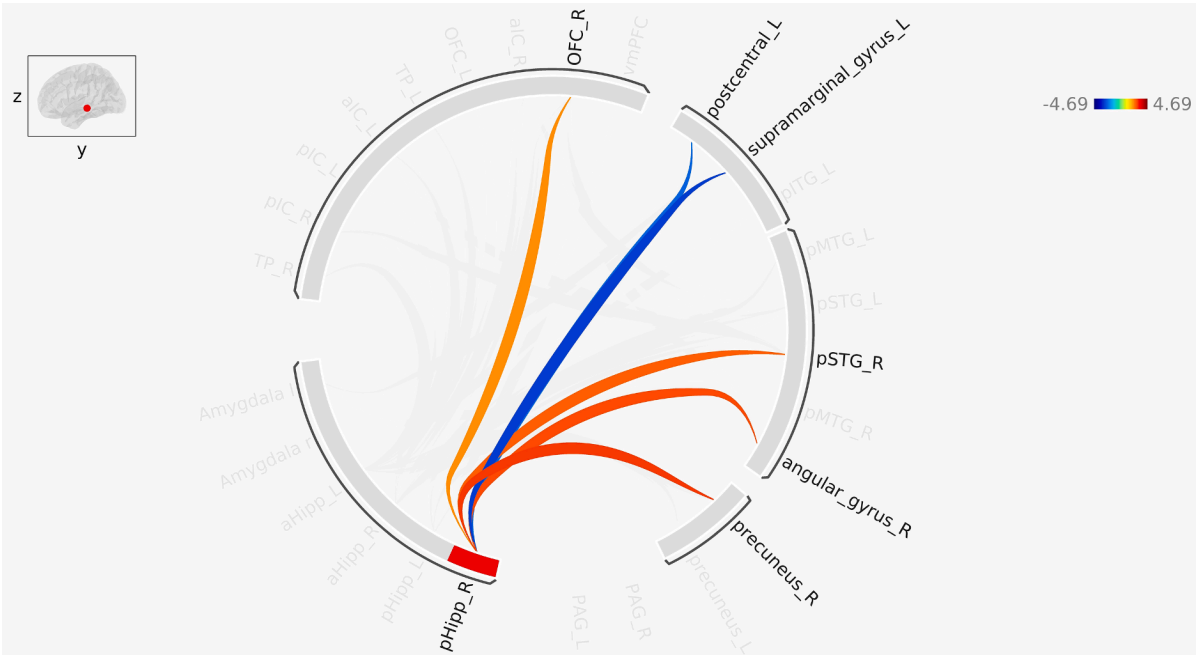

Fig. 6. Pathways identified in ROI-to-ROI functional connectivity analysis of the right posterior hippocampus. Red lines represent increased functional connectivity, and blue lines indicate decreased functional connectivity in PTSD compared to control. pHipp: Posterior hippocampus; OFC: Orbitofrontal cortex; pSTG: Posterior superior temporal gyrus. The color bar represents T-values. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

see whether PTSD is associated with changes in the topology of global connectivity, and if so, which nodes are at the center of these changes. Interestingly, only the left aHipp showed significant group differences between the PTSD and control groups. It displayed a lower average path length ($T(58) = -4.00$, p-FDR $= 0.005$) in the PTSD group relative to controls, indicating that the paths leading to the left aHipp are shorter in those with PTSD compared to controls. Similarly, the left aHipp had a higher node-wise global efficiency ($T(58) = 4.45$, p-FDR $= 0.001$), cost ($T(58) = 4.04$, p-FDR $= 0.004$) and degree ($T(58) = 4.04$, p-FDR $= 0.004$) compared to the control group. These results indicate that in PTSD, connections leading to the left aHipp become significantly more numerous and stronger (manifested in increased degree and cost), which

in turn gives rise to shorter paths leading to the left aHipp. The resultant effect of these changes is greater efficiency of information flow between these ROIs, via the aHipp (greater node-wise global efficiency). However, the left aHipp failed to show group differences for local efficiency ($T(58) = -2.39$, p-uncorrected $= 0.02$), clustering coefficient ($T(58) = -1.07$, p-uncorrected $= 0.29$), and betweenness centrality ($T(58) = 1.50$, p-uncorrected $= 0.14$). Collectively, these group differences highlight an increase in hub-like properties of the aHipp in those with PTSD as compared to trauma-exposed controls, potentially indicating an adaptive, central role of the aHipp in driving activity in a network of PSTD-relevant brain regions.

4. Discussion

This study examined the functional connectivity profile of the anterior and posterior hippocampus in individuals with PTSD and in trauma-exposed controls, using both whole-brain and post-hoc ROI-to-ROI approaches. The whole-brain seed-based analysis revealed no significant group differences when either the entire hippocampus or the posterior hippocampus (pHipp) was used as the seed ROI. In contrast, the anterior hippocampus (aHipp) was significantly more connected to affective brain regions (i.e., anterior and posterior insula and temporal pole) in PTSD compared to controls. Similarly, our post-hoc ROI-to-ROI analysis revealed more abnormal connections for the aHipp than pHipp in those with PTSD. Critically, our graph-theoretic analyses revealed that the left aHipp exhibited more hub-like properties in PTSD compared to the control group, showing lower average path length and higher global efficiency and degree. These results add to a body of evidence for increased global and local efficiency and centrality within nodes of the DMN and SN in those with PTSD, suggesting an adaptation (Suo et al., 2015; Zhu et al., 2019). Moreover, our graph-theoretic results align with a recent study that identified the entire hippocampus as a structural hub within the adult human brain (Oldham & Fornito, 2019). Here, our novel finding that the aHipp (and not the pHipp) exhibits an increase in its hubness likely signals it acquiring a more central role in communication within the brain, providing a more efficient integration of memory processes with other brain regions in PTSD relative to controls, perhaps in compensation for a possible deficit in posterior hippocampal functions, including detailed episodic retrieval. Speculatively, this could also indicate aHipp, a hippocampal sub-region linked to more emotional and schematic memory representations, taking on a more dominant role in controlling memory retrieval processes in those with PTSD, who are known to exhibit overgeneralization in memory retrieval (Schönfeld et al., 2007). On balance, the aHipp appears to be hyperconnected to emotional and other brain regions and may play a more central hub-like role in PTSD as compared to the pHipp.

4.1. Anterior hippocampus: the main player in PTSD

4.1.1. Insula

Our most robust finding was increased functional connectivity between the aHipp and anterior/posterior insula in PTSD (Fig. 1). The anterior insula is a major hub in the SN, involved in network switching and predisposing attention to salient interoceptive sensations and exteroceptive stimuli (Menon, 2011). Previous research has yielded mixed results regarding hippocampal-SN connectivity in PTSD; some studies reported hyperconnectivity (Harricharan et al., 2020; Sripada et al., 2012b), while others found hypoconnectivity (Breukelaar et al., 2021), or no differences in PTSD compared to controls (Brown et al., 2014). Our analyses, incorporating separate aHipp and pHipp seeds, offer a resolution to these discrepant findings, as we showed increased aHipp, but not pHipp functional connectivity with the anterior insula, consistent with the anterior insula's role in salience detection (Downar et al., 2002; Wiech et al., 2010), which becomes abnormal in PTSD (Russman Block et al., 2020). Abnormal salience processing could lead to benign stimuli being identified as threatening, accounting for persistent hypervigilance and hyperarousal in individuals with PTSD (Sripada et al., 2012b; Viard et al., 2019). Notably, the extensive (structural) connectivity between the insula and hippocampus (Ghaziri et al., 2018) contributes to encoding of negative stimuli (Chang & Yu, 2019; Tsukiura et al., 2013). Moreover, presentation of trauma-related cues leads to increased insula activation (Etkin & Wager, 2007), and hyperactivation of the right anterior insula, which correlates positively with state re-experiencing symptoms (Hopper et al., 2007). The anterior and posterior insula work together to accomplish important salience roles. In healthy adults, the input from the brainstem and thalamus to the posterior insula contains information about raw affective and interoceptive states, in addition to exteroceptive sensory information, which is then passed to the anterior insula where saliency of this information is assessed (Koch et al., 2016; Uddin, 2014). Here, the anterior insula is thought to "translate" this information for the prefrontal cortex, which participates in multisensory integration and emotion regulation (Harricharan et al., 2021). Thus, abnormalities in anterior insula-aHipp functional connectivity could be one of the factors underlying the misattribution of emotional salience to otherwise ordinary events in those with PTSD (Menon, 2011) and their inability to regulate emotions. Specifically, increased functional connectivity between the aHipp and the anterior insula may reduce the hippocampus' ability to discern non-threatening circumstances (Akiki et al., 2017), which could account for amplified threat processing, hypervigilance and anxiety in individuals with PTSD (Koch et al., 2016). However, heightened threat processing observed in PTSD may also result from bottom-up drive initiated by regions of the innate alarm system such as the periaqueductal grey with less top-down PFC control (Nicholson et al., 2017).

4.1.2. Temporal pole

In addition, we observed increased functional connectivity between the aHipp and temporal pole (TP). The TP has extensive connections with the amygdala and orbitofrontal cortex, and is part of the SN (Menon, 2011). It has been implicated in various functions, such as language processing, visual recognition, autobiographical episodic memories, and socio-emotional processing (Herlin et al., 2021; Olson et al., 2007). Notably, several neuroimaging studies implicated the right TP in emotional situations (Herlin et al., 2021), such as retrieval of emotional autobiographical memories (Dolan et al., 2000; Reiman et al., 1997) or watching emotional movies (Lane et al., 1997; Reiman et al., 1997). War veterans with PTSD showed higher left TP activation when viewing war-related photos compared to combat-exposed controls, with war-related pictures inducing even more TP activation versus neutral photos (Dunkley et al., 2019). Similarly, a PET study involving recalling traumatic autobiographical memories vs. neutral events found that the traumatic condition evoked higher activation in the anterior TP, with the extent of this hyperactivation being even greater in the PTSD group (Shin et al., 1999). Therefore, the increased functional connectivity between the aHipp and the right TP could partially account for the over-representation of traumatic memories in PTSD and hyper-vigilance symptoms. However, the evidence implicating the TP in functional connectivity analysis of PTSD is limited and more research is warranted to elucidate the role of the TP in PTSD.

4.1.3. PCC/Precuneus

Regarding the PCC and precuneus, we did not find any group difference in whole-hippocampal-PCC functional connectivity; however, when separately assessing a/pHipp functional connectivity, we observed elevated coupling with the precuneus in the PTSD group, especially in the aHipp (in contrast to previous findings of reduced precuneus-whole-hippocampal functional connectivity in PTSD (Akiki et al., 2018; Chen & Etkin, 2013; Miller et al., 2017; Viard et al., 2019)). Moreover, decreased functional connectivity between the aHipp and PCC/precuneus (major nodes of the DMN) was associated with increased CAPS scores (Fig. 2). While stemming from a different section of the DMN, these results align with previous findings (Sripada et al., 2012b) of

negative correlation between CAPS scores and functional connectivity between the vmPFC (another node of the DMN) and the hippocampus. The precuneus, located in the medial parietal lobe, is a major hub within multiple brain networks (Utevsky et al., 2014). According to a prominent model of spatial memory (the BBB model, (Byrne et al., 2007)), this region has been dubbed the "parietal window", operating as an egocentric window into the products of perception, and episodic and spatial memory retrieval, as well as the visual sketchpad upon which visuo-spatial working memory operates. Consequently, the precuneus is crucial for mental imagery, and increased aHipp-precuneus functional connectivity could indicate abnormal recruitment of the aHipp in central DMN functions such as mental imagery, particularly during flashbacks. Interestingly, the pulvinar-precuneus functional connectivity is lower in PTSD relative to controls (Terpou et al., 2018). The pulvinar is a thalamic structure which regulates alpha synchrony and communications between cortical areas (Saalmann et al., 2012). In this regard, we hypothesize that the reduced pulvinar-precuneus and increased precuneus-aHipp functional connectivity may indicate a shift of the precuneal representations, from thalamically-driven sensory-based representations to a heavily emotional memory-based representation scheme, with the aHipp taking on a more hub-like role in the circuit for the storage and retrieval of trauma event memories. Speculatively, the negative correlation between aHipp-precuneus/PCC functional connectivity and CAPS scores could reflect a coping mechanism orchestrated by the traumatized brain to compensate for the impaired emotional regulation circuitry (involving the aHipp) by relying more strongly upon the intact PCC/precuneus (see Akiki et al., 2018), thereby reducing the symptom severity.

4.2. Posterior hippocampus and beyond

4.2.1. vmPFC

Our analysis also showed decreased pHipp-vmPFC functional connectivity among those with PTSD compared to controls (Fig. 5). Inhibition of fear is thought to be (at least partially) dependent on hippocampus-vmPFC connectivity (Admon et al., 2013b; Kalisch et al., 2006; Milad et al., 2007), which has been reported to be reduced in PTSD (Admon et al., 2013b). Moreover, the PFC is known to regulate hippocampal processes (Spielberg et al., 2015), and during retrieval of autobiographical memories, there is evidence that the vmPFC drives hippocampal activation (McCormick et al., 2020). Similarly, strong effective connectivity from vmPFC to the hippocampus has been observed during the elaboration phase of emotionally arousing autobiographical memory retrieval (Nawa & Ando, 2020). Furthermore, the hippocampus and vmPFC are principal nodes of the DMN, which plays a major role in episodic memory, internally-directed mental activity and self-related thoughts. Hence, the disrupted vmPFC-pHipp functional connectivity in PTSD could indicate inadequate downregulation of trauma-related hippocampal activation by the vmPFC, which could consequently result in intrusive traumatic memories and impaired episodic autobiographical recall in PTSD (Abdallah et al., 2017; Akiki et al., 2018; Spielberg et al., 2015).

4.2.2. Postcentral/Supramarginal Gyri

A notable finding of this study was the reduced functional connectivity between the postcentral gyrus (primary somatosensory cortex) and the pHipp as well as between the supramarginal gyrus and a/pHipp in PTSD compared to controls. The somatosensory cortex is crucial for detecting touch stimuli and processing self-movement, and the supramarginal gyrus is implicated in bodily self-consciousness and ownership (Bekrater-Bodmann et al., 2014; Rabellino et al., 2020), coding for peripersonal space (Brozzoli et al., 2011), and visuotactile integration (Gentile et al., 2011). The weakened functional connectivity between the hippocampus and areas responsible for processing bodily sensations could partially explain the altered bodily sense and body ownership experienced by those with PTSD (Rabellino et al., 2018a; Rabellino et al., 2018b). In line with this interpretation, the somatosensory cortex was found to be less active in response to non-threatening touch in PTSD (Badura-Brack et al., 2015). The above findings are consistent with the importance of sensory-motor therapies for PTSD (Elbrecht & Antcliff, 2014; McGreevy & Boland, 2020). *Sensory Motor Arousal Regulation Therapy* (SMART) (Warner et al., 2014) is one such intervention; SMART aims to satisfy the sensory-seeking behaviours found in those with PTSD by allowing them to interact with objects that fulfill their need for sensory satiation. This multisensory approach also integrates auditory, visual and tactile information with interactive motor activities. It has been proposed (Harricharan et al., 2021) that sensorimotor interventions for PTSD can ameliorate deficits in emotional self-regulation by re-engaging otherwise "offline" areas such as the prefrontal cortex, which are normally involved in multisensory integration, emotion regulation, and conscious top-down reappraisal. This promotes reintegration of traumatic memories while reducing their negative affect. Based on the results discussed in this study, we hypothesize that the posterior hippocampus may be a critical brain region that is relatively "offline" in those with PTSD and that clinical interventions targeting this region could potentially have enhanced therapeutic efficacy. More specifically, the decreased connectivity observed between the somatosensory cortex and the posterior hippocampus, which contains more detailed contextual representations, might be a prime target for improved sensorimotor interventions that could potentially result in a contextualized sensory representation of trauma memories. In addition, sensory-motor therapies have focused particularly on treating childhood trauma, where trauma memories are often unreachable by verbal recall (Norton et al., 2011). Here, the stimulation of somatosensory and motor pathways may act as a gateway into otherwise inaccessible trauma memories, perhaps by a restoration of the diminished functional connectivity between the hippocampus and somatosensory areas.

4.2.3. Orbitofrontal cortex

In addition, those with PTSD showed increased a/pHipp functional connectivity with the lateral orbitofrontal cortex (lOFC), a brain region associated with obsession, appraisal and moderating reaction to negative affective states (Milad & Rauch, 2007; O'Doherty et al., 2001). It is also activated in anticipation of (Nitschke et al., 2006) and reaction to (Rolls et al., 2003a; Rolls et al., 2003b) unpleasant stimuli (Milad & Rauch, 2007), and in the absence of an expected reward (Milad & Rauch, 2007). In rats, hyperactivation of the lOFC has been shown to impair fear extinction (Chang et al., 2018). Moreover, higher OFC activation is seen in recalling traumatic autobiographical vs. neutral events in both PTSD and control groups, with the PTSD group showing even more OFC hyperactivation (Shin et al., 1999). Thus, increased coupling between hippocampus subregions and the lOFC could explain abnormal fear regulation, a characteristic symptom of PTSD.

4.2.4. Superior temporal gyrus

Furthermore, the superior temporal gyrus (STG) showed increased functional connectivity with the pHipp and especially with the aHipp. STG, the locus of primary and secondary auditory areas (De Bellis et al., 2002; Reale et al., 2007), is the source of the P300 (O'Donnell et al., 1999), an event-related potential (ERP) component elicited by unexpected stimuli (Van Petten & Luka, 2012). Interestingly, combat veterans with PTSD have shown amplified P300 responses when exposed to both trauma-related (Bleich et al., 1996) and novel stimuli (Kimble et al., 2000). Similarly, women with sexual assault-linked PTSD exhibited escalated mismatch negativity, a pre-conscious ERP originating from the auditory cortex in response to a stimulus that differs from a set of identical stimuli (Morgan & Grillon, 1999), aligning with hyper-vigilance often seen in PTSD. Supporting these findings of altered auditory perception in PTSD, one study reported increased STG gray matter volume in children and adolescents with maltreatment-related pediatric PTSD (De Bellis et al., 2002). Another study on those with Acute Stress Disorder found that activity in STG was positively

correlated with PTSD severity (Cwik et al., 2017). Taken together with the above, our findings of greater aHipp- and pHipp-STG functional connectivity in PTSD underscore the importance of the STG in the neurocircuitry of PTSD. Furthermore, trauma memories are often accompanied by acoustic components. Thus, it is conceivable that increased hippocampal-STG functional connectivity could reflect this aspect of the trauma memory, especially given that the individuals with PTSD in our sample were combat-exposed war veterans, many of whom would have suffered from exposure to blasts.

4.2.5. Ramification for dual representation theory

Our findings also relate to the Dual Representation Theory (DRT) of PTSD (Brewin, 2014; Brewin et al., 2010), which essentially designates two types of memory that are differentially impaired in PTSD. The first is a perceptual memory system, containing relatively unprocessed and raw sensory and perceptual representations of events *("S-reps"),* while the second consists of contextualized and verbally accessible representations of events *("C-reps")*. S-reps chiefly rely on the dorsal visual stream, the amygdala, and the insula, while the hippocampus and surrounding areas in the medial temporal lobe largely maintain C-reps. Flashbacks are viewed as amplified S-reps that, owing to the extreme stress during the encoding of the traumatic event, are not appropriately paired with the associated C-reps (which themselves are weakly encoded because of the stress), and are hence lacking due context. While the DRT does not posit a role for the hippocampus in flashbacks, our results suggest a refinement of this theory, whereby the aHipp plays a central role in flashbacks. Our finding of increased insula-aHipp functional connectivity is consistent with this, and it would be interesting to explore the directionality of our observed increased functional connectivity between the aHipp and the insula/sensory areas. However, we did not see increased amygdala-aHipp functional connectivity in PTSD, perhaps because they are already strongly connected in the healthy brain. In any case, our findings do not entirely support DRT, as the aHipp is abnormally hyper-connected to affective and multisensory areas in PTSD and is likely to drive trauma memories; this proposition requires further empirical confirmation, e.g., by conducting effective connectivity analyses during both resting-state and tasks involving trauma-related memory recall. Given the extensive and direct connectivity of the aHipp with the amygdala and the insula and the involvement of the aHipp in emotional memory encoding, it is conceivable that trauma memories are over-represented in the aHipp at a "gist-like'' level while being under-represented in the pHipp, which is thought to contain detailed representations (Poppenk et al., 2013). By this account, trauma-related cues would activate the aHipp, and due to its elevated connectivity with emotional circuitry and sensory areas, the ensuing recollection would be rich in emotional and sensory details. As a refinement of the DRT to incorporate our findings, this would imply improper contextualization of trauma memories, with an over-representation of raw sensory and emotional components in (anterior) hippocampal representations. Conversely, the pHipp would be less involved than normal in retrieving the contextual details of the trauma event memory, aligning with the report that synapses in dorsal CA1 in rodents (analogous to the pHipp in primates) are particularly damaged due to short, concurrent stress relative to ventral CA1 (Maras et al., 2014). This proposal, however, needs to be experimentally confirmed by assessing hippocampal activation and connectivity in individuals with PTSD during trauma memory recall.

Interestingly, we did not find altered hippocampal functional connectivity with the amygdala in those with PTSD compared to controls. As discussed earlier, the findings in the literature surrounding the role of the amygdala in the neurocircuitry of PTSD are mixed (Lee et al., 2021; Schulze et al., 2019; Stark et al., 2015; Suarez-Jimenez et al., 2020; Thome et al., 2019), possibly due to variations in tasks performed during scans. Nonetheless, these discrepant findings hint at a departure from an abnormal amygdala-centric view of PTSD dysfunction. For instance, while Suarez-Jimenez et al. (Suarez-Jimenez et al., 2020) reported occasional amygdalar involvement in some phases of fear conditioning and extinction, they primarily highlight a hypoactive thalamus as a core finding, suggesting it to be the nexus of problematic salience. Collectively, evidence points to more heterogeneous and distributed disruptions in cognitive, behavioural, memory and sensorimotor processes in those with PTSD, which could include both the amygdala and hippocampus.

4.3. Limitations and future directions

Although the present results provide valuable insights regarding abnormal hippocampal functional connectivity in PTSD, we were unable to distinguish the dissociative sub-type of PTSD (PTSD + DS) (Lanius et al., 2012). This sub-type afflicts 14–30% of individuals with PTSD and is associated with symptoms of depersonalization and derealization, characterized by experiences of "out-of-body" feelings and/or feelings of themselves or their surroundings as being "dream-like" and not real (Harricharan et al., 2021). It is likely that some participants within this study were from this sub-group. However, we were unable to identify them since the two items addressing depersonalization and derealization in the CAPS questionnaire were not recorded in ADNI. This limitation should be kept in mind when interpreting the presented results since PTSD + DS has a distinct neurological signature compared to PTSD. Evidence suggests that PTSD + DS symptoms originate from excessive top-down prefrontal inhibition on limbic and brainstem regions (Nicholson et al., 2017). Future work is needed to characterize abnormal hippocampal functional connectivity in the PTSD + DS subtype. Moreover, because the analyses reported here were conducted on previously collected publicly available data, we did not have access to some key details of the scanning conditions, such as the instructions given to the participants or whether they were monitored to prevent them from falling asleep. Additionally, since our participant cohort was comprised of elderly (average participant age 68.3 years), combat-exposed male Vietnam war veterans, our results might not be readily generalizable to females, younger individuals and civilians with PTSD. We particularly caution against generalizing the present results to female populations with PTSD, as a recent study (Helpman et al., 2021) found a significant group-by-sex interaction in the effect of PTSD on functional connectivity between the hippocampus and the precuneus, as well as the hippocampus and the angular gyrus (for a review of sex differences in PTSD, see Seligowski et al., 2020). Furthermore, several participants from the PTSD group in the present study suffered from comorbid conditions such as depressive symptoms, which may have affected our results. Also, while functional connectivity can be built upon structural connectivity, we did not assess structural pathways and therefore cannot determine if the functional connectivity patterns were influenced by their anatomical distances, which could be investigated in future studies. Moreover, rsFC analysis merely estimates the temporal correlation between activations of brain areas and does not reveal the direction of these correlations, warranting further investigation using effective connectivity measures. Finally, rsFC may overlook aberrant activation and functional connectivity patterns that manifest during the performance of specific cognitive tasks such as recalling trauma memories.

4.3.1. Is deliberate retrieval of trauma memories less coherent? Possible role for the pHipp

It has been argued (Bisby et al., 2020) that emotionally arousing and aversive memories, particularly traumatic ones, are less coherent compared to emotionally neutral memories. Three lines of evidence support this view:

1. Normally, episodic memory retrieval is thought to be a holistic, multifaceted phenomenon wherein multiple item-item and item-context associations combine to produce a single "all-or-none" re-experiencing of the event (Horner et al., 2015). Importantly, binding of these multi-modal items together and to the context is thought

to be primarily governed by the hippocampus (Cohen & Eichenbaum, 1995).

2. In healthy individuals, negative emotional content differentially impacts memory for sensory constructs versus higher levels of encoding, where the sensory-perceptual encoding of individual items is enhanced at the cost of item-to-item and item-context associations (Bisby & Burgess, 2013). Similarly, the administration of cortisol 30 min before a memory-encoding task decreased item-context associations (Van Ast et al., 2013). Moreover, in healthy individuals, episodic memories with negative content reportedly had lower coherence than neutral memories (Bisby et al., 2018).
3. In those with PTSD, memory deficits extend beyond negative, everyday episodic memories. For instance, their memory for paired associates of emotionally neutral items was reportedly weaker (Golier et al., 2002; Guez et al., 2011), and their allocentric memory processing (which depends on hippocampal functioning (Byrne et al., 2007)) was impaired, while their memories for individual items and egocentric memories remained unaffected (Smith et al., 2015). The adverse effects of high stress on memory were further confirmed by a report of firefighters whose memories concerning the fires they had just fought were more impaired with increasing stress (Metcalfe et al., 2019).

While the above studies have, for the most part, not considered the functional differences between the aHipp and pHipp, recent studies have begun to do so. These investigations suggest that while both regions are involved in encoding spatial context, the posterior hippocampus is more involved in the encoding of fine details and detailed spatial relational information (see, e.g. Nadel et al., 2013). For instance, the ratio of pHipp volume to that of the aHipp was positively correlated with item-context retrieval (Snytte et al., 2020), and the volume of the pHipp mediated between age and spatial context memory performance (Snytte et al., 2022). Moreover, children who performed a colour context encoding task showed recruitment of the pHipp during context encoding whereas those exposed to interpersonal violence had impaired memory of contexts (realistic background scenes) associated with violence (Lambert et al., 2017). Another study reported the recruitment of the pHipp (and the posterior parahippocampal cortex) during retrieval of item-context relations, while the aHipp (and the perirhinal cortex) was activated during retrieval of item-item relations (Sheldon & Levine, 2015).

Considering the evidence on aHipp versus pHipp roles in contextual memory, coupled with memory deficits in PTSD, such as fragmented or incoherent autobiographical memory retrieval, the underperformance of the pHipp (and not the aHipp) might be one of the leading causes of these memory impairments. Arguably, PTSD itself is an adaptive response to trauma exposure, which could manifest as a compensatory over-recruitment of the aHipp in PTSD to support processing of events in threatening situations, coupled with an under-recruitment of pHipp. This hypothesis merits further investigation.

Future studies should examine the differential roles of the anterior and posterior hippocampus in a sample including both PTSD without dissociation and the PTSD + DS sub-type, as well as healthy controls, with a focus on prefrontal-hippocampal functional connectivity. Secondly, to capture the direction of connectivity between the anterior/posterior hippocampus and target ROIs, effective connectivity analyses can be performed using multivariate Granger causality (MVGC) (Barnett & Seth, 2014) and/or Dynamic Causal Modelling (DCM) (Friston et al., 2003). Thirdly, future studies could extend beyond our post-hoc analyses, exploring a wider set of ROIs that could characterize the differential role of the hippocampal subregions in large-scale ROI-to-ROI connectivity in those with PTSD. Finally, it is important to assess activation and connectivity patterns beyond the resting state, particularly during trauma memory recall, as well as in a wider range of participants, including females and those with childhood trauma.

5. Conclusion

In summing up our main findings, the current study highlighted aberrations in the functional connectivity of hippocampal sub-regions that could underlie some core symptoms of PTSD. Here, we focused on the anterior versus posterior hippocampus, hypothesizing that they might be differentially affected by PTSD due to their unique connectivity profiles and functional roles. We found that the aHipp is the predominant locus of abnormal functional connectivity in PTSD, showing heightened functional connectivity with many brain regions, including affective areas (i.e., insula, orbitofrontal cortex and temporal pole), sensory areas, and nodes associated with the DMN in those with PTSD. In stark contrast, the abnormal connections of the pHipp were not as numerous as those of its anterior counterpart. Thus, our findings hint at abnormal recruitment of the aHipp in retrieving trauma memories in those with PTSD, while the pHipp might not be as involved in contextual retrieval as it normally should. We also observed decreased functional connectivity between regions responsible for bodily self-consciousness and the anterior/posterior hippocampus, potentially accounting for the altered sense of self and somatosensory symptoms in PTSD. Additionally, our study indicates that disrupted DMN and SN connections, mainly via the aHipp, could be regarded as a neural correlate of PTSD, with the left aHipp taking on a more hub-like role. Finally, the current study also found evidence of a link between reduced symptom severity and increased functional connectivity between the aHipp and PCC/Precuneus, which we speculate could reflect a compensatory mechanism in the brain's attempt to restore DMN recruitment in memory functions within this altered circuit. These abnormal functional connectivity profiles of hippocampal sub-regions could be predictive of symptom severity and may serve as a biomarker of the disorder. They also have important implications for neuroscientifically-guided therapeutic efforts targeting dysfunctional networks and connectivities, particularly highlighting the advantage of sensory-motor integration therapies for PTSD.

CRediT authorship contribution statement

Mohammad Chaposhloo: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Andrew A. Nicholson:** Writing – review & editing. **Suzanna Becker:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Margaret C. McKinnon:** Funding acquisition. **Ruth Lanius:** Writing – review & editing. **Saurabh Bhaskar Shaw:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Used publicly available data set

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Chapter 3

Unraveling Trauma Memory: Differential Roles of Anterior and Posterior Hippocampus in Trauma Recall in Post-traumatic Stress Disorder and Its Dissociative Subtype

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Introductory note: The work presented in the following chapter is currently in preparation, to be submitted pending final revisions from co-authors. Data for this Chapters was previously collected as part of a collaboration between Dr. Ruth Lanius and Dr. Margaret

McKinnon, and were accessed for the present purposes under a data sharing agreement between Dr. Becker and and Dr. Lanius. M. Chaposhloo was responsible for generating the research questions, performing the analyses, and drafting the original manuscripts under the supervision of Dr. Becker and the co-supervision of Dr. Shaw. M. Chaposhloo, Dr. Becker, Dr. Lanius, and Dr. Shaw were jointly involved in the conceptualization of the studies. Dr. Becker, Dr. Lanius, Dr. Shaw, Dr. Breanne E. Kearney and Dr. M. McKinnon contributed to the data interpretation and revision of the manuscripts.

This chapter addresses two of the limitations of the previous chapter: the absence of a group comprising individuals with PTSD+DS, and the limitation of analyzing only resting state data as opposed to scanning participants during the recall of trauma memories. Here, we investigated the functional connectivity of the aHPC and pHPC during the recall of trauma and neutral memories in two samples: those with classic PTSD and those with PTSD+DS. The results of this chapter test the hypotheses we made based on the findings of the previous chapter about the differential roles of the aHPC and pHPC during trauma memory recall in PTSD.

Abstract

Post-traumatic stress disorder (PTSD) has long been viewed by many as a disorder of memory. Consequently, the hippocampus has been an important focus of research on the neural circuitry of PTSD given its core involvement in episodic memory and mechanisms underlying traumatic memory. The primate hippocampus is functionally divided along its long axis into the anterior (aHipp) and posterior parts (pHipp), with the anterior portion playing a greater role in emotion-related memories while the posterior region is more involved in cognitive and spatial processing. Given this, one might predict greater involvement of the aHipp in PTSD. However, little research has investigated the differential involvement of these hippocampal subregions in PTSD, and most research in this area has been conducted during rest rather than during the recall of traumatic or extremely emotional memories. It is an open question whether anterior and posterior hippocampal regions might play differential roles during trauma-related memory recall. Here, we addressed this question by investigating the activity and the whole-brain functional connectivity of the aHipp and pHipp during the recall of moral injury (MI) related trauma memories versus neutral memories in three groups: those with PTSD (n=49), those with its dissociative subtype (PTSD+DS; n=19), and healthy controls (n=36). The left pHipp showed decreased activity during the recall of MI memories versus neutral memories in PTSD+DS compared to controls, whereas the right pHipp exhibited the opposite pattern. Additionally, both anterior and posterior hippocampal subregions displayed abnormal functional connectivity with various brain regions during trauma memory recall. For example, the right aHipp showed decreased connectivity with the dorsal anterior and midcingulate cortices in PTSD compared to controls, while the pHipp showed abnormal connectivity with areas such as the cerebellum, the parahippocampal and

fusiform gyri, somatomotor cortex, and early visual areas of the occipital lobe in PTSD+DS compared to PTSD alone and controls during the recall of MI memories. Collectively, these results suggest differential involvement of the anterior and posterior hippocampus in the recall of traumatic memories in MI-related PTSD and its dissociative subtype, which may relate to the decontextualized and fragmented nature of traumatic memories.

Introduction

Post-traumatic Stress Disorder (PTSD) is a psychiatric disorder that can develop following exposure to a traumatic event(s). It is characterized by persistent symptoms including intrusive memories of the traumatic event, avoidance of trauma reminders, pervasive negative cognition and mood, severe anxiety, hypervigilance and hyperarousal (American Psychiatric Association, 2013; Yehuda et al., 2015). Additionally, a more severe form of PTSD, known as the "dissociative subtype" (PTSD+DS), afflicts around 38% of those with PTSD (White et al., 2022) and is characterized by symptoms of depersonalization (feeling detached from one's own body) and derealization (feeling detached from one's surroundings and perceiving them as dream-like or surreal), emotional numbing, and general patterns of hypoarousal in response to trauma-related cues (Lanius et al., 2012; Schiavone et al., 2018). The trauma memories in PTSD and PTSD+DS often manifest as vivid, intense, and fragmented somatosensory and emotional recollections of the trauma. Such "flashbacks" are involuntary, triggered by the mere presence of trauma reminders despite a safe present-day environment, and are subjectively experienced as unfolding in the present moment, i.e. they are relived instead of being remembered.

Generally, PTSD symptoms coincide with maladaptive alterations in several core cognitive and emotional functions, including fear learning/extinction, threat detection, executive function,

emotional regulation, contextual processing, and associative learning (Kunimatsu et al., 2020; Lambert & McLaughlin, 2019); these functional alterations are accompanied by structural and functional abnormalities in brain regions and large-scale networks that support these functions (Akiki et al., 2017; Bremner et al., 1995, 1999, 2005; Etkin & Wager, 2007; Geuze et al., 2007; Karl et al., 2006; Kasai et al., 2008; Lanius et al., 2003; Lindauer et al., 2008; Milad et al., 2009; Rauch et al., 2006; Shin et al., 2004, 2005; Whalley et al., 2009). The hippocampus is one such region that plays a major role in the neurocircuitry affected in PTSD due to its critical involvement in episodic memory processes and many of the impaired functions (Garfinkel et al., 2014; Milad et al., 2009; Norrholm et al., 2011; Petzold & Bunzeck, 2022; Shepherd & Wild, 2014; Shin et al., 2004; Wicking et al., 2016), including fear extinction, emotional regulation, contextual and spatial processing, and visual scene construction (Kolibius et al., 2023; Marlatte et al., 2022; Milad et al., 2007; Odriozola et al., 2024; Wixted et al., 2018). PTSD has also been consistently associated with alterations in large-scale intrinsic connectivity networks (ICNs), including the default-mode network (DMN), the salience network (SN), the central executive network (CEN), and the sensorimotor network (SMN) (e.g., Akiki et al., 2017; Bao et al., 2021; Daniels et al., 2010; Koch et al., 2016). In addition, PTSD+DS has recently garnered significant research interest due to its distinct neurobiological signature from PTSD, indicating an overmodulation of limbic and subcortical areas such as the periaqueductal gray (PAG – a key region in the "innate alarm system") by cortical areas (Nicholson et al., 2017). Also, those with PTSD+DS exhibited altered functional connectivity of the cerebellum, subcortical regions, SMN, DMN, and areas implicated in bodily self-consciousness in comparison to classic PTSD (Rabellino et al., 2018, 2023; Shaw et al., 2023), with a pattern of widespread hyperconnectivity between these regions that was absent in those

with PTSD (Shaw et al., 2023). Nevertheless, the neurocircuitry of PTSD+DS, particularly during the recall of traumatic memories, remains significantly under-studied.

PTSD as a partial disorder of memory processes

Consistent with the view that PTSD, at least in part, is a disorder of memory processes, a multitude of memory functions in PTSD are known to be compromised. These include trauma memories, negative non-trauma memories, and even neutral memories of everyday events (Lambert & McLaughlin, 2019; Moore & Zoellner, 2007; Pitts et al., 2022). Notably, deficits in hippocampus-dependent associative learning for cues and contexts, which are not exclusively tied to trauma-related or emotional stimuli, have been proposed as one of the core dysfunctions in PTSD (Golier et al., 2002, 2003; Guez et al., 2011; Lambert & McLaughlin, 2019; Yehuda et al., 2006). PTSD is also associated with a tendency towards over-general and less specific autobiographical memory (AM) recall (Barry et al., 2018; Brown et al., 2013; Harvey et al., 1998; Kangas et al., 2005; McNally et al., 1994, 1995; Moore & Zoellner, 2007; Ono et al., 2016). In addition to the aforementioned deficits in non-traumatic memories, it has been consistently reported that the episodic recall of trauma memories in PTSD is a flawed process, rendering these memories unique (Lanius & Kearney, 2024; Perl et al., 2023). Specifically, those with PTSD often struggle to recall important and specific details of the traumatic event, failing to provide a coherent and organized narrative of the event (Harvey & Bryant, 1999; van der Kolk & Fisler, 1995). Those narratives are described as “fragmented” (i.e., full of repetitions, speech fillers, and lack flow), with therapy-related reductions in fragmentation correlating with decreased trauma-related anxiety (Foa et al., 1995). Trauma memories in PTSD are also frequently relived or re-experienced as if unfolding in the present moment, although in a manner that is atypical of autobiographical memories: they are

described as being intensely vivid, decontextualized, non-verbal and comprised of fragmented sensorimotor and emotional representations that are not adequately integrated into an embodied and unitary AM (van der Kolk & Fisler, 1995). These atypical, decontextualized memories would suggest an abnormal hippocampal role in trauma memory recall (Brewin et al., 2010). Moreover, PTSD has been associated with impairments in other hippocampus-dependent functions, such as spatial processing and scene construction (Marlatte et al., 2022).

Several studies that have analyzed data from a script-driven memory retrieval paradigm have shed light on the neurocircuitry underlying trauma memory recall in individuals with moral injury (MI)-related PTSD, a specific trauma type involving transgression of one's moral code (Andrews et al., 2023; Kearney et al., 2023; Lloyd et al., 2021; Terpou et al., 2022). These studies reported increased activation in areas involved in salience detection and visceral processing (dorsal ACC and posterior insula), executive functions (dlPFC), and somatomotor areas (postcentral gyrus) during the MI recall in those with PTSD compared to controls (Lloyd et al., 2021). Further, increased functional connectivity between the DMN and periaqueductal grey (PAG) and cerebellar lobule IX was found in participants with civilian-related PTSD (Terpou et al., 2022), while hyperconnectivity between the SMN and posterior DMN (pDMN) was found in both civilian and military-related PTSD during recall of MI memories compared to controls (Kearney et al., 2023). Together, these findings suggest atypical activation and functional connectivity of brain regions involved in viscerosensory processing and arousal regulation, as well as those involved in top-down cognitive control of emotions. Critically, however, none of the aforementioned studies have differentiated between PTSD and its dissociative subtype, nor did they specifically investigate hippocampal activity and connectivity.

The literature on PTSD, as reviewed up to this point, has not focused on the hippocampus. However, as noted previously, we would expect the hippocampus to play a central role in memory disturbances in PTSD. One crucial factor in hippocampal function that is frequently overlooked in connectivity studies is the functional segregation between the anterior and posterior portions of the mammalian hippocampus (Fanselow & Dong, 2010; Grady, 2020; Poppenk et al., 2013; Strange et al., 2014; Zeidman & Maguire, 2016). In humans, the anterior hippocampus (aHipp; analogous to the ventral hippocampus in rodents) is structurally connected to brain areas implicated in fear and emotional processing (e.g., the amygdala, insula, and lateral temporal areas; Catenoix et al., 2011; Kier et al., 2004) and plays a pivotal role in the affective dimensions of memory. Conversely, the posterior hippocampus (pHipp, corresponding to the dorsal hippocampus in rodents) is preferentially connected to the posterior midline (Ezama et al., 2021; Kahn et al., 2008) and visual regions (Dalton et al., 2022) and is involved in spatiotemporal contextual information processing (Lambert et al., 2017; Ranganath et al., 2004; Robin et al., 2018; Sheldon & Levine, 2015). Consistent with this functional segregation along the longitudinal axis of the hippocampus, evidence from diffusion-weighted MRI in humans indicates greater connections between the pHipp and visuospatial areas, whereas the aHipp was more linked to the temporal pole and lateral temporal cortex (Dalton et al., 2022). The pHipp also shows greater involvement in tasks relying on spatial navigation, as exemplified by the larger pHipp volume in London taxi drivers (Maguire et al., 2000). Additional memory-related disparities between the aHipp and pHipp have been documented. For instance, in healthy adults, better recollection memory performance has been associated with larger pHipp volume at the aHipp's expense (Poppenk & Moscovitch, 2011). Additionally, intracranial recording from patients with temporal lobe epilepsy revealed greater pHipp involvement in the encoding and retrieval of verbal memories compared to the aHipp

(Ludowig et al., 2008). Furthermore, a resting-state fMRI analysis reported higher node centrality for the pHipp than the aHipp (Qin et al., 2016). Therefore, the pHipp has been hypothesized to be more involved in representing the detailed, fine-grained, and contextual aspects of memory, while the aHipp has been suggested to encapsulate more coarse-grained, gist-list spatial representations, with a greater focus on emotional content and social-related processes (Gagnepain et al., 2017; Ludowig et al., 2008; Poppenk et al., 2010; Strange & Dolan, 2006). For a more detailed review of the distinction between the aHipp and pHipp, see Chaposhloo et al. (2023).

Despite the wealth of human studies investigating the differential activity and connectivity of the aHipp and pHipp in healthy populations, surprisingly few studies have focused on their differential roles within the neurocircuitry of PTSD, which have reported inconsistent alterations in resting-state functional connectivity between the pHipp and PCC/precuneus (Chen & Etkin, 2013; Lazarov et al., 2017; Malivoire et al., 2018). A recent study conducted by our team probed the differential connectivity of the aHipp versus pHipp during resting state using the publicly-available ADNI dataset (M. W. Weiner et al., 2014), employing a whole-brain, data-driven methodology with a substantially larger sample size compared to the aforementioned studies (Chaposhloo et al., 2023). In that study, the aHipp emerged as assuming a more hub-like role in the PTSD group compared to the control group, characterized by augmented connections with a multitude of brain regions, particularly those associated with affective processing, while the pHipp did not exhibit a comparable extent of aberrant connections. These observations have led us to hypothesize that in PTSD, the aHipp might acquire a more central role in the recollection of trauma memories, whereas the involvement of the pHipp may be diminished. In other words, we proposed a reorientation of trauma memory processing favouring the aHipp. However, that study was confined to a resting state paradigm, and, thus, was limited in the conclusions that could be drawn

regarding the mechanisms of trauma memory recall in PTSD. Another recent study assessed correlations between measurements of the subjective properties of trauma memories and subsequently collected resting-state fMRI data (Clancy et al., 2024). That study reported a negative correlation between the emotional intensity of intrusive trauma memories and the frequency and persistence of the resting-state aHipp-DMN co-activation pattern, while the reliving quality of intrusive trauma memories in the "here-and-now" was positively correlated with persistent pHipp-visual cortex co-activation pattern. These findings indicate that aHipp-DMN interactions may modulate emotional aspects of trauma memories, and the pHipp and visual cortex interactions may be responsible for the sensory richness of trauma memories. Nevertheless, no mechanistic insight regarding trauma memories can be concluded from that study since the participants recalled their trauma memories outside of the scanner. Therefore, no imaging study to this date has directly examined the differential involvement of the aHipp and pHipp during trauma memory recall in PTSD.

The present study aims to address two key research gaps, including a) the investigation of anterior and posterior subcomponents of the hippocampus during traumatic memory recall; and b) the unique neurobiological signature of the anterior and posterior hippocampus during traumatic memory recall in PTSD+DS versus PTSD and controls. We specifically explored trauma memories centred around MI, which is a condition that may arise in response to situations wherein a person causes, takes part in, fails to prevent, or merely witnesses an event that fundamentally contravenes one's moral framework and beliefs (Litz et al., 2009). To our knowledge, this is the first investigation into the activity and connectivity of the aHipp and pHipp during the recollection of traumatic events within PTSD and PTSD+DS cohorts. Based on the findings from our earlier resting-state study (Chaposhloo et al., 2023), we anticipated heightened aHipp activation during

the recall of MI memories compared to neutral memories and/or when comparing PTSD participants to controls. Conversely, we expected a decrease in pHipp activity under analogous conditions. We also hypothesized increased functional connectivity between the aHipp and affective brain areas during the recall of MI memories compared to neutral memories and/or in the PTSD group versus controls. In PTSD+DS, however, we hypothesized less activity of the aHipp during the recall of trauma memory due to the tendency toward emotional numbing. Finally, given that individuals with PTSD+DS often recall trauma memories from a third-person perspective, alongside the greater involvement of the pHipp in spatial processing, we expected increased connectivity between the pHipp and visual areas, as well as regions responsible for perspective switching, such as the precuneus and retrosplenial cortex (Byrne et al., 2007), in PTSD+DS relative to PTSD alone and controls during the recall of MI memories.

Methods

Participants

We utilized a previously collected fMRI dataset acquired from individuals with MI-related PTSD and controls that utilized a script-driven neutral and trauma memory retrieval paradigm. Participants were recruited via advertisements distributed across local mental health centres and other public places within the London, Ontario community. Our sample comprised a total of 104 participants (49 in the PTSD group, 19 in the PTSD+DS group, and 36 in the control group), all of whom had been exposed to a morally injurious event regardless of their diagnosis. Portions of the fMRI data analyzed here have been subject to prior analyses; readers are directed to those studies for fine details regarding the study protocols (Andrews et al., 2023; Kearney et al., 2023;

Lloyd et al., 2021; Terpou et al., 2022). Exclusion criteria included any history of bipolar disorder, psychotic disorder, neurodevelopmental disorder, head injury involving loss of consciousness, serious untreated medical conditions, substance use within three months preceding participation, incompatibility with MRI safety procedures, or pregnancy. All participants received financial compensation for their time and involvement in the study. This study was originally approved by the Health Sciences Research Ethics Board at Western University (HSREB Number 107575), and the acquisition and analyses of the data for the present purposes were approved by the McMaster Research Ethics Board (MREB Number 6347).

Clinical Questionnaires and Interviews

The clinical diagnosis of PTSD and the severity of its symptoms were assessed for all participants using the Clinician-Administered PTSD Scale-5 (CAPS-5; Weathers et al., 2018). MI presence and severity were assessed using The Moral Injury Events Scale (MIES; Nash et al., 2013). The Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID), along with a battery of questionnaires, were also administered, including the Multiscale Dissociation Inventory (MDI; Briere et al., 2005), the Beck Depression Inventory-II (BDI-II; Beck et al., 1997), and the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2011).

Each participant developed two personalized eight-sentence memory scripts in collaboration with the clinical assessor. Participants were provided with the definition of MI and received assistance from the clinical assessor in selecting an MI event that could evoke strong enough moral emotions without overwhelming them (SUDS [subjective units of distress scale] level 5-8 out of 10). The first script narrated a “neutral” event without any positive or negative emotional valence (e.g., a trip to the grocery store). The second script depicted a morally injurious event.

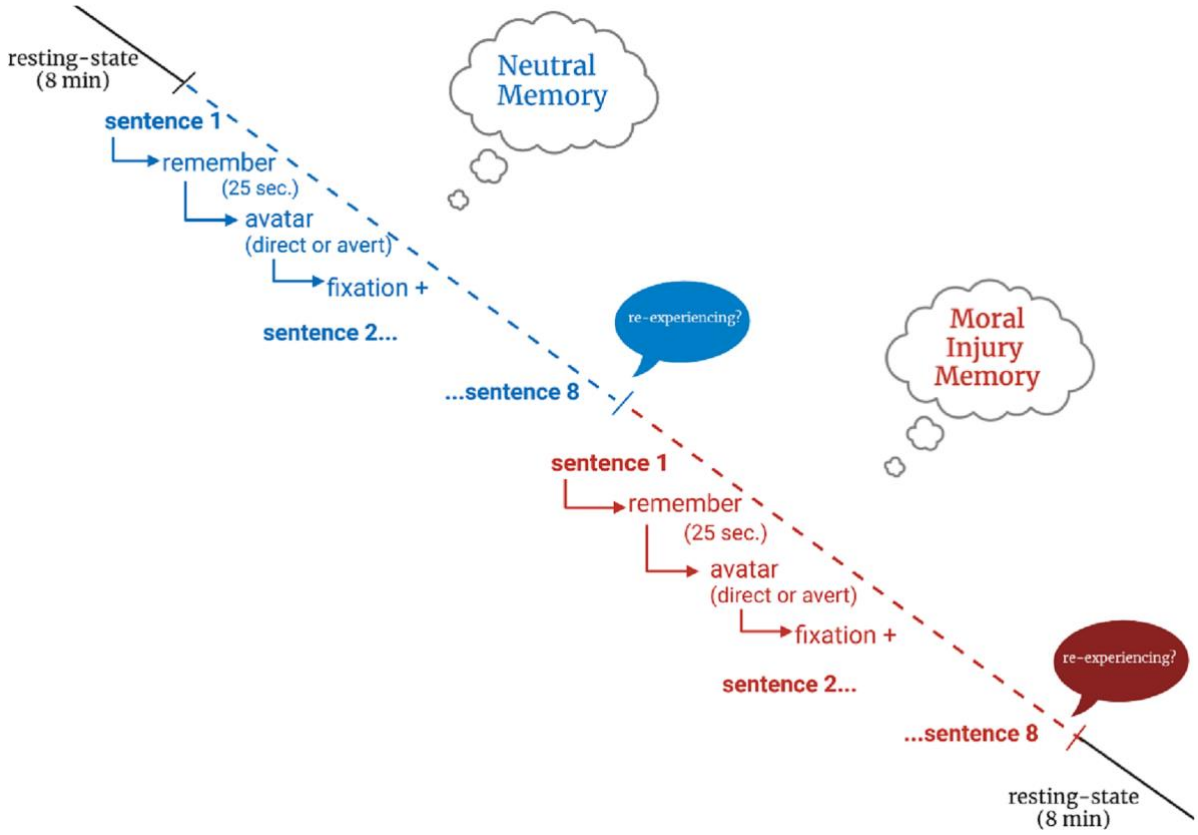

Figure 1: fMRI paradigm. Participants underwent eight-minute resting-state scans before and after the experiment. During the experiment, they first listened to their neutral memory script and then to their moral injury memory script. Each script included eight sentences, presented visually and aurally in a neutral tone, one at a time. After each sentence, participants recalled each sentence for 25 seconds. Afterward, a virtual avatar with either direct or averted gaze appeared, followed by a fixation cross. This process was repeated for each sentence in both the Neutral and Moral Injury Remember phases. Adapted from Kearney et al. (2023)

Experimental Procedure

The experimental procedure (figure 1) consisted of pre- and post-experiment resting-state scans, neutral and MI memory recall, and virtual avatar presentation. For the purposes of this study, we analyzed only the neutral and moral injury script-driven memory retrieval components of the paradigm. In the memory recall conditions, participants viewed and heard their neutral and MI memory scripts read by an experimenter in a neutral affective tone via MR-compatible headphones. The script was read and textually presented to them sentence by sentence in chronological order to evoke details of the memory as vividly as possible. After each sentence, the participants were instructed to recall the memory in detail for 25 seconds, after which a virtual avatar with either direct or averted gaze was presented, followed by a fixation cross. The gaze manipulation, a within-subject manipulation, was the focus of a previously published study (Andrews et al., 2023) but was not included in the present analyses. The same procedure was then used for the MI memory script. In addition, the Responses to Script-Driven Imagery (RSDI) Scale, a self-report measure of state PTSD and dissociative symptoms (Hopper et al., 2007), was administered after each script. Specifically, participants were instructed to rate the presence/intensity of re-experiencing symptoms using RSDI and moral emotions (e.g. shame). To prevent the emotional effects of MI retrieval from being carried over to the neutral memory recall condition, the two conditions were separated completely (neutral followed by MI).

fMRI Image Acquisition and Pre-processing

Each participant's structural and functional brain images were obtained using a 3T MRI scanner (Biograph mMR; Siemens Medical Solutions) and a Siemens 32-channel head coil. Foam paddings stabilized participants' heads and mitigated motion artifacts. T1-weighted images had a 1mm

isotropic resolution. A Gradient echo T2*-weighted blipped-echo-planar sequence was used to collect fMRI data (TR = 3000 ms, TE = 20 ms, FOV= 256 × 256 mm, flip angle= 90◦, voxel size 2 mm isotropic, parallel imaging acceleration factor = 4). For neutral and MI conditions, each run consisted of 118 volumes, each with 60 ascending interleaved slices.

fMRI data were pre-processed using SPM12 (Wellcome Centre for Human Neuroimaging, London, UK) and the CONN toolbox release 22.a (Whitfield-Gabrieli & Nieto-Castanon, 2012) within MATLAB version R2020a (The MathWorks, Inc., Natick, MA, USA). We used the default pre-processing pipeline within CONN, including realignment with correction of susceptibility distortion interactions, slice timing correction, outlier detection, direct segmentation and MNI-space normalization, and smoothing. More specifically, functional data were realigned using the SPM realign & unwarp procedure (Andersson et al., 2001), where all scans were coregistered to a reference image (first scan of the first session) using a least squares approach and a 6-parameter (rigid body) transformation (Friston et al., 1995), and resampled using b-spline interpolation to correct for motion and magnetic susceptibility interactions. Temporal misalignment between different slices of the functional data (acquired in interleaved bottom-up order) was corrected following the SPM slice-timing correction (STC) procedure (Henson et al., 1999; Sladky et al., 2011), using sinc temporal interpolation to resample each slice BOLD time-series to a common mid-acquisition time. Potential outlier scans were identified using ART as acquisitions with framewise displacement above 0.9 mm or global BOLD signal changes above five standard deviations (Nieto-Castanon, 2022; Power et al., 2014), and a reference BOLD image was computed for each subject by averaging all scans excluding outliers. Functional and anatomical data were normalized into standard MNI space, segmented into grey matter, white matter, and CSF tissue classes, and resampled to 2 mm isotropic voxels following a direct normalization procedure

(Calhoun et al., 2017; Nieto-Castanon, 2022) using SPM unified segmentation and normalization algorithm (Ashburner, 2007; Ashburner & Friston, 2005) with the default IXI-549 tissue probability map template. Finally, functional data were smoothed using spatial convolution with a Gaussian kernel of 6 mm full-width half maximum (FWHM).

In addition, functional data were denoised using the default denoising pipeline of the CONN toolbox, including the regression of potential confounding effects characterized by white matter time-series (5 CompCor noise components), CSF time-series (5 CompCor noise components), motion parameters and their first order derivatives (12 factors) (Friston et al., 1996), outlier scans (below 42 factors) (Power et al., 2014), session and task effects and their first order derivatives (8 factors), and linear trends (2 factors) within each functional run, followed by bandpass frequency filtering of the BOLD time-series (Hallquist et al., 2013) between 0.008 Hz and 0.09 Hz. CompCor (Behzadi et al., 2007; Chai et al., 2012) noise components within white matter and CSF were estimated by computing the average BOLD signal as well as the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks. From the number of noise terms included in this denoising strategy, the effective degrees of freedom of the BOLD signal after denoising were estimated to range from 178.1 to 212.5 (average 206.3) across all subjects (Nieto-Castanon, 2022).

Hippocampal Activation Analysis:

We acquired seed regions of interest (ROIs) for the left and right aHipp and pHipp from the Brainnetome atlas (Fan et al., 2016). We then used SPM12 for first-level analysis that estimated individual β weights for each condition (MI recall, neutral recall) and every voxel within each ROI. We then averaged the estimated β weights over all voxels within each ROI for each subject,

the results of which were fed into a full-factorial 3×2×4 (group×memory task×ROI) repeated measures ANOVA to carry out the group-level analysis (second-level analysis).

Functional Connectivity Analysis:

Seed-based connectivity maps (SBC) were estimated to characterize patterns of aHipp and pHipp functional connectivity. Functional connectivity strength was represented by Fisher-transformed bivariate correlation coefficients from a weighted general linear model (GLM), defined separately for each pair of seed and target areas, modelling the associations between their BOLD signal time series. Individual scans were weighted by a boxcar signal characterizing each individual task or experimental condition convolved with an SPM canonical hemodynamic response function and rectified.

At the first level, a separate GLM was estimated for each individual voxel and connectivity measures at this voxel were entered as dependent variables (one independent sample per subject and one measurement per task or experimental condition, if applicable) and groups or other subject-level identifiers were entered as independent variables. For second-level (groupwise) analyses, we employed multivariate parametric statistics with random effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual clusters (groups of contiguous voxels). Cluster-level inferences were based on parametric statistics from Gaussian Random Field theory (Worsley et al., 1996). Results were thresholded using a combination of a cluster-forming $p < 0.001$ voxel-level threshold and a familywise corrected p-FDR < 0.05 cluster-size threshold (Chumbley et al., 2010).

Results

Hippocampal Activity

We conducted a full-factorial 3×2×4 (group×memory task×ROI) repeated measures ANOVA to compare the effect of group (PTSD vs. PTSD+DS vs. control) and memory task (MI vs. neutral memory recall) on activities of four hippocampal ROIs (left and right aHipp, and left and right pHipp). The ANOVA revealed a main effect of ROI ($F(6,303)=4.28$, $p=0.00563$) and a three-way interaction ($F(6,303)=4.11$, $p=0.00056$). Post-hoc analyses, summarized in Table 1, were conducted to further investigate these significant effects. While none of the post-hoc comparisons remained significant when corrected for multiple comparisons, some noteworthy trends were observed. For example, within the PTSD+DS group, the left pHipp showed a trend toward reduced activity during MI compared to neutral memory recall (p-uncorrected=0.0379). Additionally, within the control group, the right aHipp showed a trend toward reduced activation during MI versus neutral memory recall (p-uncorrected=0.0405), an effect opposite to that observed in the right pHipp. Based on our previous findings of a more hub-like role of the aHipp in those with PTSD during resting state scans (Chaposhloo et al., 2023), we predicted greater involvement of the aHipp in MI memory recall in those with PTSD and reduced involvement in those with PTSD+DS. Interestingly, we did not observe such an effect for the aHipp, a discrepancy that will be explored in the Discussion.

Table 1: Summary statistics of the post-hoc between-group and between-condition comparisons of the hippocampal activations

Hippocampal ROI	Contrast	T-statistics	P-value	Adjusted

			(uncorrected)	P-value (FDR)
aHipp_L	PTSD+DS > PTSD; MI	t(66) = -0.3749	0.7089	0.8102
aHipp_R		t(66) = -0.7407	0.4615	0.7359
pHipp_L		t(66) = -0.9428	0.3492	0.6447
pHipp_R		t(66) = 0.6449	0.5213	0.7359
aHipp_L	PTSD+DS > Controls; MI	t(53) = -0.0599	0.9525	0.9525
aHipp_R		t(53) = 0.4781	0.6346	0.7905
pHipp_L		t(53) = -1.4018	0.1668	0.4232
pHipp_R		t(53) = 1.8169	0.0749	0.3624
aHipp_L	PTSD > Controls; MI	t(83) = 0.4560	0.6496	0.7905
aHipp_R		t(83) = 1.5675	0.1208	0.3624
pHipp_L		t(83) = -0.4432	0.6588	0.7905
pHipp_R		t(83) = 1.5906	0.1155	0.3624
aHipp_L	PTSD+DS > PTSD; Ne	t(66) = 0.3181	0.7514	0.8197
aHipp_R		t(66) = -1.7904	0.0780	0.3624
pHipp_L		t(66) = 1.6123	0.1117	0.3624
pHipp_R		t(66) = -2.4580	0.0166	0.1964
aHipp_L	PTSD+DS > Controls; Ne	t(53) = -0.1481	0.8828	0.9212
aHipp_R		t(53) = -2.3145	0.0245	0.1964
pHipp_L		t(53) = 2.7137	0.0090	0.1964
pHipp_R		t(53) = -1.3705	0.1763	0.4232

aHipp_L	PTSD > Controls; Ne	t(83) = -0.7655	0.4461	0.7359
aHipp_R		t(83) = -0.6696	0.5050	0.7359
pHipp_L		t(83) = 1.0533	0.2953	0.5905
pHipp_R		t(83) = 1.2496	0.2150	0.4690
aHipp_L	MI > Ne; PTSD+DS	t(18) = -0.2975	0.7695	0.7695
aHipp_R		t(18) = 0.8607	0.4007	0.7110
pHipp_L		t(18) = -2.2404	0.0379	0.2430
pHipp_R		t(18) = 1.7849	0.0911	0.3646
aHipp_L	MI > Ne; PTSD	t(48) = 0.4542	0.6517	0.7695
aHipp_R		t(48) = 0.3821	0.7041	0.7695
pHipp_L		t(48) = -1.0704	0.2898	0.7110
pHipp_R		t(48) = -0.2980	0.7670	0.7695
aHipp_L	MI > Ne; Controls	t(35) = -0.8097	0.4236	0.7110
aHipp_R		t(35) = -2.1275	0.0405	0.2430
pHipp_L		t(35) = 0.7238	0.4740	0.7110
pHipp_R		t(35) = -0.9719	0.3378	0.7110

aHipp_L = left anterior hippocampus, aHipp_R = right anterior hippocampus, pHipp_L = left posterior hippocampus, pHipp_R = right posterior hippocampus, MI: moral injury, Ne = neutral, FDR = false discovery rate

Examining the differences in hippocampal activity between MI and neutral recall conditions, none of the between-group comparisons survived corrections for multiple comparisons (Table 2 and Figure 2). However, some notable trends emerged. Chief among these is the finding that the left pHipp trended toward being less active during the recall of MI versus neutral memories in the

PTSD+DS group compared to the control group (p-uncorrected=0.0063). In contrast, the right pHipp trended toward being more active during MI versus neutral memory retrieval in the PTSD+DS group compared to the control group (p-uncorrected=0.02). This discordance in the activity of the left and right pHipp is intriguing and warrants further discussion, as the left and right pHipp are reported to assume different roles in memory processing.

Table 2: Summary statistics of the between-group comparisons of the MI vs. Neutral differences in hippocampal activations

Hippocampal ROI	Contrast	T-statistics	P-value (uncorrected)	Adjusted P-value (FDR)
aHipp_L	PTSD+DS > PTSD	t(66) = -0.5315	0.5968	0.7162
aHipp_R		t(66) = 0.7223	0.4727	0.6302
pHipp_L		t(66) = -1.9204	0.0591	0.1547
pHipp_R		t(66) = 1.9721	0.0528	0.1547
aHipp_L	PTSD+DS > Controls	t(53) = 0.0663	0.9474	0.9474
aHipp_R		t(53) = 1.8883	0.0645	0.1547
pHipp_L		t(53) = -2.8443	0.0063	0.0757
pHipp_R		t(53) = 2.3945	0.0202	0.1213
aHipp_L	PTSD > Controls	t(83) = 0.8815	0.3806	0.5709
aHipp_R		t(83) = 1.6410	0.1046	0.2092
pHipp_L		t(83) = -1.2253	0.2239	0.3839
pHipp_R		t(83) = 0.3836	0.7023	0.7661

aHipp_L = left anterior hippocampus, aHipp_R = right anterior hippocampus, pHipp_L =

left posterior hippocampus, pHipp_R = right posterior hippocampus, FDR = false discovery rate

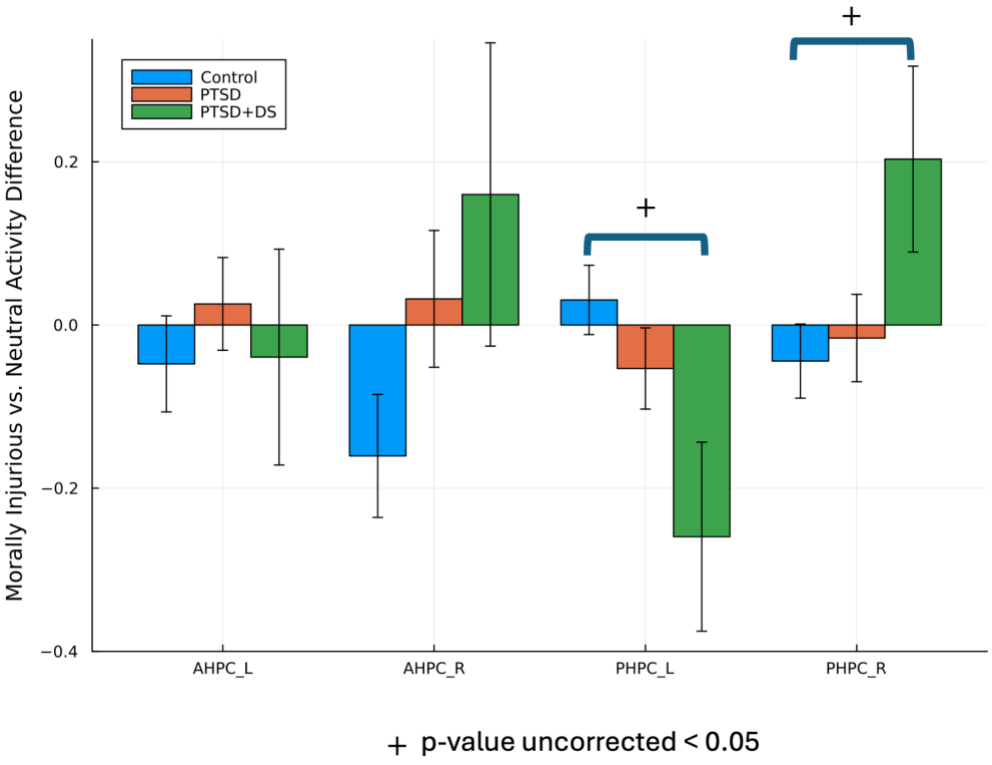

Figure 2: The difference between hippocampal activity during MI and neutral memory recall for each group and each ROI.

Whole-brain Hippocampal Functional Connectivity analyses

Results from the whole-brain aHipp and pHipp seed-based functional connectivity analysis during MI and neutral memory recall conditions are presented in Table 3. We here highlight the most significant and relevant results for each hippocampal ROI.

Table 3: Whole-brain functional connectivity of hippocampal seed ROIs

Hippocampal Seed ROI *Contrast* Target Brain Region	Target Region Cluster MNI Coordinates (mm)	Cluster Size (Voxels)	T-statistics	Increased or Decreased Connectivity	P-value (FDR)
aHipp (Left)					
PTSD+DS > PTSD; MI					
pMTG (Left)	-52 -16 -22	64	|T(66)| > 3.44	Increased	0.03817
Cerebellum Crus I/II (Left)	-16 -76 -26	60	|T(66)| > 3.44	Increased	0.03817
PTSD+DS > Controls; MI					
Cerebellum Crus I/II/VI (Left)	-16 -76 -30	199	|T(53)| > 3.48	Increased	0.00000
pTFusC (Left)	-36 -14 -28	74	|T(53)| > 3.48	Increased	0.01072
ITG (Left)	-52 -16 -22	63	|T(53)| > 3.48	Increased	0.01607
aPaHipp (Left)	-24 -20 -28	60	|T(53)| > 3.48	Increased	0.01607
PTSD+DS > PTSD; Ne					
Cerebellum IV/V (Left)	-12 -40 -18	79	|T(66)| > 3.44	Increased	0.01096
PTSD+DS > Controls; Ne					

Cerebellum III/IV/V (Left) Vermis III	-10 -48 -18	114	|T(53)| > 3.48	Increased	0.00074
aHipp (Right) *PTSD > Controls; MI* Paracingulate Gyrus (Left) dACC/MCC	-04 +14 +44	59	|T(83)| > 3.41	Decreased	0.02811
pHipp (Left) *PTSD+DS > PTSD; MI* Cerebellum IV/V/VI (Left) TOFusC (Left) OFusG (Left)	-16 -64 -18	113	|T(66)| > 3.44	Increased	0.00090
PTSD+DS > Controls; MI Cerebellum IV/V/VI (Left) pTFusC (Left) Lingual Gyrus (Left) TOFusC (Left)	-26 -44 -20	290	|T(53)| > 3.48	Increased	0.00000
Putamen (Left)	-26 -16 -18	66	|T(53)| > 3.48	Increased	0.02122
PTSD+DS > PTSD; Ne toITG (Left) TOFusC (Left) iLOC (Left) OFusG (Left) pITG (Left)	-38 -56 -08	216	|T(66)| > 3.44	Increased	0.00000
Lingual Gyrus (Left) Cerebellum IV/V/VI (Left)	-14 -66 -06	66	|T(66)| > 3.44	Increased	0.01288
PTSD > Controls; Ne Pre/postcentral Gyrus (Right)	+52 -10 +54	70	|T(83)| > 3.41	Decreased	0.00968

MI > Ne; PTSD					
pTFusC (Left) Cerebellum IV/V/VI (Left)	-34 -38 -28	88	|T(48)| > 3.51	Increased	0.00211
iLOC (Right)	+38 -82 +02	53	|T(48)| > 3.51	Increased	0.02249
aSTG (Left) Temporal Pole (Left)	-58 +02 -06	44	|T(48)| > 3.51	Increased	0.03645
pHipp (Right)					
PTSD+DS > PTSD; MI					
Intracalcarine Cortex (Left) Cuneal Cortex (Left) Occipital Pole (Left) Supracalcarine Cortex (Left)	-06 -88 +06	92	|T(66)| > 3.44	Increased	0.00393
Lingual Gyrus (Left)	-12 -72 -06	52	|T(66)| > 3.44	Increased	0.03898
PTSD+DS > Controls; MI					
Pre/postcentral Gyrus (Left)	-60 -12 +40	74	|T(53)| > 3.48	Decreased	0.00746
Intracalcarine Cortex (Left) Occipital Pole (Left)	-06 -84 +06	74	|T(53)| > 3.48	Increased	0.00746
pTFusC (Left) pITG (Left)	-46 -40 -20	44	|T(53)| > 3.48	Increased	0.04898

aHipp = anterior hippocampus; pHipp = posterior hippocampus; pMTG = posterior middle temporal gyrus; pTFusC = posterior temporal fusiform cortex; ITG = inferior temporal gyrus; aPaHipp = anterior parahippocampal gyrus; dACC = dorsal anterior cingulate cortex; MCC = midcingulate cortex; TOFusC = temporal occipital fusiform cortex; OFusG = occipital fusiform gyrus; toITG = Temporooccipital inferior temporal gyrus; iLOC = inferior lateral occipital cortex; aSTG = anterior superior temporal gyrus; MI: moral injury; Ne: neutral

The Left Anterior Hippocampus

In contrast to the lack of activation differences in the aHipp, increased connectivity was found between the left aHipp and the posterior cerebellum, temporal lobe, and occipitotemporal lobe. Specifically, in PTSD+DS compared to PTSD, the left aHipp showed increased connectivity with the left cerebellum crus I/II (p-FDR = 0.038) and the posterior division of the left middle temporal gyrus (MTG; p-FDR = 0.038) during MI memory recall. Cerebellum crus I/II is known for its role in higher cognitive functions and emotional regulation and processing (Adamaszek et al., 2017), suggesting that its enhanced connectivity with the aHipp may contribute to the distinct cognitive and emotional processing observed in PTSD+DS. The middle temporal gyrus is involved in semantic memory processing, which may indicate altered emotional and semantic content integration during trauma recall in PTSD+DS.

The contrast between PTSD+DS and controls revealed that the left aHipp again showed increased connectivity with a large cluster of voxels (p-FDR=0.000008) spanning the left cerebellum crus I/II and the left cerebellum VI during MI memory recall. In the same contrast, the left aHipp showed increased connectivity with the posterior division of the left temporal fusiform cortex (pTFusC; p-FDR=0.011), the left inferior temporal gyrus (ITG; p-FDR=0.016), and the anterior division of the left parahippocampal gyrus (aPaHipp; p-FDR=0.039). The temporal fusiform cortex and the inferior temporal gyrus are key regions for visual and object processing, suggesting that visual aspects of traumatic memories may be more pronounced in PTSD+DS.

The Right Anterior Hippocampus

During MI memory recall, the right aHipp showed decreased connectivity with a cluster of voxels (p-FDR=0.028) spanning the left paracingulate gyrus and the midcingulate/dorsal anterior

cingulate cortex in PTSD compared to controls. These regions are important for emotion regulation and salience processing. Given the role of the aHipp in processing the emotional aspect of memories, these findings may account for the reduced capacity of individuals with PTSD to effectively manage and regulate their emotions.

The Left Posterior Hippocampus

In contrasting the PTSD+DS compared to PTSD, the left pHipp showed increased connectivity with a large cluster of voxels spanning the anterior and a portion of the posterior cerebellum and visual regions (p-FDR = 0.0009), including the left cerebellum IV/V, the left cerebellum VI, the left temporal occipital fusiform cortex (TOFusC), and the left occipital fusiform gyrus (OFusG) during MI memory recall. Similarly, in the contrast between PTSD+DS versus controls, the left pHipp showed increased connectivity with the left cerebellum IV/V (p-FDR<0.000001), the left cerebellum VI, the left pTFusC, the left lingual gyrus and the left TOFusC during MI memory recall. The TOFusC and OFusG are involved in high-level visual processing and object recognition, which could underlie the more vivid recollection of trauma memories in PTSD+DS compared to PTSD alone and controls.

Moreover, within the PTSD group, the left pHipp shows increased connectivity with the left pTFusC (p-FDR = 0.002), the left cerebellum IV/V, the left cerebellum VI and the inferior division of the left lateral occipital cortex (iLOC; p-FDR = 0.02) during recalling MI memories versus neutral memories. The increased connectivity of the pHipp with visual regions, including occipital areas, and the anterior cerebellum, which is important for sensorimotor processing, could indicate the overrepresentation of raw and decontextualized sensorimotor representations in the recall of trauma memories in PTSD and its dissociative subtype.

The Right Posterior Hippocampus

Contrasting PTSD+DS to PTSD during MI memory recall, we observed the right pHipp to have increased connectivity with a relatively large cluster of voxels covering visual areas in the occipital cortex (p-FDR=0.0037), including the left intracalcarine cortex (ICC), the left cuneal cortex, the left occipital pole, the left supracalcarine cortex, and the left lingual gyrus. These regions are crucial for processing raw visual information, which may contribute to the more vivid and detailed but also more decontextualized memory recall in PTSD+DS compared to PTSD alone. In the contrast between PTSD+DS and controls, the right pHipp showed decreased connectivity with sensorimotor areas, including the pre/postcentral gyri (p-FDR=0.0075) during MI memory recall. This decreased connectivity might reflect potentially reduced integration of somatosensory and motor information in PTSD+DS, perhaps contributing to the altered sense of bodily representations reported in this subtype. In the same contrast, the right pHipp showed increased connectivity with a cluster of voxels (p-FDR=0.0075) including the left ICC, the left occipital pole, and another cluster (p-FDR=0.049) including the left pTFusC and the left posterior ITG, consistent with the heightened sensory vividness typical of trauma memory recall in PTSD+DS.

The correlation between hippocampal connectivity and clinical scores

We also investigated the correlation between hippocampal connectivity within each clinical group (PTSD and PTSD+DS) and various clinical scores: CAPS, MDI (depersonalization, derealization and memory disturbance subscores), BDI, CTQ, and RSDI reliving scores, the results of which are summarized in Table 4. Interestingly, during the recall of MI memories, in those with PTSD+DS the left aHipp-dmPFC (an area implicated in self-related thoughts) connectivity negatively correlated with CAPS scores, while in those with PTSD, the connectivity of the same pathway

positively correlated with BDI scores. In addition, in PTSD+DS during the recall of MI versus neutral memories, the left aHipp-right Angular Gyrus (a multisensory area important for the immediate sense of bodily self) connectivity was negatively correlated with MDI Derealization scores, whereas right pHipp-left Pre/postcentral gyrus (location of the primary somatosensory and motor cortex) connectivity positively correlated with the reliving subscale of RSDI scores. Therefore, it seems that the degree of reliving in those with PTSD+DS during the recall of traumatic memories may at least partially depend on this pathway connecting the pHipp to primary somatosensory regions.

Table 4: Correlation between clinical scores and hippocampal functional connectivity (with target regions revealed in the whole-brain functional connectivity analysis)

HIPP ROI-Target ROI Connectivity Clinical Scores	Group/Condition/Contrast	Target Region Cluster MNI Coordinates (mm)	Cluster Size (Voxels)	T-statistics	Positive or negative correlation	P-value (FDR)
Correlation between CAPS scores and hippocampal connectivity scores (with target regions revealed in the whole-brain functional connectivity analysis)						
aHipp_L-dmPFC CAPS	PTSD+DS; MI	+02 +56 +22	50	|T(19)| > 3.97	Negative	0.02541
Correlation between Beck Depression Inventory (BDI) scores and hippocampal connectivity scores (with target regions revealed in the whole-brain functional connectivity analysis)						
aHipp_L-dmPFC BDI	PTSD; MI	-06 +54 +36	205	|T(39)| > 3.56	Positive	0.00000
aHipp_L-dlPFC (Left) BDI	PTSD; MI	-26 +50 +30	69	|T(39)| > 3.56	Positive	0.00583

aHipp_R-dlPFC (Right) aHipp_R-dmPFC/dlPFC (Right) aHipp_R-dmPFC BDI	PTSD; MI	+40 +44 +30 +14 +54 +26 +02 +42 +38	41 48 53	|T(39)| > 3.56	Positive	0.04651 0.03525 0.03525
pHipp_L-Lingual Gyrus (Left) BDI	PTSD+DS; MI > Ne	-08 -78 -12	50	|T(17)| > 3.97	Positive	0.01591
pHipp_R-dlPFC (Left) BDI	PTSD; MI	-24 +44 +32	73	|T(39)| > 3.56	Positive	0.00823
pHipp_R-dlPFC (Left) pHipp_R-Cerebellum Crus II (Right) BDI	PTSD; MI > Ne	-22 +46 +36 +04 -86 -30	69 41	|T(39)| > 3.56	Positive	0.00480 0.03660
pHipp_R-dmPFC BDI	PTSD; MI	-04 +42 +36	51	|T(39)| > 3.56	Positive	0.01923
Correlation between Multiscale Dissociation Inventory (MDI) scores and hippocampal connectivity scores (with target regions revealed in the whole-brain functional connectivity analysis)						
aHipp_L-dmPFC/dlPFC (Left) MDI Derealization	PTSD; MI > Ne	-10 +58 +32	56	|T(40)| > 3.55	Positive	0.02277
aHipp_L-sLOC (Left) aHipp_L-SPL (Left) MDI Derealization	PTSD+DS; MI > Ne	-30 -60 +46	52	|T(17)| > 3.97	Negative	0.01228
aHipp_L-Angular Gyrus (Right) MDI Derealization	PTSD+DS; MI > Ne	+42 -52 +40	56	|T(17)| > 3.97	Negative	0.00943
aHipp_L-Precuneus MDI Derealization	PTSD+DS; MI > Ne	-12 -66 +32	46	|T(17)| > 3.97	Negative	0.01228
pHipp_R-Cerebellum VI (Right) pHipp_R-OFusG (Right) pHipp_R-Vermis VI (Right)	PTSD+DS; MI > Ne	+16 -74 -16 +02 -72 -12	57 37	|T(17)| > 3.97	Positive	0.00645 0.03562

pHipp_R-Lingual Gyrus (Right) MDI Derealization						
aHipp_R-Postcentral Gyrus (Left) aHipp_R-SPL (Left) MDI Depersonalization	PTSD; MI	-34 -36 +50	58	|T(40)| > 3.55	Positive	0.02133
aHipp_L-sLOC (Left) aHipp_L-SPL (Left) MDI Total	PTSD+DS; MI > Ne	-22 -66 +46	79	|T(17)| > 3.97	Negative	0.00104
aHipp_L-Angular Gyrus (Right) MDI Total	PTSD+DS; MI > Ne	+42 -50 +42	43	|T(17)| > 3.97	Negative	0.02237
aHipp_L-Precuneus MDI Total	PTSD+DS; MI > Ne	-04, -66 +26	37	|T(17)| > 3.97	Negative	0.03056
aHipp_R-Paracingulate Gyrus (Left) MDI Total	PTSD; MI	-04 +38 +28	61	|T(40)| > 3.55	Positive	0.02078
pHipp_R-Cerebellum VI (Right) pHipp_R-OFusG (Right) pHipp_R-Lingual Gyrus (Right) MDI Total	PTSD+DS; MI > Ne	+16 -74 -14	41	|T(17)| > 3.97	Positive	0.04380
pHipp_R-dlPFC (Right) MDI Total	PTSD; MI	+36 +42 +30	121	|T(40)| > 3.55	Positive	0.00022
Correlation between the scores of Responses to Script-Driven Imagery (RSDI) Scale and hippocampal connectivity scores (with target regions revealed in the whole-brain functional connectivity analysis)						
aHipp_R-Posterior Insula (Right) aHipp_R-Planum Polare (Right) RSDI Reliving Score (MI)	PTSD; MI	+44 +02 -04	87	|T(40)| > 3.55	Positive	0.00279
aHipp_R-toMTG (Left) aHipp_R-pMTG (Left) RSDI Reliving Score (MI)	PTSD; MI > Ne	-64 -48 -08	56	|T(40)| > 3.55	Positive	0.03111

aHipp_R-toMTG (Left) aHipp_R-pMTG (Left) RSDI Reliving Score (MI)	PTSD; Ne	-64 -46 -08	58	|T(40)| > 3.55	Negative	0.02130
aHipp_R-toMTG (Left) aHipp_R-pMTG (Left) RSDI Reliving Difference Score (MI - Neutral)	PTSD; MI > Ne	-64 -48 -08	67	|T(39)| > 3.56	Positive	0.01107
pHipp_R-vlPFC (Right) pHipp_R-Pre/postcentral gyrus (Left) RSDI Reliving Score (MI)	PTSD+DS; MI	+32 +62 +06 -38 -22 +68	49 46	|T(17)| > 3.97	Positive	0.02507
Correlation between Memory disturbance subscores of MDI and hippocampal connectivity scores (with target regions revealed in the whole-brain functional connectivity analysis)						
aHipp_L-sLOC (Left) aHipp_L-SPL (Left) Memory Disturbance	PTSD+DS; MI > Ne	-32 -62 +50	168	|T(17)| > 3.97	Negative	0.00000
aHipp_L-SPL (Left) aHipp_L-Postcentral Gyrus (Left) Memory Disturbance	PTSD+DS; MI > Ne	-46 -40 +52 -32 -36 +48	72 38	|T(17)| > 3.97	Negative	0.00125 0.02005
aHipp_L-sLOC (Right) Memory Disturbance	PTSD+DS; MI > Ne	+32 -66 +46	56	|T(17)| > 3.97	Negative	0.00431
aHipp_L-sLOC (Right) aHipp_L-Angular Gyrus (Right) Memory Disturbance	PTSD+DS; MI > Ne	+40 -56 +42	44	|T(17)| > 3.97	Negative	0.01228
aHipp_R-IFG pars triangularis (Right) aHipp_R-IFG pars opercularis (Right) OFC (Right)	PTSD+DS; MI	+50 +28 -10	62	|T(17)| > 3.97	Negative	0.00947

Memory Disturbance						
aHipp_R-IFG pars triangularis (Right) aHipp_R-IFG pars opercularis (Right) Memory Disturbance	PTSD+DS; MI > Ne	+56 +20 00	56	|T(17)| > 3.97	Negative	0.00894
aHipp_R-Parietal Operculum Cortex (Left) Memory Disturbance	PTSD+DS; MI > Ne	-52 -36 +26	44	|T(17)| > 3.97	Negative	0.01755
aHipp_R-Occipital Pole (Right) aHipp_R-sLOC (Right) aHipp_R-iLOC (Right) Memory Disturbance	PTSD+DS; Ne	+14 -92 +18 +38 -82 +04	81 43	|T(17)| > 3.97	Positive	0.00132 0.02683
pHipp_L-pMTG (Right) Memory Disturbance	PTSD+DS; MI	+62 -12 -10	66	|T(17)| > 3.97	Negative	0.00848
pHipp_L-Cerebellum Crus I (Right) Memory Disturbance	PTSD+DS; Ne	+30 -86 -26	56	|T(17)| > 3.97	Negative	0.01822
pHipp_R-dlPFC (Left) Memory Disturbance	PTSD; MI	-34 +44 +34	101	|T(41)| > 3.54	Positive	0.00107
Correlation between Childhood Trauma Questionnaire (CTQ) scores and hippocampal connectivity scores (with target regions revealed in the whole-brain functional connectivity analysis)						
aHipp_R-MTG (Right) CTQ	PTSD; MI	+58 -10 -14	66	|T(39)| > 3.56	Negative	0.01243
aHipp_R-aMTG (Right) aHipp_R-vlPFC (Left) CTQ	PTSD; MI > Ne	+60 -14 -18 -28 +48 -02	97 54	|T(39)| > 3.56	Negative	0.00107 0.02117
pHipp_R-pMTG (Right) pHipp_R-IFG pars triangularis	PTSD; MI > Ne	+56 -14 -14 +54 +24 -04	51 46	|T(39)| > 3.56	Negative	0.04280

(Right) pHipp_R-IFG pars opercularis (Right) CTQ						

aHipp = anterior hippocampus; pHipp = posterior hippocampus; pMTG = posterior middle temporal gyrus; toMTG = Temporooccipital middle temporal gyrus; OFusG = occipital fusiform gyrus; iLOC = inferior lateral occipital cortex; sLOC = superior lateral occipital cortex; dmPFC = dorsomedial prefrontal cortex; dlPFC = dorsolateral prefrontal cortex; vlPFC = ventrolateral prefrontal cortex; SPL = Superior Parietal Lobule; IFG = inferior frontal gyrus; OFC = orbitofrontal cortex; MI: moral injury; Ne: neutral;

Discussion

The present study investigated the activation and functional connectivity of the anterior versus posterior hippocampi during the recall of traumatic, morally injurious memories in PTSD and its dissociative subtype. Our findings revealed abnormal pHipp activity during the recall of MI memories versus neutral memories in PTSD+DS, which may indicate a different quality of the recall for intense emotional memories (in this case, MI memories) in individuals with the dissociative subtype. In addition to abnormalities in hippocampal activity, we observed abnormalities in hippocampal functional connectivity across various brain areas during the recall of MI memories in PTSD and its dissociative subtype.

Hippocampal Activity

Analysis of hippocampal activations revealed a significant three-way interaction (group×memory task×ROI). However, no post-hoc comparisons survived corrections for multiple comparisons. With that caveat in mind, some trends toward aHipp and pHipp activity during neutral and

traumatic memory recall are noteworthy. When subtracting hippocampal activation during neutral memory recall from MI recall, the PTSD+DS group showed more negative differential activity in the left pHipp during the recall of MI memories, in comparison to the control group. Conversely, the right pHipp showed the opposite pattern: more positive differential activation in PTSD+DS compared to controls (Figure 2). These findings support evidence suggesting functional differentiation between the left and right hippocampus, where the left hippocampus is predominantly implicated in context-dependent, verbal, and narrative episodic memory, while the right hippocampus is more closely associated with visuospatial memory and navigation (Burgess et al., 2002; Ezzati et al., 2016; Frisk & Milner, 1990; Miller et al., 2018; M. L. Smith & Milner, 1981). Therefore, attenuated activity within the left pHipp during MI memory recall in those with PTSD+DS may be indicative of these memories being less verbally articulated and contextualized and more reliant on sensory-motor fragments.

Greater activation of the right pHipp in those with PTSD+DS might also reflect the engagement of a pHipp-parietal circuit that is postulated to be involved in perspective switching (Byrne et al., 2007). Consistent with this hypothesis, those with PTSD tend to recall trauma memories from a third-person or an observer's perspective (Berntsen et al., 2003) and exhibit elevated levels of state dissociation when recalling both positive and trauma memories from this perspective, as opposed to a first-person or a field perspective (Cooper et al., 2002). In healthy populations, those with higher dissociative symptoms, such as numbness and detachment, are also more inclined to retrieve memories from an observer’s perspective and switch between first- and third-person perspectives in future thinking tasks (Kinley et al., 2021; Sutin & Robins, 2010; Williams & Moulds, 2007). Interestingly, a study reported that the left pHipp was not recruited during the recall of memories encoded amidst an illusory out-of-body experience (Bergouignan et al., 2014). It is plausible,

therefore, that the diminished left pHipp activity and the increased right pHipp activity in PTSD+DS during trauma memory recall may be attributable, at least in part, to the recollection of those memories from an observer's perspective. Additionally, it is plausible that a substantial proportion of those with PTSD+DS were experiencing dissociative states, including out-of-body experiences, during the encoding of their trauma memory. Consequently, this may predispose them to recall such memories from an observer's perspective (Bergouignan et al., 2022). The propensity for those with PTSD, particularly the dissociative subtype, to recall intense negative memories from an observer's perspective may stem from the absence of contextualized detailed information, including spatial details, necessary for "anchoring" their location and constructing the memory from a field perspective (Rubin et al., 2008). Furthermore, the act of recalling highly emotional memories from an observer's perspective has been viewed as a way to reduce the emotional intensity of those memories during retrieval (Berntsen & Rubin, 2006; Küçüktaş & St Jacques, 2022), potentially serving as an unconscious strategy by those with PTSD+DS to keep a distance from strong emotions (Eich et al., 2012). However, this strategy may be counterproductive in PTSD+DS, as such a pattern of recall could arguably render the trauma memories less grounded and tangible, thereby hindering emotional processing and the attainment of "emotional closure" for the affected individual (McCarroll, 2017). Indeed, peritraumatic dissociation—dissociative symptoms occurring during or immediately following a traumatic event—has been identified as a significant predictor of subsequent PTSD development (Koopman et al., 1994; Shalev et al., 1996) and its symptomatology (Marmar et al., 1994; Tichenor et al., 1996). Recollection of trauma memories from an observer's perspective has also been associated with heightened PTSD symptom severity (Kenny et al., 2009), including increased avoidance behaviours (Kenny & Bryant, 2007).

The right aHipp exhibited increased activity during the recall of MI memories relative to neutral memories in PTSD+DS at a trend level. Conversely, the left aHipp showed virtually no differential activity between the two groups. Based on resting-state fMRI analyses, the aHipp was observed to acquire a more hub-like role in PTSD (Chaposhloo et al., 2023), which led us to expect greater overall anterior hippocampal activity in PTSD during the recall of trauma memories. A possible reason for this apparent discrepancy might lie in the proposed roles of the aHipp and pHipp in encoding and retrieving episodic memories, respectively (Deshpande et al., 2022; Fritch et al., 2020; Kim, 2015). Alternatively, it could also mean that the hub-like role of the aHipp in PTSD observed at rest simply does not necessarily translate into increased overall activation during trauma memory recall.

Hippocampal-cerebellar connectivity

In this study, we observed strikingly aberrant hippocampal-cerebellar connectivity in PTSD+DS. To put these findings into context, we first briefly review the functional anatomy of the cerebellum. Traditionally, the cerebellum has been associated with motor coordination, control, and automation (Shadmehr et al., 2010). However, more recent evidence reveals the cerebellum to be a highly heterogeneous structure which also plays a substantial role in cognitive and affective processing and social behaviour (Adamaszek et al., 2017; Schmahmann, 2000; Schutter & van Honk, 2009; Stoodley & Schmahmann, 2009; Van Overwalle et al., 2020). While the anterior part of the cerebellum (lobules I-V, also known as the “sensorimotor cerebellum”) is involved in sensorimotor coordination, the posterior cerebellum (lobules VI-IX, including Crus I & II, also known as the “cognitive cerebellum”) is implicated in various cognitive functions, including

episodic and working memory, language, theory of mind (TOM), affective processing, and executive functions (Addis et al., 2016; Van Overwalle et al., 2022).

During MI memory recall, we found increased connectivity between the left aHipp and the left posterior cerebellum (Crus I & II) in those with PTSD+DS compared to both PTSD alone and control groups. Notably, increased baseline activity in the cerebellum, including the Crus I, has been repeatedly observed in PTSD compared to controls (e.g., Bonne et al., 2003; Wang et al., 2016). This is particularly significant because Crus I has been suggested to retain part of the original fear memory after extinction (Batsikadze et al., 2022). Moreover, the connectivity between Crus I and the precuneus–a region critical for episodic retrieval–was reported to decrease following EMDR therapy in PTSD (Verger et al., 2020). In light of our previous identification of the left aHipp as the predominant locus of abnormal connectivity in PTSD during the resting state (Chaposhloo et al., 2023), the increased connectivity observed here between the Crus I and the left aHipp in PTSD+DS compared to PTSD alone and control subjects may explain the more severe symptoms experienced by those with this subtype of PTSD; moreover, one might expect that successful therapy might be accompanied by a reduction of the strength of this connection. Somewhat contrarily, we can also view this increased connectivity from an adaptive perspective. Specifically, Andrews et al. (2023) found a negative correlation between a measure of shame and the activity of the Crus II following the recall of MI memories in PTSD. Therefore, the increased connectivity of Crus II with the aHipp in PTSD+DS may reflect an adaptive process to mitigate intense negative emotions such as shame, guilt, or disgust. This speculation is compelling considering the significant role of the aHipp in processing a memory's emotional elements and the proposed posterior cerebellar role (including Crus I & II) in emotional regulation and cognitive control. The dissociative subtype of PTSD is characterized by altered states of consciousness and

emotional detachment. Therefore, the increased connectivity of the aHipp with Crus I & II in PTSD+DS during the recall of MI memories may indicate a heightened need for cognitive control and emotional regulation. This could also represent a unique neural adaptation or compensatory mechanism to maintain emotional detachment and alleviate the intense emotional distress associated with MI memories.

Furthermore, if we consider episodic memory as an inherently predictive process aimed primarily at guiding behaviour for future events rather than faithfully recalling the past–a widely held view among memory researchers (e.g., Gershman, 2017; Schacter et al., 2007; Vecchi & Gatti, 2020)–then one can interpret the increased connectivity between the hippocampus and the cerebellum within this framework. Specifically, the cerebellum is suggested to be involved in building internal models and comparing actual outcomes with anticipated ones, using the discrepancy to update these models, ultimately aiming for automation of various functions (Koziol et al., 2014; Popa & Ebner, 2019, 2022; Welniarz et al., 2021). The posterior cerebellum, in particular, has been implicated in the affective and social aspects of this predictive processing (Haihambo et al., 2023; Van Overwalle et al., 2022). This process is strongly associated with the theory of mind, where individuals infer the internal states and intents of others in order to predict their future actions. Those with PTSD are often "on edge," especially regarding others' intentions, which may be particularly relevant in moral injury. Speculatively, the increased connectivity between the aHipp and Crus I & II during MI memory recall in PTSD+DS may represent a passive and compensatory mechanism in order to update internal models within the cerebellum, thereby better preparing the individual for future similar events.

Increased connectivity between the left anterior cerebellum (lobules IV & V) and the left pHipp was also found during trauma recall in individuals with PTSD+DS compared to those with PTSD

alone and controls. The increased cerebellar connectivity with the pHipp suggests that memory recall instantiation within the pHipp might be influenced by the more coarse and raw representation originating from the anterior cerebellum. Notably, Rabellino et al. (2018) reported increased resting-state functional connectivity between the left lobules IV & V and the right hippocampus in PTSD compared to controls. Although we did not observe such a difference localized to the right hippocampal ROIs, we did find that recalling MI memories versus neutral memories was accompanied by increased functional connectivity between the left pHipp and lobules IV & V in the PTSD-only group. Overall, the increased hippocampal connectivity with the anterior/sensorimotor cerebellum could explain why MI memories have a strong sensorimotor component in PTSD which is further elevated in PTSD+DS. In addition, those with PTSD+DS, as compared to both PTSD and control groups, exhibited greater functional connectivity between the left a/pHipp and cerebellum III/IV/V and the cerebellar vermis III during neutral memory recall. The vermis is implicated in defensive behaviour and threat reactivity via the integration of interoceptive and external sensory information, which contributes to the perception-to-action transition (Terburg et al., 2024). This abnormal connectivity suggests that those with PTSD+DS may have impairment at the cerebellar-hippocampal level, even during the processing of neutral memories.

Cortico-hippocampal Connectivity

Pre/postcentral Gyri

During the recall of MI memories, the right pHipp showed decreased functional connectivity with primary somatosensory and motor regions (the left pre/postcentral gyrus) in PTSD+DS compared to controls. Moreover, within the PTSD+DS group, the connectivity between the right pHipp and

pre/postcentral gyrus was positively correlated with the reliving subscale of RSDI scores during MI memory recall. The postcentral gyrus is the location of the primary somatosensory cortex and contains several somatotopic maps of the body in space, while the precentral gyrus is the location of the primary motor cortex and contains a corresponding body map. We also previously found decreased resting-state functional connectivity between the right pHipp and the left postcentral gyrus in PTSD (Chaposhloo et al., 2023). Collectively, these findings may explain why the recall of MI memories in PTSD+DS may differentially involve sensorimotor processes, which could map onto the clinical symptoms of reliving the past in or by the body (Kearney et al., 2023). Interestingly, these impairments might not be restricted to MI memories, as the left pHipp also showed decreased functional connectivity with the right pre/postcentral gyrus during the recall of neutral memories in PTSD compared to controls.

Fusiform Gyrus

The fusiform gyrus is a region essential for visual monitoring and recognition of shapes, particularly faces (K. S. Weiner & Zilles, 2016), as well as being implicated in monitoring the environment for safety (Porges, 2011). Here, we observed increased connectivity between the fusiform gyrus and both the aHipp and pHipp in PTSD+DS compared to both PTSD alone and controls, as well as in PTSD compared to controls, during the recall of MI memories. Our interpretation of the increased hippocampal-fusiform connectivity in PTSD and its dissociative subtype is two-fold; it may indicate heightened safety and threat monitoring and hypervigilance in PTSD and PTSD+DS, and it could also reflect the intense recall of morally distressing memories, particularly in relation to faces. Further research is required to investigate whether these alterations are specific to MI-related PTSD.

Middle Temporal Gyrus

Amongst its many functions, the MTG is involved in the audio-visual perception of emotions (Pourtois et al., 2005) and the recognition of basic facial expressions (Kitada et al., 2013). We found that during the recall of MI memories, the left aHipp exhibited increased connectivity with the left posterior middle temporal gyrus (pMTG) in PTSD+DS compared to PTSD alone. This increased connectivity might explain the enhanced recall of faces and their associated emotional expressions within the MI event. Additionally, the MTG is known to exhibit volume reduction in PTSD (Kühn & Gallinat, 2013), and the extent of this reduction correlates with re-experiencing symptoms (Kroes et al., 2011). Moreover, the MTG is implicated in AM retrieval (Holland et al., 2011) as well as language and semantic processing (Davey et al., 2016; Dronkers et al., 2004; Hoffman et al., 2012). Interestingly, in an associative learning task involving pairs of neutral words, right MTG activity was increased in the PTSD group during encoding and positively correlated with CAPS scores, whereas left pMTG activity was reduced during encoding and bilateral MTG activity was reduced during retrieval (Geuze et al., 2008). Given that PTSD+DS is characterized by emotional detachment as a coping mechanism to deal with the overwhelming stress of trauma, the increased aHipp-MTG functional connectivity may reflect an effort by the impaired MTG to connect with the aHipp and integrate emotional elements of the memory with semantic processing of the memory words, creating a more coherent narrative that can be integrated into one's life story and current sense of self and reality.

Inferior Temporal Gyrus

During the recall of MI memories, individuals with PTSD+DS showed increased connectivity between the inferior temporal gyrus (ITG) and left aHipp and right pHipp compared to controls.

The ITG is often viewed as a major part of the ventral visual stream and is implicated in the processing and perception of complex visual stimuli such as faces (Conway, 2018), including facial emotional expressions (Hadj-Bouziane et al., 2008). Thus, the increased connectivity between these areas could explain the heightened sensory load during the recall of MI memories in PTSD+DS, leading to an experience of intense emotions and vivid imagery concerning scenes and the emotions of faces associated with the MI event.

Parahippocampal areas

We observed increased functional connectivity between the left aHipp and the anterior part of the left parahippocampal gyrus in PTSD+DS compared to controls during the recall of MI memories. The parahippocampal gyrus, which surrounds the hippocampus, is crucial for memory encoding and retrieval of episodic memories (Hayes et al., 2007; Ranganath et al., 2004). In PTSD, the left parahippocampal gyrus has shown increased reactivity to masked traumatic stimuli (Sakamoto et al., 2005). Moreover, increased activation of the left hippocampus and parahippocampal gyrus has been detected during the encoding and recognition of negative emotional words in complex PTSD (Thomaes et al., 2009). Thus, this increased connectivity might explain the reason that trauma-related memories are more easily activated in PTSD+DS. Furthermore, the anterior parahippocampal gyrus corresponds to the perirhinal cortex, an area recognized for its role in visual perception (Devlin & Price, 2007), with its major input being from the ventral visual stream (Martin & Barense, 2023). The perirhinal cortex and the aHipp are also responsible for coding object identity and item-item (or object-object) associations, as opposed to the pHipp and the posterior part of the parahippocampal gyrus, also known as the parahippocampal cortex, which are involved in retrieving item-context associations (Sheldon & Levine, 2015). The fact that we observed increased connectivity between the aHipp and the area corresponding to the perirhinal

cortex, rather than the posterior parahippocampal gyrus, may indicate a lack of appropriate visually-aided context attribution in MI memories in PTSD+DS.

Midcingulate/Anterior Cingulate/Paracingulate areas

The dACC and MCC are important structures for autonomic control (which includes context-driven modulation of bodily arousal states), emotional awareness, and emotion regulation (Critchley et al., 2003; Devinsky et al., 1995; McRae et al., 2008; R. Smith et al., 2019). We observed decreased functional connectivity between the right aHipp and the left paracingulate gyrus, as well as an area at the border between the dorsal anterior cingulate cortex (dACC) and the midcingulate cortex (MCC), in PTSD compared to controls during the recall of MI memories. The dACC and paracingulate gyrus have shown hypoactivation in PTSD both in resting-state and various emotional tasks (Amad et al., 2019; Etkin & Wager, 2007). Moreover, in a fear-potentiated startle paradigm, dACC volume was inversely correlated with SCR response magnitude in PTSD (Young et al., 2018). Additionally, the MCC is important for integrating negatively valenced and motor signals (Pereira et al., 2010). Thus, we speculate that the reduced connectivity between the aHipp and dACC/MCC may reflect less integration of emotional salience into aHipp-driven processing of emotional elements.

Visual areas

We observed increased bilateral pHipp functional connectivity with several areas in the left occipital cortex during the recall of MI memories in PTSD+DS compared to both PTSD alone and controls. Those areas include the lingual gyrus, the lateral occipital cortex, intracalcarine and supracalcarine cortices, cuneal cortex and occipital pole. The pHipp is preferentially connected to these visual areas (Dalton et al., 2022). Moreover, vivid recollection of episodic memories may

depend on concurrent reactivation of low-level visual features in both the early visual cortex and the pHipp (Bone & Buchsbaum, 2021). Therefore, increased connectivity between the pHipp and visual areas in PTSD+DS may be indicative of an over-representation of raw, decontextualized, and low-level visual images during the recall of MI memories in PTSD+DS, representing the memories that are relived instead of remembered.

Limitations, Future Directions, and Conclusion

Despite these novel findings, several limitations must be addressed. Firstly, the present paradigm did not allow us to differentiate between different phases of episodic recall, namely, the elaboration and construction phases. Although these phases share some neural circuitry, they subserve different phenomenological aspects of episodic memory recall and exhibit distinct neural responses in various brain regions (Daviddi et al., 2023). Consequently, there may be unique abnormalities in brain responses during these phases that went undetected. Further, future research should investigate the directed or effective connectivity between the brain areas implicated in the neurocircuitry of traumatic memory retrieval PTSD and PTSD+DS to enable causal inferences about how abnormal activity in one brain region may affect the functions of other brain regions.

In conclusion, we detected altered activity and whole-brain functional connectivity of hippocampal subregions in PTSD, especially in its dissociative subtype. Specifically, we found abnormal pHipp activity in PTSD+DS during the recall of MI memories, which may reflect the decontextualized nature of those memories and the tendency of those with PTSD+DS to recall them from a third-person perspective. We also observed abnormal functional connectivity of hippocampal subregions with a diverse set of brain areas, including the cerebellum, parahippocampal and fusiform areas, anterior/midcingulate gyrus, lateral temporal areas, pre/postcentral gyrus, and early

visual areas. These abnormalities reflect different aspects of emotional memory recall in PTSD and PTSD+DS, suggesting an altered, maladaptive, and potentially compensatory process. In summary, these results point to the fragmented nature of emotional memory recall in PTSD, especially in its dissociative subtype, and support the notion that these memories contain raw, decontextualized sensorimotor representations that lack proper integration into one's broader sense of self and reality.

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Chapter 4

Grounding the Anterior and Posterior Hippocampus in the Brainstem: An Effective Connectivity Analysis During Trauma Memory Recall in Post-Traumatic Stress Disorder and Its Dissociative Subtype

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Introductory note: The work presented in the following chapter is currently in preparation, to be submitted pending final revisions from co-authors. Data for this Chapters was

previously collected as part of a collaboration between Dr. Ruth Lanius and Dr. Margaret McKinnon, and were accessed for the present purposes under a data sharing agreement between Dr. Becker and and Dr. Lanius. M. Chaposhloo was responsible for generating the research questions, performing the analyses, and drafting the original manuscripts under the supervision of Dr. Becker and the co-supervision of Dr. Shaw. M. Chaposhloo, Dr. Becker, Dr. Lanius, and Dr. Shaw were jointly involved in the conceptualization of the studies. Dr. Becker, Dr. Lanius, Dr. Shaw, Dr. Breanne E. Kearney and Dr. M. McKinnon contributed to the data interpretation and revision of the manuscripts.

This chapter builds upon the findings of the previous two chapters in two significant ways. First, it enables us to ask specific questions regarding the connectivity of the hippocampus with structures in the brainstem and brain areas involved in perspective transformation, questions that are often overlooked in PTSD research. Second, it allows us to study the direction of the connectivity between hippocampal subregions and the aforementioned brain regions. Here, we utilized the same dataset as in the previous chapter but restricted our analyses to hippocampal ROIs and a select number of ROIs belonging to the brainstem and areas involved in perspective switching. Furthermore, we employed a technique called multivariate Granger causality (MVGC) to infer effective connectivity between these ROIs. This technique enables us to draw causal inferences regarding the connectivity between the hippocampus and the rest of the brain, determining whether different hippocampal subregions are the driving factor, being driven, or a combination of both during the recall of trauma memories in PTSD and PTSD+DS.

Abstract

Post-traumatic stress disorder (PTSD) and its dissociative subtype (PTSD+DS) are debilitating psychiatric conditions that can develop following exposure to a traumatic event(s). PTSD+DS is characterized by the additional symptoms of depersonalization and derealization which result in the recall of trauma memories from a disembodied, third-person perspective. Here, we investigated the distinct neurocircuitry of the hippocampus, a key structure in memory and spatial processing, in PTSD and PTSD+DS during trauma memory recall. Specifically, we aimed to put the hippocampus in the context of its broader neural circuitry by employing ROI-to-ROI functional and effective connectivity between hippocampal and subcortical ROIs as well as ROIs within brain regions involved in perspective transformation. We analyzed fMRI data acquired during the recall of moral injury-related traumatic and neutral memories in participants with PTSD (n=49), participants with PTSD+DS (n=19), and neurotypical controls (n=36). Our results revealed distinct network architecture in PTSD and PTSD+DS during trauma memory recall, with the anterior hippocampus (aHipp) emerging as a prominent hub in the PTSD group. Alternatively, those with PTSD+DS exhibited a highly inefficient network that was more reliant on the posterior hippocampus (pHipp). Group differences also emerged in hippocampal functional and effective connectivity with key hubs of the innate alarm system, the vestibular system, and the perspective transformation circuitry. Collectively, our findings highlight the distinct hippocampal neurocircuitry underpinning trauma memory recall in PTSD and PTSD+DS and shed light upon the unique dissociative phenomenology of trauma memory recall in PTSD+DS.

Introduction

Post-traumatic stress disorder (PTSD) is a psychiatric condition that can develop following exposure to a traumatic event, or an event involving real or perceived threat to one's life or integrity. Its symptoms include involuntary re-experiencing of the event in the form of intrusions and/or "flashbacks", avoidance of trauma-related cues, negative alterations in cognition and mood, and hyperarousal (American Psychiatric Association, 2013; van der Kolk, 2015; Yehuda et al.,

2015). A more severe type of PTSD, the dissociative subtype (PTSD+DS), is characterized by symptoms of depersonalization (feeling detached from one's body) and derealization (perceiving surroundings as "dream-like" or surreal) in response to trauma-related stimuli (Lanius et al., 2012). Consequently, those with PTSD+DS often recall traumatic memories from a third-person or observer perspective rather than a first-person or field perspective (Frewen & Lanius, 2015), possibly to distance themselves from the intense negative emotions associated with the memory.

Importantly, many researchers consider PTSD a disorder of memory (van Marle, 2015). The recall of traumatic, emotionally negative, and even everyday memories is often impaired in those with PTSD. These impairments include over-general, less specific, and less fine-grained memory retrieval (Nixon et al., 2013; Piltan et al., 2021; Pitts et al., 2022; Schönfeld & Ehlers, 2017), which correlates with symptom severity (Schönfeld et al., 2007), predicts subsequent PTSD (Kleim & Ehlers, 2008), and is a risk factor for PTSD (Bryant et al., 2007). Additionally, individuals with PTSD often experience disorganized memories (Jelinek et al., 2009) and impairments in verbal memory (Scott et al., 2015). However, less is known about the underpinnings of the dissociative processes of depersonalization and derealization and the subsequent distortion to one's bodily and spatial awareness during traumatic re-experiencing.

The hippocampus is a core region in the episodic memory system (Burgess et al., 2002) and is thus often a primary focus in PTSD research (Rauch et al., 2006; Shin et al., 2006). Recently, the delineation between the anterior (aHipp) and posterior hippocampus (pHipp) has offered a more nuanced view of the hippocampal role in PTSD (Chaposhloo et al., 2023; Clancy et al., 2024). In healthy individuals, the aHipp is more involved in processing the emotional aspects of memories and is closely connected to regions involved in threat processing, such as the amygdala, and fear-regulation, such as the ventromedial cortex (vmPFC) (Catenoix et al., 2011; Kier et al., 2004;

Zeidman & Maguire, 2016). Conversely, the pHipp is implicated in spatiotemporal contextual processing and is preferentially connected to the posterior midline and visual areas (Dalton et al., 2022; Ezama et al., 2021; Kahn et al., 2008). Recent studies have revealed differential and task-dependent contributions of the aHipp and pHipp to the neurocircuitry of PTSD and its dissociative subtype. In PTSD, the aHipp has emerged as a hub-like area during the resting state (Chaposhloo et al., 2023). During traumatic versus neutral memory recall, those with PTSD+DS showed increased right pHipp activation compared to controls, while the left pHipp showed the opposite effect (Chaposhloo et al., in preparation). The pHipp also exhibited increased functional connectivity with visual areas in the occipital cortex in PTSD+DS compared to PTSD alone and controls, whereas the aHipp showed increased connectivity with the posterior cerebellum, an important region for cognitive and social-emotional functions. Further, decreased aHipp connectivity with the dorsal anterior/mid cingulate cortex, a region important for emotion regulation, was found in PTSD compared to controls (Chaposhloo et al., in preparation). Taken together, these findings suggest that the aHipp and related threat and fear processing areas acquire an exaggerated role in organizing memory retrieval in PTSD, whereas in PTSD+DS, the emotional areas take a back seat to the pHipp and associated visuo-spatial regions in organizing memory retrieval.

The hippocampus has also been implicated as a key node in the default mode network (DMN), an intrinsic functional connectivity network active during states of rest and self-referential memory recall (Blessing et al., 2016; Ezama et al., 2021; Huijbers et al., 2011; Norman et al., 2021); this is intriguing in the context of widespread disruptions to the DMN at rest in PTSD and PTSD+DS (Akiki et al., 2017; Bao et al., 2021; Barredo et al., 2018; Bluhm et al., 2009; Miller et al., 2017). Indeed, both the hippocampus and the posterior cingulate cortex (PCC), a key posterior node of

the DMN, show unique neurobiological activity patterns during traumatic memory retrieval which has been shown to be dissociable from negatively valenced autobiographical memories (Perl et al., 2023). At rest, the hippocampus exhibits reduced connectivity with the posterior DMN (Miller et al., 2017), and the aHipp exhibits less frequent and stable co-activation patterns with the DMN (Clancy et al., 2024) suggesting differential hippocampal involvement in broader DMN dynamics in PTSD. Subcortical regions beyond the hippocampus have also demonstrated altered functional connectivity with key nodes of the DMN in PTSD, such as the PAG (with medial prefrontal cortex, angular gyrus and precuneus) during trauma memory recall and subliminal trauma-related stimuli exposure (Terpou, Densmore, Théberge, et al., 2019; Terpou et al., 2020, 2022), and the pulvinar thalamic nuclei (with precuneus), which facilitate cortical communications by modulating alpha synchrony, at rest (Saalmann et al., 2012). These findings point to subcortico-cortical interactions that may influence hippocampal activity in the context of its role in self-referential processing subserved by the DMN (Logothetis et al., 2012; Skelin et al., 2019; Todorova & Zugaro, 2020).

The "innate alarm system" (IAS), or the neural circuitry underlying the ultra-rapid detection of subliminal threats and coordinating defensive responses (Lanius et al., 2017), is one such subcortical influence that has also previously shown alterations in PTSD. Key IAS midbrain structures, the PAG and the superior colliculus (SC), exhibited higher activation in response to subliminal trauma-related stimuli versus masked neutral stimuli in PTSD compared to controls (Terpou, Densmore, Thome, et al., 2019). This aberrant activation is not limited to subliminal threats, as the PAG and SC's activity was positively correlated with hyperarousal symptoms during the conscious processing of fearful faces in PTSD (Rabellino et al., 2016). The SC also showed increased resting-state connectivity with the temporoparietal junction (TPJ), a key region for bodily self-consciousness, in PTSD relative to PTSD+DS; conversely, in PTSD+DS, the SC

showed increased resting-state connectivity with the dorsolateral prefrontal cortex (dlPFC), a region within the central executive network (CEN) involved in executive control (Olivé et al., 2018). Thus, in PTSD there is greater involvement of regions involved in threat processing and bodily self-consciousness, whereas in those with the dissociative sub-type, executive function areas may be exerting feedback inhibitory control over these same regions.

Although much of the research surrounding hippocampal involvement in PTSD symptomatology has been in the context of memory processes, there is also rather extensive literature supporting the importance of vestibular-hippocampal interactions in spatial information processing and spatial memory (Hitier et al., 2014; Smith, 1997, 2022). The vestibular system is essential for monitoring bodily orientation in space and provides important contributions to the spatially-tuned cells of the hippocampus, such as place cells and head-direction cells (O'Mara & Aggleton, 2019). Indeed, vestibular stimulation induces strong hippocampal activity (O'Mara et al., 1994; Suzuki et al., 2001; Vitte et al., 1996), while vestibular deafferentation, particularly the right VN, results in hippocampal atrophy and impaired spatial memory (Brandt et al., 2005; Hüfner et al., 2007; Stackman et al., 2002). Of relevance, the vestibular nuclei have shown abnormal connectivity in PTSD and PTSD+DS in that those with PTSD+DS showed reduced VN connectivity with the dlPFC and parietal areas, such as the supramarginal gyrus (Harricharan et al., 2017). The vestibulocerebellum (cerebellum lobule X), another key region of the vestibular system that is intricately connected to the VN, SC, and hippocampus (Watson et al., 2019), has also shown increased connectivity with the right aHipp in PTSD+DS compared to PTSD, increased connectivity with DMN regions (mPFC, precuneus, mid/posterior cingulate) in PTSD+DS compared to controls, and decreased connectivity with the TPJ in both PTSD and PTSD+DS relative to controls at rest (Rabellino et al., 2023).

In this paper, we aimed to investigate anterior and posterior hippocampal subregions in the context of their subcortical and cortical influences in trauma memory recall. Importantly, we sought to *"ground"* the hippocampal subregions by exploring their connectivity with brainstem regions, such as the vestibular nuclei (VN), PAG, and SC, which are implicated in both spatial processing and the innate alarm system. This grounding highlights the novel focus of linking hippocampal activity with these brainstem areas, connections not previously studied in trauma memory and PTSD research. Additionally, we included the vestibulocerebellum (lobule X and fastigial nucleus) for its role spatial processing, as well as the thalamic pulvinar nuclei for being a part of the innate alarm system. We employed a region-of-interest (ROI) to ROI functional connectivity analysis between these ROIs during the recall of morally injurious (MI) trauma memories in PTSD and its dissociative subtype. We also investigated the effective connectivity between ROIs that showed significant group differences in their functional connectivity to explore causal influences within this circuitry. To our knowledge, no other study to date has examined hippocampal ROI-to-ROI functional and effective connectivity during trauma memory recall in PTSD and PTSD+DS, nor has any study directly investigated the differential role of spatial processing influences via vestibular circuits on hippocampal function in PTSD+DS, which is characterized by dissociative symptoms that distort one's sense of body in space and time. Based on our previous findings, we anticipated the aHipp would assume a more hub-like role in PTSD alone, with a more bottom-up drive of the hippocampus by the IAS, particularly the PAG, whereas in PTSD+DS, we expected a more top-down drive of the IAS by the hippocampus and altered vestibular connectivity with the hippocampus. We also hypothesized that in PTSD+DS, the pHipp would show higher connectivity with areas implicated in perspective switching, i.e., the retrosplenial cortex (RSC) and the precuneus (Byrne et al., 2007), which were also included in the effective analysis.

Methods

Here, we briefly describe the methods employed in this paper, with further details provided in the Supplementary Material. We utilized a previously collected fMRI dataset acquired from individuals with PTSD (n = 49), PTSD+DS (n = 19), and healthy controls (n = 36) while they recalled traumatic and neutral memories. First, we examined group differences in ROI-to-ROI functional connectivity between the included ROIs (PAG, SC, pulvinar, cerebellum, RSC, precuneus, vmPFC; more details on the coordinates/atlas of these ROIs to be found in Supplementary Material) using the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). ROIs showing significant group differences were then subjected to effective (i.e., directed) connectivity analysis using the Multivariate Granger Causality (MVGC; Barnett & Seth, 2014). In a system composed of multiple time series, MVGC tests the hypothesis of whether the past values of a time series are useful in forecasting another while accounting for the effects of other variables in the system. To estimate effective connectivity within each group and condition, we input the MVGC toolbox (Barnett & Seth, 2014) with a matrix containing the BOLD time series for every participant and trial within a group (8 trials per participant) for every ROI. The output comprised a 13 by 13 matrix (reflecting the 13 ROIs) of Granger causality estimates for each ROI pair, alongside another 13 by 13 matrix of FDR-corrected p-values. Next, using these Granger causality estimates, we applied graph theoretical metrics to explore whether any hippocampal ROI gained a hub-like role in PTSD or PTSD+DS during trauma recall. Specifically, we calculated a hubness score (van den Heuvel et al., 2010) for each hippocampal ROI, which included four sub-scores:

high weighted degree, high betweenness centrality, low average path length, and low clustering coefficient.

Moreover, group differences in the Granger causality estimates were calculated using Bootstrapping. Specifically, we conducted 150 runs for each group and condition, estimating Granger causality each time as previously described. Critically, in each run, a random subset of participants for each group (63% to 71% of the population within each group) and condition was selected, generating a distribution for Granger causality estimates for each group, condition, and ROI pair. Group differences in effective connectivity between hippocampal and other ROIs were compared using t-tests. The resulting p-values were corrected for a false discovery rate (FDR) of 0.05 (Benjamini & Hochberg, 1995).

Results

ROI-to-ROI functional connectivity (undirected)

Figure 1 and Table 1 present the results of the ROI-to-ROI functional connectivity analysis. In PTSD+DS compared to controls, the aHipp exhibited increased connectivity with the VN and the right SC, and decreased connectivity with the right pulvinar during the recall of MI trauma memories. The decreased aHipp-pulvinar connectivity suggests an impaired connection between the aHipp and the cortex via the pulvinar. In the same contrast, in the PTSD+DS group, the pHipp showed increased connectivity with the right SC, PAG, and the right FN. The increased pHipp-PAG connectivity in PTSD+DS is noteworthy, although it does not provide information about the directionality of this pathway, a question to be explored in the next section. Overall, the PTSD+DS group was characterized by increased brainstem/midbrain-hippocampal connectivity and

decreased connectivity of the pulvinar with the hippocampus. In PTSD alone compared to controls during the recall of MI memories, significant group differences were observed only between vestibular processing hubs (L and R VN, fatigial nucleus) and the aHipp.

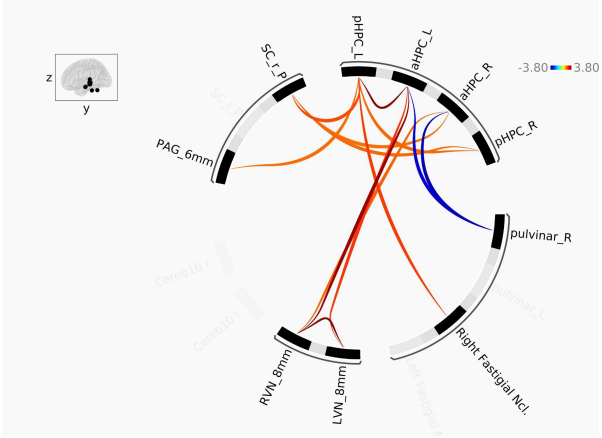

Figure 1: ROI-to-ROI analysis during recall of MI memories in PTSD+DS vs. controls (**left**) and PTSD alone vs. controls (**right**). Included ROIs are: vestibular nuclei (VN), fastigial nuclei, superior colliculus (SC), periaqueductal grey (PAG), pulvinar, cerebellum X, anterior and posterior hippocampus. Red and blue lines indicate increased and decreased connectivity, respectively.

Table 1: The ROI-to-ROI functional connectivity analysis results between the seed hippocampal ROIs and target ROIs. All prersented connections are those that are FDR-corrected at the cluster level. aHipp = anterior hippocampus; pHipp = posterior hippocampus; VN = vestibular nucleus; SC = superior colliculus; FN = fastigial nucleus; PAG = periaqueductal grey

Seed ROI	Target ROI	Contrast	F-statistics	p(FDR)
Left aHipp	Right pulvinar	PTSD+DS > Controls	F(2,52) = 5.62	0.0309
	Right VN		F(2,52) = 4.72	0.0391

	Left VN		F(2,52) = 4.72	0.0391
	Right VN	PTSD > Controls	F(3,81) = 4.98	0.0479
Right aHipp	Right pulvinar	PTSD+DS > Controls	F(2,52) = 5.62	0.0309
	Right SC		F(2,52) = 4.95	0.0391
	Right VN		F(2,52) = 4.72	0.0391
	Left VN	PTSD > Controls	F(3,81) = 4.98	0.0479
	Right FN		F(3,81) = 4.98	0.0479
Left pHipp	Right FN	PTSD+DS > Controls	F(2,52) = 5.62	0.0309
	Right SC		F(2,52) = 4.95	0.0391
	PAG		F(2,52) = 4.95	0.0391
Right pHipp	Right SC	PTSD+DS > Controls	F(2,52) = 4.95	0.0391

Multivariate Granger Causality Analysis between ROIs

The results of the MVGC analysis within each group and condition are presented in Figure 2. Notably, the left aHipp emerged as a hub during trauma memory recall in the PTSD alone group (as is clearly visible in Figure 2, top row middle panel), a pattern not observed in PTSD+DS. In fact, those with PTSD+DS exhibited a totally distinct architecture without any single apparent hub (see Figure 2, top row left panel). This suggests that trauma memory recall in PTSD alone has an increased reliance on the aHipp, highlighting a significant neurocircuitry difference between PTSD and PTSD+DS.

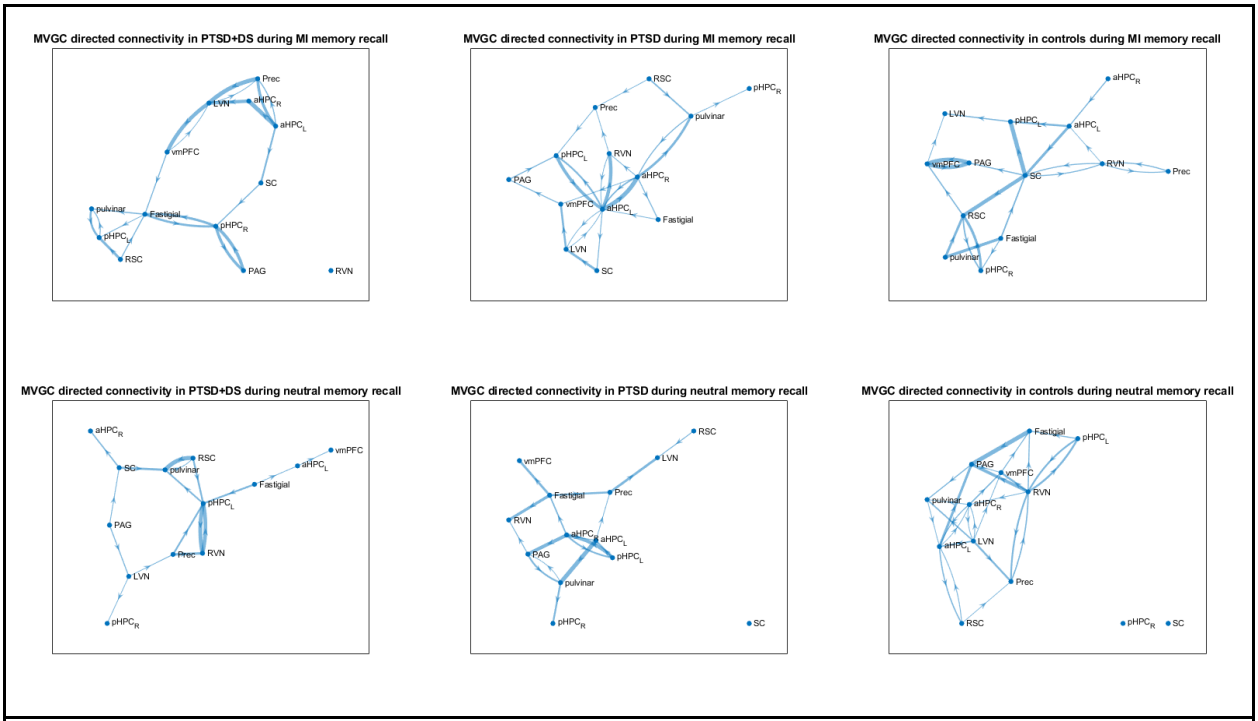

Figure 2: The results of the multivariate Granger Causality within each group and condition. The arrows represent the direction of connectivity, and line thickness indicates weights between nodes. Note that the line thickness can only be compared *within* each group and condition, not *between* groups and conditions. aHipp = anterior hippocampus; pHipp = posterior hippocampus; RVN = right vestibular nucleus; LVN = left vestibular nucleus; SC = superior colliculus; PAG = periaqueductal grey; vmPFC = ventromedial prefrontal cortex; Prec = precuneus

Group differences in MVGC connectivity between ROIs

Figure 3 presents the group differences in effective connectivity between ROIs. Critically, numerous differences were observed between groups during trauma memory recall, several of which were present but less pronounced or distinct during neutral memory recall. For instance, atypical directed connectivity between VN and hippocampal ROIs in PTSD+DS compared to PTSD alone and controls during MI memory recall potentially reflects the disembodiment experienced during trauma recall in PTSD+DS. Additionally, the directed connection from the PAG to the pHipp was decreased in PTSD+DS compared to PTSD alone during MI memory recall, whereas it was increased in PTSD alone versus controls. Interestingly, the reverse pathway from

the right pHipp to PAG showed decreased connectivity in PTSD alone compared to controls during MI memory recall. Together, the altered connectivity between the PAG and pHipp suggests a predominantly bottom-up drive by the PAG in PTSD alone, consistent with elevated threat and fear processing, which is less pronounced in PTSD+DS.

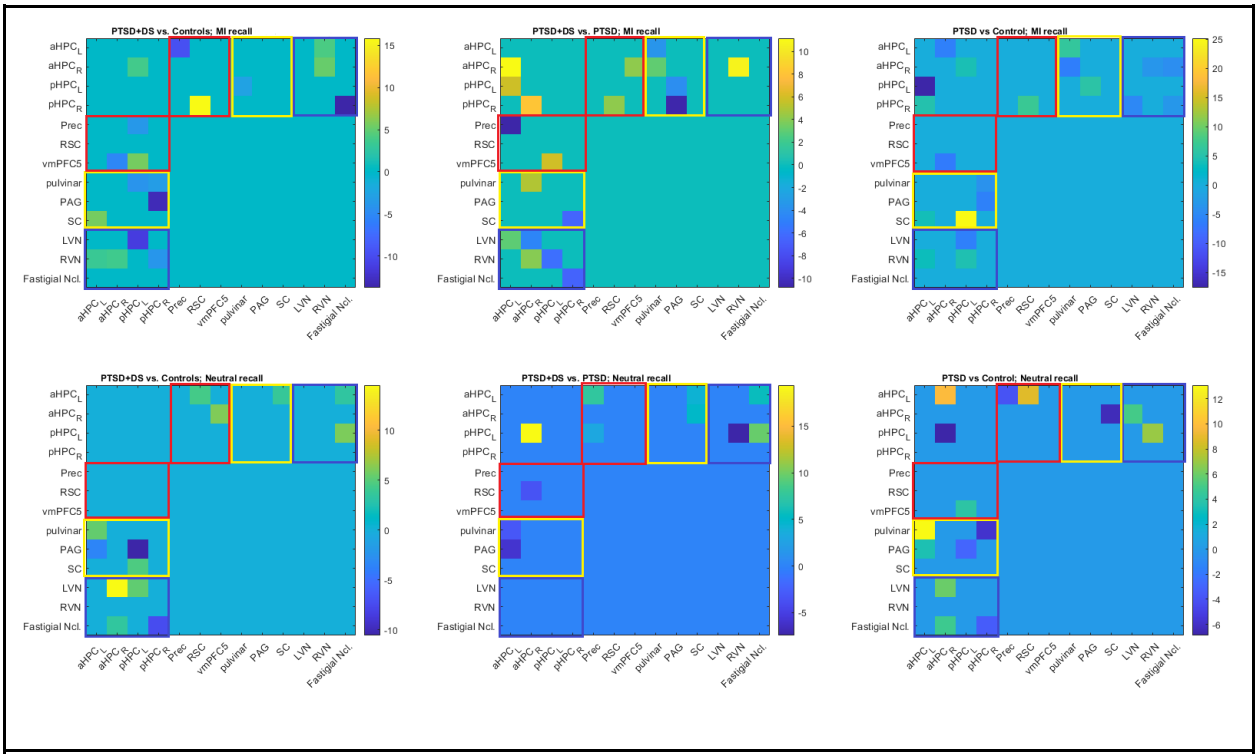

Figure 3: The results of group differences in directed connectivity between ROIs. The heatmaps illustrate the t-statistics representing the group differences in effective connectivity for each pair of ROIs during MI and neutral memory recall. All the connections shown here are significant after FDR correction (p-FDR < 0.05). Blue indicates lower connectivity, and yellow indicates higher connectivity. The columns represent the source of the connection, and the rows represent the targets. For better visibility, we grouped non-hippocampal ROIs based on their broader function using coloured outlines (red: cortical ROIs belonging to the DMN, yellow: innate alarm system, blue: vestibular ROIs). aHipp = anterior hippocampus; pHipp = posterior hippocampus; RVN = right vestibular nucleus; LVN = left vestibular nucleus; SC = superior colliculus; PAG = periaqueductal grey; vmPFC = ventromedial prefrontal cortex; Prec = precuneus.

The net causal flow of the hippocampal ROIs

We also calculated the causal net flow for each hippocampal ROI by subtracting the sum of incoming weights affecting a node from the sum of outgoing weights emanating from that node (Figure 4). During trauma memory recall, the pHipp showed a significant decrease in net causal flow in PTSD+DS compared to other groups and the aHipp. This shows that the pHipp is mainly driven by the rest of the ROIs during trauma memory recall in PTSD+DS.

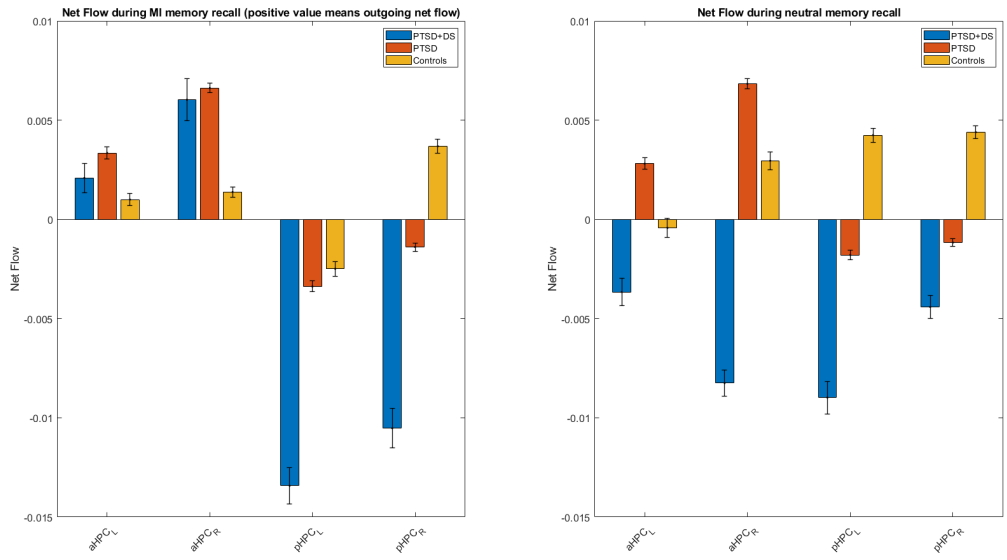

Figure 4: The causal net flow for each hippocampal ROI during the recall of MI (**left**) and neutral memories (**right**). Positive and negative values indicate a net outgoing and incoming flow, respectively.

The hubness scores for each hippocampal ROI

Figure 5 shows the composite hubness scores for each hippocampal ROI during the recall of MI memories. The aHipp exhibited significantly higher hubness scores in PTSD alone compared to

other groups and the pHipp, demonstrating that trauma memory recall in PTSD alone has an increased reliance on the aHipp. In PTSD+DS, however, the hubness scores were evenly distributed between the aHipp and pHipp, suggesting that the functional division between the aHipp and pHipp is less pronounced in PTSD+DS.

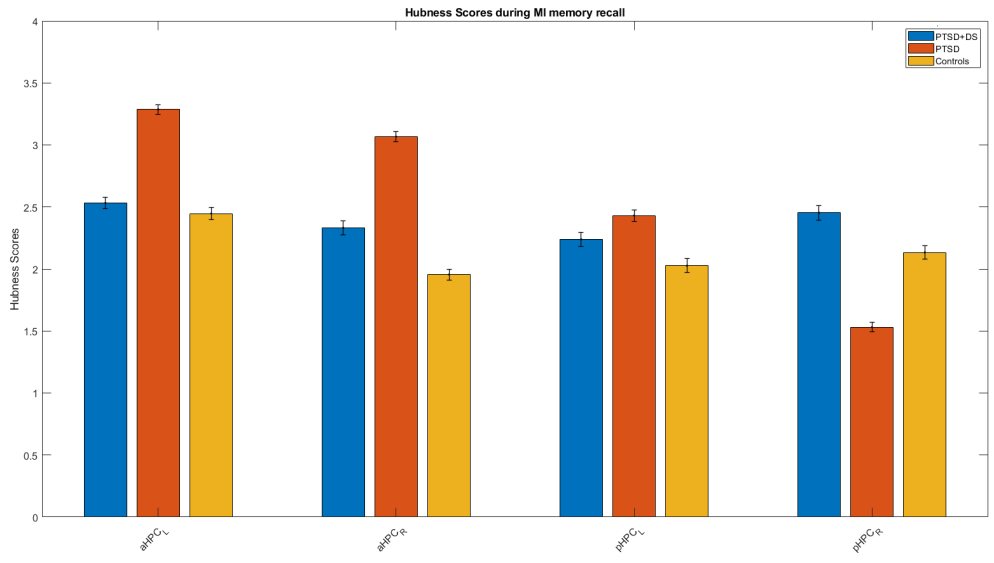

Figure 5: The hubness scores for each hippocampal ROI during the recall of MI memories. All the between group contrasts were significant after FDR correction (p-FDR < 0.05), except for PTSD+DS vs. Controls comparison in the left aHipp.

Discussion

This analysis of the hippocampus in the context of subcortical influences, the DMN, and cortical perspective transformation circuitry shed light on the unique hippocampal signatures of PTSD and its dissociative subtype relative to neurotypical controls during neutral and traumatic memory

recall. By *"grounding"* the analysis in the hippocampal connectivity with key brainstem structures, we revealed a novel aspect of hippocampal function that may underlie distinct PTSD subtypes. Employing ROI-to-ROI functional and effective connectivity, we uncovered a disparity between PTSD and its dissociative subtype, which is characterized by depersonalization and derealization symptomatology impacting one's spatial awareness and bodily orientation. During MI memory recall, the left aHipp emerged as a hub only in the PTSD alone group. Conversely, the PTSD+DS group displayed a profoundly different neural circuitry which relied more on the pHipp at the expense of the aHipp as a hub, dramatically increasing the average path length across the circuit (data shown in Supplementary Material), thereby exhibiting a profoundly more inefficient network in terms of information transfer. Significant differences were also observed between all groups (i.e., between classic PTSD and PTSD+DS, highlighting the unique neural abnormalities in PTSD+DS compared to classic PTSD, as well as between the two PTSD groups and the healthy control group) in the ROI-to-ROI effective connectivity during traumatic memory recall, which differed or was present to a lesser extent during neutral memory recall. Critically, these differences reflect the unique phenomenology of trauma recall in PTSD+DS relative to PTSD and neurotypical controls.

The hub-like role of the anterior hippocampus during the recall of trauma memories in PTSD

Our analysis of the effective connectivity using MVGC during trauma memory recall revealed that the left aHipp (and, to a lesser extent, the right aHipp) assumed a hub-like role in the PTSD alone group, in contrast to the PTSD+DS group where this was not observed. This was supported by significantly higher hubness scores of the aHipp in PTSD alone compared to other groups. These

findings corroborate our earlier findings of the aHipp's more hub-like role during the resting state in PTSD (Chaposhloo et al., 2023) in a completely different sample, but add nuance in that this role does not appear to be present in PTSD+DS. In contrast, those in the PTSD+DS group did not appear to engage the aHipp as a hub of information flow during trauma memory retrieval, appearing to leave the network in a less efficient state compared to PTSD alone. These findings support our previous hypothesis (Chaposhloo et al., 2023) about the central role of the aHipp in trauma memory recall in PTSD alone, which may relate to its unique involvement in altered emotional memory processing. Intriguingly, those with PTSD+DS displayed a completely distinct network pattern, possibly due to the unique manner in which they re-experience trauma memories. Finally, a recent study reported a psilocybin-driven reduction in functional connectivity between the aHipp and DMN (Siegel et al., 2024). It is plausible, therefore, that the aHipp losing its central role could contribute to the weakened sense of space, time, and self in PTSD+DS during trauma memory recall.

More PTSD+DS' reliance on the posterior hippocampus?

During MI memory recall, the aHipp did not serve as the dominant hub of the network in PTSD+DS. Instead, hubness scores were more evenly distributed across all four hippocampal ROIs. Relatedly, we observed increased intrahippocampal connectivity and increased weighted degree of hippocampal ROIs in PTSD+DS compared to PTSD alone (data available in supplementary material), as well as significantly more negative net causal flow of the pHipp in PTSD+DS both in comparison to PTSD alone and the aHipp, during MI memory recall. These findings suggest that traumatic memory retrieval exhibits a unique neurobiological signature in PTSD+DS at the level of the hippocampus in that the aHipp does not play a central role, while the

pHipp is uniquely more involved. Hypothetically, the lack of aHipp involvement in those with PTSD+DS may be due to the characteristic symptoms of emotional numbing and detachment. Conversely, given the pHipp's stronger involvement in spatial processing, we hypothesize its necessity for trauma memory recall in a third-person perspective in PTSD+DS. This hypothesis is further reinforced considering the right Hippocampus's known role in visuospatial memory over the left hippocampus (Burgess et al., 2002), alongside the higher hubness score of the right pHipp in PTSD+DS compared to PTSD alone in the present study. Overall, these adaptations are intriguing in the context of depersonalization and derealization symptoms and may relate to the recall of trauma memories from a third-person perspective.

A more detailed look at the group differences in effective connectivity between hippocampal ROIs and the rest of the brain

The Innate Alarm System

Here, we delve deeper into the group differences in hippocampal functional and effective connectivity during trauma memory recall, focusing primarily on the contrast between PTSD+DS and PTSD. Overall, there was an overall reduction in the connectivity from the IAS to the hippocampus in PTSD+DS compared to PTSD alone during MI memory recall. Below, we explore each IAS-related ROI separately.

The PAG

Effective connectivity from the PAG to the bilateral pHipp was reduced in PTSD+DS compared to PTSD alone; this pattern was not observed during neutral memory recall. These findings are of

interest in the context of those reported by Nicholson et al. (2017) and Terpou et al. (2020), which showed a bottom-up influence of the PAG on the amygdala and medial prefrontal cortex, the anterior hub of the DMN, in PTSD but an opposite pattern of top-down predominance in PTSD+DS. Thus, it appears that bottom-up PAG influence is reduced to the pHipp as well in PTSD+DS, which may hamper raw affective (emotional) and somatosensory information flow to this higher-order region; this may manifest as DMN-mediated memory alterations as well as sensory and affective anesthesia or numbing during traumatic memory retrieval.

The pulvinar

We also observed reduced functional connectivity between the pulvinar and the aHipp in PTSD+DS compared to controls during trauma memory recall. The pulvinar, a thalamic structure known for integrating sensory information, maintains extensive connections throughout the cortex (Froesel et al., 2021; Homman-Ludiye et al., 2020). The diminished aHipp-pulvinar connectivity in PTSD+DS suggests disruption in integrating sensory and emotional components of trauma memories, possibly reflecting reduced emotional impact during dissociative states. Moreover, the pulvinar regulates cortical communication through alpha synchrony (Saalmann et al., 2012). This may imply decreased hippocampal communication via the pulvinar with the rest of the DMN and the cortex at large, potentially cascading into impaired temporal and spatial binding of trauma memories.

Finally, the pulvinar has been implicated in fear saliency and threat anticipation (Hakamata et al., 2016; Koizumi et al., 2019) through a “low road” pathway from the SC to the amygdala via the pulvinar (Bertini et al., 2018; Kragel et al., 2021). Examining the effective connectivity graph during trauma memory recall in PTSD+DS (Figure 2, top left), we observe a clique comprising

the FN, RSC, left pHipp, and the pulvinar. Speculatively, the pulvinar may contribute to fear saliency within this clique, triggering the viewpoint transformation circuit and thereby facilitating dissociative recall of trauma memories from a third-person perspective.

The Retrosplenial Cortex

Moreover, compared to PTSD alone, those with PTSD+DS exhibited increased effective connectivity from the RSC to the right pHipp during MI memory recall. This altered connectivity was notably absent during neutral memory recall. The RSC is pivotal in transforming egocentric representations from the precuneus, a posterior hub of the DMN, to allocentric representations of the hippocampus and vice versa (Byrne et al., 2007). We therefore hypothesize that this increased connectivity is crucial for perspective switching at the level of the hippocampus in the broader context of the DMN during traumatic memory retrieval in PTSD+DS.

The Vestibular Nuclei

Compared to PTSD alone and controls, those with PTSD+DS exhibited increased effective connectivity from the VN to the aHipp, and decreased effective connectivity from the pHipp to the VN during traumatic memory recall. Given the role of the vestibular system in bodily orientation in space and maintaining an integrated sense of bodily self (Day & Fitzpatrick, 2005; Pfeiffer et al., 2014), these findings have implications for the hallmark symptoms of altered bodily self-awareness in PTSD+DS (i.e., depersonalization and derealization). Interestingly, the aHipp is proposed to preferentially process vestibular information while the pHipp preferentially processes visual cues (Hitier et al., 2014; Hüfner et al., 2011). Speculatively, the decreased connectivity from the pHipp to the VN may indicate a reduced ability of the pHipp to provide the VN with detailed,

spatially contextualized information. Overall, our findings point to a disembodiment and a compromised relation between one's self, environment, and physical orientation during trauma memory recall in PTSD+DS which may contribute to its characteristic symptoms of depersonalization and derealization.

Conclusion

In synthesis, these findings point to a unique hippocampal circuitry during traumatic memory recall in both PTSD and its dissociative subtype. While the aHipp plays a central role in trauma memory recall in PTSD alone, this pattern is not apparent in PTSD+DS, resulting in a much more inefficient mode of brain communication in PTSD+DS. In addition, those with PTSD+DS exhibit alterations in connectivity between the hippocampus and regions within the vestibular system, IAS, and perspective transformation circuitry compared to controls and PTSD alone. These functional neurobiological differences may reflect a key role of the anterior and posterior hippocampus in the unique phenomenology of traumatic memory retrieval in PTSD and PTSD+DS.

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Chapter 5

Conclusion

Conclusion

This thesis is dedicated to addressing the following question: what are the differential roles of the aHipp and pHipp during trauma memory recall in PTSD? The hippocampus is one of the core brain areas consistently implicated in the neurocircuitry of PTSD. However, there remains a lack of consensus regarding its abnormal functioning in PTSD, including during trauma memory recall. The anterior and posterior portions of the hippocampus exhibit distinct functional profiles, suggesting that inconsistencies in the field may stem from overlooking the functional division along the hippocampal long axis. Investigating these divisions separately within the context of PTSD may provide a more nuanced understanding of the hippocampus's role. Moreover, prominent theories of PTSD have neglected this functional difference along the hippocampus's long axis. They similarly remain silent regarding the dissociative subtype of PTSD, which shows unique phenomenology in trauma memory recall. This thesis addresses these gaps through three distinct methodologies, each detailed in the major chapters of the thesis.

Chapter Two (Chaposhloo et al., 2023) investigated the functional connectivity of the aHipp and pHipp during the resting state in elderly Vietnam War veterans diagnosed with PTSD. It has been established that the default-mode network, which is primarily active during rest, overlaps with many regions involved in episodic memory recall and, indeed, is active during such recall (Buckner et al., 2008). Thus, examination of the hippocampal role during the resting state was an appropriate initial step to explore functional differences between the aHipp and pHipp. Based on the aHipp's role in processing the emotional aspects of memories, we anticipated it would exhibit more pronounced functional abnormalities than the pHipp, particularly in its functional connectivity with affective brain areas. The data supported our prediction: the aHipp showed

abnormal functional connectivity, primarily increased functional connectivity, with numerous brain areas in PTSD, especially affective areas such as the insula, while the pHipp displayed far fewer abnormal connections. Furthermore, graph-theoretic analyses revealed the aHipp to take on a network hub in those with PTSD, reinforcing our prediction of its central role in the neural circuitry of PTSD compared to the pHipp. However, the study had a number of limitations. Firstly, the data set analyzed for this study came from the rather narrow population of male elderly war veterans. Secondly, while the resting state provided valuable insights into the neurocircuitry of PTSD, it cannot fully capture neural activity during the actual recall of trauma memories; thus, a paradigm involving active trauma memory recall was necessary. Thirdly, we were unable to distinguish between classic PTSD and PTSD+DS, missing the distinct neural circuitry of the dissociative subtype. Finally, resting-state functional connectivity analysis cannot indicate the directionality of connections, preventing us from answering questions such as whether the aHipp is predominantly a driving factor, is driven, or is a combination of both in PTSD.

Chapter Three addressed the first three limitations. We utilized a previously collected fMRI dataset of individuals with PTSD and PTSD+DS, both males and females of various ages, with a variety of trauma types (e.g. first responders, war veterans), as they recalled a moral injury-related trauma memory and a neutral memory. We again predicted that the aHipp would play a hub-like role during trauma memory recall in PTSD and show increased activity and functional connectivity with affective brain areas. Conversely, we expected the aHipp to be less active and less functionally connected to affective brain areas in PTSD+DS. Moreover, given the pHipp's role in spatial processing, and considering that individuals with PTSD+DS often recall trauma memories from a third-person perspective, we anticipated that the pHipp would exhibit increased activity and functional connectivity with areas involved in visuospatial processing, imagery, and

perspective switching (such as the retrosplenial cortex and the precuneus) in PTSD+DS. In contrast, we expected the pHipp to be underactive in classic PTSD. The results supported our predictions to a large degree. Although we did not observe significant differences in aHipp activity between groups or conditions, the left pHipp showed decreased activation during trauma memory versus neutral memory recall in PTSD+DS compared to controls. This finding is noteworthy because the left pHipp specifically is associated with context-dependent, verbal and narrative episodic memory, features lacking in PTSD+DS during trauma memory recall. In contrast, the right pHipp, being more involved in visuospatial memory and navigation, exhibited the opposite pattern: it was more active during trauma memory versus neutral memory recall in PTSD+DS compared to controls. This likely reflects the need for the right pHipp to perform the perspective switching that happens when individuals with PTSD+DS recall trauma memories from an observer perspective. Additionally, abnormalities in hippocampal functional connectivity were primarily observed in PTSD+DS compared to the PTSD-only group or controls. Most importantly, the pHipp displayed increased functional connectivity with visual areas in the occipital lobe, such as the lingual gyrus, lateral occipital cortex, occipital pole, intracalcarine, supracalcarine, and cuneal cortices, which is consistent with the raw, low-level, and decontextualized visual fragments characteristic of trauma memory recall in PTSD+DS.

Chapter Four addressed the remaining limitation by investigating the directionality of abnormal hippocampal functional connectivity in PTSD. We used the same dataset as in Chapter Three but restricted the analysis to a set of predefined ROIs—in contrast to the whole-brain approach we used in Chapter Three—including hippocampal, subcortical, and cortical areas known to be involved in perspective switching during visuospatial imagery. Notably, the investigation of hippocampal connections with brainstem areas is often overlooked in studies of episodic memory

and PTSD. Moreover, we utilized multi-variate granger causality (MVGC) analysis to infer the direction of altered functional connectivity between hippocampal ROIs and the other ROIs. The results revealed three main themes. First, the aHipp again emerged as the hub in the PTSD-only group during trauma memory recall. This major finding completely aligns with our previous results from Chapter Two (Chaposhloo et al., 2023), highlighting the aHipp's dominant role in classic PTSD, most likely due to its unique function in processing the emotional aspects of episodic memories. This consistency is remarkable given the aHipp's hub-like properties across two different datasets with age-diverse populations, one during resting state and the other during trauma memory recall, and in two distinct sets of ROIs, one predominantly cortical and the other subcortical. Second, individuals with PTSD+DS exhibited a completely different, rewired, and less efficient network architecture. The aHipp was no longer the obvious hub during trauma memory recall. Compared to the PTSD-only group, the network in the PTSD+DS group was less reliant on the aHipp and more on the pHipp, as evidenced by comparable hubness scores between these hippocampal subregions. We interpreted this as reflective of the unique phenomenology of trauma memory recall in PTSD+DS, which involves recalling memories from a third-person perspective, thus requiring greater pHipp involvement. Third, there were altered connections between the hippocampal ROIs and those belonging to the IAS, vestibular system, and perspective-switching circuitry. Specifically, the strength of connections from the PAG to the pHipp was diminished in the PTSD+DS group compared to the PTSD-only group. This finding aligns with previous research by Nicholson et al. (2017) and Terpou et al. (2020), which reported bottom-up driving of prefrontal areas by the PAG in the PTSD-only group but not in PTSD+DS. To our knowledge, this is the first investigation of effective connectivity between the IAS and the hippocampus during trauma memory recall in PTSD. Finally, the altered effective connectivity we

observed between the vestibular and hippocampal ROIs can be understood in terms of the altered sense of bodily awareness in individuals with PTSD+DS when recalling trauma memories.

Having discussed the main findings from all three studies included in this thesis, we now turn our attention to the dual representation theory of PTSD (Brewin et al., 2010) and how our findings would inform this prominent theory, calling for its refinement. The dual representation theory posits that "C-reps," containing the contextual component of memories and supported by the entire hippocampus (since the theory does not differentiate between the aHipp and pHipp), are weakened or "offline" in PTSD. Our findings, however, clearly indicate that the aHipp (and not the pHipp) functions as the hub in classic PTSD during trauma memory recall, driving and being driven by other cortical and subcortical areas and coordinating the information transfer between them. The aHipp is known for its crucial role in the emotional aspects of episodic memory processing, while the pHipp is more involved in detailed spatial and contextual processing. We therefore propose that it is more specifically the pHipp that supports C-reps and is offline in classic PTSD, whereas the aHipp, containing the emotional component of the traumatic event, takes on a more central role both during the resting state and in the active recall of trauma memories. In this refined framework, the situation becomes more nuanced in PTSD+DS. Due to the emotional numbing characteristic of trauma memory recall in those with PTSD+DS, we postulate that the aHipp becomes less engaged. Moreover, trauma memories in PTSD+DS are still devoid of contextual representations, perhaps even more so than in classic PTSD. These memories are often recalled from a third-person perspective as a part of the out-of-body experience characteristic of PTSD+DS. This is thought to be a means of achieving emotional distancing from the trauma event. Consistent with this, we found that the right pHipp, crucial for spatial processing, became more active, postulated to support

trauma memory recall from an observer's perspective. In contrast, the left pHipp, more involved in context-dependent, verbal and narrative episodic memory, was under-active.

Synthesizing our findings from all three studies, what are their main messages? First is the drastically different neurocircuitry between PTSD and PTSD+DS, which has been discovered previously on other brain regions (e.g., Nicholson et al., 2017) but is now examined through the lens of hippocampal function for the first time. The differences in hippocampal activity, functional and effective connectivity between classic PTSD and PTSD+DS reflect their profound behavioural variations. One of the dimensions of dissociation is out-of-body experience. Individuals with PTSD+DS likely experience this from the moment of trauma memory encoding, which helps them to distance themselves from the sheer amount of intense and negative emotions coming from the traumatic event. However, this comes at a cost, as out-of-body encoding of memories is inherently flawed (Bergouignan et al., 2014), leading to disembodiment and emotional detachment during subsequent memory recall. This places individuals with PTSD+DS at a disadvantage, reducing their chances of healing in therapeutic settings. Our data reflect these adverse effects. For instance, the functional connectivity of the left aHipp with the right angular gyrus (located in the temporoparietal junction) was negatively correlated with derealization scores in those with PTSD+DS. The temporoparietal junction is crucial for bodily self-awareness (Blanke et al., 2004). Therefore, it seems that the aHipp's ability to integrate emotional aspects of trauma memory into a coherent self-concept diminishes as dissociative symptoms intensify. In stark contrast, individuals with classic PTSD exhibit a dominance of the aHipp during rest and trauma memory recall. While this is less than ideal as trauma memories remain very much vivid and emotionally charged, at the very least, and perhaps thanks to the aHipp, those with classic PTSD are still able to keep those memories emotionally alive, resulting in less disembodiment. This could better

position them to later, in therapeutic settings, integrate those memories into a coherent sense of autobiographical self.

Several limitations of the current thesis and directions for future research should be acknowledged. First, the limitations of the functional and effective connectivity techniques used in this study must be addressed. Specifically, functional connectivity analysis only reveals correlations between signals from various brain regions, without distinguishing between direct (monosynaptic) and indirect (multisynaptic) anatomical connections, a limitation also relevant to measures of effective connectivity. Future work should integrate fMRI with methods capturing anatomical connectivity, such as diffusion MRI tractography, to potentially identify precise pathways involved in PTSD and target them for interventions.

Second, our studies did not assess the behavioral aspects of trauma memory retrieval, including memory specificity, fragmentation, field versus observer perspective, construction versus elaboration phase, and sensory and motor details. Future studies should measure these qualities during scanning, which could provide insights into the impact of abnormal neural activity on the qualities and phenomenology of trauma memory recall.

Third, fMRI is known for its low temporal resolution due to two main factors. First, the sluggish nature of the hemodynamic response peaks approximately 5-6 seconds after a neural stimulus (Glover, 2011). Second, the long repetition time (TR) in fMRI, which indicates the duration to capture one brain volume, typically ranges from 1 to 3 seconds. This limitation is significant compared to the millisecond dynamics of neural activity and is particularly challenging for tasks such as episodic memory recall, where each trial often lasts less than 30 seconds, allowing for only about 10 time points per trial. Moreover, the technique we used to infer effective connectivity,

MVGC, also has limitations. It can only detect excitatory connections and is unable to identify inhibitory connections. Additionally, it assumes that the temporal order of neural activity in different brain regions is preserved in the BOLD signal (Wen et al., 2013). These limitations could be addressed by simultaneous recording of fMRI with another imaging modality, such as EEG, which offers millisecond-level temporal resolution. This would allow for the alignment of neural events with cognitive processes in real-time, revealing the exact sequence of neural events during trauma memory recall. Additionally, methods like dynamic causal modeling (Friston et al., 2019), despite their own limitations, can infer inhibitory effective connections.

Fourth, the sample populations in the datasets used in this thesis may limit the generalizability of the findings to a broader population. For example, Chapter Two utilized a dataset from elderly male participants. This presents limitations from two perspectives: first, there are significant gender-related variations in fear discrimination (Krueger & Sangha, 2021), extinction recall (Shvil et al., 2014), and the neural circuitry of PTSD (Seligowski et al., 2020). Second, the functional connectivity profile of the anterior and posterior hippocampus in healthy populations appears to depend on age (Blum et al., 2014). Consequently, the results regarding gender and age may not be fully generalizable to the broader population.

Fifth, we did not explore differences in trauma exposure. Early childhood trauma may affect brain development differently than adult-onset trauma, potentially leading to distinct patterns of connectivity and symptomatology. Similarly, prolonged trauma exposure might result in more pervasive neural changes compared to brief incidents. Future studies should investigate these variations to inform targeted therapeutic strategies tailored to specific trauma profiles, thereby improving treatment efficacy.

Sixth, future research should focus on developing computational models and simulations of trauma recall in PTSD. Computational modeling offers several advantages: it can generate novel predictions that can be empirically tested, such as altering specific pathways in the simulation and observing behavioral changes, which can later be verified in clinical populations using techniques like TMS. Computational models also allow for the simulation of intervention effects, providing a virtual testing ground for new therapeutic approaches. Moreover, applying machine learning to hippocampal connectivity patterns can extract features for accurately classifying PTSD, PTSD+DS, and healthy controls. This method has been used for amygdala connectivity patterns (Nicholson et al., 2019), insula (Harricharan et al., 2020) and large-scale connectivity networks (Nicholson, Harricharan, et al., 2020). Utilizing hippocampal connectivity in machine learning models could enhance diagnostic accuracy. Additionally, machine learning algorithms could be employed to predict PTSD severity and symptoms (Park et al., 2023), enabling personalized interventions and predicting patient responses.

Seventh, our investigation of trauma memory recall in PTSD did not examine the temporal dynamics of neural activity during the recall process. Future research should address this, as it has been shown that initial memory retrieval phase is supported by the default-mode network, followed by a memory maintenance phase, supported by the central executive network (Shaw et al., 2021). It is plausible that hippocampal activity and connectivity are affected by these different phases of episodic memory recall, warranting further investigation.

Eighth, future research should explore hippocampal activity and connectivity throughout treatment to determine if therapy resolves any observed hippocampal abnormalities. This could enhance understanding of the hippocampus's role in recovery mechanisms and help predict treatment success, optimizing therapeutic strategies for better outcomes. Finally, future studies should

leverage results such as our findings to identify suitable targets for neurofeedback (e.g., Nicholson, Ros, et al., 2020).

In conclusion, the findings of this thesis elucidate the differential roles of the anterior and posterior hippocampus in the neurocircuitry of trauma memory recall in PTSD and PTSD+DS. The aHipp was more dominant in PTSD during trauma memory recall, while the pHipp was more involved in PTSD+DS. These findings refine prominent theories of PTSD and could pave the way for developing more accurate biomarkers and potentially more effective interventions.

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