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Neurobiology of Stress

Variations in response to trauma and hippocampal subfield changes

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A B S T R A C T

Models of posttraumatic stress disorder (PTSD) suggest that the hippocampus is key to the persistence of traumatic memory. Yet very little is known about the precise changes that take place in this structure, nor their relation with PTSD symptoms. Previous studies have mostly used magnetic resonance imaging (MRI) at low resolutions, making it impossible to identify sensitive anatomical landmarks, or compared groups often unequally matched in terms of traumatic exposure. The present cross-sectional study included 92 individuals who had all been exposed to the terrorist attacks in Paris on November 13, 2015 (53 of whom subsequently developed PTSD) and 56 individuals who had not been exposed. Hippocampal subfield volumes were estimated using cross-validated automatic segmentation of high-resolution MRI images. Results revealed changes in CA1 and CA2-3/dentate gyrus (DG) volumes in individuals with PTSD, but not in resilient (i.e., exposed but without PTSD) individuals, after controlling for potential nuisance variables such as previous traumatic exposure and substance abuse. In line with current models of hippocampal subfield functions, CA1 changes were linked to the uncontrollable re-experiencing of intrusive memories, while CA2-3/DG changes, potentially exacerbated by comorbid depression, fostered the overgeneralization of fear linked to avoidance and hypervigilance behaviors. Additional analyses revealed that CA1 integrity was linked to optimum functioning of the memory control network in resilient individuals. These findings shed new light on potential pathophysiological mechanisms in the hippocampus subtending the development of PTSD and the failure to recover from trauma.

1. Introduction

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), trauma is sudden or repeated exposure to actual or threatened death, serious injury or sexual violence (Pai et al., 2017). In some individuals, exposure to trauma causes overwhelming amounts of stress and fear that can lead to profound neurobiological and psychological damage. This further cascades into posttraumatic stress disorder (PTSD) (Yehuda and LeDoux, 2007). Reduction in the volume of the hippocampus, whether pre-existing or sequelae of the trauma, is thought to foster the development and maintenance of PTSD (Fenster et al., 2018; Gilbertson et al., 2002; Logue et al., 2018; O'Doherty et al., 2015; Szeszko et al., 2018; van Rooij et al., 2015). Some individuals, by contrast, show an ability to adapt successfully to trauma, but little is yet

known about the relationship between these variations in response to trauma and specific changes in the hippocampus.

One difficulty in characterizing these pathological and resilient outcomes in response to trauma relates to the broad spectrum of neurobiological, psychological and emotional damage associated with different types of trauma. Depending on the nature, chronicity or onset of traumatic exposure, there may be substantial variations in the prevalence of PTSD, its clinical manifestations, and the pattern of brain alterations (Liu et al., 2017; Meng et al., 2016; Yehuda et al., 2015). In practice, however, it is often challenging to compare groups of individuals with and without (i.e., resilient) PTSD that would be matched for nature, onset, and duration or chronicity of traumatic exposure. These variations may therefore limit the characterization of hippocampal alteration in PTSD, thereby blurring the boundary between the contributions of this specific psychiatric condition and the effects of the

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trauma itself.

The hippocampus is divided into three histological subfields, namely the dentate gyrus (DG), CA (1, 2 and 3), and subiculum (Duvernoy, 2005). However, to date, evidence regarding the relationship between changes in hippocampal subfields and adult PTSD remains quite scarce, and the investigation of this relationship is prone to methodological challenges. Studies using high-resolution magnetic resonance imaging (MRI) have reported mixed findings when combat veterans with PTSD are compared with combat-exposed veterans without PTSD. One study reported changes in CA3/DG (Wang et al., 2010), a result consistent with neurobiological models of PTSD suggesting that the dysfunction of this hippocampal subregion may exacerbate the overgeneralization of fear to nontraumatic reminders, a central feature of PTSD symptoms (Besnard and Sahay, 2016; Liberzon and Abelson, 2016). This deficit would be rooted in the disruption of hippocampal functions that normally support the ability to separate and restore memory traces (Carr et al., 2010). Another study, however, failed to find any significant atrophy in hippocampal subfields (Mueller et al., 2015). Although these two studies were conducted on high-resolution images (Mueller et al., 2015; Wang et al., 2010), the discrepancies in the results and the fact that they both restricted the segmentation process to the anterior part of the hippocampus prevent us from drawing any clear conclusions about hippocampal subfield alterations in PTSD.

Segmentation of hippocampal subfield volumes using lower resolution (1 mm³) MRI (Ahmed-Leitao et al., 2019; Chen et al., 2018; Hayes et al., 2017; Salminen et al., 2019), has also been performed to characterize hippocampal changes in individuals with PTSD. These studies have reported either reduced volume of the DG (Hayes et al., 2017), CA1 and CA3 (Chen et al., 2018), or no differences in subfield volumes in the PTSD population (Ahmed-Leitao et al., 2019). A recent report also suggested that changes in CA1 are rooted in the interaction between comorbid depression and PTSD (Salminen et al., 2019). However, given that the most important anatomical landmarks for subfield labeling (i.e., the thin band formed by the inner lamina of the CA and the outer lamina of the DG) are not visible at this lower resolution, the segmentation process is less reliable and consistent across individuals (de Flores et al., 2015; Iglesias et al., 2015; Wisse et al., 2014). Considering these methodological limitations, it remains unclear which hippocampal subfields are the most changed in adults with PTSD.

Hippocampal changes that predate the trauma may precipitate the development of PTSD (Gilbertson et al., 2002; Szeszko et al., 2018). By the same token, chronic stress following the trauma, owing to either prolonged activation of the hypothalamic-pituitary-adrenal axis and release of glucocorticoid stress hormones (Sapolsky, 1996; Steudte-Schmiedgen et al., 2016) or hypersensitivity of glucocorticoid receptors (Szeszko et al., 2018), may cause different types of damage in the hippocampus (McEwen et al., 2015). These stress-induced hippocampal changes are well described in animal models, and vary across subfields (Cohen et al., 2014; Gould, 2007; McEwen et al., 2016a; Sapolsky et al., 1990). In the CA, these changes range from dendritic retraction and spine loss to cell death (McEwen et al., 2016a; Schoenfeld et al., 2017; Sousa et al., 2000). In the DG, chronic stress can also prevent the production of new neurons (Heine et al., 2004; Schoenfeld et al., 2017). These changes constitute a potential mechanism for the hippocampal atrophy observed in patients with PTSD. However, given that the hippocampus is highly plastic, it may be possible to halt and even reverse some of these changes (Gould, 2007; Ortiz and Conrad, 2018; Sousa et al., 2000). Hence, identifying and treating certain symptoms may accelerate the restoration of normal hippocampal functioning or prevent further change. However, the relationship between specific hippocampal subfield alterations and PTSD symptoms has yet to be fully elucidated.

The expression of an excessively strong, persistent, and uncontrollable traumatic memory trace is an important pathogenic mechanism in the development of PTSD, and plays a central role in the neurobiological manifestation of stress (Levy and Tasker, 2012; Southwick, 1993). Current gold-standard treatments mainly focus on traumatic memory and are aimed at reducing its distressing and intrusive impact (Brewin, 2018; Foa et al., 2009; Yehuda et al., 2015). However, the potential connection between the presence of intrusive memories and hippocampal damage remains largely hypothetical to date. Hippocampal changes preceding the trauma may be a risk factor, exacerbating its impact on mental health and promoting the formation and re-experiencing of traumatic memory. From this perspective, PTSD can be seen as the result of an exaggerated pathological response that aggravates negative outcomes and risks (i.e., hippocampal changes). By contrast, protective factors or resilience mechanisms may either contribute to recovery from stress or promote resistance to stress in the first place, thereby reducing the impact of the risk factors and negative outcomes. These mechanisms may reflect pre-traumatic events or have been acquired in the face of adversity, and remain poorly understood and described (Kalisch et al., 2017). From this perspective, PTSD can also be characterized as an inability to rely on or develop mechanisms that counter risk and promote recovery from trauma. One of these key resilience mechanisms, which we recently observed in a sample of 175 participants who had or had not been exposed to the terrorist attacks in Paris on November 13, 2015, is the ability to engage frontally mediated inhibitory control processes to interrupt and suppress memory processing during the re-experiencing of intrusive memories (Mary et al., 2020). In this study, participants learned a series of neutral words paired with pictures of objects. Immediately after this learning phase, they were instructed to suppress the unwanted re-experiencing of intrusive memories that had been artificially created and involuntarily triggered by cue words. Functional and effective connectivity in the brain was measured during this suppression phase using functional magnetic resonance imaging (fMRI). Resilient individuals exhibited an increase in top-down inhibition-an effect orchestrated by the right middle frontal gyrus (MFG) that targeted the hippocampus. This controlled down-regulation of intrusive memories was considerably compromised in individuals who had developed PTSD, as there was no difference in brain dynamics between the intrusive and nonintrusive cue word conditions. Nevertheless, the efficacy of such top-down mechanisms, characterized by increased inhibitory coupling between the right MFG and hippocampus during the suppression of intrusive memories, varies drastically across healthy individuals, calling for greater scrutiny of the protective role of memory control in shielding against PTSD and potential damage to the hippocampus.

The first aim of the current study, conducted among the same participants matched on traumatic exposure than our previous study (Mary et al., 2020), was to measure the volumes of hippocampal subfields in resilient individuals and those who developed PTSD, compared with nonexposed individuals. The second aim of this study was to understand the link between individual variations in hippocampal subfield volumes and PTSD symptom clusters (i.e., intrusion, avoidance, negative impairment of cognition and mood, reactivity, and arousal), and to relate this link to neurobiological models of hippocampal subfield

functions. A third exploratory aim was to investigate the relationship between individual variations in hippocampal subfield volumes and the brain connectivity marker of memory suppression previously analyzed in the same sample (Mary et al., 2020). Participants were 92 individuals who had been exposed to the terrorist attacks in Paris on November 13, 2015 and 56 nonexposed healthy controls (see Table 1 for participants' characteristics). Exposed participants underwent the Structured Clinical Interview (SCID) for DSM-5 (American Psychiatric Association, 2013), which revealed that 53 of them had full or partial (Brancu et al., 2016) PTSD (PTSD+ subgroup), and 39 did not (PTSD- group). Data were acquired 7–18 months after the attacks (PTSD+: mean (SD) = 14.30 (3.28) months; PTSD-: mean (SD) = 13.48 (3.08) months; t(90) = 1.20, p = 0.22).

To determine the nature of changes in hippocampal subfields in PTSD, participants underwent a high-resolution MRI sequence centered on the hippocampus (resolution: 0.39 × 0.39 × 2 mm). The ASHS (Yushkevich et al., 2015) software package for automatic segmentation of hippocampal subfields was applied to delineate and compute the volume of the CA1, CA2-3/DG, subiculum, and tail subregions of the hippocampus (see Methods; Fig. 1). We used scores on the PTSD Check List for DSM-5 (PCL-5; Blevins et al., 2015) and Beck Depression Inventory (BDI; Beck and Beck, 1972) to investigate the relationship between volumetric differences and PTSD symptom clusters and comorbid depression. To assess the link between hippocampal subfield changes and memory suppression, we reutilized connectivity data yielded by our recent fMRI study based on the same brain imaging protocol and acquired in the same participants (Mary et al., 2020). For this particular study, we measured effective connectivity between the right MFG, the core hub of the inhibitory control system (Gagnepain et al., 2017), and the right hippocampus (see Fig. 5 in Mary et al., 2020), during participants' attempts to suppress neutral and inoffensive intrusive memories triggered by cue words in a think/no-think (TNT) task (Gagnepain et al., 2017).

2. Material and methods

2.1. Participants

A total of 120 individuals who had been exposed to the terrorist attacks in Paris on November 13, 2015 and 80 nonexposed individuals took part in a large biomedical project investigating the neurofunctional network responsible for memory control (Mary et al., 2020) and structural brain changes in PTSD. Exposed participants were recruited through the Programme 13-Novembre cross-disciplinary and longitudinal research initiative (http://www.memoire13novembre.fr/). The hippocampal volumetric analyses described in this study were conducted among 148 participants (see below for detailed description of inclusion and exclusion criteria). The final sample consisted of 92 participants who had been exposed to the terrorist attacks and 56 nonexposed healthy controls (see Table 1 for participants' characteristics). Exposed participants were diagnosed using the SCID (American Psychiatric Association, 2013) by a trained psychologist, supervised by a psychiatrist. All exposed participants met DSM-5 Criterion A indicating that they had experienced a traumatic event (see Table 1 for type of exposure). Trauma-exposed participants (see Table 1 for demographic and clinical characteristics) were divided into two subgroups: participants with full or partial PTSD symptoms (Brancu et al., 2016) according to DSM-5 criteria, and participants without PTSD. The study therefore included 53 trauma-exposed participants with PTSD (PTSD+ subgroup), 39 trauma-exposed participants without PTSD (PTSD- subgroup), and 56 nonexposed control participants (control group). It should be noted that the nonexposed participants were not present in Paris on November 13, 2015. The study was approved by the regional ethics committee (Comité de Protection des Personnes Nord-Ouest III, sponsor ID: C16-13, RCB ID: 2016-A00661-50, clinicaltrial.gov registration number: NCT02810197). All participants gave their written informed consent before taking part, in line with French ethical guidelines.

Table 1
Demographic and clinical characteristics of the nonexposed (Non-Exp.), trauma-exposed without PTSD (PTSD-) and trauma-exposed with PTSD (PTSD+) participants. PCL-5: Posttraumatic Stress Disorder Checklist for DSM-5. BDI: Beck Depression Inventory.

	Non-Exp. (n = 56)		PTSD- (n = 39)		PTSD+ (n = 53)		
	Mean	SD	Mean	SD	Mean	SD	Group differences*
Sex F/M	30/26		18/21		31/22		–
Age in years	32.30	11.51	36.15	7.06	36.94	8.46	1 < 3
Education level in years	6.96	1.65	7.56	1.89	7.28	1.70	–
AUDIT	4.04	2.6872	5.46	4.72	4.87	4.10	–
CAST	0.02	0.1336	0.36	1.39	0.42	1.42	–
Total intracranial volume (mm³)	1517.25	125.71	1574.12	120.21	1530.06	169.56	–
BDI (13 items)	2.16	2.76	3.92	4.12	8.75	5.25	1, 2 < 3
PCL-5 total	4.77	7.02	13.89	10.67	37.41	13.33	1 < 2 < 3
PCL-5 subscores							
Intrusion	0.79	1.65	2.36	2.16	9.19	4.25	1 < 2 < 3
Avoidance	0.50	1.29	2.00	2.15	3.98	2.58	1 < 2 < 3
Alteration of mood/cognition	2.19	3.33	4.23	4.08	12.02	5.64	1 < 2 < 3
Hypervigilance	1.29	2.38	5.31	4.42	12.23	4.26	1 < 2 < 3
Exposure type**							
A1			n = 19		n = 40		
A2			n = 7		n = 7		
A3			n = 1		n = 4		
A4			n = 12		n = 2		
Previous traumatic exposure score	6.71	7.03	12.72	9.05	11.32	9.31	1 < 2.3
Stressful childhood and adolescence event score	1.30	1.50	1.92	1.72	2.15	1.84	1 < 3

PCL-5 = Posttraumatic Stress Disorder Checklist for DSM-V; BDI = Beck Depression Inventory; AUDIT = Alcohol Use Disorders Test; CAST = Cannabis Abuse Screening Test.

* Significant differences (p < 0.05); Between-groups comparisons were assessed with a chi-square test for sex, and an analysis of variance followed by post hoc tests for the numerical variables.

** Type of exposure according to DSM-5. Criterion A1: individual directly targeted by the terrorist attacks; Criterion A2: witnessed the attacks; Criterion A3: close relative of a deceased victim of the attacks; Criterion A4: individual indirectly exposed to the attacks who assisted and rescued the victims and was exposed to aversive scenes (mainly first responders and police officers).
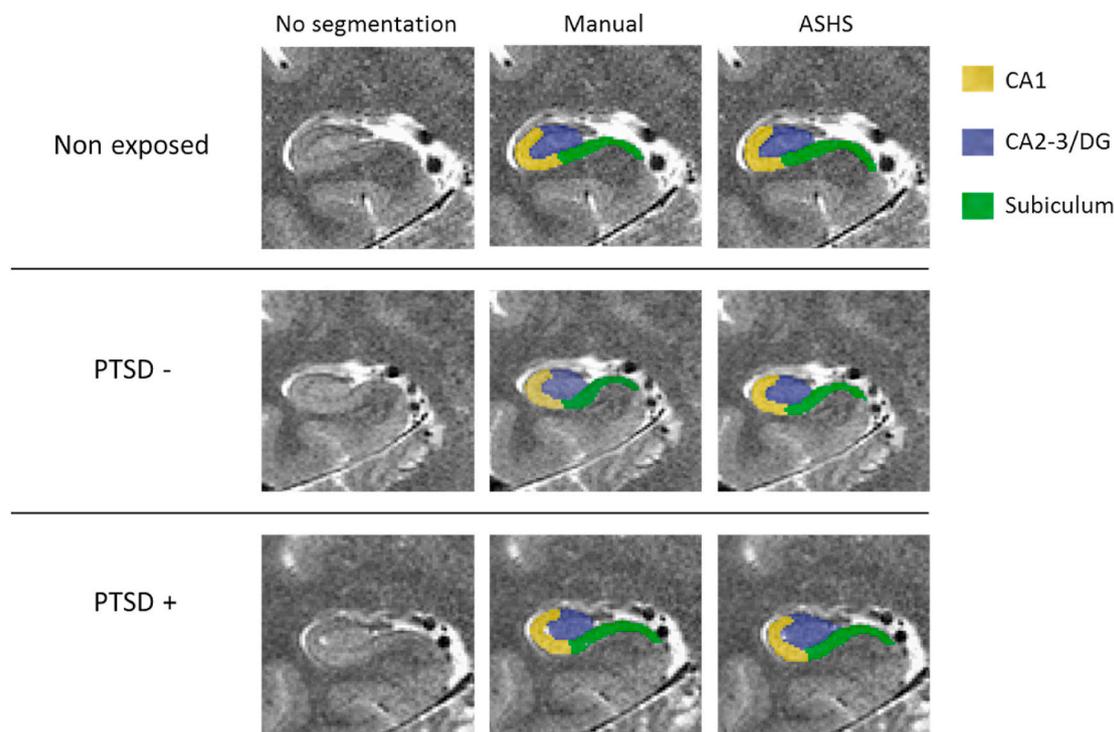
Fig. 1. Examples of manual (i.e., gold standard) and automatic (ASHS) segmentation (output of leave-one-out cross-validations) of the hippocampus for each group, illustrating the ability of the ASHS automatic segmentation software to successfully delineate hippocampal subfields (see Supplementary Table 4 for ASHS segmentation accuracy).

2.2. Inclusion/exclusion criteria

All participants were aged 18–60 years, right-handed, and French speaking. Participants were not included if they reported prior psychiatric (e.g., psychotic, bipolar, obsessive-compulsive disorders) or neurological diseases, traumatic brain injury (with loss of consciousness > 1 h), alcohol or substance abuse (other than nicotine), or MRI contraindications. In addition to the above-mentioned criteria, neither nonexposed nor exposed participants were included if they had any history of PTSD, anxiety or depressive symptoms prior to the attacks. A medical doctor applied the inclusion/exclusion criteria during a medical examination. Participants were financially compensated for taking part the study. Exclusions were made for the following reasons: no acquisition of T2 images ($n = 7$), artefacts on the T1 images ($n = 4$), motion artefacts on the T2 images (anatomical landmarks used for segmentation not visible, $n = 27$), misplacement of the saturation band on the T2 images ($n = 7$), and failure to meet inclusion criteria in the case of exposed participants ($n = 7$; 6 met the criteria for re-experiencing symptoms, but without the presence of other symptom categories, including functional impairment, i.e., Criterion G, and 1 was actually not exposed to the attacks, i.e., Criterion A).

2.3. Diagnosis of full or partial PTSD

Participants were diagnosed with PTSD in its partial form ($n = 23$) if they had re-experiencing symptoms (Criterion B), with persistence of the symptoms for more than 1 month (Criterion F) that caused severe distress and functional impairment (Criterion G). More than 80% of the individuals with this partial form also met two of the other symptom criteria, namely avoidance (C), negative alterations in cognition and mood (D), or hyperarousal (E). *Subthreshold* (also referred to as *partial* or *subsyndromal*) PTSD has been associated with clinically severe psychological, social and functional impairments (for a review, see Brancu et al., 2016). Although participants with a partial PTSD profile did not exhibit the full clinical symptoms of PTSD, the intrusive symptoms identified in each participant caused considerable distress that can be associated with high levels of social and work morbidity comparable to full PTSD (Zlotnick et al., 2002). The concept of subthreshold PTSD suggests that an individual may still display considerable clinical impairment (Cukor et al., 2010; Mota et al., 2016; Zhang et al., 2004), especially in relation to the re-experiencing and intrusive symptoms, despite not meeting the criteria for either avoidance or hyperarousal symptoms (Blanchard et al., 1996; Pietrzak et al., 2012). Therefore, trauma-exposed participants with full ($n = 30$) and partial ($n = 23$) PTSD profiles were brought together in a single clinical group (*PTSD group*) for the purpose of statistical analyses.

2.4. Questionnaires

In addition to the SCID, participants completed the PCL-5 (Blevins et al., 2015) to quantify the severity of their symptom cluster. Scores for items within a given cluster were summed as follows: Cluster B (*intrusive re-experiencing*; Items 1–5), Cluster C (*avoidance*; Items 6–7), Cluster D (*negative alteration of cognition and mood*; Items 8–14), and Cluster E (*alteration of arousal and reactivity*; Items 15–20). Severity of depressive symptoms was quantified using the BDI (Beck and Beck, 1972). These scores were used as predictor variables of hippocampal subfield volumes in our statistical models (see section below). Two other complementary questionnaires were administered to assess stressful events that had been experienced during childhood and adolescence and previous traumatic exposure (see supplementary file for further details). The first questionnaire was a measure of childhood adversity that had already been used in research on trauma and depression (e.g., Dayan et al., 2010), inspired by the literature on vulnerability in adulthood caused by adverse events in childhood (Yehuda et al., 2001). Adverse events were rated yes/no, and these binary scores were then summed. The second questionnaire was a classic and widely used list of traumatic events occurring during the lifespan, based on the DSM-5. Participants rated their degree of exposure to 18 potential traumatic events on a 4-point scale, and we computed the total score. Two other questionnaires, one

measuring alcohol consumption (Saunders et al., 1993), the other cannabis consumption (Legleye et al., 2007), were also administered. These addiction scores, together with the scores on the traumatic life events questionnaires, were used as nuisance covariates in our statistical analyses (see section below). This ensured that differences in hippocampal volumes observed between the groups were independent of the potential effects of addiction or previous traumatic exposure.

2.5. Neuroimaging data acquisition

All participants were scanned with a 3T Achieva MRI scanner (Philips) at the Cyceron Center (Caen, France). T1-weighted anatomical volumes were acquired using a three-dimensional fast-field echo sequence (3D-T1-FFE sagittal; repetition time (TR) = 20 ms, echo time (TE) = 4.6 ms, flip angle = 10°, in-plane resolution = 1 × 1 mm^2, slice thickness = 1 mm, no gap, 192 slices, field of view = 256 × 256 mm^2). This acquisition was followed by four TNT functional sessions acquired using an ascending T2-star EPI sequence (MS-T2-star-FFE-EPI axial; TR = 2050 ms, TE = 30 ms, flip angle = 78°, 32 slices, slice thickness = 3 mm, 0.75 mm gap, 64 × 64 × 32 matrix, FoV = 192 × 192 × 119 mm3, 310 vol per run). A high-resolution proton density-weighted sequence was also acquired perpendicularly to the long axis of the hippocampus (TR = 6500 ms, TE = 80 ms, flip angle = 90°, in-plane resolution = 0.391 × 0.391 mm^2, slice thickness = 2 mm, no gap, 30 slices), in order to segment hippocampal subfields.

2.6. Creation of ASHS atlas package and hippocampal subfield segmentation

Hippocampal subfields were automatically segmented using ASHS software (Yushkevich et al., 2015). As no existing ASHS atlas package was based on PTSD or trauma-exposed populations, we created an atlas package on a subsample (n = 22) of participants, using the ASHS training pipeline (instructions on https://sites.google.com/site/hippos ubfields/building-an-atlas; Supplementary Tables 3 and 4). We first manually segmented the scans of 22 participants (7 healthy controls, 7 PTSD- and 8 PTSD+, similar in age, sex and education level across groups; see Supplementary Table 3). Hippocampal subfields were manually delineated following the procedure developed in our laboratory (de Flores et al., 2015; La Joie et al., 2010; Postel et al., 2019) using ITK-snap software (version 3.6.0; Yushkevich et al., 2006). From the most anterior part of the hippocampus to the colliculi, the hippocampus was segmented into three subregions: subiculum, CA1, and a region combining CA2, CA3 and the DG (*CA2-3/DG*). Segmenting the individual CA2, CA3 and DG subfields is inaccurate, unreliable and difficult, owing to the absence of useful anatomical landmarks and the very small size of CA2 and CA3 (de Flores et al., 2015; La Joie et al., 2010). This is why we combined CA2, CA3 and DG into a single subregion. Moreover, because it is particularly difficult to differentiate between the subfields in the tail of the hippocampus, the most posterior part of the hippocampus (posterior to the colliculi) was also treated as a single subregion (*tail*). The volume of the whole hippocampus corresponded to the sum of these four segmented subregions (subiculum, CA1, CA2-3/DG, and tail). The adjacent entorhinal cortex, perirhinal cortex and parahippocampal cortex were also included in this atlas, as in the segmentation protocol developed by Berron et al. (2017). The segmentation of the parahippocampal gyrus went beyond the scope of the present study, and is not reported in here. Manual delineation was performed by a single expert rater (CP), who was blind to participants' clinical status.

Once the atlas package had been created, we assessed the accuracy of ASHS automated segmentation (relative to manual segmentation) with the subsample of 22 participants, using leave-one-out cross-validations as described in Wisse et al. (2016). We compared the automated segmentations of the 22 images (outputs of the leave-one-out cross-validations) and the corresponding manual segmentations using the dice similarity coefficient (see Supplementary Table 4 and Fig. 1). The

general coefficient was 0.86 for each hemisphere. Mean overlap measures were above 0.82 for hippocampal subfields and 0.74 for all the regions of the parahippocampal gyrus in the whole subsample. Dice similarity coefficients did not significantly differ between groups (group effect tested with analysis of variance for each region: p > 0.05).

ASHS automatically segmented the images of the remaining participants. Automatic segmentations were all visually checked before we extracted the volumes for statistical analysis. In two participants, voxels labeled as CA1 that were outside the hippocampus were manually removed.

2.7. Memory control task (think/no-think) and fMRI connectivity analysis

The data from the memory suppression task and their analysis have been described in depth elsewhere (Mary et al., 2020). Here, our goal was to use the very same data describing the effective connectivity between the right MFG and the hippocampus to study the potential relationship between this connectivity marker of memory suppression and the hippocampal subfield volumes. We therefore briefly describe the TNT task and the analysis of effective connectivity here. More details on this procedure can be found elsewhere (Mary et al., 2020).

Before the fMRI acquisition, participants intensively learned 72 neutral French word-object pairs. This overtraining procedure was intended to ensure that each cue word would automatically trigger the retrieval of the associated object. We recorded fMRI activity during the TNT task. During this task, if the cue word was shown in green (think condition), participants had to visualize and recall the associated object with as many details as possible. However, if the word was printed in red, participants had to try and stop the memory of the object from entering awareness and maintain their attention on the cue word (no-think condition). If the object came to mind anyway during suppression attempts, they were asked to push it out of their mind and report after the end of the trial that the reminder had aroused awareness of its paired object, allowing us to isolate the no-think trials that triggered intrusions.

We then used dynamic causal modelling to separately analyze top-down and bottom-up influences during attempts to downregulate intrusive memories. As this type of modelling can only handle a limited number of nodes, we designed simple 4-node DCM models to study changes in connectivity associated with memory suppression. We used the right anterior MFG as the reflection of the control systems, and the right rostral hippocampus, parahippocampal cortex and precuneus as representative nodes of the memory systems (see Mary et al., 2020, for precise definitions of these regions). We calculated how the control of intrusive memories influenced the bottom-up and top-down connections between the anterior MFG and memory targets. However, given that we were primarily interested in whether the regulation of memory activity during inhibitory control is related to the preservation/alteration of hippocampal subfield volumes, we focused here on the top-down connection between the right MFG and hippocampus. The modulator acting on this connection reflected the difference in coupling between intrusion and nonintrusion trials. Thus, a negative coupling would reflect an increase in the top-down regulation of intrusive memories consistent with an inhibitory influence. It should be noted that owing to technical or behavioral issues or image artefacts, effective connectivity analysis of TNT data was only possible for 140 of the 148 participants (nonexposed group: n = 55; PTSD-group: n = 35; PTSD+ group: n = 50).

2.8. Statistical analyses of hippocampal subfield volumes

Between-group differences were first analyzed with a repeated-measures analysis of covariance (ANCOVA), with regions of interest and hemisphere as within-participant factors, and group as a between-participants factor. Covariates included age, sex, education level, type of traumatic exposure to the attacks, previous traumatic exposure, stressful events experienced during childhood and adolescence, alcohol

(Saunders et al., 1993) and cannabis (Legleye et al., 2007) consumption, and intracranial volume (as measured with ASHS) (see Table 1). Critical interactions (Group * Region and Group * Region * Hemisphere) were characterized using planned comparisons based on one-sided *t* statistics, and testing the hypothesized hippocampal alterations associated with PTSD (PTSD+ vs. PTSD- or nonexposed), or traumatic exposure (PTSD-vs. nonexposed). The expected proportion of Type I error across multiple regions was controlled for using the false discovery rate (FDR) correction, with a desired FDR *q* value of .05 and assuming a positive dependency between variables (Benjamini and Hochberg, 1995). Reliability of between-group differences was quantified by bootstrapping the participant set with 10,000 iterations to compute 95% confidence intervals (CIs) of the mean. These 95% bootstrapped CIs were calculated on hippocampal volumes adjusted for nuisance covariates using a general linear model computed separately for each group comparisons.

We also investigated the relationship between hippocampal alterations and PTSD symptomatology, as well as top-down coupling parameters associated with the experimental suppression of intrusive memories (Mary et al., 2020), using a regression model that controlled for the same nuisance covariates. For this analysis, we used the four main clusters of PTSD symptoms (intrusion, avoidance, negative alterations of cognition and mood, alterations of arousal and reactivity) derived from the PCL-5, as well as the severity of depressive symptoms quantified using the BDI. Each parameter of interest was tested in isolation, and bivariate outliers were identified and removed beforehand, using orthogonal projection and the box plot rule (Pernet et al., 2013). We report the standardized beta coefficients and their associated *t* statistics and *p* values, corrected for the expected proportion of Type I error for each region across multiple testing using FDR. The reliability of the relationship was also assessed using 95% bootstrapped CIs.

3. Results

3.1. Hippocampal subfield alterations in PTSD

Preliminary analyses showed an overall decrease in hippocampal volume in the PTSD group, compared with the other two groups (statistics reported in supplementary file). To determine the nature of these hippocampal alterations, we further divided the hippocampus into four subregions (CA1, CA2-3/DG, subiculum, and tail; see Supplementary Table 1 for raw hippocampal volumes) according to an existing protocol (La Joie et al., 2010).

3.1.1. PTSD+ versus PTSD-

We first investigated differences between hippocampal subfield volumes by running an ANCOVA to compare the two trauma-exposed groups (PTSD+ and PTSD-), controlling for age, sex, education level, type of traumatic exposure to the attacks, previous traumatic exposure, stressful events experienced during childhood and adolescence, alcohol (Saunders et al., 1993) and cannabis (Legleye et al., 2007) consumption, and intracranial volume (measured by ASHS) (see Methods and Table 1). The effect of group differed according to subfield (Subfield * Group interaction, $F(3, 234) = 2.84$, $p = 0.039$), but was not lateralized (nonsignificant Hemisphere * Subfield * Group interaction, $F(3, 234) = 0.21$, $p = 0.31$). Planned comparisons revealed that this significant interaction was driven by smaller volumes of CA1, $t(79) = 2.21$, $p_{FDR} = 0.048$, bootstrapped 95% CI [6.78, 54.28], and CA2-3/DG, $t(79) = 2.01$, $p_{FDR} = 0.048$, bootstrapped 95% CI [9.46, 58.6], in the PTSD+ group, compared with trauma-exposed individuals without PTSD (see Fig. 2A). No group differences were found for the tail, $t(79) = 0.30$, $p_{FDR} = 0.38$, bootstrapped 95% CI [-12.84, 17.38], or the subiculum, $t(79) = 1.16$, $p_{FDR} = 0.16$, bootstrapped 95% CI [-5.51, 27.79]. Although we controlled for type of exposure in the analyses comparing the trauma-exposed groups (PTSD+ and PTSD-), we performed complementary analyses that only considered individuals who had been directly exposed to the attacks (Criterion A1), in order to confirm that the CA1 and CA2-3/DG alterations reported above were specific to the pathology and were not related to any variations in the degree and nature of exposure. These additional analyses confirmed that directly exposed participants with PTSD had smaller volumes of CA2-3/DG, $t(49) = 1.72$, $p_{FDR} = 0.046$, bootstrapped 95% CI [5.24, 71.69], and CA1, $t(49) = 2.11$, $p_{FDR} = 0.040$, bootstrapped 95% CI [11.56, 83.93], than those without (PTSD-).

3.1.2. PTSD+ versus nonexposed

The ANCOVA comparing the PTSD+ group with nonexposed individuals also revealed a significant Subfield * Group interaction, $F(3, 291) = 7.99$, $p < 0.001$, and a nonsignificant Hemisphere * Region * Group interaction, $F(3, 291) = 0.21$, $p = 0.89$. The volumes of CA2-3/DG, $t(99) = 4.27$, $p_{FDR} < 0.001$, bootstrapped 95% CI [36.4, 88.9], CA1, $t(99) = 3.63$, $p_{FDR} < 0.001$, bootstrapped 95% CI [25.5, 75.9], and subiculum, $t(99) = 2.03$, $p_{FDR} = 0.029$, bootstrapped 95% CI [3.6, 35.3], were significantly smaller in the PTSD+ group than in the nonexposed group (see Fig. 2B). No significant difference was found for the tail of, $t(99) = 0.30$, $p_{FDR} = 0.38$, bootstrapped 95% CI [-11.4, 15.6].
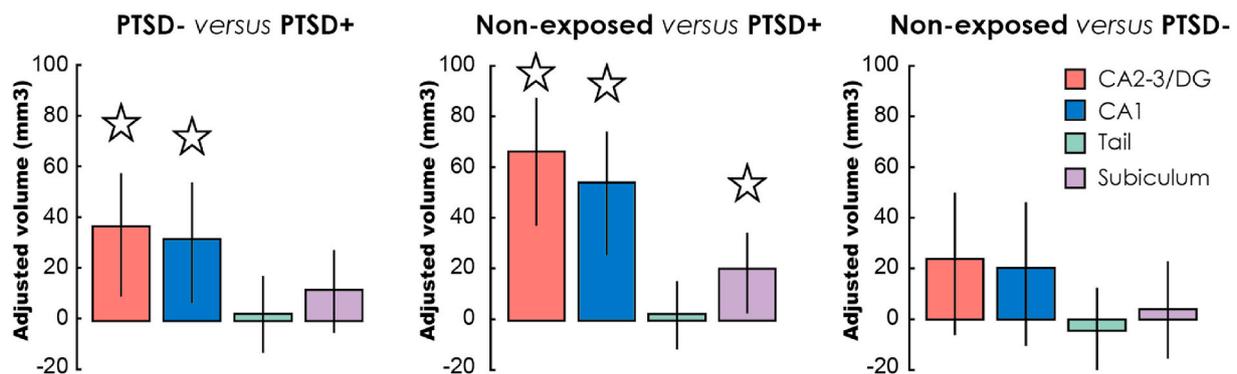
Fig. 2. Between-group differences in adjusted volume for each comparison and subfield. Subfield volumes were adjusted for nuisance covariates for each group comparison, ensuring that group differences were independent of age, sex, education level, type of traumatic exposure to the attacks, previous traumatic exposure, stressful events experienced during childhood and adolescence, alcohol and cannabis consumption, and total intracranial volume (see Methods). The bars therefore reflect the mean differences in adjusted hippocampal volume for a given contrast of interest: PTSD- > PTSD+ (left panel); Nonexposed > PTSD+ (middle panel), Nonexposed > PTSD- (right panel). Bootstrap samples were also generated for each group. Volume adjustment was performed for each bootstrap sample to generate a bootstrap distribution of the adjusted volume differences. This distribution was used to calculate the bootstrapped 95% CIs of the adjusted mean volume (i. e., error bars in the figure), which indicate significance when they do not encompass zero. Star indicates significant group difference at $p_{FDR} < .05$.

3.2. Hippocampal changes following traumatic stress exposure?

The ANCOVA comparing resilient trauma-exposed individuals (PTSD-) with nonexposed individuals revealed no significant main effect of group, $F(1, 258) = 0.99$, $p = 0.32$, and no Subfield * Group, $F(3, 252) = 1.29$, $p = 0.28$, or Hemisphere * Region * Group, $F(3, 252) = 0.54$, $p = 0.66$, interaction. Isolated testing of hippocampal subfields in the PTSD-group did not reveal any significant reduction in the volume of CA1, $t(85) = 1.18$, $p_{FDR} = 0.24$, bootstrapped 95% CI [-9.6, 47.5], CA2-3/DG, $t(85) = 1.34$, $p_{FDR} = 0.24$, bootstrapped 95% CI [-5.9, 50.8], tail, $t(85) = -0.44$, $p_{FDR} = 0.36$, bootstrapped 95% CI [-20.7, 12.34], or subiculum, $t(85) = 0.34$, $p_{FDR} = 0.36$, bootstrapped 95% CI [-14.6, 23.9] (see Fig. 2C).

3.3. Relationship between CA1 and CA2-3/DG changes and symptom severity

In the PTSD+ group, regression models using PCL-5 subscores (i.e., intrusion, avoidance, mood, hyperarousal) and the BDI score (i.e., depression), revealed that CA1 volume was negatively associated with intrusion symptoms ($\beta_{standardized} = -0.27$), $t(41) = -2.46$, $p_{FDR} = 0.045$, bootstrapped 95% CI [-0.41, -0.08], but not with other psychopathological dimensions (see Fig. 3 and Supplementary Table 2 for a detailed statistical report). However, changes in the CA2-3/DG subregion were significantly related to avoidance behavior ($\beta_{standardized} = -0.41$), $t(37) = -2.81$, $p_{FDR} = 0.02$, bootstrapped 95% CI [-0.68, -0.04], hyperarousal symptoms ($\beta_{standardized} = -0.26$), $t(36) = -1.96$, $p_{FDR} = 0.049$,

bootstrapped 95% CI [-0.49, 0.005], and depression ($\beta_{standardized} = -0.30$), $t(38) = -2.30$, $p_{FDR} = 0.033$, bootstrapped 95% CI [-0.51, -0.10]. In the PTSD-group, a reduction in CA2-3/DG volume was significantly related to increased depressive symptoms ($\beta_{standardized} = -0.40$), $t(22) = -2.56$, $p_{FDR} = 0.043$, bootstrapped 95% CI [-0.68, -0.11], and marginally related to an increase in hyperarousal ($\beta_{standardized} = -0.33$), $t(24) = -2.05$, $p_{FDR} = 0.06$, bootstrapped 95% CI [-0.62, 0.02]. However, no significant association was found between CA1 volume and PTSD or depressive symptoms (Fig. 3 and Supplementary Table 2) in the PTSD-group.

3.4. Relationship between CA1 changes and a brain connectivity marker of memory suppression capacity

MFG-hippocampal connectivity was quantified by analyzing effective connectivity in an experimental model of intrusion control (TNT task). These data were extracted from our previous study in the same sample of participants (and with the same brain imaging protocol), and reflected the right MFG's top-down negative influence over hippocampal activity to suppress involuntary and intrusive memories (Mary et al., 2020). In a previous study featuring the same neuroimaging experiment, we found that this inhibitory control over memory systems was altered in PTSD+ but preserved in PTSD-, suggesting that this function plays an important role in post-trauma adaptation (Mary et al., 2020). We therefore expected memory suppression abilities in resilient individuals (PTSD-) to have a protective effect on hippocampal subfields, and specifically on CA1, given that intrusion symptoms were related to CA1 changes. Confirming this expectation, memory suppression capacity was related to larger CA1 volumes in PTSD- ($\beta_{standardized} = -0.41$), $t(21) = -2.07$, $p = 0.025$, 90% CI [-0.70, -0.08], but not in PTSD+ ($\beta_{standardized} = 0.16$), $t(33) = 1.23$, $p = 0.11$, bootstrapped 95% CI [-0.08, 0.36] (see Fig. 4). Critically, this relationship was not observed in nonexposed individuals ($\beta_{standardized} = 0.008$), $t(42) = 0.01$, $p = 0.47$, bootstrapped 95% CI [-0.17, 0.17], suggesting that this pattern was specific to trauma-exposed, but resilient, individuals.

4. Discussion

Our findings suggest that the CA1 and CA2-3/DG subregions are specifically damaged in PTSD, even after carefully controlling for the degree and nature of exposure, or previous traumatic exposure. Changes in CA1 volume in PTSD+ were related to intrusion symptoms, but not to the comorbid effect of depression. Although the origin (pre-existing risk factor vs. stress-induced) of hippocampal alteration in PTSD remains elusive (Admon et al., 2013; Gilbertson et al., 2002; Pitman et al., 2012; Szeszko et al., 2018), we discuss here what might mediate such relationship.

One hypothesis is that intrusions caused these CA1 changes. The severe distress and fear that accompanies the recurrent re-experiencing of the trauma may well contribute to stress-induced damage in CA1, via an excessive stress response (Southwick, 1993) or the hypersensitivity of glucocorticoid receptors (Szeszko et al., 2018). In line with this idea, we also found that preservation of CA1 integrity was associated with enhanced memory control over intrusive memories, reflected in greater frontally mediated down-regulation of hippocampal activity in an experimental model of memory suppression. However, this effect was only observed in resilient individuals (PTSD-) and not in PTSD+ or nonexposed participants, suggesting that the ability to effectively block the retrieval of unwanted and intrusive memories contributes to better recovery from the trauma, by limiting stress-induced changes in CA1. Healthy individuals with better engagement of the control system experience fewer memory intrusions, greater disruption of perceptual memory, and greater forgetting (Anderson and Hulbert, 2021). Here, we can extend these conclusions to the preservation of hippocampal subfields in the face of trauma.

A second hypothesis, by contrast, is that CA1 changes cause
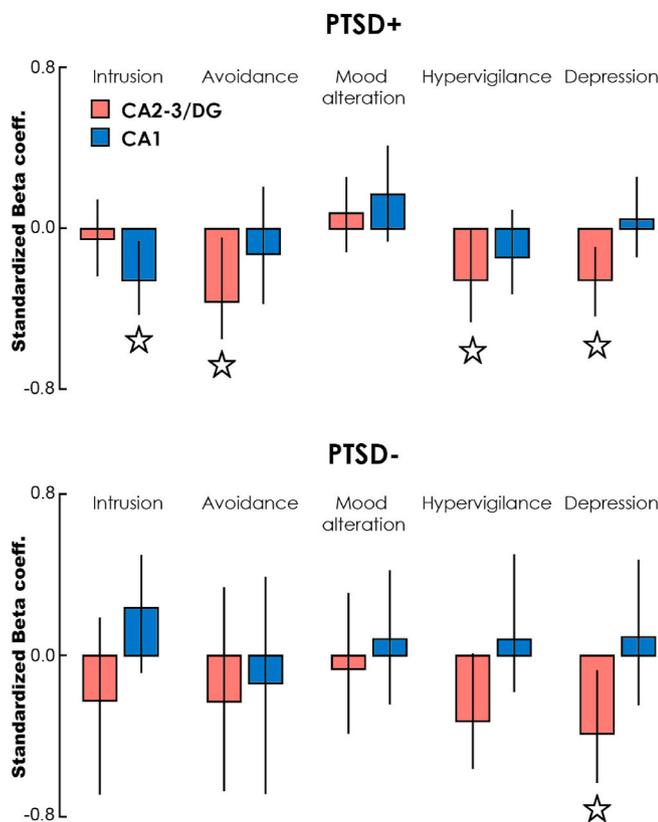
Fig. 3. Relationships between hippocampal subfield volumes and symptoms in PTSD+ and PTSD-. A regression was performed to predict subfield volumes from symptom scores, controlling for nuisance covariates (see Method). Standardized beta coefficients were estimated for each symptom, and their distribution was computed by bootstrapping the participant set to calculate the bootstrapped 95% CIs (i.e., error bars in the figure), which indicate significance when they do not encompass zero. Star indicates significant relationship at $p_{FDR} < .05$.
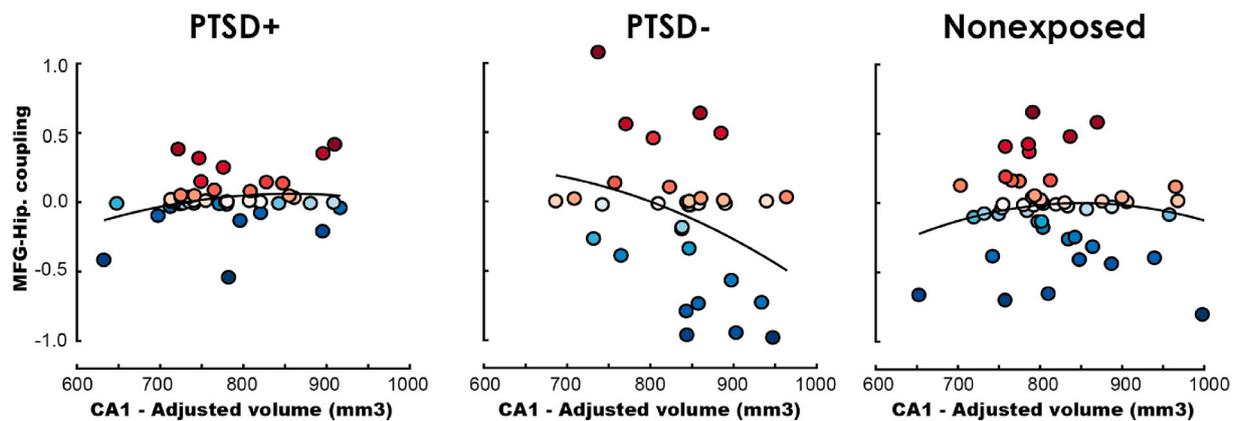
Fig. 4. Relationship between CA1 volumes and MFG-hippocampus top-down memory suppression in PTSD+, PTSD- and nonexposed. These scatterplots with fitted lines illustrate the relationship between CA1 volume, adjusted for nuisance covariates (see Method), and the magnitude of top-down memory suppression between the right MFG and hippocampus. Top-down memory suppression was estimated using a model of effective connectivity while participants attempted to suppress neutral and inoffensive intrusive memories in a TNT task administered in a laboratory setting (Mary et al., 2020). Greater inhibitory control over intrusive memories is reflected here by greater negative couling parameters (i.e., from red to blue dots).

intrusions. CA1 is preferentially involved in pattern completion, namely, the neural mechanisms that restore memory traces from partial cues (Carr et al., 2010). Intrusive re-experiencing corresponds to dysregulated memory reactivation that can be thought of as an excessive and aberrant form of pattern completion. How could reduced CA1 volume be related to excessive pattern completion? Interestingly, animal models suggest that chronic stress damages not only dendritic branching in CA1, but also GABAergic interneurons (Czéh et al., 2015; Gould, 2007; Hu et al., 2010; McEwen et al., 2016b). GABA neurotransmitters mediate memory control mechanisms (Schmitz et al., 2017), but also regulate the synchronization of precise activity across hippocampal subfields (Sik et al., 1994). We can therefore assume that if CA1 changes are preferentially mediated by alteration of the GABAergic system, the resulting disturbance of the excitation and inhibition balance in CA1 promotes the recurrent, involuntary and disinhibited reactivation of the traumatic memory.

CA2-3/DG changes in PTSD+ could not be disambiguated from the effect of comorbid depression. Depressive symptoms also affected the CA2-3/DG subregion in PTSD-. Major depressive disorder is indeed associated with smaller DG volume and fewer granule neurons in this region (Boldrini et al., 2013; Huang et al., 2013), and could be linked to reduced neurogenesis (Miller and Hen, 2015; Thomas and Peterson, 2003). Although the pathogenic mechanisms underlying CA2-3/DG changes may result from the combined effects of exposure to traumatic stress and comorbid depression, we also observed that changes in the CA2-3/DG subregion in PTSD+ were associated with behavioral avoidance and hyperarousal. This finding fits in well with the proposed role of CA3 and DG in pattern separation, a mechanism that reduces interference between new and old memory traces (Besnard and Sahay, 2016; Yassa and Stark, 2011). Alteration of this mechanism, through the maladaptive effects of stress on DG neurogenesis and CA3-DG circuitry, could affect the ability to discriminate novel and safe experiences from traumatic memories (Besnard and Sahay, 2016), and foster the generalization of threat, resulting in hyperarousal symptoms (Kheirbek et al., 2012; Liberzon and Abelson, 2016) or avoidance behaviors (Grupe et al., 2019). It should, however, be noted that another study using automatic segmentation of low-resolution MRI images (1 mm^3), found no modification of hippocampal subfields in individuals with major depressive disorder (Cao et al., 2017). Further studies are therefore needed to understand whether volume change in the CA2-3/DG subregion is specific to the conjunction of PTSD and depressive symptoms. Interestingly, in mood disorders involving the formation of problematic intrusive thoughts in addition to depression (e.g., bipolar disorder), lower CA2-3 volumes have also been found, in comparison with healthy controls

(Haukvik et al., 2020).

The cross-sectional and correlational nature of the present study meant that it did not provide any insight into the origin of the hippocampal changes seen in PTSD. Interestingly, these changes remained significant after controlling for earlier exposure to traumatic and stressful events in our statistical model. This finding suggests that the hippocampal changes observed in the PTSD+ group were not related to earlier traumatic exposure, a well-known risk factor for developing PTSD (Kessler et al., 2018) and hippocampal damage (Teicher and Samson, 2016). However, we cannot determine whether these changes were genetic in nature or resulted from a maladaptive stress response to the terrorist attacks. Hence, further studies, ideally using prospective designs to assess hippocampal volumes and functions before and after trauma, are needed to shed light on the origin and causal role of these changes in the development and persistence of PTSD symptoms.

The main strength of our study is that it provided a unique opportunity to observe variations in hippocampal phenotypes among individuals who had all been exposed to the same acute and unique traumatic event, but who responded differently to the trauma, exhibiting outcomes that ranged from the pathological to the resilient. The short interval between the traumatic event and the brain imaging (<18 months) allowed for better control over a potential time confound, and ensured that the two outcomes (i.e., absence vs. presence of PTSD) were adequately matched in terms of trauma onset. The short interval also allowed us to confidently link the absence of PTSD to resilience. The longer this interval, the harder it is to be sure that individuals found to be asymptomatic at the time the study did not develop-and recover from-PTSD in the intervening period. However, given that studies usually include participants several years after the trauma, our results are more difficult to compare with other findings. Moreover, the present sample did not reflect chronic and multiple-trauma PTSD, constituting another potential source of discrepancy and undermining the generalization of our results. Finally, owing to the proximity of the hippocampus to main arteries and the sensitivity of the imaging sequence, the data of many participants had to be discarded because of motion artefacts (see methods). Although a high exclusion rate has already been reported in hippocampal subfield studies (Yushkevich et al., 2015), this may constitute another limitation of the present study.

5. Conclusion

The first main conclusion of our study is that CA1 volume is specifically implicated in the pathological response to trauma and the development of PTSD, a relationship mediated by the expression of traumatic

memories through intrusive re-experiencing. This is in line with the role that CA1 is known to play in memory reactivation through pattern completion (Carr et al., 2010). However, further studies are needed to determine whether intrusive re-experiencing does indeed trigger stress-induced damage, or whether pre-existing damage favors the formation of traumatic memories. The former would have potential implications for the treatment of PTSD, and suggest that treatment aimed at reducing the re-experiencing of the traumatic event quickly after the traumatic event may prevent further CA1 atrophy. This is in line with current gold-standard treatment and international guidelines, which mainly focus on treating the trauma to reduce its distressing impact (Yehuda et al., 2015). However, these treatments do not fully address all the symptoms and adequately help all patients, and there is therefore a need for complementary treatments focusing on protective and resilience factors (Yehuda et al., 2016).

In line with this idea, the second conclusion concerns the relationship we observed between brain connectivity markers of memory suppression and CA1 volume in resilient individuals. The fact that this relationship was not observed in nonexposed individuals and was specific to resilient individuals suggests that this is not a trivial relationship, but one that emerges to protect individuals after traumatic exposure. While caution should be exercised when interpreting the directionality of this relationship, which will need to be elucidated in future research, this resilience-specific pattern suggests a potentially promising protective role of control processes. However, we do not suggest that traumatic memories should be treated with suppression techniques (Mary et al., 2020). Suppression mechanisms are compromised in individuals with PTSD (Mary et al., 2020) and may have limited or even aggravating impact on traumatic memories. Moreover, traumatic memories are decontextualized, and we can assume that they are primarily stored in the emotional brain system outside the hippocampus (Brewin et al., 2010; Mary et al., 2020). Therefore, they probably cannot be modulated through updating or reconsolidation mechanisms (Phelps and Hofmann, 2019). Nevertheless, recontextualizing traumatic traces by stimulating hippocampal formation through standard exposure therapy sessions (Desmedt et al., 2015) in parallel with training memory control mechanisms might not only promote more efficient regulation of the fear response (Goosens, 2011), but also create an opportunity for a remediated control system to disrupt and update the traumatic engram through reconsolidation (Phelps and Hofmann, 2019).

The third main conclusion of our study is that changes in the CA2-3/DG subregion of the hippocampus are related to avoidance and hypervigilance behaviors. This relationship is in line with the proposed role of this subregion in fear generalization, a maladaptive behavior that is presumably mediated by the alteration of pattern separation mechanisms implemented in CA2-3/DG (Besnard and Sahay, 2016). However, our study further suggests that comorbid depression may have a catalytic effect on the functional impairment of individuals with PTSD (Blanchard et al., 1998) through increased atrophy in the DG and surrounding regions. This directional interpretation of our findings should be further investigated in the future, but is supported by the established impact of depression on the production of new neurons in this subregion (Miller and Hen, 2015; Thomas and Peterson, 2003). This relationship suggests that pre-emptive monitoring and treatment of depressive symptoms following trauma could help to limit its catalytic effect, even in the absence of a formal PTSD diagnosis, thereby preserving the DG and surrounding regions and limiting the maladaptive development of avoidance behaviors.

CRediT authorship contribution statement

Charlotte Postel: Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Alison Mary:** Investigation, Writing – review & editing. **Jacques Dayan:** Writing – review & editing, Conceptualization. **Florence Fraisse:** Project administration, Data curation. **Thomas Vallée:** Investigation, Data curation. **Bérengère**

Guillery-Girard: Supervision. **Fausto Viader:** Investigation. **Vincent de la Sayette:** Investigation. **Denis Peschanski:** Funding acquisition. **Francis Eustache:** Funding acquisition, Conceptualization, Writing – review & editing. **Pierre Gagnepain:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization, Supervision, Funding acquisition.

Declaration of competing interest

The authors report no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2021.100346.

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