






## Structural brain changes with lifetime trauma and re-experiencing symptoms is 5-HTTLPR genotype-dependent

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### ABSTRACT

**Background:** Findings on structural brain alterations following trauma are inconsistent due probably to heterogeneity in imaging studies and population, clinical presentations, genetic vulnerability, and selection of controls. This study examines whether trauma and re-experiencing symptoms are associated with specific alterations in grey matter volumes and if this varies according to 5-HTTLPR genotype.

**Methods:** Structural MRI was used to acquire anatomical scans from 377 community-dwelling older adults. Quantitative regional estimates of 22 subregional volumes were derived using FreeSurfer software. Lifetime trauma was assessed using the validated Watson's PTSD inventory, which evaluates the most severe trauma experienced according to DSM criteria. Analyses adjusted for age, sex, total brain volume, head injury, and comorbidities.

**Results:** Of the 212 participants reporting lifetime trauma, 35.4% reported re-experiencing symptoms and for 1.9%, this was severe enough to meet criteria for full threshold PTSD. In participants with the SS 5-HTTLPR genotype only, re-experiencing symptoms were associated with smaller volumes in middle and superior temporal, frontal (lateral orbital, rostral and caudal middle) and parietal (precuneus, inferior and superior) regions. The trauma-exposed participants without re-experiencing symptoms were not significantly different from the non-trauma-exposed participants except for smaller precuneus and superior parietal region in traumatized participants and a larger amygdala in traumatized women specifically.

**Conclusions:** In the non-clinical sample, lifetime trauma and re-experiencing symptoms were associated with smaller volume in prefrontal, temporal and parietal cortex subregions, and this varied according to serotonergic genetic vulnerability, 5-HTTLPR SS individuals being most susceptible.

### Los cambios estructurales cerebrales con trauma en la vida y síntomas de reexperimentación son dependientes del genotipo 5-HTTLPR

**Antecedentes:** Los hallazgos sobre las alteraciones estructurales cerebrales luego del trauma son inconsistentes debido probablemente a heterogeneidad en los estudios de imagen y población, presentaciones clínicas, vulnerabilidad genética y selección de los controles. Este estudio examina si el trauma y los síntomas de reexperimentación están asociados con alteraciones específicas en los volúmenes de materia gris y si esto varía de acuerdo al genotipo 5-HTTLPR.

**Métodos:** Se utilizó IMR estructural para adquirir mapeos anatómicos de 377 adultos mayores residentes en viviendas comunitarias. Se derivaron estimados regionales cuantitativos de 22 volúmenes sub-regionales usando el software FreeSurfer. Se evaluó trauma a través de la vida utilizando el inventario para TEPT validado de Watson, que evalúa el trauma más severo experimentado de acuerdo a criterios DSM. Se ajustaron los análisis por edad, sexo, volumen cerebral total, trauma encefálico y comorbilidades.

**Resultados:** De los 212 participantes que reportaron trauma en la vida, un 35.4% reportó síntomas de reexperimentación y para el 1.9% fueron lo suficientemente severos para cumplir los criterios para el umbral completo del TEPT. Sólo en los participantes con el genotipo SS 5-HTTLPR, los síntomas de reexperimentación se asociaron con menores volúmenes en las regiones temporal media y superior, frontal (orbitolateral, rostral y caudal medial) y parietal (precúneo, inferior y superior). Los participantes expuestos a trauma sin síntomas de reexperimentación no variaron significativamente respecto a los

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### PALABRAS CLAVE



Envejecimiento; cohorte; volumen de materia gris; trauma a través de la vida; reexperimentación; región promotora asociada al transportador de serotonina; stress; IMR

### 关键词

老化; 队列; 灰质体积; 终身创伤; 再体验; 五羟色胺转运体启动子区; 应激; MRI

### HIGHLIGHTS

- Lifetime trauma has long-term consequences on grey matter volumes.
- Prefrontal, temporal and parietal cortex volume are especially reduced.
- The strongest effect is for individuals with re-experiencing symptoms.
- However, effects differ according to serotonergic vulnerability.

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no expuestos a trauma excepto por menor tamaño del precúneo y región superior parietal en los participantes traumatizados y un mayor tamaño de la amígdala específicamente en mujeres traumatizadas.

**Conclusiones:** En una muestra no-clínica, el trauma a través de la vida y los síntomas de reexperimentación se asociaron con menor tamaño en sub-regiones corticales prefrontales, temporales y parietales, y esto varía de acuerdo a la vulnerabilidad genética serotoninérgica, siendo más susceptibles los individuos 5-HTTLPR SS.

### 伴终身创伤和再体验症状的脑结构改变取决于5-HTTLPR基因型

**背景:** 可能由于影像学研究和人群, 临床表现, 遗传易损性及对照选择的异质性, 关于创伤后脑结构改变的研究结果不一。本研究考查了创伤和再体验症状是否与灰质体积的特定变化有关, 以及这种变化是否依据5-HTTLPR基因型而不同。

**方法:** 使用结构性核磁共振成像 (MRI) 获取了377名社区老年居民的解剖学图像。使用FreeSurfer软件得出了22个亚区体积的分区定量估计。终身创伤使用经验证的Watson的PTSD量表, 根据DSM标准评估所经历过最严重的创伤。以年龄, 性别, 全脑体积, 头部外伤及并发症为分析的调节变量。

**结果:** 在212名报告终身创伤的参与者中, 35.4%报告有再体验症状, 1.9%的严重程度足以满足PTSD完全临界值的标准。仅在具有SS 5-HTTLPR基因型的参与者中, 再体验症状与颞叶中上回, 额叶 (眶外侧, 延髓和尾状中) 和顶叶 (楔前叶, 下回, 上回) 的较小体积相关。没有再体验症状的创伤暴露参与者和未经创伤的参与者无显著差异, 除受创伤参与者顶叶上回区域更小和特别是受创伤妇女的杏仁核更大。

**结论:** 在非临床样本中, 终身创伤和再体验症状与前额叶, 颞叶和顶叶皮层亚区的体积较小有关, 并且依据五羟色胺遗传易感性而变化, 其中5-HTTLPR SS型患者最易感。

## 1. Introduction

Posttraumatic stress disorder (PTSD) is a trauma- and stressor-related psychiatric disorder associated with high co-morbidity and disability (Kessler, 2000). There is also evidence to suggest that even subthreshold presentations may be associated with substantial clinical impairment and distress, requiring treatment (American Psychiatric Association, 2013). Unlike other affective disorders, PTSD can present with a constellation of symptoms and there are no core symptoms that are essential for a PTSD diagnosis according to DSM criteria (American Psychiatric Association, 2013). Hence, individual clinical presentations may vary widely, leading to diagnostic heterogeneity. Re-experiencing of the trauma maintains repeated stress and constitutes the most common, clinically relevant, and debilitating of the symptom clusters characterizing PTSD (Kroes, Whalley, Rugg, & Brewin, 2011; Lanius, Bluhm, Lanius, & Pain, 2006). Re-experiencing can bring about other symptoms (avoidance and certain arousal criteria, e.g. sleep disturbance) and has less overlapping diagnostic characteristics with cognitive or mood disorders (Kroes et al., 2011; Lanius et al., 2006). Re-experiencing is unique to PTSD and may be more predictive of brain alterations in PTSD than any other symptom cluster (Kroes et al., 2011; Lanius et al., 2006) however, structural evidence is lacking.

Neuroimaging has the potential to provide crucial insights into the pathophysiology of posttraumatic symptomatology and to allow a better understanding of the aetiology of the disease, as well as why certain individuals develop PTSD symptoms and others remain disease-free even in the face of severe adversity. Most previous structural imaging studies have focused on the hippocampus, amygdala and medial prefrontal and insular cortex with some inconsistent results (Admon,

Milad, & Hendler, 2013; Li et al., 2014; Menon, 2011; O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015; Pitman et al., 2012). Conversely, structural alterations in temporal, parietal and other subcortical regions have received little attention although such regions have been implicated in emotional regulation, memory retrieval and suppression, which are altered in PTSD (Brewin, 2001; Gilmore, Nelson, & McDermott, 2015; Kuhn & Gallinat, 2013; Li et al., 2014; Logue et al., 2018). The most consistent findings suggest that PTSD is associated with smaller hippocampus and anterior cingulate cortex (ACC) volumes (Li et al., 2014; O'Doherty et al., 2015). However, such alterations have been reported in depressed patients (Schmaal et al., 2016) raising the question of specificity. Inconsistencies may also be related to study design and size, heterogeneity in population, trauma, as well as methodological issues, including small effect sizes or insufficient power to examine confounding factors (O'Doherty et al., 2015). Another factor is the variability in diagnosis (symptom severity or dimensional approach, acute/chronic, current or lifetime/remitted PTSD). So far, only a few very small studies have investigated brain morphological abnormalities in individuals with re-experiencing symptoms and only in relation to a small number of brain regions. The lack of appropriate control groups (both non-trauma exposed and trauma-exposed without re-experiencing) is another cause for concern, as it precludes a distinction between disease- and stress-related neural mechanisms (Li et al., 2014).

Genetic vulnerability to PTSD or resilience could also constitute a buffering factor but has seldom been considered (Brouwer et al., 2017; Logue et al., 2015). Imaging studies suggest increased serotonin synthesis

in multiple brain regions in PTSD, lower serotonin transporter (5-HTT) availability and correlations between 5-HTT and symptom severity (Davis, Holmes, Pietrzak, & Esterlis, 2017). The gene encoding this transporter contains a polymorphism (5-HTTLPR), which consists of a 44 bp insertion/deletion referred to as long (L) and short (S) allele, respectively, the latter being associated with reduced 5-HTT activity and serotonin reuptake. The S allele has been associated with fear learning in healthy volunteers and with reduced likelihood of successful psychotherapy or pharmacological treatments in patients (Wilker, Elbert, & Kolassa, 2014). A direct effect of 5-HTTLPR polymorphisms on PTSD although commonly reported (Pitman et al., 2012), was not supported by two meta-analyses but this may be due to study heterogeneity. Indeed, sensitivity analyses showed that risk was significantly increased in the SS patients without psychotic comorbidity or with current PTSD or high trauma exposure (Gressier et al., 2013; Navarro-Mateu, Escamez, Koenen, Alonso, & Sanchez-Meca, 2013). However, despite some evidence for altered serotonergic function in PTSD and a pivotal role of 5-HTTLPR in emotional learning processes, its implication in the association between structural brain region alterations and PTSD has not been examined.

This study aimed to determine if lifetime history of trauma and re-experiencing symptoms are associated with grey matter volume (GMV) alterations in specific brain regions, independently of comorbidity, and whether this may be specific to the carriers of the SS 5-HTTLPR genotype.

## 2. Methods

### 2.1. Study population

The data were derived from a longitudinal study of neuropsychiatric disorders in community-dwelling French elderly, the Esprit study (Ritchie et al., 2004). Eligible participants, who were at least 65 years of age and non-institutionalized, were recruited by random selection from the electoral rolls between 1999 and 2001. Ethics approval for the study was given by the national ethics committee and written informed consent was obtained from all participants. Of the 1863 participants recruited, only those aged  $\leq 80$  years were invited for an MRI; 760 participants were randomly selected of whom 668 had complete volumetric data. The participants diagnosed with dementia ( $n = 14$ ), left-handed ( $n = 16$ ), without genotyping data ( $n = 81$ ), having not completed the PTSD-I questionnaire ( $n = 135$ ) or with missing covariate data ( $n = 45$ ) were excluded from this analysis. Compared to the excluded participants, the 377 participants included were younger ( $p < 0.0001$ ), less frequently living alone ( $p = 0.0005$ ), and less likely to have cognitive

impairment ( $p < 0.0001$ ), diabetes ( $p = 0.04$ ), and cardiovascular ischaemic pathologies ( $p = 0.02$ ).

### 2.2. MRI protocol and image analysis

All the neuroimaging scans were acquired using the same scanner and analysed as described previously (Ancelin et al., 2019). Briefly, a 1.5 T GE Signa Imaging system (General Electric Medical Systems, Milwaukee, WI) was used to acquire a contiguous AC-PC aligned axial IR-prepared SPGR T1-weighted sequence for volumetric estimations (TR = 12, TE = 2.8, IT = 6000, matrix, size = 256 x 256, pixel spacing = 0.9375 x 0.9375 mm, NEX = 1, slice thickness = 1.0 mm). Regional reconstruction and segmentation was performed with the FreeSurfer 5.3 image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>). Twenty-two regions of interest (ROIs) defined using Desikan's Atlas (Desikan et al., 2006) were selected based on prevailing neurocircuitry models of PTSD (Admon et al., 2013; Kuhn & Gallinat, 2013; Li et al., 2014; Logue et al., 2018; Meng et al., 2014; Menon, 2011; O'Doherty et al., 2015). Total brain volume (grey+white matter) was computed using the segment m-file of the SPM5 software (Wellcome Department of Cognitive Neurology, UK).

### 2.3. Severe lifetime traumatic events and PTSD diagnosis

PTSD diagnosis was assessed by psychologists and psychiatric nurses using the self-report version of the Watson's PTSD Inventory (PTSD-I), which evaluates the most severe lifetime traumatic event or frightening experience according to DSM criteria (Watson, Juba, Manifold, Kucala, & Anderson, 1991). The PTSD-I used in this study shows high internal consistency ( $\alpha = 0.92$ ) and test-retest reliability (total score = 0.95) (Watson et al., 1991), in addition to being previously validated for a French population (Jehel, Duchet, Paterniti, & Louville, 1999). The first question identifies past traumatic events spontaneously evoked by the participants. If no such event was identified, participants were directed to state the most frightening event that they have experienced. The most severe trauma was then explored in the next 17 items, which correspond to specific symptoms. Appropriate for non-clinical community samples, this questionnaire allows the measurement of subsyndromic PTSD based on the cluster B of re-experiencing symptoms and records the age of the first traumatic event (Chaudieu et al., 2011).

### 2.4. Sociodemographic and clinical variables

The standardized interview included information on socio-demographic characteristics, physical health,

and medical history on cardiovascular ischaemic pathologies (angina pectoris, myocardial infarction, stroke, cardiovascular surgery, and arteritis). All drugs used in the preceding month were recorded from medical prescriptions and drug packaging. Weight and height were measured and body mass index was calculated and expressed as kg/m<sup>2</sup>. Global cognitive function was evaluated using the Mini-Mental State Examination, a score <26 indicating cognitive impairment (Folstein, Folstein, & McHugh, 1975). Lifetime major depression and anxiety disorder (phobia, generalized anxiety disorder, panic disorder or obsessive compulsive disorder) were diagnosed by psychologists and psychiatric nurses according to DSM-IV criteria and using the Mini-International Neuropsychiatric Interview (MINI, French version 5.00), a standardized psychiatric examination validated in the general population (Sheehan et al., 1998).

### 2.5. 5-HTTLPR genotyping

Blood samples were collected at baseline, enabling DNA extraction and 5-HTTLPR genotyping and data was validated using replicate independent genotyping of buccal DNA extracted from the same participants (Ancelin et al., 2019, 2017).

### 2.6. Statistical analysis

Brain volume measurements were normally distributed. Associations between brain regions and exposure to severe traumatic events were evaluated using ANCOVA adjusted for age, sex, total brain volume, and covariates which may modify the associations, e.g. lifetime major depression and anxiety disorder, head injury, and cardiovascular ischaemic pathologies. Given the frequent report of heterosis for 5-HTTLPR due to multiple sources of interacting effect (epistasis, sex, childhood adversity ...) (Ancelin & Ryan, 2018), the modifying effect of 5-HTTLPR was evaluated by stratification into three genotypes (*LL*, *SL*, and *SS*) as described (Ancelin et al., 2019, 2017). To account for the multiple brain regions examined, we adjusted the significance levels using the false discovery rate (FDR) method (Benjamini & Hochberg, 1995). All tests were 2-sided and SAS (v9.4, SAS Institute, Inc., North Carolina) was used for the statistical analyses.

## 3. Results

### 3.1. Participant characteristics

Baseline characteristics of the 377 community-dwelling participants are summarized in Table 1. Fifty-six percent reported having experienced trauma

according to DSM IV criteria during their life-time, at a median (IQR) age of 25 (17–46) years. Of the traumatized participants, 35.4% reported re-experiencing symptoms and severe enough to meet criteria for full threshold PTSD for 1.9%. Forty-five of the traumatized participants reported specific war-related traumas as the most prevalent traumatic event, 34% learning of the unexpected death or serious accident of a close relative, and 13% experiencing themselves a serious disease, an accident, or aggression (data not shown).

### 3.2. Subregional volumes according to lifetime trauma and re-experiencing symptoms

We examined GMV differences according to 5-HTTLPR in non-traumatized (NT), trauma-exposed controls without (TEC) and with re-experiencing (T + R). In the SS participants specifically, re-experiencing symptoms were associated with smaller volumes in the frontal (lateral orbital, rostral and caudal middle), parietal (precuneus, inferior and superior), and temporal (middle, superior) regions (Table 2). The T + R group had 7–11% smaller volumes compared to the control groups. The TEC participants generally did not significantly differ from the NT participants except for the precuneus and superior parietal region, which were smaller in traumatized participants irrespective of re-experiencing symptoms. A significant sex interaction was found for amygdala ( $p = 0.004$ ), with significantly larger volumes in TEC compared to NT or T + R in SS women only (global  $p$ -value = 0.001 compared to 0.095 in men). There were no significant associations according to traumatic experience in the participants with the *LL* and *SL* genotype (Supplementary Table S1). Similar results were found in the multivariate models further adjusted for antidepressant or anxiolytic medications (data not shown).

## 4. Discussion

In this non-clinical older community-dwelling population, lifetime traumatic experience was associated with many GMV abnormalities which were specific to the SS genotype. The most robust finding was observed with subregions in prefrontal cortex (PFC) (rostral and caudal middle frontal and lateral orbitofrontal), superior, inferior and medial (precuneus) parietal, as well as middle temporal cortex, whose volumes were smaller in the T + R SS participants. These findings were notably independent of psychiatric comorbidity and quite distinct from abnormalities associated with lifetime major depression recently reported in this Esprit population (Ancelin et al., 2019). This suggests a specific enduring effect of lifetime trauma on brain structure.

**Table 1.** Characteristics of the 377<sup>a</sup> community-dwelling participants according to trauma status<sup>b</sup>.

	No Trauma N = 165	Trauma without re-experiencing N = 137	Trauma with re-experiencing N = 75	p-value <sup>c</sup>
Median (IQR)				
Age, years	71 (68–73)	71 (68–74)	70 (68–74)	0.83
Body mass index, kg/m <sup>2</sup>	24.5 (22.5–26.7)	25.1 (22.7–27.4)	25.2 (22.6–27.2)	0.45
Cortex, cm <sup>3</sup>	360 (337–386)	362 (344–382)	355 (329–377)	0.10
Grey matter brain volume, cm <sup>3</sup>	458 (414–497)	469 (418–501)	453 (418–497)	0.61
Total brain volume, cm <sup>3</sup>	881 (812–964)	890 (830–960)	872 (815–942)	0.32
%				
Sex (male)	42.4%	56.2%	36.0%	0.008
Education level ( $\leq$ 5 years)	23.6%	20.4%	24.0%	0.76
Living alone	18.8%	16.2%	30.7%	0.04
Head injury	10.3%	12.4%	8.0%	0.60
Smoking				
Never	60.6%	43.1%	57.3%	0.04
Past	33.3%	48.9%	34.7%	
Current	6.1%	8.0%	8.0%	
Lifetime major depression <sup>d</sup>	24.9%	18.3%	49.3%	<0.0001
Lifetime anxiety disorder <sup>d</sup>	25.5%	20.4%	40.0%	0.008
Antidepressant or anxiolytic use	11.5%	10.2%	17.3%	0.30
Hypertension ( $\geq$ 140/90 or treatment)	68.5%	65.7%	74.7%	0.40
Cardiovascular ischaemic pathology <sup>e</sup>	10.9%	11.7%	13.3%	0.86
Diabetes <sup>f</sup>	6.1%	9.6%	4.0%	0.27
Cognitive impairment (MMSE score < 26)	13.9%	6.6%	14.7%	0.08
5-HTTLPR genotype <sup>g</sup>				
LL	24.2%	26.3%	33.3%	0.44
SL	47.9%	51.8%	41.3%	
SS	27.9%	21.9%	25.3%	

IQR = Interquartile range; MMSE = Mini-Mental State Examination.

<sup>a</sup>Except for age at first trauma (n = 29 missing data), body mass index (n = 4) and living status (n = 1).

<sup>b</sup>Severe lifetime traumatic events were assessed with Watson's PTSD Inventory according to DSM criteria (Watson et al., 1991).

<sup>c</sup>Kruskal–Wallis tests for continuous variables and Chi-square tests for categorical variables.

<sup>d</sup>Diagnosis of lifetime major depression or anxiety disorder (phobia, generalized anxiety disorder, panic disorder or obsessive compulsive disorder) according to DSM-IV criteria and using the MINI (Sheehan et al., 1998).

<sup>e</sup>History of cardiovascular ischaemic pathologies (angina pectoris, myocardial infarction, stroke, cardiovascular surgery, arteritis).

<sup>f</sup>Fasting glucose  $\geq$ 7.0 mmol/L or treatment.

<sup>g</sup>The 5-HTTLPR genotype frequency did not significantly deviate from Hardy–Weinberg equilibrium ( $p = 0.44$ ).

**Table 2.** Cortical ROI volumes<sup>a</sup> in SS homozygotes according to trauma diagnosis (n = 95)<sup>b</sup>.

	No Trauma (n = 46)		Trauma without re-experiencing (n = 30)		Trauma with re-experiencing (n = 19)		p <sup>c</sup>	FDR p <sup>d</sup>
	Mean	SD	Mean	SD	Mean	SD		
Superior frontal	35,608.69	670.31	35,031.00	684.06	33,776.99	825.56	0.074	0.148
Rostral middle frontal	24,731.60	508.29	24,513.95	518.71	22,904.02	626.01	0.011¶¶	0.038
Caudal middle frontal	9745.53	302.59	9134.41	308.79	8749.07	372.67	0.012¶	0.038
Lateral orbitofrontal	12,201.57	212.19	11,965.00	216.54	11,387.03	261.33	0.007¶¶	0.035
Medial orbitofrontal	9050.25	226.17	8896.26	230.81	8694.81	278.56	0.401	0.519
Rostral anterior cingulate	3465.00	141.35	3411.58	144.25	3216.83	174.09	0.334	0.459
Caudal anterior cingulate	2765.49	140.32	2974.57	143.20	2540.05	172.82	0.052	0.114
Posterior cingulate	4884.67	152.45	5033.24	155.57	4617.71	187.75	0.106	0.194
Superior parietal	21,279.62	470.18	20,042.26	479.82	19,877.51	579.08	0.008¶¶¶¶	0.035
Inferior parietal	21,503.36	538.44	21,433.94	549.48	19,524.34	663.15	0.007¶¶¶	0.035
Precuneus	15,433.95	300.58	14,669.04	306.75	14,371.43	370.20	0.004¶¶¶¶	0.035
Insula	11,757.67	256.25	11,852.16	261.50	11,618.16	315.60	0.772	0.815
Superior temporal	18,148.78	417.39	18,095.99	425.94	16,924.54	514.06	0.040¶	0.103
Middle temporal	17,410.96	421.98	17,872.64	430.63	16,110.41	519.71	0.005¶¶¶	0.035
Inferior temporal	16,861.70	488.48	16,683.67	498.49	16,290.45	601.61	0.613	0.710
Hippocampus	6915.95	147.23	7114.87	150.25	6893.62	181.33	0.329	0.459
Amygdala	2531.15	74.37	2686.82	75.89	2471.82	91.59	0.042	0.103
Thalamus	11,541.68	217.58	11,706.61	222.04	11,387.56	267.97	0.500	0.611
Caudate	6885.61	237.08	6908.00	241.94	6498.62	291.99	0.331	0.459
Nucleus accumbens	871.37	35.41	941.17	36.13	894.97	43.61	0.140	0.237
Putamen	9110.33	265.29	9110.09	270.73	9130.41	326.73	0.998	0.998
Pallidum	2796.16	89.81	2783.84	91.65	2861.30	110.61	0.778	0.815

SD = Standard Deviation; FDR = False Discovery Rate.

<sup>a</sup>Mean (SD) values expressed as mm<sup>3</sup>.

<sup>b</sup>Model adjusted for age, sex, total brain volume, head injury, lifetime major depression and anxiety disorder, and cardiovascular ischaemic pathologies.

<sup>c</sup>Global raw p-values when comparing no lifetime trauma (0), trauma without re-experiencing (1) and trauma with re-experiencing symptoms (2); significant 2 by 2 comparisons (Bonferroni-adjusted p-value, <0.05): ¶2 vs. 0, ¶¶2 vs. 0 and 2 vs. 1, ¶¶¶2 vs. 0 and 1 vs. 0.

<sup>d</sup>p-Values after FDR correction.

#### 4.1. 5-HTTLPR genotype

Imaging and experimental studies suggest increased 5-HT synthesis in multiple brain regions in PTSD, lower 5-HTT availability and correlations between 5-HTT and symptom severity (Davis et al., 2017). In addition, the S allele of *5-HTTLPR* is associated with decreased transcription efficiency and less 5-HTT production and subsequently to less 5-HT reuptake (Lesch et al., 1996). Despite accumulated evidence for altered serotonergic function in PTSD, an effect of *5-HTTLPR* polymorphisms on PTSD has, however, not been demonstrated, possibly due to study heterogeneity. This includes age, sex, study design (cohort vs. case-control), type and severity of trauma, blind assessment, ethnicity, PTSD diagnosis (current or lifetime), potential confounders and comorbidity, group comparability (healthy or trauma-exposed controls and use of same diagnostic instrument) as well as genetic models (Gressier et al., 2013; Navarro-Mateu et al., 2013). Two meta-analyses reported a significant increased risk with the SS genotype when analyses were restricted to cohorts (less biased than case-control studies), to participants without psychotic comorbidity (less diagnostic heterogeneity), or having experienced high trauma exposure or with current PTSD (Gressier et al., 2013; Navarro-Mateu et al., 2013). The S allele has also been associated with emotional learning processes in healthy volunteers and treatment issues in patients (Wilker et al., 2014). However, the link between PTSD and brain regions has not been reported according to *5-HTTLPR* vulnerability. Our data showing specific abnormalities in the T + R but not in the NT group further suggest that *5-HTTLPR* could be a vulnerability factor for re-experiencing rather than a plasticity gene affecting brain development.

#### 4.2. Trauma- vs. disease-related differences

Several studies have reported that stressful life events could have a substantial impact on brain function and structure, regardless of whether the criteria for a psychiatric disease were met (Li et al., 2014; Stark et al., 2015). Of the few studies having included both controls (NT and TEC), some reported differences in hippocampus, amygdala or ACC after severe external events or childhood abuse (Li et al., 2014). The structural characteristics of TEC and NT participants did not differ significantly except for the precuneus and superior parietal subregion. These regions were smaller in traumatized SS participants regardless of re-experiencing symptoms, suggesting a stress-related effect linked to the trauma. For other ROIs, smaller volumes were found in the T + R compared to TEC participants, more likely to be disease-related, as both groups have experienced traumatic events. Whether this could constitute a premorbid predisposition factor

for the development of re-experiencing or a marker of pathophysiology remains to be examined.

#### 4.3. Lifetime exposure to trauma and GMV alterations

Previous reports of morphological alterations associated with posttraumatic experience were mostly based on small case-control studies in young adults and focused on hippocampus, amygdala and certain PFC regions (Kuhn & Gallinat, 2013; Li et al., 2014; Logue et al., 2018; Meng et al., 2014; O'Doherty et al., 2015). Meta-analyses usually reported significantly smaller hippocampi in PTSD compared to TEC or NT individuals (by -1.5% in a recent ROI meta-analysis (Logue et al., 2018)). Findings on amygdala are inconsistent, showing smaller, larger or preserved volumes (O'Doherty et al., 2015; Pitman et al., 2012), possibly depending on type and age at trauma, comorbidity, sex, and genetic vulnerability (Logue et al., 2018). Larger amygdalae have been reported in TEC compared to NT or in children with PTSD (Morey, Haswell, Hooper, & De Bellis, 2016) and in adults without PTSD who experienced childhood adversity (Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014). Sex could modulate the effects of serotonergic polymorphisms implicated in the risk for emotional disorders and their interactions with environmental stress factors (Perry, Goldstein-Piekarski, & Williams, 2017). Larger amygdalae have been reported in SS women with subclinical anxiety (Cerasa et al., 2014). We found larger amygdalae in TEC compared to NT and T + R women, even after controlling for depression and anxiety comorbidity but the small number of SS re-experiencing women ( $n = 14$ ) precluded drawing a definite conclusion. Increased amygdala volume and hyper-responsivity to emotional stimuli have been associated with fear expression and fear inhibition (Admon et al., 2013). Whether our finding may reflect sex difference in vulnerability (or resilience) to psychopathology upon stress remains to be explored.

The effects of severe or repeated stress at different stages in life could depend on the brain areas that are developing at the time of the exposure. The hippocampus is most vulnerable before 2 years of age, the amygdala continues to develop from birth to late childhood, whereas PFC and precuneus are among the last regions to mature (Cavanna & Trimble, 2006; Lupien, McEwen, Gunnar, & Heim, 2009). In our sample, the median age at first trauma was 25 years, which may explain why we found abnormalities in prefrontal but not hippocampal volume. Hippocampal normalization after recovery from traumatic experience could, however, not be excluded (Thomaes et al., 2014).

We found multiple abnormalities in the PFC, an area known to be rich in serotonergic neurons; volumes of rostral and caudal middle frontal, lateral orbitofrontal, and caudal ACC were smaller in SS

participants with lifetime re-experiencing compared to non-traumatized participants. Smaller volumes in some PFC regions have been reported in one ROI (O'Doherty et al., 2015) and three VBM meta-analyses (Kuhn & Gallinat, 2013; Li et al., 2014; Meng et al., 2014) focused on PTSD in young adults with some differences, depending on age, trauma and clinical characteristics (Li et al., 2014; Meng et al., 2014). Abnormalities in dorsal ACC were suggested to be a predisposing factor for hyperarousal and ventromedial PFC, a consequence of re-experiencing and avoidance symptoms (Admon et al., 2013). Our data in a non-clinical elderly population suggest long-lasting effects in several PFC regions specifically in SS homozygous with re-experiencing symptoms.

Two VBM meta-analyses have reported smaller middle temporal gyrus in PTSD compared to TEC subjects (Kuhn & Gallinat, 2013; Li et al., 2014), and this has also been associated with greater re-experiencing scores in 28 PTSD outpatients (Kroes et al., 2011). Smaller superior temporal cortex has been observed in veterans with current PTSD compared to TEC veterans (Woodward, Schaer, Kaloupek, Cediell, & Eliez, 2009). We found smaller middle temporal volumes in T + R compared to TEC participants and NT as well as a nominal association with superior temporal cortex and this was specific to SS participants.

Additional original findings were those for parietal cortex volumes, which were smaller in SS participants with lifetime re-experiencing compared to non-traumatized participants. Structural abnormalities in parietal volumes have rarely been examined in PTSD and the lack of significant association may depend on the selection of controls, especially if T + R are compared to TEC. Smaller inferior parietal volume has been reported in two case-control studies ( $\leq 30$  current PTSD) compared to NT controls (Cheng et al., 2015; Eckart et al., 2011), and this appeared to be specific following comparisons with obsessive compulsive and social anxiety disorders (Cheng et al., 2015). Comparison of PTSD patients who experienced flashback/reliving/hyperarousal responses with dissociative patients shows a greater activation in the inferior parietal lobule in the former group and in the superior parietal lobule in the latter one (Lanius et al., 2006). Precuneus abnormalities have been associated with social anxiety disorder and avoidance behaviour in healthy subjects (Irle, Barke, Lange, & Ruhleder, 2014). Whether smaller parietal volumes may be shared with other symptom cluster or constitute a common transnosographic feature to stress-related disorder remains to be examined.

#### 4.4. Context of the findings

Our study in a non-clinical population revealed multiple traumatic stress-related morphological alterations in

the prefrontal, temporal and parietal cortex, consistent with neuroimaging studies of current PTSD (Kuhn & Gallinat, 2013; Pitman et al., 2012; Yehuda et al., 2015) and further indicate that these regions remain structurally smaller in SS older adults several decades after trauma. The GM profile associated with re-experiencing overlaps with brain networks of emotional processing and regulation, memory, and fear (Admon et al., 2013; Etkin & Wager, 2007; Hayes, Hayes, & Mikedis, 2012; Shin & Liberzon, 2010). A causal model of PTSD has been proposed (Admon et al., 2013), in which smaller ventromedial PFC volume and connectivity with the hippocampus represent neural abnormalities that, if acquired following stress exposure, may lead to impaired fear inhibition and, thus to PTSD susceptibility due to re-experiencing and avoidance symptoms. The manipulation of highly emotional memories in the aftermath of traumatic experiences not only relies on the interplay between medial temporal and prefrontal cortices, but also on the 'parietal memory network' involved in multiple stages of mnemonic processing during both initial encoding and later retrieval (Gilmore et al., 2015). Medial temporal allocentric (context-dependent) representations were suggested to be used in long-term storage, and parietal egocentric (person-dependent) representations to imagine, manipulate and re-experience the products of retrieval (Vann, Aggleton, & Maguire, 2009). The precuneus has been implicated in imagery and visualization of visuo-spatial information in perception and memory, familiarity, and self-representation (Summerfield, Hassabis, & Maguire, 2009). Disturbances in these networks might explain some of the memory disturbances associated with PTSD, such as the fragmentation of traumatic memories (Brewin, 2001), the generally less detailed retrieval of autobiographical memories or the high occurrence of recurrent, intrusive recollection of traumatic memories (Eckart et al., 2011).

#### 4.5. Limitations and strength

Due to the cross-sectional design of the study, we could not ascertain whether GMV abnormalities may be a consequence or a predisposing/pre-existing vulnerability factor to re-experiencing expression. The retrospective report of a traumatic experience may introduce recall bias and lead to an underestimation of the associations, although we have excluded participants with probable/possible dementia to minimize inaccuracies. Re-Experiencing was assessed from the worst traumatic exposure, we did not collect information on the number of lifetime traumatic events and could not study the impact of cumulated burden of lifetime trauma. We have no information on the duration of traumatic exposure and symptoms. Current symptomatology could not be examined due to the low prevalence in this

community sample and it is possible that the lack of significant association with some ROIs could be related to normalization after recovery or remission. This study focused on re-experiencing symptoms in a non-clinical sample, which may limit the generalizability to PTSD patients. Further studies are needed to replicate our data in younger population samples. Finally, multiple analyses have been performed increasing the risk of type 1 error, although we have attempted to minimize this by correcting for multiple comparisons using FDR.

This is the largest structural MRI study targeting lifetime trauma and re-experiencing, in terms of the number of participants and ROIs examined within a single study and the first one to consider 5-HTTLPR. Lifetime PTSD diagnosis as well as major depression and anxiety disorder were assessed by trained staff using validated questionnaires based on DSM criteria and information on trauma was collected through a clinical interview. We adjusted for numerous potential confounders and controlled for genotyping accuracy. Finally, we have distinguished the effects of trauma exposure from those of symptom expression.

## 5. Conclusions

This study allowed a better understanding of the neurobiological underpinnings of PTSD re-experiencing and brain response to trauma in a non-clinical sample. The structural correlates reported in this study may constitute useful imaging phenotypes of re-experiencing symptoms, and possibly PTSD or resilience. Further large studies are required to evaluate the specific impact of other symptoms clusters or neural features, which may be common to other stress-related disorder. Knowledge of genetic and environmental architecture of PTSD symptomatology could advance our understanding of the pathophysiology of the disorder. This may help in the identification of reliable structural biomarkers that could be used in prognosis, diagnosis or to better inform treatment development and possibly improve personalized medicine with existing treatments.

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No potential conflict of interest was reported by the authors.

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