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Research paper

Macro- and microstructural gray matter alterations in sexually assaulted women

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ABSTRACT

Background: Studies with trauma survivors documented structural alterations in brain regions involved in posttraumatic stress disorder (PTSD) neurocircuitry. Nonetheless, whether such alterations exist in women who were sexually assaulted in adulthood is not clear. We investigated the macro- and microstructure of key regions implicated in PTSD pathophysiology, namely the amygdala, hippocampus, anterior cingulate cortex (ACC), and insula, in this population.

Methods: Thirty-eight sexually assaulted women (PTSD, $n = 25$; non-PTSD, $n = 13$) and 24 non-exposed controls (NEC) were studied with T1- and diffusion-weighted MRI. Gray matter volume, mean diffusivity (MD), and fractional anisotropy (FA) were calculated for each region. Between-group comparisons and correlations with PTSD symptom severity were performed.

Results: Volumetric analyses revealed lower amygdala and insula volumes in the PTSD compared with the non-PTSD group. In contrast, altered microstructure was observed in both traumatized groups compared with NEC, including higher MD and lower FA in the right amygdala, and higher FA in the ACC bilaterally. Finally, the non-PTSD group had higher FA in the right insula compared with the PTSD group. PTSD symptom severity was correlated with amygdala and insula volumes, as well as with hippocampal FA and MD.

Limitations: Sample size may have led to reduced statistical power.

Conclusions: Sexual assault and the development of PTSD in women are linked with structural alterations in key regions implicated in PTSD following other trauma types (e.g., combat), though hippocampal and ACC volumes were preserved. Further studies are needed to disentangle the unique contribution of trauma type and of sex/gender to these observations.

1. Introduction

Over the past few decades, numerous magnetic resonance imaging (MRI) investigations have characterized brain alterations in traumatized individuals (for review see, Kolassa and Elbert, 2007; Stark et al., 2015). Studies of individuals who developed posttraumatic stress disorder (PTSD) following combat exposure or other types of trauma experienced in adulthood have repeatedly documented neuroanatomical abnormalities, most consistently in the amygdala, the medial prefrontal cortex including the anterior cingulate cortex (ACC), the hippocampus, and, more recently, the insula (Baldaçara et al., 2014; Bremner et al., 1995; Chen et al., 2006, 2012; Depue et al., 2014; Gurvits et al., 1996; Herringa et al., 2012; Kasai et al., 2008; Levy-Gigi et al., 2013; Lindauer et al., 2005; Luo et al., 2016; Morey et al., 2012; Mueller et al., 2015; O'Doherty et al., 2017; Wignall et al., 2004; Winter and Irle, 2004; Woodward et al., 2013; Yamasue et al., 2003; Zhang et al., 2011, 2014). PTSD-related structural aberrations in the hippocampus, amygdala, and anterior cingulate and orbitofrontal cortices have also been reported in individuals who suffered childhood trauma, including sexual abuse (CSA, Aghajani et al., 2016; Bremner et al., 1997, 2003; Rinne-Albers et al., 2017; Stein et al., 1997; Thomaes et al., 2010; Vermetten et al., 2006; Weniger et al., 2008). Using positron emission tomography and functional MRI, functional aberrations have been consistently observed in these key regions, including hyper-responsivity of the amygdala and the insular cortex, hypo-responsivity of the top-down regulatory regions in the ACC, and a deficiency in hippocampus

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activation (e.g., Bremner et al., 1999; Bruce et al., 2013; Shin et al., 2004).

Interestingly, although meta-analyses of volumetric abnormalities in PTSD have confirmed its association with volume reductions in the key structures mentioned above (Karl et al., 2006; Kühn and Gallinat, 2013; Meng et al., 2014; O'Doherty et al., 2015), several studies have failed to find gray matter alterations in female and gender-mixed samples of CSA survivors, as well as in female survivors of a related condition, namely, intimate partner violence, whether with or without PTSD (Bremner et al., 1997; De Bellis et al., 2001; Fennema-Notestine et al., 2002; Flegar et al., 2011; Landré et al., 2010; Pederson et al., 2004). Consequently, suggestions have been raised that females with intimate partner violence/CSA-related PTSD may be less prone to macrostructural gray matter alterations (Landré et al., 2010), and, more specifically, that stress may have weaker effects on the female hippocampus (Karl et al., 2006; Teicher and Samson, 2016).

Sexual assault during adulthood is a common interpersonal trauma, reported by 22% to 27% of women in the United States (Elliott et al., 2004; Koss et al., 1991), and a major risk factor for mental health disorders (Black et al., 2011; Kilpatrick et al., 2007; for review see Dworkin et al., 2017). Although among the different types of trauma, sexual assault is associated with the highest rates of PTSD symptoms (Moor and Farchi, 2011), little research examined the neuroanatomical consequences of sexual assault in adulthood. In fact, to the best of our knowledge, only one study to date has assessed the structural brain alterations in survivors of adulthood sexual assault. Using a whole-brain approach, this study reported reduced gray matter in several anatomical regions among sexually assaulted women with PTSD, but surprisingly did not show alterations in the hippocampus, amygdala, ACC, and/or insula (Sui et al., 2010).

While the commonly used volumetric measures provide information on abnormalities in gross brain structure (Mechelli et al., 2005), advances in diffusion tensor imaging (DTI) provide a method for detecting differences in microscopic properties (Alexander et al., 2007) of white and gray matter (e.g., Bozzali et al., 2002; Caverzasi et al., 2014; Cavallari et al., 2014; Ciccarellu et al., 2001; Hasan et al., 2011; Whitwell et al., 2010). Studies employing DTI commonly use fractional anisotropy (FA), a measure of the directionality of diffusion which reflects myelination and axonal density, and mean diffusivity (MD), which measures general diffusion of water molecules. Recently, several studies have used DTI to explore gray matter microstructural abnormalities in humans with PTSD and in a PTSD mouse model (Ding et al., 2013; Lei et al., 2015; Waltzman et al., 2017), revealing MD and FA alterations in the insula, amygdala, hippocampus, and ACC, alongside alterations in diffusion indices in other subcortical, parietal and frontal regions. In light of the suggestions that females may be less vulnerable to stress- and/or PTSD-related structural alterations, it may be hypothesized that the use of DTI could aid in detecting subtle alterations associated with these conditions in a more sensitive manner.

The aim of the present study was to assess the macro- and microstructural properties of gray matter in four PTSD-related key structures (amygdala, hippocampus, ACC, and insula) in survivors of sexual assault in adulthood, with and without PTSD and to compare them to non-exposed controls. Given previous findings from related populations (i.e., individuals who suffered CSA, or other types of trauma experienced in adulthood), we hypothesized that lower volume and altered microstructure will be observed in these structures in the PTSD group and possibly also in the trauma-exposed non-PTSD group. We also hypothesized that among the sexually assaulted participants, these regions' macro- and microstructure would be correlated with PTSD symptom severity.

2. Methods

2.1. Participants

Sixty-eight women were recruited for participation in the study: 38 survivors of adult sexual assault and 30 non-exposed controls (NEC), which were matched to the sexually assaulted participants for age, education, and handedness. Participants were recruited via advertisements in social media and in the Tel Aviv Rape Crisis Center. Trauma-exposed individuals were included in the study if they experienced sexual assault(s) in the past three years and after the age of eighteen. Participants who also experienced CSA were not excluded, given that CSA histories are highly common among survivors of adult sexual assault (e.g., Elliot et al., 2004). Exclusion criteria for both groups included MRI contraindications, a history of neurological disorder or any pervasive developmental disorder, head injury, fibromyalgia, any significant physical condition that is not being treated, and a frequent use of alcohol during the past six months. Additional exclusion criteria for the NEC group were current or past anxiety, mood, or psychotic disorders, and exposure to potentially traumatic events (including but not limited to sexual assault), which the participants perceived to be significant. Exposure to potentially traumatic events was assessed with the Childhood Trauma Questionnaire (Bernstein and Fink, 1998) and a modified version of the Life Events Checklist (Gray et al., 2004), revised to also address events which are relatively common to Israeli residents (e.g., exposure to rocket attacks). Some of the participants indicated that they have experienced some of these potentially traumatic events, but did not consider them as significant. These participants were therefore not excluded from analysis. Four NEC participants had above-cutoff scores in the PTSD Checklist, and thus were excluded from analyses. Following the exclusion of two additional NEC participants due to neurological abnormalities discovered after scanning, the final sample included 38 Sexual Assault and 24 NEC participants. Among these, two participants from the Sexual Assault group were excluded from the microstructural analyses due to severe artifacts in their DTI images. One participant from each Sexual Assault and NEC groups had ADHD. The use of psychotropic medications was reported by seven participants in the Sexual Assault group and one in the NEC group. Use of the following medications was reported: Sertraline, Clonazepam, Duloxetine, Citalopram, Escitalopram, and Methylphenidate. Among the Sexual Assault participants, mean time since last assault was 18.29 months (SD: 10.04, range: 2–36). Twenty-five participants (66%) in the Sexual Assault group scored above the probable PTSD diagnostic cutoff and were included in the PTSD group. The remaining 13 participants consisted of the trauma-exposed non-PTSD (TENP) group. All participants were provided with full details about the study and gave informed written consent prior to enrollment. Upon completion, participants were debriefed, thanked and compensated for their time. The study was approved by the Sheba hospital Helsinki committee and the Tel Aviv University ethical board.

2.2. Measures

Posttraumatic stress symptoms were assessed with the PTSD Checklist (PCL-5; Weathers et al., 2013), a widely used self-report measure with good psychometric properties (e.g., Bovin et al., 2016; Keane et al., 2014). Participants from the Sexual Assault group were instructed to fill out the questionnaire with regard to their most recent experience of sexual assault, while NEC participants were instructed to fill it out with regard to a self-chosen difficult event, which they have experienced sometime along their lives. Probable PTSD was determined according to a PCL-5 cutoff score of 31, which is in agreement with a cutoff score of 44 in the PCL-Specific for DSM-IV (Weathers et al., 1993). A cutoff score of 44 in the PCL-Specific is the recommended cutoff for use with female civilian sample (Blanchard et al., 1996; Hoge et al., 2014). A cutoff score of 31 in the PCL-5 was found most

efficient for diagnosing PTSD in correspondence to diagnoses made with the Clinician-Administered PTSD Scale (Bovin et al., 2016). Depressive symptoms were assessed with the commonly used Patient Health Questionnaire – depression module (PHQ-9; Kroenke et al., 2001). The Childhood Trauma Questionnaire (CTQ; Bernstein and Fink, 1998) was used to retrospectively assess the total frequency of traumatic experiences in childhood, including sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect. Questionnaires were administered in their Hebrew versions, which have been found reliable and are extensively used (e.g., Besser and Neria, 2010; Shrira et al., 2016; Somer and Herscu, 2017).

2.3. Image acquisition and preprocessing

A 3 T Magnetom Prisma scanner (Siemens, Germany) equipped with a 64-channel head coil was used. T1-weighted images were acquired in the axial plane using a 3 D magnetization-prepared rapid gradient-echo sequence with the following parameters: TR = 2530 ms; TE = 2.88 ms; TI = 1100 ms; flip angle = 7°; matrix size = 224 x 224; voxel size = 1 x 1 x 1 mm^3; iPAT = 2. Diffusion-weighted images were acquired with spin-echo echoplanar imaging with the following parameters: 75 interleaved axial slices, no gaps; matrix size = 132 x 132; FOV = 224 x 224 mm^2; TR = 7000 ms; TE = 54 ms; voxel size = 1.7 x 1.7 x 1.7 mm^3; iPAT = 2. Diffusion gradients were applied along 64 noncollinear directions using a *b*-value of 1000s/mm^2. Three additional sets of images with no diffusion encoding ($b = 0$) were acquired.

In order to estimate macroscopic regional tissue alterations, voxel based morphometry (VBM, Ashburner and Friston, 2000) was performed with SPM8 (Wellcome Department of Cognitive Neurology, London, UK) and MATLAB 2013b (MathWorks, Natick, MA, USA), using the optimized VBM protocol (Good et al., 2001). Preprocessing included a segmentation of images into gray matter, white matter and cerebrospinal fluid, a high-dimensional DARTEL spatial normalization to Montreal Neurological Institute (MNI) space and modulation for the non-linear components only, allowing for the analysis of gray matter volume (GMV) corrected for individual brain size. Prior to smoothing, a quality check was performed to examine for any artifacts in the normalization procedure. Lastly, images were smoothed with a 8 mm Gaussian kernel. Volumetric analyses were performed using the resulting preprocessed gray matter maps.

For the assessment of microstructural tissue abnormalities, diffusion weighted images were preprocessed using ExploreDTI v4.8.6. (Leemans et al., 2009). Images were regularized and corrected for eddy currents and echo planar imaging distortions and participant motion utilizing the participant's high-resolution T1-weighted image. Next, the diffusion orientation was estimated in each voxel, and FA, MD and mean diffusion-weighted images (DWIs) maps were extracted from diffusion images.

Analyses were conducted on four pre-selected regions of interest (ROIs), bilaterally: amygdala, hippocampus, insula and ACC[1] (Fig. 1). For all types of analyses, the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) was used to map whole brain voxels into 116 regions, including the ROIs. For volumetric analysis, an in-house MATLAB script was used to overlay the atlas on participants' normalized gray matter maps, and to extract mean GMV for each ROI for each participant. For diffusion metrics analysis, mean FA and MD values for each ROI were extracted from each participant's native space maps, in order to avoid normalization-induced distortions to the diffusion maps. To this aim, the AAL atlas was warped individually for each participant, using her mean DWIs as the reference image. Next, gray matter binary masks were constructed in each participant's native space using her gray matter map created during the T1-weighted image preprocessing and the warped atlas. These masks were used in the in-house MATLAB script to extract mean gray matter FA and MD values for each ROI for each participant. Each ROI's GMV, FA and MD values for each participant were exported to SPSS.

[1] Using the AAL atlas nomenclature, the term "ACC" refers to the rostral parts of the anterior cingulate cortex.

2.4. Statistical analyses

Demographic and psychological measures were compared between the Sexual Assault and NEC groups as well between the Sexual Assault PTSD and TENP subgroups using Student's t-tests for continuous variables and chi-square tests for categorical variables, performed with SPSS v20 (IBM Corp., Armonk, NY, USA). These analyses were considered significant at a false discovery rate (FDR)-corrected threshold of $p < .05$, and reported p-values in the text are FDR-corrected unless otherwise specified. One-way ANCOVAs were used to assess differences between PTSD, TENP and NEC in ROIs' structural indices. In order to rule out the possible effects of childhood trauma and age on between-group differences, CTQ and age were used as covariates of no interest. In the analysis of between-group differences in ROIs' GMV, total intracranial volume (ICV) was used as an additional covariate. Significant between-group differences ($p < .05$) were further analyzed with Sidak post-hoc tests.

In addition, in order to assess the relationship of each ROI's structural characteristics with PTSD symptom severity, partial correlations were calculated in SPSS between each ROI's structural measures and PCL total score across the Sexual Assault group, with CTQ and age as covariates of no interest. In the analyses involving ROIs' GMV, ICV was used as an additional covariate.

3. Results

There were no group differences in demographic variables between the Sexual Assault and NEC groups, as well as between the PTSD and TENP subgroups (Table 1). In addition, the PTSD and TENP groups did not differ in months since last assault (PTSD, $M = 18.7$, $SD = 10.0$; TENP, $M = 17.5$, $SD = 10.5$; $t_{36} = 0.362$, $p = .719$). As expected, higher levels of total PTSD symptoms and all PTSD subscales, as well as depression symptoms, were reported in the Sexual Assault compared with the NEC groups ($p's < 0.00001$), as well as in the PTSD compared with the TENP subgroups ($p's < 0.003$). Exposure to childhood trauma was higher in both the PTSD and TENP groups compared with NEC ($p's < 0.00001$), with no difference between the two sexually assaulted subgroups ($p = .677$).

3.1. Gray matter macrostructure

Significant between-group differences in GMV were found in the right amygdala ($F_{2,56} = 7.80$, $p = .001$) and left insula ($F_{2,56} = 3.94$, $p = .050$) (Fig. 2A, Table 2). Post hoc pairwise comparisons showed that the PTSD group had lower GMV in these structures compared with the TENP group ($p = .001$ and $p = .021$, respectively), with the NEC group not being different from any of these groups. No significant differences were observed for GMV in the left amygdala, right insula, and the hippocampus and ACC bilaterally ($p's > 0.099$).

3.2. Gray matter microstructure

One way ANCOVAs revealed a significant between-group difference in MD in the right amygdala ($F_{2,55} = 6.96$, $p = .002$) (Fig. 2B, Table 2). Post hoc pairwise comparisons showed that both the PTSD and TENP groups had higher MD compared with NEC ($p = .002$ and $p = .030$, respectively), with no difference between the sexually assaulted subgroups ($p = .835$). No between-group differences were found in mean MD of all other ROIs ($p's > 0.196$).

FA significantly differed between the groups in the right amygdala ($F_{2,55} = 8.95$, $p < .001$) and in the bilateral ACC (left ACC:

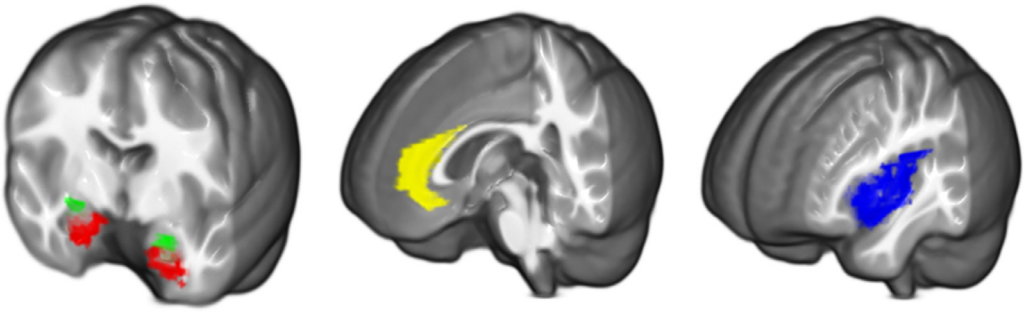

Fig. 1. Study ROIs (green: amygdala, red: hippocampus, yellow: anterior cingulate cortex, blue: insula), overlaid on the study T1 template.

Table 1
Demographic and psychological characteristics of the sample.

Measures	Sexual Assault (n = 38)	NEC (n = 24)	p	PTSD (n = 25)	TENP (n = 13)	p
Age, years	25.31 ± 4.46	25.06 ± 4.01	.826	24.72 ± 3.89	26.42 ± 5.39	.271
Handedness						
Left	9 (24%)	6 (25%)	.906	8 (32%)	1 (8%)	.095
Income						
Below median	28 (74%)	19 (79%)		19 (76%)	9 (69%)	
Similar to median	7 (18%)	3 (13%)	.749	4 (16%)	3 (23%)	.784
Above median	2 (5%)	2 (8%)		1 (4%)	1 (8%)	
Education						
High school	9 (24%)	5 (20%)		7 (28%)	2 (15%)	
Some academic	16 (42%)	12 (50%)	.757	11 (44%)	5 (39%)	.534
B.A.	10 (26%)	4 (17%)		6 (24%)	4 (31%)	
M.A. or above	3 (8%)	3 (13%)		1 (4%)	2 (15%)	
PCL Total	37.11 ± 17.56	8.29 ± 7.08	< **0.0001**	46.96 ± 12.03	18.15 ± 8.39	< **0.0001**
Intrusion	8.92 ± 4.98	1.88 ± 2.31	< **0.0001**	11.00 ± 4.05	4.92 ± 4.17	< **0.001**
Avoidance	4.68 ± 2.37	1.58 ± 1.98	< **0.0001**	5.56 ± 1.69	3.00 ± 2.65	< **0.001**
Negative Alterations in Cognitions and Mood	12.5 ± 7.11	3.04 ± 2.76	< **0.0001**	16.44 ± 5.25	4.92 ± 2.50	< **0.0001**
Alterations in Arousal and Reactivity	11.00 ± 6.69	1.79 ± 2.21	< **0.0001**	13.96 ± 6.11	5.31 ± 3.20	< **0.0001**
PHQ-9	12.32 ± 6.87	3.57 ± 3.23	< **0.0001**	15.44 ± 5.46	6.31 ± 5.15	< **0.0001**
CTQ	63.82 ± 23.10	40.25 ± 11.16	< **0.0001**	67.36 ± 24.23	57.00 ± 19.86	.097

CTQ: Childhood Trauma Questionnaire; PCL: PTSD Checklist; PHQ-9: Patient Health Questionnaire – depression module. Uncorrected p-values are displayed, FDR-corrected $p < .05$ are marked in bold.

$F_{2,55} = 6.61$, $p = .008$; right ACC: $F_{2,55} = 6.77$, $p = .005$) (Fig. 2C, Table 2). Post hoc pairwise comparisons revealed that compared with NEC, both the PTSD and TENP groups had lower FA in the right amygdala ($p = .006$ and $p = .001$, respectively) and higher FA in the left and right ACC (left ACC: $p = .005$ and $p = .013$, respectively; right ACC: $p = .008$ and $p = .006$, respectively), with no difference between the sexually assaulted subgroups. In contrast, the TENP group displayed higher FA in the right insula in comparison with the PTSD group and at a trend-level, also compared with the NEC ($F_{2,55} = 4.85$, $p = .046$, post hoc pairwise comparisons: $p = .013$ and $p = .058$, respectively). No between-group differences were found in mean FA of the left amygdala, left insula and bilateral hippocampus (p's > 0.084).

3.3. Correlations of ROIs macro- and microstructure with ptsd severity

Among the trauma-exposed participants, PTSD severity was negatively correlated with GMV of the bilateral amygdala (right: $r = -0.47$, $p = .005$, left: $r = -0.39$, $p = .040$) and insula (right: $r = -0.56$, $p < .001$, left: $r = -0.42$, $p = .018$) (Fig. 3, Table 3). PTSD severity also showed a negative correlation with FA and a positive correlation with MD of the left hippocampus ($r = -0.32$, $p = .032$ and $r = 0.34$, $p = .026$, respectively). No other significant correlations were observed between ROIs' macro- and micro-structure and PTSD severity (p's > 0.090).

3.4. Assessment of potential confounders

To assess the possible confounding effect of left-handedness, psychotropic medication use, time since assault, and therapy, we repeated our analyses controlling for each of these variables. While the addition of handedness as a covariate did not alter any of the results, adding medication use reduced the previously significant findings of higher left insula GMV and right insular FA among the TENP group compared with the PTSD group to a trend level ($F_{2,55} = 3.67$, $p = .064$ and $F_{2,54} = 4.34$, $p = .072$, respectively). To assess the possible confounding effect of time since assault and therapy, we compared the PTSD and TENP groups with and without these variables as covariates (the NEC group was not included in these analyses because time since assault and therapy are not applicable for this group). In both cases, the comparisons between the PTSD and TENP groups yielded similar results, whether with or without the addition of the covariate. Moreover, these results were identical to the ones reported above (i.e., when the NEC were included), with the only exception that a difference in the right insular GMV, which in the 3-groups design did not survive FDR correction, has now became significant, indicating lower GMV in the PTSD group compared with the TENP group (all p's < 0.05)

4. Discussion

This is the first study to examine whether there are alterations in the macro- and micro-structure of key structures of the PTSD neurocircuitry in survivors of sexual assault in adulthood. The main findings are: lower volume of the amygdala and insula in the PTSD group compared with the TENP group, with the NEC group in-between the two Sexual Assault groups; differences in microstructure in both traumatized groups compared with NEC, including higher MD and lower FA in the right

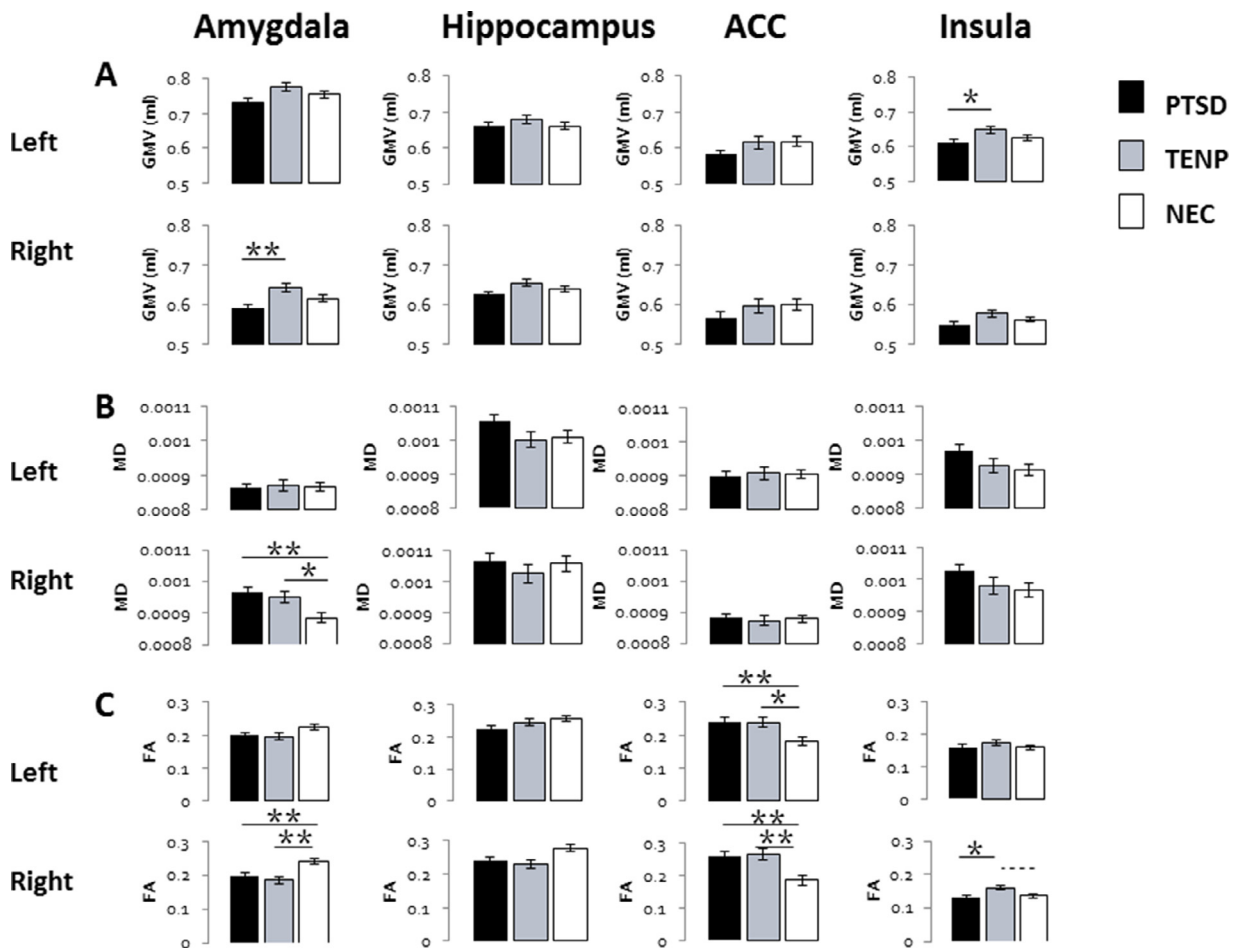

Fig. 2. Between-group comparisons of gray matter macro- and microstructure of study's ROIs. Between-group comparison of ROIs' (A) mean GMV, (B) mean MD, and (C) mean FA. *$p < 0.05$. **$p < 0.01$, FDR-corrected. ACC: anterior cingulate cortex; FA: fractional anisotropy; GMV: gray matter volume; MD: mean diffusivity.

Table 2
Comparison of ROIs' macro- and microstructure between the PTSD, TENP, and NEC groups.

	Amyg R		Amyg L		Hippo R		Hippo L		ACC R		ACC L		Insula R		Insula L	
	F	*p*	F	*p*	F	*p*	F	*p*	F	*p*	F	*p*	F	*p*	F	*p*
GMV	7.80	.001**	3.48	.038	2.98	.059	1.01	.372	1.55	.221	1.84	.168	3.63	.033	3.94	.025*
MD	6.96	.002**	0.55	.946	.055	.582	2.35	.105	0.15	.861	.078	.926	1.81	.173	2.43	.098
FA	8.95	<0.001***	2.16	.126	4.41	.017	2.86	.066	6.77	.002**	6.61	.003**	4.85	.012*	0.85	.434

Controlling for childhood trauma and age, and, in GMV ANCOVAs, also for total intracranial volume. Uncorrected p-values are displayed, FDR-corrected *p*'s < 0.05 are marked. * < 0.05, ** < 0.01, *** < 0.001. ACC: anterior cingulate cortex; FA: fractional anisotropy; GMV: gray matter volume; MD: mean diffusivity.

amygdala, and higher FA in the ACC bilaterally; higher FA in the right insula in the TENP compared with the PTSD group, and a tendency towards higher FA in this region in the TENP group also compared with the NEC; and correlations of the severity of PTSD symptoms with GMV of the amygdala and insula, as well as with hippocampal FA and MD.

The present findings are in line with previous studies reporting smaller amygdala and insula volumes in PTSD (Chen et al., 2006; Herringa et al., 2012; Morey et al., 2012, 2016; Mueller et al., 2015; O'Doherty et al., 2017; Rogers et al., 2009), and correlations of these structures' GMV with PTSD symptom severity (Akiki et al., 2017; Herringa et al., 2012; O'Doherty et al., 2017; Pietrzak et al., 2015; Rogers et al., 2009). They are also consistent with previous DTI studies that found FA increase in the anterior cingulum, subjacent to the ACC gray matter, in individuals with PTSD due to terrorism (Abe et al., 2006), and changes in amygdala FA (an increase followed by a decrease) and an increase in FA of the cingulate gyrus in a fear conditioning mouse experimental model of PTSD (Ding et al., 2013).

In contrast to many previous studies (Baldaçara et al., 2014; Bremner et al., 2003; Chen et al., 2012; Gurvits et al., 1996; Herringa et al., 2012; Mueller et al., 2015; Mutluer et al., 2017; O'Doherty et al., 2017; Rinne-Albers et al., 2017; Thomaes et al., 2010) we did not observe smaller hippocampal and ACC volumes in the PTSD group, nor a correlation between hippocampal GMV and PTSD symptoms, which was reported in traumatized men (e.g., Akiki et al., 2017; Gilbertson et al., 2002; Gurvits et al., 1996). Although it is possible that for both ACC and hippocampus GMV the present study was underpowered to detect between-group differences, our observations are consistent with previous studies in women with PTSD, which did not observe lower hippocampal volume or a correlation between hippocampal volume and PTSD symptoms (Akiki et al., 2017; Fennema-Notestine et al., 2002; Flegar et al., 2011; Landré et al., 2010). Our findings are thus in line with the hypothesis that women, or alternatively individuals with CSA- or interpersonal violence-related PTSD, may be less prone to stress-related macrostructural atrophy, especially

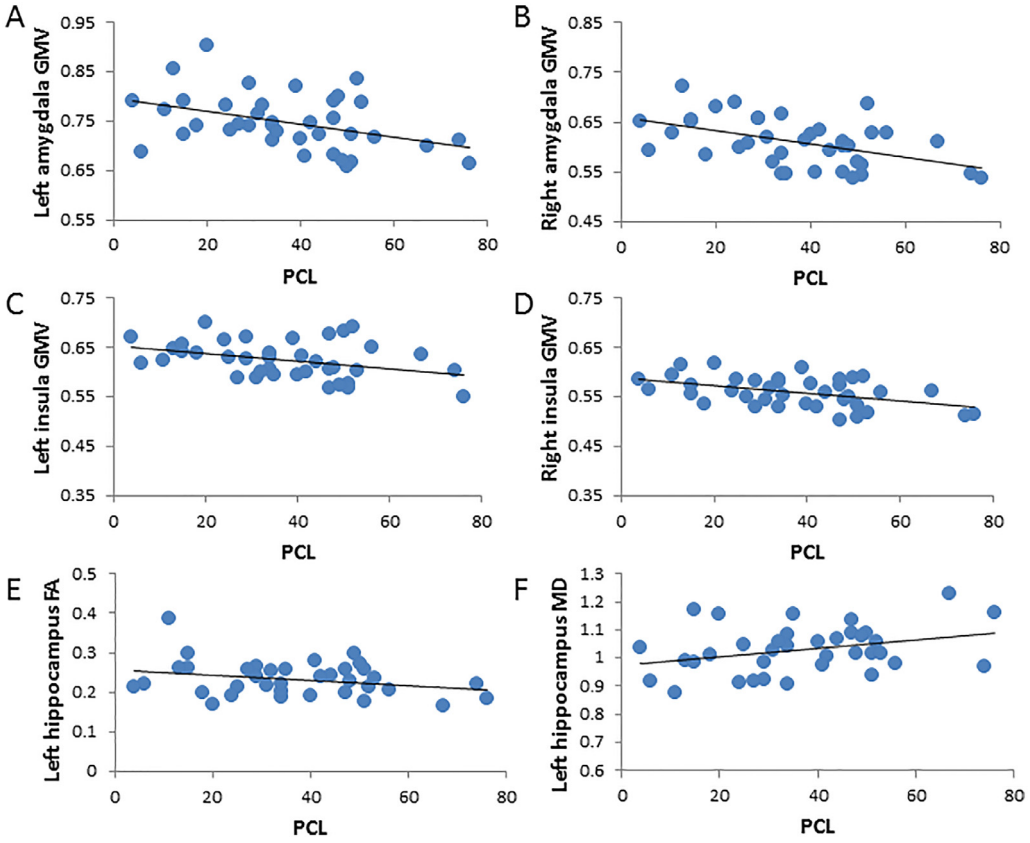

Fig. 3. Correlational analysis between ROIs' macro- and microstructure and PCL scores in the sexually assaulted participants. Mean GMV (A-D), FA (E), and MD (F) in ROIs extracted for each participant plotted against PCL scores, for significant correlations (corrected *p*'s < 0.05). MD values are presented as $mm^2/s \times 10-3$.

in the hippocampus (Karl et al., 2006; Landré et al., 2010; Teicher and Samson, 2016). The lack of reduced hippocampal GMV in the PTSD group also suggests that in contrast to previous observations in combat-exposed men (Gilbertson et al., 2002), lower hippocampal volumes may not act as a predisposing factor for developing PTSD following trauma exposure among sexually assaulted women.

We did find, however, correlations between microstructural characteristics of the left hippocampus and PTSD symptom severity among the trauma-exposed participants. This lateralized effect is in line with previous studies reporting reduced volume in PTSD and association between symptom severity and hippocampal volume for the left hippocampus only (e.g., Li et al., 2014; Lindauer et al., 2004; Zhang et al., 2011). Our finding may suggest that while hippocampal macrostructure may be preserved in women and/or in individuals with PTSD following sexual assault or interpersonal violence, there are changes to the microstructure of this region. These findings raise the possibility that sex/gender or trauma type may interact with different stress-related neural processes. Given that subtle hippocampal neuronal abnormalities were previously observed in males with combat-related PTSD (Schuff et al., 2001) and the ample evidence for complex interactions between neural characteristics, sex, and environmental events gathered from animal studies (e.g., Reich et al., 2009; Shors et al., 2001; for a review, see Joel, 2011; Joel and Yankelevitch-Yahav, 2014), this suggestion clearly warrants further studies. In any case, our observations support the utility of multimodal MRI methodology in neuroanatomical studies of trauma-exposed individuals.

An additional new finding is the higher FA in the insula among the TENP group. A previous study reported lower MD in the insula of children with PTSD compared with children without PTSD (Lei et al., 2015). The different pattern of microstructural change in the two studies may be related to the different developmental stage of the participants at the time of exposure to trauma and/or neuroanatomical assessment.

Although current literature regarding gray matter microstructure in PTSD is limited, the existence of subtle abnormalities among both traumatized groups compared with the NEC group may suggest that trauma exposure could have possibly led to the observed altered microstructure in the amygdala and ACC. This hypothesis is strongly supported by evidence from the non-human literature, where stress exposure was consistently shown to cause tissue reorganization in these structures, including alterations in dendritic morphology and damage to neurons (e.g., Cook and Wellman, 2004; Liston et al., 2006; Vyas et al., 2002). Such tissue changes were previously associated with functional impairments including anxiety-like behaviors and deficits in

Table 3
Partial correlations between PTSD symptom severity and ROIs' GMV, MD, and FA among the sexually assaulted participants.

	Amyg R	Amyg L	Hippo R	Hippo L	ACC R	ACC L	Insula R	Insula L
PTSD-GMV	−0.47**	−0.39*	−0.26	−0.16	−0.23	−0.26	−0.56***	−0.42*
PTSD-MD	.30	−0.03	.08	.34*	−0.01	−0.02	.22	.29
PTSD-FA	−0.03	−0.07	−0.06	−0.32*	.10	.19	−0.15	−0.09

Controlling for childhood trauma and age, and, in correlations with GMV, also for total intracranial volume.*$p < .05$. **$p < .01$. ***$p < .001$, FDR-corrected. ACC: anterior cingulate cortex; FA: fractional anisotropy; GMV: gray matter volume; MD: mean diffusivity.

attentional control (Liston et al., 2006; Pascual and Zamora-león, 2007), which are evident in traumatized individuals. The PTSD-related microstructural alterations in the left hippocampus are also suggested to reflect processes that occurred as a result of the assault, consistent with studies demonstrating deficits in DWI-measured hippocampal microstructure following stress exposure in rats, and correlations between such stress-induced microstructural alterations and social avoidance (Anacker et al., 2016; Liu et al., 2018; Molet et al., 2016; Vestergaard-Poulsen et al., 2011).

In contrast to differences between the two trauma-exposed groups and the NEC group, the higher FA in the right insula in the TENP compared with the PTSD group (and a nearly significant difference from the NEC group) may reflect a resilience-related characteristic. In addition to its central role in the salience network, the right insula was shown to play a critical and causal role in the transition between the default-mode and central executive networks, which suggests a central involvement of the insula in mechanisms underlying cognitive control (Sridharan et al., 2008). Furthermore, flexible and appropriate insula responsivity to threat was previously linked with trait resilience in non-traumatized individuals (Waugh et al., 2008). In line with this, it may be speculated that higher FA in the right insula in the TENP group contributes to improved insula functioning, which may be related to a more effective monitoring of salient stimuli and improved control of mental states. It can further be speculated that these capacities may eventually assist traumatized individuals to refrain from avoiding traumatic reminders, thus promoting fear extinction and emotion regulation.

Finally, smaller amygdala and insula volumes in the PTSD group compared with the TENP group and the correlations of these structures' GMV with PTSD symptom severity may reflect either acquired neural alterations or PTSD-predisposing characteristics. Since both amygdala and insula are sensitive to stress-induced neuroplastic changes (e.g., Ansell et al., 2012; Uno et al., 1989; for reviews, see Deppermann et al., 2014; McEwen, 1999), toxic stress-related effects might have led to a structural damage in the PTSD group. This possibility is supported by studies reporting negative associations between the amount of adverse life events or recent stress exposure and amygdala and insula volumes (Ansell et al., 2012; Pietrzak et al., 2015; Sublette et al., 2016). Intriguingly, in a recent study by Morey et al. (2016), amygdala volume was larger in TENP compared with *both* PTSD and NEC. This observation led the authors to suggest that some amount of stress exposure is associated with amygdala volume enlargement, whereas further exposure to stress and/or PTSD symptoms may cause volume reductions. In contrast, others have suggested that reduced amygdala volume represents a predisposing risk factor for PTSD (Admon et al., 2013; Morey et al., 2012). In line with the latter view, greater GMV of the right amygdala was associated with increased trait resilience in non-traumatized individuals (Gupta et al., 2017). Future longitudinal studies are needed in order to shed light on this issue. Nevertheless, the pattern of results observed here further suggests that these alterations may be associated with inter-individual differences in psychological trajectories following trauma exposure. In light of the central roles of both the amygdala and insula in the salience network and in emotional reactivity, compromised volumes in the PTSD group may underlie abnormal saliency detection and subsequent emotional dysregulation, while in the TENP, enhanced volume may support adaptive functioning in these processes.

Lastly, our findings may have relevance to treatment of sexual assault survivors. Specifically, our findings suggest that some existing neural targets of treatment success in PTSD (e.g., hippocampus GMV; Lindauer et al., 2005) may be less relevant in the case of sexual assault survivors, and suggest the use of other targets (i.e., macro- and microstructure of the insula). In addition, several studies have recently shown that fMRI neurofeedback techniques can lead to symptoms reduction and neural plasticity in individuals with PTSD (Gerin et al., 2016; Nicholson et al., 2017). Our findings could thus be translated to better guide therapeutic interventions for sexually assaulted individuals.

Several limitations should be taken into consideration. First, while a relatively large sample of adult sexual assault survivors was studied, dividing the participants into PTSD and TENP subgroups yielded a small sample size in the latter group. This may have led to reduced statistical power and inability to detect certain effects. Second, relatively young, functioning survivors participated in the study; hence, the generalization of our findings to older and/or less functioning survivors may be limited. Third, a minority of our participants reported the use of psychotropic medications, which might have influenced MRI indices. However, analyses with medication as a covariate yielded the same pattern of results. Fourth, we did not statistically control for depressive symptoms, because of the high correlations between the two in the present study ($r = 0.88$) as well as in previous studies (e.g., Stein and Kennedy, 2001), and because of previous claims that PTSD and comorbid PTSD/depression are indistinguishable (O'Donnell et al., 2004) and that PTSD and depressive symptoms in trauma survivors are influenced by overlapping vulnerabilities (Breslau et al., 2000). Fifth, this study utilized self-report measures, which could have been influenced by demand characteristics. Finally, the study was cross-sectional and thus could not have determined the temporal relationship between trauma exposure and observed neural alterations.

In summary, the present study provides new evidence for structural alterations in PTSD-related neural circuitry in adult sexual assault survivors with and without PTSD. Our findings suggest that while some of these alterations resemble the ones observed among survivors of other traumatic experiences, other alterations, or lack thereof, may be unique to sexual assault-related PTSD, or alternatively may be linked with response to trauma and the development of PTSD in women. Future studies disentangling trauma type and sex/gender, as well as utilizing larger samples of sexually assaulted individuals, are needed to shed light on these observations, and to further our understanding of the neuroanatomical implications of this traumatic experience.

5. Contributors

ZB developed and designed the study, collected and analyzed the data, and wrote the manuscript. YA and RT contributed to study design and data analyses. DJ contributed to the development and design of the study, to data analyses, and to writing the manuscript.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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