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Altered default mode network connectivity in adolescents with post-traumatic stress disorder

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ABSTRACT

Post-traumatic stress disorder (PTSD) is characterized by intrusions, re-experiencing, avoidance and hyperarousal. These symptoms might be linked to dysfunction in core neurocognitive networks subserving self-referential mental processing (default mode network, DMN), detection of salient stimuli (salience network, SN) and cognitive dysfunction (central executive network, CEN). Resting state studies in adolescent PTSD are scarce and findings are inconsistent, probably due to differences in patient symptom severity. Resting state brain activity was measured in 14 adolescents with severe PTSD and 24 age-matched controls. Seed-based connectivity analyses were used to examine connectivity between the DMN and the whole brain, including regions from other networks (SN and CEN). The relationships of network properties with symptom dimensions (severity, anxiety and depression) and episodic memory were also examined. Analyses revealed decreased within-DMN connectivity (between PCC and occipital cortex) in patients compared to controls. Furthermore, within-DMN connectivity (between PCC and hippocampus) correlated negatively with symptom dimensions (severity and anxiety), while increased connectivity (DMN-SN and DMN-CEN) correlated positively with episodic memory measures. These abnormal network properties found in adolescent PTSD corroborate those previously reported in adult PTSD. Decreased within-DMN connectivity and disrupted DMN-SN and DMN-CEN coupling could form the basis for intrusive trauma recollection and impaired episodic autobiographical recall in PTSD.

1. Introduction

Post-traumatic stress disorder (PTSD) is a psychiatric disorder characterized by intrusions or re-experiencing, avoidance, hyperarousal and negative alterations in cognition and mood (Diagnostic and Statistical Manual of Mental Disorders, DSM-5, 2013). These symptoms have been linked to deficits in episodic memory, attentional control, executive functions and working memory (for reviews, Scott et al., 2015; Kavanaugh et al., 2017). Neuroimaging studies have shown that these cognitive processes are subserved by different brain regions, including the medial prefrontal cortex (mPFC), amygdala, hippocampus and insula (Patel et al., 2012). Menon (2011) proposes a triple network model that synthesizes findings into a common framework to understand dysfunction in core neurocognitive networks across multiple disorders, including PTSD. The default mode network (DMN) is anchored in the posterior cingulate cortex (PCC), mPFC, hippocampus and angular gyrus. Its role comprises different aspects of self-referential mental processing (e.g., episodic memory, autobiographical memory, social cognitive processes). The salience network (SN), anchored in the fronto-insular cortex and dorsal anterior cingulate cortex, is involved in detecting, integrating and filtering relevant interoceptive, automatic and emotional information. The central executive network (CEN), anchored in the dorsolateral PFC, lateral posterior parietal cortex and cerebellum (Habas et al., 2009), has a role in high level cognitive function, including planning, decision-making and working memory. At rest, the DMN is typically active, while the SN and CEN are quiescent. A

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powerful way to examine intrinsic connections between large brain networks is resting state connectivity (Fox and Raichle, 2007).

Resting state connectivity studies in adult PTSD are crucial to pinpoint interactions between regions at rest without the confounds of cognitive tasks during the scanning procedure that may be biased to elicit brain activity per se (e.g., hippocampus, amygdala, insula) and/or provoke PTSD symptoms. Abnormalities in functional connectivity within the DMN were reported in adult PTSD, compared to controls, whatever the neuroimaging modality used, either magnetoencephalographic (MEG; Dunkley et al., 2014, 2015; Badura-Brack et al., 2017; Huang et al., 2014), electroencephalographic (EEG; Imperatori et al., 2014; Lee et al., 2014) or functional magnetic resonance imaging studies (fMRI; Bluhm et al., 2009; Daniels et al., 2010; Lanius et al., 2010; Zhang et al., 2015; Sripada et al., 2012). The latter found reduced within-DMN connectivity and increased connectivity between DMN and SN regions in patients compared to controls (Sripada et al., 2012). The authors suggested a disruption of equilibrium between large-scale networks in PTSD subserving internally-focused thought versus salience detection. Alternatively, Reuveni et al. (2016) identified similar functional connectivity patterns in the DMN of PTSD and controls, but functional connectivity parameters were more strongly correlated with clinical measures (severity, anxiety and depression) in PTSD patients. Correlations between PTSD symptom severity and functional connectivity patterns have also been reported elsewhere (fMRI: Cisler et al., 2013; Lanius et al., 2010; Qin et al., 2012; Sripada et al., 2012; MEG: Dunkley et al., 2014; EEG: Lee et al., 2014). Within the DMN, functional connectivity of the hippocampus, a region that is particularly sensitive to chronic stress (Gould, 2007), was found to negatively (Sripada et al., 2012; Birn et al., 2014; Herringa et al., 2013) or positively (Dunkley et al., 2014) correlate with symptom severity, depending on the imaging modality, fMRI or MEG respectively, or on the nature of the trauma, military (Sripada et al., 2012; Birn et al., 2014; Dunkley et al., 2014) or interpersonal trauma (e.g., childhood abuse; Herringa et al., 2013; see Hugues et al., 2011, for a review). We, and others, have previously shown that the hippocampus presents both structural and functional abnormalities in adult (Bremner et al., 2003) and adolescent abuse-related PTSD (Dégeilh et al., 2017; Postel et al., 2019). Symptoms in adolescent PTSD largely reflect those present in adults, with deficits in attentional control (Guillery-Girard et al., 2013), autobiographical memory (Crane et al., 2014; Ogle et al., 2013) and fear extinction (Keding and Herringa, 2015). What happens at the brain level? Findings from resting state studies in adolescent PTSD are inconsistent, some results bearing similarity to those found in adult PTSD, with increased cross-network connectivity (Suo et al., 2015) and reduced within-DMN connectivity in maltreated youth (Herringa et al., 2013). However, other studies show the opposite pattern, with increased within-DMN connectivity and decreased cross-network connectivity in adolescent PTSD (Patriat et al., 2016). Adolescence is a transitional period before entering into adulthood. Chai et al. (2014) revealed that connectivity between the DMN and task-positive networks (SN and CEN) develops with age going from positive in childhood to negative connectivity in adolescents and young adults.

Discrepancies between studies may be explained by the patient group characteristics, either focusing on maltreated youth (non PTSD; Herringa et al., 2013) or on patients with short PTSD duration, distant trauma onset and low severity (Suo et al., 2015; Patriat et al., 2016). In this study, we aimed to investigate this discrepancy in the literature on adolescent PTSD by assessing functional connectivity between brain networks at rest in a group of adolescents with severe PTSD. We included only patients meeting full diagnosis of PTSD and mainly characterized by interpersonal trauma, indicating high symptom severity. Seed-based connectivity analyses were used to examine DMN connectivity with the whole brain, including regions of the SN and CEN. We also examined the relationships of network properties with symptom dimensions (severity, anxiety and depression) and episodic memory, altered in PTSD (Ogle et al., 2013; for review, Zlomuzica et al., 2014). Symptoms in PTSD adolescents bearing similarity to those present in adults, we hypothesized similar network alterations, with decreased within-DMN connectivity and increased connectivity between DMN and SN or CEN regions in patients compared to controls.

2. Materials and methods

2.1. Participants

Fifteen adolescents with PTSD aged 13 to 18 years old, were recruited through the University Hospitals of Caen, Rennes and Rouen (France). Data of one patient were not exploitable because she slept during the resting state fMRI scan. PTSD adolescents received no psychotropic medication during the previous week and were free from other mental disorders including major depression. All presented a chronic PTSD for at least 6 months. Twenty-four typically developing adolescents with no history of trauma were chosen to match the patient group in terms of age and IQ. Healthy participants were recruited by prospecting in several junior high schools of the region (Normandy, France).

Altogether, 14 PTSD patients (12 females) and 24 controls (13 females) were included in the analyses (see Table 1 for descriptive statistics). All were right-handed and French native speakers. None of them reported any prior or current neurological or learning disabilities, head trauma, and MRI contraindications. The study was approved by the local Ethics Committee (CPP Nord Ouest III). All adolescents and their parents signed informed consent after a comprehensive description of the study. Compared to our previous study on self-reference

Table 1
Demographic, psychopathological and neuropsychological measures, depicting means and standard deviations (S.D.) for patients (N = 14, 12 females) and controls (N = 24, 13 females) at a p significant threshold of $p < .05$ (bold font indicates a significant difference between groups).

	PTSD		Controls		t-test	
	Mean	S.D.	Mean	S.D.	t value	p
Population characteristics						
Age (months)	188.71	18.16	191.92	20.63	0.48	0.633
Age (years)	15.73	1.51	15.99	1.720	0.541	0.592
IQ[a]	98.92	18.66	107.83	19.43	1.33	0.192
PTSD duration (months)	27	24.54	–	–	–	–
Age of onset (years)	13.36	1.78	–	–	–	–
Index trauma (n)	Sexual abuse (11) Accident (1) Loss of loved one (1) Witness of suicide (1)		–	–	–	–
Psychopathological scores						
IES-R	51.0	18.90	12.96	8.85	8.45	< 0.001
R-CMAS	18.21	6.75	8.79	5.27	4.79	< 0.001
CDI	18.93	9.40	8.83	4.66	4.44	< 0.001
Neuropsychological scores						
Episodic Memory (CMS[a])						
Stories subtest						
Immediate recall	43.46	13.27	53.63	14.13	2.13	0.040
Delayed recall	39.36	14.30	50.21	14.38	2.19	0.035
Family Scenes subtest						
Immediate recall	44.62	3.36	44.04	3.48	−0.48	0.631
Delayed recall	44.69	3.73	43.96	3.64	−0.58	0.535

Abbreviations: CMS = Children's Memory Scale (Cohen, 1997).
[a] Missing data of one patient.

processing (Dégeilh et al., 2017), we increased our sample sizes by scanning five additional patients and 14 new controls.

2.2. Assessment

A board-certified child and adolescent psychiatrist interviewed and screened all participants, incorporating both caregiver and youth reports. Psychiatric diagnoses and trauma exposure were assessed using the Structured Clinical Interview-Clinician Version (SCID-CV; First et al., 2002; Lobbestael et al., 2011). PTSD severity was additionally examined with the French version of the Impact of the Event Scale-Revised (IES-R; Brunet et al., 2003; Weiss and Marmar, 1997). Major depression was categorically screened using the SCID-CV (First et al., 2002; Lobbestael et al., 2011) and dimensionally measured with the French version of the Children Depression Inventory (CDI; Dugas and Bouvard, 1996; Kovacs, 1981). Anxiety was scored with the French version of the Revised-Children's Manifest Anxiety Scale (R-CMAS; Reynolds and Richmond, 1997; Reynolds et al., 1999). Of note, clinical assessments for this study have been previously described (Dégeilh et al., 2017).

Episodic memory deficits being consistently reported in PTSD (for review, Zlomuzica et al., 2014), neuropsychological assessments of episodic memory were also conducted. The French version of the Children's Memory Scale (CMS; Cohen, 1997) was used to evaluate verbal episodic memory with the Stories subtest and visual episodic memory with the Family Scenes subtest. Immediate and delayed recall scores were obtained for both subtests.

2.3. Neuroimaging data acquisition

All participants were scanned with a Philips Achieva 3.0 T MRI scanner at the Cyceron Center (Caen, France). High-resolution T1-weighted anatomical volumes were acquired using a three-dimensional fast-field echo sequence (3D-T1-FFE sagittal; repetition time = 20 ms, echo time = 4.6 ms, flip angle = 10°, 180 slices, slice thickness = 1 mm, field of view = 256 × 256 mm^2, in-plane resolution = 1 × 1 mm^2).

Resting state functional volumes were obtained using an interleaved 2DT2* SENSE EPI sequence designed to reduce geometric distortions, with parallel imaging, short echo time, and small voxels (2D-T2∗-FFE-EPI axial, SENSE = 2; repetition time = 2382 ms, echo time = 30 ms, flip angle = 80°, 42 slices, slice thickness = 2.8 mm, field of view = 224 × 224 mm^2, in-plane resolution = 2.8 × 2.8 mm^2, 280 volumes). Resting state duration was 11.26 min. Participants were equipped with earplugs, their head was stabilized with foam pads to minimize head motion, and the scanner room's light was turned off. During this acquisition, which was the last one in the MRI scanning session, participants were asked to relax, lie still in the scanner, and keep their eyes closed, without falling asleep. A subsequent debriefing questionnaire allowed us to ensure that the participants had no difficulty staying awake throughout the duration of the resting state fMRI scan and that nothing particular had disturbed their attention during the scanning.

2.4. Neuroimaging data preprocessing

Individual datasets were first checked for artifacts through the application of the TSDiffana routines (http://imaging.mrc-cbu.cam.ac.uk/imaging/DataDiagnostics). For each 38 individual datasets, we verified that head motion did not exceed 3 mm (translation) and 1.5° (rotation). Data were then processed as described in Mevel et al. (2013). Briefly, the first 6 volumes were discarded because of saturation effects. The EPI volumes were corrected for slice timing and realigned to the first volume. Data were then spatially normalized using a technique designed to reduce geometric distortion effects (Villain et al., 2010; Mevel et al., 2013). This procedure includes for each individual i) a coregistration of the mean EPI volume, non-EPI T2*, T2, and T1 volumes; ii) a warping of the mean EPI volume to match the non-EPI T2* volume; iii) a segmentation of the T1 volume using voxel-based morphometry; iv) a normalization of the coregistered T1, EPI, and non-EPI T2* volumes using the parameters obtained from the T1 segmentation; v) a 4 mm full-width at half-maximum (FWHM) smooth of the EPI volumes and vii) and temporal bandpass filtering (0.01–0.08 Hz). Finally, a binary mask was created from the group segmented mean grey matter T1 volume in conjunction with the mean non EPI-T2* volume in the MNI space (including only voxels with values > 0.25 in both mean volumes; Villain et al., 2010).

2.5. Statistical analyses

2.5.1. Behavioral analyses

To compare patients and controls on the psychopathological and neuropsychological measures, unpaired two-sample t-tests were performed using Statistica (Statsoft, Tulsa, USA).

2.5.2. Seed-based connectivity analyses

Using the GIFT toolbox (http://mialab.mrn.org/software/gift/index.html), whole-brain resting state fMRI analyses were performed on both groups using a seed-based approach. DMN connectivity was calculated using 4-mm radius spheres located in the bilateral PCC. The coordinates were obtained from previous studies of the DMN in PTSD: Patriat et al. (2016) in the right PCC (MNI coordinates [2 –52 26]) and Miller et al. (2017) in the left PCC (MNI coordinates [−8 –56 26]). The PCC seeds were chosen because they represent hubs of the DMN. Seeds based on these coordinates were created using the MarsBar toolbox (Brett et al., 2002) and the 38 individual mean time courses were extracted for each seed. For all participants and each seed of interest, correlations were assessed between the mean time course in the seed and the time course of each grey matter voxel. To remove potential sources of spurious variance, the time courses from white matter, cerebrospinal fluid, their derivatives, and the six movements parameters generated from realignment of head motion were introduced as covariates. Head motion parameters were also examined across groups (Framewise Displacement rate, FWD, and Root Mean Square, RMS; Power et al., 2012, 2014; van Dijk et al., 2012; Siegel et al., 2014). Groups did not significantly differ in head motion (FWD: $t(36) = 0.4431$, $p = .66$; RMN: $t(36) = 1.2726$, $p = .21$). A Fisher's z transform, as well as a 6.9 mm FWHM smooth, were then applied to the resulting individual connectivity maps. *Z*-score images from the individual functional connectivity analyses were then entered into a two-sample *t*-test implemented in SPM12, with covariates including age and sex. Family wise error (FWE) corrected $p < .05$ significance level was used, with a cluster extent threshold of 10 voxels.

2.5.3. Correlations with neuropsychological and psychopathological scores

The relationships between connectivity measures with neuropsychological and psychopathological scores were examined within the PTSD group, adjusting for age and sex. Neuropsychological measures (episodic memory, both immediate and delayed recalls, as measured with the Stories and Family Scenes CMS subtests) and psychopathological scores (symptom severity (IES-R), anxiety (R-CMAS), depression (CDI)) were added as regressors in separate whole brain analyses of connectivity between seed regions (bilateral PCC) and the rest of the brain, adjusting for age and sex. Because of the targeted, exploratory nature of the correlation analyses, a statistical threshold of $p < .001$ uncorrected was used, with a corrected cluster extent threshold of 80 voxels. This combination of activation thresholds was determined using the 3DClustSim program (Ward, 2000) to correspond to a false positive rate of $p < .05$, corrected for multiple comparisons.

In addition, a hypothesis-driven regions of interest (ROI) analysis of the hippocampal region ($p < .05$ corrected for multiple comparisons, small volume correction or SVC) was conducted to specifically examine

the correlation between PCC-hippocampal connectivity with neuropsychological and psychopathological scores, based on a priori hypotheses regarding the implication of the hippocampus in the pathophysiology of PTSD (Etkin and Wager, 2007; Lanius et al., 2010) and its specific role in episodic autobiographical memory retrieval which is impaired in PTSD (Crane et al., 2014; Ogle et al., 2013). Right and left hippocampal ROIs were obtained from the Automated Anatomical Labeling (AAL) toolbox (Tzourio-Mazoyer et al., 2002) and used as masks for the SVC analyses. All reported voxel coordinates correspond to standardized MNI space.

3. Results

3.1. Participant characteristics

Participant characteristics are summarized in Table 1. There were no significant differences between groups for age, IQ and the Family Scenes subtest of the CMS. For psychopathological measures, PTSD patients exhibited significantly higher levels of symptom severity (IES-R scale: $t = 8.45$, $p < .001$), anxiety (R-CMAS anxiety scale: $t = 4.79$, $p < .001$) and depression (CDI score: $t = 4.44$, $p < .001$) compared to controls. For neuropsychological measures, PTSD patients had significantly lower performances for both immediate ($t = 2.13$, $p < .040$) and delayed recall ($t = 2.19$, $p = .035$) on the Stories subtest of the CMS compared to controls.

3.2. fMRI results

3.2.1. Seed-based connectivity analyses

Results of the seed-based connectivity analyses for the DMN seeds (right and left PCC) are presented in Table 2 and Fig. 1. DMN seeds in both groups separately showed significant connectivity with other DMN regions (PCC, precuneus, mPFC, angular and middle temporal gyri, hippocampus and parahippocampal gyrus) and with CEN regions (cerebellum 9 and crus 1). Direct comparisons showed no differences using the FWE stringent threshold. By lowering the threshold at $p < .001$ uncorrected, another DMN region (left middle occipital gyrus) showed decreased connectivity with both the right and left PCC seeds in patients compared to controls.

3.2.2. Correlations with neuropsychological and psychopathological scores

Relationships between connectivity measures and neuropsychological and psychopathological scores are presented in Table 3 and Fig. 2. For the right PCC seed, connectivity between the DMN (PCC) and SN regions (insula, anterior cingulate cortex or ACC) was positively correlated with episodic memory performances of the Stories subtest, both for immediate and delayed recalls, and for immediate recall on the Family Scenes subtest. Additionally, for both PCC seeds, connectivity between the DMN (PCC) and CEN regions (middle frontal gyrus) was positively correlated with the Family Scenes subtest, for immediate recall. Conversely, connectivity between the DMN (PCC) and a CEN region (cerebellum crus I) was negatively correlated with performances on the Family Scenes subtest, for immediate and delayed recalls. No significant correlations appeared for the psychopathological scores. Direct comparisons with the control group can be found in Supplemental Table 1 (see Supplemental Material). Main results from these comparisons revealed stronger positive correlations between PCC/occipital cortex connectivity with episodic memory and with psychopathological (anxiety, depression) scores in controls than patients (see Supplemental Table 1).

Results of the SVC approach centered on the hippocampus are presented in Table 4 and Figs. 3 and 4. Within-DMN connectivity between the right PCC seed and bilateral hippocampi was negatively correlated with the Stories subtest (immediate and delayed recalls), right PCC and left hippocampus with the Family Scenes subtest (immediate recall), symptom severity (IES-R) and anxiety (R-CMAS), and,

Table 2
Results of the seed-based connectivity analyses depicting the interactions between bilateral PCC and the rest of the brain, with age and sex as covariates, at $p < .05$ FWE corrected, $k > 10$. L: left; R: right.

		MNI coordinates				
Region	Side	x	y	z	k	t value
R PCC connectivity						
PTSD						
PCC	R	4	−50	26	3131	36.76
Precuneus	R	4	−60	34		17.93
	L	−4	−62	26		17.17
mPFC	L	−6	54	−12	1763	12.10
	R	2	58	−12		11.87
Superior frontal gyrus	L	−18	42	44	28	7.56
	R	20	38	42	28	6.97
Superior medial frontal gyrus	L	−6	50	48	11	6.80
ACC	L	−4	34	6	10	7.00
Angular gyrus	L	−48	−66	36	521	11.23
	R	48	−62	40	82	7.84
Middle temporal gyrus	R	62	−8	−18	178	10.09
	L	−58	0	−22	64	7.70
Temporal pole	R	−36	14	−36	11	7.16
Parahippocampal gyrus	L	−22	−22	−20	111	8.33
	R	28	−20	−20	45	7.71
Cerebellum 9	R	8	−50	−42	532	7.91
Cerebellum crus 1	L	−24	−84	−30	20	7.44
	R	32	−78	−34	57	7.35
Controls						
PCC	R	4	−50	26	3975	52.13
Precuneus	L	−4	−62	26		22.06
mPFC	R	2	64	−12	3127	14.32
	L	−6	54	−10		14.26
Angular gyrus	L	−48	−66	38	1246	14.29
	R	50	−62	36	736	11.45
Middle temporal gyrus	R	64	−6	−16	941	13.18
	L	−62	−14	−18	765	11.44
Parahippocampal gyrus	L	−22	−36	−14	44	8.28
	R	26	−18	−20	24	6.96
Hippocampus	L	−22	−18	−20	75	7.94
Cerebellum 9	R	6	−52	−42	12	7.14
Cerebellum crus 1	R	28	−78	−32	792	8.19
	L	−28	−84	−32	39	7.23
PTSD > Controls	–	–	–	–	–	–
Controls > PTSD						
Middle occipital gyrus	L	−34	−96	0	70	5.08*
L PCC connectivity						
PTSD						
Precuneus	L	−6	−54	26	3100	31.98
	R	6	−56	26		15.35
mPFC	L	−6	52	−12	876	11.58
	R	0	48	4		9.86
Angular gyrus	L	−46	−66	38	230	8.94
	R	46	−62	40	47	7.52
Middle temporal gyrus	R	66	−8	−12	19	6.73
Parahippocampal gyrus	L	−24	−26	−16	58	8.56
Controls						
Precuneus	L	−6	−54	26	4127	42.97
	R	6	−56	26		24.32
PCC	R	6	−48	24		21.03
mPFC	L	−2	60	−6	2452	14.89
	R	6	56	−6		12.57
	L	−8	48	50	65	8.20
Angular gyrus	L	−42	−66	36	1168	13.66
	R	46	−62	38	630	10.08
Middle temporal gyrus	L	−62	−14	−18	351	11.09
	R	64	−4	−18	515	10.91
Temporal pole	L	−48	10	−34	41	7.57
Parahippocampal gyrus	L	−20	36	−12	35	7.70
Hippocampus	L	−22	−22	−18	55	7.98
PTSD > Controls	–	–	–	–	–	–
Controls > PTSD						
Middle occipital gyrus	L	−38	−68	32	54	4.27*

Abbreviations: ACC: anterior cingulate cortex k: number of voxels; mPFC: medial prefrontal cortex; PCC: posterior cingulate cortex.

* $p < .001$ uncorrected.

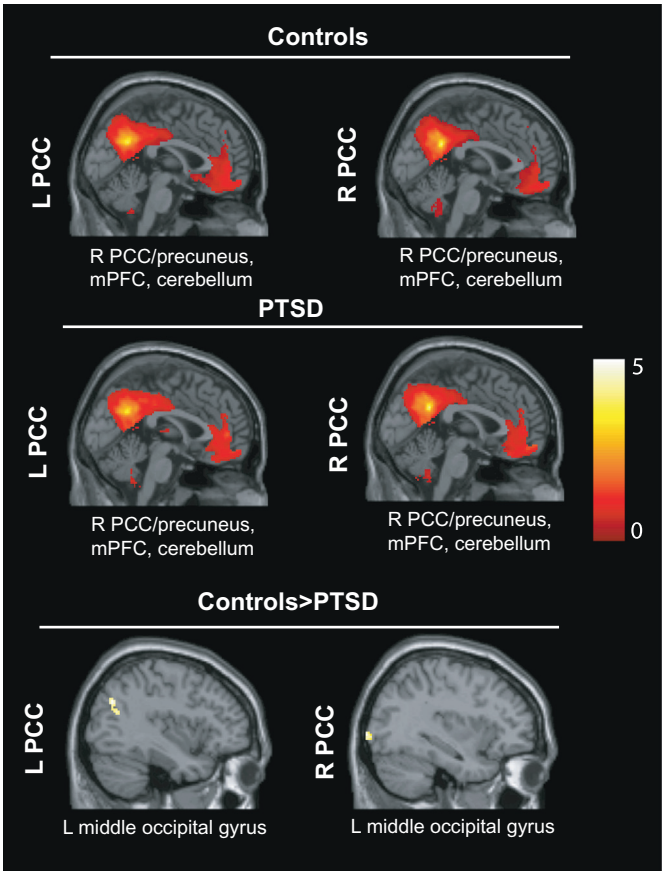

Fig. 1. Seed-based connectivity analyses between the right and left PCC and the whole brain in PTSD compared to controls, controlling for age and sex, at $p < .05$ FWE corrected, $k > 10$ voxels. R = right; L = left.

finally, the right PCC and right hippocampus with the Family Scenes subtest (delayed recall). Within-DMN connectivity between the left PCC seed and left hippocampus was negatively correlated with Stories (delayed recall), Family Scenes (immediate and delayed recalls), symptom severity (IES-R) and anxiety (R-CMAS). No significant correlations were found with depression (CDI). Direct comparisons with the control group can be found in Supplemental Table 2 (see Supplemental Material).

4. Discussion

In this study, we examined connectivity between the DMN and the whole brain in PTSD adolescents compared to healthy controls and determined if pathological scores (i.e., symptom severity, anxiety, depression and episodic memory) correlated positively or negatively with these patterns. Analyses revealed within-DMN connectivity and connectivity between the DMN and CEN regions in both groups separately. Differences between groups appeared by lowering the threshold and showed decreased within-DMN connectivity in PTSD patients compared to controls. Correlational analyses revealed that changes in functional connectivity were related to pathological patterns in patients: within-DMN connectivity between the PCC and hippocampus correlated negatively with symptom dimensions (severity and anxiety), while increased connectivity correlated positively (DMN-SN and DMN-CEN) or negatively (DMN-CEN) with episodic memory measures. We will discuss the three main findings and confront them to the existing adolescent and adult literature.

4.1. Within-DMN connectivity

In both the PTSD and control groups, we found that both PCC seeds were functionally connected with a number of regions previously identified as part of the DMN, including other regions in the PCC, precuneus, mPFC, angular gyri, middle temporal gyri and medial temporal lobe. These results confirm prior findings in adult PTSD which showed that DMN seeds, such as the PCC, were functionally connected with other DMN areas in controls and in PTSD patients at rest (Bluhm et al., 2009; Reuveni et al., 2016; Badura-Brack et al., 2017). By lowering the threshold at $p < .001$ uncorrected, direct statistical

Table 3
Results of the correlations between PCC connectivity and neuropsychological (Stories and Family Scenes subtests) and psychopathological scores (severity, anxiety, depression) within the PTSD group, adjusting for age and sex, at $p < .001$ uncorrected, cluster-level corrected ($p < .05$, $k > 80$ voxels). L: left; R: right.

		MNI coordinates				
	Side	x	y	z	k	t value
R PCC connectivity						
Stories immediate recall						
Positive correlations						
Insula	L	−42	14	−2	161	5.15
	L	−32	12	4		5.04
	L	−34	4	2		4.24
ACC	R	4	22	28	105	4.80
	L	−12	22	26		3.81
Stories delayed recall						
Positive correlations						
Insula	L	−44	14	−2	198	5.36
	L	−32	12	4		5.33
	L	−34	4	2		4.47
ACC	R	4	22	28	122	4.49
	L	−4	22	30		4.39
	R	2	16	44		4.32
Family scenes immediate recall						
Positive correlations						
Insula	R	28	22	−12	148	5.10
	R	30	24	−2		5.08
	R	36	22	10		4.17
ACC	R	10	38	14	127	4.89
	R	0	40	10		4.10
	R	4	30	22		3.71
Middle frontal gyrus	R	28	46	14	138	4.90
	R	40	44	14		4.70
	R	36	56	24		4.30
Negative correlations						
Cerebellum crus 1	R	22	−84	−26	82	4.46
	R	4	−84	−30		4.21
	R	12	−86	−30		4.02
Family scenes delayed recall						
Negative correlations						
Cerebellum crus 1	R	22	−90	−24	107	4.90
	R	22	−82	−26		4.89
	R	4	−84	−30		4.46
Severity	–	–	–	–	–	–
Anxiety	–	–	–	–	–	–
Depression	–	–	–	–	–	–
L PCC connectivity						
Stories immediate recall	–	–	–	–	–	–
Stories delayed recall	–	–	–	–	–	–
Family scenes immediate recall						
Positive correlations						
Middle frontal gyrus	R	34	56	24	237	5.51
	R	38	44	10		4.58
	R	28	46	12		4.23
Inferior frontal gyrus	R	52	26	6	256	5.02
	R	50	18	6		4.64
	R	54	22	−4		4.60
Family scenes delayed recall	–	–	–	–	–	–
Severity	–	–	–	–	–	–
Anxiety	–	–	–	–	–	–
Depression	–	–	–	–	–	–

Abbreviations: ACC: anterior cingulate cortex; PCC: posterior cingulate cortex; k: number of voxels.

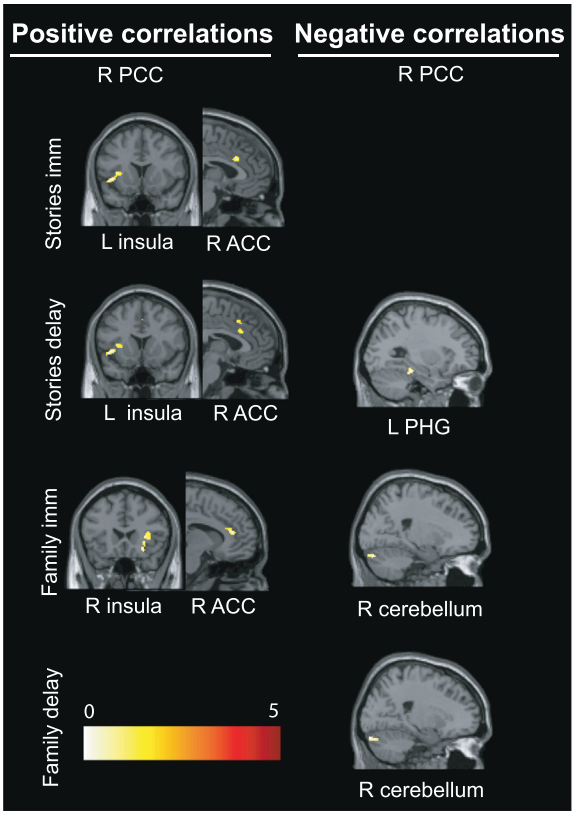

Fig. 2. Results of the correlations between PCC connectivity and episodic memory scores (Stories and Family Scenes subtests of the Children's Memory Scale, CMS) within the PTSD group, adjusting for age and sex, at $p < .001$ uncorrected, cluster-level corrected ($p < .05$, $k > 80$ voxels). R = right; L = left. For representational purposes, only connectivity with the right PCC seed is shown.
Abbreviations: family delay: family scenes delayed recall; family imm: family scenes immediate recall; stories delay: stories delayed recall; stories imm: stories immediate recall; PCC: posterior cingulate cortex; PHG: parahippocampal gyrus.

comparison showed that PTSD patients exhibited weakened within network DMN connectivity between the (right and left) PCC seeds and another DMN area (middle occipital gyrus) in PTSD compared to controls. Although this result was obtained at a lower threshold, it is nonetheless consistent with prior resting state fMRI (Mueller-Pfeiffer et al., 2013) or MEG (Badura-Brack et al., 2017; Dunkley et al., 2015) studies reporting abnormal connectivity with the visual cortex in PTSD. Moreover, correlation analyses revealed stronger positive correlations between PCC/occipital cortex connectivity with episodic memory and with psychopathological scores in controls than patients. Decreased connectivity of the PCC with occipital areas, both known for their role in visual mental imagery (Brewin et al., 2010), may be related to distorted images, dysfunctional autobiographical memory retrieval (e.g., gist memory) or flashbacks. Distortions in trauma memory may lead to inadequate contextualization of the memory trace in time, place and relative to other autobiographical memories (Ehlers and Clark, 2000). Weakened DMN functional integration during resting state (Bluhm et al., 2009; Sripada et al., 2012; Lui et al., 2009; Miller et al., 2017) or alterations in DMN function more generally (Daniels et al., 2010; Wu et al., 2011) have been previously shown in adult PTSD and Patel et al. (2012) suggested that increased suppression of DMN regions may serve as a reliable neural marker of reduced cognitive flexibility in PTSD. Our results in adolescent PTSD resonate with these findings, but must be replicated at a more stringent threshold to be considered solid.

Additional analyses revealed a negative correlation between PCC-hippocampal connectivity and symptom dimensions (severity and anxiety): higher pathological scores corresponded to less within-DMN connectivity between the bilateral PCC and left hippocampus. These findings mirror prior research showing that less DMN connectivity to the hippocampus was associated with higher scores on the Clinician Administered PTSD Scale (CAPS) in adult PTSD (Sripada et al., 2012; Birn et al., 2014), although other studies showed the opposite pattern with increased hippocampal connectivity associated with greater severity (fMRI: Shin et al., 2004; Osuch et al., 2001; MEG: Dunkley et al., 2014). Hughes and Shin (2011) reviewed these inconsistencies and suggested that "the direction of hippocampal functional abnormalities depends on the type of tasks and analyses employed." Our findings in adolescent PTSD nonetheless confirm those in adult PTSD suggesting that the reduced cohesiveness of DMN may be associated with greater symptom severity in PTSD (see also Miller et al., 2017).

A negative correlation also emerged between PCC-hippocampal connectivity and episodic memory scores (both for the Stories and Family Scenes subtests): the better patients' performances were on either episodic memory test, the more DMN-DMN connectivity decreased. The fact that greater episodic memory performances was associated with lower connectivity of the PCC with the anterior hippocampus, known for its role in autobiographical memory retrieval (Viard et al., 2007, 2012), may contribute to the intrusive nature of trauma recollection in PTSD (Patel et al., 2012). An fMRI study in adult PTSD showed that reduced hippocampal activity was associated with high arousal symptoms on the CAPS (Hayes et al., 2011). Altered activity in hippocampus during encoding of traumatic memories may contribute to the development and maintenance of the disorder. These results support neurobiological theories which propose that stress may be responsible for inhibiting hippocampal activity (Rauch et al., 2006).

Table 4
Results of the small volume correction (SVC) analysis centered on the hippocampus ($p < .05$ corrected for multiple comparisons) depicting negative correlations between PCC connectivity with neuropsychological (Stories and Family Scenes subtests) and psychopathological scores (severity, anxiety, depression) within the PTSD group, adjusting for age and sex. L: left; R: right.

			MNI coordinates			
		Side	x	y	z	t value
R PCC connectivity						
Stories immediate recall	HPC ant	R	28	−20	−10	5.30
	HPC ant	L	−12	−4	−12	4.61
Stories delayed recall	HPC ant	R	28	−20	−10	5.94
	HPC post	L	−16	−36	0	3.74
Family scenes immediate recall	HPC ant	L	−34	−12	−22	3.72
Family scenes delayed recall	HPC ant	R	28	−18	−12	3.55
Severity	HPC ant	L	−20	−2	−26	4.79
Anxiety	HPC ant	L	−18	0	−26	4.06
Depression	–	–	–	–	–	–
L PCC connectivity						
Stories immediate recall	–	–	–	–	–	–
Stories delayed recall	HPC ant	L	−36	−10	−22	3.80
Family scenes immediate recall	HPC ant	L	−34	−10	−22	3.56
Family scenes delayed recall	HPC ant	L	−14	−4	−16	3.69
Severity	HPC ant	L	−18	−2	−28	4.64
Anxiety	HPC ant	L	−18	−2	−28	4.42
Depression	–	–	–	–	–	–

Abbreviations: CDI: Children Depression Inventory; HPC ant: anterior hippocampus; HPC post: posterior hippocampus; IES-R: Impact of the Event Scale-Revised; PCC: posterior cingulate cortex; R-CMAS: Revised-Children's Manifest Anxiety Scale.

4.2. DMN connectivity with SN regions

A positive correlation was detected between PCC connectivity and SN regions (insula and ACC) with episodic memory performances for

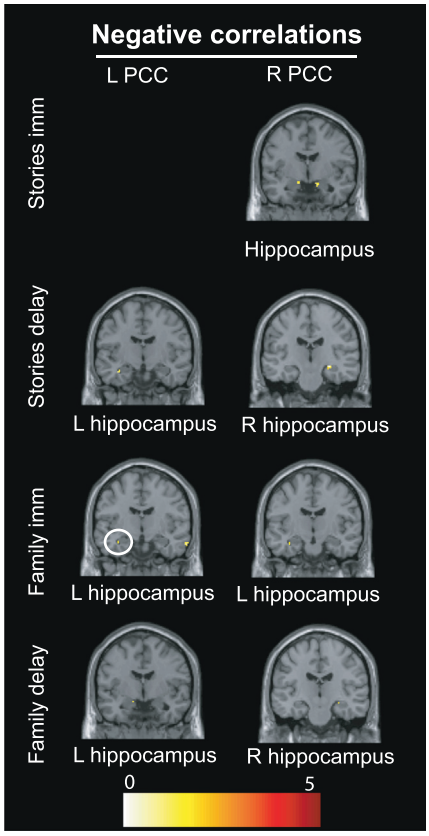

Fig. 3. Results of the small volume correction (SVC) analysis centered on the hippocampus depicting the correlations between PCC-hippocampal connectivity and episodic memory scores (Stories and Family Scenes subtests) within the PTSD group, adjusting for age and sex. R = right; L = left.
Abbreviations: Family delay: Family Scenes immediate recall; Family imm: Family Scenes immediate recall; PCC: posterior cingulate cortex; Stories delay: Stories delayed recall; Stories imm: Stories immediate recall.

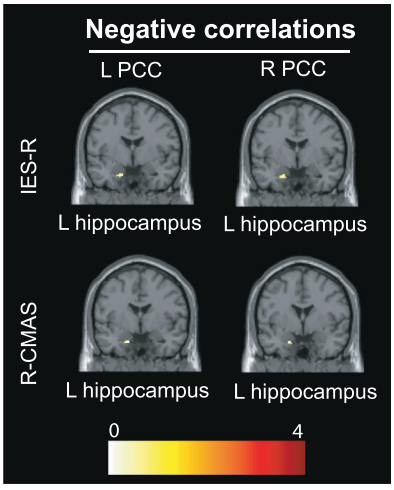

Fig. 4. Results of the small volume correction (SVC) analysis centered on the hippocampus depicting the correlations between PCC-hippocampal connectivity and psychopathological scores (IES-R, R-CMAS, CDI) within the PTSD group, adjusting for age and sex. R = right; L = left.
Abbreviations: CDI: Children Depression Inventory; IES-R: Impact of the Event Scale-Revised; PCC: posterior cingulate cortex; R-CMAS: Revised-Children's Manifest Anxiety Scale.

both tests (Stories and Family Scenes subtests). The insula is implicated in disparate cognitive and affective functions, including interoceptive awareness, emotional and empathetic responses (Menon and Uddin, 2010). As part of the SN, it biases attention towards emotionally salient stimuli or internal mental events (Menon, 2011). The insula has been frequently involved in the pathophysiology of PTSD (see meta-analysis, Etkin and Wager, 2007) and activation studies have shown increased activity in areas of the SN (insula, ACC), suggesting they may underlie disruption in conflict monitoring, autonomic regulation and reward processing (Patel et al., 2012). At rest, the SN is typically anti-correlated with the DMN in healthy subjects and likely supports the switching between large-scale networks (Menon and Uddin, 2010). In PTSD however, our findings show that the lower patients' performances were on either episodic memory test, the more DMN-SN connectivity decreased, suggesting a disruption of equilibrium between these networks as shown in adult PTSD (Sripada et al., 2012). This imbalance may help to explain sustained hypervigilance and hyperarousal in PTSD patients (Sripada et al., 2012). This positive correlation also suggests that the higher patients' performances were on either episodic memory test, the more DMN-SN connectivity increased. This connectivity increase was efficient in normalizing performances for the Family Scenes subtest (patients' performances were not different from controls), but was inefficient for the Stories subtest (patients' performances were significantly lower than controls). It is also plausible that behavioral differences may result from the nature of the task: the Family Scenes subtest, in which participants are shown family scenes close to real-life experiences, may appear more self-referential than the Stories subtest in which a factual story is presented (e.g., hot air balloon story or buffalos story).

4.3. DMN connectivity with CEN regions

Findings also revealed, in both groups, functional connectivity between both PCC seeds and a region identified as part of the central executive network (CEN), the cerebellum crus I (Stoodley and Schmahmann, 2005; Habas et al., 2009). In healthy adults, DMN and CEN are anti-correlated, meaning that these networks are competing and switching during external versus internal processing of stimuli (Fox et al., 2009; Whitfield-Gabrieli and Ford, 2012; Chai et al., 2012). Activation studies have shown increases in CEN and SN regions during stimulus-driven cognitive processes, while DMN activation decreases (Menon, 2011). In our PTSD adolescents, seed-based analyses revealed a negative correlation between connectivity of the right PCC (DMN) and cerebellum crus I (CEN) with episodic memory performances on the Family Scenes subtest (both immediate and delayed recalls). Behaviorally, patients had high performances on the Family Scenes subtest which did not significantly differ from controls. Hence, high episodic memory scores corresponded to lower DMN-CEN connectivity between the PCC seed and cerebellum crus I. The cerebellum is not frequently recruited in episodic memory tasks (unlike, for example, PFC or hippocampus) and decreasing connectivity with this region could serve to “facilitate” performances on the episodic memory tests. This decrease in DMN-CEN connectivity could be an effective way to normalize episodic memory performances in our patients.

Results also showed a positive correlation between both PCC seeds and the middle frontal gyrus (in another terminology also referred to as the dorsolateral PFC, also part of the CEN) - and additional inferior frontal gyrus (or ventrolateral PFC) for the left PCC seed - with episodic memory performances on the Family Scenes subtest (immediate recall). Behaviorally, patients did not significantly differ from controls on this subtest, suggesting that high episodic memory scores corresponded to high DMN-CEN connectivity between the bilateral PCC and lateral PFC. Episodic memory tasks, such as the Family Scenes subtest, may rely more on prefrontal regions, than the cerebellar area (see above). Hence, this DMN-CEN connectivity could be a compensatory mechanism which was effective in normalizing patients' performances. To sum, the DMN-

CEN connectivity showed both positive (PCC-dorsolateral PFC) and negative (PCC-cerebellum) correlations with episodic memory scores in patients. The imbalance between DMN and CEN connectivity patterns may be explained by a "contamination" of autobiographical remembering while performing the episodic memory tasks in PTSD, i.e. autobiographical remembering interferes with the episodic memory tasks. Of interest, Bluhm et al. (2009) reported a positive correlation between DMN connectivity with the dorsolateral PFC and frequency of dissociative experiences in adult PTSD. They suggest that dissociative experiences may involve alterations in the relation between the DMN and CEN, which may relate to difficulties switching between DMN and CEN.

Overall, our results confirm findings of resting state studies in adult PTSD, but are partly contrary to a recent adolescent PTSD study (Patriat et al., 2016) using a similar method (seed-based connectivity analyses). These authors found increased within-DMN connectivity, as found in healthy adults, but inconsistent with adult PTSD studies. These discrepancies between our results and those of Patriat et al. (2016) can be explained by the characteristics of our patient groups, in terms of origin, severity of trauma and percentage of full PTSD diagnosis. First, the origin of trauma in our sample was sexual abuse in the majority of cases (11/14 = 78%) compared to Patriat's sample (13/29 = 44%). Interpersonal trauma has been identified as the most severe type of childhood trauma compared to others (e.g., accident, death of a loved one, witness of suicide) (see McGloin and Widom, 2001; Fischer et al., 2016; Hagenaars et al., 2011). Second, using comparable tests (IESR in our study; PTSD-RI in Patriat et al., 2016), trauma severity was highest in our sample (mean severity score: 51, cut-off > 37) compared to Patriat's patients (mean severity score: 47, cut-off > 38). Third, with regard to DSM-5, 2013 criteria, 76% of patients met full diagnosis of PTSD in Patriat et al. (2016) versus 100% for patients in our study, indicating higher symptom severity in our sample. Hence, patient characteristics (origin, severity and percentage of full PTSD diagnosis) are clinically meaningful differences in trauma severity and indicate that our patients had a more severe PTSD compared to Patriat's group of patients, which may help to explain why our results mirror findings in adult PTSD, while Patriat's results bear similarities with healthy adults.

5. Limitations

Limitations of the current study should be mentioned. First, our sample size for the patient group was relatively small (N = 14) which has the risk that the study is under-powered. Our results should thus be confirmed in future studies with greater cohorts. Second, our sample was predominantly female and consisted of sexually-abused adolescents. This is characteristic of most resting state studies in adolescent PTSD in which more females than males are included (Patriat et al., 2016; Aghajani et al., 2016; Thomason et al., 2015; Suo et al., 2015). It is unknown whether the findings would generalize to males. We have re-analyzed the whole dataset including females only and results remain broadly the same (data not shown), suggesting that gender does not have an effect on the present results. Indeed, it has been previously shown that sex differences do not have major effects on DMN connectivity in healthy controls (Bluhm et al., 2009). Nevertheless, to account for this imbalance between groups, sex was added as nuisance variable in all analyses to control the gender effect. Third, to test if the age of participants could have a differential effect on each group, we performed two different analyses: setting age as a covariate of interest and performing mediation analyses. Both analyses showed that age does not have a significant effect on our results, neither on the patient nor on the control group (data not shown). Finally, the direct group comparisons and correlation analyses used an uncorrected height threshold ($p < .001$) associated to a corrected extent threshold ($p < .05$), commonly used in resting state studies on adolescent PTSD (Patriat et al., 2016; Aghajani et al., 2016; Nooner et al., 2013). It will be important for future studies to validate these findings with other statistical methods.

6. Conclusions

In summary, we report functional connectivity alterations selective to the PCC subsystem of the DMN in adolescent PTSD. Specifically, PTSD showed reduced within-DMN functional connectivity between the PCC and occipital cortex compared to controls and connectivity between the PCC and hippocampus was associated to increased trauma severity and anxiety. In addition, we found disruptions in functional connectivity between the DMN (PCC), SN (insula, ACC) and CEN (lateral PFC, cerebellum) associated to episodic memory deficits. Our results corroborate abnormal network properties previously reported in PTSD adults. Hence, both in adolescent and adult populations, PTSD pathophysiology is associated to a disruption in within-DMN connectivity, subserving internally-focused thought, and connectivity to other areas subserving salience detection (SN) and executive control (CEN). The association between decreased within-DMN connectivity and disrupted DMN-SN and DMN-CEN coupling could form the basis for intrusive trauma recollection and impaired episodic autobiographical recall in PTSD. This disrupted DMN connectivity observed in both adults and adolescents could thus represent a hallmark of PTSD leading to disrupted episodic memory and PTSD symptomatology.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101731.

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