Brain alterations in pediatric PTSD Functional brain alterations during self-reference processing in adolescents with sexual abuse related posttraumatic stress disorder: A preliminary report

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Functional brain alterations during self-reference processing in adolescents with sexual abuse related posttraumatic stress disorder: A preliminary report

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Abstract: Interpersonal childhood traumas are associated with more severe post-traumatic stress disorder at adulthood and have a critical impact on the development of the self. Weproposed to explore the functional brain changes during a self-reference processing taskin adolescents with sexual abuse related post-traumatic stressdisorder (N = 10), compared to healthy adolescents (N = 10). While patients showed no behavioral disturbances in self-reference processing, they exhibited changes in activity and connectivity in regions involved in emotional regulation (amygdala and dorsalprefrontal cortex) and semantic memory (temporal and ventrolateral prefrontal regions). These preliminary resultssuggest that these alterations may have an effect on self-esteemwhich may contribute to a possible retentionandimpairmentof symptoms in adulthood.

1. Introduction

Post-Traumatic Stress Disorder (PTSD) is a trauma and stress related disorder that develops following a traumatic experience.Negative self-appraisal may underlie the development and maintenance of PTSD(Ehlers & Clark, 2000). In addition, negative self-appraisals prior to trauma is a risk factor for PTSD development (Bryant & Guthrie, 2005). Patients often exhibit disturbances in self-reference processing (SRP;(Bryant & Guthrie, 2005; Lanius, Bluhm, & Frewen, 2011)which is the ability to distinguish self-relevant from non-self-relevant information and is proposed to be at the core of one's identity(Northoff et al., 2006). Maladaptive SRP in PTSD is apparent through negative self-reference or negative beliefs about the self(Ehlers & Clark, 2000; Frewen et al., 2011) andnegative emotions, including guilt and shame(Andrews, Brewin, Rose, & Kirk, 2000).

Thisnegative self-appraisal observed in PTSD is associated with functional brain abnormalities. Common findings in adult PTSDinclude greater amygdala activity and reduced activity in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) compared to controlsduring emotional processing(Hayes, Hayes, & Mikedis, 2012; Pitman et al., 2012) and have been integrated into a neurocircuitry model of PTSD (Rauch, Shin, & Phelps, 2006)Only two neuroimaging studies have explored SRP in adults with PTSD. The first reports lower activity within the vmPFC during SRP in PTSD patients(Bluhm et al., 2012). The second study focused onemotionally valenced SRP and observed that relative to women without PTSD, women with PTSD endorsed more negative and less positive trait-adjectives as self-descriptive and active right amygdala during SRP(Frewen et al., 2011).

These studies were exclusively conducted in adults with PTSD providing some highlights on the impact of trauma on an elaborated self, but no neuroimaging study has yet examined SRP in pediatric PTSD to identify the impact of trauma on the developing self. Adolescence is a core period of life for the development of the self (Dégeilh et al., 2015;

Pfeifer & Peake, 2012). recent findings point to serious impairments in representations of self in adolescents with PTSD(Saigh, Yasik, Oberfield, & Halamandaris, 2008; Shafran, Shahar, Berant, & Gilboa-Schechtman, 2015).

The few neuroimaging studies on cognitive and emotional processes conducted in youth with post-traumatic stress symptoms (PTSS) or full PTSD point to functional and developmental alterations of the emotion regulation network including amygdala and PFC regions. Pediatric PTSD is associated with higher amygdala and ventral PFC activity, as well as reduced dorsal PFC activityduring emotional processing (Crozier, Wang, Huettel, & De Bellis, 2014; Garrett et al., 2012; Wolf & Herringa, 2015). Wolf and Herringa (2015) reported thatactivity in dorsomedial PFC (dmPFC)decreased with age in PTSD patients, but not in controls. In addition, reduced amygdala-PFC functional connectivity associated with pediatric PTSD(Aghajani et al., 2016; Cisler, Scott Steele, Smitherman, Lenow, & Kilts, 2013)worsens with age, suggesting an abnormal development of emotional regulation processing in pediatric PTSD (Wolf & Herringa, 2015).

Accordingly, thisabnormal emotional regulation of the amygdala by the PFC,which increases with age,may have an impact on the development of the self and participate inthe maintenance and worsening of PTSDsymptoms. Some studies suggest that childhood traumas, particularlywhen they are interpersonal, have a critical impact on the development of the self, notably physicalabuse that rapidly affects self-esteem(J. Kim & Cicchetti, 2006). From the attachment theoretical viewpoint(Bowlby, 1969/1982), children who are reared in stressful home environments and/or have experimented childhood traumas may develop more negative representations of self and are at multiple risks for behavioraland psychological maladjustment(Cicchetti & Rogosch, 1994). There are some evidence that childhood traumasare associated with more severePTSD at adulthood(De Bellis & Zisk, 2014; McGloin & Widom, 2001).In this context, we investigatedthe functional brain substrates ofemotionally

valencedSRP inpediatric PTSD related to interpersonal trauma.We conducteda cross-sectional fMRI study to examine changes in regional brain activity and connectivity during emotionally valenced SRP in adolescents with sexual abuse related PTSD compared to non-traumatized healthy adolescents. Based on previous work in PTSDand theoretical models of self-development after childhood traumas, we hypothesized that behavioral and neuroimaging abnormalities observed in adult PTSD would be detected sooner, at the period of adolescence. Hence, PTSD adolescents would endorse more negative and less positive trait adjectives as self-descriptive than controls.Concerning neuroimaging analyses, we predicted greater amygdala activity and lower PFC activity during SRP in PTSD patients compared to controls. In addition, we hypothesized that alterations in the amygdala-PFC connectivityassociated with adult PTSD would also be observed inour pediatric population.

2. Method

2.1. Participants

Eleven adolescents with sexual abuse related 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 fMRI task. 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. Ten controls were chosen from a group of 30 typically developing adolescents with no history of trauma to strictly match the patient group in terms of age, gender and IQ. Healthy participants were recruited by prospecting in several junior high schools of the region (Normandy, France).

Altogether, 10 PTSD patients (8 females), and 10 controls were included in 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.

2.2. Assessment

All participants underwent a clinical interview with a child psychiatrist. The positive diagnosis of PTSD (categorical approach) was assessed with the Structured Clinical Interview-Clinician Version (SCID-CV: inter-rater reliabilityKappa value = .77;First, Spitzer, Miriam, & Williams, 1996; Lobbestael, Leurgans, & Arntz, 2011). PTSD severity (dimensional approach) was additionally examined with the French version of the Impact of the Event Scale-Revised (IES-R: internal consistencyalpha coefficient= 0.93 and test–retest reliability$r$ = 0.76 for total score; Brunet, St-Hilaire, Jehel, & King, 2003; Weiss & Marmar, 1997).Major depression was categorically screened using the SCID-CV (inter-rater reliabilityKappa value = .66;First et al., 1996; Lobbestael et al., 2011) anddimensionally measured with the French version of the Children Depression Inventory (CDI: internalconsistency alpha coefficients ranging from .71 to .83and test–retest reliabilityranging from 0.38 to 0.83 for periods of one to four weeks;Dugas & Bouvard, 1996; Kovacs, 1981). Anxiety was scored with the French version of the Revised-Children's Manifest Anxiety Scale (R-CMAS:internal consistencyalpha coefficient=.84and test–retest reliability$r$ =.83; Reynolds & Richmond, 1997; Reynolds, Richmond, & Castro, 1999). Finally, self-esteem was measured with the French version of the Rosenberg Self-Esteem scale (RSE: internal consistencyalpha coefficients rating from .83 to .90and satisfactory test–retest reliability$r$ = .84;Rosenberg, 1965; Vallieres & Vallerand, 1990).

2.3. Experimental task

In the scanner, participants performed an event-related self-reference paradigm followed by a recognition test detailed inDégeilh et al. (2015).The self-reference paradigm consisted in indicating whether or not negative and positive trait adjectives non relative to their traumatic

event*i)* characterized themselves ("self" condition)*, ii)* characterized French celebrities ("other" condition) or *iii)* were positive ("semantic" condition). Considering we aimed to explore the impact of PTSD on brain activity and connectivity during SRP, the recognition test was not considered in the present study.

After a training session outside the scanner to familiarize participants with the task, the acquisition session took place and consisted in two runs (7 minutes each) with presentation of 72 stimuli with equal proportion of negative and positive adjectives (12 adjectivesby condition and valence). Each adjective was presented for 3.5 seconds, followed by a fixation cross jittered between 1 and 3 seconds.

Trait adjectives were presented visually using E-Prime (Psychology Software Tools, Pittsburgh, PA) implemented in IFIS System Manager (Invivo, Orlando, FL). Lists of adjectives displayed for each condition and the yes/no answers on the keyboard were counterbalanced across participants and for each participant, valence of trait adjectives was counterbalanced across conditions.

2.4. MRI acquisition

Imaging data were collected using an 8 channel head coil on a Philips Achieva 3T MRI scanner (Eindhoven, Netherlands). For each participant, a high resolution T1-weighted anatomic image was acquired using a three-dimensional fast field echo sequence (3D-T1-FFE sagittal), followed by a high-resolution T2-weighted spin echo anatomical acquisition (2D-T2-SE sagittal) and a non-Echo-Planar Imaging (non-EPI) T2-star volume (2D-T2*-FFE axial). In the functional acquisition session, data were acquired with an interleaved two-dimensional T2* SENSitivity Encoding (SENSE) EPI sequence designed to reduce geometrical distortions and magnetic susceptibility artefacts (2D-T2*-FFE-EPI axial, SENSE factor: 2; TR: 2382ms; TE: 30ms; flip angle: 80°; 42 slices; slice thickness: 2.8mm; no gap; matrix: 80×80; FoV: 224mm²; in-plane resolution: 2.8mm²; 172 per run).

2.5. Behavioral analysis

Repeated measures ANOVAs onresponse times and proportion of "yes" responses were performed using Statistica (Statsoft, Tulsa, USA). To test the positivity bias in the self-appraisal, we performed repeated measures ANOVAs on response times and t-tests on the proposition of positive self-appraisal (proportions of "no" responses for negative traits and "yes" responses for positive traits) and negative self-appraisal (proportions of "yes" responses for negative traits and "no" responses for positive traits).When ANOVAs revealed significant effects, post-hoc pairwise comparisons were performed using Fisher's LSD test.

2.6. fMRI pre-processing

Data pre-processing and statistical analyses were performed with SPM5 (Wellcome Trust Centre for Neuroimaging, London, UK).For pre-processing (see Dégeilh et al. 2015), the EPI volumes were corrected for slice timing and realigned to the first volume. Then, spatial normalization was carried out for each participant as follows: (1) coregistration of the mean EPI, non-EPI-T2*, the T2 and the T1 volumes, (2)geometric EPI distortions were corrected by warping the mean EPI image to match the non-EPI-T2* volume(Villain et al., 2010), (3) segmentation of the T1 image using an age-appropriate stereotactic template (NIHPD 13-18.5: http://www.bic.mni.mcgill.ca/ServicesAtlases/NIHPD-obj1)(Fonov et al., 2011), (4) resulting parameters were applied to normalize the coregistred T1, EPI and non-EPI-T2* volumes, and (5) 8mm FWHM smoothing of the EPI images. Additionally, an individual grey matter (GM) mask was created for each participant by conjunction of the GM segments of T1 and non-EPI-T2*volumes including only voxels with values greater than 0.15 and 0.05, respectively. This individual GM mask was used as an explicit mask during first level analyses.

2.7. fMRI analysis

Considering the aim of the study was to explore the impact of PTSD on brain activity and connectivity during negative and positive SRP, we focused our analyses on the encoding phase.The semantic condition was used as a reference condition, rather than the other condition,since this latteralso engages self-reference processes. Indeed, appraisal of self (SRP) and others involved a common network including medial PFC, PCC and precuneus(Benoit, Gilbert, Volle, & Burgess, 2010; Dégeilh et al., 2015). As note, results from Self versus Other analysis are presented in supplementary information (see Table S1).

2.7.1. Brain activity changes

For the first level analyses, a whole brain voxel-by-voxel general linear model was applied to each participant. The individual model included six experimental conditions of interest for negative and positive items of each condition (self-negative, self-positive, other-negative, other-positive, semantic-negative, semantic-positive) and one non-interest condition (non-responses). Movement parameters and depression scores were added as covariates of non-interest. For the second level analysis, all individual contrasts were entered in ANOVA with conditions (self-negative, self-positive, other-negative, other-positive, semantic-negative, semantic-positive) as within-subject factor, groups as between-subject factor and subjects as random factor.

2.7.2. Functional connectivity changes

We performed psychophysiological interactions (PPI) analyses(Friston et al., 1997; Gitelman, Penny, Ashburner, & Friston, 2003)to explore group differences in functional connectivity between seed regions and the rest of the brain during negative and positive SRP. We selected regions showing significant differences their activity between PTSD and controls in the previous analysisof SRP-related activity and that were of particular interest givenour hypotheses (see introduction). The seeds used for the PPI analyses were the leftamygdala at the coordinates [-26 -14 -10] forthe self-negative>semantic contrast and [-26 -14 -8] for the

self-positive>semantic contrast.For each subject and for each seed, the neuronal activity for the corresponding contrast was extracted from a volume of interest (VOI 6 mm radius sphere) centered on sphere center coordinates detailed above. Then, a linear model was built for each subject using threeregressors: *i)* the psychological regressor corresponding to experimental conditions (self-negative or self-positive *versus*semantic), *ii)* thephysiological regressor corresponding to individual mean neuronal activity in each VOI, and *iii)* the psychophysiological regressor representing the interaction between the psychological and physiological regressors. The model also included movement parameters. To identify group differences in amygdala connectivity during self-negative and self-positive conditions, we performed second level t-test analyses foreach seed. Depression scores were added as covariates of non-interest.

For analyses of activity and connectivity, group effects were masked using a GM mask based on the mean normalized GM (i1), white matter (i2) and CSF (i3) maps from the T1 images of 30 healthy adolescents aged between 13 and 18 yearsrecruited for a study focused on healthy development (see Dégeilh et al., 2015), from which 10controls were selected for the present study. GM mask was calculated with the following formula: (i1>i2)*(i1>i3)*(i1>0.3). Based on our a priori hypotheses, resulting statistical maps were thresholded at an uncorrected voxel-level p value of 0.001 and an extent threshold of 20 voxels.

3. Results

3.1. Participant characteristics

Participant characteristics are summarized in Table 1. There were no significant differences between groups for age, perceptual reasoning and verbal comprehension (p >0.05).PTSD patients exhibited significantly higher levels of anxiety (R-CMAS anxiety scale: t_{18}= -3.75, p = 0.001) and depression thancontrols (CDI score: t_{18}= -4.05, p < 0.001). No significant group

difference was observed for social desirability (R-CMAS lie score: $t_{18}= 0.08$, $p = 0.93$) and self-esteem (RSE score: $t_{18}= 0.99$, $p = 0.33$).

3.2. Behavioral results

Regarding the proportion of "yes"responses during self and semantic conditions (Figure 1),the analysisrevealed a significant main effect of valence ($F (1,18) = 477.63$, $p <0.001$), an interaction effect between condition and valence ($F (1,18) = 26.94$, $p <0.001$) and no significant effect of group. Both patients and controlsendorsed more positive than negative adjectives as self-descriptive ($p <0.001$). T-tests on the propositions of positive self-appraisal revealed no significant difference between patients and controls ($t_{18}= 1.8$, $p = 0.09$; Figure 1).

Regarding the response timesduring the self and semantic conditions (Figure 1), results showed a significant interaction between group and valence ($F (1,18) = 4.85$, $p = 0.04$), with slower responses for negative than positive adjectives in PTSD patients ($p = 0.018$), but not in controls ($p = 0.6$). There were no group, condition or valence main effects, or any other interactions between group, condition and valence (all $p > 0.13$). ANOVAs on response times for positive and negative self-appraisal revealed a significant main effect of valence ($F (1,18) = 17.36$, $p < .001$; Figure 1), with faster responses during positive than negative self-appraisal in both groups. There was no significant group effect.

3.3. fMRI results

3.3.1. Brain activitychanges

During negative SRP, PTSD patients showed higher activation in the left amygdala than during the semantic condition, contrary to controls who equally recruited the amygdala during both conditions (Figure 2, Table 2). During positive SRP compared to the semantic condition, PTSD patients showed stronger activationin the left amygdala and superior temporal gyrus, contrary to controls who equally recruited these regions during both conditions (Figure 2, Table 2).

3.3.2. Amygdala functional connectivity

During negative SRP, compared to controls, PTSD patients showed reduced left amygdala connectivity with the dlPFC, right dmPFC, left rostral PFC, angular gyrus, left superior parietal lobule andright precuneus (Figure 3, Table 3). Overall, these couplings were negative in PTSD patients. During positive SRP, comparedtocontrols,PTSD patients showed stronger positive connectivity between the left amygdala and bilateral middle temporal gyrus and left ventrolateralPFC (vlPFC) (Figure 3, Table 3).

4. Discussion

The aim of thispreliminary fMRI study was to explore neural substrates associated to emotionally valencedSRP in pediatric PTSD with the hypothesis that significant impairments of self-appraisal may be observed in adolescence. To pursue this issue, we selected a homogenous group of adolescents with full chronic PTSD related to sexual abuse, a clinical condition whichis known to critically impact self-development(J. Kim & Cicchetti, 2006).

Our findings suggest that while PTSD adolescents showed no behavioral disturbance in SRP, they exhibited changes in functional brain activity andconnectivity during SRP. Theyshowed greater left amygdala activity during SRP independently of valence.However, this was associated with two different patterns of activity and connectivity according to the valence.During negative SRP, the left amygdala was less connectedto a large network including dorsal PFC, angular and precuneus.During positive SRP, PTSD patients exhibited higher left superior temporal activity andstronger amygdala-vlPFC connectivity. Overall, these results show that pediatric PTSD may becharacterized by early functional abnormalities in regions involved in emotional regulation and memoryduring SRP that may subtend symptom development and lead to the maladaptive SRP observed in adult PTSD.

4.1. Preserved behavioral SRP

Unlike our predictions, adolescents with PTSD showed no behavioral disturbance in SRP. They endorsed more positive and less negative trait adjectives as self-descriptive, like controls. Yet, unlike healthy controls, patients exhibited slower responses for negative than for positive adjectives (independently of the condition). This may reflect an attention bias for negative information largely describedin PTSD(Hayes, Vanelzakker, & Shin, 2012). However, changes in brain activity and connectivity observed in the PTSD group suggest that they used different neurofunctional processes and strategies during SRP than controls.

4.2. Emotion regulation deficit during negative SRP

During negative SRP, PTSD adolescents exhibited greater left amygdala activationand reduced functional amygdala connectivitywith the dmPFC, the precuneusand the angular gyrus.

The PFC and amygdala are core brain structures involved in emotional regulation(M. J. Kim, Gee, Loucks, Davis, & Whalen, 2011). Effectivedown regulation of negative emotion is characterized by PFC activityincrease, together with amygdala activitydecrease (Ochsner, Bunge, Gross, & Gabrieli, 2002) and stronger amygdala–dmPFC connectivity(Lee, Heller, van Reekum, Nelson, & Davidson, 2012). The dmPFC, precuneusand angular gyrusare key components of the "default mode network" (DMN) involved in introspective processing, self-reflection, emotion regulation and memory retrieval (Buckner, Andrews-Hanna, & Schacter, 2008). Disequilibrium between the disengagement of the DMN and hyperactivity in the amygdala may be associated with PTSD etiology (Patel, Spreng, Shin, & Girard, 2012).Thus, increased amygdala activation, reduced dmPFC-amygdala connectivity and disconnection between the amygdala and DMN regions observed here in PTSD adolescents could reflect an emotional regulation deficit during negative SRP.

Our results are concordant with previous studies showing thatpediatric PTSD is associated with age-related decrease in dmPFC activation and amygdala-PFC functional

connectivity (Aghajani et al., 2016; Cisler et al., 2013; Wolf & Herringa, 2015). Over time, this may interrupt the protracted maturation of themPFC which subtends the development of the self (Dégeilh et al., 2015; Pfeifer & Peake, 2012)and may disturb the increase of PFC-amygdala connectivity associated with emotional regulation development (Ahmed, Bittencourt-Hewitt, & Sebastian, 2015). We hypothesize that these neurodevelopmental impairments focused on cortical midline structures would result in maladaptive SRP with a deterioration of self-esteem reported in adult PTSD. This hypothesis is in agreement with Lanius et al.(2011) who reported that DMN connectivity in adults with PTSD resemblesthat observed in children aged 7–9 and evoked abnormal maturation related to the toxic effects of stress hormones.

4.3. Semantic processing during positive SRP

During positive SRP, patients showed higher activation in the left amygdala and left superior temporal gyruscompared to the semantic condition.This activation of the amygdala extends the difficulties in emotion regulation observed for negative SRP to positive SRP.In addition,PTSD patients exhibited stronger positive functional connectivity between the amygdala and both the middle temporal gyrus and left vlPFC compared to controls. These regions are involved in semantic memory processes: the lateral temporal lobe is associated with retrieval of semantic knowledge(Levy, Bayley, & Squire, 2004) and the left vlPFC is involved in cognitive control access to semantic memory(Badre, Poldrack, Paré-Blagoev, Insler, & Wagner, 2005; Greenberg et al., 2005).These results suggest that PTSD adolescents may base their judgment mainly on general semantic information during positive SRP, rather thanon their own self properties.

4.4. Methodological considerations and future directions

Our findingsbring interesting perspectives to study self in pediatric PTSD in a more comprehensive way. This study was strengthened by including solely full chronic PTSD

relative to sexual abuse and unmedicated patients at the time of the study with no comorbid diagnoses. However, the inclusion criteria were particularly restrictive and led to a difficulty in recruitment which limited the size of our sampleaffecting statistical power (as depicted by the use of an uncorrected $p = 0.001$). Hence, this studyneeds to be extended with a larger sample. In addition, it would be interesting to include another comparison group of traumaexposednon-PTSD subjectsto evaluate the effect of trauma exposure *per se* separately from PTSD. Thus, the present findings,while in need of replication, neverthelesssuggestthat self-distortion may have a role in the maintenance of PTSD symptoms relative to childhood abusein adulthood.

5. Conclusion

Activity and connectivity changes in amygdala-prefrontal regions during negative SRP observed in the present studymay reflect a deficit in cognitive regulation of negative emotion. These results showthat abnormalities,which characterize PTSD adults,are also observed in pediatric PTSD. In addition, our functional data suggest that this deficit in emotion regulation implicates compensatory processes and probably, the use of an automatic process of judgment based on semantic information for positive information related to the self. Overall, pediatric PTSD may becharacterized by functional abnormalities which may underlie pathology symptoms development and maintenance. These alterations may lead to self-esteem deterioration and a possible worsening of symptoms observed in adult PTSD relative to interpersonal traumas.Converging results would motivate an early care in pediatric PTSD to limit possible functional changes which may impact cognitive development with, for example, apsychotherapyfocused on introspection and self-awareness to promote positive self processing.

Acknowledgments

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Table 1

Demographic and psychological data

	PTSD (n = 10)		Controls (n = 10)		t-test	
	Mean	S.D.	Mean	S.D.	t (18)	p
Age (months)	190.60	19.18	192.00	22.19	0.15	0.88
WISC-IV[§]						
Perceptual reasoning	93.00	19.81	96.60	19.40	0.39	0.69
Verbal comprehension	95.22	17.15	114.00	23.60	1.96	0.07
IES-R	52.40	14.51	11.80	8.32	-7.67	<0.001
R-CMAS						
Anxiety scale	18.30	5.14	8.90	6.10	-3.75	0.001
Lie scale	3.00	2.54	3.10	2.96	0.08	0.93
CDI	18.30	5.93	8.80	4.47	-4.05	<0.001
RSE[§]	28.11	6.03	30.50	4.43	0.99	0.33

[§]Missing data of one patient.

Table 2

Brain activity changes in PTSD patients compared to controls during negative and positive self-reference processing.

Region	Side	BA	MNI (voxels)			k	t-values
			x	y	z		
Self-Negative>Semantic							
PTSD>Controls							
Amygdala	L		−26	−14	−10	37	4.19
Controls>PTSD							
Dorsolateral PFC	L	8	−28	12	46	50	4.08
Self-Positive>Semantic							
PTSD>Controls							
Amygdala	L		−26	−14	−8	26	4.09
Superior temporal gyrus	L	22	−62	−10	0	53	3.70
Controls>PTSD							
-	-		-	-	-	-	-

Abbreviations: BA, Brodmann area; PFC, prefrontal cortex.

Table 3

Amygdala functional connectivity changes in PTSD patients compared to controls during negative and positive self-reference processing.

Region	Side	BA	MNI (voxels)			k	t-values
			x	y	z		
Self-Negative> Semantic							
PTSD>Controls							
-	-		-	-	-	-	-
Controls>PTSD							
Angular gyrus	R	39	42	−54	32	109	6.42
Superior parietal lobule	L	5	−18	−54	66	150	6.10
Rostral PFC	L	10	-30	62	4	47	5.44
Dorsomedial PFC	R	8	6	46	40	52	4.97
Angular gyrus	L	39	−42	−76	32	31	4.67
Superior parietal lobule	L	7	−16	−80	46	57	4.52
Precuneus	R	7	2	-46	52	92	4.43
Dorsolateral PFC	R	9	16	46	40	28	4.32
Dorsolateral PFC	L	9	-24	48	38	22	4.15
Self-Positive>Semantic							
PTSD>Controls							
Middle temporal gyrus	L	21	-54	-24	-2	33	5.47
Middle temporal gyrus	R	21	66	-18	-12	34	5.15
Ventrolateral PFC	L	45	54	30	-2	24	4.14
Controls>PTSD							
-	-		-	-	-	-	-

Abbreviations: BA, Brodmann area; PCC, posterior cingulate cortex; PFC, prefrontal cortex.

Figure 1: Proportion of responses (top) and response times (bottom) during self and semantic conditions (left) and propositions of positive and negative self-appraisal (right) in PTSD patients and controls group.
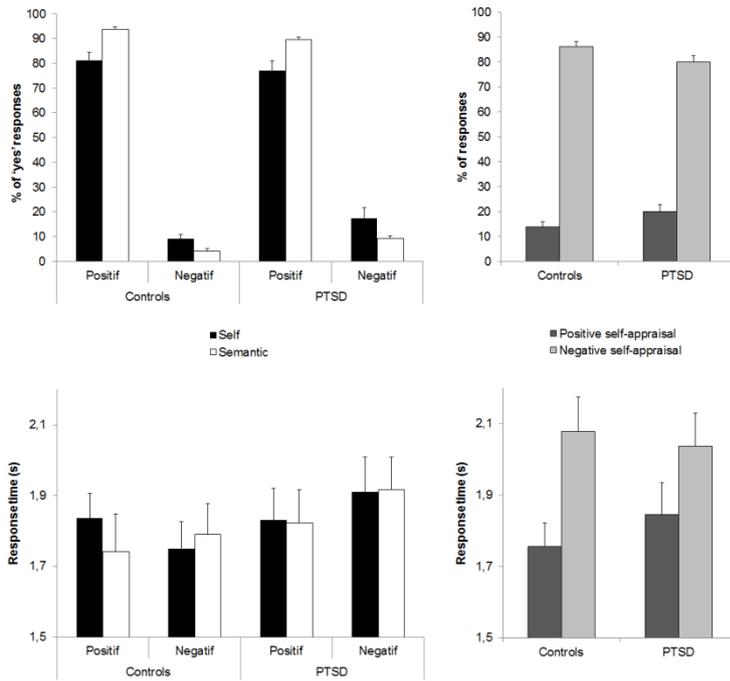
Figure 2: Brain activity changes during positive (A) and negative (B) self-reference processing.

Brain activation changes

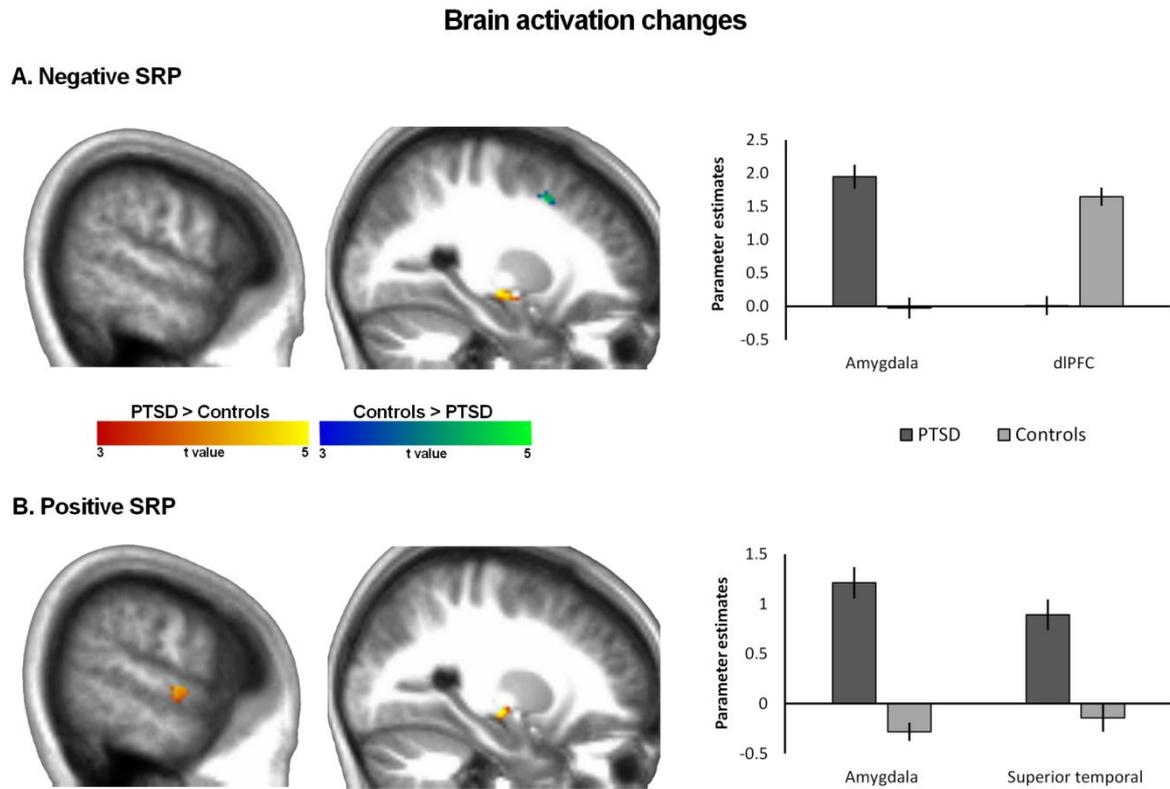**A. Negative SRP**

B. Positive SRP

Figure 3: Left amygdala functional connectivity during positive (A) and negative (B) self-reference processing.
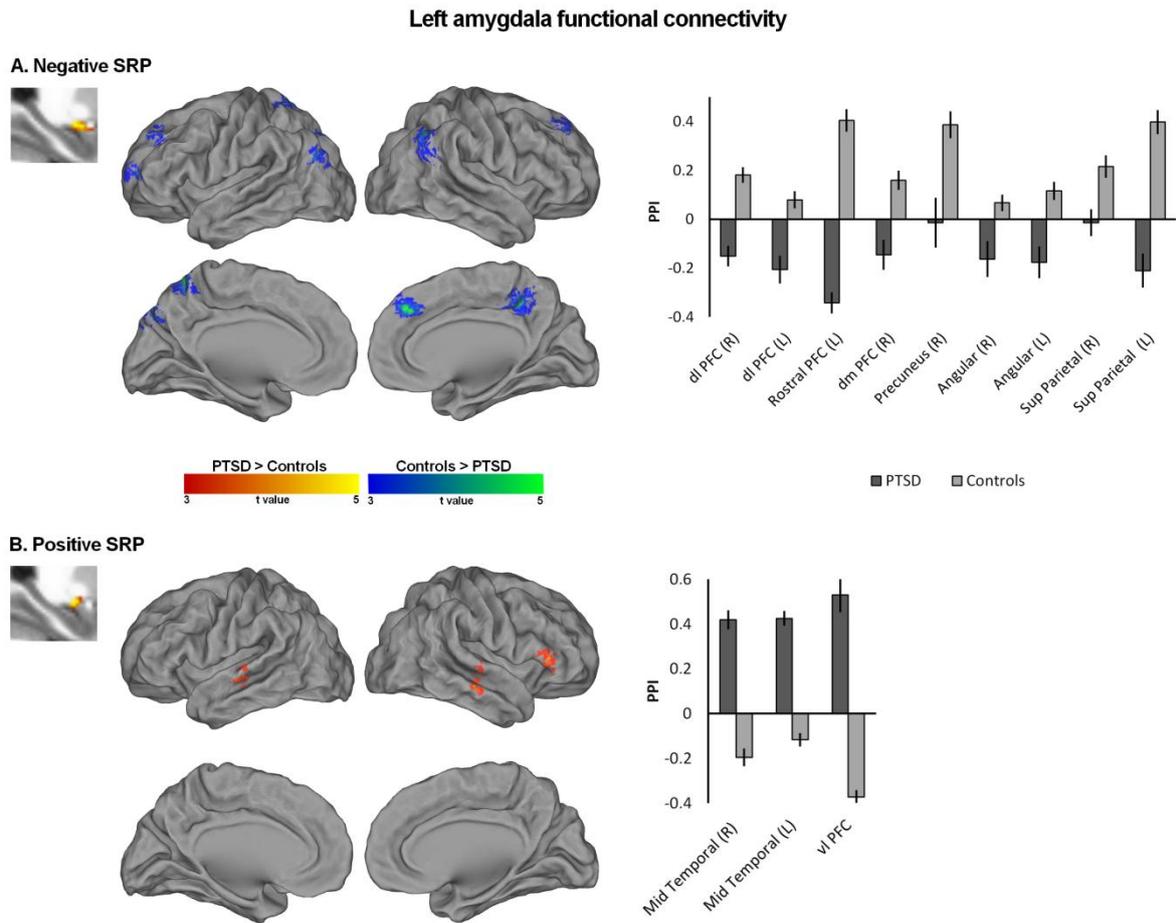
Table S1: Brain activity changes in PTSD patients compared to controls during negative and positive self-reference processing compared to other-reference processing.

Region	Side	BA	MNI (voxels)			k	t-values
			x	y	z		
Self-Negative> Other							
PTSD>Controls							
-	-		-	-	-	-	-
Controls>PTSD							
-	-		-	-	-	-	-
Self-Positive> Other							
PTSD>Controls							
Cerebellum 4, 5	R		18	-36	-24	33	4.03
Controls>PTSD							
-	-		-	-	-	-	-