

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

Fanny Dégeilh, Armelle Viard, Fabian Guénolé, Malo Gaubert, Pierre-Jean Egler, Stéphanie Egret, Priscille Gerardin, Jean-Marc Baleyte, Francis Eustache, Jacques Dayan, et al.

► **To cite this version:**

Fanny Dégeilh, Armelle Viard, Fabian Guénolé, Malo Gaubert, Pierre-Jean Egler, et al.. Brain alterations in pediatric PTSD Functional brain alterations during self-reference processing in adolescents with sexual abuse related posttraumatic stress disorder: A preliminary report. Neurocase, Taylor

Francis (Routledge), 2017, [Epub ahead of print]. <inserm-01470285>

HAL Id: inserm-01470285

<http://www.hal.inserm.fr/inserm-01470285>

Submitted on 17 Feb 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Fanny Dégeilh^{1,2,3,4}, Armelle Viard^{1,2,3,4}, Fabian Guénolé^{1,2,3,4,5}, Malo Gaubert^{1,2,3,4}, Pierre-Jean Egler⁵, Stéphanie Egret^{1,2,3,4}, Priscille Gerardin⁶, Jean-Marc Baleyte^{1,2,3,4,5}, Francis Eustache^{1,2,3,4}, Jacques Dayan^{1,2,3,4,7*}, Bérengère Guillery-Girard^{1,2,3,4*}

¹Inserm, U1077, Caen, France

²Université de Caen Normandie, UMR-S1077, Caen, France

³Ecole Pratique des Hautes Etudes, UMR-S1077, Caen, France

⁴CHU de Caen, UMR-S1077, Caen, France

⁵CHU de Caen, Service de Psychiatrie de l'Enfant et de l'Adolescent, Caen, France

⁶CHU de Rouen, Fédération hospitalo-universitaire de psychiatrie de l'enfant et de l'adolescent, Rouen, France

⁷CHGR Rennes-I, Service de Psychiatrie de l'Enfant et de l'Adolescent, Rennes, France

* Co-last authors

Corresponding author: B. Guillery-Girard, Inserm-EPHE-UNICAEN-U1077, PFRS, 2, rue des Rochambelles, F-14032 Caen Cedex, France. Tel: +33 (0)2.31.56.83.99, Fax: +33 (0)2.31.56.83.91. E-mail: berengere.guillery@unicaen.fr

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. We proposed to explore the functional brain changes during a self-reference processing task in adolescents with sexual abuse related post-traumatic stress disorder (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 dorsal prefrontal cortex) and semantic memory (temporal and ventrolateral prefrontal regions). These preliminary results suggest that these alterations may have an effect on self-esteem which may contribute to a possible retention and impairment of symptoms in adulthood.

Key words: Post-Traumatic Stress Disorder, functional magnetic resonance imaging, functional connectivity, amygdala, prefrontal.

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) and negative emotions, including guilt and shame (Andrews, Brewin, Rose, & Kirk, 2000).

This negative self-appraisal observed in PTSD is associated with functional brain abnormalities. Common findings in adult PTSD include greater amygdala activity and reduced activity in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) compared to controls during 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 on emotionally 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 activity during emotional processing (Crozier, Wang, Huettel, & De Bellis, 2014; Garrett et al., 2012; Wolf & Herringa, 2015). Wolf and Herringa (2015) reported that activity 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, this abnormal emotional regulation of the amygdala by the PFC, which increases with age, may have an impact on the development of the self and participate in the maintenance and worsening of PTSD symptoms. Some studies suggest that childhood traumas, particularly when they are interpersonal, have a critical impact on the development of the self, notably physical abuse 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 experienced childhood traumas may develop more negative representations of self and are at multiple risks for behavioral and psychological maladjustment(Cicchetti & Rogosch, 1994). There are some evidence that childhood traumas are associated with more severe PTSD at adulthood(De Bellis & Zisk, 2014; McGloin & Widom, 2001). In this context, we investigated the functional brain substrates of emotionally

valenced SRP in pediatric PTSD related to interpersonal trauma. We conducted a 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 PTSD and 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 connectivity associated with adult PTSD would also be observed in our 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 reliability Kappa 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 consistency alpha 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 reliability Kappa value = .66; First et al., 1996; Lobbestael et al., 2011) and dimensionally measured with the French version of the Children Depression Inventory (CDI: internal consistency alpha coefficients ranging from .71 to .83 and test-retest reliability ranging 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 consistency alpha coefficient = .84 and 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 consistency alpha coefficients ranging from .83 to .90 and 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 in Dégeilh et al. (2015). The self-reference paradigm consisted in indicating whether or not negative and positive trait adjectives non relative to their traumatic

eventi) 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 adjectives by 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 on response 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 proportion 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 coregistered 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 latter also 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 analysis of SRP-related activity and that were of particular interest given our hypotheses (see introduction). The seeds used for the PPI analyses were the left amygdala at the coordinates [-26 -14 -10] for the 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 three regressors: *i*) the psychological regressor corresponding to experimental conditions (self-negative or self-positive *versus* semantic), *ii*) the physiological 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 for each 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 (*i*1), white matter (*i*2) and CSF (*i*3) maps from the T1 images of 30 healthy adolescents aged between 13 and 18 years recruited for a study focused on healthy development (see Dégeilh et al., 2015), from which 10 controls 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 than controls (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 analysis revealed 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 controls endorsed more positive than negative adjectives as self-descriptive ($p < 0.001$). T-tests on the proportions of positive self-appraisal revealed no significant difference between patients and controls ($t_{18} = 1.8$, $p = 0.09$; Figure 1).

Regarding the response times during 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 activity changes

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 activation in 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 and right precuneus (Figure 3, Table 3). Overall, these couplings were negative in PTSD patients. During positive SRP, compared to controls, PTSD patients showed stronger positive connectivity between the left amygdala and bilateral middle temporal gyrus and left ventrolateral PFC (vlPFC) (Figure 3, Table 3).

4. Discussion

The aim of this preliminary fMRI study was to explore neural substrates associated to emotionally valenced SRP 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 which is 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 and connectivity during SRP. They showed 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 connected to a large network including dorsal PFC, angular and precuneus. During positive SRP, PTSD patients exhibited higher left superior temporal activity and stronger amygdala-vlPFC connectivity. Overall, these results show that pediatric PTSD may be characterized by early functional abnormalities in regions involved in emotional regulation and memory during 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 described in 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 activation and reduced functional amygdala connectivity with the dmPFC, the precuneus and the angular gyrus.

The PFC and amygdala are core brain structures involved in emotional regulation (M. J. Kim, Gee, Loucks, Davis, & Whalen, 2011). Effective down regulation of negative emotion is characterized by PFC activity increase, together with amygdala activity decrease (Ochsner, Bunge, Gross, & Gabrieli, 2002) and stronger amygdala–dmPFC connectivity (Lee, Heller, van Reekum, Nelson, & Davidson, 2012). The dmPFC, precuneus and angular gyrus are 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 that pediatric 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 the mPFC 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 resembles that 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 gyrus compared 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 vIPFC 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 vIPFC 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 than on their own self properties.

4.4. Methodological considerations and future directions

Our findings bring 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 sample affecting statistical power (as depicted by the use of an uncorrected $p = 0.001$). Hence, this study needs to be extended with a larger sample. In addition, it would be interesting to include another comparison group of trauma-exposed non-PTSD subjects to evaluate the effect of trauma exposure *per se* separately from PTSD. Thus, the present findings, while in need of replication, nevertheless suggest that self-distortion may have a role in the maintenance of PTSD symptoms relative to childhood abuse in adulthood.

5. Conclusion

Activity and connectivity changes in amygdala-prefrontal regions during negative SRP observed in the present study may reflect a deficit in cognitive regulation of negative emotion. These results show that 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 be characterized 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, a psychotherapy focused on introspection and self-awareness to promote positive self processing.

Acknowledgments

This study was supported by the University Hospital of Caen, the Caen school district and the Mutuelle Générale de l'Éducation Nationale (mutual insurance company). We would like to thank C. Lebouleux, F. Mézenge, M.H. Noël, M.C. Onfroy and C. Tomadesso for their help in testing participants and data acquisition. We are also thankful to the adolescents and institutions that took part in our research.

References

- Aghajani, M., Veer, I. M., van Hoof, M.-J., Rombouts, S. A. R. B., van der Wee, N. J., & Vermeiren, R. R. J. M. (2016). Abnormal functional architecture of amygdala-centered networks in adolescent posttraumatic stress disorder. *Human Brain Mapping, 37*(3), 1120–1135. <http://doi.org/10.1002/hbm.23093>
- Ahmed, S. P., Bittencourt-Hewitt, A., & Sebastian, C. L. (2015). Neurocognitive bases of emotion regulation development in adolescence. *Developmental Cognitive Neuroscience, 15*, 11–25. <http://doi.org/10.1016/j.dcn.2015.07.006>
- Andrews, B., Brewin, C. R., Rose, S., & Kirk, M. (2000). Predicting PTSD symptoms in victims of violent crime: The role of shame, anger, and childhood abuse. *Journal of Abnormal Psychology, 109*(1), 69–73. <http://doi.org/10.1037/0021-843X.109.1.69>
- Badre, D., Poldrack, R. A., Paré-Blagoev, E. J., Insler, R. Z., & Wagner, A. D. (2005). Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. *Neuron, 47*(6), 907–18. <http://doi.org/10.1016/j.neuron.2005.07.023>
- Benoit, R. G., Gilbert, S. J., Volle, E., & Burgess, P. W. (2010). When I think about me and simulate you: Medial rostral prefrontal cortex and self-referential processes. *NeuroImage, 50*(3), 1340–1349. <http://doi.org/10.1016/j.neuroimage.2009.12.091>
- Bluhm, R. L., Frewen, P. A., Coupland, N. C., Densmore, M., Schore, a N., & Lanius, R. a. (2012). Neural correlates of self-reflection in post-traumatic stress disorder. *Acta Psychiatrica Scandinavica, 125*(3), 238–246. <http://doi.org/10.1111/j.1600-0447.2011.01773.x>
- Bowlby, J. (1969). *Attachment and loss* (Vol. I). New York: Basic Books.
- Brunet, A., St-Hilaire, A., Jehel, L., & King, S. (2003). Validation of a French version of the impact of event scale-revised. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie, 48*(1), 56–61. <http://doi.org/10.1177/070674370304800111>

- Bryant, R. A., & Guthrie, R. M. (2005). Maladaptive appraisals as a risk factor for posttraumatic stress: a study of trainee firefighters. *Psychological Science, 16*(10), 749–52. <http://doi.org/10.1111/j.1467-9280.2005.01608.x>
- Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences, 1124*, 1–38. <http://doi.org/10.1196/annals.1440.011>
- Cicchetti, D., & Rogosch, F. A. (1994). The toll of child maltreatment on the developing child: Insights from developmental psychopathology. *Child and Adolescent Psychiatric Clinics of North America, 3*, 759–776.
- Cisler, J. M., Scott Steele, J., Smitherman, S., Lenow, J. K., & Kilts, C. D. (2013). Neural processing correlates of assaultive violence exposure and PTSD symptoms during implicit threat processing: A network-level analysis among adolescent girls. *Psychiatry Research - Neuroimaging, 214*(3), 238–246. <http://doi.org/10.1016/j.psychresns.2013.06.003>
- Crozier, J. C., Wang, L., Huettel, S. A., & De Bellis, M. D. (2014). Neural correlates of cognitive and affective processing in maltreated youth with posttraumatic stress symptoms: Does gender matter? *Development and Psychopathology, 26*(2), 491–513. <http://doi.org/10.1017/S095457941400008X>
- De Bellis, M. D., & Zisk, A. (2014). The biological effects of childhood trauma. *Child and Adolescent Psychiatric Clinics of North America, 23*(2), 185–222, vii. <http://doi.org/10.1016/j.chc.2014.01.002>
- Dégeilh, F., Guillery-Girard, B., Dayan, J., Gaubert, M., Chételat, G., Egler, P.-J., ... Viard, A. (2015). Neural Correlates of Self and Its Interaction With Memory in Healthy Adolescents. *Child Development, 86*(6), 1966–1983. <http://doi.org/10.1111/cdev.12440>
- Dugas, M., & Bouvard, M. (1996). French version of the Children Depression Inventory

- Bouvard. In J. D. Guelfi (Ed.), *L'évaluation clinique standardisée en psychiatrie* (pp. 543–8). Boulogne: Pierre Fabre.
- Ehlers, A., & Clark, D. M. (2000). A cognitive model of posttraumatic stress disorder. *Behaviour Research and Therapy*, 38(4), 319–345. [http://doi.org/10.1016/S0005-7967\(99\)00123-0](http://doi.org/10.1016/S0005-7967(99)00123-0)
- First, M. B., Spitzer, R. L., Miriam, G., & Williams, J. B. W. (1996). *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)*. (Inc., Ed.) (American P). Washington, D.C.
- Fonov, V., Evans, A. C., Botteron, K., Almli, C. R., McKinstry, R. C., & Collins, D. L. (2011). Unbiased average age-appropriate atlases for pediatric studies. *NeuroImage*, 54(1), 313–327. <http://doi.org/10.1016/j.neuroimage.2010.07.033>
- Frewen, P. A., Dozois, D. J. A., Neufeld, R. W. J., Densmore, M., Stevens, T. K., & Lanius, R. a. (2011). Self-referential processing in women with PTSD: Affective and neural response. *Psychological Trauma: Theory, Research, Practice, and Policy*, 3(4), 318–328. <http://doi.org/10.1037/a0021264>
- Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage*, 6(3), 218–29. <http://doi.org/10.1006/nimg.1997.0291>
- Garrett, A. S., Carrion, V. G., Kletter, H., Karchemskiy, A., Weems, C. F., & Reiss, A. (2012). Brain activation to facial expressions in youth with PTSD symptoms. *Depression and Anxiety*, 29(5), 449–459. <http://doi.org/10.1002/da.21892>
- Gitelman, D. R., Penny, W. D., Ashburner, J., & Friston, K. J. (2003). Modeling regional and psychophysiological interactions in fMRI: the importance of hemodynamic deconvolution. *NeuroImage*, 19(1), 200–207. [http://doi.org/10.1016/S1053-8119\(03\)00058-2](http://doi.org/10.1016/S1053-8119(03)00058-2)
- Greenberg, D. L., Rice, H. J., Cooper, J. J., Cabeza, R., Rubin, D. C., & LaBar, K. S. (2005).

- Co-activation of the amygdala, hippocampus and inferior frontal gyrus during autobiographical memory retrieval. *Neuropsychologia*, 43(5), 659–674.
<http://doi.org/10.1016/j.neuropsychologia.2004.09.002>
- Hayes, J. P., Hayes, S. M., & Mikedis, A. M. (2012). Quantitative meta-analysis of neural activity in posttraumatic stress disorder. *Biology of Mood & Anxiety Disorders*, 2(1), 9.
<http://doi.org/10.1186/2045-5380-2-9>
- Hayes, J. P., Vanelzakker, M. B., & Shin, L. M. (2012). Emotion and cognition interactions in PTSD: a review of neurocognitive and neuroimaging studies. *Frontiers in Integrative Neuroscience*, 6(October), 89. <http://doi.org/10.3389/fnint.2012.00089>
- Kim, J., & Cicchetti, D. (2006). Longitudinal trajectories of self-system processes and depressive symptoms among maltreated and nonmaltreated children. *Child Development*, 77(3), 624–39. <http://doi.org/10.1111/j.1467-8624.2006.00894.x>
- Kim, M. J., Gee, D. G., Loucks, R. a., Davis, F. C., & Whalen, P. J. (2011). Anxiety Dissociates Dorsal and Ventral Medial Prefrontal Cortex Functional Connectivity with the Amygdala at Rest. *Cerebral Cortex*, 21(7), 1667–1673.
<http://doi.org/10.1093/cercor/bhq237>
- Kovacs, M. (1981). Rating scales to assess depression in school-aged children. *Acta Paedopsychiatrica*, 46(5–6), 305–15.
- Lanius, R. a, Bluhm, R. L., & Frewen, P. A. (2011). How understanding the neurobiology of complex post-traumatic stress disorder can inform clinical practice: a social cognitive and affective neuroscience approach. *Acta Psychiatrica Scandinavica*, 124(5), 331–48.
<http://doi.org/10.1111/j.1600-0447.2011.01755.x>
- Lee, H., Heller, A. S., van Reekum, C. M., Nelson, B., & Davidson, R. J. (2012). Amygdala-prefrontal coupling underlies individual differences in emotion regulation. *NeuroImage*, 62(3), 1575–81. <http://doi.org/10.1016/j.neuroimage.2012.05.044>

- Levy, D. a, Bayley, P. J., & Squire, L. R. (2004). The anatomy of semantic knowledge: medial vs. lateral temporal lobe. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(17), 6710–5. <http://doi.org/10.1073/pnas.0401679101>
- Lobbestael, J., Leurgans, M., & Arntz, A. (2011). Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). *Clinical Psychology & Psychotherapy*, *18*(1), 75–79. <http://doi.org/10.1002/cpp.693>
- McGloin, J. M., & Widom, C. S. (2001). Resilience among abused and neglected children grown up. *Development and Psychopathology*, *13*(4), 1021–38. <http://doi.org/10.1017/S095457940100414X>
- Northoff, G., Heinzl, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006). Self-referential processing in our brain--a meta-analysis of imaging studies on the self. *NeuroImage*, *31*(1), 440–57. <http://doi.org/10.1016/j.neuroimage.2005.12.002>
- Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. E. (2002). Rethinking feelings: an fMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*, *14*(8), 1215–29. <http://doi.org/10.1162/089892902760807212>
- Patel, R., Spreng, R. N., Shin, L. M., & Girard, T. a. (2012). Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, *36*(9), 2130–42. <http://doi.org/10.1016/j.neubiorev.2012.06.003>
- Pfeifer, J. H., & Peake, S. J. (2012). Self-development: integrating cognitive, socioemotional, and neuroimaging perspectives. *Developmental Cognitive Neuroscience*, *2*(1), 55–69. <http://doi.org/10.1016/j.dcn.2011.07.012>
- Pitman, R. K., Rasmusson, A. M., Koenen, K. C., Shin, L. M., Orr, S. P., Gilbertson, M. W., ... Liberzon, I. (2012). Biological studies of post-traumatic stress disorder. *Nature Reviews. Neuroscience*, *13*(11), 769–87. <http://doi.org/10.1038/nrn3339>

- Rauch, S. L., Shin, L. M., & Phelps, E. a. (2006). Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research--past, present, and future. *Biological Psychiatry*, 60(4), 376–82. <http://doi.org/10.1016/j.biopsych.2006.06.004>
- Reynolds, C. R., & Richmond, B. O. (1997). What I think and feel: A revised measure of children's manifest anxiety. *Journal of Abnormal Child Psychology*, 25(1), 15–20. <http://doi.org/10.1023/A:1025751206600>
- Reynolds, C. R., Richmond, B. O., & Castro, D. (1999). *Echelle Révisée d'Anxiété Manifeste pour Enfants (R-CMAS)* (Les Editio). Paris.
- Rosenberg, M. (1965). *Society and the adolescent self-image*. PrincetonN.J.: Princeton University Press.
- Saigh, P. a, Yasik, A. E., Oberfield, R., & Halamandaris, P. V. (2008). The self-concept of traumatized children and adolescents with or without PTSD. *Behaviour Research and Therapy*, 46(10), 1181–6. <http://doi.org/10.1016/j.brat.2008.05.003>
- Shafran, N., Shahar, G., Berant, E., & Gilboa-Schechtman, E. (2015). Representations of Self and Parents, and Relationship Themes, in Adolescents with Post Traumatic Stress Disorder (PTSD). *Journal of Abnormal Child Psychology*. <http://doi.org/10.1007/s10802-015-0100-1>
- Vallieres, E. F., & Vallerand, R. J. (1990). Traduction et Validation Canadienne-Française de L'échelle de L'estime de Soi de Rosenberg. *International Journal of Psychology*, 25(2), 305–316. <http://doi.org/10.1080/00207599008247865>
- Villain, N., Landeau, B., Groussard, M., Mevel, K., Fouquet, M., Dayan, J., ... Chételat, G. (2010). A simple way to improve anatomical mapping of functional brain imaging. *Journal of Neuroimaging : Official Journal of the American Society of Neuroimaging*, 20(4), 324–33. <http://doi.org/10.1111/j.1552-6569.2010.00470.x>
- Weiss, D. S., & Marmar, C. R. (1997). The Impact of Event Scale-Revised. In J. P. Wilson

&T. M. Keane (Eds.), *Assessing Psychological Trauma and PTSD: A Practitioner's Handbook* (pp. 399–411). New York City: Guilford Press.

Wolf, R. C., & Herringa, R. J. (2015). Prefrontal-Amygdala Dysregulation to Threat in Pediatric Posttraumatic Stress Disorder. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, 1–10.
<http://doi.org/10.1038/npp.2015.209>

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.

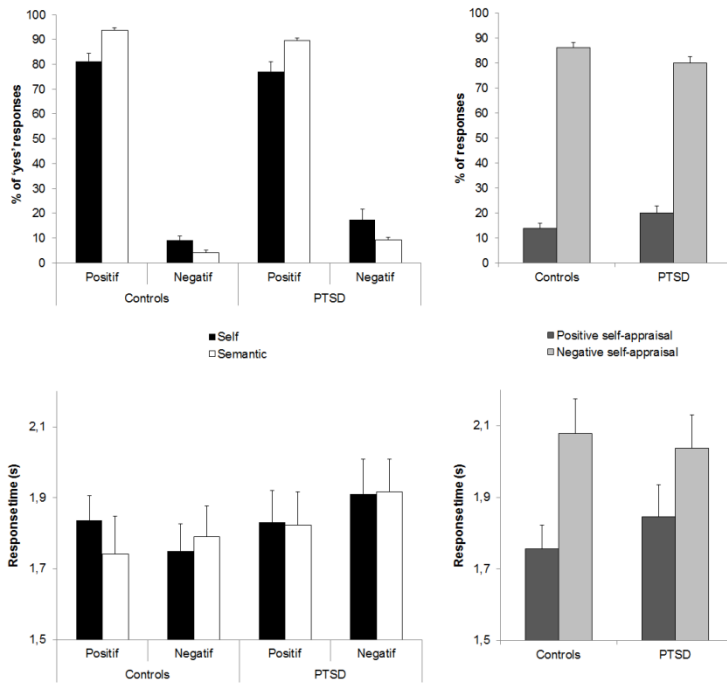


Figure 2: Brain activity changes during positive (A) and negative (B) self-reference processing.

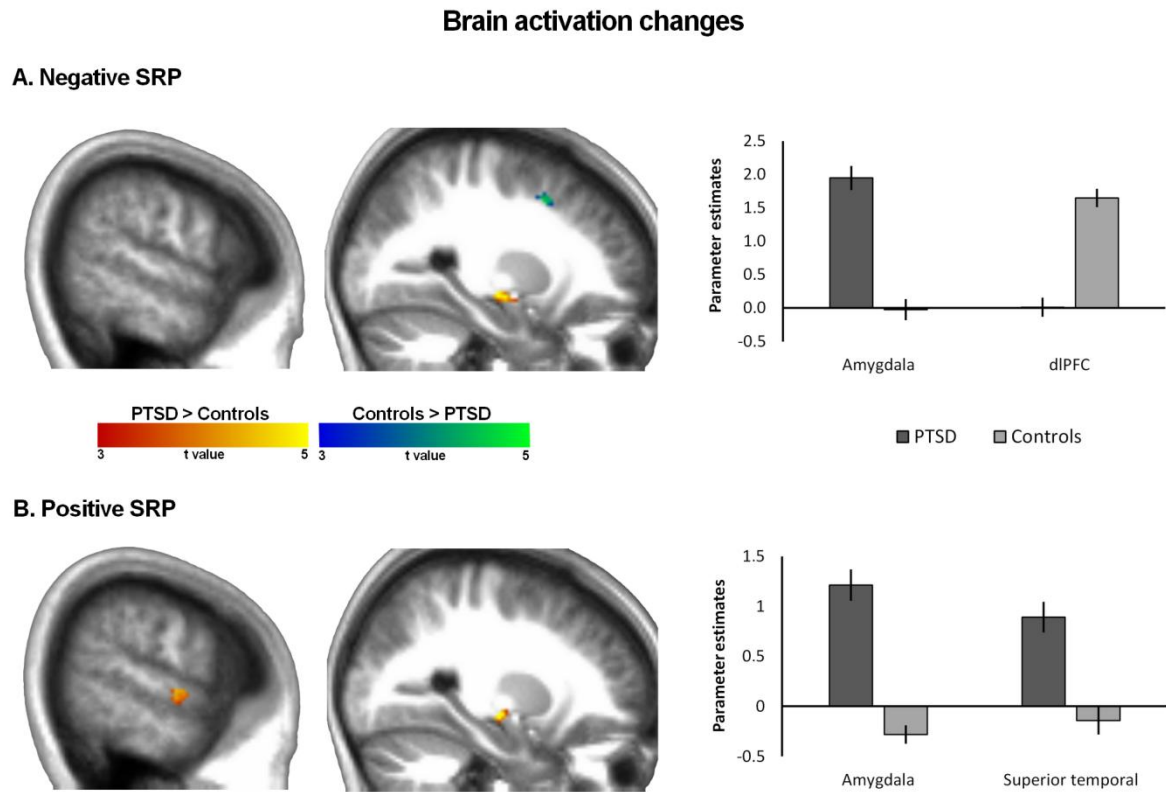


Figure 3: Left amygdala functional connectivity during positive (A) and negative (B) self-reference processing.

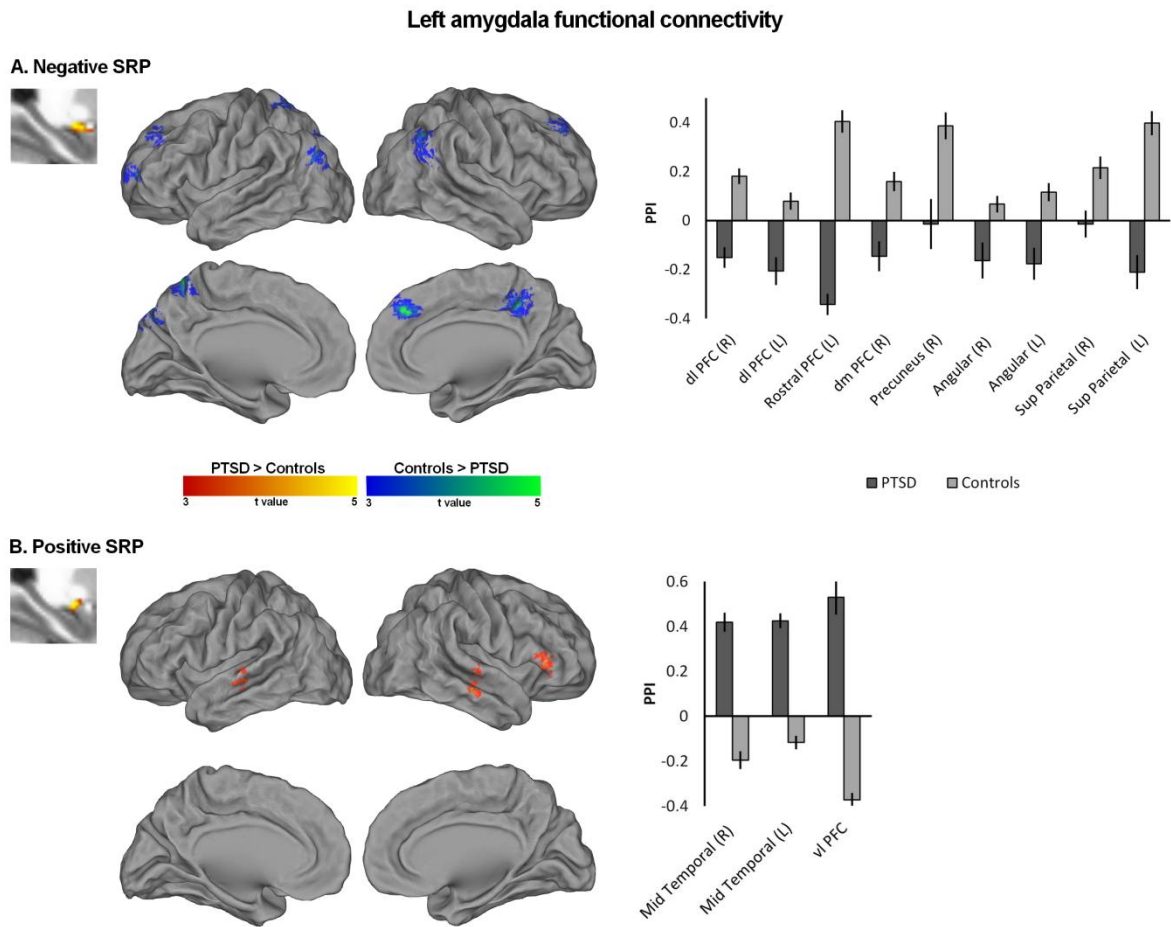


Table S1: Brain activity changes in PTSD patients compared to controls during negative and positive self-reference processing compared to other-reference processing.

| 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 | | | | | | | |
| - | - | | - | - | - | - | - |