

3-19-2015

The Dissociative Subtype of Posttraumatic Stress Disorder: Unique Resting-State Functional Connectivity of Basolateral and Centromedial Amygdala Complexes.

Andrew A Nicholson

Maria Densmore

Paul A Frewen

Jean Théberge

Richard W J Neufeld

See next page for additional authors

Follow this and additional works at: <https://ir.lib.uwo.ca/biophysicspub>



Part of the [Medical Biophysics Commons](#)

Citation of this paper:

Nicholson, Andrew A; Densmore, Maria; Frewen, Paul A; Théberge, Jean; Neufeld, Richard W J; McKinnon, Margaret C; and Lanius, Ruth A, "The Dissociative Subtype of Posttraumatic Stress Disorder: Unique Resting-State Functional Connectivity of Basolateral and Centromedial Amygdala Complexes." (2015). *Medical Biophysics Publications*. 57.
<https://ir.lib.uwo.ca/biophysicspub/57>

Authors

Andrew A Nicholson, Maria Densmore, Paul A Frewen, Jean Théberge, Richard W J Neufeld, Margaret C McKinnon, and Ruth A Lanius



**The Dissociative Subtype of Posttraumatic Stress Disorder:
Unique Resting-State Functional Connectivity of Basolateral
and Centromedial Amygdala Complexes**

Andrew A Nicholson, Maria Densmore, Paul A Frewen, Jean
Th  berge, Richard W J Neufeld, Margaret C McKinnon,
Ruth A Lanius

Cite this article as: Andrew A Nicholson, Maria Densmore, Paul A Frewen, Jean Th  berge, Richard W J Neufeld, Margaret C McKinnon, Ruth A Lanius, The Dissociative Subtype of Posttraumatic Stress Disorder: Unique Resting-State Functional Connectivity of Basolateral and Centromedial Amygdala Complexes, *Neuropsychopharmacology* accepted article preview 19 March 2015; doi: [10.1038/npp.2015.79](https://doi.org/10.1038/npp.2015.79).

This is a PDF file of an unedited peer-reviewed manuscript that has been accepted for publication. NPG are providing this early version of the manuscript as a service to our customers. The manuscript will undergo copyediting, typesetting and a proof review before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers apply.

Received 1 October 2014; accepted 16 March 2015; Accepted article preview online 19 March 2015

The Dissociative Subtype of Posttraumatic Stress Disorder: Unique Resting-State Functional
Connectivity of Basolateral and Centromedial Amygdala Complexes

Andrew A. Nicholson, B.Sc., Western University

Maria Densmore, B.Sc., Lawson Health Research Institute

Paul A. Frewen, Ph.D., Western University, Lawson Health Research Institute

Jean Théberge, Ph.D., St. Joseph's Health Care London Department of Diagnostic Imaging,
Western University Departments of Medical Imaging, Medical Biophysics and Psychiatry

Richard W.J. Neufeld, Ph.D., Departments of Psychology and Psychiatry, Neuroscience
Program, Western University

Margaret C. McKinnon, Ph.D., McMaster University,

St. Joseph's Healthcare Hamilton, Homewood Research Institute

Ruth A. Lanius*, M.D. Ph.D., Western University, Lawson Health Research Institute

*Corresponding Author

Ruth.lanius@lhsc.on.ca, 519-663-3306

339 Windermere Road, PO Box 5339

University Hospital

London, ON N6A 5A5

Abstract

Previous studies point towards differential connectivity patterns among basolateral (BLA) and centromedial (CMA) amygdala regions in patients with posttraumatic stress disorder (PTSD) as compared to controls. Here, we describe the first study to compare directly connectivity patterns of the BLA and CMA complexes between PTSD patients with and without the dissociative subtype (PTSD+DS and PTSD-DS, respectively). Amygdala connectivity to regulatory prefrontal regions and parietal regions involved in consciousness and proprioception were expected to differ between these two groups based on differential limbic regulation and behavioural symptoms. PTSD patients ($n = 49$), with ($n = 13$) and without ($n = 36$) the dissociative subtype, and age-matched healthy controls ($n = 40$) underwent resting-state fMRI. Bilateral BLA and CMA connectivity patterns were compared using a seed-based approach via SPM Anatomy Toolbox. Among patients with PTSD, the PTSD+DS group exhibited greater amygdala functional connectivity to prefrontal regions involved in emotion regulation (bilateral BLA and left CMA to the middle frontal gyrus and bilateral CMA to the medial frontal gyrus) as compared to the PTSD-DS group. In addition, the PTSD+DS group showed greater amygdala connectivity to regions involved in consciousness, awareness, and proprioception –implicated in depersonalization and derealization (left BLA to superior parietal lobe and cerebellar culmen; left CMA to dorsal posterior cingulate and precuneus). Differences in amygdala complex connectivity to specific brain regions parallel the unique symptom profiles of the PTSD subgroups and point towards unique biological markers of the dissociative subtype of PTSD.

Introduction

The dissociative subtype of posttraumatic stress disorder (PTSD+DS) – exhibited by 13-30% of PTSD patients – has recently been added to the fifth revision of the Diagnostic and Statistical Manual (American Psychiatric Association, 2013; Lanius et al., 2012; Stein et al., 2013; Steuwe et al., 2012; Wolf et al., 2012). In addition to genetic predispositions associated with the emergence of PTSD+DS (Wolf et al., 2014), epidemiological evidence points to several risk factors also associated with PTSD+DS, including prior trauma, childhood adversities, and childhood onset of PTSD (Stein et al., 2013).

Numerous studies point towards differential patterns of neural activation of the amygdala, prefrontal cortex (PFC), anterior cingulate cortex (ACC), precuneus, and parietal lobe in PTSD patients who exhibit dissociative responses during traumatic script-driven imagery or fear processing as compared to those who instead demonstrate re-experiencing symptoms (Felmingham et al., 2008; Hopper et al., 2007; Lanius et al., 2002; 2005; 2010a). This observation led to the identification of two types of emotion and amygdalar dysregulation among PTSD patients, proposed to occur at baseline as well as in response to trauma reminders: undermodulation and overmodulation (Lanius et al., 2010b; 2012). Emotional undermodulation consists of reliving traumatic experiences with related hyperarousal, characteristic of non-dissociative PTSD patients (PTSD-DS). This behavioural response is associated with decreased activation of PFC regions and ACC, thereby decreasing top-down inhibition of the amygdala and leading to hyperactivation of the limbic system (Lanius et al., 2010b; 2012; Shin and Liberzon, 2005; 2010; also see Birn et al., 2014; Stevens et al., 2013; Yan et al., 2014). Here, Lévesque et al. (2003) report increased activation within the right dorsolateral prefrontal cortex (dlPFC) when healthy participants were asked to suppress negative emotions that were associated with

increased amygdala activity. Similarly, Banks et al. (2007) show that the dlPFC exhibits connectivity to the amygdala when healthy participants were asked to regulate negative affect, suggesting top down PFC inhibition of the amygdala. A recent study has also reported that hyperarousal is associated with negative mPFC-amygdala coupling in PTSD (Sadeh et al., 2014). In contrast to emotional undermodulation, overmodulation is associated with emotional detachment and hypoarousal involving symptoms of depersonalization and derealization characteristic of PTSD+DS. Emotional overmodulation is thought to be mediated by increased PFC and ACC activation, resulting in excessive top-down inhibition of the amygdala (Lanius et al., 2010b; 2012). Right amygdala activity has also been shown to be negatively correlated with trait dissociative symptoms during exposure to thermal pain in PTSD patients (Mickleborough et al., 2011). Additionally, findings from a meta-analysis examining neuroimaging findings in PTSD have demonstrated a dorsal hypoactive amygdala region, comprising the centromedial complex (CMA; see below), which was suggested by the authors to be related to autonomic blunting associated with emotional numbing and dissociation (Etkin and Wagner, 2007). Taken together, these findings suggest that the amygdala may exhibit differential neuromodulation in PTSD+DS and PTSD-DS.

The amygdala can be classified into two subdivisions, forming the basolateral (BLA) and CMA amygdala complexes. The BLA and CMA have differential patterns of functional and structural connectivity, in addition to unique roles in fear processing (Roy et al., 2007; Phelps et al., 2004), which are altered in PTSD patients (Milad, 2014; Sripada et al., 2012). The BLA evaluates sensory information and mediates cortical integration of fear and other emotions (Jovanovic and Ressler, 2010). The BLA is regulated by feedforward inhibition from the medial PFC via somatostatin connections, with outputs to the thalamus, striatum, and PFC (Duvarci and

Pare, 2014). The CMA is involved in the execution of fear responses, with GABAergic outputs to the brainstem and periaqueductal gray involved in descending pain modulation (Duvarci and Pare, 2014; LeDoux, 1998; Milad, 2013). The CMA also receives thalamic projections and mediates major nociceptive pathways (Duvarci et al. 2014). Notably, deactivation of the CMA results in the impairment of fear expression and acquisition (Duvarci and Pare, 2014).

A novel study by Brown et al. (2014) reported differential resting-state connectivity of the BLA but not the CMA between military-trauma exposed PTSD patients and veteran controls, where the PTSD group showed greater connectivity to the pregenual ACC, dorsomedial PFC, and dorsal ACC, and controls showed stronger connectivity to the left inferior frontal gyrus. These findings suggest that the BLA and CMA complexes may exhibit unique roles in relation to PTSD symptomatology.

Critically, no studies have compared directly patterns of amygdala complex (BLA and CMA) resting-state connectivity in PTSD+DS versus PTSD-DS, which is the objective of the current study. Due to the proposed differential PFC- and ACC-mediated inhibition of the amygdala in PTSD+DS and PTSD-DS (exacerbated inhibition and attenuated inhibition, respectively), connectivity between the BLA and PFC (dlPFC) and ACC was expected to be greater in the PTSD+DS as compared to the PTSD-DS group. Moreover, given that patients with PTSD+DS and PTSD-DS exhibit unique behavioural symptoms, connectivity of the CMA was predicted to differ between these groups. Finally, we hypothesized altered amygdala connectivity (BLA and CMA) to lateral and midline parietal regions involved in consciousness, awareness, and proprioception among PTSD patients — which may contribute to the unique symptoms observed between the two patient groups.

Methods

Participants

Participants were recruited between 2009 to 2013 from the Department of Psychiatry London Health Services Center (LHSC), through family physicians, mental health professionals, psychology/psychiatric clinics, community programs for traumatic-stress survivors, and posters/advertisements, all within the London, ON community. The sample consisted of 49 PTSD patients and 40 age-matched healthy controls (demographic and clinical information are summarized in Table 1). Exclusion criteria for all participants included: any implants or metal that do not comply with 3T fMRI safety standards, a history of head injury with any loss of consciousness, significant untreated medical illness, a history of neurological disorders, a history of any pervasive developmental disorders, pregnancy, and current use of any psychotropic or cardiovascular medications within one month prior to the study. The exclusion criteria for PTSD patients included: history of bipolar disorder or schizophrenia, alcohol or substance dependence/abuse not in sustained full remission within 6 months prior to participation in the study. Exclusion criteria for the control group consisted of current or past Axis-I or Axis-II disorders. Participants were assessed using the DSM-IV Structured Clinical Interview (SCID) (First, 1997), the Clinical Administered PTSD Scale (CAPS) (Blake et al., 1995), Beck's Depression Inventory (BDI) (Beck et al., 1997), and the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). Additionally, the Multiscale Dissociation Inventory (MDI) (Briere, Weathers et al., 2005) was administered - which is a standard 30-item test of 6 types of dissociative responses: Disengagement (DENG), Depersonalization (DEPR), Derealization (DERL), Emotional Constriction (ECON), Memory Disturbance (MEMD), and Identity Dissociation (IDDIS). All PTSD participants met criterion A in the DSM-IV and had a CAPS

score of greater than 50. To be classified as PTSD+DS, PTSD patients required a score of at least 2 on both frequency and intensity for either the CAPS depersonalization or derealization items, a conservative standard method of DSM-IV PTSD+DS characterization (Steuwe et al., 2012), which restricts false positives. All scanning took place at the Robarts Research Institute's Center for Functional and Metabolic Mapping in London, Ontario, Canada. The research ethics board at the University of Western Ontario approved the current study, and all participants provided written informed consent.

fMRI Data Acquisition

Functional images were collected using a 3.0 T, whole-body MRI scanner (Magnetom Tim Trio, Siemens Medical Solutions, Erlangen, Germany) with the manufacturer's 32-channel phased array head coil. BOLD fMRI images were acquired with the manufacturer's standard gradient-echo EPI pulse sequence (single-shot, blipped-EPI, interleaved slice acquisition order and tridimensional prospective acquisition correction). Participants' heads were immobilized with foam padding within the head coil. EPI volumes were acquired with 2 mm isotropic resolution with the following parameters: FOV = 192 mm X 192 mm X 128mm (94 x 94 matrix, 64 slices), TR/TE = 3000 ms/ 20 ms, flip angle = 90°, 120 volumes. Participants were asked to close their eyes, relax and let their minds wander during the 6-minute (120-volume) scan. After the scan, participants were asked whether they had been able to comply with the instructions and whether they felt as though they had drifted out of wakefulness (all participants had been able to comply with the instructions, and no participant reported having drifted out of wakefulness).

fMRI Data Preprocessing

Image preprocessing and statistical analyses were conducted using Statistical Parametric Mapping (SPM8 and SPM12, Wellcome Department of Neurology, London, UK:

<http://www.fil.ion.ucl.ac.uk/spm>) within Matlab 8.3 (The Mathworks Inc., MA). For each participant, all functional images were realigned to the first image in the series, resliced, and mean functional images were created. Functional images were further motion corrected using the ART software (Gabrieli Lab. McGovern Institute for Brain Research, Cambridge, MA), which computes motion outlier regressors to be used in the 1st level analysis as a covariate of no interest. Movement did not differ between participant groups based on SPM and ART parameters. The images were then spatially normalized. The mean image was co-registered to the SPM EPI template and the resulting deformation matrix was applied to the functional images. All images were then smoothed using a 6mm full-width-half-maximum isotropic Gaussian filter. Band-pass filtering was conducted using successive application of a high-pass and low-pass filter with frequency cut-offs of 0.012 Hz and 0.1 Hz respectively (in-house software by co-author Jean Théberge). Seed region-of-interest masks were created using SPM's Anatomy Toolbox (Eickhoff et al., 2005) featuring cytoarchitectonically-based probability maps of the amygdala. Connectivity correlations were standardized using a Fisher Z transformation in SPM8.

Statistical Analyses

Subject-level analyses were conducted separately for each amygdala ROI. For each participant, a mean signal intensity time course was extracted from SPM's Anatomy Toolbox for each of four seed regions (bilateral BLA and bilateral CMA) and then used as a regressor in a correlation analysis with the whole-brain resting scan data for that participant. Connectivity is thus indicative of a correlation between amygdala seed regions and other brain areas. Both positive correlations and anti-correlations were examined. A whole-brain 3 (group) × 2 (complex) full-factorial analysis of variance (ANOVA) was conducted in the second level analyses. The between-group factor consisted of 3 levels: PTSD+DS, PTSD-DS, and controls, and the within-

group factor consisted of 2 levels: BLA and CMA. The variance for the between-group factor was set to unequal in order to account for the unequal sample size (Milligan et al., 1987). Here, a restricted maximum likelihood adjustment was made to the degrees of freedom during inference, using weighted least squares to produce Gauss-Markov estimators. The group \times complex interaction yielded 8 significant (FWE-corrected $p < .05$, $k = 10$) gray matter clusters (see Table 2 for ANOVA results). Follow-up comparisons for the 8 coordinates meeting the above error rate protection were then conducted examining connectivity values in one- and two-sample t-tests. Follow-up analyses utilized p -uncorrected $< .005$ $k = 10$, as following the suggestion of Lieberman and Cunningham (2009) to balance the relative risk of Type I versus II error rates. One-sample within-group analyses were conducted for each PTSD patient group and control group, individually for each amygdala seed region. Two-sample between-group contrasts were explored for each seed region, comparing both PTSD patient groups, and each patient group to the control group. Similarly, bilateral dlPFC coordinates were specified a-priori and used to conduct small volume correction analyses with an 8-mm radius sphere (MNI 36 25 30: Lévesque et al, 2003; MNI 48 28 36 and MNI -12 22 60: Banks et al., 2007) (FWE-corrected $p < .05$ $k = 10$). This region was chosen as the model postulated by Lanius et al. (2010) hypothesizes that PFC regions exhibit differential top down inhibition in PTSD+DS versus PTSD-DS. Critically, Lévesque et al. (2003) report increased activation within the right dlPFC when participants were asked to voluntarily suppress negative emotion – where negative emotion was associated with increased amygdala activation. Banks et al. (2007) show that bilaterally the dlPFC exhibits connectivity to the amygdala when participants were asked to regulate negative affect.

Baseline amygdala activity was also compared across groups for each seed to avoid potential confounding factors when drawing inferences about activity correlations. This is

important as differences in connectivity between groups may be driven by the unique baseline activity of the seed region (see Supplemental Methods). To measure baseline amygdala complex activity, mean signal intensity time courses were extracted for each amygdala seed on the participant level to compare across groups. In addition, clinical variables CAPs, CTQ, MDI, and BDI were compared across groups. One-way independent analyses of variance (ANOVAs) were used to compare baseline amygdala activity and clinical variables (see Supplemental Methods for statistics protocol). Furthermore, subscale MDI depersonalization and derealization items were averaged for each participant and evaluated as a predictor of amygdala connectivity in a multiple regression including data from all PTSD (PTSD-DS and PTSD+DS) patients, examining the 8 FWE-corrected clusters reported from the group \times complex interaction and coordinates from the dlPFC a-priori region-of-interest.

Results

Clinical Variables and Baseline Amygdalar Activity

All clinical variables (CAPS, BDI, CTQ, and MDI) yielded significant values for Levene's test of homogeneity of variance (means and standard deviations are presented in Table 1, statistics are presented in Table 3). Via Games-Howell comparisons, no significant differences were found between PTSD+DS and PTSD-DS groups in regard to CAPS, BDI, and CTQ scores. MDI scores were significantly higher in the PTSD+DS as compared to PTSD-DS group. MDI and CTQ scores were higher in the PTSD+DS and PTSD-DS group as compared to the control group. There were no between-patient group differences in baseline amygdala activity (see Supplemental Results: Table s5 for means and standard deviations, Table s6 for statistical details) and, therefore, connectivity comparisons between patient groups could be interpreted with confidence in this regard.

One-Sample Functional Connectivity Within the Dissociative Subtype, Non-Dissociative PTSD and Control Groups

Resting-state activity in the BLA and CMA predicted widespread activation in multiple cortical and subcortical regions within all participant groups for both the coordinates extracted from the ANOVA interaction and the a-priori dlPFC region. These results generally replicated findings by Brown et al., (2014) and Roy et al., (2009). As they are not the main focus of the current study, within-group data are reported in Supplemental Results (see Tables s1, s2, s3). There were no significant anti-correlations for within-group connectivity maps.

Dissociative Subtype and Non-dissociative PTSD Group Differences in Functional Connectivity

When examining connectivity values from the ANOVA interaction coordinates, the PTSD+DS group showed greater functional connectivity between the left BLA and the left superior parietal lobe (SPL) (BA 5), and the left culmen of the cerebellum (Figure 1a; Table 4a) as compared to the PTSD-DS group. The PTSD+DS also showed greater functional connectivity between the left CMA and the left dorsal posterior cingulate (BA 24), left medial frontal gyrus (BA6), and the left precuneus (BA 7) (Figure 1c), while the right CMA showed greater functional connectivity to the left medial frontal gyrus (BA 32) (Figure 1d) as compared to the PTSD-DS group. The PTSD-DS group did not show any significantly greater connectivity patterns to any of the amygdala complexes as compared to the PTSD+DS group.

In addition, when examining the dlPFC a-priori region, the PTSD+DS group showed greater functional connectivity between both the left and right BLA and the right middle frontal gyrus (BA 9) (Figure 1a and 1b; Table 4b). The PTSD+DS group also showed greater connectivity between the left CMA and the right middle frontal gyrus (BA 9) (Figure 1c).

MDI Correlations to Functional Connectivity Within PTSD Patients

Higher depersonalization and derealization MDI scores predicted increased connectivity between the left BLA and right middle frontal gyrus – a region showing one of the strongest between-patient group differences in connectivity in the main analysis (see Table 5).

Control Group and PTSD Patient Group Differences in Functional Connectivity

When investigating between-group BLA and CMA functional connectivity, widespread cortical and subcortical differences were found when comparing the control group to both the PTSD+DS and PTSD-DS groups, for both the coordinates extracted from the ANOVA interaction and a-priori dlPFC region. Control group comparisons are similarly reported in Supplemental Results (see Table s4).

Discussion

The primary aim of the present study was to compare connectivity patterns of the BLA and CMA complexes between individuals exhibiting PTSD+DS and PTSD-DS. As compared to the PTSD-DS group, the PTSD+DS group exhibited greater amygdala functional connectivity to prefrontal regions involved in emotion regulation (bilateral BLA and left CMA to the middle frontal gyrus and bilateral CMA to the medial frontal gyrus). In addition, the PTSD+DS group showed greater amygdala connectivity to regions involved in consciousness, awareness, and proprioception (left BLA to superior parietal lobe and cerebellar culmen; left CMA to dorsal posterior cingulate and precuneus) as compared to the PTSD-DS group.

In keeping with our hypothesis, we found increased functional connectivity between the amygdala and PFC regions in PTSD+DS as compared to PTSD-DS. This finding is in line with the proposed increased versus decreased PFC inhibition of limbic regions in PTSD+DS versus

PTSD-DS, respectively (Lanius et al., 2010b). There was also greater connectivity in the PTSD+DS group between both bilateral BLA and left CMA to the right middle frontal gyrus and between bilateral CMA and the left medial frontal gyrus as compared to the PTSD-DS group. This parallels previous findings in terms of structural connectivity of the BLA, which projects outputs to the PFC and receives feedforward somatostatin inhibition from cortical inputs (Duvarci and Pare, 2014). Etkin et al. (2011) suggest that there is an imperfect separation of function in ventral and lateral PFC with regard to appraisal/expression and regulation of emotion, respectively. Group differences in amygdala connectivity with the middle and medial frontal gyri in the present study may therefore underlie emotional appraisal/expression and/or regulation. Previously, Lévesque et al. (2003) also report that the lateral portion of the right dlPFC is associated with the voluntary suppression of negative emotion when healthy participants were asked to suppress sadness, where increased sadness was associated with activation in the amygdala. In a connectivity analysis by Banks et al. (2007), prefrontal dorsolateral and dorsomedial cortices, as well as ACC, showed increased connectivity to the amygdala when healthy participants were asked to regulate their negative affect, suggesting top-down inhibition of the amygdala. Notably, a recent meta-analysis suggests that the supplementary motor area may mediate dlPFC emotion regulatory effects on the amygdala (Kohn et al., 2014). Finally, it is worth noting that in the present study, the PTSD+DS group did not display increased connectivity between the BLA and the ACC, as we had hypothesized based on the Lanius et al. (2010b) model. Future studies will therefore be required to determine whether the presence of an emotional stimulus (as opposed to resting state) will lead to altered amygdala-ACC connectivity in PTSD+DS.

We had further hypothesized that there would be altered between-group connectivity with regard to the BLA and CMA and parietal regions responsible for regulating consciousness, awareness, and proprioception — phenomena central to depersonalization and derealization experiences. The PTSD+DS group showed greater connectivity as compared to the PTSD-DS group between the left BLA and the left SPL. The SPL is involved in spatial orientation and is characterized by visual and sensory inputs (Wolbers et al., 2003), where damage to the SPL results in astereognosis – the inability to recognize objects through touch (Davis et al., 2006). The SPL also plays a significant role in motor imagery, monitoring of imagined limb configuration, and proprioception (Wolbers et al., 2003). Increased connectivity between the BLA (which mediates cortical integration of fear and emotional responses) and the SPL may therefore be directly related to symptoms of depersonalization, where alterations in SPL function may occur during an out-of-body experience and would thus need to be integrated by the BLA.

The PTSD+DS group showed greater connectivity between the left CMA and the precuneus as compared to the PTSD-DS group. The precuneus has been shown to be involved in first-person perspective taking, consciousness, and self-related mental representations during rest (Cavanna and Trimble, 2006). This finding parallels our hypotheses, where those functions subtending consciousness and formation of perspective are likely altered in depersonalization responses, characteristic of PTSD+DS. In support of this finding, Medford et al. (2006) report altered precuneus activity in depersonalization disorder patients as compared to controls when performing an emotional verbal memory task.

The dorsal PCC also showed greater functional connectivity between the left CMA in the PTSD+DS group as compared to the PTSD-DS group. Generally, the PCC has been shown to be associated with visuospatial orientation that is mediated through its extensive parietal lobe

connections and assessment of self-relevant sensations (Vogt, 2005), and recently, it has been suggested that the dorsal PCC is involved in conscious, awareness, and attention (Leech and Sharp, 2014). Moreover, the dorsal PCC is implicated in orienting the body toward innocuous and noxious somatosensory stimuli, and mediates nociception — the encoding and processing of harmful stimuli (Vogt, 2005). This also parallels previous structural findings suggesting the CMA to be implicated in major nociceptive pathways (Duvarci and Pare, 2014). Therefore, the PTSD+DS group may encode harmful stimuli and traumatic experiences in a unique, i.e. detached way. Notably, the mid-cingulate cortex is very close to the dorsal PCC coordinate reported in the current study and is involved in reward value of behavioural outcomes during performance of cognitive tasks (Vogt, 2005). Thus, through the encoding of reward, the brain may characterize dissociation as an adaptive response that mitigates overwhelming experience via emotional detachment. On balance, the current results suggest that the orchestration of fear responses via connectivity between the CMA and dorsal PCC may be unique in PTSD+DS patients, where self-relevant sensations, consciousness, awareness, and attention may be altered in dissociative states. These findings are consistent with results previously reported by Lanius et al. (2005) in which PCC activity was greater in PTSD patients who showed depersonalization/derealization responses during traumatic recall relative to those PTSD patients who exhibited flashback/re-living symptoms.

Finally, the left BLA displayed increased connectivity between the culmen of the cerebellum in the PTSD+DS group as compared to the PTSD-DS group. The cerebellum has been previously shown to be involved in proprioception – the perception of limb configuration. Therefore, increased connectivity to the BLA may be important for integrating culmen functions of imagined limb configuration during PTSD+DS symptoms of depersonalization.

The between PTSD patient group comparisons in the current study revealed BLA connectivity to similar prefrontal brain regions reported by Brown et al. (2014), albeit the current study does not report group differences to ACC, and Brown et al. (2014) do not report any between group differences in CMA connectivity. These connectivity differences between studies may be due to the use of trauma-exposed control participants in Brown et al.'s (2014) study as opposed to healthy controls in the current study and/or to different types of trauma exposure (military versus civilian). Furthermore, it is not clear whether the Brown et al. (2014) study included patients with PTSD+DS.

Several limitations of the current study are worth noting. Seed-based analyses have revealed significant sex-related differences in amygdala functional connectivity such that the amygdala exhibits greater functional connectivity at rest among females to the subgenual PFC and hypothalamus, when compared to males (Kilpatrick et al., 2006). Considering that the current sample is 75% female, the results may be biased towards the detection of differences in connectivity to prefrontal regions and may not be as sensitive to alterations in amygdala connectivity characteristic of males. In addition, the current study utilizes the DSM-IV CAPS as a diagnostic criteria for PTSD+DS. Subsequent studies should replicate the current findings using DSM-5 diagnostic criteria. Dynamic causal modeling should also be conducted in order to ascertain amygdala connectivity directionality in both PTSD groups in larger samples. It is also critical to note that our analyses do not provide information on whether connectivity is inhibitory or excitatory. Moreover, cardiac and respiratory physiological-related changes in BOLD signal were not corrected for. There is a mixed consensus in the field of functional connectivity regarding the need to correct for cardiac and respiratory-related changes in BOLD signal (Birn et al., 2006; 2008; 2009; 2012; Cordes et al. 2001) – which is also reflected in the PTSD literature –

where some studies remove physiological noise (e.g., Roy et al., 2009; Sripada et al., 2012) and others do not (e.g., Brown et al., 2014; Philip et al., 2013). Finally, future studies will need to examine how amygdala connectivity may change over the course of PTSD and also elucidate connectivity differences in response to emotional/traumatic triggers within PTSD+DS and PTSD-DS groups.

In conclusion, the results of the current study point toward unique amygdala connectivity of both the BLA and CMA complexes among individuals with the dissociative subtype. Differences in amygdala complex connectivity to specific brain regions parallel unique symptoms of trauma within this PTSD group. Amygdala complex resting state connectivity may serve as a biological marker for PTSD+DS, and the identification of specific patterns of BLA and CMA connectivity may help to further characterize PTSD patient groups. Critically, these findings emphasize the importance of employing a heterogeneous conceptualization of PTSD patient groups when designing neurobiological and clinical studies – as opposed to studying one amalgamated patient group. Moreover, our results may point to unique treatment avenues for various types of PTSD patients, such as using neurofeedback via real-time fMRI to mediate different connectivity patterns. Such studies are currently underway in our laboratory.

Funding and Disclosure

Funding for the current study was provided by Canadian Institutes of Health Research (CIHR), and the authors declare no conflicts of interest.

Supplementary information is available at the *Neuropsychopharmacology* website.

Acknowledgements

The authors would like to thank Daniela Rabellino for her contributions to the manuscript.

References

- American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn. American Psychiatric Publishing: Washington, DC
- Banks SJ, Eddy KT, Angstadt M, Nathan PJ, Phan, KL (2007). Amygdala-frontal connectivity during emotion regulation. *Social Cognitive and Affective Neuroscience* **2**: 303-312.
- Beck AT, Guth D, Steer RA, Ball R (1997). Screening for major depression disorders in medical inpatients with the beck depression inventory for primary care. *Behaviour Research and Therapy* **35**: 785-791.
- Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T *et al* (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse and Neglect* **27**: 169-90.
- Birn RM (2012). The role of physiological noise in resting-state functional connectivity. *NeuroImage* **62**: 864-870.
- Birn RM, Diamond JB, Smith MA, Bandettini PA (2006). Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. *NeuroImage* **31**: 1536-1548.
- Birn RM, Murphy K, Bandettini PA (2008). The effect of respiration variations on independent component analysis results of resting state functional connectivity. *Human Brain Mapping* **29**: 740-750.
- Birn RM, Murphy K, Handwerker DA, Bandettini PA (2009). fMRI in the presence of task-correlated breathing variations. *NeuroImage* **47**: 1092-1104.
- Birn RM, Patriat R, Phillips ML, Germain A, Herringa RJ (2014). Childhood maltreatment and

- combat posttraumatic stress differentially predict fear-related fronto-subcortical connectivity. *Depression and Anxiety* **31**: 880-892.
- Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS *et al* (1995). The development of a Clinician-Administered PTSD Scale. *Journal of Trauma Stress* **8**: 75-90.
- Briere J, Weathers FW, Runtz M (2005). Is dissociation a multidimensional construct? data from the multiscale dissociation inventory. *Journal of Traumatic Stress* **18**: 221-231.
- Brown VM, LaBar KS, Haswell CC, Gold AL, McCarthy G, Morey RA *et al* (2014). Altered resting-state functional connectivity of basolateral and centromedial amygdala complexes in posttraumatic stress disorder. *Neuropsychopharmacology* **39**: 351-359.
- Cavanna AE, Trimble MR (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain: A Journal of Neurology* **129**: 564-583.
- Cordes D, Haughton VM, Arfanakis K, Carew JD, Turski PA, Moritz CH *et al* (2001). Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. *American Journal of Neuroradiology* **22**: 1326-1333.
- Davis A, Whited A, Williams R, Pass L, Dean R, Hudson B (2006). Evaluating the presence of astereognosis in patients with multiple sclerosis. *Archives of Clinical Neuropsychology* **21**: 519-519.
- Duvarci S, Pare D (2014). Amygdala microcircuits controlling learned fear. *Neuron* **82**: 966-980.
- Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K *et al* (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage* **25**: 1325-1335.

- Etkin A, Egner T, Kalisch R (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences* **15**: 85-93.
- Etkin A, Wager T (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry* **164**: 1476-1488.
- Felmington K, Kemp A, Williams L, Falconer E, Olivieri G, Peduto A *et al* (2008). Dissociative responses to conscious and non-conscious fear impact underlying brain function in post-traumatic stress disorder. *Psychological Medicine* **38**: 1771-1780.
- First MB (1997). *User's guide for the structured clinical interview for DSM-IV axis I disorders SCID-I: Clinician version*. American Psychiatric Press: Washington, DC.
- Hopper JW, Frewen PA, van der Kolk BA, Lanius RA (2007). Neural correlates of reexperiencing, avoidance, and dissociation in PTSD: Symptom dimensions and emotion dysregulation in responses to script-driven trauma imagery. *Journal of Traumatic Stress* **20**: 713-725.
- Jovanovic T, Ressler KJ (2010). How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. *American Journal of Psychiatry* **167**: 648-662.
- Kilpatrick LA, Zald DH, Pardo JV, Cahill LF (2006). Sex-related differences in amygdala functional connectivity during resting conditions. *NeuroImage* **30**: 452-461.
- Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, Habel U (2014). Neural network of cognitive emotion regulation - An ALE meta-analysis and MACM analysis. *NeuroImage* **87**: 345-355.
- Lanius RA, Bluhm RL, Coupland NJ, Hegadoren KM, Rowe B, Theberge J *et al*

- (2010a). Default mode network connectivity as a predictor of post-traumatic stress disorder symptom severity in acutely traumatized subjects. *Acta Psychiatrica Scandinavica* **121**: 33-40.
- Lanius RA, Brand B, Vermetten E, Frewen PA, Spiegel D (2012). The Dissociative Subtype of Posttraumatic Stress Disorder: Rationale, Clinical and Neurobiological Evidence, and Implications. *Depression and Anxiety* **29**: 701-708.
- Lanius RA, Vermetten R, Loewenstein RJ, Brand B, Schmahl C, Bremner JD *et al* (2010b). Emotion modulation in PTSD: Clinical and neurobiological evidence for a dissociative subtype. *The American Journal of Psychiatry* **167**: 640-647.
- Lanius RA, Williamson PC, Bluhm RL, Densmore M, Boksman K, Neufeld RWJ *et al* (2005). Functional connectivity of dissociative responses in posttraumatic stress disorder: A functional magnetic resonance imaging investigation. *Biological Psychiatry* **57**: 873-884.
- Lanius RA, Williamson PC, Boksman K, Densmore M, Gupta M, Neufeld RWJ *et al* (2002). Brain activation during script-driven imagery induced dissociative responses in PTSD: A functional magnetic resonance imaging investigation. *Biological Psychiatry* **52**: 305-311.
- LeDoux J (1998). Fear and the brain: where have we been, and where are we going? *Biological Psychiatry* **44**: 1229-1238.
- Leech R, Sharp DJ (2014). The role of the posterior cingulate cortex in cognition and disease. *Brain: A Journal of Neurology* **137**: 12-32.
- Lévesque J, Eugène F, Joannette Y, Paquette V, Mensour B, Beaudoin G *et al* (2003). Neural circuitry underlying voluntary suppression of sadness. *Biological Psychiatry* **53**: 502-510.
- Lieberman MD, Cunningham WA (2009). Type I and Type II error concerns in fMRI

- research: re-balancing the scale. *Social Cognitive and Affective Neuroscience* **4**: 423-8.
- Medford N, Brierley B, Brammer M, Bullmore ET, David AS, Phillips ML (2006). Emotional memory in depersonalization disorder: A functional MRI study. *Psychiatry Research: Neuroimaging* **148**: 93-102.
- Mickleborough MJ, Daniels JK, Coupland NJ, Kao R, Williamson PC, Lanius UF *et al* (2011). Effects of trauma-related cues on pain processing in posttraumatic stress disorder: an fMRI investigation. *Journal of Psychiatry Neuroscience* **36**: 6-14.
- Milad, M (2013). Amygdala metabolism and associative fear learning in PTSD. *Biological Psychiatry* **73**: 124S-124S.
- Milad, M (2014). Functional connectivity of the fear extinction network in PTSD patients using dynamic causal modeling. *Biological Psychiatry* **75**: 13S-13S.
- Milligan GW, Wong DS, Thompson PA (1987). Robustness properties of nonorthogonal analysis of variance. *Psychological Bulletin* **101**: 464-470
- Phelps EA, Delgado MR, Nearing KI, LeDoux JE (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron*, 43:897–905.
- Philip NS, Kuras YI, Valentine TR, Sweet LH, Tyrka AR, Price LH *et al* (2013). Regional homogeneity and resting state functional connectivity: Associations with exposure to early life stress. *Psychiatry Research* **214**: 247.
- Roy AK, Shehzad Z, Margulies DS, Kelly AMC, Uddin LQ, Gotimer K *et al* (2009). Functional connectivity of the human amygdala using resting state fMRI. *NeuroImage* **45**: 614-626.
- Sadeh N, Spielberg JM, Warren SL, Miller GA, Heller W (2014). Aberrant neural connectivity during emotional processing associated with posttraumatic stress. *Clinical Psychological Science* **2**: 748-755.

Shin LM, Liberzon I (2010). The neurocircuitry of fear, stress, and anxiety disorders.

Neuropsychopharmacology **35**: 169-191.

Shin LM, Wright CI, Cannistraro PA, Wedig MM, McMullin K, Martis B *et al* (2005).

A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Archives of General Psychiatry* **62**: 273-281.

Sripada RK, King AP, Garfinkel SN, Wang X, Sripada CS, Welsh RC *et al* (2012).

Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. *Journal of Psychiatry & Neuroscience* **37**: 241-249.

Stein DJ, Koenen KC, Friedman MJ, Hill E, McLaughlin KA, Petukhova M *et al* (2013).

Dissociation in posttraumatic stress disorder: Evidence from the world mental health surveys. *Biological Psychiatry* **73**: 302-312.

Steuwe C, Lanius RA, Frewen PA (2012). Evidence for a dissociative subtype of PTSD by latent profile and confirmatory factor analyses in a civilian sample. *Depression and Anxiety*, **29**: 689-700.

Stevens JS, Jovanovic T, Fani N, Ely TD, Glover EM, Bradley B, Ressler KJ (2013). Disrupted amygdala-prefrontal functional connectivity in civilian women with posttraumatic stress disorder. *Journal of Psychiatric Research* **47**: 1469-1478.

Vogt BA, Laureys S. (2005). Posterior cingulate, precuneal and retrosplenial cortices: cytology and components of the neural network correlates of consciousness. *Progressive Brain Research* **150**: 205-17

Wolbers T, Weiller C, Büchel C (2003). Contralateral coding of imagined body parts in the superior parietal lobe. *Cerebral Cortex* **13**: 392-399.

Wolf EJ, Miller M, Reardon AF, Rybchenko KA, Castillo D, Freund R (2012). Latent class analysis of dissociation and PTSD: Evidence for a dissociative subtype. *Archives of General Psychiatry* **69**: 698-705.

Wolf EJ, Rasmusson AM, Mitchell KS, Logue MW, Baldwin CT, Miller MW (2014). A genome-wide association study of clinical symptoms of dissociation in a trauma-exposed sample. *Depression and Anxiety* **31**: 352-360.

Yan X, Lazar M, Shalev AY, Neylan TC, Wolkowitz OM, Brown AD *et al* (2014 In Press). Precuneal and amygdala spontaneous activity and functional connectivity in war-zone-related PTSD. *Psychiatric Research: Neuroimaging*.

Table 1.

Demographic and Clinical Information

Measure	PTSD-DS (n = 36)	PTSD+DS (n = 13)	Controls (n = 40)
Age	$M = 37 \pm 12.9$	$M = 37 \pm 12.7$	$M = 32.3 \pm 11.4$
Sex	Females = 26	Females = 11	Females = 29
CAPS	69.0 ± 13.2	79.5 ± 20.2	0.7 ± 3.0
CTQ	63.0 ± 25.9	71.2 ± 20.2	31.6 ± 8.4
BDI	24.3 ± 8.1	33.5 ± 11.6	1.6 ± 2.6
MDI- DENG	14.0 ± 5.3	17 ± 4.6	8.0 ± 2.4
MDI- DEPR	7.0 ± 3.2	12.3 ± 4.5	5.3 ± 0.7
MDI- DERL	9.0 ± 3.7	13.8 ± 4.0	5.3 ± 0.7
MDI- ECON	11.0 ± 5.6	17.25 ± 5.3	5.3 ± 0.8
MDI- MEMD	9 ± 3.7	14.8 ± 4.0	5.7 ± 1.1
MDI- DDIS	6 ± 2.3	9.4 ± 5.1	5.0 ± 0.0
MDD	n = 1	n = 1	n = 0
Panic Disorder	n = 1	n = 0	n = 0
Agoraphobia	n = 0	n = 0	n = 0
Social Phobia	n = 0	n = 2	n = 0
OCD	n = 0	n = 0	n = 0
GAD	n = 0	n = 0	n = 0
Somatization Disorder	n = 0	n = 0	n = 0
Somatoform Disorder	n = 0	n = 1	n = 0
Eating Disorders	n = 0	n = 0	n = 0

Abbreviations: CAPS = Clinician Administered PTSD Scale, CTQ = Childhood Trauma Questionnaire, BDI = Becks Depression Inventory, MDI = Multiscale Dissociation Inventory, DENG = Disengagement, DEPR = Depersonalization, DERL = Derealization, ECON = Emotional Constriction, MEMD = Memory Disturbance, DDIS = Identity Dissociation, MDD = Major Depressive Disorder, OCD = Obsessive Compulsive Disorder, GAD = Generalized Anxiety Disorder, n = Number of Participants Corresponding to a group, PTSD+DS = dissociative subtype PTSD group, PTSD-DS = non-dissociative PTSD group, Control = age-matched control group.

Table 2.

3 (Group) × 2 (Complex) Full Factorial ANOVA

Analysis	Gyrus/Sulcus	H	BA	Cluster Size	MNI Coordinate			F(2, 344)	Z score	p FWE
					x	y	z			
Main Effect of Group	Middle Occipital Gyrus	L	19	16836	-32	-82	16	24.53	6.35	<.0001
	Middle Temporal Gyrus	L	21	16836	-60	-22	-8	21.32	5.90	<.0001
	Clastrum	L		604	-28	20	-8	10.53	3.97	<.0001
Group × Complex Interaction	Inferior Parietal Lobule	L	40	3716	-46	-50	54	28.38	6.84	<.0001
		R	40	4276	56	-38	50	23.81	6.25	<.0001
	Superior Parietal Lobule	L	7	3716	-36	-52	62	25.83	6.52	<.0001
	Cerebellum, Tonsil	L		1811	-36	-48	-40	18.53	5.47	<.0001
	Cerebellum, Declive	R		1811	18	-54	-20	17.96	5.38	<.0001
	Temporal Gyrus	R	22	4276	58	-50	8	19.17	5.57	<.0001
		L	21	384	-52	4	-24	15.90	5.03	<.0001
	Dorsal Posterior Cingulate	L	24	705	-6	4	40	15.10	4.88	<.0001

Full factorial analysis of variance displaying FWE-corrected gray matter clusters. Abbreviations: BA =

Broadmann area, FWE = family-wise error cluster-corrected threshold, H = Hemisphere.

Table 3.

Clinical Variables

Variable	Levene's Homogeneity Test	ANOVA	Post Hoc Comparisons	Tukey-Kramer HSD	Games-Howell
CAPS	$F(2, 86) = 36.067, p < .001$	N/A	PTSD-DS & PTSD+DS	N/A	$t(3, 22) = 2.473, ns$
BDI	$F(2, 81) = 17.439, p < .001$	N/A	PTSD-DS & PTSD+DS	N/A	$t(3, 15) = 2.530, ns$
CTQ	$F(2, 86) = 19.499, p < .001$	N/A	PTSD-DS & PTSD+DS	N/A	$t(3, 27) = 1.475, ns$
			PTSD-DS & Control	N/A	$t(3, 41) = 6.93, p < .001$
			PTSD+DS & Control	N/A	$t(3, 13) = 6.880, p < .001$
MDI Total	$F(2, 85) = 18.724, p < .001$	N/A	PTSD-DS & PTSD+DS	N/A	$t(3, 17) = 4.700, p = .001$
			PTSD-DS & Control	N/A	$t(3, 38) = 7.250, p < .001$
			PTSD+DS & Control	N/A	$t(3, 34) = 9.238, p < .001$

Abbreviations: PTSD+DS = dissociative subtype PTSD group, PTSD-DS = non-dissociative PTSD group, Control = Age-matched control group, CMA= Centromedial amygdala baseline activity, BLA= Basolateral amygdala baseline activity, N/A = not applicable, CAPS = Clinician Administered PTSD Scale, CTQ = Childhood Trauma Questionnaire, BDI = Becks Depression Inventory, MDI = Multiscale Dissociation Inventory, DENG = Disengagement, DEPR = Depersonalization, DERL = Derealization, ECON = Emotional Constriction, MEMD = Memory Disturbance, IDDID = Identity Dissociation, MDD = Major Depressive Disorder, OCD = Obsessive Compulsive Disorder, GAD = Generalized Anxiety Disorder.

Table 4.

Dissociative Subtype and Non-dissociative subtype PTSD Between-Group Connectivity Differences

Table 4 A)													
Seed Region	Contrast	Gyrus/Sulcus	H	BA	Cluster Size	Beta Values		MNI Coordinate			t(47)	Z score	p Unc.
						PTSD-DS	PTSD+DS	X	Y	Z			
Left BLA	PTSD-DS>PTSD+DS	<i>ns</i>											
	PTSD-DS<PTSD+DS	Superior Parietal Lobe	L	5	10	0.011	0.086	-22	-48	64	4.79	4.30	<.0001
		Cerebellum, Culmen	L		10	0.043	0.115	-28	-46	-30	3.23	3.06	=.001
Right BLA	PTSD-DS>PTSD+DS	<i>ns</i>											
	PTSD-DS<PTSD+DS	<i>ns</i>											
Left CMA	PTSD-DS>PTSD+DS	<i>ns</i>											
	PTSD-DS<PTSD+DS	Dorsal Posterior Cingulate	L	24	23	-0.015	0.024	-14	-4	48	3.76	3.50	=.0002
		Medial Frontal Gyrus	L	6	23	0.003	0.053	-8	6	48	3.00	2.90	=.002
		Precuneus	L	7	18	-0.012	0.055	-32	-50	50	3.09	3.00	=.002
Right CMA	PTSD-DS>PTSD+DS	<i>ns</i>											
	PTSD-DS<PTSD+DS	Medial Frontal Gyrus	L	32	11	-0.001	0.055	-8	10	48	3.00	2.83	=.002

Table 4 B)													
Seed Region	Contrast	Gyrus/Sulcus	H	BA	Cluster Size	Beta Values		MNI Coordinate			t(47)	Z score	p FWE
						PTSD-DS	PTSD+DS	X	Y	Z			
Left BLA	PTSD-DS>PTSD+DS	<i>ns</i>											
	PTSD-DS<PTSD+DS	Middle Frontal Gyrus *	R	9	17	0.003	0.106	38	32	32	3.50	3.28	=.042
Right BLA	PTSD-DS>PTSD+DS	<i>ns</i>											
	PTSD-DS<PTSD+DS	Middle Frontal Gyrus *	R	9	13	-0.020	0.114	38	32	32	3.42	3.21	=.045
Left CMA	PTSD-DS>PTSD+DS	<i>ns</i>											
	PTSD-DS<PTSD+DS	Middle Frontal Gyrus *	R	9	20	0.015	0.071	38	28	30	3.37	3.17	=.041
Right CMA	PTSD-DS>PTSD+DS	<i>ns</i>											
	PTSD-DS<PTSD+DS	<i>ns</i>											

A) Follow-up comparisons from the ANOVA interaction, $p < .005$, $k = 10$.

B) Small volume correction a-priori analysis, FWE-corrected $p < .05$, $k = 10$. Abbreviations: BLA = Basolateral amygdala, CMA = Centromedial amygdala, PTSD-DS > PTSD+DS = Contrast images representing greater connectivity in the non-dissociative PTSD group compared to the dissociative subtype, PTSD-DS < PTSD+DS = Contrast images representing greater connectivity in the dissociative subtype PTSD group compared to the non-

dissociative PTSD group, H = Hemisphere. Unc = Uncorrected for multiple comparisons, FWE = family-wise error corrected, BA = Broadmann Area.

Accepted manuscript

Table 5.

*Subscale MDI Depersonalization and Derealization Correlation to PTSD Amygdala**Connectivity*

Seed Region	Gyrus/Sulcus	H	BA	Cluster Size	MNI Coordinate			t(47)	Z score	p <i>Uncorrected</i>
					x	y	z			
Left BLA	Middle Frontal Gyrus*	R	9	14	38	32	32	3.34	3.15	<.001

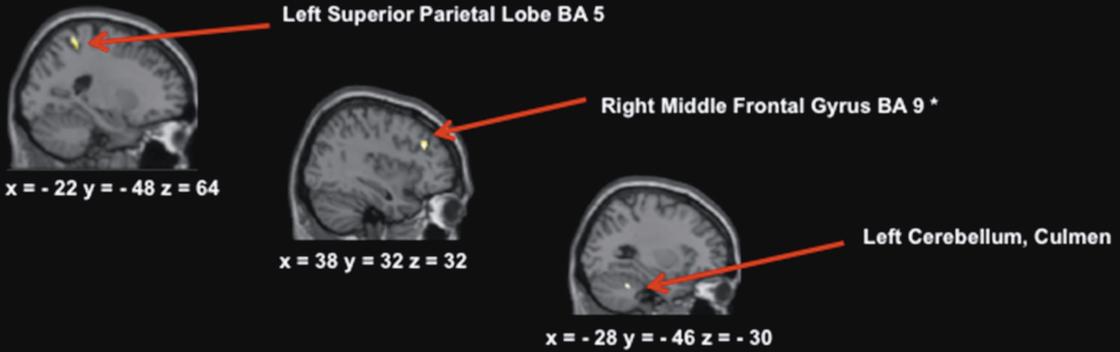
Subscale MDI depersonalization and derealization items averaged for each participant and evaluated as a predictor of amygdala connectivity including data from all PTSD (PTSD-DS and PTSD+DS) patients. Abbreviations: H = Hemisphere, BLA = Basolateral amygdala, BA = Brodmann Area.

* Indicates the a-priori analysis.

Figure 1. a) Brain areas representing greater connectivity to the left basolateral amygdala within PTSD+DS as compared to PTSD-DS; b) Brain areas representing greater connectivity to the right basolateral amygdala within the PTSD+DS as compared to PTSD-DS; c) Brain areas representing greater connectivity to the left centromedial amygdala within PTSD+DS, as compared to PTSD-DS; d) Brain areas representing greater connectivity to the right centromedial amygdala within PTSD+DS as compared to PTSD-DS. Statistical threshold $p < .005$ uncorrected, $k = 10$ for all 2-sample t-tests. Abbreviations: PTSD+DS= dissociative subtype posttraumatic stress disorder group PTSD-DS = non-dissociative posttraumatic stress disorder group, BLA = basolateral amygdala, CMA = centromedial amygdala, PCC = posterior cingulate cortex.

* Indicates the a-priori region-of-interest analysis.

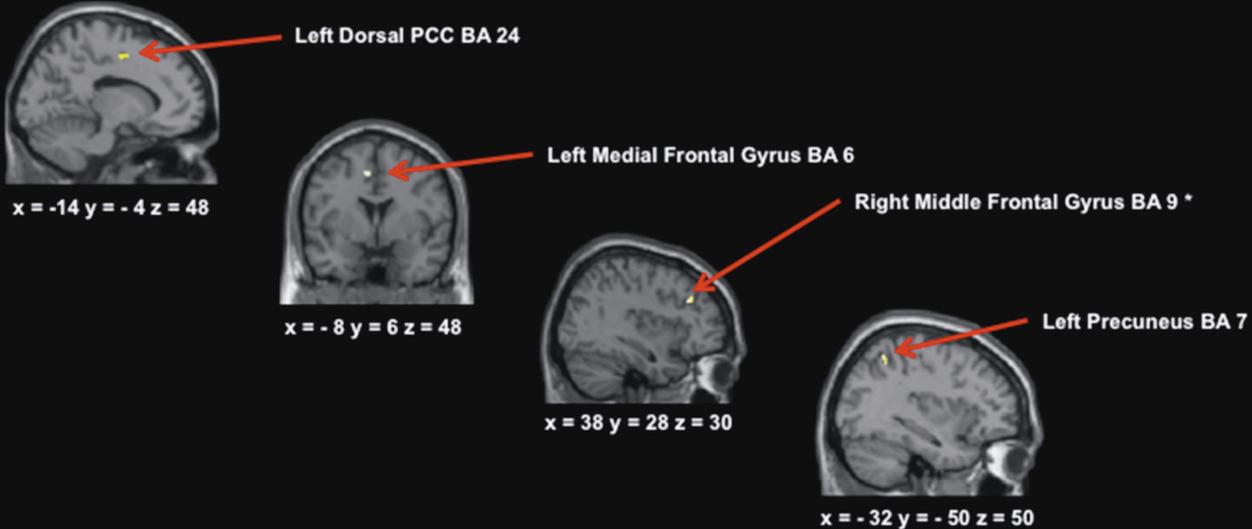
a) Left BLA PTSD+DS > PTSD-DS



b) Right BLA PTSD+DS > PTSD-DS



c) Left CMA PTSD+DS > PTSD-DS



d) Right CMA PTSD+DS > PTSD-DS

