2009

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Original Publication Citation

Bluhm, R. L., Williamson, P. C., Osuch, E. A., Frewen, P. A., Stevens, T. K., Boksman, K., . . . Lanius, R. A. (2009). Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. *Journal of Psychiatry & Neuroscience, 34*(3), 187-194.

Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma

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Background: The "default network" consists of a number of brain regions that exhibit correlated low-frequency activity at rest and that have been suggested to be involved in the processing of self-relevant stimuli. Activity in many of these areas has also been shown to be altered in individuals with posttraumatic stress disorder (PTSD). We hypothesized that the posterior cingulate cortex (PCC)/precuneus, part of the default network, would exhibit altered connectivity at rest with other areas of the default network and regions associated with PTSD. **Methods:** Seventeen medicated and unmedicated female patients with chronic posttraumatic stress disorder (PTSD) related to early-life trauma and 15 healthy female controls underwent a 5.5-minute functional magnetic resonance imaging scan with their eyes closed. We assessed areas of the brain whose activity positively and negatively correlated with that of the PCC/precuneus in both groups. **Results:** At rest, spontaneous low-frequency activity in the PCC/precuneus was more strongly correlated with activity in other areas of the default network in healthy controls than in patients with PTSD. Direct comparison of the 2 groups showed that PCC/precuneus connectivity was also greater in healthy controls than in patients with PTSD in a number of areas previously associated with PTSD, including the right amygdala and the hippocampus/parahippocampal gyrus. **Limitations:** Because our PTSD sample comprised only women with chronic early-life trauma exposure, our results may not be generalizeable to male patients, to a population with single trauma exposure or to those who were adults when the trauma occurred. In addition, our sample included patients taking medication and it is not yet clear how altered connectivity is affected by medication. **Conclusion:** Spontaneous activity in the default network during rest, as measured using PCC correlations, is altered in patients with PTSD. The potential effects of psychotropic medications on default network connectivity in the present sample remain unknown. In this patient population, the observed alterations may be associated with the disturbances in self-referential processing often observed in patients with chronic PTSD related to early-life trauma.

Contexte : Le «réseau par défaut» englobe plusieurs régions du cerveau qui manifestent une activité de basse fréquence corrélée au repos et qui, comme le suggèrent certains, joueraient un rôle dans le traitement des stimuli autoréférentiels. Dans bon nombre de ces régions, l'activité s'est également révélée perturbée chez les individus atteints de syndrome de stress post-traumatique (SSPT). Selon notre hypothèse, le cortex cingulaire postérieur (CCP) et le précunéus, éléments du réseau par défaut, manifesteraient au repos une connectivité altérée avec les autres régions du réseau par défaut et les régions associées au SSPT. **Méthodes :** Dix-sept patientes (dont certaines traitées pharmacologiquement) atteintes d'un syndrome de stress post-traumatique chronique lié à un traumatisme subi en bas âge, de même que 15 participantes témoins en bonne santé, ont subi une épreuve d'imagerie par résonance magnétique fonctionnelle de 5,5 minutes, les yeux fermés. Nous avons examiné les régions du cerveau dont l'activité était en corrélation positive et négative avec le CCP/précunéus dans les 2 groupes. **Résultats :** Au repos, l'activité de basse fréquence spontanée du CCP/précunéus a été en plus

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J Psychiatry Neurosci 2009;34(3):187-94.

Submitted Jun. 27, 2008; Revised Oct. 20, 2008; Accepted Oct. 24, 2008

forte corrélation avec celle des autres régions du réseau par défaut chez les témoins en bonne santé que chez les patientes atteintes de SSPT. Une comparaison directe entre les 2 groupes a révélé que la connectivité CCP/précunéus était également plus grande chez les témoins en bonne santé que chez les patientes atteintes de SSPT dans un certain nombre de régions auparavant associées avec le SSPT, y compris l'amygdale cérébrale droite et la région hippocampe/gyrus parahippocampique. **Limites :** Étant donné que notre échantillon de patientes atteintes de SSPT ne comprenait que des femmes présentant un syndrome chronique consécutif à un traumatisme subi en bas âge, nos résultats pourraient ne pas s'appliquer aux hommes, aux victimes de traumatismes simples ou aux patients qui étaient adultes lors du traumatisme. De plus, notre échantillon incluait des patientes qui prenaient des médicaments; or, l'impact potentiel de ceux-ci sur la connectivité est inconnu. **Conclusion :** L'activité spontanée du réseau par défaut au repos, mesurée par l'analyse de ses corrélations avec le CCP, est altérée chez des patientes atteintes de SSPT. Les effets potentiels des psychotropes sur la connectivité du réseau par défaut dans le présent échantillon demeurent inconnus. Chez cette population de patients, les altérations observées peuvent être associées à des déréglements du traitement des stimuli autoréférentiels souvent observés chez les patients atteints de SSPT chronique consécutif à un traumatisme subi en bas âge.

Introduction

Recent research has suggested that, in the absence of heavy processing demands, activity in the brain is characterized by positively correlated, low-frequency (> 0.1 Hz) oscillations within functional neural networks. Of particular interest in psychiatric research is the so-called "default network," which includes the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC)/precuneus and lateral parietal cortices.[1–3] Subjective reports indicate that mental activity occurring during such periods of rest is characterized by self-referential thought,[4,5] and these reports are further substantiated by the involvement of default network regions in tasks requiring self-reflection.[6,7]

Neuroimaging studies provide evidence of altered function in brain regions that have been implicated in the default network in participants with posttraumatic stress disorder (PTSD) (reviewed in Lanius and colleagues,[8] Nemeroff and colleagues[9]). Although most studies have only employed standard subtraction analyses, more recent studies have also identified disturbances in brain functional connectivity among those with PTSD; these include disturbances between the mPFC and amygdala during facial expression processing[10] and trauma script–driven imagery,[11,12] and among the thalamus, anterior cingulate cortex, PCC and left middle frontal cortex during trauma script–driven imagery.[13,14] Therefore, these studies may indicate abnormal functional connectivity within many of the default network regions in participants with PTSD.

It remains unclear, however, whether these disturbances in functional connectivity are task-dependent or rather reflect a more generalized disturbance that would also be evident while participants are at rest. Recent studies have identified disturbances in the default network during the resting state in patients with other psychiatric disorders, including major depression,[15] schizophrenia[16–18] and autism,[19] that are cardinally associated with disturbances in self-reflection. In addition, resting-state activity in some areas of the default network has been shown to be altered in participants with PTSD,[20,21] though these studies did not examine functional connectivity. Thus to our knowledge no previous studies have yet investigated resting-state functional connectivity in the default network among people with PTSD.

Previous studies provide a clear rationale for extending such investigations to PTSD, as significant disturbances in self-referential processing[22–26] often accompany this disorder. In particular, a substantial percentage of patients with PTSD respond to reminders of their trauma with dissociative symptoms,[14,27] which may include altered self-perception of their bodies or their perceptual and emotional experiences. Neuroimaging studies suggest that dissociative experiences involve brain regions also implicated in the default network, including the mPFC[28,29] and the dorsolateral prefrontal cortex.[29]

Therefore, in the present study we sought to investigate potential disturbances in functional connectivity within the default network during the resting state in individuals with PTSD. We chose the PCC/precuneus as the primary seed region for the investigation of default network connectivity for two reasons. First, it is the seed region most commonly used in studies of the default network and has been reliably shown to correlate with the rest of the default network in healthy adults.[18,30–33] Second, alterations in PCC activity have been shown in patients with PTSD in response to trauma reminders[8,9] and have also been shown to vary with the degree of alexithymia in such patients,[22] reinforcing the suggestion that this region is involved in self-reflection.[7] Thus we hypothesized that patients with PTSD would exhibit reduced and/or altered low-frequency blood-oxygen-level-dependent functional connectivity of the PCC, particularly with respect to the PCC and precuneus themselves, the mPFC and bilateral lateral parietal cortices, all brain regions that have previously been shown with positron emission tomography and functional magnetic resonance imaging to be functionally coactive during the resting state in healthy individuals.[30–34] We also investigated whole-brain connectivity of the PCC/precuneus to determine whether there were alterations in connectivity between the default network (via the PCC/precuneus) and other brain regions associated with PTSD. Finally, because the mPFC has also shown altered activity in various tasks among patients with PTSD,[8,9] we conducted a second set of analyses using the mPFC as the seed region.

Methods

Participants

We recruited female patients with a primary diagnosis of PTSD as a result of childhood abuse and healthy controls for

inclusion in the study. We assessed participants using the DSM-IV Structured Clinical Interview (SCID),[35] the Clinician-Administered PTSD Scale (CAPS),[36] the Dissociative Experiences Scale (DES),[37] the Toronto Alexithymia Scale (TAS)[38] and the Childhood Trauma Questionnaire – Short Form (CTQ-SF).[39] We excluded those with a history of head injury or neurologic disorders or a history of drug or alcohol abuse in the 6 months preceding the scan. We also excluded those with a history of bipolar disorder, schizophrenia or present or past Axis-I psychiatric disorders.

We recruited participants via advertisement in the community and within the health care network in London, Ontario. All scanning took place at Robarts Research Institute. The research ethics board at the University of Western Ontario approved our study, and all participants provided written, informed consent.

Procedure

We obtained images using a 4.0 Tesla UNITY INOVA whole-body imaging system (Varian) equipped with Siemens Sonata actively shielded gradient coils. We used a single-tuned, ^{1}H quadrature birdcage volume head-coil (16 leg, 21 cm in length) for transmission and detection of signals. We immobilized participants' heads with foam padding and an acrylic plastic head cradle. We adapted imaging parameters from Fox and colleagues.[30] We continuously collected functional images using a segmented (2-shot) gradient echo (T_2-weighted) sequence with spiralled gradient waveforms (64×64 matrix size, field of view 25.6 cm, echo time 15 ms, volume acquisition time 3 s, tip-angle 60°). We acquired 26–29 slices, depending on the number of slices needed to achieve whole-brain coverage. Slice thickness was 4 mm, resulting in $4 \times 4 \times 4$–mm isotropic voxels.

We asked participants to close their eyes, relax and let their minds wander during the 5.5-minute (110 volume) scan. If they found that they were "focusing too long on any one subject," they were to "pull their minds away" from it. To ensure that participants were able to relax and enter a resting state, we took several steps to minimize conditions that might interfere with such a state. First, to allow participants to acclimatize to the scanner environment, we conducted a high-resolution anatomic scan before the resting-state functional scan. Second, before the functional scan, we asked participants whether they were relaxed and ready for the upcoming scan. Neither healthy controls nor participants with PTSD reported anxiety before or during the functional run. Finally, after the scan, we asked participants whether they had been able to comply with the instructions, and participants in both groups reported being able to do so. In addition, no PTSD participant reported intrusive, trauma-related recollections during the scan.

Statistical analysis

We conducted image preprocessing steps and statistical analyses using Statistical Parametric Mapping (SPM2, Wellcome Department of Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm) based on methods reported previously.[18,31] For each participant, we realigned all functional images to the first image in the series to reduce the effects of head motion, resliced the images and created a mean functional image. We then coregistered images to the mean functional image and normalized them to the echo-planar imaging template in SPM2. To compensate for residual within-subject variability, decrease high spatial frequency noise and allow for the application of Gaussian random field theory, we smoothed the functional images using a 12-mm full-width at half-maximum isotropic Gaussian filter.[18]

After preprocessing, we conducted an analysis modelled on methods previously reported[31] to identify brain regions in which low-frequency oscillations occurred at rest and to ensure that there were no differences in the extent of this activity between groups. Briefly, we used a set of 60 cosine regressors to model activity in the frequency range of 0.012–0.100 Hz in each participant. We created a composite image from the β images for the regressors spanning this frequency range, which identified all areas of the brain in which there was low-frequency activity. We then used these composite images to compare activity between groups in a second-level, 2-sample t test. This method is more sensitive to the existence of low-frequency activity than that used by Fransson[31] to identify areas of low-frequency oscillation in healthy controls and thus less likely to result in false-negative results that would obscure between-group differences.

Having established that there were no between-group differences in low-frequency activity, we assessed connectivity of the PCC/precuneus. First, we conducted a single-subject stage of analysis to identify areas of low-frequency connectivity with the seed region. The PCC/precuneus has been previously shown[18,30–34] to have positive correlations in low-frequency activity at rest with other areas implicated in the default network, and negative correlations in low-frequency activity at rest with areas known to be active during performance of cognitive tasks. The specific seed region used in this study, a 10-mm sphere centred at 0, –56, 20 (Montreal Neurological Institute [MNI] coordinates) was previously used in a study comparing default network connectivity in patients with schizophrenia with that in healthy controls.[18] We extracted a mean signal intensity time course from this seed region and then inserted it as a regressor into correlation analyses of the "resting" data, which we had previously filtered with a phase-insensitive passband to include only frequencies in the range of interest (0.012–0.100 Hz). We then conducted a second-level, mixed-effects analysis in which individual participants were treated as random variables. This involved entering contrast images obtained for each participant during the first level analysis into a model comparing positive correlation with the PCC seed regions between groups. The resulting maps of t statistics were thresholded at $p < 0.05$, corrected for multiple comparisons using a false discovery rate correction, with an extent threshold of 10 voxels.

We conducted the same set of correlational analyses using a seed region in the mPFC, centred at MNI coordinates of –2, 48 and –4 based on a previous study.[30]

To control for the potential effects of a diagnosis of depression in the PTSD group, we performed an analysis of covariance for the between-group differences in PCC/precuneus

connectivity. To establish that differences in susceptibility artifact were not responsible for the observed between-group differences, we compared mean T_2-weighted images for each participant both by creating a mean image for each group and by conducting a 2-sample t test to compare these mean images across groups.

We conducted several supplementary exploratory analyses in the PTSD group only, in which connectivity of the PCC was correlated with scores on the DES, TAS and CAPS. These analyses were thresholded at $p < 0.001$, uncorrected for multiple comparisons, with an extent threshold of 10 voxels.

Results

Participants

We included in our study 17 women with PTSD as a result of childhood abuse (mean age 39, standard deviation [SD] 9, range 20–53 yr) and 15 healthy controls (mean age 38, SD 13, range 21–59 yr). All participants were right-handed.

The patients with PTSD had a chronic history of early life trauma, as shown by the CAPS interview (mean score 76.88, SD 19.75) and by high mean scores on all subscales of the CTQ (Table 1). The control and PTSD groups differed significantly on their scores on the CAPS, CTQ, DES and TAS-20 (Table 1). Because of the chronic nature of the traumata experienced by these participants, we do not report specific time since an index trauma event. Current comorbidities of the PTSD group were major depressive disorder ($n = 6$), dysthymic disorder ($n = 1$), depression disorder not otherwise specified ($n = 1$), panic disorder ($n = 8$), agoraphobia ($n = 3$) and generalized anxiety disorder ($n = 2$). Past Axis-I disorders were alcohol dependence ($n = 5$), alcohol abuse ($n = 2$), substance dependence ($n = 3$), substance abuse ($n = 3$), major depressive disorder ($n = 3$), panic disorder ($n = 2$) and bulimia nervosa ($n = 2$). Thirteen of 17 patients in the PTSD group were taking medications at the time of the scan: citalopram ($n = 4$), clonazepam ($n = 2$), fluoxetine ($n = 1$), lithium carbonate ($n = 1$), lorazepam ($n = 1$), paroxetine ($n = 2$), quetiapine ($n = 3$), risperidone ($n = 2$), sertraline ($n = 1$) and venlafaxine ($n = 1$). The inclusion of patients on medications is consistent with other studies of the default network in psychiatric disorders,[15,16,18] and little is yet known about the possible effects of psychotropic medication on default network connectivity.

Table 1: Participant scores on clinical scales

Scale*	Group; mean (SD)	
	Control	PTSD
CAPS[36]	1.1 (2.6)	76.9 (19.8)
CTQ†[39]		
Emotional abuse	6.2 (1.5)	17.9 (4.6)
Physical abuse	5.5 (0.9)	12.6 (6.4)
Sexual abuse	5.5 (0.6)	18.1 (7.3)
Emotional neglect	6.3 (2.1)	17.4 (3.9)
Physical neglect	5.8 (1.4)	10.8 (4.0)
Total score‡	29.0 (8.8)	76.9 (8.8)
TAS[38]	33.5 (7.0)	65.5 (9.6)
DES[37]	2.0 (2.0)	28.5 (19.3)

CAPS = Clinician-Administered PTSD Scale; CTQ = Childhood Trauma Questionnaire; DES = Dissociative Experiences Scale; PTSD = posttraumatic stress disorder; SD = standard deviation; TAS = Toronto Alexithymia Scale.
*Scores between groups significant at $p < 0.001$.
†CTQ scores compared for a total of 5 subscales presented; scores missing for 2 participants in each group.
‡Includes minimization/denial scale.

Low-frequency oscillations in seed regions during the resting state

We observed low-frequency oscillations (0.012–0.100 Hz) in both groups in widespread regions of grey matter. There were no significant between-group differences in low-frequency oscillations in either seed region (PCC/precuneus and mPFC).

Low-frequency connectivity of the PCC/precuneus

In the control group, we found activity in the PCC/precuneus seed region to correlate positively with activity in a number of regions previously identified as part of the default network, including other regions in the PCC/precuneus, mPFC (Brodmann area [BA] 10, 11), anterior cingulate gyrus (BA 24), bilateral lateral parietal cortex (BA 39), inferior temporal gyrus (BA 20) and the thalamus. We also found positive correlations between the PCC/precuneus and bilateral hippocampus, right insula and visual cortex (Table 2, Fig. 1).

In patients with PTSD, positive correlations with activity in the PCC/precuneus seed region were limited to areas within the PCC, right superior frontal gyrus (BA 9) and left ventrolateral thalamus (Table 2, Fig. 1).

Direct statistical comparison of connectivity with the PCC/precuneus seed region revealed greater connectivity in healthy controls than in patients with PTSD in a number of regions, including the PCC/precuneus, mPFC, bilateral lateral parietal cortex, bilateral middle temporal gyrus, right parahippocampal gyrus and hippocampus, right insula and right amygdala (Table 2, Fig. 2). Controlling for the effects of a diagnosis of depression in the PTSD group through an analysis of covariance did not alter the regions in which we observed diminished PCC/precuneus connectivity.

Connectivity of the mPFC

In healthy controls, we observed connectivity of the mPFC with other areas of the default network similar to that of the PCC/precuneus seed region. In participants with PTSD, connectivity of this seed region was limited to the mPFC. Direct comparison of the 2 groups showed decreased connectivity of the mPFC with other regions of the default network, particularly the bilateral lateral parietal cortex, mPFC and PCC (data not shown).

Correlation of PCC/precuneus connectivity with DES, TAS and CAPS scores

Connectivity with the PCC was positively correlated with increased DES scores in the right superior temporal gyrus

(BA 38; maximum activation at MNI coordinates of 56, 22 and –24) and in the right inferior frontal gyrus (BA 45, 46; maximum activation at MNI coordinates of 66, 18 and 6) (Fig. 3).

There were no regions of interest for which connectivity with the PCC/precuneus varied with CAPS and TAS scores.

Discussion

Our study examined the low-frequency blood-oxygen-level-dependent functional connectivity of the default network during the resting state in participants with and without PTSD. During rest in healthy controls, the activity in the PCC/precuneus was correlated with a set of regions implicated in the default network, including the mPFC, precuneus, lateral parietal cortices, inferior and middle temporal cortices, thalamus and cerebellum, replicating previous work.[30–34] In contrast, in patients with PTSD, we observed correlation with the PCC/precuneus only with the right superior frontal gyrus (BA 9) and left ventrolateral thalamus, as well as within the PCC itself. Furthermore, direct group contrasts confirmed a greater positive functional connectivity of the PCC with the precuneus, mPFC and bilateral lateral parietal cortex (all areas considered to be part of the default network) among healthy controls than among patients with PTSD.[1,4,30–34] We observed similar alterations in connectivity between the control and the PTSD groups for connectivity of seed regions in both the PCC/precuneus and the mPFC. The focus of the present manuscript is on the former seed region, as it has been the focus of most previous analyses of the default network in healthy individuals and because of the frequent observation of task-related differences in activity of this region between patients with PTSD and healthy controls.

Altered functional connectivity of midline cortical structures, including the PCC and the mPFC, has previously been demonstrated in patients with PTSD during emotion-relevant paradigms such as facial affect perception and

Table 2: Areas of correlation with posterior cingulate cortex/precuneus

Group	MNI coordinates			*z* score	Brain region
Controls only	8	–44	28	6.79	Posterior cingulate gyrus (BA 31)
	0	–30	32	5.87	Posterior cingulate gyrus (BA 23)
	46	–68	30	6.13	Right angular gyrus (BA 39)
	–40	–74	30	6.04	Left precuneus (BA 39)
	–2	60	10	5.61	Left mPFC (BA 10)
	22	40	29	5.28	Right superior frontal gyrus (BA 9)
	–26	34	44	5.47	Left middle frontal gyrus (BA 8)
	–64	–12	–24	5.69	Left inferior temporal gyrus (BA 20)
	68	–12	–28	4.93	Right inferior temporal gyrus (BA 20)
	58	–62	10	5.18	Right middle temporal gyrus (BA 39)
	–22	–36	–4	4.89	Left parahippocampal gyrus
	12	–20	8	5.11	Thalamus
	54	–64	–28	2.83	Cerebellum
	–54	–64	–32	2.81	Cerebellum
	–38	–18	30	2.71	Cerebellum
PTSD only	6	–48	26	4.66	PCC (BA 31)
	–14	–16	16	3.74	Thalamus
	24	40	38	4.10	Left superior frontal gyrus (BA 9)
Controls > PTSD	–2	–28	36	3.48	Posterior cingulate gyrus (BA 23)
	4	–62	34	3.67	Precuneus (BA 7)
	–40	–76	30	4.37	Left angular gyrus (BA 39)
	44	–68	28	4.31	Right angular/middle temporal gyrus (BA 39)
	10	60	18	3.74	Right mPFC (BA 10)
	20	58	–10	3.65	Right superior frontal gyrus (BA 11)
	8	28	66	2.95	Right superior frontal gyrus (BA 6)
	28	26	44	2.92	Right middle frontal gyrus (BA 8)
	–24	24	40	3.54	Left middle frontal gyrus (BA 8)
	–46	6	40	2.63	Left middle frontal gyrus (BA 9)
	–62	–13	–24	4.07	Left inferior temporal gyrus (BA 20)
	68	–14	–26	3.73	Right inferior temporal gyrus (BA 20)
	70	–38	–6	3.48	Right middle temporal gyrus (BA 21)
	10	–22	0	3.91	Thalamus
	–12	–38	–10	4.03	Cerebellum
	26	–8	–18	4.49	Right amygdala
	30	–22	–24	3.82	Right parahippocampal gyrus (BA 36)
	40	18	10	3.14	Right insula (BA 13)

BA = Brodmann area; MNI = Montreal Neurological Institute; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; PTSD = posttraumatic stress disorder.

trauma script–driven imagery.[11–14] However, the extent to which such disturbances in functional connectivity are circumscribed to these tasks, as opposed to reflecting a more generalized disturbance that might also be observable at rest, has been thus far unknown. The present evidence suggests that PTSD is characterized by altered connectivity in a robust neural network previously associated with self-referential processing in the resting state.[1,4,30–34]

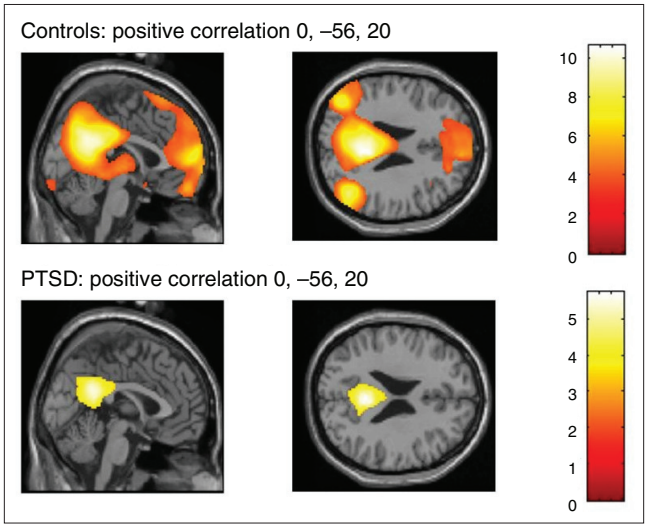

Fig. 1. Areas of correlation with posterior cingulate cortex/precuneus in healthy controls and in patients with posttraumatic stress disorder, thresholded at $p < 0.05$, corrected using false discovery rate correction.

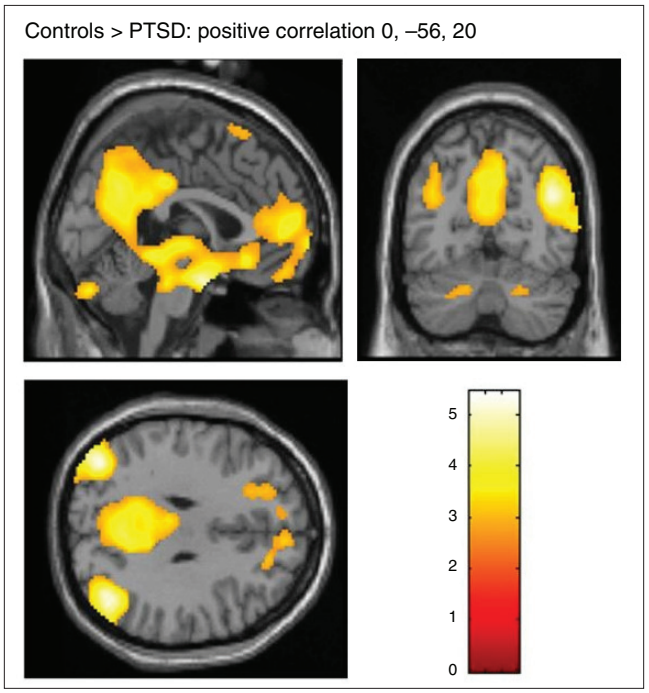

Fig. 2. Areas in which correlation with the posterior cingulate cortex/precuneus is stronger in healthy controls than in patients with posttraumatic stress disorder, thresholded at $p < 0.05$, corrected using false discovery rate correction.

We also observed between-group differences in PCC connectivity between the PCC seed region and a number of regions previously associated with PTSD. In particular, patients with PTSD showed less connectivity than controls between the PCC and right amygdala, right hippocampus and right insula. This involvement of the right-hemisphere may be important given the suggestion that the early-life trauma experienced by the patients with PTSD may have interfered primarily with the development of the right hemisphere.[40] Greater connectivity of the default network with the amygdala and hippocampus in healthy controls may be particularly interesting in light of the suggestion that a function of the default network is to maintain the organism in a state of readiness for expected future events.[41] Moreover, functional neuroimaging studies have implicated the PCC in the assessment of self-reflection[42] in addition to (and perhaps via relations with its role in) episodic memory.[43] These studies suggest that the PCC may be a crucial node in the default network, linking past information with current environmental events and assessing these events with regard to their relevance to the self. Drawing on these studies, our findings may help to explain the hypervigilance and the hypersensitivity to trauma reminders that are central characteristics of PTSD in terms of an increased likelihood of an emotional response to environmental stimuli due to the altered connectivity between the default network and the amygdala, hippocampus and insula.

The association of the default network with self-reflection and self-monitoring also suggests that alterations in the activity of this network may be implicated in dissociative symptoms in patients with PTSD. The dorsolateral prefrontal cortex is part of a second resting state network that consists of areas associated with cognitive processing and that has previously been shown to be negatively correlated with the

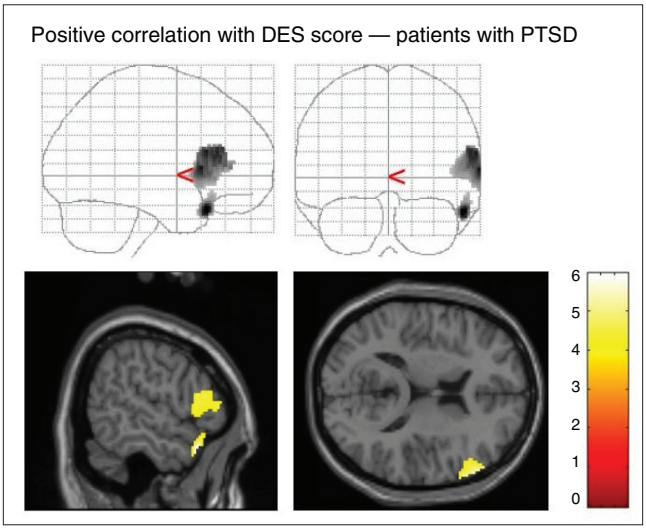

Fig. 3. Areas of positive correlation of Dissociative Experiences Scale[37] score with posterior cingulate cortex/precuneus connectivity in patients with posttraumatic stress disorder, thesholded at $p < 0.001$, uncorrected.

default network in healthy controls.[30,31] In this study, however, among patients with PTSD, scores on the DES,[37] which measures trait dissociation, were positively correlated with the extent of connectivity between the PCC/precuneus and a region of the right dorsolateral prefrontal cortex (BA 45/46). A study of working memory in patients with dissociative disorder showed increased activation in the left dorsolateral prefrontal cortex, which was also associated with better working memory performance, in this patient group.[29] Although the present study and the working memory study suggest that the right and the left dorsolateral prefrontal cortices, respectively, may be involved in dissociation, the specific results of the 2 studies may be task-dependent manifestations of a common underlying deficit. Moreover, these findings raise the hypothesis that dissociation may involve alterations in the relation between the default network and brain regions subserving cognitive activity.

Previous studies examining alterations of the default state in psychiatric conditions have examined autism,[19] schizophrenia,[16–18] major depressive disorder[15] and attention deficit hyperactivity disorder.[44] These studies, together with the present study of default network alterations in PTSD, suggest that examination of the activity of this network may help to distinguish between these disorders on the basis of neuropathophysiology. Whereas all of the studies cited above report alterations in the default network associated with psychiatric disorders, there may also be alterations in resting-state connectivity unique to different disorders. In particular, we found less correlation in patients with PTSD than in healthy controls between the PCC/precuneus and the right amygdala, hippocampus and insula. All of these regions have been previously implicated in PTSD[10–12] (reviewed in Lanius and colleagues,[8] Nemeroff and colleagues[9]), and have not shown altered relations with the default network in other psychiatric disorders.[15–19] It should be emphasized, however, that this line of research is still in its early stages, and that published studies to date have used a variety of task conditions (including both rest and cognitive tasks) and different analytic techniques to probe the activity of the default network.

Limitations

To our knowledge, ours is the first study to show that connectivity within the default network at rest is impaired in patients with PTSD. However, our study has certain limitations and also raises questions to be addressed in future studies of the default network. In particular, the PTSD group in our study comprised only women, and all had chronic, early-life trauma exposure. Thus, it may be that the results do not generalize to a population whose trauma exposure was a single incident or those who were adults at the time of trauma exposure. Future studies should also consider the potential effects of sex, as our results cannot be generalized to male patients with PTSD. The effects of comorbid psychiatric conditions and of physiologic and hormonal differences should be addressed in future research. In addition, like previous studies of the default network in patients with psychiatric disorders, our study included medicated patients.[15,16,18] It is not yet clear how alterations in default mode connectivity observed to date have been affected by participants' medication status, as there has not yet been a study that compares medicated and unmedicated patients for any disorder or any medication type. In our study, most patients were taking one or more medications at the time of the scan; however, all of them remained symptomatic, as evidenced by scores on the CAPS and measures of dissociation and alexithymia. Because the PTSD sample in our study included both unmedicated and medicated patients , it is less likely that the alterations in default network connectivity observed here were a result of medication status. However, future work examining the default network in PTSD and other psychiatric disorders should not only include cohorts of unmedicated patients, but also directly examine the potential impact of different psychotropic medications on resting state networks.

We should also note that studies of resting-state activity, as with other studies that do not incorporate an objective behavioural assessment of participants' compliance with instructions (e.g., script-driven imagery), depend on the assumption that participants did engage in the required task. Finally, future research should examine the complexities of the default network in light of recent reports that suggest that although the 2 seed regions included in our study both correlate with other areas of the default network at rest, they show different patterns of anticorrelations with so-called "task-positive" brain regions and they appear to modulate activity in negatively correlated networks, rather than vice versa.[45]

In summary, the present evidence suggests that patients with chronic PTSD related to early-life trauma display significantly reduced functional connectivity within the default network during the resting-state. These brain regions, including the PCC, precuneus, and mPFC have been associated with self-referential processing during the resting-state. Accordingly, the present evidence is consistent with the altered forms of self-perception and consciousness accompanying more severe and chronic PTSD. Future studies will also examine whether patterns of default network activation may usefully predict persistence of PTSD symptoms or related post-traumatic symptomatology in acutely traumatized populations.[46]

Competing interests: None declared.

Contributors: Drs. Bluhm, Williamson, Frewen, Boksman, Neufeld, Théberge and Lanius designed the study. Drs. Bluhm, Williamson, Frewen, Stevens, Boksman, Neufeld and Lanius acquired the data, which all authors analyzed. Drs. Bluhm, Williamson, Frewen, Boksman, Neufeld, Théberge and Lanius wrote the article. All authors reviewed the article and provided approval for publication.

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