Functional Connectivity of Dissociative Responses in Posttraumatic Stress Disorder: A Functional Magnetic Resonance Imaging Investigation

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Background: *The purpose of this study was to assess interregional brain activity covariations during traumatic script-driven imagery in subjects with posttraumatic stress disorder (PTSD).*

Methods: *Functional magnetic resonance imaging and functional connectivity analyses were used to assess interregional brain activity covariations during script-driven imagery in PTSD subjects with a dissociative response, PTSD subjects with a flashback response, and healthy control subjects.*

Results: *Significant between-group differences in functional connectivity were found. Comparing dissociated PTSD patients and control subjects' connectivity maps in the left ventrolateral thalamus (VLT) [−14, −16, 4] revealed that control subjects had higher covariations between activations in VLT and in the left superior frontal gyrus (Brodmann's area [BA] 10), right parahippocampal gyrus (BA 30), and right superior occipital gyrus (BA 19, 39), whereas greater covariation with VLT in dissociated PTSD subjects occurred in the right insula (BA 13, 34), left parietal lobe (BA 7), right middle frontal gyrus (BA 8), superior temporal gyrus (BA 38, 34), and right cuneus (BA 19). Comparing dissociated PTSD and flashback PTSD connectivity maps in the right cingulate gyrus [3, 16, 30] revealed that dissociated PTSD subjects had higher covariations between activations in this region and the left inferior frontal gyrus (BA 47).*

Conclusions: *Greater activation of neural networks involved in representing bodily states was seen in dissociated PTSD subjects than in non-PTSD control subjects. These findings might illuminate the mechanisms underlying distorted body perceptions often observed clinically during dissociative episodes.*

Key Words: PTSD, dissociation, functional connectivity, neuroimaging, fMRI, anterior cingulate, insula

Neuroimaging has become an important technique for understanding altered brain functions underlying posttraumatic stress disorder (PTSD). Although a number of neuroimaging studies have examined alterations in brain functioning in PTSD patients during resting conditions (Lucey et al 1997; Semple et al 1993, 1996) and in response to pharmacologic challenges (Bremner et al 1997), cognitive tasks (Clark et al 2003; Shaw et al 2002; Shin et al 2001), or masked facial emotional stimuli (Hendler et al 2003; Rauch et al 2000), in the majority of studies investigators have used trauma-specific symptom provocation paradigms (Bremner et al 1999a, 1999b; Gilboa et al 2004; Lanius et al 2001, 2002, 2003b, 2004; Liberzon et al 1997, 1999; Osuch et al 2001; Pissiota et al 2002; Rauch et al 1996; Shin et al 1997, 1999, 2004).

Studies of neural activation patterns in PTSD patients during recall of traumatic memories have reported alterations in a number of limbic, paralimbic, and prefrontal areas as compared with control subjects. These include the anterior cingulate gyrus (Brodmann's area [BA] 24, 32) (Bremner et al 1999a, 1999b; Lanius et al 2001, 2002, 2003b; Liberzon et al 1999), the medial prefrontal cortex (Bremner et al 1999a, 1999b; Lanius et al 2001, 2002, 2003b; Shin et al 1997, 1999, 2004), the amygdala (Liberzon et al 1999; Pissiota et al 2002; Rauch et al 1996; Shin et al 1997, 2004), and the thalamus (Bremner et al 1999b; Lanius et al 2001, 2003a; Liberzon et al 1999).

We have recently reported that the patterns of brain activation in patients who dissociate in response to traumatic script-driven imagery can be strikingly different from those observed in patients who relived their traumatic experience through flashbacks after being exposed to the traumatic script (Lanius et al 2001 vs. Lanius et al 2002). The group of PTSD subjects who dissociated from the memory and their emotions in response to traumatic script-driven imagery exhibited greater levels of brain activation in the superior and middle temporal gyri (BA 38), the inferior frontal gyrus (BA 47), the occipital lobe (BA 19), the parietal lobe (BA 7), the medial prefrontal cortex (BA 10), and the anterior cingulate gyrus (BA 24). In contrast, a group of PTSD patients who had a flashback/reliving experience to the traumatic script, involving intense emotions and arousal, exhibited significantly less activation of the thalamus, anterior cingulate gyrus (BA 32), and medial prefrontal cortex (BA 10, 11) as compared with control subjects (Lanius et al 2001).

In all of these studies, however, the traditional "subtraction analysis" approach was used, which can delineate specific brain regions involved in different responses to recall of a traumatic memory. To assess interregional covariations in brain activity and thus to look at the behavior of entire networks, functional connectivity analyses are required. To date, neuroimaging studies in PTSD have just begun to address the functional connectivity underlying the recall of traumatic memories (Gilboa et al 2004; Lanius et al 2004; Shin et al 2004) and working memory (Shaw et al 2002). Abnormal connectivity among regions involved in different responses to trauma-related stimuli might characterize the neuronal networks underlying distinctive flashback/reliving and dissociative responses. Alternatively, patterns

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of functional connectivity among brain regions during responses to trauma-related stimuli in PTSD might not be abnormal or dysfunctional per se; rather, they might reflect functionally significant and integrated responses that are "normal" in their connectivity and coordinated activity but "abnormal" in the sense of being extreme or inappropriate to the current situation. In the latter case, such integrated network responses might be repetitions of those that were adaptive—or at least functionally coherent attempts at adaptive responding—during the original trauma(s) and that have become conditioned responses that are "abnormal" in their behavioral consequences while retaining functional significance and coherence (Lanius et al 2003a). Much more than subtraction analyses, functional connectivity analyses, particularly when combined with grouping responses into distinct subtypes, holds the promise of shedding considerable light on these issues.

The purpose of this study was to use functional connectivity analyses to assess interregional brain activity covariations during traumatic script-driven imagery in subjects with PTSD exhibiting dissociative responses, as compared with both PTSD subjects who experienced a flashback/reliving response and with trauma-exposed control subjects without PTSD. Because individuals who dissociate in response to reminders of a traumatic event often report symptoms of depersonalization, including disconnection from emotions and bodily sensations, we hypothesized that functional connectivity analyses of dissociated PTSD patients would implicate neuronal networks involved in conveying bodily states to the brain, compared with control subjects, who were hypothesized to exhibit networks of activation more consistent with a pattern of verbal autobiographical memory recall. For functional connectivity analyses comparing dissociated and flashback/reliving PTSD groups, we hypothesized that functional connectivity analyses of dissociated PTSD patients would implicate neuronal networks involved in conscious experience, compared with flashback/reliving PTSD subjects, who were hypothesized to exhibit networks of activation more consistent with a pattern of nonverbal autobiographical memory recall.

Methods and Materials

Subjects

Three groups of subjects were included in this study. The first group of subjects exhibited a dissociative response to the traumatic script-driven imagery symptom provocation paradigm. To be included in this group, subjects had to give a description consistent with a dissociative episode and also endorse a minimum of 15 symptoms on the Clinician-Administered Dissociative States Scale (CADSS; Bremner et al 1998) during the traumatic script-driven imagery paradigm. Each item on the CADSS was scored as present or absent. The subjects in this group had developed PTSD as a result of sexual abuse or assault ($n = 8$) or motor vehicle accidents (MVA; $n = 2$). The 2 subjects in this group who developed PTSD as a result of a MVA also had histories of childhood sexual abuse. The second group of subjects had a flashback/reliving response to the scripts. To be included in this group, subjects had to give a clear description consistent with a flashback/reliving experience and rate the recall of the memory as a reliving experience as at least 5 out of 6 on a 6-point scale (0–6). Moreover, they had to endorse fewer than 15 items on the CADSS during the traumatic script-driven imagery paradigm. The subjects in this group had developed PTSD as a result of sexual abuse or assault ($n = 6$) or an MVA ($n = 5$). Of the 11 subjects in this group, 9 reported a history of childhood emotional, physical, or sexual abuse. The third group of subjects consisted of 10 subjects who met criterion A for PTSD (as a result of sexual abuse or assault [$n = 7$] or MVAs [$n = 3$]) but who never met DSM-IV criteria for PTSD.

Written informed consent was obtained from all participants after a detailed description of the study, which was approved by the Office of Research Ethics at the University of Western Ontario. Subjects with PTSD and control subjects were assessed with the Structured Clinical Interview for DSM-IV (SCID; First et al 1997); the Clinician-Administered PTSD Scale (CAPS; Blake et al 1995) (mean [SD] CAPS scores were 90 [7] for the dissociated PTSD group; 72 [14] for the flashback/reliving PTSD group; and 4 [1.5] for the control group); and the Dissociative Experience Scale (DES; Bernstein and Putnam 1986) (DES scores were 34.8 [20] for the dissociated PTSD group, 17.9 [13.5] for the flashback/reliving PTSD group, and 3 [2.8] for the control group). Please see Table 1 for the comorbid conditions, time elapsed since the traumatic event, and medication use prior to the washout period of the PTSD patients. A structured interview was used to determine all subjects' medical and neurologic conditions. There was no medical or neurologic morbidity or cerebral damage associated with past drug or alcohol use in the patients with a history of substance abuse. The control subjects were of similar age (37.7 [11.1] years for the dissociated PTSD group, 36 [12] years for the flashback/reliving PTSD group, and 35.2 [12.3] years for control group), gender, and race, and were free of any psychiatric illness. All subjects were right handed. The gender distribution was as follows: the dissociated PTSD group consisted of all female subjects; the flashback/reliving group included two male subjects; and the control group included one male subject. All PTSD subjects who were receiving medications except for one had undergone a supervised drug washout for at least 2 weeks before scanning. One of the subjects was too acutely ill to be without medication; this subject's medication regimen was bupropion 150 mg and mirtazapine 15 mg. None of the subjects were receiving fluoxetine before the drug washout (see Table 1). Patients with a history of psychosis, bipolar disorder, and substance use disorder in remission for less than 6 months were excluded from the study, as were patients with any significant medical conditions, neurologic illness, or history of head injury. Seven of the dissociative PTSD subjects, 11 of the flashback/reliving subjects, and 10 of the control subjects included in the analyses for the present article were also included in a previous publication (Lanius et al 2002 or Lanius et al 2004). The functional connectivity analyses used in this study give different information about the patterns of brain activation observed in traumatic script-driven imagery than do the subtraction analyses used in previous reports. This study re-analyses the data from the same scanning session previously reported for each subject, with a new technique that shows covariation in activation among different brain areas.

Functional Magnetic Resonance Imaging Data Acquisition

All imaging data were acquired on a 4-T whole-body magnetic resonance imaging (MRI) system (Varian, Palo Alto, California; Siemens, Erlangen, Germany) with a 90-cm diameter horizontal bore and a whole-body 68-cm diameter gradient set with a maximum strength of 40 mT/m and a slew rate of 120 mT/m/sec. A transmit–receive cylindrical hybrid birdcage radio frequency coil (Barberi et al 2000) was used for transmission and detection of signal. Foam padding was fit snugly between the subject's head and a Plexiglas head cradle within the head coil to immobilize the subject's head.

Table 1. DSM-IV Diagnoses, Time Elapsed Since Onset of Trauma, and Medications Administered Before Supervised Washout of Dissociated and Flashback/Reliving PTSD Patients

Subject No.	Current and Past Diagnoses	Time Since Trauma (Onset)	Psychiatric Medications Prior to Washout
Dissociative PTSD Group			
1	PTSD, dysthymia, past major depression	57 y	None
2	PTSD, current major depression, dysthymia, past major depression	24 y	Triamazepam
3	PTSD, past major depression, past alcohol abuse, past eating disorder NOS	41 y	Triamazepam 15 mg Olanzapine 2.5 mg Venlafaxine 75 mg (Not taking medications 3 weeks before scan)
4	PTSD, current major depression, past major depression	43 y	None
5	PTSD, dysthymia	10 y	Sertraline 150 mg
6	PTSD, past major depression, past eating disorder NOS	24 y	None
7	PTSD, past major depression	31 y	None
8	PTSD	23 y	None
9	PTSD, current major depression	3 y	Bupropion 150 mg
10	PTSD, current major depression, past alcohol abuse, past major depression	47 y	Bupropion 150 mg Mirtazapine 15 mg (on medications during study)
Flashback/Reliving PTSD Group			
1	PTSD, past major depression	2 mo	Clonazepam .5 mg
2	PTSD, panic disorders, past major depression, past drug abuse/dependence	26 y	Amitriptyline 50 mg
3	PTSD	9 mo	Paroxetine 20 mg
4	PTSD, current major depression, past drug abuse/dependence	16 y	None
5	PTSD, eating disorder NOS, dysthymia, past major depression	15 y	None
6	PTSD	2 mo	None
7	PTSD, current major depression, dysthymia, past major depression, past alcohol abuse/dependence	32 y	None
8	PTSD, past major depression	21 y	None
9	PTSD, current major depression, dysthymia, panic disorder, past alcohol abuse/dependence	34 y	None
10	PTSD	37 y	Clonazepam 3 mg Amitriptyline 75 mg
11	PTSD, current major depression	2 y	None

PTSD, posttraumatic stress disorder; NOS, not otherwise specified.

Imaging planes for the functional scans were prescribed from a series of sagittal anatomic images acquired with high gray/white matter contrast (i.e., T1-weighted). The functional planes were 12 contiguous, 6-mm-thick axial slices oriented in a plane approximately parallel to the anterior commissure–posterior commissure (AC-PC) line centered on a plane level with the anterior cingulate. Before further imaging, a constrained, three-dimensional phase shimming procedure (Klassen et al 2004) was performed to optimize the magnetic field homogeneity over the prescribed functional planes. During each functional task, blood oxygenation level–dependent (BOLD) images (T_2*-weighted) were acquired continuously with an interleaved, four-segment, optimized echo planar imaging (EPI) protocol (128 × 128 matrix size, repetition time [TR] = 1250 msec, echo time [TE] = 15 msec, flip angle = 45°, field of view = 24.0 cm, volume collection time = 6 sec). Each image was corrected for physiologic fluctuations with a navigator echo collected at the beginning of every EPI train. During each experimental session, a T1-weighted anatomic reference volume was acquired along the same orientation as the functional images with a three-dimensional fast low-angle shot (FLASH) acquisition sequence (256 × 256 × 64 matrix size, 3.0-mm reconstructed slice thickness, inversion time = 500 msec, TR = 10 msec, TE = 4.0 msec).

Script-Driven Imagery

The script-driven imagery procedure was adapted to functional MRI (fMRI) according to previously published methods (Lanius et al 2001, 2002, 2003b). Please see Figure 1 for details of the boxcar design.

Scanning of traumatic and neutral imagery conditions was repeated three times. Each scan proceeded as follows: each subject was instructed to lie still and allow himself/herself to

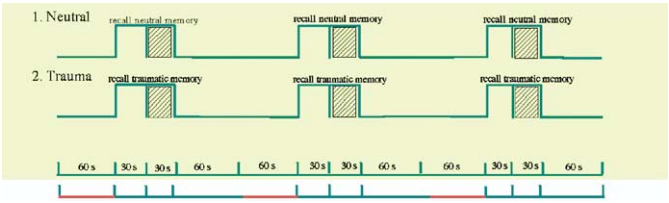

Figure 1. Visual representation of neutral and traumatic script paradigms. Red lines represent the "implicit baseline" scans that were used for SPM99 analyses. Hatched boxcars represent the recall only of neutral or traumatic memory used in the basis function, lasting 30 sec (six volumes).

begin focusing on the traumatic script as soon as the script was read. Reading of the script lasted 30 sec. As soon as the subject heard the script of the traumatic or neutral event that the individual had experienced, he/she was encouraged to remember olfactory, auditory, somatosensory, and visual sensations that were associated with the traumatic event for 60 sec. Measurements of heart rate occurred during this time. A period of 120 sec was allowed to pass until the script was repeated. During this time, the subject was asked to lie still, breathe through his/her nose, and "let go" of the traumatic event. Baseline brain activation was calculated according to the average activation patterns 60 sec before each recollection of the traumatic event. Brain activation during the recall of the traumatic event was calculated according to the average activation patterns during the final 30 sec of the recall of the traumatic event. Subjects were assessed for dissociative symptoms during the recall of the traumatic memory with the CADSS after each scan. Each item was scored as absent or present.

Autonomic responsivity to script-driven memories was assessed by averaging the change in heart rate from baseline across the three provocations, and *t* tests were used to compare the responsivity of PTSD patients with that of control subjects.

SPM99 Analyses

Subtraction Analyses (Fixed Effects Model). These statistical analyses use voxel-wise general linear models (Talairach and Tournoux 1988) with design matrices composed of epoch-related regressors. Regional activations attributable to traumatic memory recall for each subject group (dissociated and flashback/reliving PTSD patients and control subjects) and between groups (dissociated and flashback/reliving PTSD patients compared with control subjects) were ascertained by use of basic subtraction analyses.

Linear contrasts were used to test within- and between-group hypotheses about significant differences in location and intensity of BOLD response during the script-driven imagery task, relative to BOLD response measured during baseline.

These linear contrasts yield statistical parametric maps of the *t* statistic, SPM(*t*). The group SPM(*t*) maps were thresholded at $p < .001$ and corrected for multiple comparisons.

The differences in heart rate were not included in the fMRI analyses because previous studies have shown that the range of changes in heart rate (−14 to 32 bpm) as reported in this study do not have a significant effect on global blood flow (King et al 2001; Ploghaus et al 1999).

Functional Connectivity Analyses. Subtraction analyses address signal elevation and differences in elevation. Functional connectivity analyses, on the other hand, isolate intervoxel correspondence across measurement times, in a configuration of the data that forms the voxel's respective elevations (see Neufeld 1977 [chapter 10] for a discussion). A detailed description of functional connectivity analyses is beyond the scope of this article but can be found in the original literature describing SPM psychophysiologic interactions (Friston et al 1994, 1997; Kirk 1995; Hayasaka and Nichols 2003). A core datum for the functional connectivity analysis comprises the difference between the within-subject regression of the reference voxel signals or the postnarrative–imagine period and that of the baseline period (Friston et al 1997). Time-series data for the imaging period comprise 18 pairs of values emanating from six postnarrative measures obtained across three repetitions; similarly, 36 pairs of baseline values comprise 12 measures obtained across three repetitions.

We have previously reported functional connectivity/neuronal networks underlying flashback/reliving responses in PTSD patients who had a traumatic script-driven imagery-induced flashback/reliving response as compared with control subjects (Lanius et al 2004). Functional connectivity analyses can detect regions whose BOLD response activity covaries with the activity of a selected reference voxel in a brain region of interest. Regions that exhibit significant covariation with the activity of the reference voxel over the time course of the task being studied but not during the baseline condition scans are inferred to be functionally connected to the region represented by the reference voxel. The approach of choosing a seed voxel and computing time-dependent (dynamic) co-activations with the seed voxel is one of many approaches used to determine functional connectivity (Buechel and Friston 1997; Friston et al 1994). These range from nondirectional multivariate analyses (e.g., principal component analysis and certain versions of canonical covariation [see Shaw et al 2002]) to path analytic approaches (for a general description see Neufeld 1977). This study uses the same methods (psychophysiologic interactions [PPI], SPM99) as our previous functional connectivity analyses (Lanius et al 2004).

To determine which voxel's time series data could be used in the PPI analyses, a large subtraction analysis was conducted, within which all subjects' data were analyzed together to determine areas of commonly significant BOLD response elicited by performance of the script-driven imagery task relative to baseline BOLD response. When examining the dissociated PTSD and control groups, the subtraction analyses in which all subjects' baseline scans were averaged and subtracted from all subjects' averaged activation scans yielded a maximally activated left ventral lateral thalamic nucleus voxel at coordinates [−14, −16, 4]. The thalamus is highly relevant to the study of dissociation and is often referred to as the sensory gateway to the cortex (Kandel et al 1991). It has been suggested to play a key role in core consciousness (Damasio 1999) and to mediate the interaction between attention and arousal (Portas et al 1998), phenomena that are of importance to dissociation.

When examining the dissociated and flashback/reliving PTSD groups, the subtraction analyses in which all subjects' baseline scans were averaged and subtracted from all subjects' averaged activation scans yielded a maximally activated right cingulate gyrus voxel at coordinates [3, 16, 30]. The affective division of the anterior cingulate gyrus has been shown to be affected during the recall of traumatic material in PTSD (Bremner et al 1999a, 1999b; Lanius et al 2001; Liberzon et al 1999; Shin et al 1997, 1999), and reciprocal connections between the cognitive and affective division of the anterior cingulate gyrus have been described (Bush et al 2000). In addition, the affective division of the anterior cingulate gyrus plays a role in the conscious experience of emotion and in

linking autonomic changes to emotional stimuli (Bush et al 2000; Lane et al 1997).

Dissociative PTSD Group Versus Control Group Comparison. For each subject, BOLD response time series values were extracted from the thalamic voxel outlined above. After data extraction, each subject's vector of voxel activity values was normed, yielding 20 vectors, one per subject, each of whose elements have means of 0 and SDs of 1 (Friston et al 1997). Each normed vector was multiplied in a point-wise fashion by the hemodynamically convolved (measurement period that is registered is temporally offset to accommodate the hemodynamically induced lag in the BOLD response in the associated activation) boxcar-shaped vector that was originally used in the subtraction analysis to estimate the effects attributable to the traumatic script-driven imagery transaction. These vectors were entered into a group SPM analysis as "covariates of interest," to produce SPMs of the left ventral lateral thalamic nucleus functional connectivity for the dissociated PTSD and control subjects. For each subject group, linear contrasts were used to display the location and extent of brain regions whose activity demonstrated a significant dynamic co-activation with the left ventral lateral thalamic nucleus, in the form of SPM(t) maps. Threshold t scores for these maps were set to control for a region-wise false-positive rate of .001.

Dissociative PTSD Group Versus Flashback/Reliving PTSD Group Comparison. For each subject, BOLD response time series values were extracted from the right cingulate voxel outlined above. After data extraction, each subject's vector of voxel activity values was normed, yielding 20 vectors whose elements have means of 0 and SDs of 1. Each normed vector was multiplied in a point-wise fashion by the hemodynamically convolved (measurement period that is registered is temporally offset to accommodate the hemodynamically induced lag in the BOLD response in the associated activation) boxcar-shaped vector that was originally used in the subtraction analysis to estimate the effects attributable to the traumatic script-driven imagery transaction. These vectors were entered into a group SPM analysis as "covariates of interest," to produce SPMs of the right cingulate functional connectivity for the dissociated PTSD and flashback/reliving PTSD subjects. For each subject group, linear contrasts were used to display the location and extent of brain regions whose activity demonstrated a significant dynamic co-activation with the right cingulate gyrus, in the form of SPM(t) maps. Threshold t scores for these maps were set to control for a region-wise false-positive rate of .001.

We had also hoped to compare functional connectivity patterns between dissociative PTSD subjects and control subjects in other regions; however, there were no common areas of activation between groups (as shown by subtraction analysis) in such areas as the amygdala and the hippocampus, which might have been expected to be implicated in alterations in brain connectivity during recall of a traumatic memory.

Results

All PTSD patients who were included in the "dissociative" group exhibited dissociative responses to the traumatic script-driven imagery. They reported feeling like "I was looking down at my body," "I was out of my body," or "I was completely zoned out and could not recall the memory." All PTSD patients who were included in the "flashback/reliving" group reported feeling like "I was back at the scene of the accident" or "it felt like I was back in the past." None of the control subjects reported reliving or dissociative symptomatic responses, and all reported recalling the traumatic event as an ordinary autobiographical memory.

CADSS Scores

Dissociative responses to the script-driven imagery symptom provocation paradigm were assessed with the CADSS (scored as absent or present) and were compared with baseline CADSS scores before exposure to the script-driven imagery. The mean (SD) baseline CADSS score was 2.2 (1.9) for the dissociated PTSD group, 2.45 (2.11) for the flashback/reliving PTSD group, and .3 (.48) for the control group. The mean CADSS score during the traumatic script-driven imagery-induced memory recall was 18.2 (2.6) for dissociative PTSD subjects, 5.8 (2.9) for the flashback/reliving PTSD group, and .4 (.5) for control subjects. One-way analyses of variance (ANOVAs) showed a significant difference in CADSS scores before and during exposure to the traumatic script among groups [CADSS prior to script: $F(2,28) = 5.060$, $p < .13$; CADSS during script: $F(2, 28) = 190.77$, $p < .000$]. Independent t tests comparing the control and the flashback/reliving PTSD groups showed significant differences in CADSS scores before and during exposure to the traumatic script [prior to script: $t(19) = -3.2$, $p < .007$; during traumatic script: $t(19) = -6.2$, $p < .005$]. Independent t tests comparing the control and the dissociated PTSD groups also showed significant differences in CADSS scores before and during exposure to the traumatic script [before script: $t(18) = -3.1$, $p < .01$; during traumatic script: $t(18) = -24.9$, $p < .000$]. Independent t tests comparing the flashback/reliving and the dissociated PTSD groups showed significant differences in CADSS scores during but not before the exposure to the traumatic script [prior to script: $t(19) = .29$, $p = .773$; during traumatic script: $t(19) = -11.5$, $p < .000$].

Heart Rate

Changes in heart rate from baseline to the traumatic script-driven imagery condition were assessed in each group (dissociated PTSD group: mean [SD] 3.9 [12.5]; flashback/reliving PTSD group: 13.5 [12.5]; control group: 2.1 [2.24]). One-way ANOVAs showed a significant difference in heart rate among groups [$F(2,27) = 5.991$, $p < .007$]. Independent t tests comparing the control and the flashback/reliving PTSD groups showed significant differences in heart rate [$t(19) = -5.15$, $p < .000$]. In contrast, independent t tests comparing the control and the dissociated PTSD group did not show significant differences in heart rate [$t(17) = -.45$, $p = .683$]. Independent t tests comparing the flashback/reliving and the dissociated PTSD groups showed differences in heart rate approaching significance [$t(18) = 2.06$, $p = .062$].

Although some of the dissociated PTSD patients showed no change or a decrease in heart rate from baseline to the traumatic script-driven imagery condition, 4 of the 10 dissociated PTSD subjects showed mean heart rate increases ranging from 2 to 32. There did not seem to be any clinical features that distinguished these 4 subjects from the rest of this group; however, we have observed that dissociative subjects can have a variety of heart rate responses, including a decrease, no change, or an increase in heart rate. Future studies will have to address these complexities further.

Brain Activation During Script-Driven Imagery

Both the subtraction analyses and the subsequent functional connectivity analyses were conducted with and without the single dissociative PTSD patient receiving medication included in the group. There were no significant differences between these two sets of analyses.

Subtraction Analyses

Baseline Brain Activation. There were no differences in baseline brain activation between both groups of PTSD patients and control subjects (data not shown).

Neutral Memory Recall. Recalling a neutral memory resulted in the activation of the right anterior cingulate gyrus (BA 24) [4, 16, 26], right cingulate gyrus (BA 23) [4, −16, 30], left posterior cingulate gyrus (BA 23) [2, 30, 26], right posterior cingulate gyrus [4, −46, 4], and left superior temporal gyrus (BA 22, 38) [−52, 12, −6] in both the dissociative PTSD group and the control subjects. Control subjects showed significantly ($p < .001$) more activation in the right anterior cingulate gyrus (BA 24, 32) [10, 8, 38] [12, 22, 34] during the recall of a neutral memory, as compared with the dissociative PTSD group. The dissociative PTSD group showed significantly ($p < .001$) more activation in the right superior and middle temporal gyri (BA 21, 22) [58, −30, 0], right and left anterior cingulate gyrus (BA 24) [2, −4, 32], as well as in the right cingulate gyrus (BA 33) [4, 10, 26] during the recall of a neutral memory as compared with the control subjects (data not shown). Thus, activation of the right anterior cingulate gyrus differed between the two groups in two distinct areas. In one of these, the dissociative PTSD group showed greater activation than control subjects, whereas in the other, activity was greater in control subjects than in the dissociative PTSD subjects. Brain activations for the neutral memory condition in the flashback/reliving PTSD group have been previously described (Lanius et al 2004).

Traumatic Memory Recall. Table 2 shows regions of activation during the traumatic memory recall in the control ($n = 10$), dissociated PTSD ($n = 10$), and flashback/reliving PTSD groups ($n = 11$). Both the dissociated PTSD and the control groups showed activation in the left ventrolateral thalamus [−14, −16, 4]. This area was subsequently chosen as a reference voxel for the functional connectivity analyses comparing dissociated PTSD and control subjects. Both the dissociated and flashback/reliving PTSD groups showed activation in the right cingulate gyrus [3, 16, 30]. This area was subsequently chosen as a reference voxel for the functional connectivity analyses comparing dissociated and flashback/reliving PTSD subjects.

Functional Connectivity Analyses

Dissociative PTSD Subjects Versus Control (non-PTSD) Subjects. The SPM(t) map examining PPIs between the left ventral lateral nucleus of the thalamus [−14, −16, 4] activity and traumatic script-driven imagery in control subjects was compared with the same SPM(t) map in dissociated PTSD subjects (see Table 3 and Figures 2 and 3). Comparison of functional connectivity maps showed that control subjects showed more significant covariation than the dissociated PTSD subjects in the left superior frontal gyrus (BA 10), right parahippocampal gyrus (BA 30), and the right superior occipital gyrus (BA 19, 39). In contrast, comparison of functional connectivity maps revealed that dissociated PTSD subjects showed greater covariation than the control subjects between the reference voxel and the right insula (BA 13, 34), left parietal lobe (BA 7), right middle frontal gyrus (BA 8), superior temporal gyrus (BA 38, 34), and right cuneus (BA 19).

Dissociative PTSD Subjects Versus Flashback/Reliving PTSD Subjects. The SPM(t) map examining PPIs between the right cingulate gyrus [3, 16, 30] activity and traumatic script-driven imagery in dissociated PTSD subjects was compared with the same SPM(t) map in flashback/reliving PTSD subjects (see Table 4 and Figures 4 and 5). Comparison of functional connectivity maps showed that dissociated PTSD subjects showed more significant covariation than the flashback/reliving PTSD subjects in the left inferior frontal gyrus (BA 47). In contrast, comparison of functional connectivity maps revealed that the flashback/reliving PTSD subjects showed greater covariation than the dissociated PTSD subjects between the reference voxel and the posterior cingulate gyrus (BA 31), the right precuneus (BA 7), the left inferior frontal gyrus (BA 45), and the right middle temporal gyrus (BA 35).

Discussion

One group of PTSD patients in this study experienced a dissociative response to the script-driven traumatic memory, whereas the non-PTSD control subjects recalled the traumatic event as an ordinary autobiographical memory. Corresponding comparisons of functional connectivity maps, with a voxel in the left ventrolateral thalamic nucleus used as a seed voxel, showed distinctly different functional connectivity patterns in the two groups. This nucleus was chosen because the thalamus serves functions that are clearly relevant to dissociation. The thalamus is also thought to function as the principal synaptic relay station for sensory information reaching the cerebral cortex (Kandel et al 1991); however, it also receives a large number of projections from the neocortex itself, particularly from layer 5 (Sherman and Guillery 1996) and also from layer 6. Because the thalamus is fairly uniform in its anatomy and physiology, Adams and Cox (2002) have suggested that its functions are probably also general, rather than varying between different regions. One function that has been suggested is that the thalamus might play a key role in core consciousness (Damasio 1999) and also mediate the interaction between attention and arousal (Portas et al 1998).

It has also been suggested that during the alert, waking state, stimuli generated naturally in the external world commonly lead to synchronous, high-frequency discharges in the 40-Hz range in discrete relay neurons of the thalamus and in the cortical areas to which these project (Usrey and Reid 1999). It is these temporally coherent events that have been hypothesized to bind, in the time domain, the fractured components of external and internal reality into the experience of a single constructed reality (Llinas 2002). Thus, the alterations in functional connectivity observed in the dissociative PTSD subjects in this study, as compared with control subjects, might reflect their altered conscious experience during traumatic script-driven imagery. Furthermore, it has been reported (Johnson and Ojemann 2000) that stimulation of the dominant ventrolateral thalamus results in disruptions of language-processing abilities. Traumatic memories in PTSD have often been described as having a sensory, nonnarrative, or nonlinguistic form. Control subjects in this study reported experiencing the memory for this event in a verbal/narrative form with few sensory images. Although previous work (including work from our laboratory, e.g., Lanius et al 2004) has focused on traumatic memories in patients who respond to trauma cues by "reliving" the event, the dissociative experiences reported by the patients in the dissociative PTSD group in this study might also be interpreted as representing a nonverbal response to the memory. Further studies are required to elucidate the differences between—and similarities in—the mechanisms that give rise to these two different pathologic responses in PTSD, and research into the functions of the thalamus might assist in this goal.

Comparison of dissociated PTSD and control functional connectivity maps at coordinates [−14, −16, 4] (left ventral lateral thalamic nucleus) showed that control subjects exhibited greater covariation than the dissociated PTSD subjects between the

Table 2. A Summary of Areas of Significantly Increased BOLD Response Across All Subjects During the Fixed Effects Analysis, During the Final 30 Seconds of Traumatic Event Recall Relative to the Baseline in Each Subject Group

MNI	R/L	Effect Lobe	Effect Gyrus	Brodmann's Area	Local Maximum	
					p Voxel	*t* Voxel
Control Subjects ($n = 10$)						
($df = 824$, Minimum Cluster Size k = 10)						
10, −18, 0	R	Sublobar	Thalamus	Mammillary body	<.0001	6.71
−14, −16, 4	L	Sublobar	Thalamus	Ventral lateral mucleus	<.0001	5.87
−16, −10, 0	L	Sublobar	Thalamus		<.0001	10.96
40, −18, 20	R	Sublobar	Insula	13	<.0001	6.42
2, 20, 36	R	Limbic	Cingulate	32	<.0001	6.52
2, 10, 32	R	Limbic	Cingulate	24	<.0001	5.92
12, 8, 38	R	Limbic	Cingulate	24	<.0001	13.03
0, −18, 46	R/L	Limbic	Cingulate	24, 31	<.0001	11.60
−4, 40, 22	L	Limbic	Anterior cingulate	32	<.0001	6.18
32, 0, −20	R	Limbic	Parahippocampal	Amygdala	<.0001	6.41
−16, −36, 0	L	Limbic	Parahippocampal	27	<.0001	8.54
30, 40, −10	R	Frontal	Middle frontal	11, 47	<.0001	6.69
−16, 62, −6	L	Frontal	Medial frontal	10	<.0001	8.23
−8, 62, 4	L	Frontal	Medial frontal	10	<.0001	7.18
−42, 2, 36	L	Frontal	Precentral	6, 9	<.0001	7.24
−42, 10, 30	L	Frontal	Middle frontal	9	<.0001	5.75
−22, 46, −10	L	Frontal	Middle frontal	11	<.0001	7.03
−40, −10, 46	L	Frontal	Middle frontal	6	<.0001	6.53
24, −62, 54	R	Parietal	Superior parietal	7	<.0001	6.91
12, −68, 28	R	Parietal	Precuneus	7	<.0001	6.23
−4, −38, 48	L	Parietal	Precuneus	7	<.0001	6.27
40, −54, 16	R	Temporal	Superior temporal	39	<.0001	5.73
−38, −56, 16	L	Temporal	Middle temporal	22	<.0001	6.76
26, −84, 40	R	Occipital	Precuneus	19	<.0001	8.59
Dissociated PTSD ($n = 10$)						
($df = 824$, Minimum Cluster Size k = 10)						
10, −18, 0	R	Sub-lobar	Thalamus	Mammillary body	<.0001	6.43
−14, −16, 4	L	Sub-lobar	Thalamus	Ventral lateral nucleus	<.0001	5.93
−10, −2, 0	L	Sub-lobar	Lentiform nucleus	Medial globus pallidus	<.0001	6.04
0, −20, −6	R/L	Brainstem	Midbrain	Red nucleus	<.0001	7.30
0, 24, 22	R/L	Limbic	Anterior cingulate	24	<.0001	7.85
2, 10, 32	R	Limbic	Cingulate	24	<.0001	7.49
3, 16, 30	R	Limbic	Cingulate	24	<.0001	6.35
2, −2, 34	R	Limbic	Cingulate	24	<.0001	9.26
0, −48, 4	R/L	Limbic	Posterior cingulate	30	<.0001	9.26
−24, −86, 38	L	Occipital	Precuneus	19	<.0001	6.81
Flashback/Reliving PTSD ($n = 11$)						
($df = 906$, Minimum Cluster Size k = 10)						
−38, 24, −2	L	Sublobar	Insula	13	.000	6.15
2, 20, 36	R	Limbic lobe	Cingulate	32	.000	7.93
28, −46, −4	R	Limbic lobe	Parahippocampal	19	.000	6.66
0, 18, 36	R/L	Limbic lobe	Cingulate	32	.000	8.06
3, 16, 30	R	Limbic	Cingulate	24	<.0001	7.21
0, 6, 38	R/L	Limbic lobe	Cingulate	24	.000	7.21
0, −46, 10	R/L	Limbic lobe	Posterior cingulate	30	.000	6.15
−1, −20, 42	L	Limbic lobe	Posterior cingulate	24	.000	4.97
−4, −12, 38	L	Limbic lobe	Cingulate	24	.000	7.20
−6, 32, 32	L	Limbic lobe	Cingulate	32	.000	6.05
26, 56, −4	R	Frontal lobe	Superior frontal	10	.000	8.84
48, 4, 42	R	Frontal lobe	Middle frontal	9	.000	6.59
−28, 48, −8	L	Frontal lobe	Medial frontal	10	.000	7.35
−26, 52, −6	L	Frontal lobe	Middle frontal	10	.000	10.83
−18, 64, −10	L	Frontal lobe	Superior frontal	11	.000	7.06
−50, 0, 36	L	Frontal lobe	Precentral	6	.000	8.17
58, −44, 42	R	Parietal lobe	Inferior parietal	40	.000	6.74
42, −52, 50	R	Parietal lobe	Inferior parietal	40	.000	6.22
−62, −32, 22	L	Parietal lobe	Inferior parietal	40	.000	6.32

Table 2. (continued)

MNI	R/L	Effect Lobe	Effect Gyrus	Brodmann's Area	Local Maximum	
					p Voxel	*t* Voxel
−60, −48, 26	L	Parietal lobe	Inferior parietal	40	.000	5.91
8, −80, 10	R	Occipital lobe	Cuneus	17	.000	6.56

The Montreal Neurological Institute (MNI) coordinates, *p* values, and *t* values presented are those of the maximally activated voxel of each significant cluster. $p < .001$ corrected for multiple comparisons, minimum cluster size k is 10 voxels (2 × 2 × 2 mm). BOLD, blood oxygen level–dependent; PTSD, posttraumatic stress disorder; R, right; L, left.

reference voxel and the left superior frontal gyrus (BA 10), right parahippocampal gyrus (BA 30), and the right superior occipital gyrus (BA 19, 39). In contrast, comparison of functional connectivity maps revealed that dissociated PTSD subjects showed greater covariation than the control subjects in the right insula (BA 13, 34), left parietal lobe (BA 7), right middle frontal gyrus (BA 8), superior temporal gyrus (BA 38, 34), and right cuneus (BA 19).

One possible explanation for these between group differences in functional connectivity is that they are due to alterations in autobiographical memory. Functional neuroimaging techniques (positron emission tomography [PET] and fMRI) have been used to investigate the neuronal circuitry underlying autobiographical memory. Maguire (2001) notes that the most consistent result seen in eleven studies reviewed is a medial and left-lateralized activation pattern, particularly in the left medial prefrontal cortex and left hippocampus (Conway et al 1999; Fink et al 1996). In one study (Maddock et al 2001), however, subjects were instructed to recall particularly affect-laden memories, resulting in a predominantly right-hemispheric activation pattern that included activation of the prefrontal and temporal cortices, posterior cingulate gyrus, and insula. The present functional connectivity findings show primarily left-hemispheric frontal activation in the control subjects, as compared with predominantly right-hemispheric frontal and insula activation in the dissociated PTSD subjects. These findings might suggest that the memories are less affect-laden for the control subjects as compared with the dissociated PTSD subjects, and this is consistent with the subjective reports of the subjects. The control subjects recalled the traumatic memory as an ordinary autobiographical memory, whereas the dissociated PTSD subjects described symptoms of dissociation to "escape from" the overwhelming emotions associated with the traumatic memory.

The observed differences in functional connectivity patterns could be due to the effects of the traumatic memory or could be reflective of a general deficit in autobiographical memory in patients with PTSD. We addressed this problem by examining brain activation during neutral autobiographical memory recall in both PTSD and control subjects, using a subtraction analysis to determine whether there were differences in activation in the relevant brain areas. There were no significant differences in baseline activation between the two groups. During neutral autobiographical memory recall, control subjects showed significantly ($p < .001$) more activation in the right anterior cingulate gyrus (BA 24, 32) as compared with PTSD subjects. In contrast, PTSD subjects showed significantly ($p < .001$) more activation in the right superior and middle temporal gyri (BA 22), right and left anterior cingulate gyrus (BA 24), as well as in the right cingulate gyrus (BA 33), during the recall of a neutral memory as compared with control subjects (data not shown). Although areas in the right anterior cingulate gyrus and the superior temporal gyrus were also activated in dissociated PTSD subjects during recall of the traumatic memory, the specific voxels activated in response to the two different scripts (neutral vs. trauma) were different. Thus, we conclude that the patterns of activation seen in response to the trauma script are not simply due to alterations in autobiographical memory in PTSD patients but are due specifically to the effects of remembering the traumatic event.

Table 3. Brain Areas of Activation Showing Significant Differences in Connectivity/Covariation with Activation in the Left Ventrolateral Thalamus [−14, −16, 4] Between Dissociated PTSD Subjects and Control Subjects During Recall of a Traumatic Event

MNI	R/L	Effect Lobe	Effect Gyrus	Brodmann's Area	Local Maximum	
					p Voxel	*t* Voxel
Control Subjects ($n = 10$)						
> Dissociated PTSD ($n = 10$)						
($df = 1,480$, Minimum Cluster Size k = 10)						
−14, 60, 12	L	Frontal	Superior frontal	10	<.0001	6.62
18, −42, 6	R	Limbic	Parahippocampal	30	<.0001	5.89
26, −48, 2	R	Limbic	Parahippocampal	30	<.0001	5.76
44, −74, 26	R	Occipital	Superior occipital	19, 39	<.0001	6.07
Dissociated PTSD ($n = 10$)						
> Control Subjects ($n = 10$)						
($df = 1,480$, Minimum Cluster Size k = 10)						
8, −84, 34	R	Occipital	Cuneus	19	<.0001	6.13
32, 2, −16	R	Temporal	Superior Temporal	38, 34	<.0001	6.11
40, 2, −12	R	Sub-lobar	Insula	13, 34	<.0001	5.53
34, 16, 36	R	Frontal	Middle Frontal	8	<.0001	6.06
44, 16, 34	R	Frontal	Middle Frontal	8	<.0001	5.52
−6, −70, 54	L	Parietal	Superior Parietal	7	<.0001	5.91

PTSD, posttraumatic stress disorder; MNI, Montreal Neurological Institute coordinates; R, right; L, left.

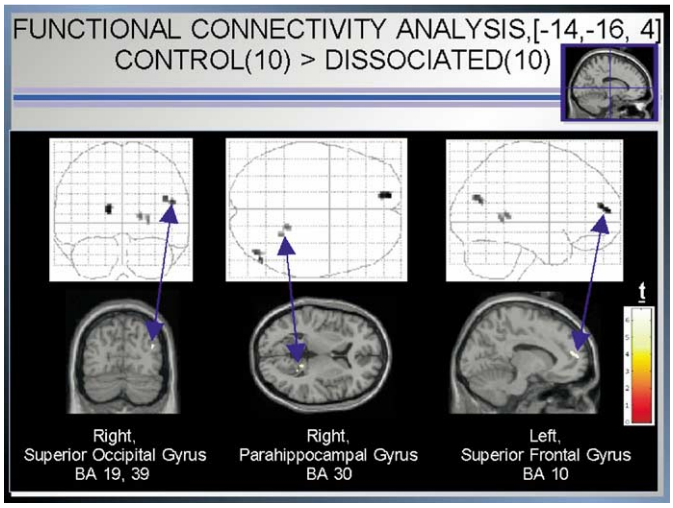

Figure 2. Brain regions with activation showing significantly greater functional connectivity/covariation with activation in the left thalamus in traumatized subjects without posttraumatic stress disorder (PTSD) than in dissociated PTSD subjects during recall of a traumatic event. Areas of functional connectivity/covariation determined by the statistical parametric map of the *t* statistic showing the psychophysiologic interaction between activity in the left thalamus (Talairach coordinates x = −14, y = −16, z = 4) and activity in other brain regions. The grid diagrams show all areas with significantly greater covariation in the subjects without PTSD. The cross-sectional brain images show sites of significant covariation in areas of interest. BA, Brodmann's area.

In addition to the changes in regions associated with autobiographical memory, differences in functional connectivity patterns involving the insula were observed between dissociative PTSD and control subjects, with activation in the right insula in dissociated PTSD but not in control subjects, correlating with activity in the left ventrolateral thalamus. This is particularly interesting in light of the insula's role in two processes relevant to the dissociative response: bodily perception (interoception) and perception of emotions. The insula has been shown to receive signals related to pain states, body temperature, and visceral sensations, as well as signals regarding the state of the smooth musculature in blood vessels and other viscera (described in Craig 2003).

The role of the insula in perception of internal states has also been supported in a PET study by Critchley et al (2001), who measured state-dependent regional brain activity in subjects with pure autonomic failure (PAF). These patients cannot modulate their bodily state through the autonomic nervous system, owing to peripheral autonomic degeneration. Compared with control subjects, subjects with PAF showed less activity in the right insula and left somatosensory cortex. These differences occurred consistently across a number of task conditions, thus indicating an alteration in the cortical mapping of bodily states, rather than a task-specific response. Critchley et al (2001) also found differences in regional brain activity across tasks in the right anterior cingulate and left posterior cingulate.

Damasio (1999) has emphasized the role of the insula and the somatosensory cortices in processing signals regarding bodily state and suggests that these signals form the basis for emotions. In this study, the dissociative PTSD subjects reported that they experienced both changes in their perception of their own bodily states and an inability to feel emotion. In a PET study of brain activity during self-generated emotion, Damasio (2000) found insula activation across a range of emotions. Bilateral activation of the insula was seen during recall of memories causing sadness and anger; right hemispheric activation was seen during recall of happiness and fear. Subjects in this study were healthy volunteers, and care was taken (with the use of both subjective reports and objective measures of psychophysiological arousal) to ensure that subjects were actually experiencing the emotion during data acquisition. The dissociated PTSD subjects in this study, however, reported difficulties in feeling emotions. Thus, the insula activation seen in this study might reflect this altered perception or possibly alterations in the "body map" constructed by the insula, which has been hypothesized by Damasio (1999) to contribute to emotional experiences. In fact, the subjective reports of the dissociated PTSD subjects in this study suggest that they experienced alterations in both bodily perceptions and emotions during recall of the traumatic memory.

It is interesting to note that patients in a dissociative state often have difficulties with perception of internal bodily states, for example recognizing pain states. Seven out of 10 dissociated PTSD patients included in the present study reported on the DES (Bernstein and Putnam 1986) that they are sometimes able to ignore pain. Moreover, patients in dissociative states often have significant difficulties experiencing feelings of emotion. In fact, all of the dissociative subjects in this study reported being "removed" from their experience of their traumatic memory.

In the functional connectivity analysis comparing dissociative PTSD patients with those PTSD patients who exhibited a flashback/reliving response, we used as a seed voxel an area in the right anterior cingulate gyrus that was close to the area that we used in a previous study (Lanius et al 2004) to compare functional connectivity in flashback/reliving PTSD patients with that seen in control subjects. The anterior cingulate has often been implicated in the pathophysiology of PTSD (Bremner 1999a, 1999b; Lanius et al 2001, 2002, 2003; Liberzon et al 1999; Shin

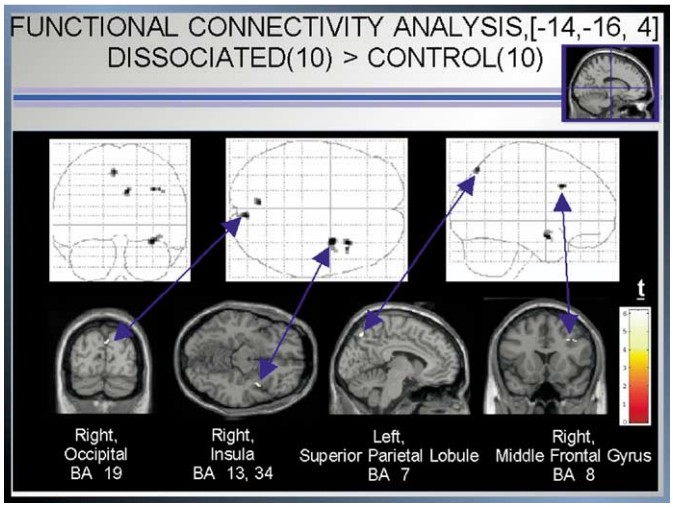

Figure 3. Brain regions with activation showing significantly greater functional connectivity/covariation with activation in the left thalamus in dissociated posttraumatic stress disorder (PTSD) subjects than in traumatized subjects without PTSD during recall of a traumatic event. Areas of functional connectivity/covariation determined by the statistical parametric map of the *t* statistic showing the psychophysiologic interaction between activity in the left thalamus (Talairach coordinates x = −14, y = −16, z = 4) and activity in other brain regions. The grid diagrams show all areas with significantly greater covariation in the subjects without PTSD. The cross-sectional brain images show sites of significant covariation in areas of interest. BA, Brodmann's area.

Table 4. Brain Areas of Activation Showing Significant Differences in Connectivity/Covariation with Activation in the Right Cingulate Gyrus [3, 16, 30] Between Dissociated PTSD and Flashback/Reliving PTSD Subjects During Recall of a Traumatic Event

MNI	R/L	Effect Lobe	Effect Gyrus	Brodmann's Area	Local Maximum	
					p Voxel	*t* Voxel
Flashback/Reliving PTSD ($n = 11$) > Dissociated PTSD ($n = 11$) ($df = 1,584$, Minimum Cluster Size k = 10)						
20, −34, 44	R	Limbic	Cingulate	31	<.000	5.94
20, −64, 18	R	Limbic	Posterior Cingulate	31	<.000	6.58
−22, 56, 6	L	Frontal	Superior Frontal	10	<.000	5.60
−42, 16, 2	L	Frontal	Inferior Frontal	47	<.000	6.50
−54, 24, 10	L	Frontal	Inferior Frontal	45	<.000	6.17
22, −70, 48	R	Parietal	Precuneus	7	<.000	6.96
24, −70, 28	R	Parietal	Precuneus	7	<.000	5.46
28, −60, 50	R	Parietal	Precuneus	7	<.000	6.62
24, −76, 36	R	Parietal	Precuneus	19	<.000	5.64
42, −66, 16	R	Temporal	Middle Temporal	39	<.000	6.71
48, −70, 18	R	Temporal	Middle Temporal	39	<.000	6.41
4, −84, 28	R	Occipital	Cuneus	18	<.000	6.01
30, −82, 24	R	Occipital	Superior Occipital	19	<.000	6.23
Dissociated PTSD ($n = 11$) > Flashback/Reliving PTSD ($n = 11$) ($df = 1,584$, Minimum Cluster Size k = 10)						
−34, 32, −8	L	Frontal	Inferior Frontal	47	<.000	6.14

PTSD, posttraumatic stress disorder; MNI, Montreal Neurological Institute coordinates; R, right; L, left.

1999). The anterior cingulate cortex has also been shown to play a key role in the representation of subjective experience, in the integration of bodily responses with behavioral demands (Critchley et al 2001), and emotion. Because the anterior cingulate gyrus is involved in the experiential and/or expressive aspects of emotion, it might be that the disruption in its functioning observed in patients with PTSD reflects emotion dysregulation, including extremes of re-experiencing and avoiding emotionally distressing memories.

In this study, we found that the flashback/reliving PTSD group, as compared with the dissociative PTSD group, exhibited greater covariation with the seed voxel in the right anterior cingulate, including the right posterior cingulate, right parietal, and occipital cortex. These regions were also found to be more

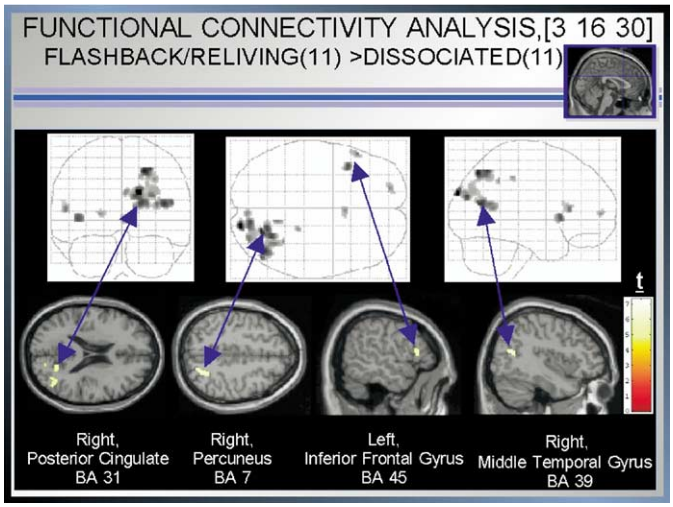

Figure 4. Brain regions with activation showing significantly greater functional connectivity/covariation with activation in the right cingulate gyrus in flashback/reliving posttraumatic stress disorder (PTSD) subjects than in dissociated PTSD subjects during recall of a traumatic event. Areas of functional connectivity/covariation determined by the statistical parametric map of the *t* statistic showing the psychophysiological interaction between activity in the right cingulate gyrus (Talairach coordinates x = 3, y = 16, z = 30) and activity in other brain regions. The grid diagrams show all areas with significantly greater covariation in the flashback/reliving PTSD subjects. The cross-sectional brain images show sites of significant covariation in areas of interest. BA, Brodmann's area.

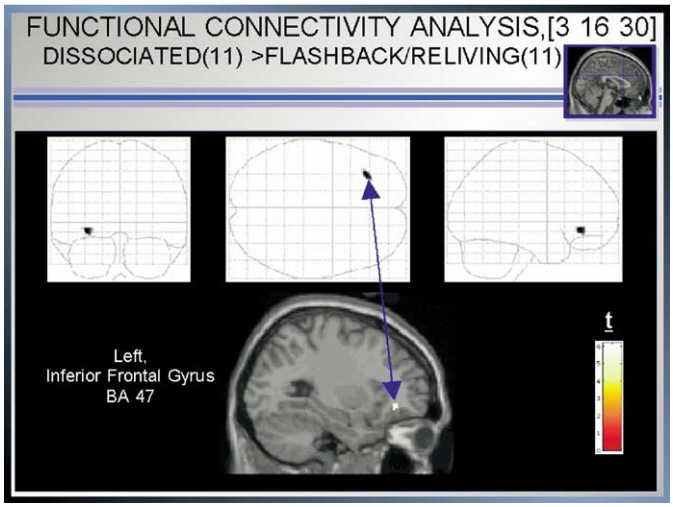

Figure 5. Brain regions with activation showing significantly greater functional connectivity/covariation with activation in the right cingulate gyrus in dissociated posttraumatic stress disorder (PTSD) subjects than in flashback/reliving PTSD subjects during recall of a traumatic event. Areas of functional connectivity/covariation determined by the statistical parametric map of the *t* statistic showing the psychophysiologic interaction between activity in the left thalamus (Talairach coordinates x = 3, y = 16, z = 30) and activity in other brain regions. The grid diagrams show all areas with significantly greater covariation in the dissociated PTSD subjects. The cross-sectional brain images show sites of significant covariation in areas of interest. BA, Brodmann's area.

strongly correlated with a different, but nearby (x = 2, y = 20, z = 36), seed voxel in the right anterior cingulate than in the flashback/reliving PTSD group than in healthy control subjects (Lanius et al 2004); however, the patterns in the control subjects in the earlier analysis, in whom greater covariation with the right anterior cingulate occurred in the left superior frontal gyrus (Brodmann's area 9), left anterior cingulate gyrus (BA 32), left striatum (caudate), left parietal lobe (BA 40 and 43), and left insula (BA 13) did not resemble the connectivity patterns observed in the dissociative PTSD group analyzed in this study. In this latter group, only one area was found to have activation more strongly correlated with the right anterior cingulate than in the flashback/reliving PTSD group; this was the left inferior frontal gyrus (BA 47). This region has previously been implicated in the determination of relevance to self of verbal statements of differing emotional valence (Blackwood et al 2000). This is of interest because the dissociative PTSD subjects used dissociation to distance themselves from the emotional content of the traumatic memory.

Unfortunately, it was not possible to conduct a functional connectivity analysis of all three groups based on the same seed voxel, or even the same region (there were no voxels in the right anterior cingulate that were activated in all three groups); this limits the degree to which the connectivity patterns in all three groups can be compared.

There are several further limitations of the present study. One of the limitations is that the sample size of the groups was relatively small. This did not allow application of alternative statistical models, such as random or mixed effects models (Friston et al 1999; Kirk 1995). The latter afford generalization to the population of PTSD patients through statistical generalization theory, as opposed to logical deductive considerations of sample to population comparability (Neufeld 1970). Although it is unfortunate that a larger sample size could not be used, the effects reported in the analyses are quite large indeed. As such, our highly significant results provide enormous protection at the cluster level against type I error. Further limitations have to do with the characteristics of the study subjects themselves. Some of the PTSD subjects included in the present study had comorbid disorders, including dysthymia, lifetime history of polysubstance dependence, and major depression. Axis II comorbidity, especially borderline personality disorder, will also have to be evaluated in future studies. Further studies will also need to address covariations between clinical symptoms and brain activation patterns. Such covariation analyses often require larger sample sizes than used in the present study, and investigations with larger sample sizes are currently in progress. In addition, there are limitations to the information that can be obtained through the use of functional connectivity analyses. These analyses provide information about regions in the brain whose activity covaries during performance of a task of interest (in this case, recall of a traumatic event). They do not, however, give any insight into the causes of the distinct covariation patterns observed between groups. In particular, although the left ventrolateral thalamus contained the voxel used as the "seed" voxel in the comparison of the dissociative PTSD and the control groups, it should not be concluded that this region is the cause of the between-group differences observed.

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