Brain Activation during Script-Driven Imagery Induced Dissociative Responses in PTSD: A Functional Magnetic Resonance Imaging Investigation

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Background: *The goal of this study was to examine the neuronal circuitry underlying dissociative responses to traumatic script-driven imagery in sexual-abuse-related posttraumatic stress disorder (PTSD). Pilot studies in our laboratory have shown that PTSD patients had very different responses to traumatic script-driven imagery. Approximately 70% of patients relived their traumatic experience and showed an increase in heart rate while recalling the traumatic memory (Lanius et al 2001). The other 30% of patients had a dissociative response with no concomitant increase in heart rate. This article focuses on the latter group.*

Methods: *The neuronal circuitry underlying dissociative responses in PTSD was studied using the traumatic script-driven symptom provocation paradigm adapted to functional magnetic resonance imaging (fMRI) at a 4 Tesla field strength in 7 subjects with sexual-abuse-related PTSD and 10 control subjects.*

Results: *Compared with control subjects, PTSD patients in a dissociative state showed more 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 frontal gyrus (BA 10), the medial cortex (BA 9), and the anterior cingulate gyrus (BA 24 and 32).*

Conclusions: *These findings suggest that prefrontal and limbic structures underlie dissociative responses in PTSD. Differences observed clinically, psychophysiologically, and neurobiologically between patients who respond to traumatic script-driven imagery with dissociative versus nondissociative responses may suggest different neuronal mechanisms underlying these two distinct reactions.* Biol Psychiatry 2002;52:305–311 © *2002 Society of Biological Psychiatry*

Key Words: PTSD, neuroimaging, psychophysiology, anterior cingulate, dissociation, temporal lobe

Introduction

Dissociation is a common feature of posttraumatic stress disorder (PTSD). Dissociation often involves a disruption in the usually integrated function of consciousness, memory, identity, or perception of the environment. Acute dissociative responses to psychologic trauma have been found to predict the later development of chronic PTSD (Bremner et al 1992, 1997; Koopman et al 1994; Marmar et al 1994; Shalev et al 1996). Moreover, individuals who experienced acute dissociative responses to psychologic trauma have been shown to develop a chronic pattern of dissociation in response to minor stressors or reminders of the original trauma (Bremner et al 1997). Bremner hypothesized that there may be two subtypes of acute trauma response, one primarily dissociative and the other predominantly intrusive or of hyperarousal, that represent unique pathways to chronic stress–related psychopathology (Bremner 1999). Interestingly, the DSM-IV acute stress disorder has a prominent emphasis on dissociative symptoms, whereas DSM-IV PTSD has no dissociative symptom cluster.

In addition to PTSD, dissociative responses can accompany a multitude of other psychiatric disorders, including panic disorder, mood disorders, and psychoses. In addition, dissociative responses have been reported to occur in several neurologic conditions such as temporal lobe epilepsy (TLE), migraines, and cerebral vascular disease (for review see Sierra and Berrios 1998).

Although the neuronal circuitry underlying dissociative phenomena are not well understood, a recent study examined brain glucose metabolism in DSM-IV depersonalization disorder. Significantly lower metabolic activity was observed in the right superior and middle temporal gyri (areas 21, 22). Increased metabolic activity was seen in parietal areas (area 7B, 39) and left occipital cortex (area 19). Dissociation and depersonalization scores were significantly positively correlated with metabolic activity in area 7B. The authors suggested that depersonalization is associated with functional abnormalities in sequential hierarchical areas of the sensory cortex as well as in areas responsible for multimodal sensory integration (BA7B;

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Simeon et al 2000). This study has the limitation of solely focusing on depersonalization disorder without examining this disorder in context with various comorbidities often observed with depersonalization disorder.

The pattern of brain activation associated with dissociative responses in PTSD has been largely unexplored. To our knowledge, this is the first functional magnetic resonance imaging (fMRI) neuroimaging study to examine dissociative responses in PTSD at a 4-Tesla field strength. Based on the previous literature on dissociative mechanisms as well as our pilot work (Bremner et al 1997; Simeon et al 2000), we hypothesized functional abnormalities in the medial prefrontal, superior and middle temporal gyri, as well as the anterior cingulate gyrus in dissociative PTSD patients compared with control subjects.

Methods and Materials

Subjects

All PTSD subjects described in our study had a dissociative response to the traumatic script-driven imagery as assessed by a modified version of the Clinician-Administered Dissociative State Scale (CADSS; Bremner et al 1998) in which each item was scored as present or absent. Pilot studies in our laboratory showed that PTSD patients had very different responses to traumatic script-driven imagery. Approximately 70% of patients relived their traumatic experience and showed an increase in heart rate response after being exposed to the traumatic script (see Lanius et al 2001). The other 30% of patients had a dissociative response with no concomitant increase in heart rate. This article focuses on the latter group.

Seven female subjects who had developed PTSD as a result of sexual/physical abuse were studied. All of the PTSD subjects had a childhood history of chronic sexual, physical, and emotional abuse. The control group consisted of 10 (9 female, 1 male) subjects who met criterion A (as a result of sexual abuse/assault ($n = 7$) or a motor vehicle accident ($n = 3$) for PTSD but who did not meet DSM-IV criteria for PTSD. The extent of the traumatic experiences for the control subjects was less chronic and severe. IRB approval and informed consent were obtained. Subjects were diagnosed and assessed for dissociative pathology using the Structured Clinical Interview for DSM-IV (SCID; First et al 1997), the Clinician Administered PTSD Scale (CAPS; Blake et al 1995), the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D; Steinberg 1994), and the Dissociative Experience Scale (DES; Bernstein and Putnam 1986). The mean CAPS score was 87 (SD 15.3) for the PTSD subjects and 4 (SD 1.6) for the control subjects. Dissociative experience scale (DES) scores were 43 (SD 17.6) for the PTSD and 3 (SD 2.8) for the control group. Usually DES scores of 30 or greater indicate a dissociative disorder (Bernstein and Putnam 1986). Dissociative responses to the script-driven symptom provocation were assessed using the CADSS and compared with baseline CADSS scores before script-driven imagery as described in a recent positron emission tomography (PET) study of sexual-abuse-related PTSD (Bremner et al 1998). Three of the seven patients met criteria for current dysthymia and two for panic disorder. All seven patients met criteria for current dissociative disorder NOS (not otherwise specified). Four patients fulfilled a lifetime history of polysubstance dependence, five fulfilled lifetime history of major depression, two fulfilled lifetime history of eating disorder NOS, and two fulfilled lifetime history of panic disorder. The control subjects were of comparable age (36 [SD 10.9] for PTSD group and 35 [SD 12.3] for control group), gender, and race; none met criteria for any DSM-IV mental disorder. All subjects were right-handed. Patients had undergone a supervised drug washout for at least 2 weeks before scanning. Patients with a history of psychosis, bipolar disorder, and substance use disorder in remission for less than 6 months were excluded from the study. Moreover, patients with any significant medical conditions, neurologic illness, or a history of head injury were excluded from the study.

fMRI Procedures

We performed the MR imaging studies on a 4-Tesla whole body Varian/Siemens imaging system 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/mins. A whole-head hybrid birdcage radio frequency (RF) coil was used for transmission and detection of signal. Before imaging, a global shimming procedure, using first and second order shims, were performed to optimize the magnetic field over the imaging volume of interest. Subjects' heart rates were monitored using a fiber-optic pulse oximeter.

The subjects' heads were placed into a head cradle and packed tightly with copious amounts of foam to reduce motion. The RF coil was subsequently placed around the subject's head. Each functional brain volume was acquired using a navigator echo corrected, interleaved multishot (four shots) echo planar imaging pulse sequence with a 128×128 matrix size and a total volume acquisition time of 5 sec [echo time (TE) = 15 msec, flip angle = 45°, FOV [field of vision] = 24.0 cm]. During each imaging session, high-resolution (256×256), three-dimensional, T1-weighted anatomic volumes were acquired in the same FOV and orientation as the functional images [TE = 4.5 msec, repetition time (TR) = 9.0 msec; inversion time (TI) = 500 msec, flip angle = 11°]. The resulting acquisition produced 64 contiguous structural images each with a slice thickness of 1.25 mm.

Functional maps of the activated pixels were constructed by comparing, on a pixel-by-pixel basis, the signal intensity in the baseline and task-related images, using statistical methods (SPM 99; Ashburner et al 2000). Basis functions representing epochs of interest were entered into SPM. Variability in scans attributed to each basis function relative to SPM99's implicit baseline were revealed using contrasts. Fixed-effects analyses were performed by modeling each group's evoked blood oxygenation level dependent (BOLD) response using hemodynamically convolved boxcar basis functions (see Figure 1).

Script-Driven Imagery

The script-driven imagery procedure was adapted to fMRI according to previously published methods (Lanius et al 2001).

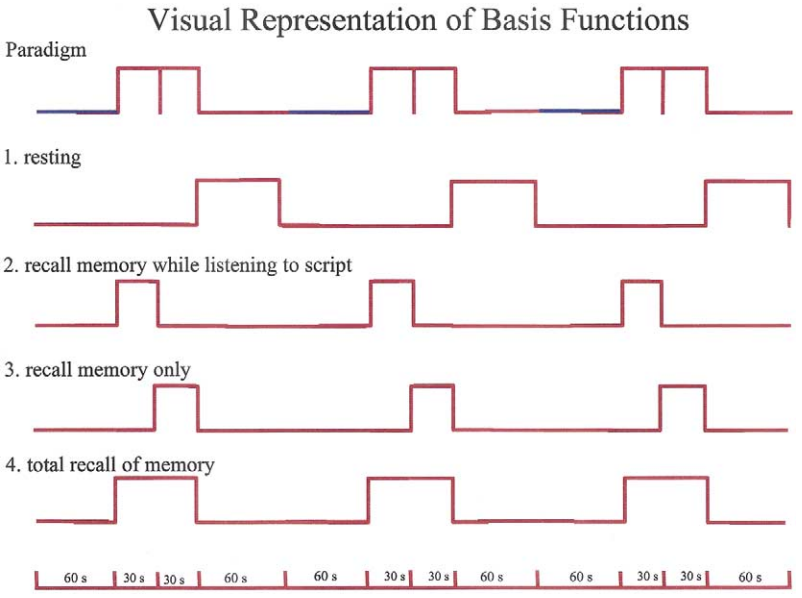

Figure 1. Blue scans represent the "implicit baseline" used for SPM99 analysis. Boxcars in line 3 represent the recall of neutral or traumatic memory only. The TR was 5 sec per image volume. TR, repetition time.

Scanning of the traumatic imagery condition was repeated three times. Each scan proceeded as follows (see Figure 1): 1) Each subject was instructed to lie still, breathe through his or her nose, and to begin focusing on the traumatic script as soon as it was read. Reading of the script lasted 30 sec. As soon as the subject heard the script, he or 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. We allowed 120 sec to pass until the script was repeated. During this time, the subject was asked to lie still, breathe through his or her nose, and let go of the traumatic event. Subjects were assessed for dissociative symptoms using the CADSS after each scan. Baseline brain activation was calculated based on average activation patterns 60 sec before each recollection of the traumatic event. Brain activation during the recall of the traumatic event was calculated based on average activation patterns during the final 30 sec of the recall of the traumatic event.

Analyses of Script Responses

Two-tailed *t* tests were used to compare dissociative responses to the scripts in PTSD patients versus control subjects, both at baseline and for change from baseline in response to scripts. 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 responsivity of dissociative PTSD patients versus control subjects.

Results

Table 1 shows regions of activation during the script-driven imagery versus implicit baseline where the PTSD group ($n = 7$) shows greater, lesser, or equal levels of activation compared with the control group ($n = 10$) during the final 30 sec of the recall of the traumatic memory. The dissociated PTSD group showed greater activation than the control group in the right superior and middle temporal gyri (BA 38), the inferior frontal gyrus (BA 47), the occipital lobe (BA 19), the right parietal lobe (BA 7), the right medial frontal gyrus (BA 10), the right medial prefrontal cortex (BA 9), and the right anterior cingulate gyrus (BA 24 and 32).

Dissociative responses to the script-driven imagery symptom provocation paradigm were assessed using the CADSS and were compared with baseline CADSS scores before exposure to the script-driven imagery. The mean baseline CADSS score was 3.1 (SD 1.3) for PTSD patients and 0.3 (SD 0.48) for control subjects. The mean CADSS score during the traumatic script-driven imagery-induced memory recall was 19.6 (SD 1.4) for dissociative PTSD subjects and 0.4 (SD 0.51) for control subjects. Dissociative PTSD subjects showed a significant increase in CADSS scores during script-driven imagery-induced dissociation as compared with baseline ($p < .0.000$, $t = 31.1$, $df = 6$ (t test, one-tailed)). Control subjects did not show a significant increase in CADDS scores during script-driven imagery-induced memory recall compared with baseline ($p > .34$; $t = 1$, $df = 9$ (t test, one-tailed)).

Figure 2 shows regions of activation where the extent threshold (k) is greater than 10 voxels during the traumatic memory recall while PTSD patients dissociated versus implicit baseline where the PTSD group ($n = 7$) showed greater activation than the control group ($n = 10$). Figure 2 shows the areas listed in Table 1.

The PTSD patients did not show a significant increase in heart rate during script-driven imagery-induced dissociation (dissociative PTSD group: mean 4.1; SD 14.2; control group: mean 2.1; SD 2.25) from baseline com-

Table 1. Regions of Activation during Memory Recall Versus Implicit Baseline Where the Dissociated PTSD Group (n = 7) Shows Greater, Less, or Equal Activation to the Control Group (n = 10)

Talairach	R/L	Effect Lobe	Effect Gyrus	Brodmann's Area	*p* voxel	*t* voxel
D-PTSD group ($n = 7$) > control group ($n = 10$) $df = 1401$, $k > 10$						
12, 40, 18	R	Limbic lobe	Anterior cingulate	BA 32	6.73E-006	6.34
4, −4, 36	R	Limbic lobe	Cingulate gyrus	BA 24	1.22E-005	6.24
52, 24, −16	R	Frontal lobe	Inferior frontal gyrus	BA 47	1.56E-012	8.56
4, 54, 12	R	Frontal lobe	Medial frontal gyrus	BA 9, 10	5.12E-011	8.11
2, −66, 46	R	Parietal lobe	Precuneus	BA 7	1.81E-012	8.54
50, −72, 24	R	Temporal lobe	Middle temporal gyrus	BA 39	4.89E-015	9.27
54, 12, −16	R	Temporal lobe	Superior temporal gyrus	BA 38	5.32E-013	8.69
−4, −76, 34	L	Occipital lobe	Cuneus	BA 19	8.37E-013	8.64
−26, −84, 36	L	Occipital lobe	Cuneus	BA 19	7.30E-010	7.74
D-PTSD ($n = 7$) < control group ($n = 10$) $df = 1401$, $k > 10$						
−18, −34, −6	L	Limbic lobe	Parahippocampal gyrus	BA 35	4.42E-005	6.01
44, 12, 36	R	Frontal lobe	Middle frontal gyrus	BA 8, 9	7.49E-010	7.74
−42, −26, 8	L	Temporal lobe	Superior temporal gyrus	BA 41, 13	1.06E-005	6.27
D-PTSD ($n = 7$) = control group ($n = 10$) $df = 1401$, $k > 10$						
12, −18, 2	R	Sublobar	Thalamus		1.78E-015	9.39
18, −10, 4	R	Sublobar	Thalamus		9.97E-010	7.70
14, −6, 16	R	Sublobar	Thalamus		5.19E-009	7.46
0, −14, 10	R, L	Sublobar	Thalamus		3.07E-004	5.65
−14, −10, 2	L	Sublobar	Thalamus		4.50E-012	8.42
−6, −10, 4	L	Sublobar	Thalamus		2.78E-006	6.49
2, 26, 24	R	Limbic lobe	Anterior cingulate	BA 24, 32	3.33E-016	9.67
2, 10, 32	R	Limbic lobe	Cingulate gyrus	BA 24	3.33E-016	9.77
0, −4, 32	R, L	Limbic lobe	Cingulate gyrus	BA 24	3.22E-015	9.32
14, −38, 0	R	Limbic lobe	Parahippocampal gyrus	BA 27, 30	9.59E-014	8.91
−14, −36, 2	L	Limbic lobe	Parahippocampal gyrus	BA 27, 30	3.11E-010	7.86
8, −44, 8	R	Limbic lobe	Posterior cingulate	BA 29	7.06E-005	5.93
−2, 42, 20	L	Frontal lobe	Medial frontal gyrus	BA 9	3.03E-007	6.85

D-PTSD, dissociated posttraumatic stress disorder; R, right; L, left; BA, Brodmann's Area.

pared with control subjects ($p > .71$, $t = 0.3$, $df = 6$ (t test, one-tailed)).

Time courses of activation showed that brain activation returned to baseline during rest periods in all brain areas studied for both PTSD and control groups. These time courses indicate that 60 sec was sufficient time for subjects to recover from the traumatic, script-driven memories. Baseline brain activation did not differ between PTSD patients and control subjects (data not shown). One may have expected a decrease in the signal over time due to a habituation effect as a result of repeating the scripts three times; however, the data show that the signal does not fade over time. This was true for all control and PTSD subjects in all brain areas studied thus far (data not shown).

Discussion

Compared with control subjects, PTSD subjects who dissociated in response to traumatic script-driven imagery exhibited higher 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 frontal gyrus (BA 10), the medial prefrontal cortex (BA 9), and the anterior cingulate gyrus (BA 24 and 32). These patterns of brain activation are strikingly different from those observed in patients who relived their traumatic experiences after being exposed to the traumatic script (see Lanius et al 2001). The latter group showed significantly less activation of the thalamus, anterior cingulate gyrus (area 32), and medial frontal gyrus (area 10, 11) during script-driven recall of traumatic events compared with control subjects (Lanius et al 2001). Lower levels of anterior cingulate activation and medial prefrontal activation in this group were consistent with previous PET studies of sexual abuse- and combat-related PTSD (Bremner et al 1999a, 1999b; Shin et al 1999).

Heart rate responses to the traumatic scripts also differed between these two groups of patients. The group of patients who relived their traumatic experience showed an increase in heart rate in response to the traumatic script (see Lanius et al 2001). Patients with a dissociative response to the traumatic script-driven imagery showed no significant increase in heart rate. The lack of autonomic response observed in the PTSD patients during dissocia-

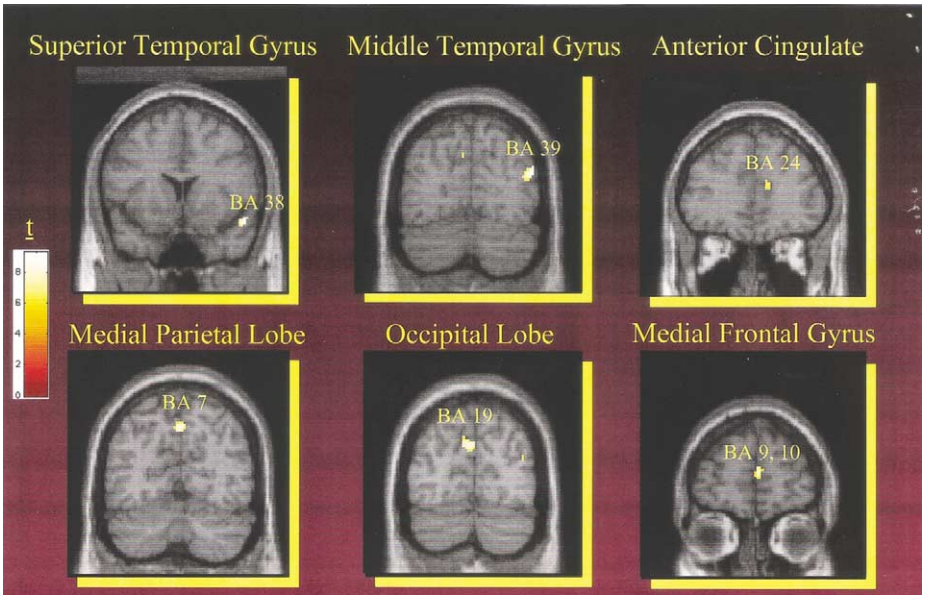

Figure 2. Regions of activation during memory recall versus implicit baseline where the dissociated posttraumatic stress disorder group ($n = 7$) shows greater activation than the control group ($n = 10$), $k > 10$. BA, Brodmann's area.

tive states is consistent with previous findings (Kelly and Walter 1968; Lader 1975; Lader and Wing 1966). Lader (1975) reported that depersonalization responses were associated with nonfluctuating skin conductance response. Moreover, Lader and Wing (1966) observed a decrease in heart rate when patients became depersonalized. Griffin et al (1997) found that, in contrast to rape victims with low peritraumatic dissociation during the trauma, those with high peritraumatic dissociation had suppressed skin conductance response and decreased heart rate when talking about the rape.

The differences observed clinically, psychophysiologically, and neurobiologically between patients who respond with dissociative versus nondissociative responses to traumatic script-driven imagery suggest that different neuronal mechanisms underlie these two distinct reactions. Future studies will need to replicate these findings and further elucidate the neural correlates underlying such different responses.

The results of increased 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 frontal gyrus (BA 10), the medial prefrontal cortex (BA 9), and the anterior cingulate gyrus (BA 24 and 32) in dissociative PTSD patients are consistent with the finding of increased global cerebral blood flow in the frontal lobes and anterior cingulate gyrus following THC-induced depersonalization (Mathew et al 1999). Furthermore, increased brain glucose metabolism in parietal Brodmann's areas 7B and occipital area 19 was found during states of depersonalization in DSM-IV depersonalization disorder (Simeon et al 2000). It remains unclear why dissociative PTSD patients in our study showed increased activation in the superior and middle temporal gyri, whereas patients with depersonalization disorder showed decreased metabolic activity in these regions. One possible explanation may be differences in the samples of patients studied. The comorbidity profile in the Simeon et al (2000) study is not known and may contribute to discrepancies in the results of the two studies.

Activation in the superior and middle temporal gyri during dissociative states in PTSD is consistent with the temporal lobe hypothesis of dissociation. The epilepsy literature has described dissociative symptoms with seizures of various foci, including both right and left hemispheres (Devinsky et al 1989; Kenna et al 1965). Penfield and Rasmussen (1950) also reported depersonalization like symptoms in response to stimulation of the superior and middle temporal gyris during neurosurgery. Moreover, Teicher et al (1993) explored the relationship between early abuse and limbic system dysfunction as measured by the Limbic System Checklist-33 (LSCL-33; Teicher et al 1993). This symptom checklist includes symptoms often experienced by people suffering from temporal lobe epilepsy. Results showed that LSCL-33 scores correlated well with the dissociative experience scale scores (Teicher et al 1993, 1997). Changes in brain activation of the superior and middle temporal gyri therefore may contribute to the dissociative responses experienced by the patients in our study.

Sierra and Berrios (1998) recently proposed a corticolimbic model of depersonalization. They postulated that depersonalization involves corticolimbic disconnection, such that left medial prefrontal activation with reciprocal amygdala inhibition results in hypoemotionality and decreased arousal, and right dorsolateral prefrontal cortex

activation with reciprocal anterior cingulate inhibition leads to hypervigilance, attentional difficulties, and emptiness of mental contents. In support of their model, Sierra and Berrios cited evidence for medial prefrontal involvement in both the monitoring and modulation of emotions (Damasio 1994; Reiman et al 1997). In this model, once a threshold of anxiety is reached, the medial prefrontal cortex is thought to inhibit emotional processing on limbic structures such as the amygdala, which in turn leads to a dampening of sympathetic output and reduced emotional experiencing. Finally, several studies suggest that the prefrontal cortex has inhibitory influences on the emotional limbic system, including PET studies showing a negative correlation between blood flow in the left prefrontal cortex and the amygdala (Davidson and Sutton 1995; Drevets et al 1992).

Our findings partially lend support to the above model. The dissociative PTSD patients had increased activation in the dorsolateral prefrontal cortex (BA 9) and the medial frontal cortex (BA 10). They also did not exhibit increased amygdala activation. Increased activation of the medial prefrontal cortex may underlie the lack of autonomic response observed in these patients.

It is interesting to note that the activation effects in the superior and middle temporal gyris, anterior cingulate, medial parietal lobe, and medial frontal gyrus in the dissociated PTSD subjects were lateralized to the right side. The possibility that childhood trauma sets the stage for lateralized responses is given credence by reports from Schiffer et al (1995) who showed right hemisphere activation using probe-evoked potentials during recall of unpleasant memories in adults with a history of childhood abuse. Moreover, Teicher et al (1997) and DeBellis (1999) reported reduced corpus callosum size in individuals with a history of childhood abuse.

There are several limitations of this study. The relatively small numbers of study participants ($n = 7$ in the PTSD group; $n = 10$ in the control group) did not allow for the performance of a random effects analysis. Studies using larger sample sizes are currently in progress. In addition, the comorbidity profile of the PTSD subjects may be a confounding factor in the study. All PTSD subjects included in our study had a history of chronic childhood sexual, physical, and emotional abuse. Significant comorbidity, including dysthymia, panic disorder, lifetime history of polysubstance dependence, major depression, and eating disorder NOS were therefore noted in this patient group. It has been well established that patients with dissociative disorders invariably have multiple comorbid disorders. In fact, PTSD and dissociative disorders are often referred to as "umbrella disorders" because a wide variety of symptoms may be understood as part of a traumatically based syndrome (Kessler et al 1995). Future studies will employ more rigorous assessments of the subjects' childhood traumatic experiences.

In summary, our results suggest that PTSD patients can have very different responses to traumatic script-driven imagery and may shed light on key biological dimensions of the disorder. In our laboratory's functional neuroimaging studies of PTSD, approximately 70% of patients relived their traumatic experience and showed an increase in heart rate while recalling the traumatic memory (Lanius et al 2001), while the other 30% showed a dissociative response with no concomitant increase in heart rate. Interestingly, attempts to correctly classify PTSD cases using discriminant functions based on psychophysiological responses to reminders, including expected increased heart rate, have historically resulted in false negative classifications in the range of 30% to 40% (Orr, 1997; Orr and Roth 2000). Keane and colleagues (1998) recently reported on the largest and most rigorous research of this kind, a multi-site study of 1,168 Vietnam veterans, in which the best logistic model for predicting current PTSD status exhibited an approximately two-thirds rate of correct classification (i.e., two-third agreement with DSM-IV diagnosis). The fMRI findings reported here add to the emerging evidence of experiential, psychophysiological and neurobiological differences between patients who have hyperaroused, dissociative, and other responses to traumatic reminders (Griffin et al 1997; Hopper and van der Kolk 2001). Our findings also suggest that different neuronal mechanisms may generate distinctly different reactions and, as Osuch (2001) has recently observed, that the heterogeneity of symptomatic and biological responses to traumatic reminders in PTSD should be addressed in the designs of functional imaging studies of this disorder.

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