A review of neuroimaging studies in PTSD: Heterogeneity of response to symptom provocation

R.A. Lanius a,b,*, R. Bluhm c, U. Lanius d, C. Pain a,e

Abstract

Different experiential, psychophysiological, and neurobiological responses to traumatic symptom provocation in posttraumatic stress disorder (PTSD) have been reported in the literature. Two subtypes of traumatic response have been hypothesized, one characterized predominantly by hyperarousal and the other primarily dissociative, each one representing unique pathways to chronic stress-related psychopathology. Recent PTSD neuroimaging findings in our own laboratory support this notion and are consistent with the view that grouping all PTSD subjects, regardless of their different symptom patterns, in the same diagnostic category may interfere with our understanding of posttrauma psychopathology. This review will integrate findings of different experiential, psychophysiological, and neurobiological responses to traumatic symptom provocation with the clinical symptomatology and the neurobiology of PTSD.

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1. Introduction

Neuroimaging has become an important technique in understanding the neurochemistry, and the functional changes underlying various psychiatric disorders. Both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been used in posttraumatic stress disorder (PTSD) to elucidate the neural mechanisms underlying PTSD. While a number of neuroimaging studies have examined alterations in brain functioning in PTSD patients during resting conditions (Semple et al., 1993, 1996; Lucey et al., 1997; Bonne et al., 2003), in response to cognitive tasks (Shin et al., 2001, 2004; Shaw et al., 2002; Clark et al., 2003; Bremner et al., 2003; Bryant et al., 2005), masked (Rauch et al., 2000; Hendler et al., 2001) or overtly presented (Shin et al., 2005) facial stimuli, the majority of studies have used some form of symptom provocation paradigm (Rauch et al., 1996; Liberzon et al., 1996/1997, 1999; Bremner et al., 1999a,b; Shin et al., 1997, 1999; Lanius et al., 2001, 2002, 2003a,b; Osuch et al., 2001; Pissiota et al., 2002; Gilboa et al., 2004; Shin et al., 2004; Britton et al., 2005). Our own studies, using script-driven imagery, have shown that responses to recalling traumatic experiences in chronic PTSD patients can differ significantly. Whereas many studies have pre-screened subjects for subjective or autonomic reactivity prior to scanning, we have subdivided our subjects post-scan on the basis of their description of their experience during script-driven imagery. Approximately
70% of patients reported reliving their traumatic experience in the form of intensely upsetting recollections and flashbacks, a phenomenon that has been referred to as “primary dissociation” (van der Kolk et al., 1996a). This group also showed a significant increase in heart rate while recalling the traumatic memory (Lanius et al., 2001). The other 30% of our sample exhibited a dissociative response (Lanius et al., 2002). That is, they reported such experiences as depersonalization, derealization or “zoning out,” phenomena that have been termed “secondary dissociation” (van der Kolk et al., 1996a). This group also failed to show a mean concomitant increase in heart rate when exposed to the traumatic script (Lanius et al., 2002). Bremner (1999) has previously suggested that there may be two subtypes of acute trauma response, one characterized by intrusive memories and hyperarousal and the other predominately dissociative, each representing unique pathways to chronic stress-related psychopathology. Our results indicate that these two patterns may also be seen in patients with chronic PTSD.

Most PTSD neuroimaging studies to date have focused on the hyperarousal response, in some cases, as noted above, selecting study patients for their autonomic or subjective reactivity to trauma reminders. This paper will review the literature describing both patterns with particular attention to the relationship between autonomic response, subjective experience and neural activation patterns. Several comprehensive reviews of the PTSD neuroimaging literature (see, for example, Pitman et al., 2001; Hull, 2002; Bremner, 2002, 2003, 2004; Nutt and Malizia, 2004; Liberzon and Phan, 2003; Tannev, 2003) and the acute stress response in PTSD (e.g., Vermetten and Bremner, 2002a,b) have recently been published. Thus, this review will discuss only those studies in which the authors have reported extensively on measures of autonomic reactivity and/or subjects’ phenomenological states in addition to neural activation (summarized in Table 1). All of the studies that have addressed these issues have used, not surprisingly, symptom provocation or pharmacological challenge paradigms. Autonomic measures that have been studied include heart rate, blood pressure and skin conductance. Patients’ responses to trauma cues have been measured using PTSD symptom checklists, and analogue scales for particular emotions. Several studies have made use of the “Subjective Units of Distress Scale” (SUDS), a visual analogue scale for rating current subjective distress from 0 to 100 (e.g., Bremner et al., 1999a,b). In addition, state dissociation during exposure to the traumatic stimuli has been measured using the Clinician Administered Dissociative States Scale (CADDS) (Bremner et al., 1999a,b; Lanius et al., 2002; Lanius et al., 2005). Studies discussed in this review were obtained through a MEDLINE search and through searching the references of papers thus obtained. This review will also consider separately the literature on each of the regions of the brain consistently implicated in either of the two major response patterns (hyperarousal and dissociation) in an attempt to begin to elucidate the contributions of these areas to the pathology observed in PTSD.

2. Neuroimaging of flashback/reliving/hyperarousal response to traumatic symptom provocation

2.1. Pharmacological challenge with yohimbine

In a PET study, Bremner et al. (1997) administered yohimbine, an α2-antagonist which stimulates brain noradrenaline release, to 10 subjects with combat-related PTSD and 10 age-matched controls with no history of exposure to an extreme psychological stressor. Noradrenaline is thought to be implicated in the alterations in both arousal and memory seen in patients with PTSD (Southwick et al., 1999) and also induces panic in patients with panic disorder (Gurguis et al., 1997). In the PTSD group, six patients experienced a panic attack and three experienced a flashback (compared to zero controls experiencing either a panic attack or a flashback). Only one of the PTSD patients (and none of the controls) in this study had comorbid panic disorder. PTSD subjects, but not controls, also reported increases in anxiety and panic attack symptoms after exposure to yohimbine. Neither group reported these symptoms after exposure to placebo. Metabolic patterns in response to yohimbine administration were also different between groups, with PTSD patients exhibiting a decrease in metabolism as compared to placebo and controls exhibiting a corresponding increase. These differences were seen in prefrontal, temporal, parietal and orbitofrontal cortices.

2.2. Symptom provocation using trauma reminders (photographs, sounds or script-driven imagery)

Bremner et al. (1999a) conducted a PET study in 10 Vietnam veterans with combat-related PTSD and 10 control subjects with combat experience in Vietnam but no PTSD, investigating differences in response to combat-related pictures and sounds. Prior to scanning, the PTSD subjects were screened for emotional and psychophysiological reactivity to the paradigm and included only if they demonstrated a 5 b.p.m. increase in heart rate and a 50 point increase on the SUDS. During the scanning session, PTSD symptomatology and subjective distress were measured in response to the neutral and the traumatic stimuli. Subjects in the PTSD group reported significant increases in fear, anxiety and subjective distress during the traumatic stimuli, as compared to controls. PTSD subjects also had higher scores on the CADSS than controls, and there was a
<table>
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<th>Subjects: type of trauma [n]</th>
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<td><strong>Pharmacological challenge</strong></td>
<td>Bremner et al. (1997)</td>
<td>PET Yohimbine [placebo]</td>
<td>Combat veterans PTSD [10] Controls [10]</td>
<td>PTSD patients exhibited a pattern of decreased metabolism following yohimbine administration, while control subjects exhibited an increase: there were significant metabolic differences in prefrontal, temporal, parietal and orbitofrontal cortex</td>
<td>PTSD subjects, but not controls, reported a significant increase in anxiety with yohimbine (but not placebo) Six out of 10 PTSD patients had a panic attack and 3 out of 10 had a flashback with yohimbine (compared to zero controls)</td>
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<td><strong>Trauma-related pictures/sounds</strong></td>
<td>Bremner et al. (1999a)*</td>
<td>PET Combat-related pictures/sounds [neutral slides/sounds]</td>
<td>Combat veterans PTSD [10] Combat veterans controls [10]</td>
<td>PTSD subjects showed a decrease in blood flow in the medial prefrontal cortex (BA 25). Controls showed a greater increase in blood flow than PTSD subjects in the anterior cingulate (BA 24)</td>
<td>PTSD subjects showed increased PTSD, anxiety and dissociative symptoms as well as subjective fear and distress</td>
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<td>Pissiota et al. (2002)*</td>
<td>SPECT Combat-related sounds [neutral sounds]</td>
<td>Combat veterans PTSD [7] No control group</td>
<td>Increased rCBF in right amygdala, sensorimotor cortex (BA4/6), cerebellar vermis and periaqueductal grey. Decreased rCBF in right retrosplenial cortex (BA 26/29/20). All activations reported are for trauma (compared to neutral condition</td>
<td>Increased heart rate, but not skin conductance, during combat sounds (compared to neutral sounds)</td>
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<td>Rauch et al. (1996)</td>
<td>PET</td>
<td>Trauma script [neutral script, teeth clenching]</td>
<td>PTSD – variety of traumas [8] (No control group)</td>
<td>Increased blood flow in right hemispheric limbic and paralimbic regions, visual cortex. Decreased blood flow in left inferior frontal and middle temporal cortex. All results reported are for PTSD subjects; comparison is between control conditions and trauma script</td>
<td>Increased heart rate, skin conductance and facial electromyograms during trauma script in prescan screening session</td>
<td>Distress and intense reexperiencing phenomena</td>
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<td>Shin et al. (1999)</td>
<td>PET</td>
<td>Trauma script [neutral script, teeth clenching]</td>
<td>Childhood sexual abuse PTSD [8] Childhood sexual abuse controls [8]</td>
<td>PTSD subjects showed greater increases in the orbitofrontal cortex and anterior poles than controls. The control group showed greater activation in the insular cortex and anterior cingulate gyrus. PTSD subjects, but not controls, showed rCBF decreases in the left inferior frontal gyrus. Both groups showed decreases in bilateral anterior frontal regions, but these decreases were greater in PTSD subjects</td>
<td>PTSD patients had greater heart rate increases in response to the trauma script than did controls. There was no significant difference in blood pressure change between the two groups</td>
<td>The PTSD group showed greater increases in guilt and disgust in response to the trauma script compared to the control group</td>
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<td>Bremner et al. (1999b)</td>
<td>PET</td>
<td>Trauma script [neutral script]</td>
<td>Childhood sexual abuse PTSD [10] Childhood sexual abuse controls [12]</td>
<td>PTSD subjects had greater increases in blood flow in the superior and middle frontal gyri (BA6, 9), posterior cingulate (BA 31) and motor cortex; decreased blood flow was seen in the subcallosal gyrus (BA 25) and there was no activation of the anterior cingulate gyrus (BA 32). There was also decreased blood flow in the right hippocampus, fusiform/inferior temporal gyrus, supramarginal gyrus and visual association cortex in women with PTSD compared to those without PTSD</td>
<td>Subjects with PTSD had significantly higher PTSD symptoms, dissociative symptoms, anxiety and fear in response to the trauma script</td>
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<td>Study</td>
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<td>Osuch et al. (2001)</td>
<td>PET</td>
<td>Trauma script [rest]</td>
<td>Various [11]</td>
<td>rCBF positively correlated with flashback intensity in brainstem, lingual, bilateral insula, right putamen, left hippocampal and parahippocampal, somatosensory and cerebellar areas</td>
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<td>All PTSD patients experienced significant dissociative responses as measured by the CADDs and by subjective reports</td>
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<td>Lanius et al. (2003a)</td>
<td>fMRI</td>
<td>Trauma, sad and anxious, neutral scripts [baseline]</td>
<td>Sexual abuse/assault [7] and MVA [3] PTSD</td>
<td>PTSD subjects showed significantly less activation of the thalamus and anterior cingulate gyrus (BA 32) in all three emotional states, as compared to controls</td>
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<td>Control: sexual abuse/assault [6] and MVA [4]</td>
<td>In both PTSD and comparison groups, during recall of the neutral memory, activation occurred in the right anterior cingulate gyrus (BA 32), the middle and inferior frontal gyri (BA 10), the left parietal lobe (BA 40, 7) and the occipital lobe (BA 18)</td>
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<td>PTSD subjects showed higher scores than controls on emotion analog scales (anger, fear, disgust, sadness, guilt, shame) during trauma script Hyperarousal/reliving/flashback response by PTSD patients (not reported in original paper)</td>
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significant increase in CADSS scores in these subjects after exposure to the traumatic script. In response to the traumatic stimuli, PTSD patients showed a significant decrease in blood flow in the paracingulate cortex (BA 25) and the middle temporal gyrus. There was greater activation in controls, as compared to PTSD patients, in the right anterior cingulate gyrus (BA 24 and 32). Heart rate and systolic blood pressure were not significantly different between groups during either the neutral or the trauma scripts, but PTSD subjects had significantly higher diastolic blood pressure than controls overall.

Liberzon and colleagues (1999) measured regional cerebral blood flow (rCBF) in subjects with PTSD using single photon emission computerized tomography (SPECT) with $^{99m}$TcHMPAO. Three groups were studied: Vietnam veterans with PTSD ($n = 14$), veterans without PTSD ($n = 11$) and non-combat controls ($n = 14$). Subjects were exposed to white noise and to combat sounds on two separate days. All three groups showed increases in rCBF in the anterior cingulate and medial prefrontal cortex in response to the trauma condition, but not the white noise condition. However, only the PTSD group exhibited increased rCBF in the left amygdala. During the trauma stimuli, PTSD subjects exhibited a higher skin conductance response than controls. Zubieta et al. (1999), in a SPECT study involving veterans with PTSD and both veteran and non-combat exposed controls, reported that PTSD patients exhibit significant increases in rCBF in the medial prefrontal cortex during exposure to combat sounds, but not to a white noise condition.

During debriefing, one patient studied by this group reported having experienced a full-blown flashback in response to the trauma stimuli, and rated his subjective distress during this experience as maximal. Due to the differences in both subjective experience and blood flow patterns, data for this subject was presented separately (Liberzon et al., 1996/1997). During this experience, this subject showed greater uptake in subcortical regions, particularly the thalamus, as compared to cortical areas. Interestingly, two days later the subject recalled experiencing acute fear and anxiety but denied having had a flashback at the previous session.

Pissiota et al. (2002) also conducted a study with combat veterans suffering from PTSD ($n = 7$), using combat-related and neutral sounds. No control group was used in this study. Subjects had been previously screened for physiological and emotional responsiveness to the combat sounds. Six of the subjects had a full-blown panic attack, as measured by the Panic Anxiety Scale (30) during the trauma.
stimulus and two subjects experienced a panic attack during the neutral stimulus. Subjects exhibited an increase in rCBF in the right sensorimotor cortex (BA 4, 6), extending to the primary somatosensory cortex (BA 1, 2, 3), as well as in the cerebellar vermis and periaqueductal grey. Blood flow was decreased in the right retrosplenial cortex (BA 26/29/30 and parts of BA 23). In addition, there was an increase in rCBF in the right amygdala, which was correlated significantly with self-reported anxiety. Heart rate, subjective ratings of anxiety and distress, but not skin conductance were higher during exposure to combat-related sounds than to neutral sounds.

Several studies have used a script-driven imagery paradigm based on earlier psychophysiological studies (see Pitman et al., 1987). This paradigm involves having the patient construct an autobiographical narrative about the traumatic experience (the trauma script) and, usually, a second narrative about a neutral experience. These scripts are then read to the patient during the scan and the patient is instructed to use the scripts to help him/her recall a specific memory and remember as many sensory details of the experience as possible.

In a PET study, Rauch et al. (1996) investigated changes in rCBF during script-driven imagery in eight patients with PTSD who had been previously shown to be physiologically responsive to script-driven imagery. During the pre-scan screening, these patients had significant increases in heart rate during the traumatic scripts (19.7 ± 3.5 beats per minute). Skin conductance measures and frontalis electromyograms also showed a significant increase during the traumatic scripts. Physiological measures were not, however, made during the scanning session. Alterations in rCBF occurred during exposure to the traumatic script, specifically an increase in right-sided limbic, paralimbic and visual areas and a decrease in the left inferior frontal and middle temporal cortex. The latter rCBF changes were compared to rCBF in these patients during exposure to a neutral script. The subjects in this study described their subjective experiences during the trauma script as reflective of their PTSD symptomatic state and as including intense reexperiencing phenomena. No control group was included in this study.

Shin et al. (1999) studied 16 women with histories of childhood sexual abuse, eight with and eight without current PTSD. Subjects were also asked to rate the intensity of their emotional states while listening to both the neutral and traumatic scripts, using an analogue scale of 0–10. PTSD subjects gave higher average ratings for guilt and disgust during the trauma script than did control subjects. They also reported higher overall arousal, as measured on a similar analogue scale. Changes in rCBF were reported as a comparison between the trauma script and the two control conditions (neutral script and teeth clenching) combined. Control subjects, but not PTSD subjects, exhibited significant increases in rCBF in the anterior cingulate gyrus and insular cortex. PTSD subjects, but not controls, showed decreased rCBF in the left inferior frontal gyrus. PTSD subjects showed greater regional decreases in blood flow than controls in widespread regions of frontal, temporal, and parietal cortex, while the control groups showed greater relative increases in the anterior cingulate gyrus as compared to the PTSD group. Subjects’ heart rate and blood pressure were measured throughout the experiment and compared during the neutral and trauma scripts. A significant increase in heart rate was observed in PTSD subjects, as compared to controls, during the trauma script. There was, however, no corresponding increase in either systolic or diastolic blood pressure.

Bremner et al. (1999b) conducted a PET study using a script-driven imagery paradigm in 10 women with PTSD subsequent to childhood sexual abuse and 12 women with a history of childhood sexual abuse but no PTSD. No physiological measures were obtained. A number of behavioral measures were taken before and after exposure to the traumatic script and scores were compared between the PTSD and control groups and between the neutral and trauma scripts. Patients with PTSD reported significantly higher scores than controls on a number of scales used to assess reactivity to exposure to the traumatic script, including a PTSD symptom scale, the CADDs and some emotion analogue scales.

Differences in rCBF were also seen between groups in response to the trauma scripts, with PTSD patients showing higher levels of rCBF than controls in the posterior cingulate (BA 31) and anterolateral prefrontal cortex (BA 9 and 10). PTSD patients showed a decrease in rCBF, as compared to controls, in the medial prefrontal cortex (BA 25) and failure of activation in the anterior cingulate gyrus (BA 32), as well as relative decreases in rCBF in parts of the parietal cortex (BA 40), the right hippocampus, visual association cortex (BA 19), fusiform gyrus/inferior temporal gyrus (BA 20) and dorso-lateral prefrontal cortex (BA 6 and 8).

In our studies, the neuronal circuitry underlying flashback/reliving/hyperarousal and dissociative responses in PTSD was investigated using the script-driven symptom-provocation paradigm adapted to fMRI, in subjects with sexual abuse or motor vehicle accident-related PTSD and control subjects who had a history of sexual abuse or motor vehicle accidents but who never developed PTSD.

Fig. 1 demonstrates that compared with control subjects (n = 9), patients who had a hyperarousal response and relived their traumatic experience through flashbacks after being exposed to the traumatic script (n = 9) showed significantly less activation of the thalamus, anterior cingulate gyrus (BA 32), medial frontal gyrus (BA 10, 11), occipital lobe (BA 19) and inferior
frontal gyrus (BA 47) (Lanius et al., 2001). The altered anterior cingulate cortex, medial prefrontal cortex, and thalamic activation observed during the recall of traumatic material is consistent with previous PET studies of sexual abuse and combat-related PTSD (Liberzon et al., 1996/1997, 1999; Shin et al., 1997, 1999; Bremner et al., 1999a,b; Zubieta et al., 1999; Shin et al., 2004; Britton et al., 2005). Subjects' emotional responses to the traumatic script were measured using analog scales (scale from 0 to 7). PTSD subjects reported significantly higher levels, as compared to controls, of anger, fear, disgust, sadness, guilt and shame (Lanius et al., 2003a).

PTSD subjects also exhibited an average increase in heart rate of 12 b.p.m. These physiological findings are consistent with those of Rauch et al. (1996) and Shin et al. (1999) described above. Sack et al. (2004) have further investigated the importance of altered heart rate in PTSD and have demonstrated an association between low respiratory sinus arrhythmia (RSA) and sustained heart rate increases during recall of a traumatic memory in PTSD subjects. They further found that by contrast, subjects with a higher baseline RSA returned to their baseline heart rate more quickly. Further research is required to determine whether there is a causal relationship between RSA and PTSD symptomatology; however, the findings by Sack et al. provide further evidence for the variability of response to symptom provocation among PTSD patients.

Britton et al. (2005) compared blood flow patterns in a group of combat veterans with PTSD during script-driven imagery of neutral and emotionally evocative scenes with the blood flow patterns seen in combat-exposed veterans without PTSD and non-combat-exposed controls. The control group with no combat exposure was the only group to show significantly greater left amygdala activation in the traumatic/stressful, relative to the neutral, script; by contrast the combat-exposed control group showed deactivation in the left amygdala in response to the traumatic/stressful condition (as compared with the neutral script). Of the three groups, only the PTSD group showed increased activation of the dorsal anterior cingulate in during the traumatic/stressful script and this group also was the only one to show decreased activation in the rostral anterior cingulate. Subjects' emotional experience was assessed using rating scales for the following adjectives: disgusted, sad, afraid, angry, shocked, guilty, nervous, ashamed, and disturbed. Compared with the neutral conditions, the traumatic/stressful scripts elicited greater negative emotional responses in all groups and PTSD subjects reported greater negative emotional experience than did the combat controls. Similar results were found for a separate analysis of the specific emotion of fear. An analysis of skin conductance showed that, across all subjects, skin conductance activity correlated with the peak activity in the left insula.

In addition to the traditional “subtraction analyses” used in most neuroimaging studies, some investigators have conducted correlation analyses between either neural activation and subjective reports or neural activation in two or more different regions. Osuch et al. (2001) focus on the reexperiencing phenomena of PTSD and hypothesize that differences in attention to flashback phenomena may account for diversity of findings among the neuroimaging studies to date. This study tested subjective and autonomic responses to trauma scripts to determine rCBF patterns associated with flashbacks.
During the prescan screening session, nine subjects demonstrated emotional arousal when talking about their trauma, while two exhibited objective and subjective indicators of dissociation. Neither of these subjects experienced flashbacks during the scan and so they were not included in the rCBF analysis. Overall, there was a positive correlation between flashback intensity and activity in the left inferior frontal gyrus, left hippocampal and parahippocampal gyrus, left anterior insula and right insula, right putamen, left somatosensory cortices and left cerebellum, lingula and brainstem. Negative correlations were seen between flashback intensity and activity in the bilateral superior frontal gyrus, right fusiform gyrus and right medial temporal gyrus. These correlations were slightly stronger in subjects who had a subjective/autonomic mismatch (specifically, they reported distress in response to the script-driven imagery but did not display an increase in heart rate).

Shin et al. (2004) have also conducted an analysis of correlations between different brain regions in patients with PTSD subsequent to combat exposure \( (n = 17) \) in response to script-driven imagery. They found that a relative decrease in activation in the medial prefrontal gyrus during trauma scripts was inversely correlated with rCBF changes in the left amygdala and in the right amygdala/periamygdaloid cortex. Furthermore, symptom severity was positively correlated with rCBF in the right amygdala and negatively related to rCBF in the medial frontal gyrus. Psychophysiological measurements were also taken during this study, with PTSD subjects exhibiting greater increases in skin conductance response than controls regardless of script condition. Both the PTSD and the control subjects showed greater increases in skin conductance for the trauma than the neutral script and there was also a significant group \( \times \) condition interaction, with the PTSD group showing significantly greater skin conductance increases during the trauma script. Similarly, left lateral frontal electromyographic (EMG) responses were significantly greater in the PTSD group than in controls, in both groups for the trauma script compared to the neutral (main effect for script condition) and a group \( \times \) condition interaction was also seen. The PTSD group also reported significantly higher feelings of fear, arousal, disgust and guilt during the trauma script than did the control group.

Recent studies have also begun to examine the networks of brain regions that mediate PTSD symptoms. We conducted an analysis of connectivity patterns underlying the response to script-driven imagery seen in PTSD patients with flashback/relying/hyperarousal responses \( (n = 11) \) versus controls \( (n = 13) \) (Lanius et al., 2004). The majority of neuroimaging studies to date have used “subtraction analyses,” in which brain activation during a control task (in PTSD script-driven imagery studies, usually rest or a neutral memory) have been compared with, or subtracted from, activation during the task of interest (a traumatic memory). By contrast, functional connectivity analyses allow the assessment of inter-regional brain activity correlations during the recall of traumatic events. In the particular connectivity analysis that we conducted, a “seed voxel” is chosen that is activated in both the control and the PTSD group, and regions whose activity covaries with that of the seed voxel during the task of interest are assessed. Because these analyses are based on correlation of activity, rather than increases or decreases of activity relative to a baseline task, the results of subtraction analyses and functional connectivity analyses may be different. Thus, the two approaches complement each other in giving different insights into the alterations in neural functioning associated with PTSD.

In our study, functional connectivity analyses show markedly different patterns of brain activation during recall of a traumatic memory in PTSD subjects (in whom areas of functional connectivity with the right anterior cingulate gyrus included the occipital lobes, right parietal lobes and posterior cingulate gyrus) and in controls (in whom areas showing functional connectivity with the right anterior cingulate gyrus included the left prefrontal cortex and left anterior cingulate gyrus). These differences can be explained with reference to the phenomenological aspects of the memory in the two groups. The PTSD subjects experienced their memory primarily as images (usually visual), whereas ordinary memories tend to lose this imagistic quality over time and, as reflected in the experience of the control group in this study, to be recalled primarily in a narrative form (van der Kolk, 1996; Brewin et al., 1996).

A recent study by Gilboa et al. (2004) conducted both functional connectivity analyses and effective connectivity analyses of script-driven imagery in subjects with a history of road or work accidents. The statistical methodology of this study was different than that described above, as it used partial least squares to identify brain regions that covaried in activation with the reference voxel and thus identified latent variables (i.e., theoretical variables that were not explicitly measured) in the neuroimaging data. Using a seed voxel in the right prefrontal cortex, this group found significant two latent variables. Both of these included regions of positive salience in the visual cortex; that is, activation in these regions correlated positively with activation in the seed voxel. The second latent variable included areas negative salience in the bilateral anterior cingulate gyrus. In a second analysis using a seed voxel in the right amygdala, functional connectivity analyses showed negative salience between this area and bilateral cuneus (BA 17/18) and effective connectivity analyses suggested that the amygdala has direct influences on visual cortex, subcallosal gyrus and anterior cingulate in PTSD subjects but not in control subjects. The PTSD
subjects participating in this study also had significantly higher heart rates during both neutral and trauma scripts than did the healthy control group; there was also a group X script interaction (with the heart rate of the PTSD subjects being slightly higher during the trauma than during the neutral script and that of the control subjects being slightly lower during the trauma script than during the neutral script). Although this study does not report phenomenological responses to script-driven imagery, the physiological measures suggest that the PTSD subjects in this study likely had a flashback/reliving/hyperarousal response to the trauma script. Moreover, the relationship between activation in the visual cortices and each of the seed voxels used in this study (both of which were selected on the basis of their role in modulating the expression of emotional states in response to both current circumstances and past experiences), is similar to the relationship found by Lanius et al. (2004) using a seed voxel in the anterior cingulate gyrus.

Overall, the studies described above indicate that one pattern of physiological activity, associated with subjective arousal and reexperiencing, involves an increase in heart rate and skin conductance. However, the range of physiological responses to exposure to traumatic scripts may be more complex than these studies indicate, particularly since these studies often selected only subjects who had been previously shown to experience hyperarousal in response to trauma cues (Rauch et al., 1996; Bremner et al., 1999a,b; Pissiota et al., 2002). A more varied pattern of response was described by Osuch et al. (2001), who tested subjective and autonomic responses to trauma scripts to determine rCBF patterns associated with flashbacks. Seven of 11 subjects had an increase in heart rate in response to the traumatic scripts (average 20 b.p.m.), with the other four having no heart rate response. One subject had an increase in heart rate, despite reporting no subjective distress. Two subjects experienced subjective distress, but did not display an increase in heart rate.

Together, the results of these studies suggest that symptom scales and measures of autonomic reactivity may be important in distinguishing between the hyperarousal and the dissociative response to symptom provocation in PTSD patients. While there are cases of mismatch between autonomic activity and subjective reports, closer attention to the relationships between subjective, autonomic and neurophysiological responses may help to clarify the variety of responses that may be observed to trauma reminders in this group. Moreover, because this variability of response may not have been adequately appreciated in the past, it may be that the differences in reported group averages in neural activation patterns that occurred in different studies was due in part to heterogeneity of subjects, in terms of their subjective and autonomic responses to trauma reminders, both between and within studies.

It is also interesting to note that the subjects who showed flashback/reliving/hyperarousal responses exhibited significantly less activation of the thalamus and the anterior cingulate gyrus (BA 32) not only during traumatic memory recall, but across three different script-driven imagery-induced emotional states (sad, anxious, and traumatic) (Lanius et al., 2003a). These findings may suggest that anterior cingulate and thalamic dysfunction in the recollection of traumatic as well as other negative events may underlie the emotion dysregulation often observed clinically in PTSD. The function of these brain structures and their potential contribution to the flashback/reliving/hyperarousal response are discussed below.

2.3. Key brain areas involved in hyperarousal responses

2.3.1. Anterior cingulate cortex

The anterior cingulate gyrus is a complex structure with multiple functions (Vogt and Gabriel, 1993). Animal research has suggested that the anterior cingulate gyrus has extensive connections with multiple brain structures, including the amygdala, hypothalamus, nucleus accumbens, ventral tegmental area, substantia nigra, raphe, locus ceruleus, periaqueductal grey, and brain stem autonomic nuclei (Carmichael and Price, 1995; Frysztak and Neafsey, 1994; Sesack et al., 1989, 1992; Neafsey et al., 1993). Thus, the anterior cingulate gyrus is part of a system that orchestrates the autonomic, neuroendocrine, and behavioural expression of emotion and may play a key role in the visceral aspects of emotion (Vogt and Gabriel, 1993).

The anterior cingulate cortex has been shown to play a key role in the representation of subjective experience, in the integration of bodily responses with behavioural demands (Critchley et al., 2002), and emotion. Lane et al. (1998) have reported positive correlations between scores on the Levels of Emotional Awareness Scale and cerebral blood flow in BA 24 of the anterior cingulate gyrus during film- and recall-induced emotion. These results indicate that the anterior cingulate cortex may also play a role in the experiential aspects of emotion. On the basis of the key involvement of the anterior cingulate gyrus in the experiential and/or expressive aspects of emotion, it is possible that disruption in its functioning as observed in PTSD may provide a neural basis of emotion dysregulation, including extremes of re-experiencing and avoiding emotionally distressing memories, as well as generalized problems with physiologic hyperarousal and emotional numbing in this disorder. It should also be noted, however, that in addition to its role in the experience of and reflection on one’s emotions, the anterior cingulate gyrus also plays an important role in cognitive functions, including performance...
monitoring (van Veen and Carter, 2002) and working memory (Hartley and Speer, 2000). In light of work showing that PTSD patients have altered activation in the anterior cingulate cortex during a Stroop task that uses trauma cues, but not a traditional colour Stroop task (Bremner et al., 2004), it seems probable that the cognitive deficits observed in PTSD patients have a state dependent, emotional component.

The subgenual region of the anterior cingulate cortex, in particular, has been shown to be activated during induction of sad mood in healthy control subjects (Liotti et al., 2000), but to fail to activate in a similar task in subjects with current or remitted major depressive disorder (Liotti et al., 2002). Altered activation, as compared with that observed in control subjects, in this region in PTSD neuroimaging studies using traumatic symptom provocation may reflect the negative aspects of trauma reminders. It is of note, however, that comorbid depression is common in PTSD patients, thus making it difficult to interpret the finding of pathological activation of the subgenual anterior cingulate in PTSD neuroimaging studies.

2.3.2. Medial prefrontal cortex

Moscovitch and Winocur (2002) note that the medial prefrontal cortex is important in retrieval of episodic memories (Tulving et al., 1994) and may be involved in temporal segregation (Schnider et al., 2000), so that “currently relevant memories can be differentiated from memories that may have been relevant once but are no longer” (Moscovitch and Winocur, 2002). Although these authors do not discuss the timeless nature of traumatic memories experienced by patients with PTSD, their suggestion has clear relevance to the alterations in activity seen in PTSD patients during traumatic recollections.

It is also interesting to note that the medial prefrontal cortex is active during the explicitly self-referencing processing of stimuli (Taylor et al., 2002; Northoff and Bermpohl, 2004). Given that PTSD is said to involve a loss of one’s pretrauma self (van der Kolk et al., 1996b), differences in activation in this area between PTSD subjects and control subjects may also be a reflection of the self-relevant nature of the traumatic stimuli presented during symptom provocation paradigms, particularly script-driven imagery experiments.

Medial prefrontal cortex dysfunction has been described in many PTSD neuroimaging studies (Shin et al., 1997, 1999; Bremer et al., 1999a,b; Liberson et al., 1999; Zubieta et al., 1999; Lanius et al., 2001, 2002, 2003a; Shin et al., 2004) and has been hypothesized to be associated with attentional and frontal deficits sometimes associated with a quasi dementia-like syndrome in PTSD (Markowitsch et al., 2000). In addition, the medial prefrontal cortex has been shown to be able to suppress the hypothalamic-pituitary-adrenal axis in response to stress (Crane et al., 2003). Finally, it has been suggested that the medial prefrontal cortex is involved in the extinction of conditioned fear responses (Morgan et al., 1993); this function will be discussed below in the section on the amygdala. Several studies have also suggested that the medial prefrontal cortex has inhibitory influences on the emotional limbic system, including the amygdala. PET studies have shown negative correlations between blood flow in the left prefrontal cortex and the amygdala (Davidson and Sutton, 1995; Drevets et al., 1992).

2.3.3. Amygdala

The amygdala is reciprocally connected with many areas of the brain, including the hypothalamus, hippocampus, neocortex and the thalamus. The amygdala has been shown to play a crucial role in fear conditioning (Le Doux, 2002). Le Doux also describes the amygdalas’ relevance to contextual learning. Moreover, the basolateral amygdala has been shown to play a role in stress-mediated alterations of memory, including post-event memory consolidation (Cahill, 2000).

PTSD neuroimaging studies have led to contradictory findings with regards to amygdala activation. Some studies have reported increased amygdala activation (Rauch et al., 1996, 2000; Shin et al., 1997; Liberson et al., 1999; Pissiota et al., 2002; Shin et al., 2004; Gilboa et al., 2004; Britton et al., 2005) whereas other studies have not found altered amygdala activation (Shin et al., 1999; Bremner et al., 1999a,b; Lanius et al., 2001, 2002, 2003a). Protopopescu et al. (2005) suggest that the time course of amygdala activation in response to negative emotional stimuli may also differ between PTSD and controls subjects. We did not observe amygdala activation in either the chronic flashback/reliving/hyperarousal nor the dissociative subjects (Lanius et al., 2001, 2002). However, we have reported a case study that describes two subjects (husband and wife) who developed acute PTSD secondary to an identical stressor. Even though both subjects experienced the identical motor vehicle accident, their subjective, psychophysiological, and neurobiological responses to traumatic script-driven imagery differed significantly. The husband exhibited a flashback/reliving/hyperarousal response with concomitant amygdala activation, and the wife showed a numbing response with no concomitant amygdala activation (Lanius et al., 2003b). These findings are consistent with Foa et al.’s (1995) notion of different patterns of post-trauma response, one characterized by numbing and the other being essentially phobic.

Differences in amygdala activation are also seen in emotional responses in non-PTSD samples. Williams et al. (2001) examined the amygdala response to fearful faces in healthy adults and demonstrated two distinct response systems, depending on arousal levels. When
exposure to these faces was accompanied by arousal, as measured by a change in skin conductance, the pattern of neural activation involved activation in the amygdala and medial prefrontal cortex. In contrast, if no skin conductance response occurred, activity was seen in the hippocampus and lateral prefrontal cortex. These authors hypothesize that their data reflect a dissociation in these networks in the “visceral experience” versus the “declarative fact” processing of fearful stimuli. Given these findings, future studies in PTSD patients may find more consistency in amygdala response by measuring arousal levels.

The alterations in activation that have been observed in both the medial prefrontal cortex and the amygdala in PTSD may reflect a functional relationship between these two structures, in which the medial prefrontal cortex exerts a modulatory or inhibitory activity on the amygdala (Milad and Quirk, 2002). Rauch et al. (2000) have, however, also shown that PTSD patients exhibit greater amygdala response than controls to masked faces with a fearful expression (as compared with masked happy faces), suggesting that amygdala hyperreactivity occurs in a “bottom up” fashion in addition to any alterations in activation that result from the loss of regulation of the amygdala by the frontal cortex.

2.3.4. Thalamus

The thalamus is “the principal synaptic relay for information reaching the cortex” (Kandel and Schwartz, 1991). All sensory information, except for olfaction, is routed through the thalamus to the cerebral cortex, and thus the thalamus is often referred to as the sensory gateway to cortex. The thalamus has also been suggested to be involved in mediating the interaction between attention and arousal (Portas et al., 1998), both of which are clearly relevant to the phenomenology of traumatic stress syndromes. In particular, the dorsomedial nucleus of the thalamus has been shown to be implicated in limbic cortical–subcortical circuitry (Alexander et al., 1990); however, many neuroimaging studies are unable to distinguish between thalamic nuclei.

Thalamic dysfunction in PTSD has previously been shown by both Brenner et al. (1999a) and Liberzon et al. (1996/1997), as well as by our own laboratory (Lanius et al., 2001, 2003a), but has not been noted by other authors. The relative paucity of thalamic findings in neuroimaging studies may be attributable to a number of reasons, including inherent differences in targeted response variables (e.g., metabolism, blood oxygenation) and their relative time courses. Moreover, variability among experiments may be caused by differences in scanner resolution that affects spatial and temporal resolution (see, e.g., Krasnow et al., 2003). Differences between study samples, including chronicity of illness, comorbidity, or type of trauma, may play a role in different thalamic activation patterns. On the basis of a comparative review of neuroimaging studies of emotional recall and of hypnotic response that showed that similar brain regions (e.g., thalamus, amygdala, hippocampus, medial prefrontal cortex, anterior cingulate gyrus) are activated during both types of task, Vermetten and Bremner (2004) suggest that attention should be paid to differences in hypnotisability of subjects. In addition, the use of trauma-exposed controls, which is common in symptom provocation studies, may obscure differences between adaptive and pathological responses to trauma reminders (Britton et al., 2005), though it should also be noted that PTSD subjects also exhibit pathological responses to negative emotional memories that are not specifically trauma-related (Lanius et al., 2003a,b).

The thalamus may also be an important factor in the etiology of PTSD. High levels of arousal during traumatic experiences have been hypothesized to lead to altered thalamic sensory processing (Krystal et al., 1995), which in turn results in a disruption of transmission of sensory information to the frontal cortex, cingulate gyrus, amygdala, and hippocampus. Krystal et al. (1998) have hypothesized that this mechanism underlies dissociative symptoms and may be one of the mechanisms underlying flashbacks in PTSD.

van der Kolk (1996) has suggested that the experience of day-to-day, nontraumatic events are integrated into consciousness without the sensory aspects of the event being registered separately. Flashbacks on the other hand lack such integration of experience. Indeed, they have been described as timeless, predominantly nonverbal, imagery-based memories (van der Kolk and Fisler, 1995; Brewin et al., 1996). These descriptions are consistent with functional connectivity findings described above in our flashback/reliving/hyperarousal PTSD group (Lanius et al., 2004), whose activation patterns in response to their traumatic script showed neuronal networks consistent with a nonverbal pattern of memory retrieval. Thus, our findings lend support to the notion that the failure to integrate traumatic memories into the present context accounts for their ongoing disturbing nature.

The inability to integrate memories into the present context may be related to disruptions in thalamic-mediated temporal cognitive binding. “a temporally coherent event that binds, in the time domain, the fractured components of external and internal reality into a single construct...the “self”” (Llinas, 2002; see also Joliot et al., 1994). Such a lack of temporal cognitive binding and the resulting lack of corticothalamic dialogue may underlie flashback experiences or primary dissociation (Van der Hart et al., 1996; van der Kolk et al., 1996a), a phenomenon that has been described as an inability to integrate the totality of what is happening into personal memory and identity; thus these memories remain isolated from ordinary consciousness. Such a conceptu-
alization raises the question whether dynamic state changes in the corticothalamic system may account for the fragmented nature of memory observed in PTSD and whether PTSD is a neuropsychiatric disorder that can be characterized by thalamocortical dysrhythmia (Llinas et al., 1998).

Overall, then, the current literature on PTSD indicates that the hyperarousal response we have discussed above is characterized by specific neural, autonomic and subjective responses to reminders of a traumatic event. In particular, some subjects report that during exposure to trauma reminders, they have sensory and/or emotional experiences that reflect their initial experience of the trauma. The intensity of these experiences may vary, with some subjects experiencing distress and emotional arousal, some experiencing particularly vivid memories involving visual, auditory, tactile or olfactory experiences from the trauma. In extreme cases, subjects may experience a full-blown flashback in which the trauma is relived in its entirety. This pattern of phenomenological response appears to occur together with autonomic changes indicative of arousal, such as increased heart rate or skin conductance and also tends to involve certain regions of the brain, including the anterior cingulate cortex, medial prefrontal cortex, thalamus and amygdala. It is important to note, however, that some subjects who experience this pattern of response, which we have termed the “flashback/reliving/hyperarousal” response, may show what Osuch et al. (2001) have termed a subjective/autonomic mismatch, in which, for example their phenomenological experience involves reliving or hyperarousal but they do not have an autonomic response that reflects their hyperarousal, or vice versa. Further work is required to tease apart aspects of this pattern of response and to determine how the autonomic and phenomenological responses are related to patterns of brain activation. The increasing use of techniques in the analysis of neuroimaging data such as correlation of brain activation with subjective reports of the intensity of an experience (e.g., Osuch et al., 2001) or autonomic reactivity (e.g., Williams et al., 2001), may help to distinguish the neural correlates of different aspects of PTSD patients’ responses to trauma reminders.

Furthermore, the flashback/reliving/hyperarousal pattern of response, while the most commonly studied, is not the only one seen in PTSD patients. We have found that approximately 30% of patients experience a dissociative response to the script-driven imagery paradigm. The next sections of the paper will review the neuroimaging literature on dissociation, including two studies of dissociation in PTSD, the physiological changes associated with this type of response and the possible role of several key brain areas involved in this dissociative response.

3. Neuroimaging of dissociative responses in PTSD

The bulk of the PTSD neuroimaging literature to date has focussed on what we have termed the flashback/reliving/hyperarousal response. Some imaging studies of dissociative phenomena have been conducted in pharmacologically induced depersonalisation (Mathew et al., 1999), depersonalisation disorder (Hollander et al., 1992; Simeon et al., 2000; Phillips et al., 2001), and dissociative identity disorder (DID) (Saxe et al., 1992; Sar et al., 2000; Reinders et al., 2003). These have identified several brain regions that our own studies have also shown may be implicated in the dissociative response to symptom provocation in PTSD.

In our study of PTSD subjects who experienced dissociative responses to the traumatic script-driven imagery (Lanius et al., 2002), participants reported that “I was looking down at myself from above,” “I was detached from my body,” “I was completely zoned out and floating,” or “I was emotionless” during the script-driven imagery procedure. All PTSD patients included in this study had chronic histories of emotional, physical, and sexual abuse beginning in childhood and often continuing to the present. They reported that dissociation had been a defense they had used throughout their lives to escape overwhelming experiences.

Fig. 2 shows that PTSD patients who reported dissociative responses to the traumatic script-driven imagery (n = 10) showed very different patterns of brain activation than those seen in control subjects (n = 10). Moreover, the alterations in neural activation observed in subjects who dissociated in response to an autobiographical trauma script were different than those observed in subjects who exhibited flashback/reliving/hyperarousal responses (see Fig. 1). The dissociated PTSD patients 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 BA 32) as compared to control subjects. 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 findings of increased global cerebral blood flow in the frontal lobes and anterior cingulate gyrus following THC-induced depersonalization (Mathew et al., 1999) and increased activation of the frontal cortex in depersonalization disorder (Hollander et al., 1992; Phillips et al., 2001). Phillips et al. (2001) also report decreased activation in emotion-responsive brain regions, such as the insula, in response to aversive emotional stimuli in patients with.
depersonalization disorder. Moreover, increased brain glucose metabolism in parietal Brodmann areas 7B and occipital area (BA 19) was found during states of depersonalization in DSM-IV depersonalization disorder (Simeon et al., 2000). In two of the DID studies, however, increased activation was localized to the left temporal lobes (Saxe et al., 1992; Sar et al., 2000). By contrast, Reinders et al. (2003) found that activation in the medial prefrontal cortex and in the posterior association cortices differed in two different “senses of self” experienced during a scanning session.

Direct comparison of a sample of PTSD subjects who experienced a flashback/reliving/hyperarousal response with a sample of dissociative PTSD subjects (Fig. 3) shows that dissociative PTSD subjects show greater activation in the thalamus, the right superior parietal lobule (BA 7) and cingulate gyrus (BA 24), the left angular gyrus (BA 39) and bilateral medial prefrontal cortex (BA 10). By contrast, the flashback/reliving/hyperarousal PTSD group showed greater activation than the dissociative group in the left inferior parietal lobule (BA 40), left precentral gyrus (BA 6) and bilateral prefrontal cortex (BA 9, 10, 11) (Fig. 4).

We have also conducted functional connectivity analyses (see description above) comparing dissociative PTSD patients to healthy control subjects and to PTSD subjects who experienced a flashback/reliving/hyperarousal response to script-driven imagery. Connectivity shows that dissociative PTSD subjects show greater activation in the thalamus, the right superior parietal lobule (BA 7) and cingulate gyrus (BA 24), the left angular gyrus (BA 39) and bilateral medial prefrontal cortex (BA 10). By contrast, the flashback/reliving/hyperarousal PTSD group showed greater activation than the dissociative group in the left inferior parietal lobule (BA 40), left precentral gyrus (BA 6) and bilateral prefrontal cortex (BA 9, 10, 11) (Fig. 4).
maps for the dissociative PTSD subjects and the control subjects using a seed voxel in the left ventrolateral thalamus (VLT) were distinct. The control subjects had higher covariances between activations in VLT and in the left superior frontal gyrus (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). Usrey and Reid (1999) have suggested that stimuli generated naturally in the external world lead, in the alert, waking state, to synchronous discharge of neurons in the thalamus and in the cortex that occur in the 40 Hz range and that serve to temporally bind information from different modalities, leading to a coherent phenomenal experience of the world. It may be, then, that the alterations in functional connectivity of the thalamus underlie the dissociative experiences of the PTSD subjects observed in this study. Furthermore, Johnson and Ojemann (2000) reported that stimulation of the dominant ventrolateral thalamus results in a disruption of language abilities. Traumatic memories in PTSD patients experienced in a sensory, non-verbal manner, whereas control subjects report experiencing their memories of a traumatic event primarily in a verbal or narrative form. Thus, the alterations in thalamic activation and connectivity observed in PTSD patients may be a reflection of the altered phenomenology of traumatic memories in PTSD patients.

For the comparisons between the dissociative PTSD group and the flashback/reliving/hyperaroused PTSD group, a seed voxel in the right cingulate gyrus was used. Dissociated PTSD subjects had higher covariances between activations in this region and the left inferior frontal gyrus (BA 47) than did the other PTSD group. These results are similar to those reported in Lanius et al. (2004) for a comparison of the flashback/reliving/hyperaroused PTSD group with a group of healthy controls, which are described above.

The dissociative group of PTSD subjects described above showed no average increase in heart rate as compared to the control group. Recent data from our laboratory, however, suggests that dissociative subjects can have a variety of heart rate responses, including a decrease, no change or an increase in heart rate. Some subjects are showing a mixed hyperarousal/dissociative response during which there appears to be a continued re-experiencing in the disembodied mental state that is associated with an increase in heart rate. Subjects who showed such a mixed response reported “I was looking down on my own body while being back at the scene of the trauma”. In other subjects as described above, however, the disembodied mental state becomes predominant with a lack of reexperiencing and is associated with no increase in heart rate. This phenomena may be evidence for the suggestion that some individuals can experience both depersonalization and arousal responses [Reinders et al., unpublished results, quoted in Nijenhuis et al. (2002)]. Future studies will have to address these complexities further.

The lack of mean heart rate increase in the dissociative PTSD group (Lanius et al., 2002) is consistent with a recent case series studying psychophysiological reactivity in subjects with PTSD as a result of childhood abuse, in which one subject dissociated and demonstrated a significant decline in heart rate and diastolic blood pressure (Schmahl et al., 2002). Griffin et al. (1997) also 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 lack of autonomic response often observed in the PTSD patients during dissociative states is also consistent with previous findings in depersonalization responses (Lader, 1975; Lader and Wing, 1966; Kelly and Walter, 1968). Lader (1975) reported that depersonalization responses were associated with non-fluctuating skin conductance response. Moreover, Lader and Wing (1966) observed a decrease in heart rate when patients became depersonalized.

Sierra et al. (2002) recently examined autonomic responses to emotional stimuli in depersonalization disorder. Results showed that skin conductance response to unpleasant pictures was significantly reduced in patients with depersonalization disorder and that the latency of response was significantly prolonged. In contrast, latency to non-specific stimuli, such as a clap or a sigh, was significantly shorter in the depersonalization group as compared to controls. The authors suggest that a heightened state of alertness may contribute to the earlier response to startling noise and that reduced response to unpleasant stimuli may be caused by a selective inhibitory mechanism on emotional processing in depersonalization disorder. Although the subjects in this study are not described as having a history of trauma, the phenomenology and physiology of depersonalization seen in this group of patients is similar to those with symptoms of dissociation due to traumatic experiences.

The two responses to traumatic memories that have been described in this review as they are manifested in adults may also reflect response to trauma early in life. It has been proposed that an infant’s psychobiological response to trauma is composed of two sequential response patterns, hyperarousal and dissociation (Schore, 2001c). Dissociation is a process during which the overwhelmed child disengages from external stimuli in the environment and escapes by altering his or her internal organization (Schore, 2003). Such a disengagement is thought to be mediated by a parasympathetic dominant state. This primitive defensive state is a primary hypometabolic regulatory process, used throughout the life span, in which the stressed individual passively disengages in order “to conserve energies...to foster survival by the risky posture of feigning death, to allow healing of wounds and restitution of depleted resources by immobility” (Powles, 1992).

It is this parasympathetic mechanism that mediates the “profound detachment” (Barach, 1991) of dissociation. Activity of the dorsal vagal complex in the medulla in the dissociative state are hypothesized to increase dramatically, thus leading to decreases in blood pressure, metabolic activity, and heart rate, despite increases in circulating adrenaline (Schore, 2001b).

3.1. Key brain areas involved in dissociative processes in PTSD

3.1.1. Parietal and occipital cortex

The parietal and occipital cortices play an important role in a hierarchy of sensory processing that begins with primary sensory areas and continues in unimodal and polymodal association areas as well as the prefrontal cortex (Fuster, 2003). The higher order sensory areas are involved in the integration of information coming from the primary sensory cortex and coordinate aspects of multimodal somatosensory–visual–auditory integration. Alterations in the occipital area BA 19 and the parietal area BA 7 may affect the process of integration in higher-order cortices. It is well known that dissociation involves dysregulation of the visual and somatosensory modalities (Bremer et al., 1998; Bernstein and Putnam, 1986). Reinders et al. (2003) also report alterations in activation in posterior association cortex in DID patients across different “self” states. Alterations in these brain areas, as described during dissociative responses in PTSD (Lanius et al., 2002) as well as in the work of Simeon and colleagues (2000), may therefore reflect the visual and somatosensory disturbances described by the patients. It is not clear on the basis of the evidence currently available, however, whether dissociation is the result of abnormal activation in the parietal and occipital cortices or whether both dissociation and activation in these cortical regions are the result of a common cause, such as abnormalities in activation in other regions of the brain (particularly the temporal cortex and the limbic system).

3.1.2. Temporal cortex

Much of the literature on dissociation has examined dissociative phenomena in patients with temporal lobe epilepsy. Dissociative symptoms have been reported during seizures of various foci, in either the right or the left hemisphere (Devinsky et al., 1989; Kenna and Sedman, 1965). In a series of 32 cases of temporal lobe epilepsy, eleven cases exhibited symptoms of depersonalization, four with a left-sided focus, three with a right-sided focus, and four with general dysrhythmia (Kenna and Sedman, 1965). In another series of 71 epileptic patients in whom dissociative symptoms were quantified, depersonalization was most commonly induced by partial complex seizures, more so with left-sided foci. Dissociative Experience Scale scores in this patient population were lower than those seen in patients with psychiatric dissociative disorders (Devinsky et al., 1989).

In addition to the evidence from the epilepsy literature for the role of the temporal lobe in dissociation, Penfield and Rasmussen (1957) have reported depersonalization-like symptoms in response to stimulation of the superior and middle temporal gyrus during neurosurgery. Patients reported “queer sensations of not
being present and floating away” and “far off and out of this world” in response to stimulation of the superior and middle temporal gyri, respectively. Penfield and Rasmussen postulated that depersonalization states involve an “alteration in the usual mechanism of comparison of immediate sensory perception with memory records” (Penfield and Rasmussen, 1957; cited in Simmons et al., 2000).

There is also some evidence that links the dissociative phenomena observed in epileptic patients with the type of psychological trauma commonly observed in PTSD patients. Teicher and colleagues (1993) used the Limbic System Checklist-33 (LSCL-33), which includes symptoms often experienced by people suffering from temporal lobe epilepsy, to explore the relation between early abuse and limbic system dysfunction. Results showed that LSCL-33 scores correlated well with the dissociative experience scale scores (Teicher et al., 1993, 1997). This suggests that there may be a link between the activity of temporal cortex and of the limbic system, underlying dissociation in epilepsy, PTSD and depersonalization disorder. Further, the functional connectivity analysis conducted by Lanius et al. (2005) shows that activation in the right superior temporal gyrus and the right insula correlated with the activity of the seed voxel in the left ventrolateral thalamus, suggesting that temporal/limbic structures may contribute to patients’ dissociative responses.

3.1.3. Corticolimbic model of dissociation

Sierra and Berrios (1998) have proposed a corticolimbic model of depersonalization. They postulated that depersonalization involves corticolimbic disconnection. In this model, left medial prefrontal activation with reciprocal amygdala inhibition results in hypoemotionality and decreased arousal, whereas right dorsolateral prefrontal cortex activation with reciprocal anterior cingulate inhibition leads to hypervigilance, attentional difficulties and emptiness of mental contents. In this model, once a threshold of anxiety is reached, the medial prefrontal cortex inhibits emotional processing on limbic structures such as the amygdala, which in turn leads to a dampening of sympathetic output and reduced emotional experiencing. In support of this hypothesis, Sierra and Berrios note that the medial prefrontal cortex has been shown to be involved in both the monitoring and the modulation of emotions (Damasio, 1994; Reiman et al., 1997). Moreover, several studies have shown 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). In PTSD patients, Shin et al. (2004) have also found a reciprocal relationship activity in the medial prefrontal cortex and amygdala function.

In summary, our findings in the subtraction analysis of script-driven imagery in PTSD patients show some similarities with the above model. The dissociative PTSD patients had increased activation in the dorsolateral prefrontal cortex (Fig. 2, BA 9) and the medial frontal cortex (Fig. 2, BA 10). They also did not exhibit increased amygdala activation. The functional connectivity analysis, by contrast, shows that there is covariation in activity between the right superior temporal cortex (BA 34, 38) and the right insula. Thus, it appears that the results of our neuroimaging studies in dissociative PTSD patients support some aspects of both the corticolimbic model and the hypothesis that dissociation is mediated by activity in the temporal lobes.

4. Conclusions

In summary, our results suggest that PTSD patients can differ strikingly in their responses to traumatic script-driven imagery. These varied responses may shed light on key biological dimensions of the disorder. Our results are consistent with Bremner’s previous hypothesis describing two subtypes of acute trauma response, one primarily dissociative and the other characterized predominantly by intrusions and hyperarousal, each representing unique pathways to chronic stress-related psychopathology. Moreover, the results support Foa and colleagues’ (1995) notion that different PTSD symptoms such as intense hyperarousal or numbing may represent distinct pathological processes and that grouping PTSD subjects with different symptom patterns in the same diagnostic category may interfere with our understanding of post-trauma psychopathology. The fMRI findings reported here add to the emerging evidence of experiential, psychophysiological and neurobiological differences between patients who have flashback/reliving/hyperarousal responses versus dissociative responses to traumatic reminders. Our findings also suggest that different neuronal mechanisms may generate these two distinct reactions and that the heterogeneity of somatic and biological responses to traumatic reminders in PTSD need to be addressed in the designs of functional imaging studies.

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