

Hippocampal Function in Posttraumatic Stress Disorder

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ABSTRACT: Recent studies have reported memory deficits and reduced hippocampal volumes in posttraumatic stress disorder (PTSD). The goal of the current research was to use functional neuroimaging and a validated explicit memory paradigm to examine hippocampal function in PTSD. We used positron emission tomography (PET) and a word-stem completion task to study regional cerebral blood flow (rCBF) in the hippocampus in 16 firefighters: 8 with PTSD (PTSD group) and 8 without PTSD (Control group). During PET scanning, participants viewed three-letter word stems on a computer screen and completed each stem with a word they had previously encoded either deeply (High Recall condition) or shallowly (Low Recall condition). Relative to the Control group, the PTSD group exhibited significantly smaller rCBF increases in the left hippocampus in the High vs Low Recall comparison. However, this finding reflected relatively elevated rCBF in the Low Recall condition in the PTSD group. Collapsing across High and Low Recall conditions, (1) the PTSD group had higher rCBF in bilateral hippocampus and left amygdala than the Control group, and (2) within the PTSD group, symptom severity was positively associated with rCBF in hippocampus and parahippocampal gyrus. The groups did not significantly differ with regard to accuracy scores on the word-stem completion task. The PTSD group had significantly smaller right (and a trend for smaller left) hippocampal volumes than the Control group. The results suggest an abnormal rCBF response in the hippocampus during explicit recollection of nonemotional material in firefighters with PTSD, and that this abnormal response appears to be driven by relatively elevated hippocampal rCBF in the comparison condition. Published 2004 Wiley-Liss, Inc.[†]

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INTRODUCTION

Posttraumatic stress disorder (PTSD) is a potentially debilitating psychiatric condition that can occur after experiencing, witnessing, or being confronted with events involving actual or threatened death or serious injury (American psychiatric Association [APA], 1994). PTSD is characterized by reexperiencing symptoms such as intrusive recollections of trauma, avoidance of trauma-related stimuli and/or emotional numbing, and heightened arousal. Despite accelerated neuroscience investigation over the past decade, the pathophysiology of PTSD remains incompletely understood.

Given that PTSD is marked by several symptoms involving the construct of memory, researchers recently have begun to systematically examine memory function in individuals with this condition. The literature currently contains several reports of impaired performance on neuropsychological tests of verbal and visual memory in PTSD (Gil et al., 1990; Sutker et al., 1991, 1995; Bremner et al., 1993, 1995; Gurvits et al., 1993; Uddo et al., 1993; Yehuda et al., 1995; Barrett et al., 1996; Jenkins et al., 1998; Vasterling et al., 1998; Moradi et al., 1999; Bustamante et al., 2001; Gilbertson et al., 2001; but see also Stein et al., 1999). For example, Bremner et al. (1993) reported that Vietnam veterans with PTSD exhibited poorer performance on the Logical Memory subtest of the Wechsler Memory Scale and on verbal and visual versions of the Selective Reminding Test than did non-veterans without PTSD. Jenkins et al. (1998) found that rape victims with PTSD performed more poorly than both rape victims without PTSD and nontraumatized control participants on a delayed free recall measure of the California Verbal Learning Test; performance in the PTSD group improved with cueing and recognition testing. Although consistently reported, memory deficits in PTSD may be fairly circumscribed, occurring on some neuropsychological measures and not others (e.g., Stein et al., 1999; Yehuda et al., 1995).

Researchers studying the neurobiology of PTSD have begun to examine the integrity of brain regions that are critical to memory processes. Several magnetic resonance imaging (MRI) studies have reported decreased hippocampal volumes in individuals with PTSD (Bremner

et al., 1995, 1997b; Gurvits et al., 1996; Stein et al., 1997; Gilbertson et al., 2002; Villarreal et al., 2002a). Two magnetic resonance spectroscopy (MRS) studies have reported decreased neuronal integrity in hippocampus, as measured by decreased N-acetyl aspartate (NAA) levels (Schuff et al., 2001; Villarreal et al., 2002b). Volumetric reductions of hippocampus have ranged from 5% to 26% and have been found bilaterally across studies. However, a few studies have not replicated the finding of decreased hippocampal volumes in PTSD (DeBellis et al., 1999, 2001; Bonne et al., 2001; Carrion et al., 2001). These mixed results have suggested that hippocampal volumetric changes may be restricted to only some subgroups (e.g., adults with chronic PTSD), or that they may be secondary to comorbid conditions, or that hippocampal pathology may be relatively subtle and not always detectable by standard morphometric MRI procedures. The latter possibility is consistent with the finding of decreased hippocampal NAA levels in the absence of volumetric changes in a sample of veterans with PTSD (Schuff et al., 2001).

Although several studies have examined possible structural pathology of the hippocampus in PTSD, little is known about hippocampal function in this disorder. Semple et al. (1993) reported a trend for decreased left/right ratios of hippocampal blood flow during a word-generation task in veterans with PTSD and substance abuse histories. In a symptom provocation study, Bremner et al. (1999) found that patients with PTSD exhibited greater blood flow decreases in the right hippocampus than did control participants. The same research group reported decreased glucose metabolism in the hippocampus following administration of yohimbine vs placebo in PTSD (Bremner et al., 1997a). Osuch et al. (2001) reported a positive correlation between flashback intensity and rCBF in a left perihippocampal region in patients with chronic PTSD. Needed in the literature are studies in which validated memory tasks are implemented in the context of functional neuroimaging specifically to examine the functional integrity of the hippocampus in this disorder.

The main goal of the current study was to use positron emission tomography (PET) and a well-validated explicit memory paradigm (Schacter et al., 1996a,b; Heckers et al., 1998, 2002) to measure regional cerebral blood flow (rCBF) within the hippocampus in firefighters with and without PTSD. Firefighters report experiencing a variety of horrific events in which they risk their own lives, as well as witness the injury, mutilation and death of others (Bryant and Harvey, 1996; Beaton et al., 1998). Although a relatively large percentage of firefighters meet diagnostic criteria for PTSD (18–32%; McFarlane, 1986; Wagner et al., 1998; al Naser and Everly, 1999), surprisingly little research has been conducted on this group of individuals. Furthermore, none of the existing studies of firefighters has examined the neurobiology of those with PTSD.

In the current investigation, participants viewed a series of three-letter word stems (e.g., DRA_) on a computer screen and completed each stem with a word that they had previously encoded either deeply (High Recall condition) or shallowly (Low Recall condition). Previous research on healthy individuals has demonstrated that both recall accuracy and rCBF in the hippocampus are greater in the High Recall than in the Low Recall condition (Schacter et al., 1996). We hypothesized that, relative to firefight-

ers without PTSD, firefighters with PTSD would exhibit smaller rCBF increases in hippocampus in the High vs Low Recall comparison. Given that our word stem completion task differs from neuropsychological tasks that have revealed memory impairment in PTSD (i.e., our task involved cued recall, which improves accuracy in PTSD patients; see Jenkins et al., 1998) and given that not all memory tests reveal impairment in this disorder, we had no a priori prediction regarding group differences in recall accuracy.

MATERIALS AND METHODS

Participants

Participants were 16 right-handed (Oldfield, 1971) firefighters without a history of head injury, neurological disorders, or other major medical conditions. Eight of the participants (7 M, 1 F) met DSM IV diagnostic criteria for current PTSD (PTSD group) and 8 participants (8 M, 0 F) never had PTSD (Control group) according to the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995). Participants were recruited via advertisement from the greater Boston area and southern New Hampshire. No participant had taken psychotropic or cardiovascular medication within 4–6 weeks prior to participation. All participants were exposed to several types of specific firefighting-related traumatic events (e.g., witnessing the death or serious injury of others, handling burned bodies); in the PTSD group, symptoms were directly related to those events. Only one participant with PTSD was still working as a firefighter at the time of participation.

The groups did not significantly differ in age (mean \pm SD; 50.5 years \pm 10.3 [PTSD] and 43.5 years \pm 8.8 [Control]; $t[14] = 1.5$, $P = 0.17$) or in number of years of education (13.7 years \pm 1.4 [PTSD] and 14.8 years \pm 1.8 [Control]; $t[14] = 1.3$, $P = 0.21$). Consistent with the PTSD diagnosis, the PTSD group had a higher mean PTSD severity (CAPS) score than the Control group (52.6 \pm 22.7 [PTSD] and 2.1 \pm 4.0 [Control]; $t[14] = 6.2$, $P < 0.001$) and a trend for a higher mean score on the Beck Depression Inventory (Beck and Steer, 1987; 11.9 \pm 13.0 [PTSD] and 2.4 \pm 2.6 [Control]; $t[14] = 2.0$, $P = 0.07$). The groups did not significantly differ with respect to scores on the Beck Anxiety Inventory (Beck and Steer, 1990; 8.6 \pm 10.8 [PTSD] and 3.0 \pm 4.0 [Control]; $t[14] = 1.4$, $P = 0.19$), or age at time of trauma onset (27.6 \pm 7.0 [PTSD] and 28.6 \pm 9.9 [Control]; $t[12] = 0.3$, $P = 0.83$ [data missing for 1 subject per group]).

The presence of other psychiatric disorders was assessed with the Structured Clinical Interview for DSM-IV (First et al., 1995). Participants in the PTSD group met criteria for the following current comorbid diagnoses: major depression ($n = 2$), panic disorder ($n = 1$) and specific phobia ($n = 1$). Participants in the Control group did not meet criteria for any current psychiatric disorders.

This study was approved by the Institutional Review Boards of the Massachusetts General Hospital, Boston, MA and the Veterans Affairs Medical Center, Manchester, New Hampshire. Written informed consent was obtained from each participant.

Explicit Memory Task

The design and procedures of the explicit memory task were identical to those previously reported (Heckers et al., 1998). PET data were acquired during three conditions: High Recall, Low Recall, and Baseline (described below). Each participant was scanned twice per condition, yielding a total of six scans per participant.

Participants completed two separate unscanned study sessions, each of which was followed by two scanned recall sessions. In a study session, participants viewed 40 different neutral words presented sequentially on a computer screen. Half of the words were presented once and half were presented four times each. For the words that were presented once, participants were asked to count the number of T junctions contained in the letters of the word (a T junction occurs when two perpendicular lines cross, as in the letter "T"); this represents a perceptual (shallow) encoding task. For the words that were presented four times each, participants were asked to count the number of meanings the word had; this represents a semantic (deep) encoding task.

During PET data acquisition, participants viewed three-letter word stems (e.g., DRA_) and were asked to complete each stem with a word that they saw previously (either once [Low Recall condition] or four times [High Recall condition]). The order of the Low Recall and High Recall conditions was counterbalanced across participants and groups. For all participants, the first and last scans involved completing word stems with the first word that came to mind (Baseline condition). Given that we were interested in examining how depth of processing (High vs Low Recall) modulated hippocampal rCBF during recall in the Control vs PTSD groups, and given that the Baseline condition did not involve the recollection of previously studied material, the Baseline condition was not expected to yield data critical to our hypotheses and is not the focus of the current manuscript. We briefly note, however, that the High-Baseline comparison (both within and across groups) yielded similar, albeit less significant, hippocampal activations compared to the High-Low comparison. This is identical to the findings of a previous study using the same design (Heckers et al., 1998). Second, the Low-Baseline comparison yielded no hippocampal activation both within and across groups, which again is consistent with previous studies (Schacter et al., 1996a,b; Heckers et al., 1998). PET scans were separated by at least 10 min, to allow for radiation decay.

PET Procedures

The PET equipment and procedures have been described previously (Rauch et al., 1994; Shin et al., 1997, 1999). Briefly, PET data were gathered by a 15-slice, whole-body tomograph (Scanditronix PC 4096, General Electric, Milwaukee, WI). The camera produced contiguous slices 6.5 mm apart, with axial resolution at 6.0-mm full-width half maximum (FWHM; axial field, 97.5 mm). Images were reconstructed using a measured attenuation correction and a Hanning-weighted reconstruction filter set to allow for 8-mm in-plane spatial resolution (FWHM).

After entering the scanner, each participant was fitted with a thermoplastic custom-molded face mask, an overlying face mask

attached to a vacuum, and nasal cannulae (placed in the mouth) which delivered the $^{15}\text{O-CO}_2$. The concentration of the $^{15}\text{O-CO}_2$ was 2,960 MBq/L; the flow rate was 2 L/min. Each participant's head was aligned in the scanner relative to the canthomeatal line, and transmission measurements were made using an orbiting pin source.

PET Data Analysis

Statistical analysis of the PET data was conducted using the SPM99 software package (Wellcome Department of Cognitive Neurology, London, UK; Friston et al., 1991, 1995). PET images were motion corrected, spatially normalized, and smoothed to 15-mm width (FWHM). At each voxel the PET data were normalized by the global mean and fit to a linear statistical model by the method of least squares. Planned contrasts at each voxel were conducted; this method fits a linear statistical model, voxel-by-voxel, to the data. Hypotheses were tested as contrasts in which linear compounds of the model parameters were evaluated using *t*-statistics, which were then transformed to *z*-scores.

The main contrast of interest in the current study was that of High Recall vs Low Recall. Specifically, we predicted that relative to the Control group, the PTSD group would exhibit smaller rCBF increases in the hippocampus in the High Recall vs Low Recall comparison.

To obtain an estimate of the location of hippocampal activation that was unbiased with regard to group, we first pooled data from all participants together and compared the High vs Low Recall conditions. This comparison resulted in a statistical parametric map that was examined for activation in the hippocampus and parahippocampal gyrus. (Given the limited spatial resolution of PET as well as the size of our smoothing kernel, our a priori search volume included both regions.) If such activation was found, we planned to create a region of interest (ROI) around the maximum voxel, extract blood flow data from that ROI, and use a planned *t*-test to evaluate our prediction of smaller rCBF difference scores (High-Low Recall) in the PTSD group, compared to the Control group. Given that this a priori prediction was specific and directional, the associated *P*-value was one-tailed.

In addition to these analyses, the main effect of group (collapsing across conditions) was assessed in order to clarify results of the previous analyses. We also computed the High vs Low Recall contrast within each group separately, and then assessed the Condition \times Group interaction (voxel-by-voxel). Although the hippocampus was our only a priori ROI, for the sake of completeness, we also report activations with *z*-scores greater than 3.09 ($P < 0.001$, uncorrected for multiple comparisons) in other brain regions. ROI-based as well as whole-brain, voxel-wise correlational analyses were conducted to determine whether clinical variables were significantly related to hippocampal rCBF changes in the High vs Low Recall comparison. Whole-brain, voxel-wise SPM "covariates only" analyses were conducted to determine whether clinical variables were significantly related to hippocampal rCBF in both the High and Low Recall conditions combined.

TABLE 1.

Mean Recall Accuracy Rates*

Group	PTSD (n = 8)	Control (n = 8)
High recall	71% (11)	67% (5)
Low recall	23% (9)	28% (7)

*PTSD, posttraumatic stress disorder. Standard deviations are given in parentheses.

Structural MRI

To help clarify the source of group differences in hippocampal function, we also obtained structural MRI data on 15 participants (one control participant had metallic implants and could not undergo MRI). These data were collected on a Siemens Symphony/Sonata 1.5-tesla (T) whole-body high-speed imaging device with a three-axis gradient head coil. Head movement was restricted using expandable foam cushions. After an automated scout image was obtained and shimming procedures were performed to optimize field homogeneity, two high-resolution 3D MPRAGE sequences (TR, 7.25 ms; TE, 3 ms; flip angle, 7 degrees) with an in-plane resolution of 1.3 mm, and 1-mm slice thickness, were collected. The hippocampus and temporal lobes were segmented according to previously established procedures (Filipek et al., 1994; Makris et al., 1999; Seidman et al., 2002). Although these morphometric analyses were not the primary focus of this study, based on previous results in the literature, we hypothesized that the PTSD group would have smaller hippocampal volumes than the Control group. Given that this prediction was specific and directional, P -values for these analyses were one-tailed.

RESULTS

Recall Accuracy

Recall accuracy was expressed in terms of percentage of word stems completed correctly (Table 1). Accuracy data were submitted to a two-group (PTSD, Control) \times 2 Condition (High Recall, Low Recall) analysis of variance (ANOVA). The main effect of Group was not significant ($F[1,14] = 0.02, P < 0.88$). A significant main effect of Condition indicated that, as expected, accuracy rates were higher in the High Recall condition than in the Low Recall condition ($F[1,14] = 230.4, P < 0.0001$). The Condition \times Group interaction was not significant ($F[1,14] = 2.8, P = 0.12$); i.e., the difference in accuracy rates between the High vs Low Recall conditions did not significantly differ between the groups.

PET Results

We pooled all participants together and conducted the High vs Low Recall comparison. The resulting statistical parametric map revealed an activation in left hippocampus ($z = 3.88$, MNI coordinates $x,y,z = -24, -18, -22$; see Fig. 1). (This activation

persisted even when age and hippocampal volumes were included as covariates in the statistical model.) Within this activation, we then identified an ROI (radius = 2 mm) around the voxel with the maximum z -score, extracted blood flow data from that region, and calculated a High-Low Recall rCBF difference score for each subject. Consistent with our hypothesis, the PTSD group had smaller rCBF difference scores than the Control group ($t[14] = 2.1, P = 0.03$, one-tailed). This group difference remained significant even after removing from the analyses the data of two PTSD patients with current comorbid depression ($t[1,12] = 2.0, P = 0.04$, one-tailed). Follow-up paired t -tests revealed that the Control group exhibited a significant rCBF increase from the Low Recall to the High Recall condition ($t[7] = 3.3, P = 0.01$), whereas the PTSD group did not ($t[7] = 1.1, P = 0.33$) (Fig. 2).

In the PTSD group, the nonsignificant rCBF change between conditions appeared to be due to elevated rCBF in the Low Recall condition. To assess whether the PTSD group had higher rCBF in the hippocampus across conditions than the Control group, we examined the main effect of Group. This voxel-wise analysis revealed greater rCBF in the PTSD group than in the Control group in the left hippocampus ($z = 3.68$, MNI coordinates $x,y,z = -36, -26, -12$), right hippocampus ($z = 5.10$, MNI coordinates $x,y,z = +38, -12, -16$), and left amygdala ($z = 4.48$, MNI coordinates $x,y,z = -14, -2, -20$).

We also conducted the High vs Low Recall comparison within each group separately. In the Control group, this analysis revealed activations in left hippocampus ($z = 3.62$, MNI = $-24, -18, -22$) and visual cortex ($z = 3.60$, MNI = $-30, -72, +26$). In the PTSD group, activations occurred in postcentral gyrus ($z = 3.85$, MNI = $+62, -22, +26$) and lingual gyrus ($z = 4.06$, MNI = $-20, -66, -10$).

A voxel-wise Condition \times Group interaction revealed rCBF increases in the High vs Low Recall comparison that were greater in the Control group than in the PTSD group: hippocampus ($z = 2.40$, MNI = $-28, -16, -24$), fusiform gyrus ($z = 3.24$, MNI =



FIGURE 1. Results of the High vs Low comparison in positron emission tomography (PET) data pooled across all participants. The coronal image displays regional cerebral blood flow (rCBF) increases in left hippocampus ($z = 3.88$; MNI coordinates $x,y,z = -24, -18, -22$) superimposed on a canonical SPM99 T1 template. This image is displayed according to neurological convention.

+40, -48, -18), and orbitofrontal cortex ($z = 3.11$, MNI = +10, +60, -22). Regions showing greater rCBF changes in the PTSD group included: lingual gyrus ($z = 4.16$, MNI = -20, -66, -10), inferior temporal gyrus ($z = 3.84$, MNI = -50, -8, -24), and medial frontal gyrus ($z = 3.53$, MNI = -8, +54, -10). Activations in the Condition \times Group interaction persisted even when age and hippocampal volumes were included as covariates in the statistical model.

Hippocampal Volumes

Relative to the Control group, the PTSD group had significantly smaller right hippocampal volumes (right hippocampus: $t[13] = 1.86$, $P = 0.05$, one-tailed) and a trend for smaller left hippocampal volumes (left hippocampus: $t[13] = 1.42$, $P = 0.09$, one-tailed). (See Table 2). Relative to the Control group, the PTSD group had a 10.2% smaller right hippocampus and a 7.7% smaller left hippocampus.

Correlational Analyses

Both within and across groups, there were no significant correlations between rCBF changes in the region of left hippocampus that was activated in the High vs Low Recall comparison across subjects (MNI coordinates $x,y,z = -24, -18, -22$) and CAPS scores, BDI scores, recall accuracy scores, or hippocampal volumes (all P -values > 0.24). Voxel-wise correlational analyses confirmed that these latter variables were not significantly related to rCBF changes in other portions of hippocampus or parahippocampal gyrus.

Voxel-wise SPM "covariates only" analyses of rCBF in the High and Low Recall conditions combined revealed that, within the PTSD group, CAPS scores were positively associated with rCBF in

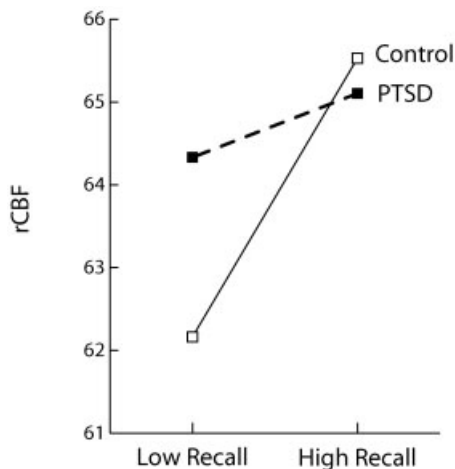


FIGURE 2. Normalized rCBF values in left hippocampus (MNI coordinates $x,y,z = -24, -18, -22$) in the High and Low Recall conditions in the posttraumatic stress disorder (PTSD) and Control groups. The mean regional cerebral blood flow (rCBF change between conditions) was significantly smaller in the PTSD group than in the Control group ($P = 0.03$, one-tailed). rCBF significantly increased between conditions in the Control group ($P = 0.01$), but not in the PTSD group ($P = 0.33$).

TABLE 2.

Mean Hippocampal Volumes*

Group	PTSD (n = 8)	Control (n = 7)
Left hippocampus	3.88 (0.49)	4.21 (0.37)
Right hippocampus	3.93 (0.43)	4.38 (0.51)

*PTSD, posttraumatic stress disorder. Volumes are expressed in cubic centimeters. Standard deviations are given in parentheses.

right hippocampus/parahippocampal gyrus ($z = 3.68$; MNI coordinates $x,y,z = +32, -16, -22$), with a similar trend in left hippocampus/amygdala ($z = 2.94$; MNI coordinates $x,y,z = -26, -6, -24$), even after controlling for BDI scores. That is, within the PTSD group, greater PTSD symptom severity was associated with greater rCBF in these regions in the High and Low Recall conditions combined.

DISCUSSION

Firefighters with PTSD exhibited smaller rCBF increases in the left hippocampus during an explicit memory recall task than did firefighters without PTSD. However, this between-group difference appeared to be driven by relatively elevated rCBF in the Low Recall condition in the PTSD group. In addition, collapsing across conditions, the PTSD group exhibited greater rCBF in the hippocampus than did the Control group, and within the PTSD group, symptom severity was positively associated with rCBF in hippocampus and parahippocampal gyrus. The latter finding resonates with a previously reported positive correlation between flashback intensity during symptom provocation and perihippocampal rCBF (Osuch et al., 2001). These findings of abnormally elevated hippocampal activity in PTSD might be consistent with reduced efficiency of hippocampus during the performance of an explicit memory task and/or with impaired integrity of inhibitory interneurons within the hippocampus (Friston et al., 1992; Heckers et al., 1998). Our results might be at least partially consistent with the view that anxiety may be mediated by hyperactivity of the septohippocampal system (McNaughton, 1997) and with a recent neuroanatomical model of PTSD, in which an abnormally functioning hippocampus and medial prefrontal cortex fail to inhibit a hyperresponsive amygdala (Rauch et al., 1998, 2000; Shin et al., 2001). Critical tests of this model will come from future cognitive activation studies of the functional interrelationships among these three brain regions.

The relationship between hippocampal function and volume in PTSD appears to be complex at best, and the current study can offer only preliminary data in this regard. We have found that, relative to the Control group, the PTSD group exhibited abnormal modulation of rCBF in left hippocampus during an explicit memory task (driven primarily by elevated rCBF in the Low Recall condition), greater rCBF in hippocampus (bilaterally) across conditions, and smaller right (and a trend for smaller left) hippocampal volumes. One might speculate that rCBF abnormalities in the

hippocampus might reflect a functional compensation for reduced hippocampal volumes. If this were the case, (1) hippocampal rCBF changes should be correlated with hippocampal volumes and (2) statistically controlling for hippocampal volumes should eliminate the group difference in rCBF increases. However, neither of these possibilities was true in the current study. Further research on a larger sample will be needed to address this issue adequately.

We did not find significant group differences in recall accuracy. Although this may seem inconsistent with previous reports of verbal memory deficits in PTSD (e.g., Bremner et al., 1993; Gurvits et al., 1993; Vasterling et al., 1998), individuals with PTSD do not exhibit impairment on all measures of memory ability (e.g., Yehuda et al., 1995; Stein et al., 1999). In addition, individuals with PTSD show improvement in memory task performance with cueing and recognition testing, as opposed to recall testing (Jenkins et al., 1998). In the current task, cueing (with word stems) may have improved performance in the PTSD group. Lastly, previous memory research on PTSD has focused mainly on combat veterans, rape survivors, or abuse survivors. It is possible, although unlikely, that memory performance could be different in firefighters with PTSD. An alternative explanation for the lack of group differences in recall accuracy might be low statistical power due to the relatively small number of subjects studied. However, the current finding of no significant group differences in recall accuracy is consistent with that of a larger ($n = 36$) word-stem completion study of explicit memory in sexual-abuse related PTSD (L.M. Shin, unpublished observations).

Although abnormal recruitment of the hippocampus in the current study is consistent with previous reports of structural abnormalities in the hippocampus in PTSD, the etiology of functional and/or structural abnormalities in PTSD is far from clear (see Bremner, 2001; McEwen, 2001; Pitman, 2001; Yehuda, 2001). Basic research has demonstrated hippocampal damage in animals exposed to extreme stress or administration of glucocorticoids (e.g., Uno et al., 1989; Woolley et al., 1990; Sapolsky et al., 1990; Watanabe et al., 1992; Sapolsky, 2000). Although these findings have led some researchers to hypothesize that hippocampal abnormalities in PTSD are due to stress-induced neurotoxicity, there is some support for the notion that hippocampal abnormalities may be present in individuals prior to trauma exposure and act as a vulnerability factor for the development of PTSD (Pitman, 2001). Compelling evidence for this possibility comes from a recent study of hippocampal volumes in male Vietnam combat veterans and their combat unexposed monozygotic twins. Gilbertson et al. (2002) found that unexposed co-twins of veterans with PTSD had smaller hippocampal volumes compared to the unexposed co-twins of veterans without PTSD. It would be of interest to examine hippocampal function in a similar twin design.

Reports of hippocampal abnormalities in PTSD should be interpreted with caution, especially in light of the high rates of comorbid depression in this disorder (e.g., Kulka et al., 1990; Kessler et al., 1995). Several recent MRI studies have reported decreased hippocampal volumes in patients with major depressive disorder (Sheline et al., 1996, 1999; Shah et al., 1998; Bremner et al., 2000; Mervaala et al., 2000; Steffens et al., 2000; Frodl et al., 2002), although there have been some failures to replicate this finding

(Axelson et al., 1993; Vakili et al., 2000; Rusch et al., 2001). Interestingly, one recent study has reported decreased hippocampal volumes in depressed women with histories of childhood abuse, but not in depressed women without such histories (Vythilingam et al., 2002). This finding highlights the need to assess trauma histories in studies of the hippocampus in depression. Reports of functional abnormalities in the hippocampus in major depression have been limited. Vindebech et al. (2001) reported higher resting blood flow in the hippocampus in depressed patients relative to healthy control participants. De Asis et al. (2001) found that, compared to control participants, elderly patients with depression displayed diminished hippocampal activation during a word generation task. In the current study, two patients with PTSD had current comorbid major depression. However, between-group differences in hippocampal activation remained significant even after data from the two PTSD patients with comorbid major depression were removed from the analyses. Therefore, it seems unlikely that the current finding of abnormal hippocampal recruitment in PTSD is solely attributable to the presence of comorbid major depression.

Structural and functional abnormalities in the hippocampus also have been reported in schizophrenia (e.g., Nelson et al., 1998; Heckers et al., 1998, 1999; Heckers, 2001; Wright et al., 2000). Using the exact paradigm described in the current study, Heckers et al. (1998) found diminished rCBF increases in the High-Low Recall contrast in patients with schizophrenia relative to control participants, an effect that was later demonstrated in schizophrenia patients both with and without the deficit syndrome (Heckers et al., 1999). Interestingly, functional impairment of the hippocampus appears to be accompanied by a recall accuracy deficit in schizophrenia (Heckers et al., 1998), but not in PTSD, according to the current results. Thus, it is important to note that functional abnormalities in the hippocampus do not appear to be specific to PTSD, as they have been observed in patients with depression and schizophrenia. Whether the etiology of hippocampal abnormalities differs between these psychiatric disorders is currently unknown.

Limitations of this study include relatively small sample sizes and, as mentioned above, the presence of comorbid disorders in the PTSD group. Future studies ought to include larger sample sizes, as well as psychiatric control groups. In addition, response times were not measured in the current work. Although accuracy is typically considered the most important behavioral dependent variable in this type of study, an examination of response times might have revealed significant differences between groups or correlations with hippocampal rCBF. Finally, PET studies in general are limited by modest spatial resolution, head movement, and stereotactic transformation. In addition, normalizing rCBF values based on whole-brain blood flow precludes the detection of absolute blood flow changes between conditions and groups.

In conclusion, we found that relative to firefighters without PTSD, firefighters with PTSD exhibited abnormal rCBF responses in the left hippocampus during the explicit recollection of nonemotional material, and that this abnormality was driven by relatively higher hippocampal rCBF in the comparison condition in the PTSD group. Future research ought to investigate the spec-

ificity of functional hippocampal abnormalities to PTSD, as well as determine the clinical implications of such abnormalities.

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