Regional Cerebral Blood Flow Correlated with Flashback Intensity in Patients with Posttraumatic Stress Disorder

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Background: *Nuclear imaging studies have examined cerebral blood flow (rCBF) in subjects with posttraumatic stress disorder (PTSD) using symptom evocation paradigms. To date, no such studies have investigated rCBF as related to subjects' reports of flashback intensity.*

Methods: *Subjects with varying traumatic histories and longstanding PTSD were studied using [^{15}O]-H_2O positron emission tomography with an auditory script of their traumatic event. Eight subjects had three resting scans followed by their script and additional scans. Heart rate responses as well as the presence of flashbacks and their intensity were recorded. rCBF was correlated with flashback intensity in each subject's scan. Combined analysis of all subjects' data yielded common regions related to the flashback experience.*

Results: *rCBF correlated directly with flashback intensity in the brainstem, lingula, bilateral insula, right putamen and left hippocampal and perihippocampal, somatosensory and cerebellar regions. Inverse correlations with rCBF were found in bilateral dorsolateral prefrontal, right fusiform and right medial temporal cortices.*

Conclusions: *This study correlated flashback intensity and rCBF in a group of patients with chronic PTSD suggesting involvement of brainstem, and areas associated with motor control, complex visual/spatial cues and memory.* Biol Psychiatry 2001;50:246–253 © *2001 Society of Biological Psychiatry*

Key Words: PTSD, trauma provocation, PET, cerebral perfusion, functional neuroimaging

Introduction

Numerous groups have studied cerebral blood flow in subjects with chronic posttraumatic stress disorder (PTSD) using a script or medication challenge to reproduce subjects' symptoms (Brannan et al 1999; Bremner et al 1997, 1999a, 1999b; Engdahl et al 1999; Liberzon et al 1997, 1999; Rauch et al 1996; Shin et al 1997, 1999; Zubieta et al 1999). Other groups have performed functional neuroimaging of PTSD without symptom evocation (Lucey et al 1997; Semple et al 1993, 1996), or with fluorodeoxyglucose positron emission tomography (PET) or fMRI (Bremner et al 1997; Rauch et al 2000; Shin et al 1999).

There is some agreement in the findings of functional imaging studies of PTSD despite different experimental variables including type of eliciting stimulus, order of neutral and symptom evocation conditions, type of traumatic event to which subjects were initially exposed, length of time since the traumatic event, and whether or not physiologic nonresponders to traumatic stimuli were included in the sample population. In general, studies support activation in the right (Rauch et al 1996; Shin et al 1997) or left (Liberzon et al 1999) amygdala, and in the sensorimotor cortex (Rauch et al 1996; Bremner et al 1999a, 1999b).

There is also considerable diversity in the literature reporting cerebral function in response to symptom exposure. The anterior cingulate, middle and superior temporal, middle frontal, right orbitofrontal, occipital, hippocampal, parahippocampal, anterior temporal, and inferior frontal cortices have been implicated in different studies, demonstrating either increases or decreases in perfusion depending on the study conditions and sample population.

Vivid re-experiencing phenomena, sometimes called flashbacks, are one of the hallmarks of PTSD and are perhaps the most subjectively distressing symptom for patients. They are distinct from regular memories in that patients report that "they feel like they are back there" (i.e., when and where the traumatic event occurred). There

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Table 1. Demographics of 11 PTSD Patients Receiving rTMS Treatment

Patient	Gender	Medications	History of childhood trauma	Index traumatic event	Years since index trauma	CAPS intrusion (max 4)	CAPS avoidance (max 7)	CAPS hyperarousal (max 6)	Other active anxiety disorders[a]	Major depression
1	F	Serzone	yes	Suicide of relative	2	3	6	5	PD	yes
3[b]	F	Prozac, Klonopin, Doxepin	yes	Childhood abuse	48	4	5	5	PD SP SpP	yes
4	F	Elavil, Prozac	no	Adult rape	18	4	4	5	SP	yes
5	F	Medication free	yes	Childhood abuse	37	4	7	6	PD SP	yes
6	F	Effexor, Klonopin	yes	Adolescent rape	21	3	6	3	Ag	yes
7	F	Wellbutrin, Ativan	yes	Childhood abuse	29	3	6	3	PD SP	yes
8	F	Paxil, Klonopin, Ambien	yes	Adult industrial accident	4	4	5	4	PD SP	yes
9	F	Nardil	no	Adult rape	37	4	7	6	PD SpP	yes
10	F	Pamelor	no	Spousal abuse	22	4	7	5	PD SpP	yes
11	M	Doxepin, Klonopin	yes	Vietnam	32	4	5	4		yes
12	F	Effexor, Paxil, Doxepin	yes	Childhood abuse and adult rape	20	4	6	5	PD SP	yes
Mean					24.5	3.7	5.8	4.6		
SD					14.0	0.5	1.0	1.0		

[a]PD: Panic Disorder; SP: Social Phobia; SpP: Specific Phobia; Ag: Agoraphobia.
[b]Subject 2 not studied.

is a sense of loss of control, and often an autonomic response (such as tachycardia, tachypnea, and diaphoresis) that is physiologically much more similar to a panic attack than a normal memory.

Four neuroimaging studies of PTSD have reported subjects who had vivid re-experiencing phenomena or flashbacks during script or medication challenge. The remaining studies did not address this phenomenon specifically. Liberzon et al (1999) reported one flashback in 14 subjects hearing combat sounds, and published these results separately from the 13 subjects who did not (Liberzon et al 1997). Bremner et al (1997) noted that three of ten subjects with PTSD reported a flashback with yohimbine administration, and Shin et al (1999) mentions that one of eight subjects with PTSD had a flashback in response to script-driven imagery. In addition, Rauch et al (1996) noted that all eight of their subjects reported re-experiencing phenomena during the provocation scan, suggesting that they had flashbacks during the procedure. The differences in attention to flashback experiences in the subjects in these studies may help to account for the diversity of the findings among them.

In the current study, we investigated PTSD patients' subjective and autonomic responses to hearing an individualized auditory trauma script to determine the regional cerebral blood flow (rCBF) pattern specifically associated with flashback experiences. We hypothesized that subjects would have a flashback and increased heart rate upon hearing the script, and that flashback intensity would be correlated with rCBF response in visual and/or visual association areas (Liberzon et al 1997; Rauch et al 1996; Shin et al 1999b) and amygdala/parahippocampal regions as seen in previous PTSD studies (Brannan et al 1999; Bremner et al 1997, 1999; Liberzon et al 1999; Rauch et al 1996; Semple et al 1993; Shin et al 1999a, 1999b).

Methods and Materials

Subjects

Twelve subjects (ten women and two men) with chronic, longstanding PTSD that was unresponsive to standard treatment were enrolled for participation in a treatment trial using repetitive transcranial magnetic stimulation and involving PET scanning. The study protocol had been approved by the Institutional Review Board at the NIMH. The study was described to the subjects and written informed consent was obtained. Subject 2 was unable to tolerate the scan procedure and thus was not included, leaving 11 subjects in this study. All but one subject

was right-handed. Subject demographics are depicted in Table 1. Mean age was 41.1 years (SD = 11.3, range 23–56) and mean time since index traumatic event was 24.5 years (SD = 14.0, range 2–48). As illustrated, comorbid diagnoses were common, particularly other anxiety disorders and depression. In addition, all subjects had a history of substance abuse, but had not been using drugs or alcohol for at least 3 months before the study. Subject 8 was discovered to have been using alcohol during the protocol after the PET scan and may also have imbibed socially within 3 months before scanning. This subject was included in the study. Patients were tapered off of any antipsychotic and/or anticonvulsant medications before the study, but due to the severity of symptoms, antidepressants and benzodiazepines were permitted. They were on stable doses without medication changes for at least 3 weeks before scanning as summarized in Table 1. At baseline upon admission, nine of the 11 individuals described in this study had great difficulty talking about their traumatic experience(s) without becoming upset, tearful and anxious whereas two evidenced objective and subjective indicators of dissociation (subjects 1 and 5). All endorsed a history of disturbing flashbacks at the time of admission.

Subjects were evaluated with a structured diagnostic interview (Schedule for Affective Disorders and Schizophrenia, Lifetime Version, Modified to Anxiety Disorders) at the start of the study. In addition, they were given the Clinician Administered PTSD Scale (CAPS) to establish diagnostic criteria for PTSD. CAPS scores are depicted in Table 1. Symptom rating scales were utilized during PET scanning as described below.

Scanning Procedure

Patients were scanned using a GE Advance scanner (GE Medical Systems, Waukesha, WI, USA), which acquires 35 slices 4.25 mm apart, with 6 mm reconstructed transverse resolution and an in-plane resolution of 4.25 mm. A transmission scan was obtained using sources rotated around the subject's head to correct the emission scans for photon attenuation by the skull and scalp and to verify correct head positioning for the emission scan. Head movement was restricted with an individually molded thermoplastic mask and scans were obtained parallel to the canthomeatal line. Radial arterial blood sampling allowed determination of time-blood activity curves used to calculate absolute rCBF using an autoradiographic method (Herscovitch et al 1983; Raichle et al 1983).

All subjects were instructed to write or verbally describe a brief account of a focal traumatic event. This script was edited by the research team to be 1–1.5 min long when read, and to include descriptions of three to five sensory experiences, as described by the subjects. The script was read aloud by a research assistant and tape-recorded, but not played for the subjects until the day of the scan. Each subject had been brought to the PET suite several days before the actual scan and was instructed about the procedure in detail. A flashback was defined to the subjects as vivid re-experiencing during which they felt as if the traumatic event was happening again.

On the day of the procedure, after arterial line placement, subjects were brought into the PET suite and positioned on the scanner bed where they acclimated to the environment for at least 30 min before the first scan. Because one subject was not able to tolerate arterial line placement, we elected to acquire relative blood flow data. Each subject underwent three resting PET scans (each lasting 1 min after the $[^{15}O]H_2O$ activity reached the head) 12 min apart. Two minutes before the fourth scan, subjects heard their personalized trauma script recording. They then had three more scans 12 min apart for a total of six scans. Subjects heard the tape only once during the session, between scans three and four. For the scan after the audiotape, subjects were asked to focus on the contents of the script. For all other scans (including scans five and six), subjects were asked to focus on their mood. The fourth, fifth and sixth scans were designed to follow the response to the tape across time. Nine of the subjects were able to complete all six scans. Subject 11 had the first five scans only, due to technical problems and is included in the analyses. Subject 12 was only able to tolerate the first three scans. Her heart rate and subjective data are included where available, but scan data were not complete enough to be included in the rCBF analyses. Subjects 1 and 5 did not experience a flashback at any time during the scanning procedure and were thus eliminated from the rCBF analyses.

Rating and Physiologic Monitoring Procedure

Approximately 20–30 min after patients were positioned in the scanner, 5 min before the first scan, they were given a baseline subjective units of distress scale (SUDS) assessing their anxiety, panicky feelings, intrusive thoughts, calmness, feelings of unreality, talkativeness, depression, sadness and anger. In addition, they were asked if they had had a flashback since being positioned on the scanning table. If so, they were asked to rate how disturbing the flashback was on a scale from 0 (not at all) to 100 (the greatest it can be). Immediately after each scan, subjects were asked these questions again, with the modification that the flashback question referred to the time since the previous set of questions.

Heart rate was monitored throughout the scanning procedure with three baseline heart rate measures at 5-min intervals before scanning began, every 15 sec during each PET image acquisition, and 1 min, 5 min and 9 min after each of the scans. The nine intrascan heart rate measures were averaged to yield a single heart rate mean within each scan.

Statistical Analyses

Image processing and analysis were performed on a UNIX workstation (Sun Microsystems Inc., Mountain View, CA, USA) using Matlab (Mathworks, Sherborn, MA, USA) and Statistical Parametric Mapping software (SPM, courtesy of MRC Cyclotron Unit, Hammersmith Hospital, Hammersmith UK). ANALYZE (Mayo Foundation, Rochester, MN, 1991) and NIH- and NIMH-developed software were also used in the imaging processing, analysis and presentation. Scans were visually inspected for artifacts and stereotactically normalized as described previously (Ketter et al 1999) into a standard space corresponding to the human brain atlas of Talairach (Talairach and Tournoux 1988). These images were then smoothed with a Gaussian low-pass filter of 10 mm in-plane and 6 mm axial FWHM to minimize

Table 2. Brain Regions Correlated with Flashback Intensity

Brain region	Talairach coordinates			Direction of correlation	Z	
	X	Y	Z		Maxima	*p* Value
L inferior frontal	−48	+6	+12	Direct	3.60	0.000318
L insula	−34	+10	+12	Direct	3.33	0.000868
L perihippocampal region	−28	−24	−4	Direct	3.83	0.000128
L somatosensory	−48	−24	+36	Direct	4.21	0.000025
L cerebellum	−10	−56	−8	Direct	3.62	0.000294
R insula	+28	−4	+12	Direct	3.82	0.000134
R putamen	+26	0	+12	Direct	3.85	0.000118
Lingula	+6	−66	0	Direct	3.14	0.001688
Brainstem	+2	−14	−16	Direct	3.94	0.000082
L superior frontal	−16	+48	+16	Inverse	4.62	0.000004
R superior frontal	+16	+52	+16	Inverse	3.67	0.000242
R fusiform	+34	−72	−8	Inverse	4.28	0.000019
R medial temporal	+52	−52	+4	Inverse	3.40	0.000674

noise and improve between-subject spatial alignment. rCBF analyses were executed in SPM95 (Friston et al 1995). Absolute analyses were not utilized because of the lack of absolute data on all subjects and due to the potential confound of rCBF perturbations induced by the hypocapnea that occurred in many subjects who experienced flashbacks with the scans. For these relative analyses, the effect of global on regional blood flow was removed by applying a voxelwise proportional normalization of absolute flow with global flow to arrive at normalized blood flow (Fox et al 1985).

Because not all subjects were in a resting state (flashback intensity zero) before the script and not all subjects had a precipitous flashback after hearing the script, the customary pre-/postscript subtraction analysis is not presented in this study. Instead, the following approach was used. Relationships of each patient's flashback intensity during a scan (as rated immediately after the scans) to blood flow were examined with voxelwise Pearson correlations in SPM95 within each subject across the six scans. For a particular scan during which a subject did not report a flashback, blood flow was correlated with a zero score. These correlations resulted in Z-maps, each relating to the null hypothesis of no linear relationship between rCBF and flashback intensity in a particular subject. The Z-maps were then combined via meta-analysis ($\Sigma Z/\sqrt{n}$; Rosenthal 1991). This approach enabled us to use both the intrasubject scans (dependent data points) obtained by scanning each subject repeatedly in one session and intersubject scans (independent data comparisons) obtained by scanning multiple subjects. The resulting Z_{meta} map was then subjected to cluster analysis (Friston et al 1994; Maisog J, personal communication) with a Z threshold of 1.96 (two-tailed) and a cluster probability threshold of $p = .05$. Cluster analysis considers the smoothness of the Z-map, arising from the low-pass filtering applied to the input images as well as inherent spatial autocorrelation in the underlying brain function, in determining the effective independence of the multiple comparisons contained in the total brain volume analyzed. Uncorrected *p* values were then displayed (for purposes of depicting topography of the finding) for all voxels falling in clusters deemed significant by this analysis. Local maxima were located within brain regions using the Talairach and Tournoux atlas (1988) (Table 2). Demographic and clinical patient data were analyzed using SPSS with a significance threshold set at $p < .05$ (not corrected for multiple comparisons).

Results

Phenomenology

Three general response types were evident among the 11 subjects studied, as summarized in Figure 1. These types are: those who reported no flashbacks following the script ($n = 3$); those who were calm in the first three scans, but reported flashback experiences in response to the script ($n = 5$); and those who reported flashback experiences beginning early in the scanning session with exacerbation of symptoms upon hearing the script ($n = 3$). Subjects who reported flashbacks of intensity greater than about 60 were objectively anxious and almost always tearful at the times they reported these experiences. There were no cases where the subject was reporting a severe flashback but appeared outwardly calm. Conversely, those subjects not reporting flashbacks were uniformly calm in appearance. Two of the three subjects who denied flashback experiences after the tape reported the sensation of feeling that they were somewhere else in a different time and place, but not at the traumatic event (subjects 1 and 5). Subjects who reported flashbacks described the experience as identical to their flashback experiences outside the scanner occurring after external environmental cues or spontaneously as part of their PTSD symptomatology. The distribution of flashback intensity data for each scan and all subjects was bimodal with a grouping at zero (no flashback) and then a nearly normal distribution between 30 and 100 with the second modal point at 80.

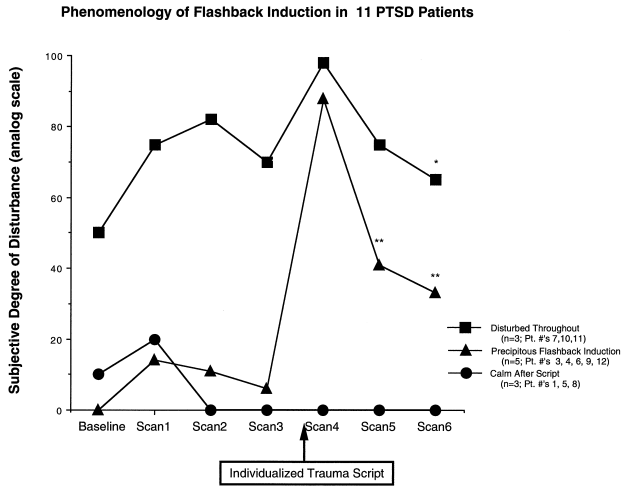

Figure 1. Phenomenology of flashback induction in 11 PTSD patients. Subjective degree of distress from vivid re-experiencing phenomena (flashbacks) is depicted across the course of the six PET scans. Individualized trauma scripts were heard between scans 3 and 4. The sample population divides into three groups: those who were calm after the script ($n = 3$; subjects 1, 5, and 8); those who were initially calm but had a precipitous flashback reaction to the auditory script ($n = 5$; subjects 3, 4, 6, 9, and 12); and those who reported flashback experiences early in the procedure (during the resting scans) and had an additional acute exacerbation with the script ($n = 3$; subjects 7, 10, and 11). *n = 2; **n = 4 (data missing for technical reasons)

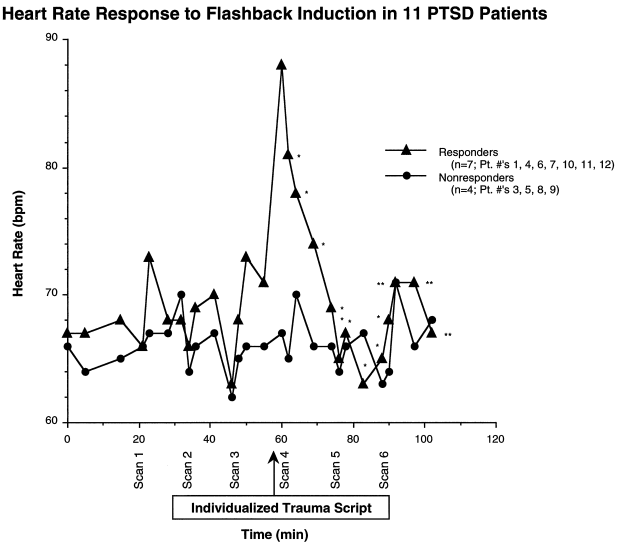

Figure 2. Heart rate response to flashback induction in 11 PTSD patients. Heart rate in beats per minute vs. time (in minutes) relative to PET scans. Individualized trauma scripts heard between scans 3 and 4. The sample population divides into two groups: those having an acute increase in heart rate response ($n = 7$; subjects 1, 4, 6, 7, 10, 11 and 12); and those without an increase ($n = 4$; subjects 3, 5, 8 and 9). *$n = 6$; **$n = 5$.

Heart Rate Response

A meta-analytic correlation between heart rate and subjective flashback intensity among all eight subjects over all scans demonstrated a Z score of 3.8, $p = .0001$; however, subjects fell into two categories: heart rate responders ($n = 7$) and nonresponders ($n = 4$) to the script, as shown in Figure 2. Responders had an acute elevation in heart rate averaging approximately 20 beats per minute between prescript and postscript conditions. Nonresponders did not have any mean elevation in heart rate after the script. It is noteworthy that one of the subjects who reported no subjective response to the script did have a heart rate response (subject 1). In addition, two subjects who had a precipitous subjective response to the audiotape had no significant elevation in heart rate (subjects 3 and 9). All three subjects who were already distressed at the beginning of the procedure and had an acute exacerbation of subjective symptoms upon hearing the script had a significant heart rate elevation.

Cerebral Perfusion

Combined correlations between subjective report of flashback intensity and rCBF in eight of the subjects are shown in Figure 3. Subject 8 was included in the analysis since she had a flashback at baseline and during scan 1, although not after hearing the script. Z-maxima, p values and exact locations of the peak and trough voxels are provided in Table 2. Positive correlations were found between flashback intensity and left inferior frontal, left hippocampal and perihippocampal, left anterior insula, right insula, right putamen, left somatosensory, left cerebellum, lingula and brainstem regions. Negative correlations were found

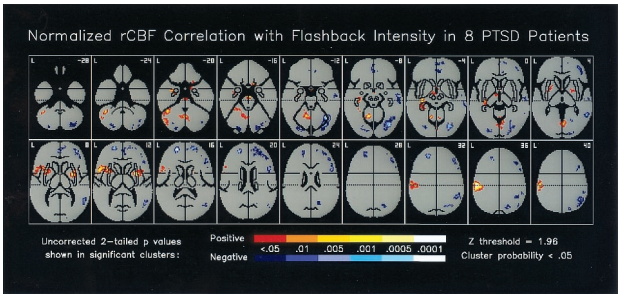

Figure 3. Normalized rCBF correlated with flashback intensity in eight PTSD patients. Statistical parametric maps displayed on transverse sections depicting regions of direct or positive (red scale) and inverse or negative (blue scale) correlations with flashback intensity as measured by subjective units of distress. Direct correlations were seen between flashback intensity and left inferior frontal, left hippocampal, left somatosensory, and left cerebellar cortices, brainstem, lingula and right putamen. Inverse correlations were seen between flashback intensity and right superior frontal, left superior frontal, fusiform and medial temporal cortices. Statistical threshold for inclusion is a Z score of > 2.33 and a p value of $< .05$ to correct for multiple comparisons using cluster analysis.

between bilateral superior frontal, right fusiform and right medial temporal cortices. All these relationships have Z-maxima greater than 3.0.

When the three subjects who had a subjective/autonomic mismatch (subjects 3 and 9; subject 5 having already been left out of the PET analysis due to all zero scores on flashback intensity) and who did not respond to the script (subject 8) were removed from the analysis, the resulting image (not shown) was almost identical to that for all eight subjects. The correlations were slightly stronger in the smaller group, suggesting that the relationships shown in Figure 3 may have been driven primarily by the subjective/autonomic responders.

When heart rate was covaryied from the analysis of flashback intensity and rCBF many of the strong correlations were diminished, as might be expected given the significant heart rate-flashback intensity association in many of these subjects. Comparison of the two probability maps show overlap in the left somatosensory, left lateral cerebellum, right superior frontal and right fusiform regions. When heart rate was covaried from the analysis of rCBF and flashback intensity, new positive correlations emerged in the left caudate/nucleus accumbens, left globus pallidus and left dorsolateral prefrontal cortex.

Discussion

This study correlating regional cerebral perfusion with flashback intensity in a group of chronic, treatment-resistant PTSD subjects with a history of flashbacks on stable doses of medications demonstrates several points. Phenomenologically, subjects had one of three responses to the auditory trauma script: they either were calm despite the eliciting stimulus, became acutely disturbed by it, or had some increased disturbance on a baseline of already moderate distress. Autonomically, subjects either had an acute elevation of their heart rate with the script or did not. Of note, two subjects with an acute subjective flashback response had no significant heart rate elevation, and one subject with an acute heart rate elevation had no significant subjective distress, indicating a lack of association between measures of flashback intensity and autonomic responsiveness in these three subjects.

Regional cerebral perfusion correlated directly with flashback intensity in the visual association areas confirming the hypothesized activation of these regions, but not the hypothesized involvement of the amygdala. rCBF also correlated directly with left hippocampal/perihippocampal areas, inferior frontal, left anterior insular, left somatosensory and left cerebellar cortices, the brainstem, right putamen and right insula. Inverse correlations with flashback intensity were prominent in the right and left superior frontal, right fusiform and right medial temporal cortices. Our findings are consistent with those works demonstrating superior frontal rCBF decreases with symptom evocation (Liberzon et al 1997; Rauch et al 1996; Shin et al 1999a) and hippocampal or parahippocampal involvement with PTSD (Bremner et al 1999; Engdahl et al 1999; Rauch et al 1996; Shin et al 1999a), but not with those implicating the anterior cingulate, superior and anterior temporal lobe or amygdala. In parallel with our observations, using other imaging methodologies, alterations in left insular activity (increased or decreased) have been found in healthy volunteers with induced anxiety (Chua et al 1999), subjects with a variety of anxiety disorders (Rauch et al 1997) and affective disorder patients with anxiety symptoms (Osuch et al 2000). The preponderance of left-sided direct and right-sided inverse correlations between flashback intensity and rCBF in our study is in contrast to Rauch's initial provocation study using pre- and postscript image analyses. Rauch et al (1996) showed increased blood flow preferentially on the right, including in the orbitalfrontal, anterior cingulate, temporal, insular, amygdalar and sensory-motor regions. These differences may be due to differences in subject population or method of data analysis. Specifically, our study has accounted for variability in the individual responses of each subject to each scan with regard to flashback experience which, as we have demonstrated, is not uniform.

Many neuroimaging studies of PTSD have focused on increasing the homogeneity of their subject population. For example, some studies have selected for physiologic responders (Brannan et al 1999; Bremner et al 1999; Rauch et al 1996; Shin et al 1999); however, comparing our subjects 4, 6 and 9 (precipitous flashback) with 7, 10 and 11 (small increased response on background distress) suggests that people who have both subjective and physiologic response to traumatic reminders can have different patterns of reaction in the scanner over time. When nonphysiologic responders are included, it becomes even more apparent that there can be highly varied subjective responses and autonomic dissociations to the same auditory script paradigm. The statistical analysis used in this preliminary study is an attempt to address this variability in a way that utilizes the differences in reactions to the evocation stimulus in a positive fashion.

The bilateral inverse relationships between frontal cortices and flashback intensity found here may be related to the loss of higher-order executive functioning as flashback intensity increases. This would be consistent with the temporary loss of present-reality orientation typically seen in subjects undergoing flashback experiences. The frontal lobes are known to be involved in hierarchical regulation of more primitive brain regions, and this relative functional decrement may indicate an inability of the frontal systems to modulate other structures (brainstem, basal

ganglia and hippocampal/perihippocampal areas) that were activated during flashback experiences. Further studies are needed to determine if this frontal hypofunction is a fundamental aspect of flashback pathophysiology.

The involvement of brain regions associated with motor control (putamen, cerebellum and somatosensory cortex) (Zigmond et al 1999), complex visual or spatial processing (right medial temporal, fusiform and lingula cortices) (Nakamura et al 2000) and memory processing (prefrontal, hippocampal cortices) (Buckner et al 1995; Lepage et al 2000) suggest the composite and multimodal nature of flashback phenomena. Further studies are needed to parcel out which of these component brain functions are related to which neural substrate.

The overlap between heart rate elevation and flashback intensity must be considered when viewing the rCBF correlations presented here. Our results were strongly influenced by the subjects who had both an autonomic and a subjective response to the testing environment. Statistical attempts to control for heart rate were limited by the strong correlation between these two variables. Comparing a group of physiologic responders with a group of nonresponders, both of who have the subjective experience of a flashback during scanning, would better clarify these relationships. This study included subjects with treatment refractory, chronic PTSD following a variety of different traumatic experiences and who were taking stable doses of antidepressants and/or benzodiazepines during the time of the scan. The use of multiple medications during the scan interval is a limitation of this study.

We focused on isolating one aspect of the phenomenology of the subjects' experiences (i.e., flashbacks and investigated regional alterations in brain activity associated with the intensity of the flashback). These preliminary findings should be confirmed in a larger group of medication-free subjects and in those with less chronic and refractory PTSD before they can be generalized to the larger population of patients with PTSD. Investigation of flashback intensity and rCBF in a group of PTSD subjects who have an autonomic response compared with those who do not will help to separate the neural substrates of autonomic aspects of flashbacks from the nonautonomic, internal experience. This may be helpful in understanding other mental phenomena of "misperception" such as hallucinations.

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