Increased Regional Cerebral Perfusion by ^{99m}Tc Hexamethyl Propylene Amine Oxime Single Photon Emission Computed Tomography in Post-Traumatic Stress Disorder

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Objective: Because of the treatment resistance and chronic affective lability of many post-traumatic stress disorder (PTSD) patients and the hypothesized association of these behaviors with temporal and limbic structures, a study was conducted to determine whether these patients would exhibit alterations in regional cerebral perfusion in the temporal and limbic regions compared with age-matched normal volunteers at rest. Method: We studied 17 patients using ^{99m}Tc hexamethyl propylene amine oxime single photon emission computed tomography. Seven of the patients were on a selective serotonin reuptake inhibitor, five were on a tricyclic antidepressant, and five were on no medication at the time of the study. Patients were compared with eight age-matched normal controls. Results: All PTSD patients showed a relative increase in regional cerebral perfusion in the anterior and posterior cingulate regions bilaterally, the right temporal and parietal regions, the right caudate/putamen region, and the left orbital and hippocampal regions compared with the control group. When the group of PTSD patients who were free of medication were compared with the control group, increased regional cerebral perfusion was found in the right and left caudate/putamen regions and the right orbital and anterior cingulate cortex bilaterally. Conclusions: PTSD is associated with increased regional blood flow in limbic areas and the right temporal and parietal cortex compared with age-matched normal volunteers.

Introduction

Post-traumatic stress disorder (PTSD) is a clinical syndrome resulting from experiencing or witnessing an extreme traumatic stressor that involved potential loss of life or serious injury to the self or others. This can include learning of an unexpected death or injury to a family member or a close associate. Persistent reexperiencing of the traumatic event accompanied by dreams of the event or feeling as if the traumatic event is recurring are characteristic of this disorder. Physiological and psychological reactivity to cues resembling the traumatic event can result in dissociative episodes, avoidance of stimuli associated with the traumatic event, and psychogenic amnesia. Sleep disturbances, inappropriate irritability, difficulty in concentration, hypervigilance, and exaggerated startle responses often accompany this disorder.[1]

The longitudinal course of PTSD highlights the complexity of the matrix onto which any neurobiological studies are superimposed. Different clinical progressions suggest that a range of modifying factors could influence individual neurobiological response. Subcategorizations by symptom cluster (intrusive, avoidant, and hyperarousal) and the frequency of comorbidity also suggest diverse neurobiological disturbances.[2] The neurobiological diversity of PTSD may reflect a similar diversity in the anxiety disorders as a group.

Despite the extensive older literature on PTSD in veterans of the Vietnam War, appreciation of the neuroanatomic and neurophysiologic features of this disorder has grown rapidly in the last decade.[3,4]

Neuroanatomic Features

Magnetic resonance imaging (MRI) studies have demonstrated a selectively smaller right hippocampal volume in some PTSD patients. No significant changes were noted in the volume of the caudate and the temporal lobes.[5-7] Others have reported an increased incidence of small clefts in the callosal-septal interface.[8] Decreased neuronal density of the right medial temporal structures was seen in combat-related PTSD.[7] Brain atrophy was not seen in combat-related PTSD. However, using quantitative volumetric MRI, both left and right hippocampi were found to be significantly smaller in PTSD subjects compared with combat control and normal subjects.[9,10] A group of 21 women with reported sexual victimization in childhood also demonstrated significantly reduced left-sided hippocampal volume compared with nonvictimized women.[11] The finding of reduced hippocampal volume in both groups serves to focus attention on the possible limbic system reactivity to extraordinary stress.

Neurophysiologic Features

Functional neuroimaging methods to study PTSD patients who were alcohol abusers demonstrated decreases of whole brain glucose metabolism and blood flow. No deficits were seen in alcoholics without neurological symptoms.[12]

Resting-state positron emission tomography (PET) studies in patients with PTSD and comorbid substance abuse have shown an increase in orbital frontal cortical blood flow and decreases in left and right hippocampal blood flow ratios.[13] PTSD patients without comorbid substance abuse studies have shown increased regional cerebral blood flow (rCBF) in the left and right parahippocampal gyrus, the left striatum, and the brain stem in the resting state.[14]

Functional challenge studies using auditory, visual, chemical, and memory-based evocative designs have shown results that appear to depend on both the type of challenge and the disease state.

Various auditory challenges have demonstrated decreased

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perfusion in the left inferior frontal and left midtemporal regions and increased perfusion in the medial prefrontal cortex, left amygdala, nucleus accumbens, right limbic, right paralimbic, and visual cortex in patients without a history of comorbid substance abuse.[15-18] In patients with PTSD and comorbid substance abuse, an increase in errors of commission as well as decreased perfusion of the right frontal and right parietal cortical regions has been reported.[19]

Visual challenge in PTSD patients has demonstrated decreased perfusion in Broca's area, left angular gyrus, operculum, and secondary somatic cortex as well as increased perfusion bilaterally in the visual cortex, left frontal-orbital region, and posterior cingulate gyrus.[20]

Memory-based challenge using visualization of combat settings demonstrated decreased perfusion of Broca's area, frontal, temporal, parietal and fusiform gyri with increased perfusion of the right amygdala, orbital-frontal, and cingulate gyri.[21,22]

Chemical challenge of PTSD patients with yohimbine has shown differentially decreased glucose metabolism in the prefrontal, temporal, and parietal regions as well as increased subjective anxiety.[23] A chemical explanation of the common finding of reduced hippocampal volume, as the result of toxic levels of glucocorticoids, was not supported in patient cortisol studies.[24]

Single photon emission computed tomography (SPECT) study of a single flashback episode during an auditory simulation of combat stimuli challenge has been reported. During this flashback, patient normalized cortical/subcortical perfusion ratios were altered.[25]

Anatomic and functional studies in other anxiety disorders have demonstrated findings that help place the PTSD findings in a more general neurobiological context.

Panic Disorder

The possibility of altered cerebral structure in panic disorder with agoraphobia was by examined by computed axial tomography. Normal ventricular brain ratios were observed in panic patients compared with published control data. Patients who had received long-term benzodiazepine therapy showed an increase in mean ventricular brain ratios consistent with a previous study.[26]

Fontaine et al. conducted MRI studies in panic disorder and found right temporal lobe atrophy as well as abnormalities in the medial temporal lobes and right parahippocampal area.[27] Reiman and colleagues conducted a PET study in eight patients with panic disorder who were vulnerable to lactate-induced panic and found a hemispheric asymmetry (decrease left to right) of parahippocampal blood flow, blood volume, and oxygen metabolism.[28] Hypoperfusion of the hippocampus has been reported in lactate-induced panic disorder, whereas increased metabolism in the basal ganglia and frontal white matter was associated with high scores on anxiety ratings, which were reversed after benzodiazepine treatment.[29,30]

Schlegel et al. found decreased benzodiazepine receptor binding in panic disorder measured by iomazenil-SPECT. Panic patients had lower iomazenil uptake rates in the frontal, occipital, and temporal cortex than epileptic patients, indicating the involvement of the benzodiazepine receptor complex in panic disorder.[31]

Benkelfat and colleagues administered the neuropeptide cholecystokinin-4 intravenously to eight healthy normal volunteers, and rCBF was determined. Cholecystokinin-4-induced anxiety was associated with increase in the claustrum-insular-amygdala regions, the cerebellar vermis, and the anterior cingulate gyrus.[32]

Kaschka et al. compared patients with panic disorder and depression with a matched control group of dysthymic patients without a history of panic attacks to evaluate panic-related abnormalities of the benzodiazepine receptor complex. The panic group had a significant decrease in the regional activity index in the lateral inferior temporal lobes, the left medial inferior temporal lobes, and the frontal lobes. The authors attributed these findings to either regional blood flow differences or benzodiazepine receptor effects.[33]

Obsessive-Compulsive Disorder

Uhde and Kellner were unable to find any significant differences compared with normal controls.[26] Garber and colleagues used MRI to characterize a small group of patients with obsessive-compulsive disorder. There were no significant differences compared with controls at the head of the caudate, the cingulate gyrus, in intracaudate/frontal horn ratios, and in areas of the corpus callosum.[34]

Baxter et al. found metabolic rates that were significantly increased in the left orbital gyrus and bilaterally in the caudate nucleus in patients with obsessive-compulsive disorder.[35]

Simple Phobia

Potts and colleagues found no statistically significant differences between social phobia patients and normal control subjects in total cerebral, caudate, putamen, and thalamic volumes. A significant negative correlation was found between age and putamen volume in patients, but none was found in control subjects. This reduction in putamen volumes was not correlated with the severity of illness.[36] Mountz et al. found that resting global and regional cerebral blood flow values in phobic subjects did not differ significantly from those of normal controls.[37] O'Carroll et al. found decreased blood flow in temporal and posterior cerebral regions in SPECT studies of patients with simple phobia listening to a relaxation tape.[38] Stein and Leslie found no significant differences with SPECT studies in generalized social phobia compared with healthy subjects.[39]

Anxiety Disorder

Gur and colleagues compared cortical activity in two samples of normal volunteers. One group was studied with noninvasive Xe^{133} inhalation for measuring blood flow and the other with PET for measuring cerebral glucose metabolic rates. The inhalation technique produced less anxiety than the PET procedure, and for low-anxiety subjects there was a linear increase in cerebral blood flow with anxiety. The PET group manifested a linear decrease in cerebral glucose metabolism with increased anxiety.[40] Reivich et al. examined the effects of vigilance or attention on cerebral metabolism. There was significantly greater metabolism in the right versus the left parietal region in subjects attending to visual auditory tasks compared with subjects who were not. Anxiety appeared to produce significantly greater glucose utilization in the right hemisphere compared with the left in very anxious subjects.[41] Giordani et al. found no significant relationship between global or regional cortical metabolic rates and anxiety.[42] Gottschalk and colleagues found high correlation

TABLE I

REGIONAL CEREBRAL PERFUSION DIFFERENCES FOR SELECTED REGIONS OF INTEREST IN PTSD PATIENTS AND CONTROLS

Region of Interest	Mean ^{99m}Tc HMPAO Relative Perfusion Ratios: All Patients (N = 17)	Mean ^{99m}Tc HMPAO Relative Perfusion Ratios: Medication-Free Patients (N = 5)	Mean ^{99m}Tc HMPAO Relative Perfusion Ratios: Controls (N = 8)	All Patients vs. Controls: Kruskal-Wallis ANOVA by ranks [H (1, N = 25), p]	Medication-Free Patients vs. Controls: Kruskal-Wallis ANOVA by ranks [H (1, N = 13), p]
Right orbital cortex	0.650	0.688	0.579	NS	6.193
Right temporal pole	0.729	0.713	0.621	6.274	NS
Right midtemporal lobe	0.759	0.739	0.647	4.902	NS
Right midparietal lobe	0.770	0.767	0.688	3.925	NS
Right caudate/putamen	0.787	0.793	0.678	8.148	5.486
Left orbital cortex	0.664	0.663	0.568	4.900	NS
Left hippocampus	0.770	0.767	0.695	5.705	NS
Left caudate/putamen	0.778	0.850	0.720	NS	3.916
Bilateral anterior cingulate	0.832	0.853	0.674	6.875	5.486
Bilateral posterior cingulate	0.753	0.751	0.620	4.900	NS

HMPAO, hexamethyl propylene amine oxime; ANOVA, analysis of variance; NS, not significant.

between anxiety scores and increased local cerebral glucose metabolic rate in the paracentral and superior frontal regions in patients with anxiety dreams.[43]

Rauch et al. analyzed pooled PET data from three different anxiety disorders: obsessive-compulsive disorder, simple phobia, and PTSD. The data indicated activation in the right frontal cortex, right posterior medial orbital-frontal cortex, bilateral lenticulate nuclei, and brain stem bilaterally during symptomatic episodes versus the control state. A positive correlation was found between rCBF at one brain stem locus and subjective anxiety scores.[10]

Materials and Methods

Subjects

Seventeen male outpatients, ages 28 to 48 years (mean, 45.8 ± 16.4 years), served as voluntary subjects for this study. All subjects were engaged in group therapy for their symptoms of PTSD. All subjects scored 107 or above on the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder and met Diagnostic and Statistical Manual of Mental Disorders criteria for PTSD.[1,44] One subject had experienced PTSD symptoms since the Panama Canal Zone action of 1987; the remainder of the patients were Vietnam-era veterans. All subjects suffered from increased startle response, flashbacks, and recurrent nightmares as documented by examination and history. Chronic dysphoria was universally comorbid in this population, both historically and at the time of study.

Twelve of the 17 patients had not abused alcohol or drugs for at least 6 years before the time of the scan, and 5 had not ingested alcohol or drugs in the preceding 1 to 3 years. Before measurement of regional cerebral perfusion (rCP), a urine sample was collected for drug testing in both patient and volunteer populations. All drug screens were negative at the time of measurement. Seven of the patients were taking a selective serotonin reuptake inhibitor (SSRI), 5 were taking a tricyclic antidepressant (TCA), and 5 were not taking any medication. All PTSD subjects underwent computed tomography before the cerebral perfusion study to rule out any preexisting focal brain lesions.

Eight male volunteers, ages 35 to 40 years, with no history of psychiatric or medical disorders served as controls for the SPECT study. Control subjects were volunteers from the hospital staff and denied any historical or current use of alcohol, drugs, or psychotropic medications. This population was unmatched for previous exposure to trauma.

SPECT Procedure

Details of the imaging techniques have been reported.[45,46] Tracer injection was made in a quiet area under conditions of low levels of ambient light and sound. No external evidence of hyperarousal was noted in either group. SPECT brain images were obtained with ^{99m}Tc bound to hexamethyl propylene amine oxime after a 50-minute image-acquisition time using a high-resolution collimator and a single-head rotating gamma camera (Siemens). Acquisition was initiated 20 minutes after the injection of 25 mCi of ^{99m}Tc using a 14-cm radius of rotation.

After completion of the acquisition of the primary data sets, a thin ^{99m}Tc-filled plastic reference tube was placed along the orbital-meatal line and imaged. Transverse slices parallel to the orbital-meatal line were then obtained. These were transformed into coronal and sagittal projections. Both processes being performed with custom software developed for this facility. Slices of 0.6 cm were preprocessed using an image-dependent Metz filter and then reconstructed by a Kalman Gaussian Fourier filter back-projection technique. Attenuation correction was performed using the Chang method. Matching landmarks on thin SPECT images to tomographic anatomy identified well-defined areas of cortex and basal ganglia, with no overlap into other cortical areas. SPECT quantification was performed using ratios of uptake in well-defined areas normalized to the uptake in the cerebellum.

The mean uptake of the six highest-intensity pixels was used in each region of interest (ROI). ROI varied, depending on the structure being measured, from 10 to 30 pixels. The same experienced observer selected each ROI. Because gray matter has the highest activity in these images, the mean value of the six highest-intensity pixels within the ROI was used to represent the local gray matter. This was found to minimize the inclusion of sulci and other lower-activity areas in the ROI, as described previously. The statistical uncertainty of sampling only six pix-

TABLE II

FINDINGS BY IMAGING METHOD

Study in Chronologic Sequence	Methodology	Frontal Cortex	Temporal Cortex	Parietal Cortex	Hippocampus and parahippocampus	Caudate/ Putamen	Disorder
Garber, 1989[a]	MRI	No significant difference				No significant difference	OCD[b]
Fontaine, 1990	MRI		↓ Medial		↓ Right hippocampus		Panic
Potts, 1993	MRI					No significant difference	Phobia
Myslobodsky, 1995	MRI	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	PTSD
Bremner, 1995	MRI		No significant difference		↓ Right hippocampus	No significant difference	PTSD
Gurvits, 1996	MRI				↓ Left and right hippocampi		PTSD
Canive, 1997	MRI				↓ Right		PTSD
Freeman, 1998	MRI				↓ Right		PTSD
Rauch, 1998	MRI				↓ Left and right hippocampi		PTSD
Mountz, 1989	rCBF	No significant difference	No significant difference	No significant difference			Phobia
O'Carroll, 1993	SPECT		↓ Temporal				Phobic, relaxation tape
Schlegel, 1994	SPECT	↓ Bilateral	↓ Bilateral	↓ Bilateral			Panic disorder
Benkelfat, 1995[c]	rCBF		↑ Claustrum-insular-amygdala region				CCK_4-induced anxiety[d]
Fig, 1995	rCBF				↑ Parahippo-campal	↑ Left striatum	Panic
Fischer, 1996[e]	rCBF	↑ Left orbito-frontal ↓ Broca's area					Viewing video of robbery
Rauch, 1996[f]	rCBF	↓ Left inferior	↓ Middle temporal				PTSD/ traumatic audio tape
Stein, 1996	SPECT	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	Social phobia
Liberzon, 1997[g]	SPECT						PTSD
Shin, 1997[h]	rCBF	↑ Orbitofrontal ↓ Middle gyrus	↑ Anterior pole ↓ Anterior and middle gyri	↓ Inferior lobule			Response to visual imagery

[a] No significant difference in cingulate noted.
[b] Obsessive-compulsive disorder.
[c] Increase in cerebellar vermis and anterior cingulate.
[d] CCK_4, cholecystokinin-4.
[e] Increase in visual cortex and posterior cingulate, decrease in left operculum and angular gyrus.
[f] Also showed increases in right limbic, paralimbic, and visual areas.
[g] Altered ratio of cortical to subcortical perfusion during induced flashback; peak activity in the thalamus.
[h] Increase in ventroanterior cingulate gyrus and right amygdala, decrease in Broca's area.
[i] Increase in anterior and posterior cingulate noted.
[j] Increase in left amygdala, nucleus accumbens, and anterior cingulate.
[k] Glucose metabolism rate.
[l] Blood flow decreased with treatment using benzodiazepines.

TABLE II

CONTINUED

Study in Chronologic Sequence	Methodology	Frontal Cortex	Temporal Cortex	Parietal Cortex	Hippocampus and parahippocampus	Caudate/ Putamen	Disorder
Stein, 1997	rCBF				↓ Hippocampal		Child sexual victimization
Sachinvala, 1999[i]	SPECT	↑ Right orbital	↑ Right	↑ Right	↑ Left	↑ Bilateral	PTSD
Liberzon, 1999[j]	rCBF and SPECT	↑ Midfrontal gyrus					PTSD/auditory combat stimulus
Zubieta, 1999	rCBF	↑ Medial prefrontal					PTSD/auditory combat stimulus
Revich, 1984	GMR[k]	↑ Right	↑ Right	↑ Right			Anxiety
Baxter, 1988	GMR	↑ Left orbital				↑ Bilateral caudate	OCD
Giordani, 1990	GMR	No significant difference	No significant difference	No significant difference			Anxiety
Gottschalk, 1991	GMR	↑ Frontal					Anxiety
Wu, 1991[l]	GMR	↑ Frontal				↑ Caudate/ putamen	Lactate-induced panic
Volkow, 1992	GMR	↓ Right	↓ Right	↓ Left	↓ Right	↓ Right	Alcohol abusers
DeCristofaro, 1992	GMR	↑ Frontal			↓ Hippocampus	↑ Basal ganglia	Lactate-induced panic
Reiman, 1986	PET	↑ Frontal			↓ Left and right parahippocampal	↓ Basal ganglia	Panic
Gur, 1987	PET	↓ Linear	↓ Linear	↓ Linear	↓ Linear	↓ Linear	Anxiety
Semple, 1993	PET	↑ Orbital			↓ Hippocampus		PTSD with substance abuse
Kaschka, 1995	PET	↓ Frontal	↓ Temporal				Panic
Semple, 1996	PET	↓ Right frontal		↓ Right parietal			PTSD with substance abuse
Bremner, 1997	PET	↓ Prefrontal and orbitofrontal	↓ Temporal	↓ Parietal			During yohimbine-induced anxiety in PTSD
Rauch, 1997	PET	↑ Right and posterior medialorbito-frontal				↑ Bilateral lenticular and brainstem foci	PTSD, simple phobia, and OCD

els was minimized by the use of filtered images. This value (mean of six highest-intensity pixels) was then expressed as a fraction of the uptake measured in the cerebellum.

The mean cortex-to-cerebellum ratios by our technique range from 0.8 to 0.9 in normal subjects. The coefficient of variation among repeated determinations in the same subject was 5%. Perfusion was determined in each of the selected 18 ROIs (for each subject) in the transverse, coronal, and sagittal views.

Analysis of Patient Data

Statistical analyses of the rCP data were performed using the Kruskal-Wallis analysis of variance by ranks for all three groups.

Results

When we compared all PTSD patients with controls, we found statistically significant increases in rCP (referenced to the cerebellum) in the PTSD patient population. These increases were in the anterior and posterior cingulate regions bilaterally, the right temporal and parietal regions, the right caudate/putamen region, and the left orbital and hippocampal regions. The rCP was statistically significantly increased in the drug-free patient population compared with normal controls in the anterior cingulate gyrus, the right orbital region, and the right and left caudate/putamen regions. There appears to be a strong predilection for increased rCP in the right hemisphere in PTSD patients (Table I).

We also separated the population into four groups: (1) those taking a SSRI, (2) those taking a TCA, (3) those who were taking no drugs, and (4) normal controls. We found no significant differences in rCP in patients who were taking a TCA or a SSRI compared with drug-free patients, possibly because of the small number of patients in each group.

Discussion

In comparing the entire patient population with normal controls, we observed significant increases in regional brain perfusion in the right cortical areas of the orbital frontal, lateral frontal, and midparietal regions. Bilaterally, the caudate/putamen regions also exhibited increased perfusion. When we restricted our analysis to drug-free patients compared with our control population, we found that the anterior cingulate, the right orbital cortex, and the caudate/putamen remained statistically significantly different in perfusion. Neither SSRIs nor TCAs had a large enough influence on the rCP to be seen in the small subsets of the 17 PTSD patients. This is of interest because of the common clinical observation that patients may continue to be symptomatic despite medications. It may be that the agents used alter rCP in areas other than those selected ROIs. Our data demonstrate that patients with PTSD had an increase in cerebral blood flow primarily in the limbic structures and the basal ganglia, with involvement of right neocortical areas.

Conclusions

Studies of rCP or rCBF in PTSD patients are better understood when they are viewed in relation to other anxiety disorders that have been the focus of similar studies. rCBF has been studied in patients with obsessive-compulsive disorder, phobia, and panic disorder. A comparison of these findings is given in Table II.

Frontal changes, as demonstrated in our study, were also seen in 10 of 15 studies using functional imaging techniques, despite there being no changes in this region in any of the structural studies. Caudate/putamen changes, as seen in our study, have been seen in other studies reporting functional changes in this region. The substantial differences we observed between the drug-free and normal control populations is probably indicative of increased regional neuronal activity in PTSD patients. We may infer that increased cerebral perfusion will be associated with hyperactive emotional states when it is found in those brain regions classically associated with the regulation of emotion. More data must be collected, using more than one physiologic imaging technique, before we can determine if there are specific brain regions associated with changes in rCP in disorders that are not associated with demonstrable neuronal loss.

Despite the limitations of this study (carrying out the perfusion studies only under resting conditions, the lack of scaled subjective report of anxiety state during the SPECT study, the use of a limited number of pixels in each ROI, and the use of the cerebellum as the reference region), the findings are consistent with the existing knowledge of anxiety disorders.

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