Traumatology, Vol. 7, No. 4, 2001

Activation of Thalamo - Cortical Systems in Post-Traumatic Flashbacks: A Positron Emission Tomography Study

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Trauma victims with post-traumatic stress disorder (PTSD) often experience 'flashbacks' that are described as being different from memories of other fearful biographic situations. We used Positron Emission Tomography and Statistical Parametric Mapping to compare in the same subject brain activation patterns during induced flashbacks with recall of fearful non-traumatic situations. During fearful recall there were significant activations of right precuneus. When traumatic memories were compared to neutral, right lingual gyrus, right thalamus / mamillary bodies, and right cerebellum were significantly activated. When brain activation during flashbacks was compared to simple fear, right mediodorsal thalamus (MD), right precuneus, and right cerebellum were significantly more active. With respect to recent experimental evidence concerning the function of thalamo-cortical systems, we hypothesize that post-traumatic flashback experiences are based on hyperactive thalamo-cortical 'closed loop' networks.

KEY WORDS: Trauma, post-traumatic stress disorder, flashbacks, memories, Positron Emission Tomography, Statistical parametric Mapping, lingual gyrus, thalamus, medidorsal thalamus, cerebellum, thalamo-cortical networks.

Previous studies using symptom provocation and positron emission tomography in post-traumatic stress disorder (PTSD) patients have compared regional cerebral blood flow (rCBF) changes during provoked re-experiencing of the trauma with response to neutral stimuli. Increased cerebral blood flow was found in limbic and paralimbic structures, the anterior cingulate cortex, as well as amygdala (Rauch, van der Kolk, Fisler, Alpert, Orr, Savage, Fischman, Jenike, and Pitman 1996). However, exposure to script-driven imagery of childhood sexual abuse trauma was shown to activate the same paralimbic regions in individuals with and without PTSD (Shin, McNally,

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Kosslyn, Thompson, Rauch, Alpert, Metzger, Lasko, Orr, and Pitman 1999). It remained unclear whether the "feeling as if the traumatic event were recurring" or the "sense of reliving the experience" represent a specific pattern of brain activation or only an intense aversive emotional state.

We used 15-O-H2O-Positron Emission Tomography (PET) and Statistic Parametric Mapping to compare in the same individual brain activation during flashback episodes provoked by induced recollection of the traumatic event with activation due to imagery of another biographical situation in which intense fear had been felt but which had not been described as traumatic by the individual nor re-experienced as intrusively distressing memory. A third, neutral condition was also tested.

Subjects

Five male right-handed, neurologically and medically well train drivers (age, 38.6 ± 11.84 y) with no psychiatric history, who had accidentally run over suicidal persons as they pulled the train into a station participated in the study. All subjects fulfilled DSM-IV criteria for post-traumatic stress disorder and all suffered from nightmares, depressed feelings, and persistent re-visualizations of the trauma. All subjects were diagnosed according to DSM-IV using the SCID interview. Time period between trauma and PET was 12 ± 8.2 ms (range, 4 - 24 ms). After complete description of the study, written informed consent was obtained. The study was approved by the Ethics Commitee of the Medical Faculty of the University of Cologne. Psychotherapeutic help was offered to all participants who stayed in the outpatient department for a couple of hours after PET measurement. We used the German version of the Impact of Event Scale (Horowitz, Wilner, and Alvarez 1979;Maercker and Schützwohl 1998) to measure the extent of impact the traumatic event had on the subject. Following Zilberg (Zilberg, Weiss, and Horowitz 1982) and Maercker we did not calculate a sum score from the three subscales of the IES, but used the equation X= -.02 * Intrusion + .07 * Avoidance + .15 * Hyperarousal - 4.36. IES scores were 50.4 ± 2.70 (range, 47 - 54), adjusted using the equation, scores were .46 ± .428 (range, .12 - 1.16), respectively.

Methods

Positron Emission Tomography Statistics

PET scanning was performed using the 15-O-H2O technique described at length in the literature (Quarles, Mintun, Larson, Markham, MacLeod, and Raichle 1993) on a CTI / Siemens ECAT EXACT HR tomograph (Wienhard, Dahlbom, Eriksson, Michel, Bruckbauer, T, Pietrzyk, and Heiss 1994). Twelve subsequent scans were reconstructed. For data analysis, statistical parametric mapping (SPM 96) was used with standard parameter settings. Reconstructed PET images were realigned, spatially normalized to the Talairach coordinate system (Talairach J and Tournoux P 1988) using a 12 parameter affine transformation, followed by non-linear matching with 8 iterations, and smoothed with a 12 mm FWHM isotropic Gaussian filter. Regional activation effects were assessed using the general linear model (Friston KJ 2000) with pair-wise contrasts of all three conditions against each other. Regional effects were accepted as significant if the p value for the effect size (z) or cluster size (k) was < 0.05 (Friston, Holmes, Poline, Price, and Frith 1996) with correction for multiple comparisons.

Stimulation paradigm

Prior to PET procedures, during a series of talks with both main investigators (MH, TS), each individual was asked to give a detailed description of the traumatic event. A second situation from each person' s biography was determined in which he had felt intense fear but which had not left him in total helplessness or subsequently had been thought of as traumatic. Thirdly, an emotionally neutral situation was identified, which was controlled for the presence of complex visual stimuli, the presence of people and of human faces. The agreed-upon situations were then labeled with a keyword and the subjects were made familiar with the instructions given during the measurements. The emotional activation paradigm consisted of 3 tasks with 4 replications each. The order of the 12 tasks was not known to the subject and was chosen to minimize 'overlapping' of emotional states especially after inducing the flashbacks (AA BB CC - AA BB CC, A= neutral, B= fearful, C= traumatic). The presentation of the keyword associated with the respective autobiographic emotional situation started 10 sec. prior to tracer injection, reliving the situation was stopped by the investigator 45 sec. after injection. At the starting of each measurement the subject was asked to imagine the respective situation as vividly as possible and to try to feel the same way he had felt at that particular time in his life. During relaxation time after each scan, subjects made a rating of their emotions during scanning using the PANAS scale (Watson, Clark, and Tellegen 1988) for multiple affects (joy, sadness, anger, surprise, disgust and fear, 1-5) and on a "sameness" scale (1-10) for similarity of induced flashbacks compared to spontaneously occurring flashbacks. Heart rate during each condition was measured.

Results

All subjects rated the induced flashbacks during PET as very similar to their spontaneously occurring flashbacks ("sameness" 9.2 ± .84). Neutral situations on the PANAS scale were rated 1 ± .54 for each of the five tested emotions. Fearful non-traumatic recall was rated 1 ± .0 for joy and disgust, 1 ± .54 for sadness and anger, 2.4 ± .55 for surprise and 3.4 ± .55 for fear. Traumatic recall was rated 1.0 ± .0 for joy and sadness, 2.8 ± .84 for anger, 4.4 ± .89 for surprise, 2.8 ± 1.3 for disgust, and 5.0 ± .0 for fear. Heart rate differed significantly (p=0.026) between neutral (58.8 ± 3.36 bpm) and traumatic (74.1 ± 5.48) recall.

During fearful non-traumatic recollection as compared to neutral (Table 1), significant increases in rCBF were seen in the right precuneus. Activations in right parahippocampal gyrus, and right cingulate gyrus approached but did not reach significance.

When traumatic memories were compared to neutral memories (table 2) a cluster of regions was activated consisting of right lingual gyrus, right thalamus / mamillary bodies, and right cerebellum. Activations in cingulate areas on both sides approached significance. Desactivations were seen in left inferior parietal and bilateral middle temporal areas.

When induced flashbacks were compared to fearful non-traumatic biographical recall (table 3) we found significantly greater activations in right medial dorsal thalamus (MD), right precuneus, right cerebellum and left precentral gyrus (BA 4). Activations in right paracentral lobule, right precentral gyrus, and right postcentral gyrus did not reach significance. Significantly greater desactivations were found in right middle temporal cortex and left angular cortex.

Table 1. Representative areas of significant rCBF changes during fearful non-traumatic episodic retrieval relative to neutral

Structure	activation / desactivation	x	y	z	Z score
Right precuneus	activation	10	- 60	18	4.29

Note: Table 1-3: Regions are identified by name of structure according to the brain atlas of Talairach and Tournoux (Talairach J and Tournoux P 1988). x = distance [mm] to the right (+) or left (-) of midline, y = distance [mm] anterior (+) or posterior (-) to the anterior commissure, z = distance [mm] superior (+) or inferior (-) to a horizontal plane through the anterior and posterior commissures. Z scores are normalized t statistics reflecting the significance of the activation effect generated by the appropriate comparison using SPM. No. of Brodmann‘s area is given according to the Talairach brain atlas. Area No. without brackets = center of activation or desactivation lies in Brodmann‘s area. Area No. with brackets [] = center of activation or desactivation lies adjacent to or in immediate vicinity of Brodmann‘s area.

Table 2. Representative areas of significant rCBF changes during traumatic episodic retrieval relative to neutral

structure	activation / Desactivation	Brodmann‘s area	x	y	z
right lingual gyrus	activation	18	8	- 100	- 4
right thalamus / mamillary bodies	activation		8	- 18	2
right cerebellum	activation		16	- 56	- 16
left inferior parietal lobe	desactivation	[40]	- 46	- 56	44
left middle temporal gyrus	desactivation	21	- 64	- 42	- 10
right middle temporal gyrus	desactivation	21	60	4	- 18

Discussion

The areas that were statistically significantly activated during fearful recall have been implicated in episodic memory, the processing of emotions (Andreasen, O'Leary, Paradiso, Cizadlo, Arndt, Watkins, Ponto, and Hichwa 1999;Andreasen, O'Leary, Cizadlo, Arndt, Rezai, Watkins, Ponto, and Hichwa 1995), and phobic fear (Rauch, Savage, Alpert, Miguel, Baer, Breiter, Fischman, Manzo, Moretti, and Jenike 1995). Our findings concerning activations during induced flashbacks are in partial accordance with recent reports in the literature. Visual cortical activations have been described by Rauch et al. (Rauch, van der Kolk, Fisler, Alpert, Orr, Savage, Fischman, Jenike, and Pitman 1996), who also reported a right hemispheric preponderance in a study using script-driven imagery in PTSD patients. The lingual gyrus which is adjacent to the parahippocampal gyrus has been implicated in visual memory, memory for faces (Kapur, Friston, Young, Frith, and Frackowiak 1995) and arousal induced by emotional pictures (Lang, Bradley, Fitzsimmons, Cuthbert, Scott, JD, Moulder, and Nangia 1998). Activation of the thalamus / mamillary bodies may point to the role of the pituitary – adrenal and pituitary – thyroid axis in post-traumatic stress disorder as described in the literature (Bremner, Southwick, and Charney 1999).

When flashback induced activation was compared to activation due to fearful non-traumatic recall, we found significantly greater activations in a cluster of regions including right medial dorsal thalamus (MD), right precuneus, right cerebellum and left precentral gyrus (BA 4). Activations in right paracentral lobule, right precentral gyrus, and right postcentral gyrus did not reach significance. Significantly greater desactivations were found in right middle temporal cortex and left angular cortex. Some of these patterns have also been reported by Bremner et al. (Bremner, Staib, Kaloupek, Southwick, Soufer, and Charney 1999) in their study of Vietnam veterans who were exposed to combat pictures. They hypothesized that activation of the left precentral gyrus was possibly due to motor aspects of memory necessary for preparation of action of right-handed subjects during stress response. The implication of the cerebellum in tasks that require attention and episodic memory is well known from several other studies (Bremner, Staib, Kaloupek, Southwick, Soufer, and Charney 1999;Andreasen, O'Leary, Paradiso, Cizadlo, Arndt, Watkins, Ponto, and Hichwa 1999).

The main finding of our study, however, is the significantly greater activation of an ensemble of right hemispheric areas that consists of medial dorsal thalamus (MD), medial parietal association cortex (precuneus), together with right cerebellum in traumatic recall as compared to a condition of simple fear. The output of MD, a limbic thalamic nucleus, is directed to proisocortical prefrontal areas (BA 9, 10, 11, 12) and the frontal eye field (BA 8), while its input comes from the amygdala, other limbic areas (Krettek and Price 1977;Krettek and Price 1977) and multisensory association cortices (Creutzfeldt 1983;Jones 1981), hence this thalamic nucleus has long been thought of as the key gate structure for sensory, mainly visual, as well as limbic input to the prefrontal cortex. Lesions of MD have been reported to decrease emotional responsiveness as well as episodic memory function (Armstrong 1990). The precuneus, a multimodal cortical association area, has often been implicated in episodic memory retrieval (Krause, Schmidt, Mottaghy, Taylor, Halsband, Herzog, Tellmann, and Muller-Gartner 1999) and memory-related imagery (Fletcher, Frith, Baker, Shallice, Frackowiak, and Dolan 1995).

Recently, Llinas and co-workers (Llinas and Ribary 1994) reviewing evidence about the functional neuroanatomy of thalamocortical systems in dreaming states and wakefulness argued that the connectivity between thalamus and cortex is mainly bi-directional. They posit that conscious sensory experience is determined by the simultaneity of activity in the thalamocortical system. During wakefulness, it is stimulated by externally induced sensory input, during dream states by the activity of neuronal ensembles that support memories. In their view dream states are characterized by an increased attentiveness to an intrinsic state which is not or not much perturbed by external stimuli. This view of thalamocortical resonance representing a ‚closed intrinsic functional state' in which sensory input from outside cannot, address the machinery that generates conscious experience' (Llinas and Ribary 1994) seems to be particularly attractive for the understanding of the neuroanatomical basis for PTSD flashback re-visualizations. From a different viewpoint, based on another network model of emotional functioning posited by Lang (Lang 1985), Pitman and others (Pitman and Orr 1995) have conceptualized emotions in PTSD as pathological emotional networks that are activated by certain stimuli and have a heightened accessibility for spontaneous processing.

From our data we postulate that the ‚nightmare-like' feeling ‚as if the traumatic event is reoccurring' in PTSD, functionally represents hyperactive ‚closed loop' systems involving limbic thalamic nuclei and multimodal cortical association areas with consequent direction of the attention to internal imagination and temporary functional withdrawal from the external world. During flashback re-visualization these loops are significantly more activated than during the experience of simple fear.

A particularly interesting feature of MD is that its lateralmost sector plays an important role in gaze-control and control for saccades and eye following movements. Paralaminar cells of the MD sustain bidirectional communication with the frontal cortical eye fields (Shook, Schlag-Rey, and Schlag 1991). Eye-tracking abnormalities in schizophrenics have been linked to MD dysfunction (Scheibel 1997). In recent years, a new empirically validated therapeutic approach has widely been adopted by clinicians for treatment of PTSD flashbacks. It is called ‚Eye Movement Desensitization and Reprocessing' (EMDR) (Shapiro 1996) and makes use of induced rhythmic saccadic eye movements while the patient holds in mind salient aspects of a traumatic memory. This often leads to a dramatic relief, reduction of anxiety and cessation of the intrusions. The data presented here may give some hints as to the neuroanatomical correlate for EMDR. We hypothesize that EMDR, by externally stimulating the MD, temporarily interrupts the closed loop of thalamo-cortical 'flashback' hyperactivity and allows for some sensory input which then facilitates reorientation to reality for the subject.

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table 3

Representative areas of significant rCBF changes during traumatic episodic retrieval relative to fearful non-traumatic retrieval.

structure	activation / desactivation	Brodmann's area	x	y	z	Z score
right thalamus med dors nucl	activation		6	- 16	2	4.54
right cerebellum	activation		8	- 66	- 22	4.19
right precuneus	activation	19	28	- 81	40	4.44
left precentral gyrus	activation	4	- 34	- 20	58	4.54
right middle temporal gyrus	desactivation	[21]	52	2	- 16	5.16
left angular gyrus	desactivation	[39]	- 40	-64	32	4.61