Cerebral Blood Flow During Anxiety Provocation

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It has been suggested that traumatic reactions result from the failure to integrate the trauma with existing cognitive schemata, whereas phobias represent biologically influenced adaptation patterns. This implies that central nervous system (CNS) organization of traumatic reactions may differ from that of phobic reactions. In this article, we review our previously published work on anxiety and regional cerebral blood flow (rCBF). By using positron emission tomography and [^{15}O]-butanol, relative rCBF was determined in 14 subjects with simple animal phobias exposed to visual phobogenic stimuli and in 6 bank officials exposed to a video showing an armed bank robbery that they recently witnessed. Subjective and physiologic indices of fear and anxiety were elevated by the activation condition in both groups. Phobic stimulation elevated rCBF bilaterally in the secondary visual cortex compared with neutral stimulation but reduced rCBF in the hippocampus and in the prefrontal, orbitofrontal, temporopolar, and posterior cingulate cortex. Compared with neutral stimulation, video of a robbery increased rCBF bilaterally in the primary and secondary visual cortex, the posterior cingulate, and the left orbitofrontal cortex. Decreased rCBF was evident in Broca's area, the left angular gyrus, the left operculum, and the secondary somatosensory cortex. Hence, visually induced fear and anxiety are associated with alterations in limbic, paralimbic, and cortical brain regions that are of relevance for cognition and affect.
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Modern brain-imaging techniques, such as positron emission tomography (PET), allow the visualization of neural activity in cortical and subcortical areas during emotional and cognitive challenge.[1] PET has vastly broadened our knowledge of the central nervous system (CNS) correlates of thoughts and feelings. Well-controlled activation studies have more frequently evaluated cognition than emotions.[2] Thus, publications focusing on cognitive neuroscience outnumber those related to affective neuroscience.[2] The reasons for this are numerous and complex but are most likely related to the difficulties associated with achieving experimental control over emotional states because of the elusive and rapidly changing nature of human emotions. However, certain emotional states can be reliably induced with a degree of experimental control over a period that allows them to be studied with PET and brain blood-flow measures.[3,4] Two such emotional states are specific phobic reactions and reexperience of trauma after a stressful event. Phobias seem to be partly related to genetic factors,[5] whereas the reaction to reexperiencing trauma after a stressful event (e.g., a robbery) seems to be due to environmental rather than genetic factors. Even though affective reactions observed during the reexperience of a stressful traumatic event are similar to phobic reactions in terms of intense discomfort,[6] it has been suggested that traumatic reactions result from the failure to integrate the trauma with existing cognitive schemata,[7] whereas phobias represent biologically influenced adaptation patterns. This implies that CNS organization of traumatic reactions may differ from that of phobic reactions.

Studies were undertaken to examine CNS correlates of specific snake and spider phobias[8–10] and of reexperiencing a traumatic[15] event using PET and [^{15}O]-butanol to measure regional cerebral blood flow (rCBF). In addition, nonfearful individuals were exposed to videotapes of spiders and of neutral scenes (park setting) (M.F., H.F., G.W. 1997. Unpublished data).

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Theories of emotion share common unifying themes. Emotions may be viewed as biologically based Darwinian-shaped patterns of adaptation that are associated with a subjective feeling state, a behavioral action propensity, and autonomic nervous system alterations; in other words, emotions have subjective, behavioral, and bodily components. Therefore, in addition to selecting biologically meaningful stimuli to elicit an emotion, we have measured subjective and autonomic nervous system components to confirm the emotional state. Because the PET technique severely restricts behavioral activity, we have not included measures of overt behavior.

METHOD

Aversive and neutral videotapes were displayed without sound on a 21-inch monitor located approximately 1 m in front of the fixated subjects and 0.5 m above eye level with the order of presentation counterbalanced between subjects. All animal phobics (6 snake phobics and 8 spider phobics) fulfilled DSM-III/IV criteria[6] for simple/specific phobia and were exposed to visual phobogenic material. Six bank officials who had recently witnessed an armed bank robbery viewed a videotape of the event that was obtained from their security system. None fulfilled the DSM-IV criteria[6] for posttraumatic stress disorder (PTSD), but all fulfilled at least one criterion. Both groups had a neutral control condition that was similar in basic sensory properties, such as color, intensity of light, and movements. Eight nonfearful individuals were recruited in a manner that was identical to the recruitment of the phobics,[8–10] but they all were in the lowest tenth percentile of spider fear as measured with a spider fearfulness questionnaire.[11] The nonfearful individuals were shown a spider video and a neutral video (park scenes). After each scan, anxiety was verbally rated using all 20 items (range, 1–4) from the state portion of the State-Trait Anxiety Inventory[12] as well as Subjective Units of Distress, ranging from 0 (no) to 100 (maximum).[8–10]

An eight-ring PET scanner (Scanditronix PC2048-15B) was used.[13] The scanner produces 15 slices with 6.5-mm slice spacing. The transaxial image resolution was 5 mm, while the axial resolution was 6 mm at full width at half maximum. The axial field of view was 10 cm. All subjects first had a transmission scan, which was used for making attenuation corrections. Within 30 seconds after the beginning of each videotape and immediately before each PET scan, approximately 25 mCi (925 MBq) of [^{15}O]-butanol was administered to the subjects. A functional blood-flow image was determined for each individual by summing uptake data covering 100 seconds. Anatomic normalization of all individual rCBF images into a standard brain shape was performed using the Greitz computerized brain atlas.[14] Adaptation to the Greitz brain atlas was performed manually on each individual PET image. A region-of-interest (ROI) approach was used to identify significantly activated areas in the studies on animal phobia.[8–10] The present approach reflects increasing methodologic sophistication. A subtractive image approach was used in the trauma experiment[15] and in the control study with nonfearful individuals. Electrodermal activity was recorded with a Hagfors-type constant voltage circuit, with isotonic electrode paste serving as the electrolyte (0.5% NaCl/100 mL H_2O) through Beckman-Offner Ag/AgCl electrodes.[16] Electrodermal activity and a continuous electrocardiogram were recorded on paper using a Siemens-Elema Mingograph. Skin conductance fluctuations exceeding 0.05 μSiemens were estimated during the exposure period and were expressed in nonspecific fluctuations per minute. Heart rate was expressed in beats per minute. Further details of these studies are outlined elsewhere.[8–10,15]

RESULTS AND COMMENTS

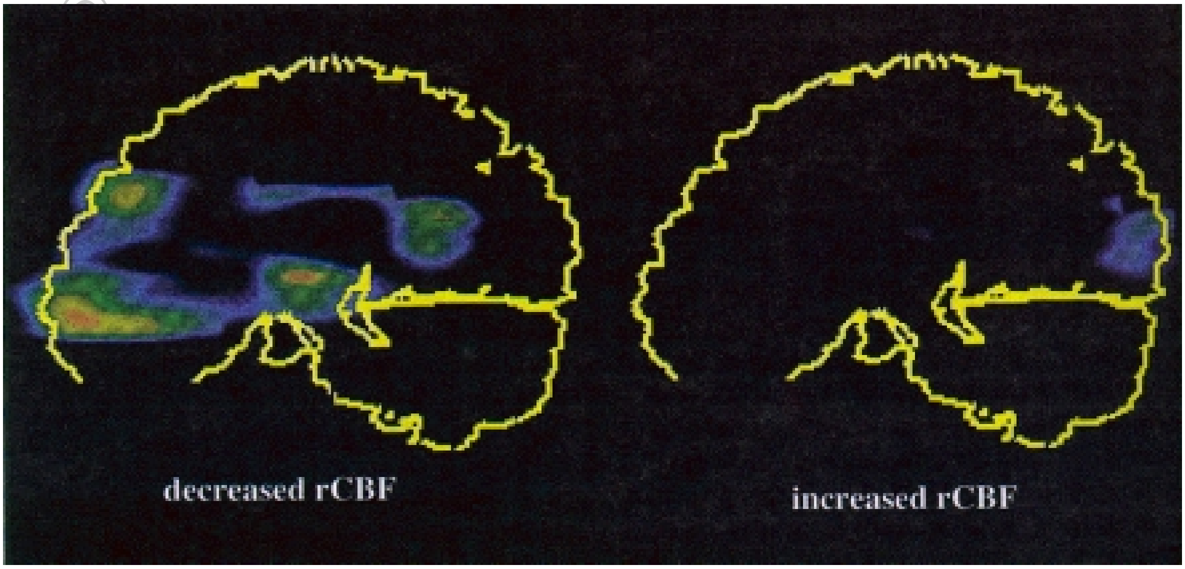
Snake and spider phobics displayed highly similar rCBF patterns during the phobic condition compared with the neutral condition.[9,10] During phobic provocation, rCBF increased in the secondary (Brodmann's areas 18 and 19) but not in the primary (area 17) visual cortex, and rCBF reductions were observed in the hippocampus and in the prefrontal (areas 9, 10, and 46), orbitofrontal (areas 11 and 12), temporopolar (anterior 20, 21, and 38), and posterior cingulate cortex (area 23) but not in the amygdala, hypothalamus, or the anterior cingulate cortex (areas 24 and 33) (Figure 1). Because both snake and spider phobics display the defense reaction when they are confronted with their phobic objects (Table 1),[4,17] we believe that the current findings demonstrate the functional neuroanatomy of the visually elicited defense reaction.

To study whether rCBF differed after viewing of the spider video compared with the neutral video, we subjected 8 nonfearful subjects to the same protocol previously used in phobics. Ratings and physiologic measures confirmed that the nonfearful group responded to the spider video and to the neutral video scenes in an emotionally similar manner (Table 2).

Subtractive image methodology did not reveal significant rCBF differences between the two conditions. This supports the theory that rCBF alterations in spider phobics during phobic fear are associated with anxiety-related emotional processes rather than with stimulus-related perceptual factors.[18,19] We have suggested that the functional correlate of the increased activity in the visual associative cortex reflects externally directed vigilance functions in fear.[8] Generalized anxiety disorder is characterized by increased neural activity in the visual cortex, which is normalized after benzodiazepine treatment,[20] and patients with obsessive-compulsive disorder show increased activity in the visual cortex.[21] This suggests that hypervigilance associated with various anxiety states is correlated with

Figure 1. Subtraction PET Image Illustrating Decreased and Increased rCBF in 14 Subjects During Visual Phobogenic as Compared With Neutral Stimulation*

Specific Phobics



*Based on combined data from references 9 and 10. The left sagittal image displays deactivation in the pre- and orbitofrontal cortex as well as in the posterior gyrus cinguli. The right sagittal image displays activation in the secondary visual cortex.

Table 1. Mean (SD) State Anxiety Ratings (range, 20–80), Subjective Units of Distress (range, 0–100), Heart Rate, and Nonspecific Electrodermal Fluctuations During Phobic and Neutral Visual Stimulation in 6 Snake Phobics and 8 Spider Phobics*

Rating	Phobic Condition	Neutral Condition	p Value
State anxiety ratings	61.8 (7.2)	37.1 (12.7)	< .0001
Subjective units of distress	69.0 (24.1)	11.6 (19.0)	< .0001
Heart rate (bpm)	74.6 (14.8)	65.8 (10.0)	< .01
Nonspecific electrodermal fluctuations (per min)	5.3 (3.2)	2.5 (2.6)	< .001

*Data from references 8–10. p Values indicate the difference based on repeated univariate analysis of variance.

Table 2. Mean (SD) State Anxiety Ratings (range, 20–80), Subjective Units of Distress (range, 0–100), Heart Rate, and Nonspecific Electrodermal Fluctuations to Videotapes of Spiders and Park Scenes in 8 Subjects Selected to Be Nonfearful of Spiders*

Rating	Spider Condition	Neutral Condition	p Value
State anxiety ratings	29.8 (3.1)	32.0 (6.1)	NS
Subjective units of distress	2.4 (2.9)	3.0 (3.1)	NS
Heart rate (bpm)	71.9 (10.3)	72.1 (9.9)	NS
Nonspecific electrodermal fluctuations (per min)	0.9 (1.0)	1.3 (1.7)	NS

*Data not published previously. p Values indicate the difference based on repeated univariate analysis of variance. Abbreviation: NS = not significant.

increased neural activity in the visual cortex. Moreover, Stewart and coworkers[22] demonstrated increased rCBF in the visual cortex during lactate-induced panic attacks. Thus, the increased neuronal activity in the secondary visual cortex seems to reflect fear and anxiety, at least in part. A study by Rauch and coworkers[23] demonstrated that in subjects with specific phobias increased neuronal activity may be linked to the sensory system stimulated; they used tactile stimulation to induce fear in subjects with specific phobias and observed increased activity in the somatosensory cortex.

The reduced neuronal activity observed in the paralimbic and limbic cortex may reflect reduced cognitive processing during the cerebral response that is associated with the defense reaction.[9] Because the hippocampus seems to form part of the behavioral inhibition system,[24] the relative rCBF reductions in limbic areas may be functionally associated with the behavioral inhibition system.[24] Decreased activity in the hippocampus should then be associated with less inhibition and would serve to support the defense reaction in preparing for the behavioral reaction, i.e., the fight/flight response. Reduced activation in the prefrontal cortex is probably associated with reduced cognitive processing[25] and may preserve fear since lesions in the prefrontal cortex in animal models result in retarded extinction of fear.[26]

It should be noted that the areas in which we observed decreased rCBF as a function of phobic fear receive afferent fibers from primary and, in particular, secondary sensory areas. It was speculated that the secondary visual cor-

Table 3. Mean (SD) Relative rCBF in the Secondary Visual Cortex (Brodmann's Areas 18 and 19) to Phobogenic and Neutral Visual Stimulation in Individuals Reporting the Presence or Absence of a Family History of Specific Animal Phobia (FH^+ and FH^-, respectively)*

Family History	Phobogenic Condition	Neutral Condition
FH^+	99.1 (7.4)	90.8 (11.4)
FH^-	93.0 (10.4)	92.0 (10.2)

*Data from references 9 and 10. The interaction between family history and stimulation condition was significant ($F = 9.53$; $df = 1.12$, $p < .01$).

Table 4. Mean (SD) State Anxiety Ratings (range, 20–80), Subjective Units of Distress (range, 0–100), Heart Rate, and Nonspecific Electrodermal Fluctuations in Individuals Reporting the Presence or Absence of a Family History of Specific Animal Phobia (FH^+ and FH^-, respectively)*

Rating	FH^+	FH^-	p Value
State anxiety ratings	64.2 (8.6)	59.4 (5.0)	NS
Subjective units of distress	61.8 (27.5)	69.9 (22.3)	NS
Heart rate (bpm)	77.7 (20.0)	71.6 (7.1)	NS
Nonspecific electrodermal fluctuations (per min)	5.6 (3.0)	4.8 (3.6)	NS

*Data from references 8–10. p Values indicate the difference based on repeated univariate analysis of variance. Abbreviation: NS = not significant.

tex may exercise control over the limbic and paralimbic cortex during the visually elicited defense reaction. The reduction of rCBF in orbitofrontal and temporopolar cortex may reflect the unreasonable nature of phobia manifested in the loss of voluntary control over fear. Findings from our studies indicate that the CNS underpinnings of snake and spider phobias are very similar.[9,10] It is not clear whether this simply reflects the similarities of those syndromes, the impact of environmental factors (indicating that phobia is learned), or hereditary factors (reflecting genetic influences). However, combined data on brain blood flow, [9,10] when related to parental history of the same specific phobia and to aversive learning experiences, indicate that parental history rather than learning-related experiences tends to account for part of the variance in rCBF in the secondary visual cortex (Table 3). Subjective ratings and physiologic responses did not differ as a function of family history (Table 4), making it unlikely that differences in rCBF only mirror differences in the level of fear, suggesting a heredity component.

To study the effect of emotionally relevant environmental impact, we investigated the effects of reexperience of a robbery on rCBF as compared with a neutral control condition.[15] Subjective and physiologic measures demonstrated that fear and anxiety were elicited during the reexperience of a robbery but not during the control condition (Table 5).

Compared with the control condition, viewing the armed robbery elevated rCBF in two clusters. One cluster was located bilaterally in the posterior gyrus cinguli (Brodmann's areas 23 and 31), the primary visual cortex

Table 5. Mean (SD) State Anxiety Ratings (range, 20–80), Subjective Units of Distress (range, 0–100), Heart Rate, and Nonspecific Electrodermal Fluctuations During Visual Reexperience of a Robbery as Compared With a Neutral Condition*

Rating	Stressful Condition	Neutral Condition	p Value
State anxiety ratings	52.2 (8.9)	39.4 (14.4)	< .05
Subjective units of distress	94.6 (47.3)	16.3 (8.6)	< .01
Heart rate (bpm)	67.2 (5.7)	62.3 (5.6)	< .05
Nonspecific electrodermal fluctuations (per min)	2.6 (1.6)	0.5 (0.2)	< .05

*Data from reference 15. p Values indicate the difference based on repeated analysis of variance.

(area 17), and the secondary visual cortex (areas 18 and 19). The other cluster was located in the left orbitofrontal cortex (areas 10 and 12). Decreased rCBF was found in a cluster in the left hemisphere in Broca's area (area 44), the secondary somatosensory cortex (area 43), operculum (area 50), and angular gyrus (area 40) (Figure 2).

Because the videotapes were visually similar and displayed moving objects, the main results are not likely to be attributed to differences in visual complexity or artifacts of eye movements or fixation.[18,19] Hence, the differences in rCBF related to reexperience of trauma seem to reflect stress-related emotions rather than stimulus-related perceptions. Furthermore, a recent study using verbal scripts to induce fear and anxiety in patients with PTSD reported a similar flow distribution pattern, with decreased activity in language processing areas and increased activity in the secondary visual cortex.[27] In comparing PTSD patients with normal controls, Bremner and coworkers[28] found decreased glucose metabolism in the temporal cortex in those with PTSD during the resting state. They speculated that this may account for the failure to extinguish trauma reactions.

The decrease in neural activity observed in areas related to speech, hearing, and somatosensory processing, on the one hand, and the increased activity of the visual and memory system, on the other, may be associated with resource allocation from an unstimulated to a stimulated sensory modality[10,29,30] and may facilitate the processing of signals with perceptual and behavioral significance[30]; it may also signify the dissociative nature of trauma reexperience.[7,28] If both accounts are correct, gating appears to be nonadaptive.

Neural activity in the occipital region suggests increased vigilance[9] activated by reminders of trauma.[31] Posterior cingulate activation indicates the retrieval of trauma-associated episodic memories,[32] and orbitofrontal activation is likely to mark the emotional nature of the reaction.[33] Increased neural activity in the orbitofrontal cortex during anxiety has been proposed to facilitate the initiation and direction of attention for behavioral action.[32] Activity in the left-sided cluster, with its maximum in the

Figure 2. Subtraction PET Image Illustrating Decreased and Increased rCBF in 6 Subjects During Visual Reexperience of a Robbery Compared With Neutral Stimulation*

Robbery Victims

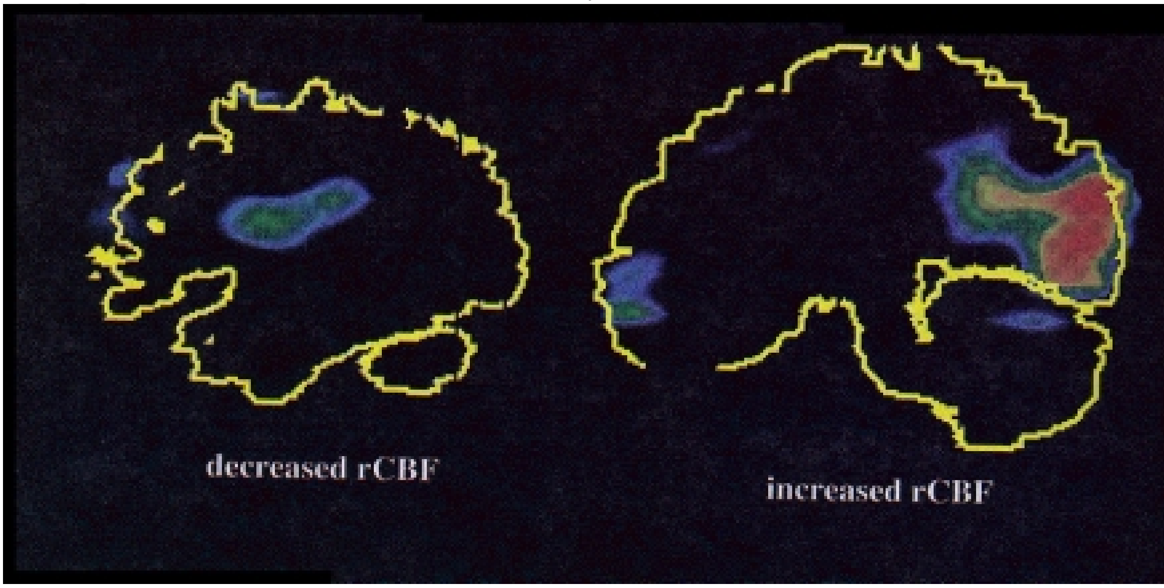


*Figure based on data from reference 15. The left sagittal image displays deactivation in a cluster consisting of Broca's area, the left operculum, the left somatosensory cortex (SII), and the angular gyrus (not in picture). The right sagittal image displays activation in two clusters, the first in the orbitofrontal cortex and the second in the posterior gyrus cinguli and the visual cortex.

left orbitofrontal cortex, is consistent with the suggestion that left prefrontal brain activity inhibits negative affect.[2] Data from our study[15] indicate that the primary inhibitory area may be the paralimbic cortex. It may be argued that there was less emotional inhibition in the subjects with specific phobias,[9,10] who actually lost emotional control, than in the robbery victims and therefore decreased orbitofrontal activity in the phobics. However, quantitative as well as qualitative aspects of anxiety may account for differences in orbitofrontal neural activity. For example, other rCBF activation studies in simple phobics[23,30,33,34,35] used exposure paradigms that included imagined or concealed rather than real phobic objects and reported enhanced orbitofrontal activity.[23] Imaging procedures seem to be driven by memory rather than by perceptions, and this may indicate that the orbitofrontal cortex is involved in the retrieval of emotional memories. It is likely that memory activation also occurs in robbery victims, but no firm conclusion could be drawn regarding whether quantitative or qualitative differences account for differences in orbitofrontal neural activity. Furthermore, the present paradigms do not address the question of whether the activation of the secondary visual cortex reflects unspecific visual arousal processes or specific mechanisms related to phobic anxiety and to the reexperience of a traumatic event.

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