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Effect of worry on regional cerebral blood flow in nonanxious subjects

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Abstract

Several studies suggest that cognitive tasks attenuate activation of the limbic system by emotional stimuli. We investigated the possibility that worry would similarly inhibit the limbic system by examining its effects on regional cerebral blood flow (rCBF). Ten nonanxious volunteers underwent four scans within one session, using positron emission tomography (PET) with $H_2^{15}O$ as tracer. The first two scans recorded emotionally neutral thinking induced after listening to tapes describing neutral statements. Preceding the third and fourth scans, subjects listened to the self-recorded tape describing their individual worries, were instructed to continue to worry, and were scanned 5 min later. Subjects rated themselves as more anxious during the worry scans but showed no significant heart interbeat or skin conductance changes. During worry, rCBF increases were found bilaterally in the medial fronto-orbital gyri and the right thalamus; rCBF decreases were found bilaterally in the hippocampi and amygdalae, in the right insula, the left and right inferior, middle and superior temporal gyri and the occipito-temporal gyri, the right inferior occipital gyrus and the left supramarginal gyrus. Activity of the left orbito-frontal gyrus was negatively correlated with activity of the amygdalae. The results support the hypothesis that worry-induced prefrontal activity suppresses affect-related subcortical regions.

Keywords: Worry; Anxiety; Normal subjects; Positron emission tomography; rCBF; Autonomic responses

1. Introduction

Worries have been described as repetitive, relatively uncontrollable thoughts and images that emerge when a person faces a potential threat (Beck et al., 1987). Being future oriented, worries of low intensity (Hoyer et al., 2002) prepare an individual for a stressful situation by encouraging the development of coping strategies (O'Neill, 1985; Segerstrom et al., 2003); however, in the presence of heightened anxiety, for instance, in generalized anxiety disorder, worry becomes a frustrating attempt to find an answer to situations for which no easy solutions exist (Borkovec, 1994) or, when the outcome appears to be beyond

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one's control, leads to unpleasant repetitive thoughts (O'Neill, 1985). Under such circumstances, worries become uncontrollable, excessive and maladaptive (Barlow, 1988; Hoyer et al., 2002).

O'Neil (1985) regarded worry to be the cognitive expression of anxiety. Wells and Papageorgiou (1995) conceptualized worry as a cognitive strategy for dealing with threats that can become problematic and subjectively uncontrollable when it is used to distract from emotional processing of other thoughts. Borkovec (1994) proposed that worry is a predominantly verbal activity that allows individuals to avoid the intrusion of more arousing material such as fear-related images. Vrana et al. (1986) found that, compared with imagery, verbal articulation of the same emotional material induces milder emotional and cardiovascular responses. Thus, worry increases anxiety, but the verbal nature of worry largely limits conscious accessibility of parallel-processed images and, when occasional catastrophic images do enter awareness, they are less vivid, intrusive, attention-grabbing, and emotionally distressing. By worrying, a person avoids more distressing anxiety-related images and their associated heightened autonomic responses (Borkovec, 1994; Borkovec et al., 2004; Borkovec and Hu, 1990). However, while worries successfully define negative events, they are ineffective in generalizing successful solutions or in generating effective coping mechanisms (Borkovec, 1985). Therefore, worries, when associated with high anxiety, do not permit the working through of anxiety-evoking situations and may contribute to the maintenance of anxiety (Borkovec et al., 2004; Wells and Papageorgiou, 1995).

Imaging studies of anxiety in healthy volunteers have produced variable results due to differences in experimental paradigm and instructions (Liotti et al., 2000). Anticipatory anxiety, imaged after the administration of randomly applied electric shocks, activated both insulae and the anterior cingulate but not the amygdala (Chua et al., 1999), while anticipation of a shock that was never given activated the amygdala (Phelps et al., 2001). Classical fear conditioning led to initial activation but, subsequently, to a gradual decrease of response in the amygdala (Büchel and Dolan, 2000). Cognitive evaluation of threatening visual stimuli increased the response of right prefrontal cortex and the anterior cingulate but attenuated the response of the amygdala (Hariri et al., 2003). Thus, cerebral responses to anxiety vary depending on the novelty of the threat, contextual memories, interoceptive sensory information, ambiguity of the situation, and cognitive elaborations.

None of the above studies examined the effect of personal worries on brain activity. Using functional magnetic resonance imaging (fMRI) in normal subjects, we found that listening to brief repetitive statements that described a personal worry, when compared with listening to neutral statements, induced greater changes in the left inferior frontal gyrus, the left globus pallidus, and the anterior and posterior cingulate but not in the amygdala (Hoehn-Saric and Schlund, 2003). However, subjects had difficulties engaging in undisturbed worry because of the noisy environment of the MRI scanner and the repetitious nature of the stimulus. As Drevets and Raichle (1998) stated, the immediate impact of potential threat may differ from the manifestations caused by subsequent cognitive elaboration.

In studies of worry, it is important to define the study population. Manifestations of worry, their intensity, controllability and content vary in normal populations that are exposed to different stressors (Hoyer et al., 2002; Andrews and Borkovec, 1988; Fresco et al., 2002; Segerstrom et al., 2000, 2003) and differ in patients with anxiety disorders (Borkovec and Inz, 1990; Hoyer et al., 2002; Segerstrom et al., 2000). Experimental settings influence worries and their effects on autonomic responses. For instance, in one study the induction of worry after reflecting on statements written on index cards led to anxiety and increased heart rate (York et al., 1987), while in another study, freely chosen worries did not (Borkovec et al., 1993). Also, for the assessment of induced worries their time course is important, as induced worry tends to increase in intensity over the first 15 min and to decline subsequently (Borkovec, 1994).

The aim of this study was to extend our understanding of the effects of worry, induced as closely as possible in its natural mode (i.e., relatively undisturbed and prolonged) on regional cerebral blood flow (rCBF) in nonanxious individuals who express worries that may be encountered in everyday life. Using positron emission tomography [PET] with $H_2^{15}O$ as tracer, we exposed normal subjects to self-recorded statements of their principal worry, instructed them to continue to worry after termination of the recording and scanned them after 5 min of undisturbed worry.

2. Methods

2.1. Subjects

Subjects were 10 nonanxious paid volunteers, recruited by newspaper advertisements. They were told that the purpose of the study was to explore the effect of a personal worry on the blood flow of the brain in persons who have no psychiatric problems. Five of the subjects were female, six were Caucasian, two were African-American and two were Asian Indian. Their mean age was 34 (20 to 40) years, and their mean educational level was 15.5 (12 to 18) years. All were right-handed according to the Edinburgh Inventory of Handedness (Oldfield, 1971). They were free of past or present psychiatric disorders, as confirmed by an interview using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1997). They also scored below 37 on the Spielberger State Trait Anxiety Inventory (STAI), Trait Form (Spielberger et al., 1970). They were in good physical health and had not used drugs affecting the central or autonomic nervous systems for at least 2 weeks. All subjects expressed a legitimate worry, such as having a close relative suffering from cancer, being a graduate student with insufficient funds to finish studies or living in a crime-ridden section of the town without means to move to a better environment. Thus, it was possible that the presented worries could be resolved in the future either through action or adaptation. Subjects signed an informed consent form approved by the university's Joint Committee for Clinical Investigations.

2.2. Measures

2.2.1. Initial evaluation

Initial measures included the following: SCID, STAI Trait Form, and Edinburgh Handedness Scale. In addition, the presence of past and present physical illnesses, as well as drug use, was systematically evaluated, and urine toxicology screens were carried out.

2.2.2. Measures during scanning

Subjective measures included the STAI State Form, concise version, consisting of the five items with the highest item-remainder correlations in the STAI normative sample (O'Neil, 1972), bipolar scales for Anxiety and Pleasantness, ranging from −5 (extremely anxious or unpleasant) to +5 (extremely relaxed or pleasant); Present State Rating Scale (PSRS), a custom-constructed self-rating scale of which six items described physical symptoms (sweating, palpitations or heart beating fast, difficulties breathing normally, feelings of sickness or nausea, shaking or trembling and muscle tension) and six described psychic symptoms (psychic tension, anxiety, irritability, depressed mood, drowsiness and mental slowness); items were each rated for severity from 0 to 10. After each scan, subjects rated the degree to which they had been able to keep their minds on the topics (from 1=not at all to 6=completely). They also rated whether they had been thinking in images; if so, they rated how often (from 0=not at all to 5=all the time) and how clear the images were (from 0=no image to 5=sharp with details).

2.2.3. Physiological measures

Skin conductance and cardiac interbeat interval were measured using an earlier described ambulatory monitor (Thakor et al., 1989).

2.3. Procedure

Subjects were prescreened by telephone. They were also asked to write down present worries on one page. Then they were screened for level of trait anxiety using the STAI and handedness using the Edinburgh Handedness Scale. They were interviewed by a psychiatrist for past and present physical illness and mental disorders using the SCID. Subjects had to be free of past or present mental illness in themselves and immediate relatives, in good health and not using any drugs. After signing the consent form, subjects were asked to make a 2-min tape of their principal worry, speaking in the first person as if they were worrying aloud by themselves, avoiding a descriptive mode. An appointment was then given to fit a mask and for the MRI.

The PET scans were conducted on a separate day. A 10-min transmission scan was performed before the emission scans and was immediately followed by four blood flow measurements: two scans which followed a recording of neutral content and two scans which

followed recordings of a subject's personal worry. For each CBF measurement, 75 mCi of $H_2^{15}O$ was injected as an intravenous bolus, and a dynamic PET emission scan was performed for 5 min using a GE 4096 Plus system (15 rings, *z*-axis of 96 mm, average axial resolution of 6.0 mm FWHM). The dynamic scan mode consisted of 41 frames (24×5s, 5×8s, 8×10s and 4×5s). The interval between $H_2^{15}O$ injections was approximately 15 min (half-life of ^{15}O is 2 min). PET data were reconstructed with 6 mm filter width (Hanning).

Subjects came to the laboratory at 7 AM and had an arterial line inserted in a radial artery by an anesthesiologist and a saline drip was inserted into a vein. Electrodes were placed on the chest for cardiac monitoring and on the index and middle fingers of the nondominant hand for skin conductance. Then subjects were placed in the scanner and baseline subjective ratings were obtained. After the transmission scan, subjects were reminded that they would hear a 2-min neutral tape, a paragraph from the Encyclopedia Britannica describing flower arrangement or a flower auction, and that they should continue to think about what they have heard until the scan was finished. The content of the neural tapes was the same for all subjects but the recordings for men were in a male and for women in a female voice. Then the tape was played for 2 min, immediately after which the ambulatory monitor and blood samplers and scanner were activated. After the 5-min scan, subjective ratings were obtained. The second neutral scan proceeded the same way. Before the third and fourth, the worry scans, subjects were told to worry as much as they could after listening to their prerecorded worry tape. They were also told that in order to give them time to fully engage in the worry, the scan would start 5 min after the tape stopped. Then subjects listened to their worry tapes. The scans were started 5 min after the termination of the tape. The two neutral scans always preceded the worry scans to assure that the effect of worry would not extend and influence the neutral scans.

2.4. Data analysis

PET data were analyzed using SPM 99 (Statistical Parametric Mapping 99, Institute of Neurology, University College of London, UK), implemented using Matlab (Mathworks Inc., USA) (Friston et al.,1995a,b). Before statistical analysis, head motion correction and spatial normalization to brain templates were performed. Head motion corrections were made using rigid body transformation. Mean images of four scans were spatially normalized to the Montreal Neurological Institute (MNI) PET template, and normalization parameters were reapplied to each PET image to remove intersubject anatomical variability (Friston et al., 1995b). Affine transformations were performed to determine the 12 optimal parameters to register the brain onto the template. Small differences between the transformed image and the template were removed using the elastic deformation method. The deformation was controlled so that it consisted of a linear combination of predefined smooth basis functions used in discrete cosine transformation. Spatially normalized images were smoothed by convolution, using an isotropic Gaussian kernel with 16-mm FWHM. The aims of smoothing were to increase the signal-to-noise ratio and to account for the subtle variations in anatomical structures. After subject-specific analysis of covariance (ANCOVA) normalization, a voxel-by-voxel comparison between neutral and worry scans was performed. A critical threshold of $P < 0.005$ and at last 100 contiguous $2 \times 2 \times 2$ mm voxels in the cluster were used to find significant differences. A probabilistic brain atlas for the MNI template was referred to for the anatomical labeling of the coordinates of the local maxima of each significant cluster (Evans et al., 1996; Kang et al., 2001). Self-report measures and physiological measures were analyzed using analysis of variance (ANOVA) for repeated measures, followed by two-tailed *t*-tests when appropriate. Physiological recordings were averaged for the first 3 min of each scan.

3. Results

3.1. Subjective and physiological changes during worrying

Fig. 1 shows self-ratings of subjects before the first scan and for worry and neutral statements while being scanned. Subjects were asked to rate themselves according to the way they felt during the scan.

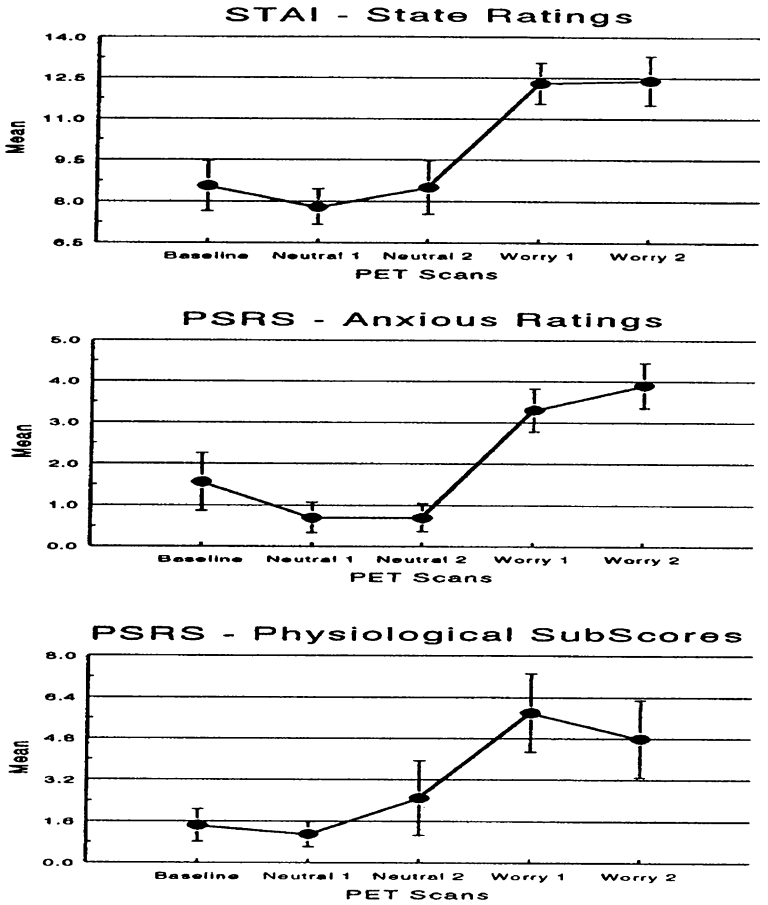

Fig. 1. Self-ratings of anxiety, state trait anxiety inventory, concise state scale (STAI), present state rating scale (PSRS) anxiety rating, and combined physiological symptoms subscore; at baselines and, retrospectively, after 2 Neutral and 2 Worry scans.

Analysis of variance with repetitive measures was performed on the five conditions (Baseline, Neutral scan 1, Neutral scan 2, Worry scan 1, Worry scan 2). Significant differences from baseline were found for both worry conditions but not for neutral conditions. Sustained decreases in pleasantness on the Analogue scale were found during the worry condition [$F(4/36)=16.14$, $P<0.001$] and increases were found during worry on the PSRS items of psychic tension [$F(4/36)=7.16$, $P<0.001$], anxiety [$F(4/36)=10.8$, $P<0.001$], irritability [$F(4/36)=8.88$, $P<0.001$] and depressed mood [$F(4/36)=3.98$, $P<0.009$) and on the STAI concise State form ($F(4/36)=9.10$, $P<0.001$]. The highest mean ratings of anxiety (3.9 ± 1.7) on the PSRS were approximately one and a half times, and twice as high, respectively, as the highest mean ratings of psychic tension (2.6 ± 2.1; $t=2.41$, $P<0.04$) or irritability (1.9 ± 1.9; $t=5.1$, $P<0.001$) and more than three times that of the depressed mood item (1.1 ± 1.73; $t=3.93$, $P<0.003$). The combined physical symptoms score of the PSRS [$F(4/36)=4.13$, $P<0.007$] increased during worry, mainly due to increased muscle tension, the only individual item that reached statistical significance [$F(4/36)=4.09$, $P<0.008$]. Most subjects were able to keep their minds on the topic, with mean ratings of 5.4 (2 to 6) for the neutral and 5.8 (2 to 6) for the worry condition, 6 meaning "completely." During the neutral condition three subjects reported thoughts but no images; during the worry condition four subjects reported the same. Frequency of perceived images was similar in both groups: 3.7 (2 to 5) for the neutral condition and 3.4 (2 to 5) for the worry condition. The

Table 1
Physiological recording during scans, 3-min averages

Physiology measures	Neutral 1	Neutral 2	Worry 1	Worry 2
IBI mean	892.6 ± 48.6	914.5 ± 40.9	864.8 ± 31.6	857.8 ± 24.1[a]
SC mean	4.58 ± 1.2	3.79 ± 1.1[b]	3.97 ± 1.1	3.91 ± 1.0
SC range	0.86 ± 0.1	0.67 ± 0.1	1.15 ± 0.2[c]	0.72 ± 0.1[d]

Means and standard deviation.
IBI: Heart interbeat interval.
SC: Skin conductance.
N: Neutral thoughts.
W: Worry thoughts.
No differences on any measures were found, using ANOVA with repeated measures. Significant differences were found using two-tailed *t*-tests: [a] N2–W2 $P<0.04$; [b] N1–N2 $P<0.001$; [c] N1–W1 $P<0.04$; [d] W1–W2 $P<0.01$.

clarity of perceived images also was similar in both groups: 3.5 (1 to 5) for the neutral and 3.4 (1 to 5) for the worry conditions. An ANOVA for repeated measures of physiological recordings obtained during the 3-min neutral and worry scans showed no significant differences between the neutral and worry scans. To examine possible trends, two-tailed *t*-tests were calculated that suggested a decrease of IBI means, i.e. an increase of heart rate, during the worry sessions and a decrease of mean skin conductance from the first to the second neutral session (see Table 1).

3.2. Changes in rCBF

Significant increases in rCBF during worry, as compared with neutral thinking, were found in left and right medial fronto-orbital gyrus and in the right thalamus (see Fig. 2A and Table 1). Initial SPM maps suggested four clusters with significantly increased rCBF. However, our interpretations suggest that two of them were located outside of the brain since the most probable structures of the local maxima were the dura matter and the fourth ventricle. We accepted all eight clusters with decreased rCBF detected by SPM based on the probabilistic labeling. Significantly reduced rCBF levels were seen in the left and right hippocampi and amygdalae, the right insula, the left and right inferior, middle and superior temporal gyri and the left anterior temporal tip, the left and right occipito-temporal gyri, the right inferior occipital gyrus, and the left supramarginal and angular gyri (see Fig. 2B and Table 2).

To examine a relationship between the amygdala and the prefrontal cortex, a correlational analysis was performed in a voxel-wise manner in which the mean count of bilateral amygdalae of all 40 scans (2 neutral and 2 worry scans × 10 subjects) was used as the covariate. The regional PET count in the amygdala adjusted by ANCOVA was obtained using sphere VOIs (radius = 5 mm) around the activated foci in bilateral amygdalae. In every voxel, correlation analyses with the mean amygdala count as the covariate were performed to examine an inverse relationship between frontal cortical and limbic activation. A significant negative correlation was found in the left orbito-frontal cortex (height threshold: $P=0.005$, uncorrected; extent threshold: $k=100$ voxels) as shown in Fig. 3.

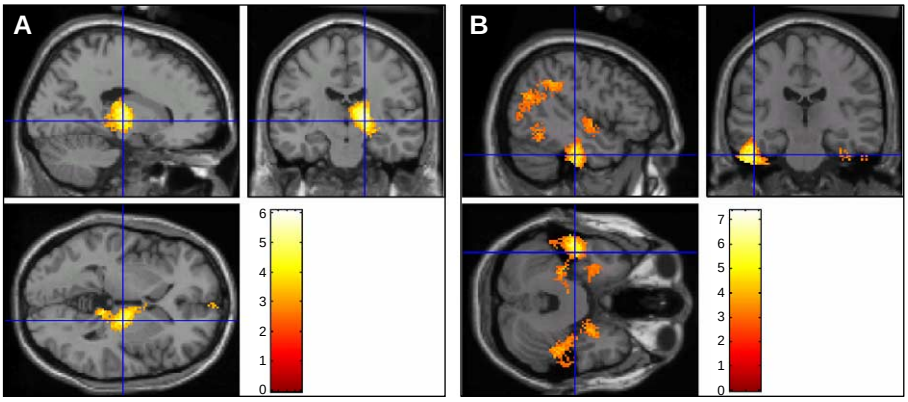

Fig. 2. (A) rCBF increase in thalamus during worry (MNI coordinate: (18, −16, 0) mm, Probable structure: right thalamus (Prob = 0.74) and right posterior limb of internal capsule (Prob = 0.23)). *T*-score was indexed by the color bar (threshold > 2.9). (B) rCBF decrease in the inferior temporal gyrus (MNI coordinate: (−46, −22, −32) mm. Probable structure: left inferior temporal gyrus (Prob = 0.57) and CSF (Prob = 0.35)).

Table 2
Brain areas with significantly increased rCBF during worry as compared with neutral thinking (height threshold: $P=0.005$, uncorrected; extent threshold: $k=100$ voxels)

Number of voxels	Brain regions included in cluster	Side	Coordinates (x, y, z)	Peak Z-value	P value (uncorrected)
1427	Thalamus	Right	18, −16, 0	4.36	0.0000
650	Orbito-frontal gyrus	Left	−2, 54, −20	3.62	0.0001
	Orbito-frontal gyrus	Right	4, 54, −32	3.47	0.0003

To examine a possible order effect affecting the results, an analysis was performed (with height threshold: $P=0.005$, uncorrected and extent threshold: $k=100$ voxels), by subtracting (Neutral scan 1+Worry scan 1)−(Neutral scan 2+Worry scan 2) (Table 3). Only the right middle temporal gyrus, the left superior parietal gyrus and precuneus, and the right anterior cingulate were found to be activated. A second analysis subtracting (Neutral scan 2+Worry scan 2)−(Neutral scan 1+Worry scan 1) showed only an activation of the left precentral gyrus.

3.3. Correlations between physiologic measures and amygdala activation

To examine possible relations between peripheral physiological measures and activation of the amygdalae, correlations were calculated between the averaged neutral scores of the cardiac interbeat interval (IBI) and skin conductance levels (SCL) during the neutral scans and the averaged amygdala metabolism. During the neutral scans, only SCL showed a significant negative correlation ($R=-0.645$, $P<0.05$) with the averaged amygdala activation. Correlations between change scores for IBI and SCL (averaged neutral to averaged worry scans) with averaged changes in amygdala metabolism (averaged neutral to averaged worry scans) yielded no significant correlations.

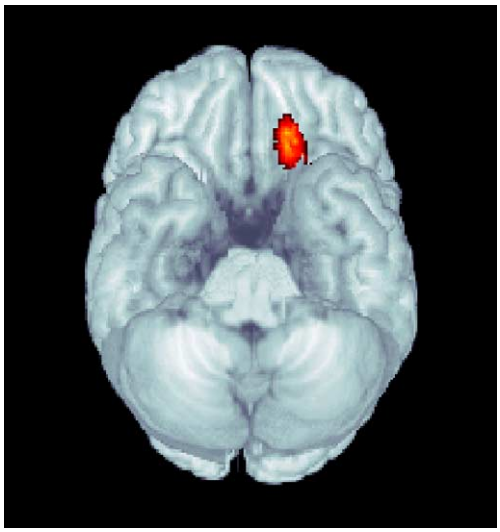

Fig. 3. Negative correlation between activated foci of the amygdalae and the left orbito-frontal cortex (height threshold: $P=0.005$; extent threshold: $k+100$ voxels).

4. Discussion

In the present study, subjects who worried quietly over several minutes rated themselves as more tense, anxious, irritable and depressed during worry than during baseline and neutral thoughts. Concomitant ratings of depression during worry have been observed in other studies (Andrews and Borkovec, 1988; Segerstrom et al., 2000), perhaps because worrying involves continuous processing of thoughts and images that can easily shift between topics and associated meanings. However, in our study ratings of anxiety during worry were significantly higher than ratings of other emotional reactions. Subjects also rated increased somatic symptoms during worry, mainly because of increased muscle tension, but registered no significant autonomic changes. However, because of a trend for increased heart rate during worry, a significant change in a larger population cannot be ruled out.

Worry, compared with neutral thoughts, increased rCBF in both, but predominantly left, middle fronto-orbital regions and the right thalamus, regions that are associated with cognitive-emotional processing (Krawczyk, 2002). In addition, worry led to widespread inhibition in the right amygdala, hippocampus

Table 3
Brain areas with significantly decreased rCBF during worry as compared with neutral thinking (height threshold: $P=0.005$, uncorrected; extent threshold: $k=100$ voxels)

Number of voxels	Brain regions included in cluster	Side	Coordinates (x, y, z)	Peak Z-value	P value (uncorrected)
1906	Inferior temporal gyrus	Left	−52, −24, −30	4.78	0.0000
	Hippocampus	Left	−26, −8, −24	4.16	0.0000
	Amygdala	Left	−28, −2, −28	3.91	0.0000
	Anterior temporal tip	Left	−26, 4, −48	3.66	0.0001
1830	Supramarginal gyrus	Left	−56, −38, 34	4.78	0.0000
	Angular gyrus	Left	−38, −48, 36	3.69	0.0001
	Occipito-temporal gyrus	Left	−44, −54, −14	3.51	0.0002
	Middle temporal gyrus	Left	−52, −62, 22	3.33	0.0004
	Superior temporal gyrus	Left	−52, −46, 18	3.20	0.0007
652	Inferior temporal gyrus	Right	48, −40, −22	4.35	0.0000
	Occipito-temporal gyrus	Right	46, −36, −20	3.57	0.0002
180	Middle temporal gyrus	Right	56, −62, 28	4.04	0.0000
358	Inferior occipital gyrus	Right	42, −88, −4	3.97	0.0000
448	Hippocampus	Right	28, −8, −32	3.46	0.0003
	Amygdala	Right	30, 0, −30	3.06	0.0011
204	Superior temporal gyrus	Left	−46, −6, −4	3.34	0.0004
658	Superior temporal gyrus	Right	48, −2, −12	3.64	0.0001
	Insula	Right	44, 0, −6	3.37	0.0004

and insula, areas that are generally activated by fear (Phan et al., 2002). Also inhibited were the left and right superior, middle and inferior temporal gyri, the left anterior temporal tip, the left supramarginal and angular gyri, the left and right occipito-temporal gyrus and the inferior occipital gyrus, areas involved with auditory and visual processing.

Several studies have linked anxiety and worry states to increased left frontal cortical activation (Borkovec et al., 1998; Carter et al., 1986; Heller et al., 1997; Tucker et al., 1978; Tyler and Tucker, 1982). In our study, worry activated both medial orbito-frontal regions, regions that are involved in episodic memory and evaluation (Zysset et al., 2002) and become activated when attention is directed towards self-referential mental activity (Maguire et al., 1999). These areas are critical in integrating affective information while preventing impulsivity in decision and action (Krawczyk, 2002). In contrast to the prolonged worry in the present study, listening repeatedly to worry statements during fMRI induced only relatively small BOLD activation in those regions (Hoehn-Saric and Schlund, 2003). In both studies, worry activated areas in the left prefrontal regions; in the fMRI study worry activated primarily the left inferior frontal gyrus, a region associated with language. On the other hand, listening to brief worry statements during fMRI recording led to activation in the right anterior and posterior cingulate, the lentiform nucleus and occipital regions. This suggests that subjects in the fMRI study responded more to the ambiguity and conflictual nature of the worry message, while in the present study prolonged worry led to greater integrative efforts to find a solution.

The activation of prefrontal regions may have been responsible for the inhibition in the limbic system, and possibly in the temporo-occipital regions. As discussed by Hariri et al. (2003), the amygdala provides direct influence over prefrontal cortical outputs, which modulate the responses of the amygdala through indirect inhibitory connections. Deactivation of the amygdala has been observed in tasks that involve higher cognitive processing (Drevets and Raichle, 1998). Taylor et al. (2003) found that activity in the amygdaloid region is attenuated while the medial prefrontal cortex and cingulate sulcus are activated during cognitive appraisal of aversive visual stimuli. Similarly, Hariri et al. (2003) demonstrated that cognitive evaluation of threatening visual stimuli increased the BOLD response of the right prefrontal cortex and the anterior cingulate but attenuated the amygdala response. We found a negative correlation between activation of the left orbito-frontal gyrus and the amygdalae, observations suggesting that the

cognitive activity of worry was responsible for the inhibition of the limbic system.

Borkovec et al. (2004) hypothesized that worry may be an attempt to suppress both the aversive images and the unpleasant somatic anxiety mechanism. Our subjects showed inhibition of the limbic system during worry but did not report the decrease in thinking in images that was found by Borkovec et al. (2004). These differences may be accounted for by the smaller number of subjects in our study and by a comparison of periods of worry with periods of active thinking about a given theme rather than with undirected thinking. Another possibility is that the repetitive theme of worries occupies one's mind and inhibits the emergence of new images and suppresses unwanted, disturbing thoughts (Anderson et al., 2004) comparable to the thought-blocking effect of the mantra in the practice of mediation-like relaxation (Benson, 1975). In this way, worry may reduce some aspects of fear while still generating an aversive emotional state.

Worry scans followed the neutral scans because we were concerned that if worry preceded neutral scans, it might have had a carryover effect and altered the neutral response. For the same reasons other investigators preceded anxiety-provoking interventions with control scans (Rauch et al., 1995). While we cannot exclude an order effect, the analyses of reversed sequences of the scan failed to show changes that would indicate that the order of the scans was responsible for the results.

In this study we were interested in the process of worrying without experimental constraints that could have modified the results. Therefore, we instructed our subjects to worry as if they would under normal conditions at home but gave no further instructions. Since worry not only contains attempts to solve a problem but also repetitive ruminative thinking, it would be of interest to expand the study and image subjects after instructing them to try to solve their problem or just ruminate about the problem. In this study, neutral statements were not of a personal nature and were not presented in the subject's voice in the first person. In further studies, neutral topics may use self-recorded self-referential statements that do not constitute worry.

Further, imaging of undisturbed worry in patients with heightened anxiety may yield different results than those in nonanxious volunteers. Using fMRI, we found in patients with generalized anxiety disorder significant differences in BOLD responses to repeated sentences describing a personal worry while they were highly anxious and after successful treatment (Hoehn-Saric et al., 2004). Therefore, the effect of undisturbed worry on cerebral blood flow, namely its ability to inhibit the limbic system or, perhaps, its failure to do so, needs to be explored in patients with generalized anxiety disorder. Of equal interest would be to explore the effect of worry in patients with obsessive–compulsive disorder. In both disorders, intrusive thoughts are difficult to control and both disorders respond to treatment with selective serotonin reuptake inhibitors. Moreover, obsessive–compulsive disorder is frequently comorbid with generalized anxiety disorder, and intrusive and obsessive thoughts may overlap. Symptom provocation in obsessive–compulsive patients increases brain activity in orbito-frontal cortex, anterior cortex and caudate (Kent and Rauch, 2004) and exposure to anxiety associated obsessive–compulsive symptom dimensions in normal volunteers activated bilateral ventral and limbic regions (Mataix-Cols et al., 2003). However, the effects of prolonged worry on the limbic system in obsessive–compulsive patients are unknown.

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