Regional Cerebral Metabolism Associated with Anxiety Symptoms in Affective Disorder Patients

Elizabeth A. Osuch, Terence A. Ketter, Timothy A. Kimbrell, Mark S. George, Brenda E. Benson, Mark W. Willis, Peter Herscovitch, and Robert M. Post

Background: We studied the relationship between regional cerebral metabolism and the severity of anxiety in mood disorder patients, controlling for depression severity.

Methods: Fifty-two medication-free patients with unipolar or bipolar illness underwent positron emission tomography with \[^{18}\text{F}\]-fluorodeoxyglucose. Hamilton Depression Rating Scale and Spielberger Anxiety-State Scale scores were obtained for the week of the scan. Analyses were performed on globally normalized images and were corrected for multiple comparisons.

Results: After covarying for depression scores, age, and gender, Spielberger Anxiety-State Scale scores correlated directly with regional cerebral metabolism in the right parahippocampal and left anterior cingulate regions, and inversely with metabolism in the cerebellum, left fusiform, left superior temporal, left angular gyrus, and left insula. In contrast, covarying for anxiety scores, age, and gender, Hamilton Depression Rating Scale scores correlated directly with regional cerebral metabolism in the bilateral medial frontal, right anterior cingulate, and right dorsolateral prefrontal cortices.

Conclusions: Comorbid anxiety symptoms are associated with specific cerebral metabolic correlates that partially overlap with those in the primary anxiety disorders and differ from those associated with depression severity. Biol Psychiatry 2000;48:1020-1023 © 2000 Society of Biological Psychiatry

Key Words: Anxiety, depression, neuroimaging, positron emission tomography, cerebral metabolism, affective disorders

Introduction

Patients with primary affective disorders often have prominent comorbid anxiety symptoms that impact behavior and response to treatment (McElroy et al, in press). Previous functional brain imaging studies in affective disorders have not always addressed the contribution of anxiety symptoms to the patterns of regional brain activity observed.

Several investigators have studied a variety of primary anxiety disorders as well as anxiety induced in normal subjects. The right, compared with the left, parahippocampal gyrus has been found to have increased regional cerebral blood flow and metabolism in subjects with primary anxiety disorders, i.e., panic disorder (Nordahl et al 1990; Reiman et al 1984, 1986). Increases in regional cerebral glucose metabolism (rCMRglu) in the insular cortex, right frontal and posterior medial orbitofrontal cortices, and lenticular nucleus have been found to be associated with symptom provocation in three anxiety disorders, including obsessive-compulsive disorder (OCD), simple phobia, and posttraumatic stress disorder (PTSD) (Rauch et al 1997). Other brain areas associated with anxiety include the left inferior parietal lobe in panic disorder (Nordahl et al 1990) and secondary visual cortex, hippocampus, prefrontal and orbitofrontal cortices, temporal poles, and posterior cingulate gyrus in simple phobias (Fredrikson et al 1995). Lucey et al (1997) found decreased regional cerebral blood flow in superior frontotemporal cortices and right caudate in both OCD and PTSD patients compared to healthy control subjects.

Studies of anxiety provoked in healthy control subjects have demonstrated increased rCMRglu in the left anterior cingulate gyrus (Chua et al 1999; Kimbrell et al 1999) left inferior frontal, temporal, and cuneus gyri (Kimbrell et al 1999), and orbitofrontal, inferior frontal, and left insula (Chua et al 1999). Kimbrell et al (1999) also showed decreased rCMRglu in right posteriortemporalparietal cortex, right superior frontal, and right medial frontal cortices with anxiety induction in these same subjects.

These findings in diverse anxiety patient populations and healthy volunteers with induction of anxiety indicate several regions of general overlap, such as frontal and
temporal cortices and insula. The purpose of this study was to identify changes in rCMRglu associated with the severity of anxiety symptoms (controlling for depression severity) in patients diagnosed with an affective disorder and to differentiate these from rCMRglu associated with severity of depression. We expected to find associations between anxiety and rCMRglu in frontal, insular, and temporal areas.

Methods and Materials
Fifty-two patients (mean age 39.8 years, SD = 12.7, range = 20–65; 23 male), with a primary affective disorder (25 unipolar, 27 bipolar), who were free of medication for at least two weeks, underwent positron emission tomography (PET) studies using [18F]-fluorodeoxyglucose (FDG) after being given a complete description of the study and giving their written informed consent. Subjects were participants in studies of treatment interventions and underwent assessments and PET scans as part of those studies. The population comprised both treatment-refractory inpatients and 18 less refractory, unipolar outpatients (Little et al 1996). The mean duration of illness was 18.4 years (SD = 9.5) for the bipolar group and 25.6 years (SD = 14.0) for the unipolar group.

Weekly modified Spielberger Anxiety-State Scale (SAnx) and weekly Hamilton Depression Rating (HAMD) Scale ratings were performed in the same week as the scan, i.e., 1 day before the scan or up to 6 days after the scan. The modified SAnx consisted of the Spielberger Anxiety-State Scale with instructions asking subjects to describe each item in reference to their symptoms in the past week (Spielberger et al 1983). This intermediate time frame was used in these subjects with affective disorders to minimize interference from previous manic episodes, previous resolved anxious depressive episodes, or previous symptom-free times that might occur if a typical Trait-Anxiety scale were used. We also wanted to focus on the subjects’ general state of baseline anxiety as distinguished from any acute anxiety related to the scan itself. Thus, the modified SAnx used here is a measure of comorbid anxiety symptoms during each patient’s affective state in the week of the scan.

PET Acquisition and Analysis
Following the injection of 5 mCi of FDG, subjects had their eyes covered and performed an auditory continuous performance task (Kimbrell et al 1999) during a 30 min uptake period. Positron emission tomography images were then obtained with a Scan-ditronix (Bartlett, TN) PC2048-15B tomograph (in-plane resolution ~7 mm), in four sets of 7 slices, to provide 28 interleaved slices 3.4 mm apart. The images were combined with measurements of arterial plasma FDG activity and glucose to obtain quantitative images of rCMRglu.

Images were resized/resliced and stereotactically normalized to the Talairach atlas (Talairach and Tournoux 1988). Voxelwise Pearson correlations were performed, covarring for age, gender, and SAnx or HAMD score, using Statistical Parametric Mapping for images normalized to their global gray matter mean resulting in Z maps (Friston et al 1991). These Z maps were then submitted to cluster analysis (Friston et al 1994) with a Z threshold of 1.96 (two-tailed p = .05) and a cluster probability threshold of p = .05. Cluster analysis considers the smoothness of the Z map in determining the effective independence of the multiple comparisons in the total brain volume analyzed.

Results
Mean SAnx was 47.1 ± 12.7 (range = 21—74) and HAMD was 22.2 ± 9.7 (range = 3—42). There was no significant difference in SAnx or HAMD scores between unipolar and bipolar groups. SAnx and HAMD were highly correlated (r = .62, p < .0001, n = 52).

SAnx correlated directly with rCMRglu in right parahippocampal gyrus and the left anterior cingulate gyrus bordering the callosum (from Talairach coordinate Z = +16 to Z = +32) after covarying for age, gender, and HAMD scores. In the same analysis, SAnx correlated inversely with rCMRglu in left fusiform gyrus, left superior temporal region, left angular gyrus, left insula, and bilateral lateral cerebellum (Figure 1, top). Alternatively, after covarying for age, gender, and SAnx, HAMD scores correlated directly with rCMRglu in bilateral medial frontal, right anterior cingulated, and right dorsolateral prefrontal cortices. There were no significant inverse correlations between rCMRglu and HAMD (Figure 1, bottom).

When the bipolar patients (n = 27) and unipolar patients (n = 25) were considered separately, the analysis was weakened by the reduced number of subjects. However, the bipolar subgroup analysis contained inverse correlations between SAnx and rCMRglu in the left superior temporal region, left insula, and bilateral lateral cerebellum. The unipolar subgroup analysis contained a direct correlation in the inferior anterior cingulate gyrus and an inverse correlation in the right cerebellum (not shown).

Discussion
Severity of anxiety symptoms in affective disorder patients was positively correlated with rCMRglu in the right parahippocampal and left anterior cingulate regions. The increase in the right parahippocampal gyrus is consistent with findings in other subject populations, such as those with panic disorder (Nordahl et al 1990; Reiman et al 1984, 1986). Increases in rCMRglu in the left anterior cingulate gyrus converge with findings in healthy control subjects with self-induced anxiety (Chua et al 1999; Kimbrell et al 1999). The mild inverse relationship between anxiety and rCMRglu in the left insula found here is interesting in light of previous findings of increases in this region with anxiety provocation in anxiety disorder pa-
Using cluster analysis.

Scores in this sample. Statistical threshold for inclusion is a
dorsolateral prefrontal regions (Z = 0.0008; X = 52, Y = 51, Z = 60, Z = 48, Y = 38, Y = 18, Z = 0), and left angular gyrus (Zmax = 3.17; p = .002; X = 38, Y = 58, Z = 52). There was also a less significant correlation in the left insula (Zmax = 2.25; p = .02; X = 38, Y = -18, Z = +12). Hamilton Depression Rating Scale score is positively correlated with the bilateral medial frontal (right and left peaks at Zmax = 3.52; p = 0.0004; X = +4, Y = +32, Z = -12 and Zmax = 3.68; p = 0.0002; X = -6, Y = +60, Z = 0, respectively), right anterior cingulate (Zmax = 3.18; p = .002; X = +2, Y = +40, Z = +4), and right dorsolateral prefrontal regions (Zmax = 3.04; p = .002; X = +42, Y = +32, Z = 0). There were no negative correlations with HAMD scores in this sample. Statistical threshold for inclusion is a Z score of >1.96 and a p value of <.05 to correct for multiple comparisons using cluster analysis.

Anxiety measured with the modified SAnx represents each subjects’ anxiety during the week of the scan, and not trait-anxiety or the state of anxiety specifically during the scan itself. This is a different representation of the level of anxiety associated with the patients’ affective states than either of the other time frames. An analysis with anxiety measured in other contexts and with other scales may yield results different from those reported here.

The heterogeneity of the subjects may have resulted in an attenuation of some of the significant differences in the relationships of anxiety to rCMRglu within different patient subgroups. It might also be argued, however, that the power offered by the large sample size and the inclusion of both bipolar and unipolar treatment refractory and treatment responsive patients, studied across a range of depression severities, adds to the validity of the results. The convergence of the findings in this preliminary study of anxiety in patients with primary affective illness with those in the literature in patients with primary anxiety disorders and with anxious healthy control subjects sug-

Figure 1. Regional cerebral glucose metabolism correlations with mood ratings in 52 mood disorder patients controlling for age and gender. Statistical parametric maps displayed on transverse sections depicting regions of direct or positive (red scale) and indirect or negative (blue scale) correlations with modified Spielberger Anxiety-State Scale (SAnx) covarying for Hamilton Depression Rating Scale (HAMD) score at the top, and correlations with HAMD covarying for SAnx at the bottom. Spielberger Anxiety-State Scale score is positively correlated with right parahippocampal (Zmax = 3.41 [maximum Z value for cluster]; p = .006; X = +38, Y = -24, Z = -8 [Talairach X, Y, Z]) and left anterior cingulate gyri (two peaks at Zmax = 3.10; p = .002; X = -10, Y = +28, Z = +20 and Zmax = 3.09; p = .002; X = -8, Y = +8, Z = +32) and negatively correlated with bilateral cerebellum (Zmax = 3.06; p = .002; X = +24, Y = -54, Z = -20 and Zmax = 2.75; p = .006; X = -32, Y = -52, Z = -20), left fusiform gyrus (Zmax = 3.35; p = .0008; X = -48, Y = -50, Z = -12), left superior temporal gyrus (Zmax = 3.24; p = .001; X = -52, Y = -18, Z = 0), and left angular gyrus (Zmax = 3.17; p = .002; X = -38, Y = -58, Z = +32). There was also a less significant correlation in the left insula (Zmax = 2.25; p = .02; X = -38, Y = -18, Z = +12). Hamilton Depression Rating Scale score is positively correlated with the bilateral medial frontal (right and left peaks at Zmax = 3.52; p = 0.0004; X = +4, Y = +32, Z = -12 and Zmax = 3.68; p = 0.0002; X = -6, Y = +60, Z = 0, respectively), right anterior cingulate (Zmax = 3.18; p = .002; X = +2, Y = +40, Z = +4), and right dorsolateral prefrontal regions (Zmax = 3.04; p = .002; X = +42, Y = +32, Z = 0). There were no negative correlations with HAMD scores in this sample. Statistical threshold for inclusion is a Z score of >1.96 and a p value of <.05 to correct for multiple comparisons using cluster analysis.

Patients (Rauch et al 1997) and with anticipatory anxiety in healthy control subjects (Chua et al 1999). It is becoming evident that these areas are consistently associated with anxiety across diverse populations and functional imaging methodologies. Contrary to our hypothesis, we found no significant correlations between SAnx and rCMRglu in frontal regions except for the anterior cingulate gyrus.

The direct and inverse relationships to anxiety symptoms were distinct from those that correlated with depressive symptoms. Depression (when controlling for anxiety), correlated positively with bilateral sub- and pregenual structures. These areas have previously been associated with severity of depression in unipolar and/or bipolar patients (Bench et al 1993; Drevets et al 1995; Mayberg et al 1997), although sometimes inversely (Drevets 1999). Because of the high comorbidity between depression and anxiety in affectively ill patients, failure to covary for anxiety symptoms when assessing cerebral correlates of depressive symptoms (and vice versa) may lead to erroneous conclusions about underlying neural substrates.
gests that right parahippocampal and left cingulate gyri, and left insula are fundamental neural substrates related to anxiety.

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References


