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Regional cerebral glucose metabolism and anxiety symptoms in bipolar depression: Effects of levothyroxine

Michael Bauer[a,b,*], Steven M. Berman[b], Florian Schlagenhauf[c], Bradley Voytek[b], Natalie Rasgon[d], Mark A. Mandelkern[e], Peter C. Whybrow[b], Edythe D. London[b]

[a] Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[b] Semel Institute for Neuroscience and Human Behavior, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA
[c] Department of Psychiatry and Psychotherapy, Charité — Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany
[d] Department of Psychiatry and Behavioral Sciences, Stanford School of Medicine, Palo Alto, CA, USA
[e] Department of Physics, University of California Irvine, Irvine, CA, USA

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ABSTRACT

We examined the relationships between regional brain activity and anxiety in bipolar depressed patients receiving adjunctive treatment with levothyroxine. Regional brain activity was assessed with positron emission tomography and [^{18}F]fluorodeoxyglucose in 10 euthyroid, depressed bipolar women before and after 7 weeks of adjunctive therapy with levothyroxine. The primary biological measures were relative (to global) regional radioactivity as a surrogate index of glucose metabolism in pre-selected brain regions. Relationships were assessed between regional brain activity and anxiety symptoms while controlling for depression severity. At baseline, Trait Anxiety Inventory measures covaried positively with relative brain activity bilaterally in the dorsal anterior cingulate, superior temporal gyri, parahippocampal gyri, amygdala, hippocampus, ventral striatum, and right insula; state anxiety showed a similar pattern. After treatment anxiety was improved significantly. Change in trait anxiety covaried positively with changes in relative activity in right amygdala and hippocampus. Change in state anxiety covaried positively with changes in relative activity in the hippocampus bilaterally and left thalamus, and negatively with changes in left middle frontal gyrus and right dorsal anterior cingulate. Results indicate that comorbid anxiety symptoms have specific regional cerebral metabolic correlates in bipolar depression and cannot only be explained exclusively by the depressive state of the patients.

1. Introduction

Epidemiological studies have widely documented a high rate of comorbidity between bipolar and anxiety disorders (Wittchen et al., 1994). An independent association of comorbid anxiety with greater severity and impairment in bipolar disorder patients (Simon et al., 2004) and an association of high anxiety levels with poor therapeutic outcome have also been demonstrated (Frank et al., 2002). Although this relationship is well established, the underlying neurobiology of anxiety in bipolar disorder has not been thoroughly studied (Freeman et al., 2002).

Functional neuroimaging studies in patients with primary anxiety disorders have provided evidence of higher rates of regional cerebral glucose metabolism, particularly in hippocampal and parahippocampal areas, compared to controls (Bisaga et al., 1998; Rauch et al., 2003). Other neuroimaging studies have identified the orbitofrontal, insular, temporal, cingulate, parietal and occipital cortices as important neural substrates of anxiety disorders (Rauch et al., 1997). In a recent positron emission tomography (PET) study, Sakai et al. (2005) showed higher [^{18}F]fluorodeoxyglucose (FDG) uptake in the amygdala and hippocampus in patients with panic disorder experiencing high state and trait anxiety before entering the scanner compared to healthy controls.

Abnormally elevated indices of glucose metabolism have also been observed in limbic and subcortical (striatum and thalamus) structures of patients with unipolar depression (Drevets, 2000) and bipolar depression (Ketter et al., 2001; Strakowski et al., 2005). Studies of bipolar disorder, however have rarely addressed the relationship between anxiety symptoms and regional brain function. One study demonstrated that comorbid anxiety symptoms in bipolar disorder are associated with specific neural correlates (Osuch et al., 2000). In that study, after covariation for depression scores, severity of anxiety correlated positively with regional glucose metabolism in right parahippocampal and left anterior cingulate regions, and inversely with glucose metabolism in the cerebellum, left fusiform gyrus, superior temporal gyrus, angular gyrus, and insula.

* Corresponding author. Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Fetscherstr. 74, 01307 Dresden, Germany. Tel.: +49 351 458 2772; fax: +49 351 458 4324.
E-mail address: michael.bauer@uniklinikum-dresden.de (M. Bauer).

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We previously reported that augmentation treatment with levothyroxine (L-T_4) improves mood (Bauer et al., 1998) and normalizes elevated relative cerebral glucose metabolism in the subgenual cingulate, amygdala, hippocampus and subcortical brain areas (thalamus, dorsal and ventral striatum, and cerebellar vermis) in women with bipolar depression (Bauer et al., 2005). The present study represents a secondary analysis of data from the same study, which used FDG and PET, and examines the relationship between parallel changes in anxiety symptoms and in relative regional activity among bipolar depressed patients receiving L-T_4 treatment. We hypothesized that in bipolar depression relative brain activity in the amygdala and its related limbic structures would be positively associated with severity of anxiety.

2. Methods and materials

2.1. Study design

This was a prospective, single-blind, 7-week study that investigated the efficacy of augmentation treatment with supraphysiological doses of L-T_4 and the relation of clinical response to alterations in regional brain function in women with bipolar depression (Bauer et al., 2005). Only women were studied because previous work had indicated that women benefit more than do men from thyroid hormone supplementation (Bauer et al., 2008). For the purpose of this secondary analysis, anxiety symptoms were analyzed for associations with regional cerebral activity while controlling for depression severity both before and after the course of L-T_4 treatment. The measure of brain function was normalized, decay-corrected, raw counts (of the radiotracer FDG) as a surrogate index of glucose metabolism. Relative activity (as used in this report) refers to this measure.

2.2. Inclusion and exclusion criteria and participants

Study inclusion required participants to be between the ages of 18 and 55 years, and to have a diagnosis of bipolar I or II disorder. The screening for positive bipolar disorder included a current depressive episode and a score $\geq$15 on the clinician-rated 21-item Hamilton Rating Scale for Depression ($HRSD_{21}$) despite antidepressant therapy ($\geq$6 weeks, standard doses of at least one antidepressant; see below). Patients had received the same antidepressant during the 6 weeks before study entry, with no changes in dose during the 3 weeks before entry. They also were euthyroid (serum TSH [thyroid-stimulating hormone] 0.3–4.7 mcIU/ml).

Participants were excluded from the study if they demonstrated any of the following: psychotic features or history of schizoaffective disorder/schizophrenia; organic brain disorder; current alcohol dependence or abuse; current dependence, or abuse with a positive urine screen on an addictive substance (illegal drugs); thyroid adenoma or hypothyroid condition; unstable medical illness; endocrine disorder; severe cardiovascular disease; intake of thyroid hormone during the 4 months immediately preceding study entry; clinical judgment of serious suicidal tendency; pregnancy, lactation, or childbirth within a year prior to study entry; or childbearing potential without use of contraception, due to the susceptibility of a fetus or nursing infant to medical harm from the injected radiotracer.

Further details of recruitment and diagnostic procedures of the UCLA Institutional Review Board-approved study were previously described in detail (Bauer et al., 2005). Of the 10 participants (mean age 39.3 $\pm$ 7.8 years, all of Caucasian descent), nine were diagnosed with bipolar I disorder, and one with bipolar II disorder (Structured Clinical Interview for DSM-IV Axis I Disorders). The mean duration of the current episode of depression at study entry was 171 $\pm$ 125 days. These 10 participants had 15.2 $\pm$ 2.4 years of education and were right handed (as determined by the Edinburgh Handedness Inventory). For screening and diagnostic purposes, participants completed a medical and physical examination, a routine laboratory evaluation (thyroid function tests, blood count, blood chemistry, and urine drug screen), examination of vital signs, and a 12-lead electrocardiogram (ECG). Anxiety was self-reported using the Spielberger State and Trait Anxiety Inventory (STAI). Participants completed the STAI-State form (STAI-S; possible total scores: 0–80) and the STAI-Trait form (STAI-T; possible total scores: 0–80) immediately after PET scanning was completed. State anxiety is supposed to measure the intensity of feelings at a particular moment (anxiety-in-progress), and trait anxiety is conceptualized as the propensity of a person to experience state anxiety and is considered to be more stable and reliable (Endler and Kocovski, 2001).

2.3. Procedures

At study visits, a clinical evaluation, including assessment of adverse event, body weight, vital signs, cardiac (including ECG) and thyroid function, was performed. Levothyroxine (Levothroid®) was administered once daily in addition to the antidepressant and mood stabilizer medication that each patient was receiving but to which he/she was not responding. The L-T_4 dose was 100 μg/day for the first week, 200 μg/day for the second week and 300 μg/day for weeks 3–7; if TSH was not suppressed by the end of week 3, the L-T_4 dose was increased to 400 μg/day.

At study entry, patients were receiving antidepressants (mostly SSRIs and venlafaxine) and mood stabilizers (mostly lithium and divalproex sodium) (for details see Bauer et al., 2005). There was no change in treatment with any of these medications throughout the study. None of the research participants received hormone replacement therapy; all were pre-menopausal (evidenced by urine ovulation test) except for one (aged 53 years) who had a hysterectomy.

2.4. MRI and PET imaging

Each participant completed two PET scanning sessions with FDG to assess relative activity, one before L-T_4 treatment and again after 7 weeks of treatment. Thyroid status and psychiatric ratings were assessed on the morning of each PET scan. Beginning before injection of the FDG and continuing during the uptake period, the participant performed an auditory continuous performance task (CPT) that was administered to provide a consistent cognitive set across all participants. PET images were acquired with a Siemens ECAT EXACT HR+ tomograph (CTI, Knoxville, TN) in 63 planes with a 15.5-cm field of view (FOV) in 3D mode, as described previously (Bauer et al., 2005). After completion of a transmission scan (for attenuation correction), the participant was removed from the gantry and seated to perform the CPT. Approximately 5 min after the CPT was started, FDG (<5 mCi, <185 MBq) was administered as an intravenous bolus. Brain images were acquired for 30 min (six 5-min frames), beginning 50 min after FDG injection. T1 volumetric structural magnetic resonance imaging (MRI) scans (3-T, General Electric) were used for co-registration with PET data.

2.5. Data analysis

Clinical anxiety measures before and after treatment with L-T_4 were compared using Student's *t* tests. Statistical significance for all analyses was set at $\alpha = 0.05$ (all tests two-tailed).

As a surrogate index for relative brain glucose metabolism, we used decay-corrected, raw counts of radioactivity, scaled to the global mean of each scan, and made comparisons between time of assay (pre- and post-treatment) using Statistical Parametric Mapping (SPM99) (Wellcome Department of Cognitive Neurology, 2000). Each PET image was co-registered to the corresponding MRI using Automated Image Registration (Woods et al., 1993). The MR images were then used to normalize each participant's PET data spatially through linear and