Decreased Occipital Cortical Glutamate Levels in Response to Successful Cognitive-Behavioral Therapy and Pharmacotherapy for Major Depressive Disorder

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Cognitive-behavioral therapy · Antidepressant · Selective serotonin reuptake inhibitor · γ-Aminobutyric acid · Glutamine · Glutamate

Abstract
Background: Previous studies have demonstrated that antidepressant medication and electroconvulsive therapy increase occipital cortical γ-aminobutyric acid (GABA) in major depressive disorder (MDD), but a small pilot study failed to show a similar effect of cognitive-behavioral therapy (CBT) on occipital GABA. In light of these findings we sought to determine if baseline GABA levels predict treatment response and to broaden the analysis to other metabolites and neurotransmitters in this larger study. Methods: A total of 40 MDD outpatients received baseline proton magnetic resonance spectroscopy (1H-MRS), and 30 subjects completed both pre- and post-CBT 1H-MRS; 9 CBT nonresponders completed an open-label medication phase followed by an additional/3rd 1H-MRS. The magnitude of treatment response was correlated with occipital amino acid neurotransmitter levels. Results: Baseline GABA did not predict treatment outcome. Furthermore, there was no significant effect of CBT on GABA levels. However, we found a significant group × time interaction (F1, 28 = 6.30, p = 0.02), demonstrating reduced glutamate in CBT responders, with no significant glutamate change in CBT nonresponders. Conclusions: These findings corroborate the lack of effect of successful CBT on occipital cortical GABA levels in a larger sample. A reduction in glutamate levels following treatment, on the other hand, correlated with successful CBT and antidepressant medication response. Based on this finding and other reports, decreased occipital glutamate may be an antidepressant response biomarker. Healthy control comparator and nonintervention groups may shed light on the sensitivity and specificity of these results. © 2014 S. Karger AG, Basel

Introduction
Major depressive disorder (MDD) has the highest worldwide morbidity among neuropsychiatric disorders across all socioeconomic strata [1–3]. Standard treatment for unipolar depression includes antidepressant medications, device-based therapies and/or psychotherapy. At
present, the selection of treatment modality for an individual patient is based primarily on patient preference and/or therapist orientation instead of a more personalized pathophysiological approach. Due to the heterogeneous nature of MDD, there remains a clinical need for trait and/or state-specific biomarkers to assist in antidepressant treatment prediction and response assessment.

The two manualized psychotherapies with the largest evidence base in MDD are interpersonal psychotherapy and cognitive-behavioral therapy (CBT). Both psychotherapies were recommended as first-line treatments in the 2010 iteration of the American Psychiatric Association’s practice guideline for MDD [4]. Additionally, CBT is associated with lower risk of relapse after remission compared to antidepressant medications [5–8]. Although a multi-site study initially suggested that CBT might be less effective in patients with severe depression [9], a subsequent meta-analysis did not support this claim [10]. As illness severity, therefore, is not a reliable predictor of response, several studies have stratified subjects into depressive subtypes as a putative enrichment strategy. Stewart et al. [11] reported that atypical depression responded more robustly to cognitive therapy than other depressive subtypes. In contrast, hypothalamic-pituitary-adrenal axis dysfunction (a biometric of melancholic depression) predicted a poorer treatment response to CBT and other psychosocial interventions [12, 13]. However, due to discrepancies in the literature [14], it remains inconclusive whether depressive subtype reliably predicts antidepressant outcomes.

As a result of the discrepancies in the literature with demographic and clinical predictors, several investigators have instead focused on neurobiological measures that might predict and/or correlate with antidepressant treatment outcomes. Several studies have demonstrated that currently depressed outpatients have lower levels of the inhibitory amino acid neurotransmitter γ-aminobutyric acid (GABA) in plasma, cerebrospinal fluid and occipital and prefrontal cortices [15–19]. We previously reported that a subgroup of MDD subjects exhibited markedly reduced occipital GABA concentrations [18]. Nearly 50% of MDD subjects had occipital GABA levels below the level found in more than 95% of healthy subjects. The reduced GABA content was especially prominent in patients diagnosed with melancholic depression [18]. Other studies have reported a normalization of occipital cortex GABA in response to somatic interventions (selective serotonin reuptake inhibitors, SSRI [20] and ECT [21]). In contrast, a preliminary study from our group [22] showed no significant cortical GABA change following a successful 12-week course of once-weekly CBT. However, this study was small (n = 8 completers) and did not investigate other amino acid neurotransmitters and their precursors, e.g. glutamate and glutamine.

Alterations in the glutamate system in MDD have been described by positron emission tomography (PET), protein biochemistry and magnetic resonance spectroscopy (MRS). Examples of such alterations include decreased metabotropic glutamate receptor type 5 (mGluR5) expression in MDD brain based on both PET (with the mGluR5 selective radioligand 11C-ABP688) and immunoblotting in postmortem samples [23], as well as reduced prefrontal cortical glutamate receptor subunit NR2A and NR2B expression and the excitatory postsynaptic density protein, PSD-95, relative to matched psychiatrically healthy subjects [24]. Prior MRS studies have shown brain region-specific alterations of glutamate and/or glutamine levels, i.e. increased glutamate/glutamine in the occipital cortex [18, 25] but decreased glutamate/glutamine levels in the prefrontal cortex [19, 26], anterior cingulate cortex [27, 28] and left amygdala [29].

Considering our preliminary evidence that successful CBT did not affect occipital GABA, and that a selective subgroup of MDD patients appears to have markedly reduced GABA levels, we sought to determine if baseline occipital GABA content could serve as a biomarker for CBT treatment efficacy. Addressing the limitations of our previous study, i.e. the small sample size and the lack of data on other neurotransmitters and metabolites, we increased our sample size of currently depressed MDD outpatients and expanded the panel beyond GABA to other proton MRS (1H-MRS)-detectable metabolites, glutamate and glutamine.

Based on these preliminary results [22], our primary hypotheses were that lower baseline GABA levels would predict a poorer antidepressant response to CBT and that a successful 12-week course of CBT would not alter occipital GABA levels. Pilot 1H-MRS studies suggesting a relationship between glutamate changes (posttreatment – pretreatment) and successful antidepressant therapies (either ECT [26, 28–30] or ECT + pharmacotherapy) led to our secondary hypothesis that a successful course of CBT will correlate with cortical glutamate changes.

**Subjects and Methods**

All study procedures were conducted at the Yale Depression Research Program and the Yale Magnetic Resonance Research Center. Subjects enrolled in this study provided written informed consent prior to all research-related procedures. The institutional

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review board/human investigations committee at the Yale University School of Medicine approved all portions of this protocol before initiation. The study was initiated prior to 2007 and was therefore not registered with ClinicalTrials.gov.

**Study Design**

This longitudinal study enrolled medication-free (≥2 weeks for typical monoaminergic antidepressants with the exception of ≥4 weeks for fluoxetine), currently depressed outpatients who presented to the clinic for initial screening and evaluation. After obtaining informed consent, subjects received baseline clinical assessments from licensed psychiatric clinicians. All rating scales were conducted by trained research staff. ¹H-MRS was obtained for baseline occipital cortical amino acid measurements. Then, participants received structured CBT as outlined in Beck et al. [31]. The psychotherapy consisted of 50-min individual sessions on a once-weekly basis for 12 weeks. Two therapists (L.R.F. and M.K.F., who were trained and certified at the Beck Institute) provided the manualized psychotherapy. The Cognitive Therapy Rating Scale (CTRS) was used to assess audiotaped copies of the sessions to ensure treatment integrity, evaluate therapist competency and provide quality control. After the end of the 12-week therapy course, all clinical assessments and ¹H-MRS were repeated (fig. 1a). CBT nonresponders were then offered an additional 6 weeks of SSRI treatment. At the end of this brief pharmacotherapy phase, a 3rd ¹H-MRS was obtained (fig. 1a).

**Subjects**

All subjects were 18–65 years old and met the DSM-IV-TR criteria for MDD in a current major depressive episode. Diagnosis was determined by face-to-face psychiatric evaluation and confirmed by the Structured Clinical Interview for DSM-IV Disorders [33]. Exclusion criteria were as follows: a current or past diagnosis of MDD with psychotic features, active suicidal ideation, a history of suicidal behavior in the preceding 2 years, current use of psychotropic medications, a history of or current uncontrolled medical or neurological problems, an alcohol or illicit substance use disorder within the preceding 6 months, current illicit substance use (as confirmed by urine toxicology), a history of psychiatric illness due to confirmed general medical condition(s), a history of primary personality disorder, and a history of psychotic spectrum illness. Predefined exit criteria for clinical deterioration were defined as follows: (1) a 25% increase over baseline Beck Depression Inventory (BDI) score at any time over the course of the trial or (2) an increase in passive suicidal ideation or the onset of active suicidal ideation at any time over the course of the trial. No subjects were excluded for clinical deterioration, and the reasons for in-protocol termination are presented in figure 1b.

**Clinical Assessments and Rating Scales**

Clinical assessments included comprehensive medical, neurological and psychiatric evaluations by experienced psychiatric research clinicians. Baseline blood and urine testing included the following: complete blood count, glucose, blood urea nitrogen, creatinine, electrolytes, liver and thyroid function tests, rapid plasma reagin, urinalysis, urine toxicology and urine pregnancy test (if applicable). Within 3 days prior to the first ¹H-MRS scan, a battery of clinician-administered psychiatric assessments was completed, including the 24-item Hamilton Depression Rating Scale (HDRS₂₄) [34] and Hamilton Anxiety Rating Scale (HAM-Å) [35] and other measures of maladaptive cognition/rumination – Dysfunctional Attitude Survey (DAS), Beck Hopelessness Scale (BHS) and Ruminative Responses Scale (RRS). Thereafter, the clinician-administered HDRS₂₄ was repeated every 4 weeks and the self-reported BDI [36] was repeated on a weekly basis to monitor clinical response. HAM-A was repeated at the end of both the psychotherapy and pharmacotherapy phases.

¹H-MRS Acquisition and Processing

The occipital cortex was selected in our initial MRS protocols due to technical limitations for the detection of amino acid neurotransmitters in other brain areas that have been more extensively studied in depression, e.g. the prefrontal cortex and amygdala. Since those initial studies, our group has consistently demonstrated decreased GABA [17, 18] and increased glutamate [18] levels with differential effects from successful antidepressant therapy [20–22, 37] (but not full restoration [25, 38]) in the MDD occipital cortex. Therefore, we continued to utilize the occipital cortex as our region of interest (ROI) in this study. ¹H-MRS was acquired with a slight modification of the J-edited method previously described [18] (two editing pulses were inserted into the sequence instead of one). Briefly, metabolite levels were measured in an occipital cortex ROI – primarily in V1 in a 13.5-ml voxel (3.0 × 1.5 × 3.0 cm) placed across the midline of the brain centered 1.5 cm from the dura. Cortical GABA content was determined using J-editing, where sub-spectra were acquired with 8,192 data points over a 410-ms acquisition, a 2.5-second repetition time, and a TE of 68 ms with a 4-tesla Bruker spectrometer, averaging data in 20-second blocks for a total of 20 min. Glutamate and glutamine were measured simultaneously using the unedited subspectra of the J-editing acquisition.

The unedited and the J-edited difference subspectra were fitted simultaneously using a basis set of metabolite spectra measured with the J-editing acquisition sequence. The metabolites fitted were aspartate, GABA, glutamate, glutamine, N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG), creatine, phosphocreatine, myo-inositol, scyllo-inositol, choline, phosphorylcholine, and glycerophosphorylcholine. The subspectrum obtained without the editing pulse was fitted simultaneously with the J-edited difference spectrum of GABA. Because of limited resolution in vivo, the results for NAA and NAAG were combined and recorded as NAA; creatine and phosphocreatine were combined and recorded as creatine, and the three choline-containing compounds were combined and recorded as choline. This implementation had no macromolecular contamination of GABA [37], so the basis set for fitting did not include a macromolecular signal. The level of aspartate, though present in the spectra, was poorly determined at the echo time of 68 ms and, therefore, was not used. Uncertainties of individual measurements were determined using a Monte-Carlo analysis as previously described [37, 39]. The means of percent solid tissue in the acquired voxel were not different between groups or assessment time points (p > 0.1). Thus, no covariance for tissue content was included. The means of creatine/water were not different between groups or assessment time points (p > 0.1). As such, the concentration of brain metabolites was estimated assuming a creatine concentration of 9 mmol/kg.

**Statistical Analysis**

Prior to conducting each analysis, the distribution of outcome measures was examined using probability plots and Kolmogorov-Smirnov test statistics. Response status was determined by 50% or...
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more reduction in the last observed HDRS24 scores. Paired t-test and related-samples Wilcoxon Signed Rank tests were used to examine pre- and post-treatment changes. General linear model (GLM) repeated-measures analyses were constructed as needed. Age and sex were considered as covariates in all models. Spearman’s rank order was used for correlational analyses. All tests were two-tailed, with a significance level set at \( p \leq 0.05 \). False discovery rate correction for multiple comparisons was used when appropriate (\( p \) adjusted).

**Results**

A total of 50 subjects were enrolled (30 women), with a mean \( \pm SD \) age of 42.6 \( \pm 11.4 \). Of these, 42 subjects had a successful baseline \( ^1 \)H-MRS scan and had at least 1 treatment follow-up visit (\( \geq 4 \) weeks of CBT); 33 subjects had a successful post-CBT \( ^1 \)H-MRS scan, and 30 subjects had...
both baseline and post-CBT $^1$H-MRS scans (fig. 1b). Subsequently, 14 CBT nonresponders entered the open-label pharmacotherapy phase, 9 of whom completed the 2nd and 3rd $^1$H-MRS and all clinical assessments (fig. 1b). The demographic and clinical features of the study sample entering and completing both the CBT and SSRI phases are provided in table 1.

As shown in table 2, CBT exerted a significant antidepressant effect ($p < 0.001$), resulting in an average 41% reduction in HDRS$_{24}$ scores and a 38% response rate ($\geq$50% reduction from baseline HDRS$_{24}$). CBT also had a significant effect on self-rated depressive symptoms (BDI) and anxiety symptoms (HAM-A), dysfunctional attitude (DAS), and hopelessness (BHS). CBT, however, did not affect total scores on the RRS (table 2). In CBT nonresponders who entered the pharmacotherapy phase, SSRIs exerted a significant antidepressant effect ($p = 0.02$), leading to an average 31% reduction in HDRS$_{24}$ scores and a 36% response rate (table 2).

**Association of Baseline Amino Acid Neurotransmitter Levels with Treatment Response**

Baseline GABA did not correlate with $\Delta$-HDRS$_{24}$ (post-treatment – pretreatment) over the CBT period ($r = -0.08$, $p = 0.66$). There was also no association between baseline glutamate and $\Delta$-HDRS$_{24}$ ($p = 0.59$). However, baseline glutamine levels were negatively correlated with $\Delta$-HDRS$_{24}$, such that patients with higher baseline glutamine exhibited a better antidepressant response to CBT ($r = -0.38$, $p = 0.03$), although this correlation did not survive correction for multiple comparisons ($p_{adjusted} = 0.06$). In addition, baseline GABA, glutamate and glutamine did not differentiate between CBT responders and nonresponders ($p > 0.05$). Pre-SSRI GABA, glutamate and glutamine were also not significantly correlated with HDRS$_{24}$ change over the pharmacotherapy phase ($p > 0.1$).

<table>
<thead>
<tr>
<th>Table 1. Demographic and clinical characteristics of study sample</th>
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<tr>
<td><strong>CBT</strong> (n = 42)</td>
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<td>Age, years</td>
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<tr>
<td>Duration of illness, years</td>
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<td>Number of MDEs</td>
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<td>Number of ADTs</td>
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<td>Current MDE, years</td>
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<tr>
<td>Female</td>
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<tr>
<td>Medication naïve</td>
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<td>Substance abuse history</td>
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Data are presented as median (with range in parentheses) or percentage. CBT: participants were treated with CBT, had pre-CBT MRS and presented for at least 1 follow-up assessment. CBT-MRS: participants were treated with CBT and completed pre- and post-CBT MRS. SSRI-MRS: participants were treated with SSRI and completed pre- and post-SSRI MRS. MDEs = Major depressive episodes; ADTs = antidepressant treatment (trials).

<table>
<thead>
<tr>
<th>Table 2. Effect of CBT and SSRIs on clinical outcome measures</th>
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<tr>
<td><strong>a CBT</strong></td>
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<td></td>
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<tr>
<td>HDRS$_{24}$</td>
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<tr>
<td>BDI</td>
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<td>HAM-A</td>
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<td>DAS</td>
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| **b SSRI** | | | |
| | Pre-SSRI | Post-SSRI | d.f. | $T^a$ | $p$ |
| HDRS$_{24}$ | 24.5±1.7 | 16.9±2.9 | 12 | −2.24 | 0.02 |
| BDI | 17.6±2.1 | 12.4±2.5 | 12 | −1.91 | 0.06 |
| HAM-A | 12.5±1.5 | 11.4±2.2 | 10 | −0.36 | 0.72 |
| DAS | 149±9.9 | 124±9.9 | 8 | −2.26 | 0.02 |
| HS | 11.2±1.8 | 7.3±1.9 | 8 | −2.17 | 0.03 |
| RRS | 24.3±1.2 | 22.2±1.5 | 8 | −1.50 | 0.13 |

Data are presented as mean ± standard error of mean. $T$: test statistics from related-samples Wilcoxon Signed Rank test (significance set at $p \leq 0.05$).
Relationship between Amino Acid Neurotransmitter Changes and the Efficacy of CBT

A repeated-measure GLM with GABA as the dependent variable, time of scans (pre-CBT vs. post-CBT) as the within-subject factor and group (responders vs. nonresponders) as the between-subject factor showed no time (p = 0.39), group (p = 0.79) or group × time interactive effects (p = 0.96). A repeated-measure GLM with glutamate as the dependent variable, time of scans (pre-CBT vs. post-CBT) as the within-subject factor and group (responders vs. nonresponders) as the between-subject factor found a significant group × time interaction (F1, 28 = 6.30, p = 0.02), demonstrating reduced glutamate in CBT responders with no significant change in CBT nonresponders (fig. 2a). The time effect was significant (F1, 28 = 5.42, p = 0.03) but there was no group effect (p = 0.98). Secondary analyses, including gender and age as covariates in the same repeated-measure GLM, showed no gender effects, no time × gender interaction, no age effect, and no time × age interaction (all p > 0.05). Over the 12-week CBT course, there was a significant correlation between Δ-glutamate and Δ-HDRS24 (rS = 0.43, padjusted = 0.02), Δ-BDI (rS = 0.46, padjusted = 0.02; fig. 2b) and Δ-HAM-A (rS = 0.48, padjusted = 0.02; fig. 2c). Secondary partial correlation analyses included gender and age as covariates. Controlling for gender, Δ-glutamate correlated with Δ-HDRS24 (rS = 0.42, p = 0.02), Δ-BDI (rS = 0.46, p = 0.01) and Δ-HAM-A (rS = 0.48, p = 0.01). Controlling for age, Δ-glutamate correlated with Δ-BDI (rS = 0.37, p = 0.046) and Δ-HAM-A (rS = 0.37, p = 0.047) but not Δ-HDRS24 (rS = 0.30, p = 0.11).

Given the small sample completing the pharmacotherapy phase (n = 9), no GLM analyses were performed. To assess the relationship between Δ-glutamate and Δ-HDRS24, we conducted a complementary correlational analysis. During the pharmacotherapy phase, there was a correlation between Δ-glutamate (post-SSRI – pre-SSRI) and Δ-BDI (rS = 0.69, p = 0.04; fig. 3a). There was a trend with Δ-glutamate and HDRS24 (rS = 0.63, p = 0.07; fig. 3b) but, unlike CBT, the change in glutamate levels did not correlate with Δ-HAM-A (p = 0.23). Given the small sample size and the exploratory nature of the pharmacotherapy phase, no correction for multiple comparisons was performed.

Discussion

This study investigated amino acid neurotransmitters at baseline, after a 12-week course of CBT and, in CBT nonresponders, a 6-week course of antidepressant medication in a well-characterized sample of currently depressed unipolar major depression subjects. Although several patients had a lengthy course of illness and index episode, our depressed outpatient sample specifically contacted our research clinic based on advertisements for evidence-based psychotherapy in lieu of antidepressant medications. This sample was also relatively treatment naïve and had lifetime rates of substance misuse consist-
Fig. 3. In CBT nonresponders, positive SSRI response is associated with decreased glutamate in the occipital cortex. Unipolar unmedicated depressed subjects in a current major depressive episode received 12 weeks of once-weekly structured CBT. Of the 14 subjects who entered phase 2 due to CBT nonresponse, 9 completed all neuroimaging and clinical assessments. In the medicated CBT nonresponders, reductions in (a) BDI and (b) HDRS were positively correlated with reductions in occipital cortical glutamate (changes are posttreatment – pretreatment).

Consistent with our preliminary report (n = 8 completers) [22], successful CBT had no effect on occipital cortical GABA levels in this larger sample. However, contrary to our a priori hypothesis, we did not find a significant relationship between baseline GABA levels and treatment outcome. The lack of CBT effects on cortical GABA measures contrasts with the findings of increased occipital GABA levels following treatment with other evidence-based therapies for depression such as SSRIs [20] and ECT [21]. Disparate effects of psychotherapy and antidepressant medications have previously been observed in the frontal cortex, cingulate cortex and hippocampus, i.e. CBT relative to the SSRI paroxetine as detected by $^{18}$fluorodeoxy glucose PET [45]. These results suggest that distinct neurotransmitter and/or neurocircuitry effects may be responsible for somatic and psychotherapeutic antidepressant response. However, it is also possible that the changes in occipital GABA associated with medications and ECT are not directly related to the antidepressant effects of the treatments. It should also be noted as a potential limitation of this study that, although pretreatment HDRS$_{24}$ scores resembled those observed in the earlier SSRI study, the current CBT study did not include subjects with melancholic, psychotic or treatment-resistant depression, which typically have been associated with the lowest levels of GABA. Therefore, the subjects in this study may have less room for improvement in GABA levels than the subjects with more severe depressive subtypes. Nevertheless, in contrast to this hypothesis, healthy subjects (who presumably have normal baseline GABA levels) exhibited increased occipital cortical GABA in response to a single intravenous administration of the SSRI citalopram [46].

We did, however, observe a robust association between changes in occipital cortex glutamate levels with CBT antidepressant response. More specifically, we found the subjects with the greatest reductions in glutamate levels during the CBT treatment period had the largest reductions in depression and anxiety symptom severity, as exemplified by decreased HDRS$_{24}$/BDI and HAM-A. This finding is of interest in light of several previous studies showing evidence of decreased prefrontal Glx content (a mixture of MRS-detectable glutamine and glutamate at lower magnetic field strengths) that subsequently normalizes following successful antidepressant treatment of unipolar depression, i.e. either ECT [26, 28–30] or ECT + antidepressant medications [29]. Similarly, the rapid but transient antidepressant effect of total sleep deprivation has also been associated with increased Glx in the dorsolateral prefrontal cortex of male depressed patients with neurovegetative symptoms consistent with melancholia [47]. Our findings, showing decreased levels of occipital cortex glutamate following CBT to be associated with treatment response, appear in contrast to the existing literature. However, studies measuring glutamate or Glx in the occipital cortex have either reported no difference or increased metabolite levels in MDD subjects [18, 25, 48]. Considering the current findings in this light, the decreased glutamate content observed following CBT might reflect a regional normalization similar to that reported in the PFC regions.

Although the small number of subjects going on to participate in the pharmacotherapy phase of the study severely limits our ability to draw any firm conclusions, we did find suggestive evidence of a similar correlation be-

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between the change in glutamate following 6 weeks of SSRI treatment and clinical response as assessed by measures of depression severity. These data suggest that the change in glutamate occipital cortex content may be associated with clinical improvement regardless of the treatment modality employed. Obviously, this correlative finding will need to be replicated before any more definitive statements can be made.

Although our study has many strengths, including a relatively large and clinically homogenous sample initially requesting evidence-based psychotherapy for the treatment of major depression, a longitudinal design, a long treatment period (4–6 months total), two evidence-based treatment modalities (depression-focused CBT and antidepressant pharmacotherapy) with no overlap between treatment periods, the use of neurobiological measures [49, 50], and an MRS sequence at 4 T that permitted specific quantification of glutamate, there are several limitations to consider. First, as with all proton MRS studies, the measures reflect total tissue content of the metabolites and do not provide any direct information related to amino acid neurotransmission. Second, our selection of a V1 occipital cortical ROI may be viewed by some as a limitation due to the primary function of the occipital cortex in vision (as opposed to other brain regions that have been more widely associated with depression, e.g. prefrontal cortex, anterior cingulate cortex and amygdala). However, as cited above, our group and others have demonstrated differential levels of amino acid neurotransmitters with response to successful antidepressant therapies in the occipital cortex. Additionally, there are several recent studies demonstrating abnormal function of the visual cortex in depression that changes [51, 52] and possibly predicts treatment outcome [53]. A third major limitation of our study is the absence of a nonintervention (‘placebo’) group in both the CBT and pharmacotherapy phases to control for nonspecific clinical and neuroimaging effects. The lack of a healthy control population does not allow us to directly make metabolite comparisons with nondepressed brains. Additionally, the fact that we excluded psychotic depression and had a limited number of subjects with melancholic or treatment-resistant depression (the subtypes that have been reported to have both the lowest GABA levels and poorest response to CBT [14, 48, 54]) limits our ability to generalize the findings to all MDD subtypes. It is unclear whether CBT success would also correlate with baseline GABA levels or decreased glutamate in these typically more severely depressed patients. Moreover, it is plausible that there was some level of selection bias because the inclusion criteria required individuals who were not currently taking psychotropic medications. Therefore, it is possible that we had a higher percentage of patients who for a variety of reasons were opposed or hesitant to seeking medication therapy [51, 52]. Finally, the SSRI exploratory analysis is hampered by the small sample size (n = 9) and data variability.

In conclusion, our observations provide exciting evidence of concordant glutamatergic effects from both evidence-based psychotherapy and antidepressant medication. Mechanistically, the relationship between the changes in occipital cortex glutamate content and successful treatment of depression may reflect several nonexclusive processes, including a recovery from an underlying pathology affecting neuronal-glial cell amino acid metabolism [55–57], changes in mitochondrial energy metabolism [58] or a change in the relative cellular composition of the tissue. Future studies are required to confirm these observations and to identify their underlying neurophysiological bases.

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Disclosure Statement

Dr. Sanacora has received consulting fees from AstraZeneca, Avanier Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Co., Hoffman La-Roche, Naurex and Noven Pharmaceuticals over the last 36 months. He has also received additional grant support from AstraZeneca, Bristol-Myers Squibb, Hoffman La-Roche, Eli Lilly and Co., Janssen, Merck Co. and Naurex over the last 36 months. In addition, he is a coinventor on filed patent application by Yale University (PCTWO0610805A1) and holds shares in Bio-Haven Pharmaceuticals Holding Company. Dr. Abdallah has received consulting fees from Genentech. None of the other authors report any potential conflicts of interest.
CBT

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