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Spectroscopic correlates of antidepressant response to sleep deprivation and light therapy: A 3.0 Tesla study of bipolar depression

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ABSTRACT

Glutamate is the primary excitatory neurotransmitter of the human brain, and recent findings suggest a role for the glutamatergic system in the pathophysiology and treatment of mood disorders. Single proton magnetic resonance spectroscopy (1H-MRS) was used to study the relative *in vivo* levels of brain neural metabolites. We evaluated the effect of antidepressant treatments on the relative concentration of unresolved glutamate and glutamine (Glx) with GABA contamination (2.35 ppm peak) using single voxel 1H-MRS at 3.0 Tesla. We studied 19 inpatients (7 males, 12 females) affected by bipolar disorder type I, current depressive episode without psychotic features, before and after 1 week of treatment with repeated total sleep deprivation (TSD) combined with light therapy (LT). Chronobiological treatment caused a significant amelioration in mood levels. Changes in the brain Glx/creatine ratio followed a general trend toward decrease, with individual variability. We observed that the decrease in the Glx/creatine ratio significantly correlated with the improvement of both objective and subjective measures of depression.
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1. Introduction

More than half of brain neurons use glutamate (Glu) as their primary neurotransmitter. Despite this predominant role in the neuronal activity of the human cerebral cortex, little is known about glutamatergic neurotransmission in mood disorders. Several lines of evidence support the importance of investigating this issue, but the reported findings do not yet allow definitive conclusions to be drawn (Krystal et al., 2002; Javitt, 2004).

In animal models several antidepressant treatments, including drugs of different classes (tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and bupropion) and electroconvulsive treatment, were able to down-regulate the glutamatergic NMDA receptor function upon repeated administration (Paul et al., 1994), to increase the expression of the vesicular Glu transporter VGLUT1 (Tordera et al., 2005), to decrease the mRNA expression for the synaptic Glu transporter (Andin et al., 2004), and to decrease the Glu outflow (Muramatsu et al., 1998; Golembiowska and Dziubina, 2000, 2001; Michael-Titus et al., 2000). Conversely, NMDA antagonists enhanced serotonergic function and down-regulated β-adrenergic receptors, and some Glu antagonists showed antidepressant effects, consistent with a model of excessive Glu-induced excitation in mood disorders (Kugaya and Sanacora, 2005). Human studies showed antidepressant effects of D-cycloserine (Crane, 1961), ketamine (Berman et al., 2000) and amantadine (Vale et al., 1971). In animal models Glu antagonists acting at both metabotropic and NMDA receptors were shown to share antidepressant-like behavioral effects and to be synergistic with tricyclic antidepressants (Chaki et al., 2004; Rogoz et al., 2004; Palucha et al., 2005; Kos and Popik, 2005).

Post-mortem studies of the human brain found NMDA receptor density lower than normal in depressed and bipolar patients (Scarr et al., 2003; Nudmamud-Thanoi and Reynolds, 2004), and in suicide victims (Nowak et al., 1995). Single case reports (Sanacora et al., 2004a; Singh et al., 2004) and two clinical trials in human subjects showed that riluzole, which inhibits Glu release, was able to promote antidepressant response both in treatment-resistant major depression

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(Zarate et al., 2004) and in bipolar depressed patients who failed to respond to lithium salts (Zarate et al., 2005).

Single proton magnetic resonance spectroscopy (1H-MRS) makes possible the study of *in vivo* relative levels of brain Glu in mood disordered patients. Alterations in Glu and glutamine (Glx) with GABA contamination are often attributed to Glu because the usual brain concentrations of the metabolites are 1 μmol/g for GABA versus 8–13 μmol/g for Glu, and the Glu-to-glutamine ratio ranges from 2.4 to 3.8 (Cooper et al., 2003; Gruetter et al., 2003). Studies providing an estimate of the unresolved relative levels of Glu plus glutamine with GABA contamination (usually referred as Glx) in unipolar depression found it to be reduced in patients affected by a major depressive episode and to normalize after electroconvulsive treatment in responders (Pfleiderer et al., 2003; Michael et al., 2003a) and to be reduced in pediatric depression (Mirza et al., 2004; Rosenberg et al., 2004). Studies attempting to measure Glu alone gave contrasting results, finding it to be lower (Auer et al., 2000; Rosenberg et al., 2005) or higher (Sanacora et al., 2004b) than normal, a discrepancy probably due to technical difficulties and to the lack of simple methods for the quantification and separation of Glu and glutamine by use of 1H-MRS (Auer et al., 2000), with better results with higher magnetic fields (3.0 T or more).

In contrast to the findings in unipolar depression, in bipolar depression Glx was found to be consistently elevated both in adult (Cecil et al., 2002; Dager et al., 2004) and pediatric (Castillo et al., 2000) patients affected by bipolar disorder. Glx was found to be more elevated also during euthymia (Bruhn et al., 1993) and during manic episodes (Michael et al., 2003b), thus suggesting that patients affected by bipolar disorder have higher Glx irrespective of the illness phase (Yildiz-Yesiloglu and Ankerst, 2006). Lithium salts, the mainstay for the treatment of bipolar disorder, were shown to decrease Glx in bipolar patients (Friedman et al., 2004), consistent with evidence that mood stabilizers can attenuate glutamatergic function either by promoting Glu uptake from the synapse or by postsynaptically reducing the intracellular signaling cascade (Krystal et al., 2002). Up to now, no study has attempted to correlate brain Glx with antidepressant response in bipolar depression.

These contrasting results have stimulated interest in the study of glutamatergic neurotransmission in mood disorders, but led to contrasting hypotheses (1) linking depression with a hyperglutamatergic activity, or conversely with a hypoglutamatergic activity, to be corrected by successful antidepressant treatment; and (2) linking the observed dysfunctions in brain Glu to the mood illness, or to the effects of drugs. Moreover, the issue of a possible unipolar–bipolar dichotomy in the role of Glu during depression has not been specifically investigated. The description of possible changes in brain 1H-MRS measures of Glx during a course of antidepressant treatment of bipolar depression, and of the possible link between changes in mood and Glx could help to clarify some of these issues.

The combination of clinical chronotherapeutic antidepressant techniques such as repeated total sleep deprivation (TSD) and light therapy (LT) has been shown to cause rapid and sustained antidepressant effects in bipolar depression. Though the exact mechanisms of action of TSD and LT are still unknown, they are likely to involve changes in the regulation of biological rhythms, and their clinical effect seems to be influenced by the same biological variables that influence response to pharmacological antidepressant treatments (Wirz-Justice et al., 2005; Benedetti et al., 2007a). The combination of TSD and LT makes it possible to study the biological correlates of antidepressant response at close time points, and in the absence of the possible confounding factors associated with prolonged drug treatments (Wirz-Justice et al., 2004).

In the present study we correlated the clinical effect of a 1-week TSD + LT treatment with changes of single voxel 1H-MRS measures of the relative concentrations of brain Glx in a homogeneous sample of patients affected by bipolar depression.

2. Methods

2.1. Sample

We studied 19 patients (7 males, 12 females) with a diagnosis of bipolar disorder type I, depressive episode without psychotic features. Diagnoses were made by trained psychiatrists using the Structured Clinical Interview for DSM Disorders (SCID-I). Clinical and demographic characteristics were (mean±S.D.) as follows: age 46.58±9.54 years; age at onset 27.21 ± 10.33 years; number of previous depressive episodes 6.26 ± 5.13; number of previous manic episodes 4.68 ± 5.60; duration of current episode 28.16 ± 35.85 weeks.

Inclusion criteria were a baseline Hamilton Depression Rating Scale (HDRS) score of 18 or higher; absence of other diagnoses on Axis I; absence of mental retardation on Axis II; absence of pregnancy, history of epilepsy, major medical and neurological disorders; no treatment with long-acting neuroleptic drugs in the last 3 months before admission; no treatment with neuroleptics or irreversible MAOIs in the last month before admission; absence of a history of drug or alcohol dependency or abuse within the last 6 months.

Physical examinations, laboratory tests and electrocardiograms were performed at admission. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Treatment and clinical assessment

All patients were administered three consecutive TSD cycles (days 1–6); each cycle was composed of a period of 36 h awake. On days 1, 3, and 5, patients were totally sleep deprived from 07:00 h until 19.00 h on the following day. They were then allowed to sleep during the night of days 2, 4, and 6. TSD was carried out in a room with 80 lux ambient light. Patients were administered LT (exposure for 30 min to a 400 lux green light) at 03:00 h during the TSD night and in the morning after recovery sleep, half an hour after the time of awakening, approximately between 08:00 and 09:00 h.

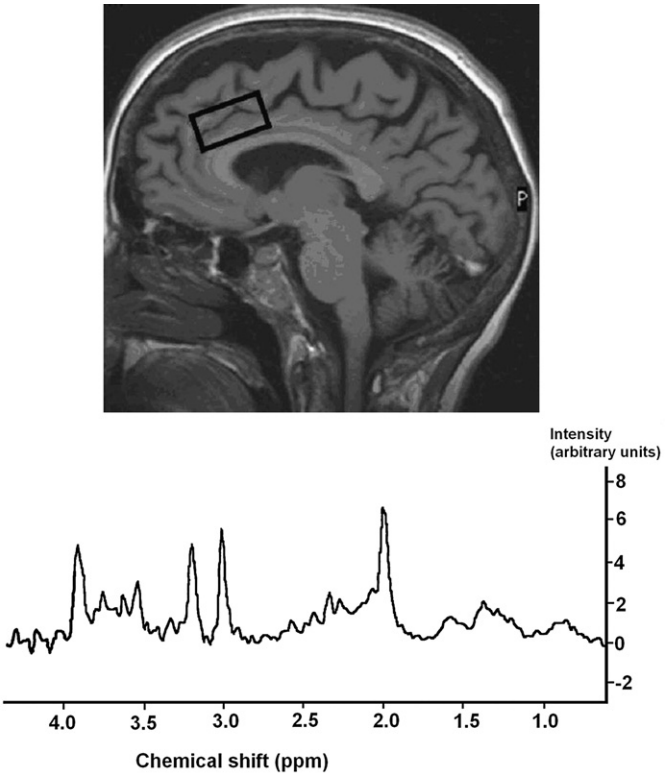

Fig. 1. Positioning of the 1H-MRS voxel and a typical spectrum.

Table 1
Metabolite ratios (means ± standard deviations) before and after treatment.

	Before treatment	After treatment	$t_{(d.f.)}$	P
NAA/Cr	1.03 ± 0.43	1.16 ± 0.33	$0.908_{(18)}$	0.376
NAA/Cho	1.11 ± 0.41	1.22 ± 0.37	$0.712_{(18)}$	0.485
Cho/Cr	0.95 ± 0.29	1.01 ± 0.37	$0.677_{(18)}$	0.507
GLX/Cr	0.39 ± 0.30	0.27 ± 0.17	$1.438_{(17)}$	0.169
Ins/Cr	0.42 ± 0.15	0.42 ± 0.21	$0.034_{(15)}$	0.974

Cho = Choline containing compounds; Cr = Creatine-phosphocreatine; GLX = Glutamate plus Glutamine; Ins = Inositol; NAA = *N*-Acetyl-Aspartate.

Patients were not taking any drug except ongoing lithium salts, which were kept in the usual therapeutic range (plasma levels 0.5–0.8 mmol/l) and remained unchanged between the two scans.

Mood was rated before and after the TSD + LT treatment by administering in the morning a modified version of the 21-item HDRS from which items that could not be meaningfully rated due to the TSD procedure and to the time frame were excluded (i.e., weight changes and insomnia: items # 4, 5, 6, and 16) (HDRS-NOW). In the same days self-ratings of perceived mood levels were assessed by a self-administered 10-cm visual analogue scale (VAS) three times a day (08:00, 13:00, and 18:00 h). Patients were instructed to rate their mood between "very sad" (on the left) and "very happy" (on the right) with a median "normal" point. Raw data were converted to a 0 to 100 rating scale, with 0, 50 and 100 denoting extreme depression, euthymia, and euphoria, respectively. Each patient's perceived mood level was calculated as the mean of the three scores for that day. A categorical response criterion of 30% decrease in HDRS score was adopted.

2.3. MR procedures

All MRI/MRS studies were performed on a 3.0 Tesla magnet (Intera Philips) with a standard quadrature head coil at baseline and the day after the end of the chronobiological treatment in the early afternoon.

The structural MRI study was performed first to rule out brain lesions and to localize the volume of interest (VOI) for the spectroscopy study, acquiring sagittal T1 images, axial T2 fast spin-echo (FSE) images parallel to the bicomessural line, and coronal fluid-attenuated inversion recovery (FLAIR) images orthogonal to the axial ones.

1H-MRS data were acquired using a point resolved spectroscopy (PRESS) sequence (TR 2000 ms, TE 30 ms, 128 acquisitions) from a single VOI of 30 × 20 × 15 mm size positioned at the level of the anterior cingulate cortex in the inter-hemispheric region (Fig. 1). Single VOI anatomical landmarks were defined on a medial sagittal image assuming the superior border of the corpus callosum as the inferior limit of the VOI and a line perpendicular to it, tangent to the genu of the corpus callosum as the anterior limit. On the transverse plane the VOI was placed symmetrically in order to include cingulate cortex on both sides. The rectangular shape of the VOI, having the major axis along the anterior–posterior direction and a relatively short axis along the lateral direction, was chosen in order to include mostly cingulate grey matter minimizing white matter contamination. The same anatomical landmarks were used in the second study: the quality of VOI repositioning was checked by comparing the images from the first and the second study in both the sagittal and axial planes. The choice of the region of interest was due to the finding that metabolic changes in this area correlate with antidepressant response to TSD (Benedetti et al., 2007b).

Proton spectra were processed by an operator blind to the treatment status, using jMRUI (http://www.mrui.uab.es/mrui), by application of 4 Hz Gaussian apodization, Fourier transform and automatic zero-order phase correction with the Hankel-Lanczos Singular Value Decomposition (HLSVD) procedure. We used a black-box approach, with no prior knowledge, and used an automated curve-fitting procedure for the following peaks: *N*-acetyl-aspartate (NAA) at 2.00 ppm, creatine-phosphocreatine (Cr) at 3.0 ppm, choline containing compounds (Cho) at 3.2 ppm, inositol (Ins) at 3.6 ppm. The peak at 2.35 ppm was considered for the overlapping resonances from glutamate and glutamine (Glx), with possible GABA contamination (Hurd et al., 2004). Peak integral ratios for NAA/Cr, NAA/Cho, Cho/Cr, Glx/Cr and Ins/Cr were calculated. The primary analysis of interest was the correlation between changes in brain Glx and changes in measures of depression (VAS, HDRS).

3. Results

The chronotherapeutic treatment was associated with significant changes of both HDRS (from 20.84 ± 4.36 to 9.42 ± 6.17, $t = 6.62$, $P < 0.00001$) and VAS (from 30.74 ± 18.22 to 40.56 ± 22.98, $t = 2.17$, $P = 0.0433$) measures of depression; 15/19 patients showed a

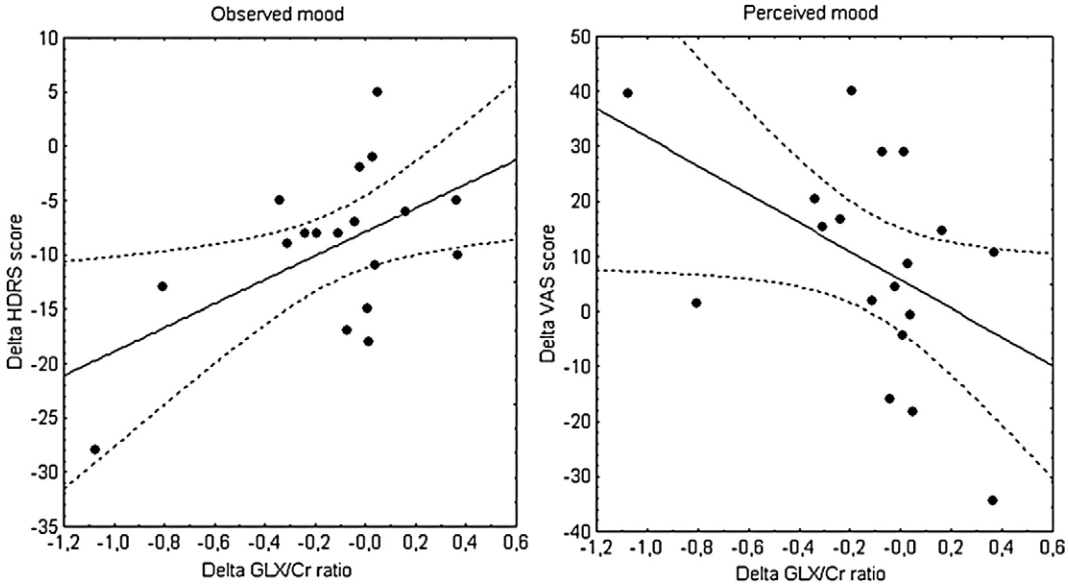

Fig. 2. Correlation between decrease in Glx/Cr ratio and clinical improvement as rated on both objective (HDRS) and subjective (VAS) measures of depression. HDRS scores correlate positively with the severity of the pathology (higher scores, more severe symptomatology) while VAS scores correlate negatively (higher scores, less severe symptomatology).

clinically relevant amelioration (HDRS score decrease of at least 30%).

All patients completed the MRI/MRS study protocol; in none of them did MRI examination show any brain abnormalities. Spectral resolution allowed the estimation of peaks both before and after treatment for NAA, Cho and Cr in all patients, for Glx in 18 patients, and for Ins in 16 patients.

Metabolite ratios before and after treatment are shown in Table 1. The individual variability in the effect of treatment on Glx/Cr ratio was significantly correlated with the individual variability in the clinical effect of treatment: higher decrease in Glx/Cr, greater decrease in depressive symptomatology on both objective (Delta HDRS scores: Pearson's $r=0.534$, $P=0.022$) and self-rated (Delta VAS scores: $r=0.470$, $P=0.049$) measures of depression (Fig. 2). Results were confirmed when the sample was stratified according to a categorical criteriom of benefit associated with treatment (HDRS score reduction of at least 30%): patients who had some benefit ($n=14$) had a higher decrease in Glx than patients who did not ($n=4$) (Delta Glx/Cr ratio: -0.17 ± 0.39 vs. $+0.05\pm0.08$; Median test: Ch-squarei=5.14, $P=0.023$).

Following usual conventions (Cohen, 1988), the effect size of the correlation between Glx and mood improvement was large for the HDRS (>0.50), and medium to large for the VAS. Post-hoc power calculations (GPOWER, Faul et al., 2007; *t*-test on correlations with two-tailed $\alpha=0.05$, $n=19$, critical $t=2.11$) resulted in power of 0.737 for the HDRS and 0.591 for the VAS.

4. Discussion

The main finding of the present study is that the mood amelioration associated with chronotherapeutic approaches (TSD+LT) in patients affected by bipolar depression was paralleled by a decrease in single voxel 1H-MRS measures of brain Glx. This finding is consistent with current hypotheses of excessive Glu-induced excitation in bipolar depression (Kugaya and Sanacora, 2005), and is in agreement with neurochemical studies that showed that antidepressant drugs decrease the Glu synaptic outflow, and that lithium salts, which are the mainstay of treatment for bipolar disorder, decrease 1H-MRS measures of Glx in patients affected by bipolar disorder (see Section 1).

In view of these findings, we might speculate that our observation of reduced Glx in bipolar depressed patients responding to TSD + LT therapy could be due to a reduction of glutamatergic system activity. Glutamate is the major excitatory neurotransmitter in the brain and a high percentage of corticofugal neurons are glutamatergic. The reduction in Glx could be due to a direct effect of treatment on glutamatergic neurons, or to the interplay between the glutamatergic system and brain monoamines that are known to be targeted by TSD, namely dopamine (DA) and serotonin (5-HT). TSD is known to cause a marked enhancement in brain levels of both DA and 5-HT (Wirz-Justice and Van den Hoofdakker, 1999), and the magnitude of this effect has been correlated with antidepressant response to TSD both by directly measuring brain metabolites (Gerner et al., 1979; Ebert et al., 1994) and by exploring the synergistic effects of TSD and drugs acting on DA and 5-HT (e.g., Smeraldi et al., 1999; Benedetti et al., 2001). Several studies using positron emission tomography have associated a decrease in metabolic rates in the cingulate cortex with response to TSD, and mobilization of DA and 5-HT has been suggested to be associated with the decrease in metabolism of the anterior cingulate seen in responders to TSD (see review in Wu et al., 2001). The decrease in cingulate Glx observed in the present study could then be part of more general changes of metabolism and neurotransmission associated with response to TSD.

Patients were taking lithium salts, which enhance and sustain the effects of TSD and LT (Benedetti et al., 2007a). One study showed that in healthy humans lithium significantly decreased Glx in basal ganglia, but not in anterior cingulate cortex (Shibuya-Tayoshi et al., 2008), while one study in bipolar patients showed that lithium is able to decrease Glx in an axial section encompassing anterior cingulate and many other brain structures (frontal cortex, caudate nuclei, putamen, insula, thalami, parietal cortex, and occiput; Friedman et al., 2004). Lithium was kept unchanged in our study, and it could have contributed to the observed decrease in cingulate Glx by potentiating the effects of TSD and LT. Whichever the exact mechanism, our data suggest that a decrease in brain Glx levels might be a neurometabolic correlate of antidepressant response to treatment of bipolar depression.

Several limitations must be considered. Fitting of a single peak in a crowded spectral region such as the 2.35 ppm peak with a black-box method is prone to possible uncontrolled influences. Large resonances from macromolecules may result, leading to increased estimates of Glx compared with other metabolites. We could not discriminate between glutamate and glutamine as their resonances overlap in the in-vivo proton spectra acquired with our PRESS sequence. Minimal contamination from GABA should be considered as well (Section 1). The use of Cr ratios rather than absolute concentrations is another limitation of this study; however, the fact that the Cho/Cr ratios do not change significantly before/after treatment would suggest that chronotherapy is not affecting Cr resonance due to circadian rhythm changes. Another limitation is the absence of segmentation which could result in an increased variability due to differential inclusion of white and gray matter in the voxel studied; careful attention to accurate repositioning of the VOI in the repeat study and the intrasubject comparison should have limited this bias.

The effect sizes of the observed correlations were large, but power was lower than the optimal 1-β value for both HDRS and VAS correlations with Glx, meaning that our experimental conditions resulted in a good protection against type I, but not against type II errors, which could then have been present for metabolites other than Glx. In the absence of any prior knowledge about the spectroscopic effects of TSD + LT, here we provide possible *a priori* effect sizes for future studies in the field. Notwithstanding the questionable assumption of retrospective power calculations that the sample effect size is essentially identical to the effect size in the population from which it was drawn, our results suggest that enlarged samples will be needed to rule out H0, but that our sample was sufficient to detect the observed differences of Glx relative concentration before/after treatment.

Finally, we studied the anterior cingulate cortex because of consistent literature that linked this area with bipolar disorder and response to antidepressant treatments, and we did not consider reference voxels in other areas. Further studies will show if these changes and their relationship with clinical response are specific to this area or are common to other regions, or to the whole brain.

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