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ABNORMAL GLUTAMATERGIC NEUROTRANSMISSION AND NEURONALGLIAL INTERACTIONS IN ACUTE MANIA

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Abstract

Background—At excitatory synapses, glutamate released from neurons is taken up by glial cells and converted to glutamine, which is cycled back to neurons. Alterations in this system are believed to play a role in the pathophysiology of bipolar disorder, but they have not been characterized *in vivo*. We examined the glutamine/glutamate ratio, and levels of other metabolites in acute mania and schizophrenia in this exploratory study.

Methods—Data were obtained from 2×2×2cm voxels in the anterior cingulate cortex (ACC) and parieto-occipital cortex (POC) using 2-dimensional *J*-resolved proton magnetic resonance spectroscopy at 4 Tesla, and analyzed using LCModel. Fifteen bipolar disorder patients with acute mania and seventeen schizophrenia patients with acute psychosis were recruited from an inpatient unit; twenty one matched healthy controls were also studied. Glutamine/glutamate ratio and N-acetylaspartate, creatine, choline, and myo-inositol levels were evaluated in a repeated-measures design. Medication effects and relationship to demographic and clinical variables were analyzed.

Results—Glutamine/glutamate ratio was significantly higher in ACC and POC in bipolar disorder, but not schizophrenia, compared with healthy controls. N-acetylaspartate was significantly lower in the ACC in schizophrenia. Patients on and off lithium, anticonvulsants, or benzodiazepines had similar glutamine/glutamate ratios.

Conclusions—The elevated glutamine/glutamate ratio is consistent with glutamatergic overactivity and/or defective neuronal-glial coupling in acute mania, although medication effects cannot be ruled out. Abnormalities in glutamatergic neurotransmission and glial cell function in bipolar disorder may represent targets for novel therapeutic interventions.

Keywords

MRS; glutamate; glutamine; glia; bipolar disorder; schizophrenia

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INTRODUCTION

Bipolar Disorder (BD) is a common disorder [1] and the sixth leading cause of disability among persons aged 15–35 [2]. Several lines of evidence implicate cellular and synaptic abnormalities in the pathophysiology of BD, including *postmortem* studies of low glial cell number in the prefrontal cortex (PFC) [3,4], abnormal PFC volume [5,6] and activity [7,8], and genetic abnormalities in synaptic proteins [9,10]. Thus, cellular and synaptic abnormalities constitute important targets for novel treatments in BD [11].

The excitatory neurotransmitter glutamate (Glu) is released into the synaptic cleft, taken up by glial cells, converted to glutamine (Gln), and cycled back to neurons [12,13]. Therefore, Gln/Glu ratios provide a window into the integrity of the glutamatergic synapse and neuronal-glial coupling. For example, rat models of cerebral ischemia are characterized by elevated Gln/Glu ratios [14] providing evidence for increased Glu release and subsequent conversion to Gln by glia during ischemia [15].

Glutamatergic neurotransmission is implicated in the pathophysiology of BD [16] and novel glutamatergic compounds are being studied as possible treatments for mood disorders [17, 18]. One recent *postmortem* nuclear magnetic resonance study reported elevated Glu levels in the dorsolateral prefrontal cortex in bipolar disorder [19]. Glutamatergic function has not been fully explored *in vivo* in BD due to paucity of measurement techniques. Signal/noise and spectral resolution limitations in magnetic resonance spectroscopy (MRS) have forced quantification of combined Glu-Gln as Glx [20]. Several studies report reductions in Glx in major depressive disorder (MDD)[21–23], while manic [24,25], depressed [26,27], and fully-recovered BD subjects [28] show elevated Glx. Children with manic symptoms have lower than normal Glx levels [29]. The physiological significance of Glx findings remains unclear and MRS techniques distinguishing Glu and Gln in the human brain therefore constitute an important advance. Using such an approach, one study found elevated Glu and non-significantly lower Gln levels in the occipital cortex in MDD [30].

There is also a large literature on glutamatergic abnormalities in schizophrenia [31]. MRS studies have reported elevations in Gln with no change in Glu in never-treated first episode schizophrenia subjects, suggesting “greater than normal glutamatergic activity” [32], and lower Gln and Glu in chronically ill subjects, suggesting neurodegeneration or chronic medication effects [33].

In this exploratory study, we quantified Glu and Gln and generated Gln/Glu ratios using *J*-resolved proton magnetic resonance spectroscopy (^{1}H MRS) (*J*=coupling constant for resonances arising from coupled spins) [34,35]. This sequence acquires spectra at multiple echo times, providing information on *J*-coupling interactions as well as chemical shift, and improving metabolite quantification [36]. To probe the anatomical extent of abnormalities, we obtained data from the ACC and POC. The ACC is considered a major locus of pathology in BD [37]; POC abnormalities have been reported in MDD [30] but not BD [38]. MRS imaging (MRSI) was not chosen because of susceptibility artifacts at higher field strengths [39]. We scanned acutely manic patients with BD, acutely psychotic patients with schizophrenia, and a matched healthy control group at 4 Tesla. We hypothesized that abnormal neuronal-glial coupling would result in Gln/Glu ratio alterations in acute mania in ACC and POC. Because previous MRS reports indicate glutamatergic abnormalities depend on stage of illness in schizophrenia [32,33], we predicted we would find normal or elevated Gln/Glu ratios in this condition.

METHODS

We first carried out a test-retest study to determine within-subject reliability. Ten healthy subjects (5M, 5F; ages 18–35) with no medical/neurological/psychiatric/substance use problems, and not taking medications, were scanned three times. Scans were conducted within one week for each subject, except for 2 female subjects whose third scan was four weeks later, at the same phase of the menstrual cycle. All scans and data analysis were identical to methods described below. The within-subject coefficients of variation (CV=standard deviation/mean of 3 scans) in ACC and POC were 11% and 7% for NAA, 9% and 7% in Cr, 8% and 4% for Cho, 9% and 9% for mI, 13% and 10% for Glu, 23% and 17% for Gln, respectively.

Subjects

Following approval by McLean Hospital IRB, 22 control, 39 bipolar I disorder, currently manic, and 20 schizophrenia subjects with acute psychosis were recruited (NC, BD and SZ groups, respectively). All patients were hospitalized in a psychiatric inpatient unit. Subjects with significant neurological or medical problems, current substance abuse or history of substance dependence were excluded. All patients had negative urine toxicology tests. We used an Informed Consent Survey which asks 10 simple questions about the study such as “What illness is being studied?” and “If you don’t want to, do you have to be in this study?” Every subject answered these questions correctly, and answers were documented. Patients were assessed using the Structured Clinical Interview for DSM-IV (SCID) [40], Young Mania Rating Scale (YMRS), Montgomery-Asberg Depression Rating Scale (MADRS), and Positive and Negative Syndrome Scale (PANSS) on scan day. The SCID substance abuse/dependence assessment did not include tobacco products; tobacco smokers were not excluded from the study. Healthy control subjects were assessed using the SCID; no family history information was obtained from healthy controls. The demographic and clinical variables and statistical comparisons are in Table 1.

Although severity of mania and psychosis cannot be directly compared, all patients were hospitalized with acute episodes, suggesting that all had pronounced psychopathology. All BD subjects met full DSM-IV criteria for current manic episode; there was no additional cutoff for YRMS scores. No patients met criteria for rapid cycling. Usable data were obtained from 21 NC, 15 BD and 17 SZ (eight diagnosed with schizoaffective disorder, not currently in a mood episode) subjects. Inability to tolerate the scanning environment due to psychiatric condition was the primary reason for dropout (N=22 for BD, 2 for SZ). BD subjects who did not complete the study were more symptomatic than those who did (YMRS:26.9; MADRS:18.4; PANSS: 82.0; compare with Table 1). Chlorpromazine (CPZ) equivalents were calculated for patients taking antipsychotic medications[41].

MRI/MRS Scans

As part of one IRB protocol, all subjects were recruited for two MRI scans on the same or consecutive days (depending on scanner availability). Subjects underwent a structural MRI in a Siemens 3 Tesla Trio scanner (Erlangen, Germany) with a quadrature radio-frequency coil using 3D inversion prepared sagittal FLASH sequence. TE/TR/TI times=2.74ms/2.1s/1.1s, echo spacing 6.3ms, 12° flip. Field of view (FOV) was 256mm with 1×1mm pixels, and 1.33 mm slices. Subjects with structural abnormalities were excluded.

^{1}H MRS acquisitions were conducted on a 4 Tesla full-body MR scanner (Varian/UnityInova, Varian Inc., Palo Alto, CA), using a 16-rung, single-tuned, volumetric-birdcage coil (Robarts Research Institute, London, Canada). 2D gradient-recalled echo images (12s) were acquired in three dimensions to ensure optimal patient positioning. Manual global shimming of unsuppressed water signal yielded an unfiltered global water linewidth of ≤30Hz. T1-weighted

sagittal images (TE/TR=6.2/11.4ms, FOV=24×24×8cm, in-plane resolution=0.94×1.88mm, slice thickness=5mm, readout points=512, flip angle=11°) and axial images (similar parameters as above, except for in-plane resolution =0.94×0.94mm, slice thickness=2.5mm) were next acquired, allowing for clear differentiation between cortical grey matter (GM) and white matter (WM), and serving as anatomical guide to positioning MRS voxels.

A 2×2×2cm single voxel was then placed on the ACC. We were interested in studying the subgenual ACC but susceptibility artifacts precluded collecting such data. We therefore placed the voxel, on midsagittal T1-weighted images, anterior to genu of the corpus callosum, with the ventral edge aligned with the dorsal corner of the genu (Figure 1), and positioned the voxel on the midline on axial images. A point-resolved spectroscopy sequence (PRESS) modified for *J*-resolved ^{1}H MRS, employing a four-pulse WET (water suppression enhanced through T1-effects) sequence [42] was used. Manual shimming within the voxel resulted in water linewidths ≤ 11 Hz. Following tip angle, water-suppression, and RF pulse power optimization using automated methods, the 2D J-resolved sequence collected 48 TE-stepped spectra from the voxel, with the echo-time ranging from 30ms to 500 ms in 10ms increments. Specifically, the second TE period in the PRESS sequence was progressively prolonged by symmetrically flanking the last 180 degree pulse prior to signal acquisition with two 5 millisecond delay periods. Acquisition parameters were: TR=2.0s, acquisition bandwidth=2kHz, repetitions=16; nominal voxel volume=8cc; approximate scan duration=28 minutes.

This process was repeated on a 2×2×2cm POC voxel. On midsagittal images we aligned the ventral edge of the voxel with the dorsal corner of the splenium of the corpus callosum, covering posterior cingulate and retrosplenial cortices, and positioned the voxel on the midline in axial images (Figure 1). Because POC spectral quality was superior, 8 repetitions were obtained in approximately 14 minutes. Total time in the magnet was 75–90 minutes.

The water resonance full width at half maxima were 9.9±1.2 and 8.7±0.8Hz for NC, 9.3±1.5 and 8.6±0.7Hz for BD and 9.4±2.3 and 8.9±0.9Hz for SZ subjects (in ACC and POC, respectively; no between-group differences). Coil loading was not quantified; this affects all metabolites similarly, and would not modify the Gln/Glu ratio.

MRS Data Processing and Analysis

All MRS processing was blinded to diagnosis. Real (not magnitude) spectra were used (Figure 2). For each voxel, the 48 TE-stepped free-induction decays (FIDs) were zero-filled to 128 FIDs in f1, Gaussian-filtered to minimize residual ringing from longer TE NAA and Cr signal, and Fourier-Transformed in f1 to produce a series of 128 *J*-resolved spectral FIDs over 100Hz bandwidth. A blinded MR physicist (JEJ) excluded spectra from 5 subjects due to low signal-to-noise and/or spectral resolution: 2 ACC and 1 POC in NC, 1 POC in BD and 1 ACC in SZ.

We used the commercial spectral-fitting package, LCModel (version 6.0–1) [43] for 2D fitting. 2D fitting improves spectral fitting by utilizing all available signal rather than fitting select single *J*-resolved extractions [35,39]. For 2D fitting, LCModel utilized GAMMA-simulated [44] theoretical *J*-resolved basis sets to fit every *J*-resolved spectral extraction. We generated basis sets for N-acetylaspartate, N-acetylaspartylglutamate, Alanine, Gamma-aminobutyric acid, Aspartate, Choline, Creatine, Glucose, Glutamate, Glutamine, Glutathione, Glycerophosphocholine, Glycine, Myo-inositol, Scyllo-inositol, Lactate, Phosphocreatine, Phosphocholine, Serine, and Taurine. We first used GAMMA to generate 48 theoretical, TE-stepped spectra ranging from 30ms to 500ms in 10ms increments [20]. Each GAMMA spectrum was modeled at 2kHz spectral bandwidth with 1024 complex pairs and a 2Hz Lorentzian lineshape, zero and first-order phased with no baseline roll. We also modeled a formate peak at 8.45ppm and a TSS reference peak at 0.0ppm to mimic the standard LCModel stock solution required for basis-set generation [45]. For each GAMMA-simulated metabolite

TE-series, we zero-filled complex time-points in each FID to 128 TE points, apodized with an exponential filter to approximate metabolite T2-decay at 4T, and Fourier-Transformed in the TE dimension to obtain basis sets sampled at nominal 0.78Hz *J*-resolution for 100Hz bandwidth. These *J*-resolved metabolite FIDs were converted into 128 separate LCModel basis sets for each metabolite. This process resulted in artifact-free and theoretically-correct *J*-resolved basis sets for each *J*-resolved spectral extraction from *in vivo* spectra. For every metabolite, we fit its spectrum over 50Hz bandwidth (−25Hz to +25Hz; 64 TE points), deriving the integrated area under the 2D-surface. Spectral regions outside this range did not contain significant metabolite signal but contributed additional noise.

LCModel provides Cramer-Rao Lower Bounds (CRLBs), an estimate of the variance associated with fitting. In our case, each 2D spectrum produced 64 CRLBs for each metabolite. These ranged from less than 5% in regions of high certainty (typically close to *J*=0Hz; Figure 3), to greater than 50% in regions of low certainty. We report the mode, median and mean CRLBs for each metabolite from the clinical study (Table 2). The results of LCModel fitting for each metabolite are reported as arbitrary units (AUs). Glu and Gln measures in the test-retest study are shown in Figure 4.

Image Segmentation

Tissue-segmentation of T1-weighted images into GM, WM, and cerebrospinal fluid (CSF) used FMRIB's Automated Segmentation Tool (Oxford, UK). Poor image quality precluded segmentation in 30 voxels. The percentage of GM in ACC and POC was 79±5% and 70±8% (NC), 76±8% and 69±8% (BD), and 77±3% and 69±7% (SZ),while that of WM was 17±6% and 28±8% (NC), 16±8% and 29±8% (BD), and 16±4% and 29±8% (SZ), respectively.

For the 73 voxels where data were available, we computed Pearson's R for percent GM and MRS measures. GM was positively correlated with all MRS measures (NAA: R=0.417, p=0.002; Cr: R=0.586, p<0.001; Cho: R=0.563, p<0.001; mI: R=0.574, p<0.001; Glu: R=0.555, p<0.001; Gln: R=0.270, p=0.046), consistent with prior literature [46–48]. No relationship existed between Gln/Glu and GM (R=−0.009, p=0.947), suggesting that Glu and Gln levels covary between GM, WM, and CSF.

Statistical Analysis

Demographic and clinical variables were compared across groups using analysis of variance (ANOVA) and chi-square tests (Table 1). There was no effect of sex on any metabolite measures. A series of correlation coefficients (uncorrected for multiple comparisons) showed that age, age at disease onset, and CPZ equivalents were not related to metabolite measures, except for a negative correlation between age and NAA levels (R=−0.208, p=0.048).

Given our *a priori* hypothesis, we considered the Gln/Glu ratio as our primary outcome measure, and did not analyze Glu or Gln separately. In addition, we examined NAA, Cr, Cho and mI levels. The effect of diagnosis on metabolite measures was investigated using repeated measures ANOVAs with brain region (ACC vs. POC) as within-subjects factor, and diagnosis as between-subjects factor. Main effects and the brain region × diagnosis interaction were explored and Dunnett's post-hoc tests were used. There was a statistical trend difference in age between diagnostic groups (Table 1). Therefore, we repeated the metabolite analyses with age as covariate.

A series of correlation coefficients showed no relationship between metabolite measures and MADRS, YMRS, and PANSS scores (uncorrected for multiple comparisons). Finally, we examined medication effects on metabolite levels using one-way ANOVAs. This was done in BD and SZ groups separately because different numbers of subjects took each medication in

the SZ and BD groups and group differences in metabolite levels could confound the medication effect.

RESULTS

Gln/Glu ratio showed a significant main effect of diagnosis (F(38,2)=4.875, p=0.013) but no main effect of brain region (F(38,1)=1.223, p=0.276) or brain region × diagnosis interaction (F(38,2)=1.819, p=0.177). Post-hoc tests revealed that Gln/Glu ratios were significantly elevated in BD but there was only a trend toward significance in SZ (Dunnett's 2-sided comparison to NC, p=0.009 and p=0.065, respectively) (Table 3; Figure 5). With age as covariate, the pattern of findings remained: significant diagnosis main effect (F(37,3)=4.655, p=0.016), no brain region × diagnosis interaction, and a significant *post-hoc* difference between BD and NC, but not SZ and NC (not shown).

On NAA levels, there was a significant main effect of brain region (F(36,1)=30.969, p<0.001), no main effect of diagnosis, and a significant diagnosis × brain region interaction (F(36,2) =3.453, p=0.042), reflecting the fact that NAA levels were lower in the ACC but not POC in patient groups. Post-hoc tests revealed that NAA levels in the ACC were significantly lower in SZ but not BD as compared with NC (Dunnett's 2-sided, p=0.031 and p=0.236, respectively) (Table 3).

The remaining 3 metabolites (Cr, Cho, mI) showed no significant main effect of diagnosis (not shown), but a strong effect of brain region (Cr: F(36,1)=191.256, p<0.001; Cho: F(36,1) =305.247, p<0.001; mI: F(34,2)=141.094, p<0.001). No diagnosis × brain region interaction existed for these metabolites (not shown).

Medication and Subgroup Effects

Since all BD subjects and all but one SZ subject were taking second generation antipsychotics, we could not examine the effect of these medications on metabolite measures. Gln/Glu ratios and metabolite levels were no different between patients who were taking benzodiazepines and those who were not (F<1.308, p>0.266 for BD and F<1.294, p>0.266 for SZ). Similarly, grouping by treatment with anticonvulsants (F<4.120, p>0.055 for BD and F<2.300, p>0.142 for SZ) or lithium (F<1.243, p>0.277 for BD and F<2.157, p>0.155 for SZ) had no effect on any measure (Figure 6).

Excluding the 8 patients with schizoaffective disorder from the SZ group, there was still a significant main effect of diagnosis on Gln/Glu (F(30,2)=6.925, p=0.003) and a significant Gln/Glu elevation in BD but not SZ (Dunnett's 2-sided comparison to NC, p=0.002 and p=0.323, respectively). In a one-way ANOVA, Gln/Glu and metabolite levels were no different between 8 schizoaffective disorder and 9 schizophrenia patients (p-values between p=0.624 (Cho) and p=0.890 (NAA)).

DISCUSSION

We found elevated Gln/Glu ratios in mania using 2D *J*-resolved ^{1}H MRS at 4 Tesla, consistent with predicted neuronal-glial coupling abnormalities. The findings were pronounced in bipolar disorder; a cohort of acutely ill schizophrenia patients showed only a trend towards abnormal Gln/Glu ratios. The abnormality existed in both brain areas, suggesting that it may be widespread in the cerebral cortex.

Glutamatergic Neurotransmission in Bipolar Disorder

Although glutamate plays a crucial role in psychiatric disorders, brain Glu levels do not reflect glutamatergic activity because Glu is also involved in cellular metabolism, and because static

Glu measures could mask dynamic changes in Glu synthesis/release/metabolism. Simultaneous Glu and Gln measurements better capture such changes, but even these measures cannot provide direct evidence of synaptic abnormalities because brain Glu and Gln are mostly intracellular. Nonetheless, specific changes in Gln/Glu taken together with known abnormalities in BD may be valuable indicators of glutamatergic function.

Our finding of elevated Gln/Glu ratio in mania is similar to that reported in animal ischemia models where excessive Glu release leads to excitotoxicity [14,15], and in first-episode schizophrenia where it may indicate “greater than normal glutamatergic activity” [32]. In mania, cerebral metabolic rate elevations accompany racing thoughts, distractibility, irritability, and insomnia [49] and our findings are consistent with excessive glutamatergic neurotransmission driven by neuronal activity. In this context, the balance between Glu-Gln conversion in glia and Gln-Glu conversion in neurons appears disrupted due to a breakdown in neuronal-glial interactions. We cannot pinpoint the site of pathology, but well-documented glial number reductions in BD are interesting [3,50] because glial cells modulate neuronal Glu release, and provide Gln to neurons for Glu synthesis [51]. The transport of Gln from glial cells to neurons is poorly understood, but may involve a neuronal Gln transporter [52].

We report elevated Gln/Glu in mania, while others have found lower Gln and higher Glu in depression [30]. The modulation of cortical Gln/Glu by mood state suggests that BD is characterized not by a simple excess or deficiency in glutamatergic signaling, but by an inability to maintain homeostasis. Therefore, therapies reducing variability in glutamatergic neurotransmission, e.g. by stabilizing Glu release through actions on presynaptic metabotropic Glu receptors may be as effective in BD as in SZ [53].

Importantly, our findings are consistent with our *a priori* hypothesis of abnormal glial-neuronal interactions in BD, but by no means provide definitive evidence for it. Elevated Gln/Glu ratios could arise from intermediary metabolism abnormalities where both molecules play a role, or from intraneuronal abnormalities, e.g. in glutaminase which converts Gln to Glu.

Neurochemical Profile of Schizophrenia and Mania

Although there is *postmortem*, biochemical and clinical evidence of glutamatergic abnormalities in schizophrenia [31], we found only a trend toward alterations in brain Gln/Glu ratios in the SZ group. Several factors are relevant: first, our work focused on one specific aspect of glutamatergic neurotransmission, Gln/Glu ratio. This is not an index of total glutamatergic function; rather a specific probe of Glu-Gln cycling. Therefore, significant abnormalities in glutamatergic function in schizophrenia may still exist at the level of the NMDA receptor or in second messenger signaling without any alteration in Gln/Glu ratios. Second, previous studies reported that first-episode schizophrenia patients have elevated Gln but normal Glu levels in ACC [32], and that chronically ill patients show lower than normal Gln and Glu levels [33]. Our finding of no statistical Gln/Glu change in SZ is consistent with this literature because we studied chronically ill patients. It is intriguing that several SZ subjects had elevated Gln/Glu ratios (Figure 5) but correlation of illness duration with Gln/Glu in SZ was not significant (not shown). Studies explicitly designed to test the effect of illness duration on Gln/Glu are needed.

Both BD and SZ showed lower than normal NAA in the ACC, although the effect was statistically significant only in the SZ group. NAA levels reflect neuronal integrity and function, and reductions are reported in several brain regions in BD and SZ [54–56]. Our replication reassures us that our cohort and methodology were consistent with previous studies. By contrast, we did not identify changes in Cho or mI. Abnormalities in both of these metabolites have been reported in some but not all BD studies [57,58]. Possible explanations

for discrepancies include subjects' clinical status (mania vs. euthymia/depression), medication effects, and differences in data acquisition/analysis.

Strengths and Limitations

This study has several strengths: high field strength, novel data acquisition and analysis techniques, and reliable metabolite measures. We evaluated the improvements in Glu and Gln quantification afforded by our approach in two ways: first, we demonstrated that our measures were reliable in a test-retest study. Our reliability measures were comparable to those previously reported for Cr, Cho, NAA, and mI, and improved upon those reported at 1.5T and 4T for Glu and Gln [59–61]. To our knowledge, no other BD or SZ study has reported such reliability estimates. Second, we examined CRLBs in patient data. CRLBs are considered excellent <20% [62]. In our study, mean CRLBs were <20% for all metabolites except for mI (POC) and Gln (both voxels) (Table 2). Both mI and Gln had lower mode/median than mean CRLBs, indicating that the mean was inflated by outliers. The CRLBs obtained for Gln in our study are lower than those in a recent *in vivo* human spectroscopic imaging study at 3T/4T (mid-30%) [46] and a single voxel study at 3T (>35%) [63]. Another 2D MRS study at 3T obtained a mean Gln CRLB of 14% from 27 healthy volunteers in a 15.625cc voxel [36]. Thus, our quantification compares favorably with other studies.

One limitation in this study is that all patients were taking medications. Psychotropic medications have complex and variable effects on glutamatergic neurotransmission, including on Glu receptors [64,65]. For example, 3.6 months of lithium but not valproate treatment in depressed BD outpatients caused a reduction in GM Glx [66]. In animal studies, lithium and valproate stimulate Glu release and inhibit uptake, although chronic treatment has opposite effects [67,68]. We found that lithium, anticonvulsants, or benzodiazepines did not impact MRS measures but this is preliminary due to small N. As for antipsychotic medications, 8 BD patients were taking risperidone, 4 olanzapine, 3 quetiapine, 2 aripiprazole, and 1 ziprasidone (3 patients on combinations). Five SZ patients were taking olanzapine, 4 clozapine, 3 aripiprazole, 2 risperidone, 2 quetiapine, and 1 haloperidol. Although many more BD patients were taking risperidone, all had Gln/Glu ratios similar to others with their diagnosis (BD=0.586, SZ=0.412; see Table 3). Likewise, 5 SZ patients took clozapine (Gln/Glu=0.589), but this did not explain our findings. Although we uncovered no evidence that psychotropic medications affect Gln/Glu ratios, it is likely that medications modulate glutamatergic neurotransmission [69]. Two factors may obscure this effect: first, the sample size in most neuroimaging studies is small and interindividual variability overwhelms all but prominent diagnosis effects. Medication-effect studies are needed to examine these changes [66]. Second, we scanned acutely ill subjects, and 7 BD and 4 SZ patients were unmedicated prior to hospitalization. Therefore, medication effects may be weaker than diagnosis effects.

We did not utilize absolute quantification; such technically demanding and time-consuming attempts were not feasible in this study. We also avoided internal referencing to Cr because of the recent reports suggesting Cr abnormalities in BD and SZ [70,71]. Finally, internal referencing to the water resonance [72] was not possible because we did not acquire water unsuppressed spectra in this study.

Grouping patients with schizophrenia and schizoaffective disorder together is another limitation. Although our analyses revealed no differences in MRS measures between these diagnoses, future studies may find such differences. Finally, because GABAergic interneurons are abnormal in BD and SZ [73,74], measuring GABA levels would be important. While *J*-resolved MRSI allowed quantification of GABA previously [39], this measure did not meet quality-control criteria in our study, possibly because of reduced information in our two-voxel design. GABA-dedicated acquisition protocols may provide further information in this regard [22,28].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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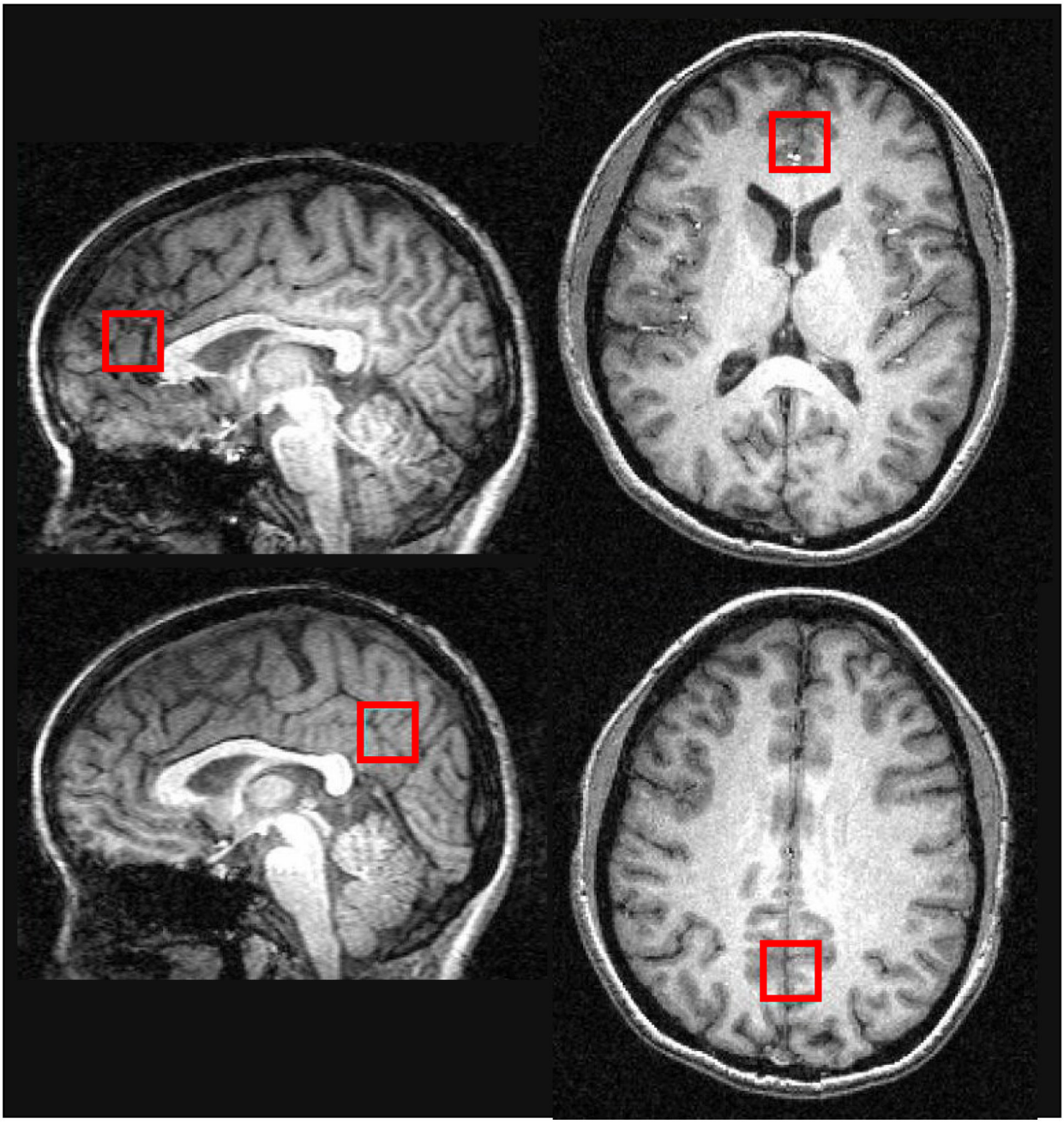

Figure 1.
Parasagittal (left) and axial (right) views of the brain from T1-weighted images illustrate ACC (top) and POC (bottom) voxel placement in one control subject.

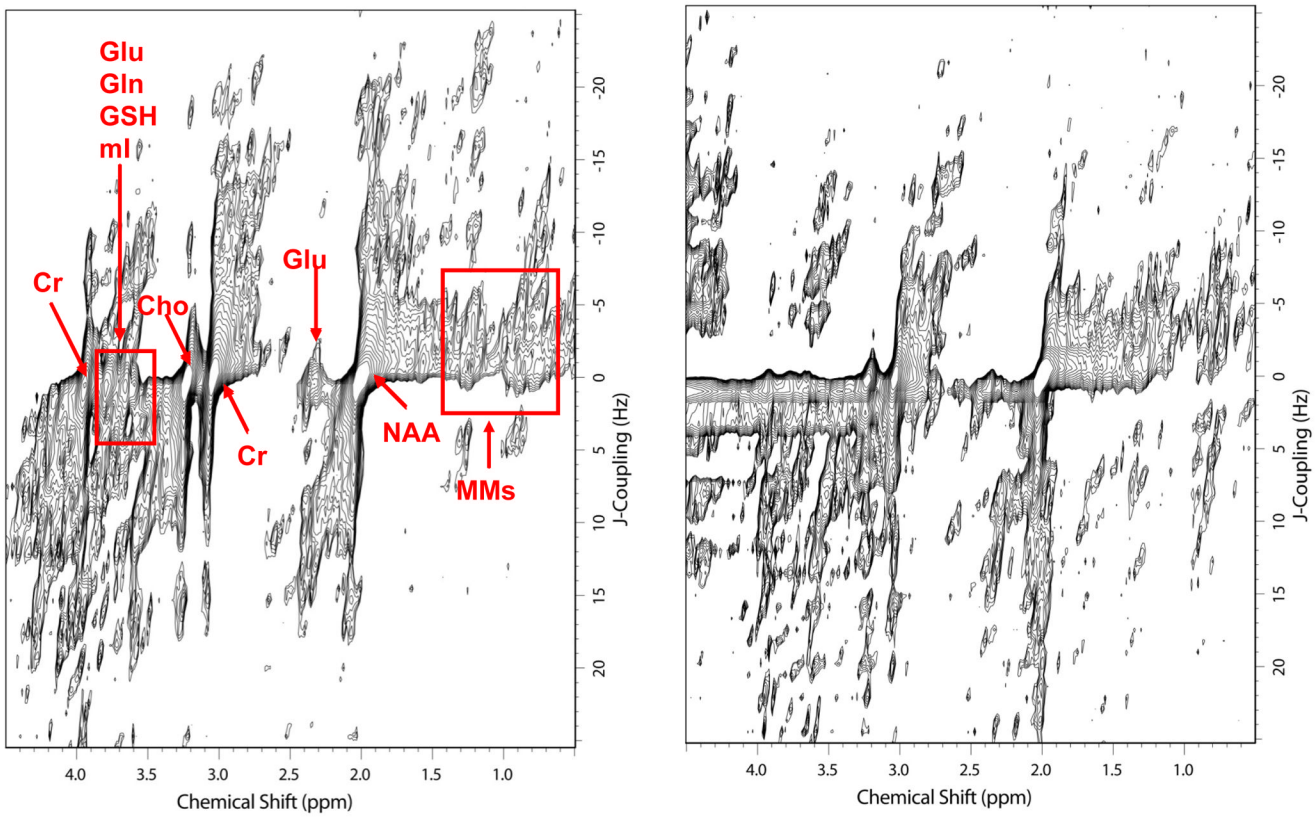

Figure 2.

Contour plots of real 2D spectra from the ACC in a control (left) and BD subject (right). In each case, the X-axis is frequency (F2 in ppm) and the Y-axis is *J* (F1 in Hz). The spectral region from about −35 to +35Hz is shown. The main metabolite resonances recognizable in the plots are labeled. Although mI and Gln resonances are not well-resolved in these plots, the additional information available from 2D MRS allows improved fitting of these metabolites as discussed in the text. Note the variable nature of the macromolecule signal profile (highlighted in a box in the left panel) between the two spectra. Abbreviations as in the text; H_2O – water, GSH – glutathione, MMs - macromolecules.

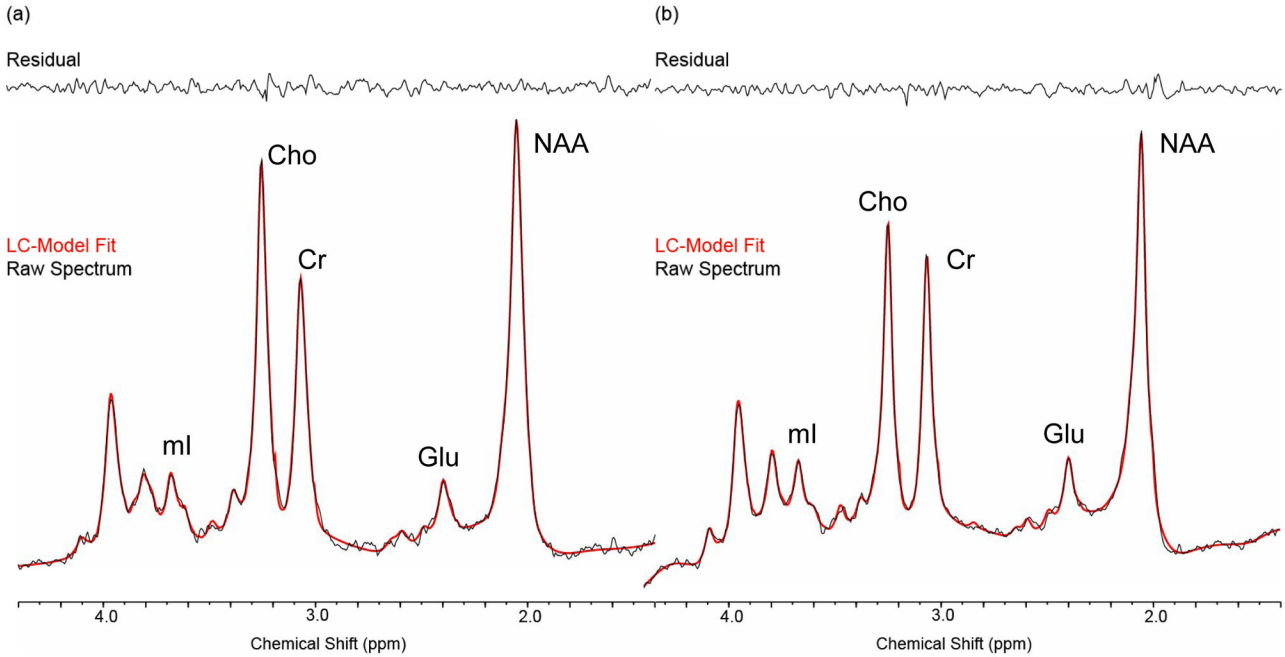

Figure 3.

Sample 1D spectra extracted from 2D datasets at *J*=0.0Hz. These spectra are from the ACC in a control (left) and BD subject (right). Raw data are visible as a black line and the LCModel spectral fit is in red, with the residual shown in the top panel. Metabolite resonances identifiable in this spectral extraction are labeled; note that Gln resonances are not apparent at *J*=0.0Hz.

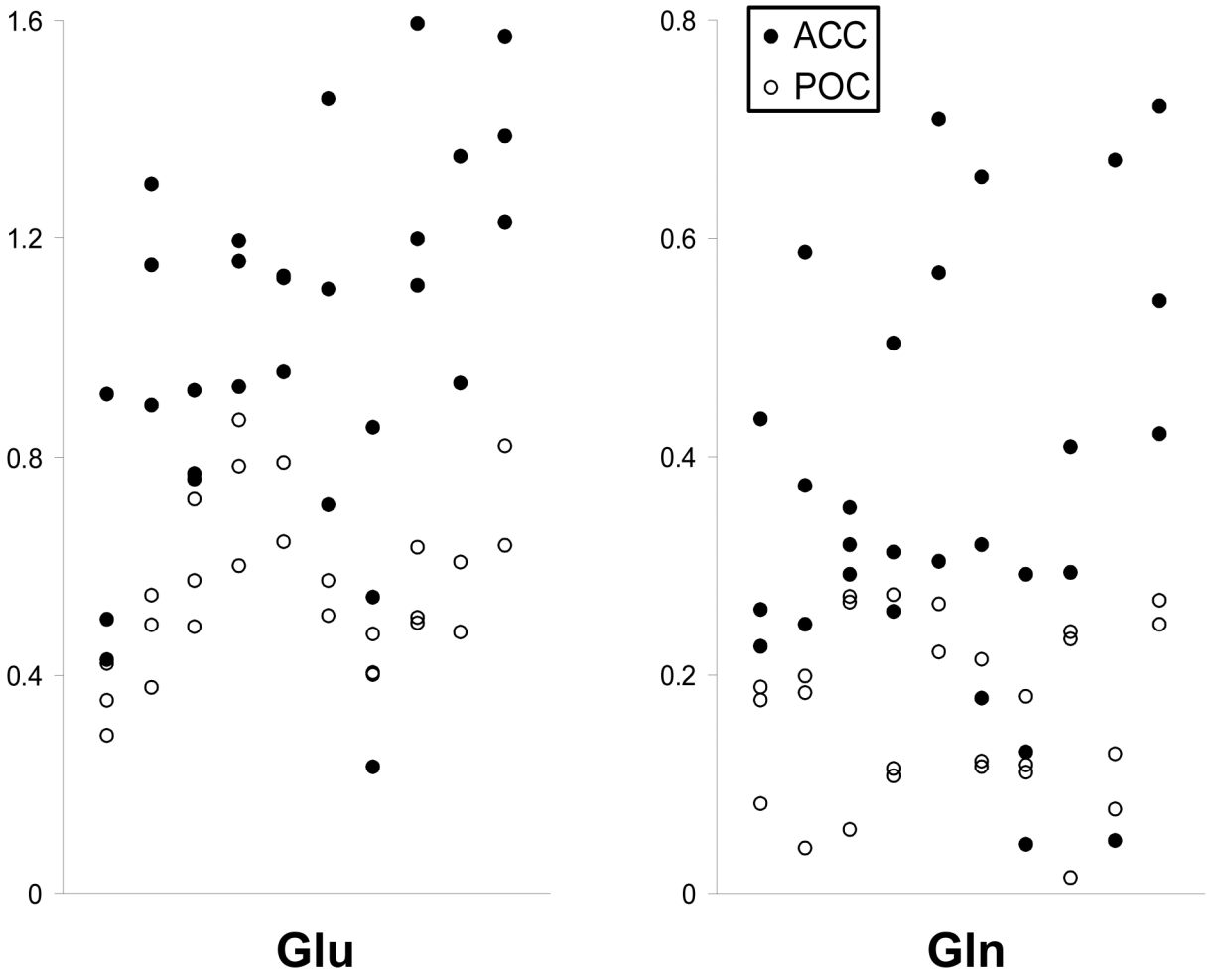

Figure 4.
Scatter plot of Glu and Gln measures expressed as Arbitrary Units (AU) for all 10 subjects in the test-retest study. See text for details. Note that in general, within-subject variability across scans is less significant than between-subject variability, Glu levels are higher than Gln levels, and ACC levels of both metabolites are higher than those in the POC.

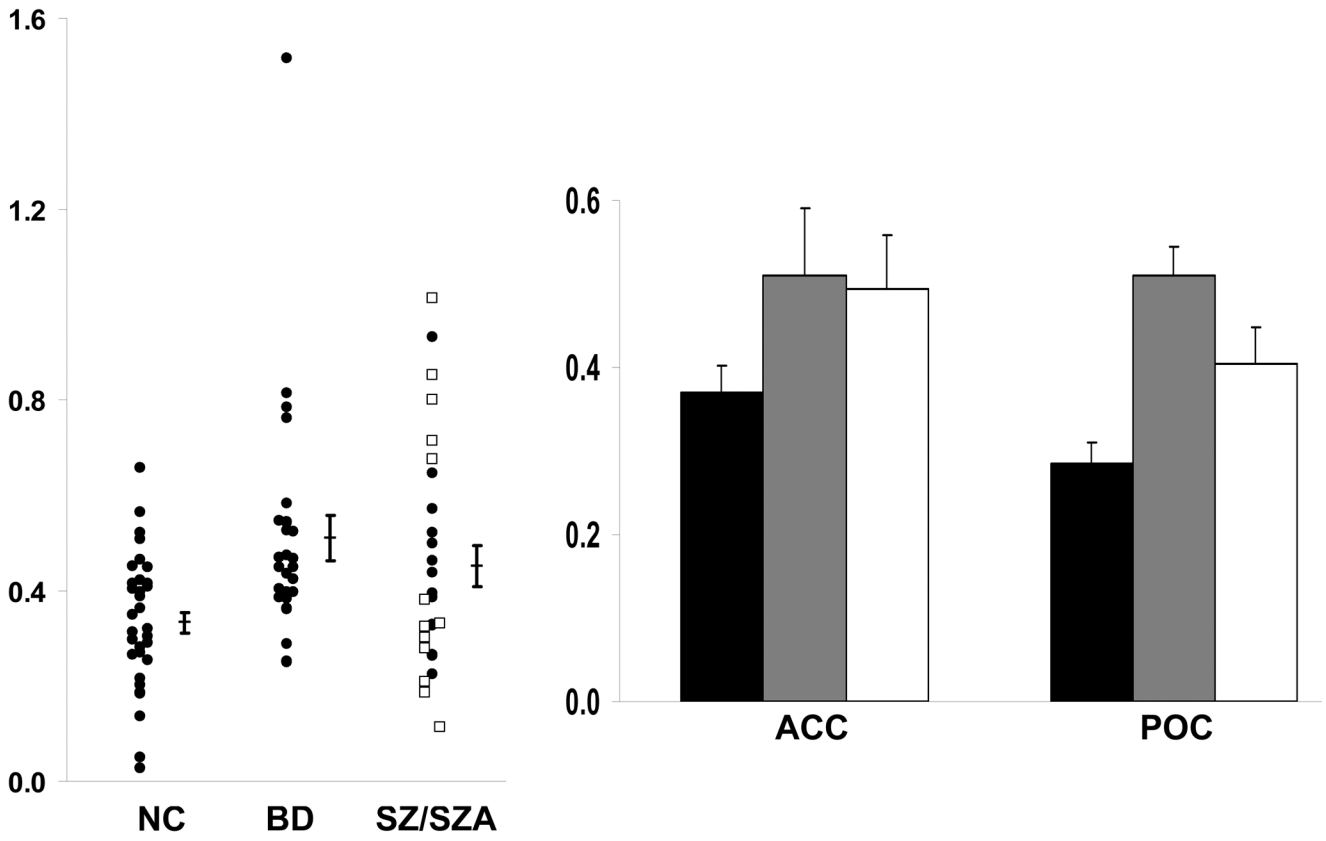

Figure 5.

Gln/Glu ratios in the three study groups. The left panel shows a scatter plot of Gln/Glu in NC, BD, and SZ groups with ACC and POC data points presented on the same graph, and mean and standard errors depicted adjacent to the data for each group. Within the SZ group, data from patients with schizoaffective disorder are depicted with open squares. The right panel shows Gln/Glu in the ACC and POC voxels in NC, BD and SZ groups (black, grey and white bars, respectively). Mean±SE are shown.

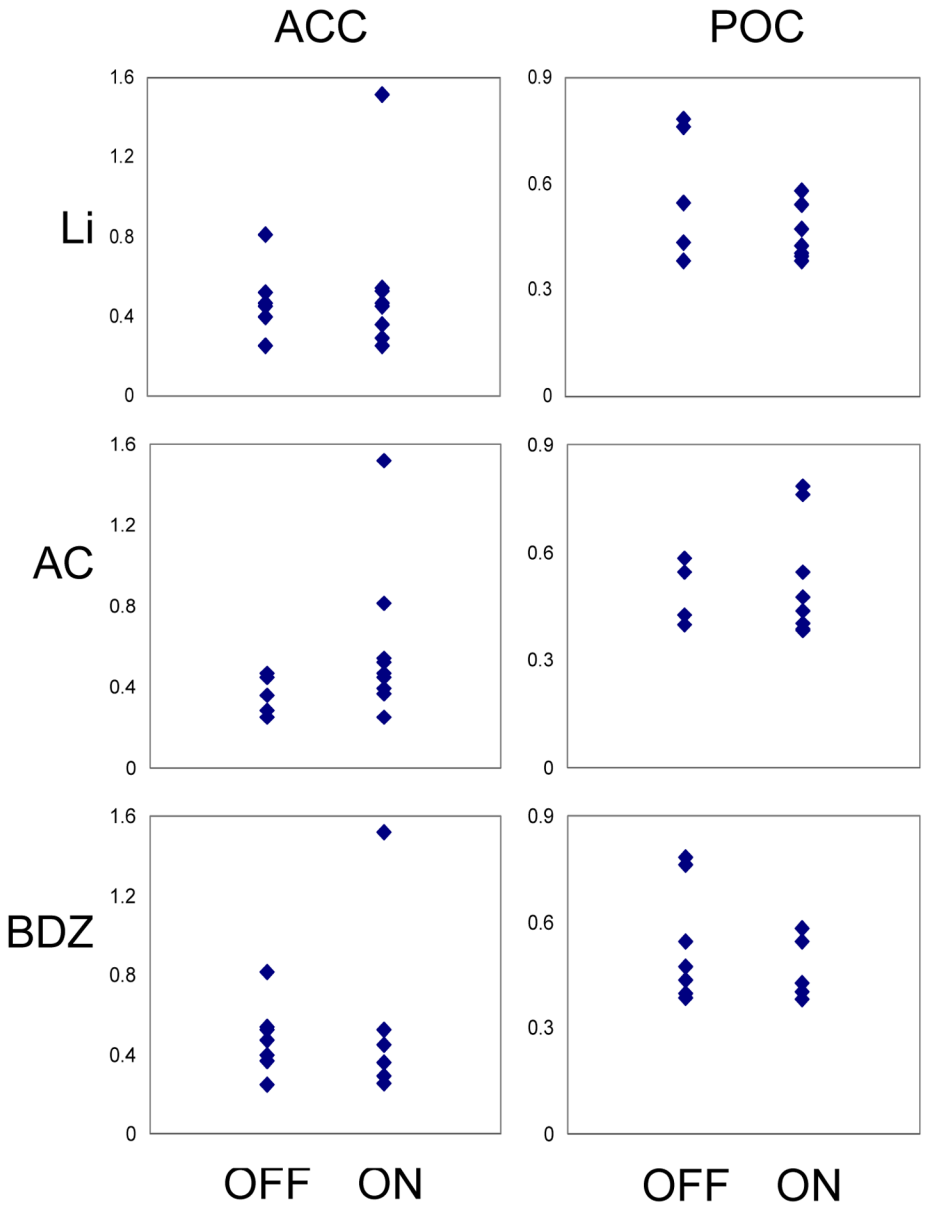

Figure 6.

Gln/Glu in BD patients grouped according to medication status. In each panel, data points on the left are from patients not taking the specified medication while those on the right are from patients taking the medication (Li – Lithium; AC – Anticonvulsants; BDZ – Benzodiazepines; left column – data from ACC; right column – data from POC).

Table 1

Subject demographic and clinical information (Mean±SD where appropriate)

	Normal Control (N=21)	Bipolar Disorder (N=15)	Schizophrenia (N=17)	Statistical Evaluation
Age	34.3±10.0	36.3±11.6	41.8±9.8	F(50,2)=2.52; p=0.10
Gender	11M, 10F	7M, 8F	10M, 7F	χ^2 0.48; p=0.79
Age of onset	--	25.5±9.5	23.5±7.7	F(26,1)=0.92; p=0.76
MADRS	--	11.1±3.6	16.6±7.3	F(29,1)=7.16; p=0.01
YMRS	--	24.7±8.9	14.8±9.0	F(29,1)=9.70; p=0.004
PANSS	--	59.6±13.9	86.0±19.8	F(29,1)=18.15; p<0.001
Lithium	--	9	3	χ^2 6.01; p=0.02
Anticonvulsants	--	10 (8 valproate)	7	χ^2 2.08; p=0.15
SGAs	--	15	16	χ^2 0.91; p=0.34
FGAs	--	0	2	χ^2 1.11; p=0.29
CPZ equivalents	--	244±122	542±412	F(28,1)=7.18; p=0.01
Benzodiazepines	--	7	9	χ^2 0.13; p=0.72

Abbreviations are as in the text. SGA: Second generation antipsychotic; FGA: First generation antipsychotic.

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Table 2

Cramer Rao Lower Bounds (in %)

	ACC			POC		
	Mode	**Median**	**Mean**	**Mode**	**Median**	**Mean**
NAA	5	5	6	3	5	6
Cr	4	4	4	4	4	5
Cho	6	6	6	9	8	8
mI	5	9	14	8	13	21
Glu	11	13	16	15	14	17
Gln	18	26	36	21	19	28

All abbreviations are as in the text.

Table 3

Metabolite levels (in AUs; Mean±SD)

	Gln/Glu	Glu	Gln	Cr	NAA	Cho	mI
ACC							
NC	0.369±0.147	1.084±0.283	0.400±0.196	1.390±0.341	1.290±0.372	1.894±0.500	1.085±0.324
BD	**0.511±0.312***	0.952±0.229	0.502±0.371	1.343±0.383	1.146±0.372	1.810±0.480	0.956±0.250
SZ	0.494±0.267	0.919±0.306	0.449±0.284	1.210±0.376	**1.000±0.423***	1.823±0.580	0.919±0.334
POC							
NC	0.286±0.117	0.533±0.162	0.160±0.098	0.657±0.198	0.824±0.247	1.289±0.402	0.487±0.177
BD	**0.510±0.140***	0.536±0.108	0.264±0.054	0.731±0.169	0.866±0.194	1.268±0.281	0.483±0.097
SZ	0.405±0.182	0.552±0.104	0.222±0.099	0.736±0.170	0.859±0.185	1.463±0.371	0.505±0.134

*Group value significantly different from Control value (see text for statistical details)