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Title: A 1H-MRS Investigation of the Medial Temporal Lobe in Antipsychotic-Naïve and Early-Treated First Episode Psychosis

Article Type: Full Length Article

Keywords: Antipsychotics, MRS, schizophrenia, early psychosis, brain metabolism

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A $^1$H-MRS Investigation of the Medial Temporal Lobe in Antipsychotic-Naïve and Early-Treated First Episode Psychosis

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2. ORYGEN Research Centre, Department of Psychiatry, University of Melbourne, Australia
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Running head: Proton spectroscopy in treated and treatment-naïve psychosis

Word count: 2380 (exc. Abstract and References)

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ABSTRACT

Schizophrenia is associated with significant brain abnormalities, including changes in brain metabolites as measured by proton magnetic resonance spectroscopy (MRS). What remains unclear is the extent to which these changes are a consequence of the emergence of psychotic disorders or the result of treatment with antipsychotic medication. We assessed 34 patients with first episode psychosis (15 antipsychotic naïve) and 19 age- and gender-matched controls using short-echo MRS in the medial temporal lobe bilaterally. Overall, there were no differences in any metabolite, regardless of treatment status. However, when the analysis was limited to patients with a diagnosis of schizophrenia, schizophreniform or schizoaffective disorder, significant elevations of creatine/phosphocreatine (Cr/PCr) and myo-inositol (mI) were found in the treated group. These data indicate a relative absence of temporal lobe metabolic abnormalities in first episode psychosis, but suggest that some treatment-related changes in mI might be apparent in patients with schizophrenia-spectrum diagnoses. Seemingly illness-related Cr/PCr elevations were also specific to the diagnosis of schizophrenia spectrum disorder and seem worthy of future study.

KEYWORDS: Antipsychotics, MRS, schizophrenia, early psychosis, brain metabolism

Word count (abstract): 167
1. INTRODUCTION

Schizophrenia is a disorder associated with significant brain abnormalities, such as enlarged lateral ventricles and reduced cortical grey matter volume (Shenton, et al., 2001). However, these changes are subtle and relatively non-specific. An alternative approach to the study of the disease is the use of magnetic resonance spectroscopy (MRS), a technique that allows the in vivo measurement of important brain metabolites such as neurotransmitters or bioenergetic molecules. The vast majority of MRS studies have used proton MRS, and have studied the amino acid N-acetylaspartate (NAA), a presumed marker for neuronal viability (Birken and Oldendorf, 1989); (although see Bhakoo and Pearce, 2000). The exact role of NAA in brain metabolism is unclear, but because its rate of production is tightly coupled with glucose metabolism (Moreno, et al., 2001), it may be an osmolyte that prevents the build up of intraneuronal water associated with neural activity (Baslow, 2003), although there is also evidence that it plays a role in myelin synthesis (Chakraborthy, et al., 2001).

In chronic schizophrenia, NAA reduction is most consistently found in the prefrontal cortex of patients with established illness (Keshavan, et al., 2000; Steen, et al., 2005), where it is associated with poorer cognition (Bertolino, et al., 2000), longer duration of illness (Stanley, et al., 1996) and greater levels of negative symptoms (Callicott, et al., 2000). There have been some studies indicating prefrontal reductions in NAA in schizophreniform disorder (Bertolino, et al., 2003), and although others have not shown this (Wood, et al., 2003), there may be an association with later clinical outcome (Wood, et al., 2006). There is also evidence for NAA reduction in the medial temporal lobes of patients with chronic schizophrenia (Keshavan, et al., 2000; Steen,
et al., 2005), but the evidence for similar reductions in the first episode is less robust. Although there is one study demonstrating hippocampal NAA reduction in schizophreniform psychosis (Bertolino, et al., 2003), we and others have failed to show this (Wood, et al., 2003; Molina, Sánchez, et al., 2005; Ohrmann, et al., 2005). One reason for this discrepancy, not yet explored, is that antipsychotic treatment might result in a decline in hippocampal NAA over a number of years (Bustillo, Lauriello, et al., 2002). However, recent work is inconsistent on this question. Some studies show a similar NAA reduction in naïve and treated patients (Cecil, et al., 1999), while others show no difference from controls (Bustillo, Rowland, et al., 2002). There are also data to suggest that antipsychotic-naïve first-episode patients already have reductions in NAA (Fannon, et al., 2003), and that treatment actually increases NAA levels in both recent-onset cases and patients with chronic illness (Fannon, et al., 2003; Szulc, et al., 2005).

Metabolites other than NAA may also be of interest, such as trimethylamines (choline-containing metabolites; TMA) or myo-inositol (mI), which both play roles in second messenger systems (Fisher, et al., 1992; Hodgkin, et al., 1998). Both metabolites have other functions; the TMA peak may represent a marker for membrane phospholipid metabolism (Berger Gregor E, et al., 2002), while mI has been implicated as an organic osmolyte (Cordoba, et al., 1996). Studies of neuroleptic-naïve patients are inconsistent with respect to these metabolites (Cecil, et al., 1999; Bustillo, Rowland, et al., 2002; Fannon, et al., 2003). Treatment with olanzapine has been shown to result in increased levels of TMA in first episode mania (DelBello, et al., 2007), while levels of mI are elevated by risperidone in chronic schizophrenia (Szulc, et al., 2005).
In this study we directly compared $^1$H-MRS derived metabolite concentrations from the medial temporal lobes of two groups of first-episode psychosis patients – one antipsychotic-naïve, and the other treated with an atypical antipsychotic medication for a maximum of 23 days. Based on our earlier findings and the published literature, we predicted that there would be reductions in NAA in the naïve but not the treated group, whilst there would be elevations of both TMA and ml in the treated group, but an elevation of TMA alone in the naïve group.

2. METHODS

2.1 Participants

Thirty-four patients who were part of a larger randomized double-blind placebo-controlled clinical trial (Berger Gregor E, et al., In press) were recruited from the Early Psychosis Prevention and Intervention Centre (EPPIC) at ORYGEN Youth Health. Study inclusion criteria were: (1) age at onset 15 – 29 years (inclusive), (2) currently psychotic as reflected by the presence of at least one of; (a) delusions, (b) hallucinations, (c) disorder of thinking/speech, other than simple acceleration or retardation, (d) disorganised, bizarre, or markedly inappropriate behaviour. DSM-IV diagnoses were obtained from all patients using the Structured Clinical Interview for DSM-IV (First, et al., 1997) three weeks after entry to the study. Diagnoses were schizophrenia (n=9), schizophreniform psychosis (n=13), schizoaffective disorder (n=3), major depression with psychotic symptoms (n=6) and psychosis NOS (n=3). Patients with a diagnosis of bipolar disorder with psychotic features were not recruited but referred to a concurrent intervention study running on site. Fifteen
patients were scanned neuroleptic-naïve (80% schizophrenia spectrum), while the remaining 19 (68% schizophrenia spectrum) had received at least one dose of an atypical antipsychotic medication (risperidone n=8, quetiapine n=5, olanzapine n=6; median number of days on medication = 6, range 1 – 23; median cumulative dose at scan (chlorpromazine equivalents) = 600mg, range 101 – 4600mg). Nineteen healthy volunteers were selected from a larger sample recruited from similar socio-demographic areas as the patients in order to match as closely as possible for age and gender.

Seven neuroleptic-naïve patients (six male, one female, all schizophrenia-spectrum diagnoses) were rescanned after twelve weeks of treatment (mean time between scan = 83 days). Three were treated with quetiapine, two with risperidone and two with olanzapine (median cumulative dose between scan (chlorpromazine equivalents) = 18270mg, range 6700 – 26200mg).

All subjects were screened for co-morbid medical conditions by clinical assessment, physical and neurological examinations. Exclusion criteria for all subjects were: a history of significant head injury, seizures, neurological diseases, impaired thyroid function and steroid use. Control subjects with a personal history of psychiatric illness or family history of psychosis were excluded. The local research and ethics committee approved this protocol, and each subject (or their guardian) provided written informed consent.
2.2 Proton Magnetic Resonance Spectroscopy

Short-echo (TE 30 ms) acquisition proton MRS was performed on a 3T GE LX Horizon scanner (GE Healthcare, Milwaukee, USA) using a PRESS sequence with two chemical-shift selective imaging pulses for water suppression. Spectra were acquired with 128 transients of 2k data points over a frequency width of 5000 Hz with TR = 3 sec. Spectra were recorded from single isotropic 2 cm voxels, placed in each temporal lobe. Three-plane localizing images were acquired to allow prescription of regions of interest (ROI) for spectra. Sagittal plane, 2 cm thick scout images (T1 spin-echo), followed by 2 cm thick coronal images, centred in the plane of the ponto-medullary junction, were acquired. A ROI in each temporal lobe was selected in the coronal plane with the lateral aspect of the hippocampus in the centre of the ROI. The sagittal image was viewed to ensure that the ROI did not include petrous temporal bone. This region of interest consisted largely of the anterior hippocampus (>50%).

Spectra were analyzed with LCModel (Provencher, 1993), using a basis set of 15 metabolites acquired on-site, incorporating the standard macromolecule and baseline fitting routines of LCModel. Metabolite concentrations were estimated following calibration using the tissue water signal as an internal standard, and corrected for the grey matter tissue fraction in the voxel as necessary. Results are presented in institutional units approximating millimolar concentration and were rejected if the Cramer-Rao lower-bound was greater than 35%. Full-width-half-maxima and signal-to-noise ratios averaged 0.092 ± 0.014 ppm and 11.4 ± 2.3 respectively across both hemispheres.
2.3 Statistical analysis

Demographic data were compared between the groups using analysis-of-variance, t-tests, Chi-square and Mann-Whitney U tests. The distribution of each metabolite concentration was inspected for outliers and checked for normality. Following this, metabolites were compared between the three groups using repeated-measures ANOVA, with hemisphere as the repeated measure. Post-hoc testing was performed with Tukey’s honestly-significant-difference test. Longitudinal analysis was conducted using single-value t-tests.

3. RESULTS

Demographic and clinical information is shown in Table 1. There were no significant differences between the groups on any of the measures.

Metabolite data for the three groups is displayed in Table 2.

3.1 NAA

Repeated-measures ANOVA demonstrated a significant effect of hemisphere (left > right; $F_{1,50}=22.38$, $p<0.001$), but no significant effect of treatment group ($F_{2,50}=2.48$, $p=0.094$) nor treatment group by hemisphere interaction ($F_{2,50}=0.90$, $p=0.415$).
3.2 TMA

Repeated-measures ANOVA demonstrated a significant effect of hemisphere (left > right; $F_{1,50} = 6.34$, $p = 0.015$), but no significant effect of treatment group ($F_{2,50} = 1.06$, $p = 0.355$) nor treatment group by hemisphere interaction ($F_{2,50} = 0.22$, $p = 0.802$).

3.3 Cr/PCr

Repeated-measures ANOVA demonstrated no significant main effect of hemisphere ($F_{1,50} = 1.53$, $p = 0.222$) or treatment group ($F_{2,50} = 2.08$, $p = 0.136$), nor a treatment group by hemisphere interaction ($F_{2,50} = 0.38$, $p = 0.684$).

3.4 mI

Repeated-measures ANOVA demonstrated no significant main effect of hemisphere ($F_{1,50} = 0.40$, $p = 0.530$) or treatment group ($F_{2,50} = 1.93$, $p = 0.156$), nor a treatment group by hemisphere interaction ($F_{2,50} = 0.66$, $p = 0.520$).

3.5 Glx

Repeated-measures ANOVA demonstrated no significant main effect of hemisphere ($F_{1,50} = 0.74$, $p = 0.394$) or treatment group ($F_{2,50} = 1.62$, $p = 0.208$), nor a treatment group by hemisphere interaction ($F_{2,50} = 0.14$, $p = 0.874$).

3.6 Schizophrenia-spectrum disorders

All analyses were repeated after excluding the nine patients diagnosed with psychosis NOS or MDD with psychotic features (see Table 3 for demographic details for this subgroup). This did not change the findings for NAA, TMA or Glx (although the treatment group effect for NAA approached significance; $F_{2,41} = 2.9$, $p = 0.067$). A
significant treatment group effect was identified, however, for both mI ($F_{2,41}=3.3$, $p=0.046$) and Cr/PCr ($F_{2,41}=3.28$, $p=0.048$). In both cases, post-hoc testing with Tukey’s h-s-d test showed significantly higher concentrations in the early-treated spectrum group compared to controls. Neuroleptic-naïve spectrum patients did not significantly differ from the other two groups (Figure 1).

--- Figure 1 about here ---

Pearson’s correlations were conducted between cumulative antipsychotic dose at time of scan (in chlorpromazine equivalents) and the concentration of NAA, Cr/PCr and mI separately (collapsed across hemisphere), for the treated group only. This was significant for mI ($r=0.601$, $p=0.03$), but not for NAA or Cr/PCr ($r=-0.168$, $p=0.58$ and $r=0.352$, $p=0.24$, respectively).

3.7 Longitudinal analysis

Percentage change in the five metabolites over 12 weeks varied between an increase of 7.5% for NAA and a decrease of 2.3% for Cr/PCr (Table 4). One-sample t-tests showed that none of these changes were significantly different to zero (all $p>0.2$). Spearman’s correlations between the cumulative antipsychotic dose and the percent change ranged from 0.571 for NAA to –0.214 for Glx; however, none of these were significant (all $p>0.15$).

4. DISCUSSION

This study demonstrates no alteration in medial temporal metabolites measured by proton spectroscopy in early psychosis, regardless of treatment status. Of particular
interest, the presumed neuronal marker NAA was unaffected at first presentation, replicating our previous finding at lower magnetic field (Wood, et al., 2003) and extending this to other metabolites. This supports our volumetric study that showed that the hippocampus is generally intact in first episode psychosis and only becomes abnormal with continued illness (Velakoulis, et al., 2006). It does, however, run counter to the findings of a recent meta-analysis (Steen, et al., 2005), perhaps due to the very short duration of untreated psychosis in the current study and/or the moderate sample size. Furthermore, we found no significant alteration in glutamate and glutamine, in line with previous studies of the medial temporal lobe (Keedy, et al., 2006; Olbrich, et al., 2007).

However, significant alterations in metabolite concentrations were found when those with affective psychosis or psychosis NOS were excluded. Specifically, we identified an increase in Cr/PCr and mI concentrations in those who had already begun treatment at the time of scanning compared to controls. Antipsychotic-naïve patients did not significantly differ from the treated patient group or the controls. It is unclear whether these findings indicate a treatment-mediated alteration, an effect of the illness or a combination of the two i.e. an enhancement of a normal illness effect by medication.

It is reasonable to believe that, for Cr/PCr, an illness effect is the most likely cause of the elevation in concentration. It has been noted previously that the Cr/PCr resonance changes with regional metabolic activity, owing to T$_2$ differences between Cr and PCr (Ke, et al., 2002). Increases in the signal intensity may therefore be the result of increased metabolic activity, rather than increased concentration. Indeed, there is
some evidence for increased metabolic activity in the temporal lobes of unmedicated schizophrenia patients (Soyka, et al., 2005) and also specifically in the hippocampi of first episode schizophrenia patients compared with non-schizophrenia patients (Molina, Sanz, et al., 2005). The fact that there was no significant correlation between concentration and antipsychotic dose, and that the effect sizes of the increase in the two groups are broadly comparable (Treated = 0.865, Naïve = 0.599), supports the notion that it is a result of the illness rather than treatment. However, the possibility that treatment accentuates the effect of the disorder cannot be discounted.

In contrast, the significant correlation between mI concentration and antipsychotic dose makes it more likely that the increase is a response to antipsychotic treatment, which would fit with the notion of mI as a second messenger (Hodgkin, et al., 1998). At least one previous study has found an effect of risperidone on mI concentration (Szulc, et al., 2005), and the effect sizes of the two groups in the current study are quite different (Treated = 0.988, Naïve = 0.433). This increase in mI may be related to astrocyte activation (Rothermundt, et al., 2007), and is also seen in other diseases where there is gliosis (e.g. hypothalamic hamartoma Freeman, et al., 2004). Potentially this could be due to the neuroprotective properties of atypical antipsychotics (for review, see Berger, et al., 2003), although chronic exposure to antipsychotics appears to result in a lower glial cell number (Konopaske, et al., 2007). Whether this effect is specific to the schizophrenia spectrum, however, is unclear. Examination of the date from the nine patients with a non-schizophrenia spectrum diagnosis shows that the six who were treated had mI concentrations that were around 15% higher than the three who were scanned neuroleptic-naïve.
4.1 Longitudinal analyses

No significant changes were identified in the seven patients for whom longitudinal data were available. Indeed, what is apparent from Table 4 is the large variation in metabolite concentration over the follow-up interval, both increases and decreases. Such variability indicates that significant longitudinal effects are only likely to be found where they are very large (such as Berger, et al., 2008), or where large samples are used (Venkatraman, et al., 2006).

4.2 Limitations

Our findings are limited by a number of factors. Firstly, we only examined the hippocampus; other regions may be differently affected by antipsychotics (Szulc, et al., 2005) or just be differently involved in the pathophysiology of psychotic disorders (e.g. differences in outcome prediction of MRS measures of frontal and temporal lobe (Wood, et al., 2006)). Secondly, the treated patients may be significantly different to naïve patients in some unmeasured way, relating to why they were unable to be scanned before starting antipsychotic medication. Further, the treated patients had varied time on treatment, and were on different atypical antipsychotics (although there may not be much effect of different treatments (Szulc, et al., 2007)). Finally, patients were recruited into the study as part of a randomised trial of essential fatty acids supplementation (Berger, et al., In press), potentially biasing participation to those willing to be involved in a long study (more than 12 weeks).

In conclusion, although first episode psychosis patients as a group show no evidence of metabolic brain changes in the medial temporal lobe (regardless of treatment status), there do seem to be effects in patients with a schizophrenia spectrum
diagnosis. In particular, significant elevations in the concentrations of Cr/PCr and mI were found in the group receiving antipsychotic medication. However, inspection of the relationship between these metabolites and dose indicates that only the changes to mI are a response to treatment.

REFERENCES


numbers in the parietal cortex of macaque monkeys.
Neuropsychopharmacology. 32 1216-1223.
magnetic resonance spectroscopy (1H MRS study). Medical Science Monitor. 13 17-22.
<table>
<thead>
<tr>
<th></th>
<th>Naïve (n=15)</th>
<th>Treated (n=19)</th>
<th>Control (n=19)</th>
<th>Test Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent male</td>
<td>80%</td>
<td>63%</td>
<td>63%</td>
<td>$\chi^2(2)=1.4$, $p=0.500$</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20.0 (4.0)</td>
<td>19.5 (3.2)</td>
<td>21.0 (4.4)</td>
<td>$F_{2,52}=0.63$, $p=0.536$</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>19.9 (4.0)</td>
<td>19.4 (3.2)</td>
<td>. . .</td>
<td>$t_{32}=0.4$, $p=0.714$</td>
</tr>
<tr>
<td>Median DUP (weeks)</td>
<td>6.0 (0.25-36)</td>
<td>3.0 (0.2-30)</td>
<td>. . .</td>
<td>$U=119.5$, $p=0.574$</td>
</tr>
<tr>
<td>Percent smokers</td>
<td>64%</td>
<td>59%</td>
<td>33%</td>
<td>$\chi^2(2)=3.7$, $p=0.161$</td>
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<tr>
<td>Percent cannabis users</td>
<td>50%</td>
<td>47%</td>
<td>22%</td>
<td>$\chi^2(2)=3.3$, $p=0.191$</td>
</tr>
<tr>
<td>GAF$^1$</td>
<td>45.9 (11.6)</td>
<td>47.0 (13.0)</td>
<td>. . .</td>
<td>$t_{30}=-0.2$, $p=0.810$</td>
</tr>
<tr>
<td>Total CDSS$^2$</td>
<td>11.4 (6.5)</td>
<td>9.0 (3.8)</td>
<td>. . .</td>
<td>$t_{21.9}=1.3$, $p=0.22$</td>
</tr>
<tr>
<td>Total PANSS$^3$</td>
<td>77.4 (13.4)</td>
<td>80.3 (17.1)</td>
<td>. . .</td>
<td>$t_{22}=-0.5$, $p=0.656$</td>
</tr>
</tbody>
</table>

Table 1. Clinical and demographic details. Data are presented as mean (standard deviation) unless otherwise noted.

1 Data unavailable for one naïve and one early-treated patient

2 Data unavailable for two early-treated patients

3 Data unavailable for three naïve and seven early-treated patients
<table>
<thead>
<tr>
<th></th>
<th>Naïve</th>
<th></th>
<th></th>
<th>Treated</th>
<th></th>
<th></th>
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<td>Right</td>
<td>Left</td>
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</tr>
<tr>
<td><em>NAA</em></td>
<td></td>
<td>6.01 (0.89)</td>
<td>5.46 (0.59)</td>
<td>6.61</td>
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<td><em>TMA</em></td>
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<td>1.19 (0.20)</td>
<td>1.11 (0.30)</td>
<td>1.27</td>
<td>1.21 (0.24)</td>
<td>1.25 (0.23)</td>
<td>1.13</td>
<td>0.17</td>
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<tr>
<td><em>Cr/PCr</em></td>
<td></td>
<td>3.95 (0.58)</td>
<td>3.92 (0.81)</td>
<td>4.11</td>
<td>4.01 (0.75)</td>
<td>3.80 (0.92)</td>
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<td><em>mI</em></td>
<td></td>
<td>3.30 (0.73)</td>
<td>3.22 (1.07)</td>
<td>3.50</td>
<td>3.59 (0.82)</td>
<td>3.24 (0.69)</td>
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<td><em>Glx</em></td>
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<td>6.38 (1.46)</td>
<td>6.69 (0.91)</td>
<td>6.93</td>
<td>7.05 (1.08)</td>
<td>6.37 (1.62)</td>
<td>6.70</td>
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Table 2. Mean (standard deviation) metabolite concentrations for the three subject groups.
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<td><strong>Percent male</strong></td>
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<td><strong>Age (years)</strong></td>
<td>20.2 (4.3)</td>
<td>20.3 (3.4)</td>
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<td><strong>Age at onset (years)</strong></td>
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<td>20.2 (3.4)</td>
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<td><strong>Median DUP (weeks)</strong></td>
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<td>2.75 (0.2-30)</td>
<td>U=52.5, p=0.259</td>
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<td><strong>Percent smokers</strong></td>
<td>58%</td>
<td>75%</td>
<td>n.a.</td>
</tr>
<tr>
<td><strong>Percent cannabis users</strong></td>
<td>50%</td>
<td>67%</td>
<td>n.a.</td>
</tr>
<tr>
<td><strong>GAF</strong>^1</td>
<td>46.7 (8.7)</td>
<td>44.3 (9.3)</td>
<td>t_{21}=0.7, p=0.516</td>
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<td><strong>Total CDSS</strong>^2</td>
<td>10.4 (6.0)</td>
<td>8.3 (2.6)</td>
<td>t_{15.3}=1.1, p=0.286</td>
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<td><strong>Total PANSS</strong>^2</td>
<td>74.4 (9.1)</td>
<td>90.3 (15.9)</td>
<td>t_{7.0}=-2.6, p=0.06</td>
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Table 3. Clinical and demographic details for the schizophrenia-spectrum patients only. Data are presented as mean (standard deviation) unless otherwise noted.

^1 Data unavailable for one naïve and one early-treated patient
Data unavailable for two early-treated patients

Data unavailable for two naïve and seven early-treated patients
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<td>-31</td>
<td>6</td>
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<tr>
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Table 4. Percent metabolite change over 12 weeks in seven individual patients
Figure 1. Metabolite concentrations for mI, Cr/PCr and NAA for the schizophrenia-spectrum diagnosis patients.
Acknowledgement

None
Conflict of interest

Both Professors McGorry and Pantelis have received funding from Eli Lilly, AstraZeneca, Bristol-Myers-Squibb, and Jansen-Cilag. All other authors declare that they have no conflicts of interest.
Contributors

Drs Wood and Berger designed the study and wrote the protocol. Drs Berger and Proffitt, and Ms McConchie, recruited the patients and collected clinical data. Dr Wellard managed the acquisition and quality of the spectroscopy data. Dr Wood performed the statistical analyses and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.
Role of funding source

This work was supported by two NH&MRC project grants (ID: 145627 & 209062), a NH&MRC program grant (ID: 350241), and the Colonial Foundation, Melbourne, Australia. Dr Wood is the recipient of National Health & Medical Research Council Career Development Award and a NARSAD Young Investigator Award. Dr Berger was supported by a Swiss National Science Foundation young investigator award, and a Margaret & Walter Lichtenstein Foundation award (University of Basel). None of these bodies had any further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.