Prediction of Functional Outcome 18 Months After a First Psychotic Episode

A Proton Magnetic Resonance Spectroscopy Study

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Context: Recent magnetic resonance imaging studies have attempted to relate volumetric brain measurements in early schizophrenia to clinical and functional outcome some years later. These studies have generally been negative, perhaps because gray and white matter volumes inaccurately assess the underlying dysfunction that might be predictive of outcome.

Objective: To investigate the predictive value of frontal and temporal spectroscopy measures for outcome in patients with first-episode psychoses.

Design: Left prefrontal cortex and left mediotemporal lobe voxels were assessed using proton magnetic resonance spectroscopy to provide the ratio of N-acetylaspartate (NAA) and choline-containing compounds to creatine and phosphocreatine (Cr) (NAA/Cr ratio). These data were used to predict outcome at 18 months after admission, as assessed by a systematic medical record audit.

Setting: Early psychosis clinic.

Participants: Forty-six patients with first-episode psychosis.

Main Outcome Measures: We used regression models that included age at imaging and duration of untreated psychosis to predict outcome scores on the Global Assessment of Functioning Scale, Clinical Global Impression scales, and Social and Occupational Functional Assessment Scale, as well as the number of admissions during the treatment period. We then further considered the contributions of premorbid function and baseline level of negative symptoms.

Results: The only spectroscopic predictor of outcome was the NAA/Cr ratio in the prefrontal cortex. Low scores on this variable were related to poorer outcome on all measures. In addition, the frontal NAA/Cr ratio explained 17% to 30% of the variance in outcome.

Conclusions: Prefrontal neuronal dysfunction is an inconsistent feature of early psychosis; rather, it is an early marker of poor prognosis across the first years of illness. The extent to which this can be used to guide treatment and whether it predicts outcome some years after first presentation are questions for further research.

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some reporting an inverse correlation between the ventricle-brain ratio and outcome,22,23 and not others.24 Some investigations were retrospective in nature or were restricted to particular subgroups of patients (eg, inpatients); therefore, it is unclear whether these relationships are the result of selection bias.

Some studies (mainly using magnetic resonance imaging) have attempted to examine the prediction of outcome in a prospective design. One study, by Mille et al,25 investigated 123 patients with a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder and attempted to predict outcome during 5 years (measured as psychosocial function, time spent as an inpatient, and duration of clinically significant symptoms) using 7 volumetric measures obtained at baseline (frontal and temporal tissue, frontal and temporal cerebrospinal fluid, cerebral and cerebellar tissue, and ventricular cerebrospinal fluid). Only temporal lobe tissue volume significantly predicted outcome, with smaller temporal volume at baseline predicting greater persistence of psychotic symptoms. However, this only explained 5.8% of the variance in persistence of hallucinations, indicating that its prognostic value was low. An additional investigation was a multicenter European study26 of 109 patients with recent-onset schizophrenia followed up 2 years later. Outcome (measured in terms of need for care and social functioning) was predicted using 7 baseline volumetric measures (intracranial, total brain, cerebral gray and white matter, lateral and third ventricles, and cerebellum), but no significant relationship was found.

Assessment of outcome in both studies,25,26 was methodologically good and included a structured interview with the patient at follow-up. This implies that the failure of these studies to find clinically significant relationships between baseline structural imaging data and outcome at least 2 years later is either because there is no such relationship to find or because of the relative insensitivity of volumetric methods to the functional integrity of the brain. An imaging tool that might have better predictive power for outcome in psychotic disorders is magnetic resonance spectroscopy (MRS). This technique assesses the concentration of various brain metabolites in vivo and as such is able to give more detailed information about the integrity of the region of interest at the cellular and metabolic levels compared with the relatively gross volumetric estimates. This is especially true for a disorder such as schizophrenia, in which the cellular abnormalities remain unclear.27 However, to date there have been no studies using this technique to predict outcome from a first psychotic episode, to our knowledge.

One metabolite that has been of particular interest in schizophrenia is N-acetylaspartate (NAA), which has long been considered a marker of neuronal integrity.28 Although it is agreed that NAA is present both intraneuronally and extraneuronally (eg, as demonstrated by Bhakoo and Pearce29), it is reduced in conditions in which there is persistent or reversible neuronal loss.30 In schizophrenia, reduction in NAA level is most consistently found in the prefrontal cortex of patients with established illness,31 where it is associated with poorer cognition,32 longer duration of illness,33 and greater levels of negative symptoms.34 These findings suggest that the level of prefrontal NAA may be associated with poor outcome, but it is unknown if this relationship is present at first onset or if it develops during the disorder. There have been some investigations indicating prefrontal reductions in NAA in schizophreniform disorder,35 but others have not shown this.36

In this study, we aimed to explore the predictive value of baseline measures that included symptoms and NAA/creatinine (Cr) ratios in the left hippocampus and prefrontal cortex for 18-month clinical and functional outcome from the earliest phase of a first episode of psychosis.

METHODS

PARTICIPANTS

Forty-six patients with first-episode psychosis (63% male) were recruited from the Early Psychosis Prevention and Intervention Centre (part of ORYGEN Research Centre), Melbourne.37 Study inclusion criteria were (1) age at onset of 15 to 29 years (inclusive) and (2) currently psychotic as reflected by the presence of at least 1 of the following 4 symptoms: (a) delusions, (b) hallucinations, (c) disorder of thinking or speech other than simple acceleration or retardation, and (d) disorganized, bizarre, or markedly inappropriate behavior. The DSM-IV diagnoses were derived from a retrospective medical record audit (described in the “Outcome Data” subsection). The mean±SD age of the group was 21.6±3.2 years, with a median DUP of 46 days (range, 0-3317 days). Diagnoses included schizophrenia (n=18), schizophreniform psychosis (n=6), schizoaffective disorder (n=7), bipolar disorder with psychotic symptoms (n=9), major depression with psychotic symptoms (n=2), delusional disorder (n=1), and psychosis not otherwise specified (n=3). All patients were being treated with atypical antipsychotic medication at the time of imaging (mainly 2-4 mg of risperidone or 5-10 mg of olanzapine). Six of the patients were also treated with lithium carbonate (500-1500 mg/d).

All subjects were screened for comorbid medical and psychiatric conditions by clinical assessment and by physical and neurological examinations. Exclusion criteria were seizures, polydipsia, neurological diseases, impaired thyroid function, corticosteroid use, a history of significant head injury, electroconvulsive therapy during the 6 months before imaging, or a DSM-IV diagnosis of alcohol or other substance dependence. The North Western Health Care Network/University of Melbourne research and ethics committees approved the research protocol, and all subjects provided written informed consent.

PROSPECTIVE DATA

Psychopathology

Levels of psychopathology were assessed at the time of imaging using the Positive and Negative Syndrome Scale38 in all but 4 patients. Rather than using the total or subscale scores, we used a 5-factor model (negative syndrome, delusions and hallucinations, cognitive disturbance, antisocial tendency, and affective syndrome) that best approximates the underlying structure of the instrument, similar to the model described by White et al.39 In particular, we used a summary score composed of emotional withdrawal, blunted affect, lack of spontaneity, passive/apathetic social withdrawal, poor rapport, motor retardation, and active social avoidance to represent the negative syndrome.40
Magnetic Resonance Spectroscopy

Proton spectra were acquired from all subjects using a 1.5-T scanner (GE Medical Systems, Milwaukee, Wis) at the Royal Melbourne Hospital, Melbourne, Australia. Two volumes of interest (dimensions, 15 × 15 × 15 mm) were obtained from the left hemisphere in each patient, one in the mediotemporal lobe and one in the middle frontal gyrus. These were localized on the T1-weighted coronal images obtained for volumetric purposes; the midpoint of the mediotemporal voxel was positioned 4.5 mm posterior to the amygdala, and the midpoint of the middle frontal voxel was positioned 7.5 mm anterior to the genu of the corpus callosum (Figure 1). The mediotemporal voxel was positioned so that the hippocampus touched the bottom and the left-hand side of the box, and the middle frontal voxel was placed as far laterally as possible without including the skull in the region of interest. Shimming was performed by an automated global shim, and water-suppressed spectra were acquired using a point-resolved spectroscopy sequence (repetition time, 1500 milliseconds; echo time, 135 milliseconds; and number of signals acquired, 128). Spectra were analyzed using the LCModel method, and data are reported as the ratio of the NAA (2.01 ppm) and choline-containing compounds (3.20 ppm) peaks to the Cr peak (3.02 ppm). The output from LCModel includes the Cramer-Rao lower bounds, which are a measure of reliability. For the hippocampal region, the mean Cramer-Rao lower bounds for each metabolite were as follows: Cr, 11.2; NAA, 8.0; and choline-containing compounds, 9.1. For the frontal region, the same metabolites had mean Cramer-Rao lower bounds as follows: Cr, 10.8; NAA, 5.7; and choline-containing compounds, 9.9. Sample spectra for both regions of interest are shown in Figure 2.

OUTCOME DATA

Outcome data were derived from the First Episode Psychosis Outcome Study, a systematic medical record audit of all patients consecutively accepted and subsequently treated at the Early Psychosis Prevention and Intervention Centre between January 1998 and December 2000. Treatment included a standardized initial psychiatric assessment (including psychiatric history and a detailed mental state examination), outpatient case management, cognitive behavioral therapy, low-dose antipsychotic therapy, an inpatient unit for acute care during crisis ad-

Figure 1. Magnetic resonance images showing the location of the midpoint of the mediotemporal voxel (A) and the dorsolateral prefrontal voxel (B). The images are presented in radiological format, with the left hemisphere on the right.

Figure 2. Sample spectra and LCModel fits (heavy line) from the mediotemporal voxel (A) and the dorsolateral prefrontal voxel (B).
missions, a mobile crisis intervention and community treatment team, acute and recovery group programs, family work, and specialized consultations to treat enduring positive psychotic symptoms, if necessary, for an episode of care of 18 months. Details of the medical record review methods, including comprehensive quality assurance strategies, are fully described elsewhere. Demographic and illness-related details were assessed using the Early Psychosis File Questionnaire, a comprehensive instrument that consists of questions from the Royal Park Multidimensional Instrument for Psychosis, the Drug and Alcohol Assessment Schedule, a modified version of the Brief Psychiatric Rating Scale, the Clinical Global Impression (CGI)–Schizophrenia Scale, the CGI–Bipolar Illness Scale, the Global Assessment of Functioning (GAF) Scale, the Social and Occupational Functional Assessment Scale (SOFAS), the Premorbid Adjustment Scale, the Vocation and Location Index, a modified version of the Udvalg for Kliniske Undersøgelser Adverse Effect Scale, and measures of level of engagement (score range, 1-5), compliance (on a 4-point scale ranging from 0 [total noncompliance] to 3 [full compliance] with antipsychotic treatment), current drug use (type of substance and modification of use), and traumatic life events. The North Western Health Care Network/University of Melbourne approved the study.

Interrater reliability was established for all primary and secondary outcome scales used in the study by randomly selecting 40 medical records stratified by time. Each of these medical records was assessed independently by the 2 main investigators (M.L. and P.C.), who gave ratings related to the situation at enrollment in the Early Psychosis Prevention and Intervention Centre on the following scales: CGI–Schizophrenia, CGI–Bipolar Illness, GAF, SOFAS, Premorbid Adjustment, and Insight. Analysis revealed good to very good interrater reliability, with κ values ranging from 0.82 to 0.92 (CGI–Schizophrenia, 0.87; CGI–Bipolar Illness mania severity, 0.89; CGI–Bipolar Illness depression severity, 0.87; GAF, 0.88; SOFAS, 0.92; Premorbid Adjustment, 0.82; and Insight, 0.89).

Concurrent validity was examined by assessing the correlation between CGI–Schizophrenia, GAF, and SOFAS scores at baseline and at discharge or loss to follow up. Correlation coefficients between those scales were high (>0.78), and scores on the scales were all significantly correlated with one another (P<.001).

Validity of the diagnosis was also examined. Between 1998 and 2000, 230 patients at the Early Psychosis Prevention and Intervention Centre were included in prospective trials and were assessed using a Structured Clinical Interview for DSM-IV Axis I disorders for psychotic and comorbid diagnoses soon after entry to the service (weeks 2-4). In 115 medical records randomly selected from the 230 medical records, the assessed diagnoses were compared with those given in the First Episode Psychosis Outcome Study. The κ values revealed good concordance for psychosis diagnoses (κ=0.795) and for comorbid substance abuse diagnoses (κ=0.736).

In this study, outcome data included GAF, SOFAS, and CGI scores at discharge, and the number of inpatient admissions during the 18-month treatment period. The number of inpatient admissions was selected (rather than a measure such as the number of days hospitalized during the treatment period) because it represented a measure of successive psychotic exacerbations.

**STATISTICAL ANALYSIS**

The statistical analyses were conducted in similar fashion to those of Miley et al. We first tested if there was an effect of each regional metabolite ratio on the outcome variables as a whole (discharge GAF, CGI, and SOFAS scores, and the number of acute admissions). For each of the 4 metabolite ratios, we performed a joint omnibus multivariate regression test, which assessed the effect of the metabolite ratio on all 4 outcome variables simultaneously. For ratios in which this test was significant at P=.05, follow-up analyses were performed with each outcome variable independently. Duration of untreated psychosis and age at the time of MRS imaging were entered as covariates in all analyses (it was previously shown that there is no effect of DUP on spectroscopy variables in this cohort).

Within the regression-based analysis, we introduced model terms that represented the interaction between diagnostic group and regional metabolite ratios. In effect, this amounted to fitting separate regression lines (between metabolite ratio and outcome) for each diagnostic group and then testing whether the slopes of those regression lines were the same.

Outcome variables for the sample at discharge are summarized in Table 1, along with the same variables at intake. There were no significant sex or diagnostic (schizophrenia spectrum vs nonschizophrenia spectrum) differences for any of the 4 outcome measures or on covariates such as age at MRS, CGI scores at intake, GAF scores at intake, or any of the 5 symptom scale scores. However, DUP significantly differed between the diagnostic groups (Mann-Whitney test, 144.5; P=.04), with the nonschizophrenia spectrum group having a median DUP of 30 days compared with 61 days in the schizophrenia spectrum group.

Left mediotemporal MRS data were available from all but 1 patient, whose data were unusable (because of poor shim, broad line widths, and a signal-noise ratio of 1), and left prefrontal MRS data were available from all but 5 patients (unusable in 1 patient [failed water suppression] and not performed in 4 patients). The 6 patients for whom complete MRS data were unavailable were significantly older than the remaining 40 patients (24.1 vs 21.3 years; t44=-2.1, P=.04) and had significantly higher scores on the antisocial tendency syndrome (14.3 vs 10.3; 0.78).
charge (F1,40 = 7.94, \( P = .01 \)) However, they were not receiving significantly higher doses of antipsychotic medication.

Four joint omnibus tests for effects of each metabolite ratio in each region of interest on all 4 outcome measures were performed. Duration of untreated psychosis and age at MRS were included in the analyses. Of all spectroscopy measures, only the NAA/Cr ratio in the left frontal region of interest was significantly related to outcome (F4,40 = 4.30, \( P = .006 \); \( P > .2 \) for all other measures). Each outcome measure was then individually tested using the left frontal NAA/Cr ratio. There were statistically significant effects of the NAA/Cr ratio on CGI scores at discharge (F1,40 = 5.67, \( P = .02 \)), GAF scores at discharge (F1,40 = 7.94, \( P = .008 \)), SOFAS scores at discharge (F1,40 = 13.27, \( P = .001 \)), and the number of admissions during the treatment period (F1,40 = 10.73, \( P = .002 \)). Figure 3 shows the relationship between the frontal NAA/Cr ratio and the GAF score at discharge.

Because negative symptoms at baseline assessment and premorbid functioning (assessed by GAF score) have previously been related to outcome in studies of schizophrenia, both factors were entered as additional covariates in the omnibus regression test. Table 1 gives the mean values for both of these variables. The frontal NAA/Cr ratio continued to have a significant effect on GAF scores at discharge (F1,36 = 5.99, \( P = .02 \)), SOFAS scores at discharge (F1,36 = 8.97, \( P = .005 \)), and the number of admissions (F1,36 = 5.11, \( P = .03 \)). The frontal NAA/Cr ratio no longer significantly predicted CGI scores at discharge, but this effect was still a trend (F1,36 = 3.21, \( P = .08 \)). Together, the 5 predictive factors (frontal NAA/Cr ratio, baseline negative symptoms, premorbid GAF score, age at imaging, and DUP) explained more than 60% of the variance in GAF scores at discharge, 63% of the variance in SOFAS scores at discharge, 38% of the variance in CGI scores at discharge, and 54% of the variance in the number of admissions, with the frontal NAA/Cr ratio alone explaining 17%, 17%, 24%, and 30%, respectively (Table 2).

There were no diagnostic subgroup (schizophrenia spectrum vs nonschizophrenia spectrum) effects in the relationships between the frontal NAA/Cr ratio and outcome variables (\( P > .75 \) for all). Adding the remaining 4 symptom factors from the Positive and Negative Syndrome Scale (cognitive disturbance, delusions and hallucinations, affective symptoms, and antisocial tendency) did not alter our findings, and none of these factors significantly predicted any outcome variable. Furthermore, the results were unchanged when the 6 patients treated with lithium were excluded from the analyses.

**COMMENT**

To our knowledge, this is the first study to use proton MRS data, acquired early in the first episode of a psychotic illness, to predict functional outcome after 18 months of optimal treatment. We demonstrated that the NAA/Cr ratio in the left prefrontal cortex is related to clinical severity and to global function at the end of the treatment phase and is predictive of the number of acute inpatient admissions during the same period. These findings are independent of baseline levels of negative symptoms, age, and DUP, suggesting a primary role of prefrontal neuronal dysfunction in patients with poor outcome.

These data suggest that a lower frontal NAA/Cr ratio (presumably a result of lower NAA) may be a marker of an intermediate phenotype of patients with first-episode psychosis with poor response to optimal treatment. This may explain the more consistent MRS findings in chronic illness and the considerable variability in studies of first-episode patients.\(^{31,36}\) In the absence of differences when compared with controls, there is an association between greater prefrontal NAA reductions and greater symptom severity (and poorer social functioning) in deficit schizophrenia.\(^{37}\) A similar result was obtained in inpatients.\(^{39}\) Both studies\(^{34,37}\) and the present findings implicate prefrontal neuronal or synaptic dysfunction as a potential component of poor outcome. The results of our study further suggest that this association can be identified early on with the emergence of frank psychotic symptoms. Therefore, patients included in most imaging studies of chronic schizophrenia may have more severe illness and poorer prognosis, characterized by prominent negative symptoms and neuropsychological deficits implicating frontal systems (eg, as demonstrated by Pantelis et al\(^{39}\)). It is likely that such patients at onset of illness showed more prominent negative symptoms and had compromised frontal lobe integrity. One study has suggested a decline in the frontal NAA/Cr ratio with continued illness on the basis of cross-sectional data from a few patients.\(^{59}\) However, close examination of those data reveals that the patient with chronic schizophrenia did not have NAA/Cr ratios that fell below the range of the recent-onset group; instead, they were equal to the bottom 30% to 40%, suggesting that poor outcome is associated with lower NAA/Cr ratios early in the course of illness. Previous work from our group identified poorer prefrontal cortical function in prodromal patients who later become psychotic, suggesting that poor outcome and poor prefrontal cortex integrity are linked before frank psychosis.\(^{60,61}\)

The lack of association between mediotemporal metabolite ratios and outcome may reflect a lesser degree...
of impairment in this region early in the course of illness. Although mediomental lobe structures, including the hippocampus, have been reported as being reduced in volume from illness onset, recent work among our large cohort suggests that such abnormalities are not found at the earliest phases of the illness. Instead, mediomental lobe abnormalities may arise over time with continued illness.

It is unclear what a lower NAA/Cr ratio is signaling in terms of underlying neuronal function. The rate of NAA production seems to be tightly coupled to the rate of glucose metabolism, which has led to the suggestion that permetabolic state, which is an uncommon finding in schizophrenia research. Fourth, because the outcome data were obtained using the GAF Scale and SOFAS are global and do not capture the many dimensions of functioning. However, the use of more detailed scales would have been inappropriate in the context of a medical record audit. Fifth, the MRS voxel was fairly large, and we did not interpret the correlation between outcome and NAA/Cr ratio, suggesting that the degree of shared variance is small. Third, because we used a ratio rather than an absolute quantification of metabolites, a poor outcome might be associated with an increased Cr peak rather than lower NAA. However, this would likely reflect a hypermetabolic state, which is an uncommon finding in schizophrenia research. Fourth, because the outcome data were obtained using medical record audit, the measures obtained using the GAF Scale and SOFAS are global and do not capture the many dimensions of functioning. However, the use of more detailed scales would have been inappropriate in the context of a medical record audit. Fifth, all the analyses assume a linear relationship between outcome and the predictive variables, which may not be the case for DUP. Sixth, given recent reports of progressive brain change in the disorder, the relationship we identified may have an association with the degree of change. Within-subject longitudinal studies are needed to adequately address this issue.

In summary, we have shown that prefrontal neuronal and synaptic integrity early in a first psychotic episode, as assessed by the NAA/Cr ratio, is predictive of functional outcome 18 months later. This has a high degree of relevance to our understanding of the variability in outcome from first-episode psychosis, suggesting that impaired prefrontal function is associated with poor prognosis. It also opens the way for possible clinical applications of in vivo brain MRS in the treatment of psychotic disorders.

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Table 2. Regression Variables for the Prediction of the Outcome Measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>GAF Scores at Discharge</th>
<th>CGI Scores at Discharge</th>
<th>No. of Admissions</th>
<th>SOFAS Scores at Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P$ Value, $\beta$</td>
<td>Variance, %</td>
<td>$\chi^2$</td>
<td>$P$ Value, $\beta$</td>
</tr>
<tr>
<td>Frontal NAA/Cr ratio</td>
<td>0.002 0.32</td>
<td>16.6</td>
<td>0.002 0.25</td>
<td>29.7 &lt;.001</td>
</tr>
<tr>
<td>Age at imaging</td>
<td>0.18 0.19</td>
<td>2.4</td>
<td>−0.33 10.6</td>
<td>&lt;.01 0.68</td>
</tr>
<tr>
<td>Duration of untreated psychosis</td>
<td>0.66 −0.05</td>
<td>3.1</td>
<td>0.19 3.5</td>
<td>&lt;.01 0.58</td>
</tr>
<tr>
<td>Premorbid GAF Scale</td>
<td>0.48 0.04</td>
<td>32.0</td>
<td>−0.30 9.7</td>
<td>−0.35 34.9</td>
</tr>
<tr>
<td>Baseline negative symptoms</td>
<td>0.31 0.19</td>
<td>6.8</td>
<td>0.27 &lt;.01</td>
<td>−0.04 10.5</td>
</tr>
</tbody>
</table>

Abbreviations: CGI, Clinical Global Impression scales; GAF, Global Assessment of Functioning Scale; NAA/Cr, $N$-acetylaspartate–creatine and phosphocreatine; SOFAS, Social and Occupational Functional Assessment Scale.
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Author Contributions: Dr Wood takes responsibility for the integrity of the data and the accuracy of the data analysis for this study. All authors had full access to all the data in the study.

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