King's Research Portal

DOI:

[10.1016/j.biopsych.2010.10.004](https://doi.org/10.1016/j.biopsych.2010.10.004)

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Brugger, S., Davis, J. M., Leucht, S., & Stone, J. (2011). Proton Magnetic Resonance Spectroscopy and Illness Stage in Schizophrenia-A Systematic Review and Meta-Analysis. *Biological psychiatry*, 69(5), 495 - 503. [N/A]. <https://doi.org/10.1016/j.biopsych.2010.10.004>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Proton Magnetic Resonance Spectroscopy and Illness Stage in Schizophrenia – A Systematic Review and Meta-Analysis

Stefan Brugger^{1,2}
 John Davis^{3,4}
 Stefan Leucht⁵
 James M Stone^{1,6*}

¹King's College London Institute of Psychiatry
 De Crespigny Park
 London
 SE5 8AF

²St George's, University of London
 Cranmer Terrace
 London
 SW17 0RE

³Psychiatric Institute,
 Department of Psychiatry,
 University of Illinois at Chicago,
 Chicago, IL
 USA

⁴University of Maryland Psychiatric Research Center,
 Baltimore, MD
 USA

⁵Department of Psychiatry and Psychotherapy,
 Technische Universität München,
 Germany

⁶Imperial College London
 Hammersmith Hospital
 Du Cane Road
 London
 W12 0NN

*Corresponding Author:
 E517
 Burlington Danes Building
 Hammersmith Hospital
 Du Cane Road
 London
 W12 0NN

Tel: 020 7594 7087
 Fax: 020 7594 6548
james.m.stone@imperial.ac.uk

number of words in the abstract: 234
 number of words in the text: 3998
 number of tables: 5
 the number of figures: 8
 number of supplementary material: 1

Key Words: Schizophrenia, Psychosis, MRS, Spectroscopy, NAA, Abstract:

Background

It is not known whether regional brain N-acetyl aspartate (NAA) changes in the progression from prodrome to chronic schizophrenia. We used effect size meta-analysis to determine which brain regions show the most robust reductions in NAA first episode and chronic schizophrenia as measured by proton magnetic resonance spectroscopy (1H-MRS), and to determine whether these changes are present in individuals at high risk of developing schizophrenia.

Methods

We identified 131 papers of which 97 met inclusion criteria. Data were separated by stage of illness (at risk, first episode schizophrenia, chronic schizophrenia) and by brain region. For each region, mean and standard deviation of the NAA measure was extracted.

Results

Significant reductions in NAA levels were found in frontal lobe, temporal lobe and thalamus in both patient groups (effect size > 0.3 ; $p < 0.01$). In individuals at high risk of schizophrenia (of whom approximately 20% would be expected to undergo transition to psychosis), significant NAA reductions were present in thalamus (effect size = 0.78; $p < 0.05$), with reductions at trend level only in temporal lobe (effect size = 0.32; $p < 0.1$), and no reductions in frontal lobe (effect size = 0.05; $p = 0.5$).

Conclusions

These data suggest that schizophrenia is associated with loss of neuronal integrity in frontal and temporal cortices and in the thalamus, and suggest that these changes in the frontal and temporal lobe may occur in the transition between the at-risk phase and the first episode.

Introduction

Proton magnetic resonance spectroscopy (1H-MRS) studies in patients with schizophrenia have frequently reported regional reductions in N-acetyl aspartate (NAA), a brain metabolite present at very high concentrations in neurons in the CNS. Reductions in NAA levels measured by 1H-MRS are associated with ischemic brain injury and dementia, leading to the suggestion that NAA represents a surrogate marker of neuronal integrity (1). NAA also plays a role in myelin lipid synthesis, the control of osmolality, energy metabolism and neurotransmission (through the synthesis of NAAG by combination with glutamate) (1). An earlier meta-analysis, by Steen and colleagues, of frontal and medial temporal lobe 1H-MRS findings in patients with schizophrenia and first episode schizophrenia (FES) revealed that NAA levels were reduced in both regions, but that there was not any difference between FES and chronic schizophrenia (2).

Recent years have seen an explosion of interest in the prodrome of schizophrenia, with many groups studying individuals with attenuated psychotic symptoms and people at risk of schizophrenia due to their family history. Of course, only a proportion of these individuals eventually go on to develop schizophrenia (3). Nonetheless, several MRI studies have shown that people at risk of developing schizophrenia have alterations in gray matter volume compared to healthy controls (4-6), and that they have further reductions in gray matter volume associated with transition to psychosis (5).

Reductions in NAA reported in 1H-MRS studies of individuals at risk of schizophrenia suggest that these grey matter changes may have a neuronal basis (7),

perhaps representing the loss of dendritic arborization that has been reported in schizophrenia (8). It should be noted that not all 1H-MRS measures in people at risk of schizophrenia have been in agreement (9-10). Given the wide variance with 1H-MRS, and the requirement for relatively large sample sizes to obtain data with reasonable power (11), this is not altogether surprising.

Here, using a meta-analysis of the current literature, we test the hypothesis that regional reductions in NAA are associated with illness progression. We hypothesize that NAA reductions are most marked in patients with chronic schizophrenia, and are less evident in individuals with FES and in individuals at risk of schizophrenia.

Methods

Selection of studies

We selected all English-language studies published (or made available electronically) before 31st August 2009, of proton spectroscopy in patients with schizophrenia and individuals at high risk of schizophrenia compared to normal controls. We employed a search strategy using PubMed with keywords “MRS” and one of “schizophrenia”, “psychosis”, “UHR”, “ARMS”, “ultra high risk”, “prodromal”, “prodrome” or “schizoaffective”, obtaining hard-copies of all papers reporting NAA levels in patients with schizophrenia. We also obtained all papers referenced in two previous systematic reviews of the field (12-13). We selected all papers reporting mean and standard deviation for NAA in patients with schizophrenia, FES, and high risk of schizophrenia with a matched control group. Where mean and/or standard deviations for NAA were not reported, the authors of the papers were contacted. Efforts were made not to double-count subject data – papers in which this was suspected to have

occurred were excluded from the analysis.

Methodological considerations

Analysis of proton magnetic resonance spectroscopy data is complicated by the fact that the brain chemicals detected by ^1H -MRS (termed metabolites) occur in grey and white matter but not in CSF. If the area from which the spectrum is acquired (voxel) contains a large percentage of CSF, the estimated metabolite concentrations measured using ^1H -MRS will underestimate their actual concentration in brain tissue (14).

There are two methods commonly used to correct for this problem. The first is to report a ratio of the metabolite of interest to one of the other metabolites that are thought to remain relatively constant (either creatine - Cr, or less commonly choline - Cho). This has the potential drawback that if Cr or Cho levels are altered by illness state, the resultant ratio will be affected. The second method is to correct metabolite measures (either water-scaled or “absolute”) for the amount of CSF and brain tissue in the voxel by dividing the metabolite measure by the percent tissue volume in the voxel, sometimes with a further correction made for the relative grey and white matter content of the voxel (voxel brain tissue corrected) (14).

The fact that there are different methods for correcting ^1H -MRS data for voxel brain tissue content makes combination of papers in a meta-analysis problematic. However, NAA results using scaled to Cr measures and voxel brain tissue corrected values were not found to differ significantly when analysed separately by Steen and colleagues (2). They combined data from studies using different methods by calculating the ratio of patient to control NAA levels (regardless of voxel tissue correction method). Here,

rather than calculate a ratio for each study, we performed a meta-analysis of effect size derived from each study, calculated from the absolute mean and SD values for patients and controls regardless of outcome method.

Proton magnetic resonance spectroscopy studies require selection of the voxel for spectrum acquisition at the time of scanning. Many studies in patients with schizophrenia and in individuals at high risk of schizophrenia acquire spectra from slightly different brain regions, leading to difficulties in comparing findings. Steen and colleagues combined ¹H-MRS data acquired from all frontal and all temporal lobe regions into two main brain regions. Although this approach could mask findings that are specific to a particular subregion of frontal or temporal cortices, they found that regardless of subregion chosen, the NAA findings were similar within each overall region. We took a similar approach, combining NAA findings into seven regions – frontal lobe, temporal lobe, thalamus, cerebellum, parietal lobe, occipital lobe and basal ganglia.

Identification of individuals at high risk of schizophrenia

There are two current methods of identifying individuals at high risk of schizophrenia. The first is to identify teenage relatives of patients with schizophrenia (high genetic risk of schizophrenia), and the second is to select subjects on the basis of their clinical presentation – either having attenuated (subthreshold) psychotic symptoms, or a brief (less than 7 day) psychotic episode, which resolved without intervention (“BLIP”), so-called ultra high risk (UHR) patients (15). In the present study, we included both high risk groups.

Identifying individuals with First Episode Schizophrenia

Criteria for FES were not explicitly reported in any of the studies identified. Where authors reported the research subjects as being FES they were included as such for the purposes of the present analysis. We also included subjects reported as having schizophreniform disorder. Studies that included patients with non-schizophrenic psychosis were excluded from the analysis unless data from the patients with FES could be extracted.

Analysis

Data were separated by phase of illness (at risk of schizophrenia, FES, chronic schizophrenia), and by brain region (thalamus, basal ganglia, cerebellum, parietal lobe, occipital lobe, temporal lobe, frontal lobe). Where a study reported measures from more than one subregion (e.g. anterior cingulate cortex and DLPFC), these were entered into the appropriate meta-analysis (i.e. frontal lobe) as two (or more) independent datasets. Studies reporting metabolite values from different brain hemispheres, different subdivisions of patients (within each broad group of at risk, FES and chronic schizophrenia), or different outcome measures were treated in the same manner. Sample sizes for both patients and controls were adjusted to ensure that participants in such studies were not double-counted. This is an accepted strategy for handling such data (16).

We conducted a meta-analysis of effect size, using the *meta* (version 1.5-0) and *metafor* (version 1.1-0) packages for the R statistical programming language (17). A random effects model was used for the analyses, as it was considered likely that variation in subregion, hemisphere, and choice of outcome measure could potentially

introduce significant heterogeneity (18). The standardized mean difference (SMD) effect size (Hedge's g) was calculated for each study and combined as a weighted mean by the inverse variance method.

Meta-regression was used to test the hypothesis that the degree of reduction in NAA levels relative to healthy controls would increase with illness phase from risk of developing psychosis to chronic schizophrenia. Where evidence for such a relationship was found, the timing of these NAA losses was examined using further meta-regressions.

Publication bias

Publication bias was investigated qualitatively using funnel plots for each group and brain region. Funnel plot asymmetry was assessed quantitatively by linear regression analysis(19) and the Duval and Tweedie trim and fill procedure (20).

Analysis of heterogeneity

Cochran Q and I^2 statistics were calculated in order to evaluate within study heterogeneity. Meta-regression of experimental variables was performed to investigate possible sources of heterogeneity, including effects of laterality, echo time, 1H-MRS acquisition technique (PRESS, STEAM), outcome measure (scaled to creatine vs. voxel brain tissue correction) and subregion. The influences of important demographic and clinical variables (age, age of onset, genetic vs. clinical at risk group, duration of medication and PANSS subscales) were investigated using meta-regression. It was not possible to compare NAA levels in patients treated with typical vs. atypical antipsychotics using meta-regression as most studies did not report

metabolite values for these treatment groups separately. Results were corrected for multiple comparisons using the Holm-Bonferroni method, in order to guard against type I errors (21).

Outliers and sensitivity analysis

Where significant heterogeneity was found the papers contributing to this were identified by visual inspection and cumulative meta-analysis. Outliers were examined in order to determine possible explanations for their results. We then repeated the meta-analyses with the outliers excluded, in order to assess the extent to which their findings were dependent upon the influence of such outliers.

To investigate the effect of our use of a random effects meta-analysis, we reanalyzed the data using fixed effects meta-analysis.

Lastly, to investigate the effect of treating multiple results from a single study as separate dataset, we repeated the meta-analyses using a single ‘composite’ measure from each study: where studies reported results from different subregions or using different outcome measures in the same paper, these were combined into a single value and analyzed using a random effects meta-analysis.

Results

Study selection

The literature search described above yielded 269 papers, of which 131 were potentially suitable for this study. Of these, 12 papers were excluded because of overlapping or suspected overlapping data with other papers from the same research

group. Eleven were excluded for lack of a control group. Six were excluded because mean and standard deviation of NAA levels were not reported and 5 were excluded as it was impossible to separate patients with schizophrenia from those with other diagnoses. A total of 97 papers met the inclusion criteria and were thus included in further analysis (7, 9-10, 22-115).

NAA measures by region and illness phase

Frontal lobe

In keeping with previous reports, NAA in frontal lobe was significantly reduced compared to controls in patients with chronic (fig. 1) and FES (fig. 2). No significant reduction in NAA was found in individuals at high risk of schizophrenia, whether due to a genetic or clinical risk (figure 3).

Temporal lobe

NAA in temporal lobe was reduced significantly in patients with chronic (fig. 4) and FES (fig. 5). In individuals at risk of developing schizophrenia, a reduction at trend level was found, although the effect size was comparable to that reported FES and chronic groups (fig. 6).

Thalamus

Significant NAA reductions in thalamus were present in patients with chronic schizophrenia (fig. 7) and in patients with first-episode schizophrenia (fig. 8). Only two studies measuring NAA in thalamus in individuals at high risk of schizophrenia have been published to date, but both showed a significant reduction compared to healthy controls (table 1).

Other regions

One group reported significant reductions in NAA in patients with chronic schizophrenia, FES, and in individuals with an at risk mental state in corpus callosum (113-114). There are no replications of these data by other groups at present.

Studies reporting NAA data in basal ganglia, cerebellum, parietal and occipital lobe have been published in patients with chronic schizophrenia and FES.

A trend for lower NAA in cerebellum compared to healthy controls was found in studies of first episode and chronic schizophrenia, becoming significant when the two groups were combined (table 1). There was no evidence for a reduction in basal ganglia NAA levels in patients with chronic or first-episode schizophrenia (table 1). A single study examining the basal ganglia in individuals at risk of developing schizophrenia has been published, although its results are non-significant (24). Pooled results of studies examining patients with both first-episode and chronic schizophrenia, either taken separately or combined, found no evidence for a reduction in NAA levels in occipital or parietal lobe (table 1).

Difference in NAA measures with stage of illness

A statistically significant difference in NAA levels with illness phase was found in frontal lobe only, with NAA reductions being present in FES patients but not in the at risk group (table 2). No significant differences in NAA levels were found in the patients with first episode compared to chronic schizophrenia.

Publication Bias

Funnel plots revealed no obvious signs of publication bias for any phase of illness or region (see supplemental materials eFigures 1-7). The linear regression test for funnel plot asymmetry confirmed this finding for all regions except frontal lobe, where a trend towards asymmetry was found for patients with chronic schizophrenia (Table 2). However, the trim and fill procedure estimated the number of missing studies to be zero. It was therefore considered unlikely that significant publication bias existed.

Heterogeneity

Significant heterogeneity was found in frontal lobe for all phases of illness. In temporal lobe significant heterogeneity was found for patients with first-episode schizophrenia and chronic schizophrenia but not for individuals at increased risk of developing schizophrenia (table 3).

Meta-regression

This meta-analysis included studies of two different categories of individuals considered to be at heightened risk of developing schizophrenia – those related to patients diagnosed with schizophrenia and those experiencing prodromal symptoms of schizophrenia. Meta-regression revealed no significant effect of these categories on NAA levels. Furthermore, no significant effect of hemisphere or variation in frontal lobe subregion was found for any patient group (Table 3), in line with previous findings (116). We therefore felt justified in our decision to include results from both hemispheres and from different frontal subregions in a single analysis. In temporal lobe an effect of outcome measure (ratio to Cr vs. voxel brain tissue correction) was found (uncorrected $p < 0.5$) for both patients with FES and individuals at risk of

schizophrenia, with studies employing ratio to Cr reporting a greater effect size, although this was not statistically significant after correction for multiple comparisons (table 4).

One significant effect was found for chronic patients: that of negative symptoms (as measured by PANSS) on NAA levels in the temporal lobe (with lower NAA being associated with higher levels of negative symptoms). For first episode patients, in frontal lobe, significant effects of age of onset of illness (lower NAA with earlier onset) and duration of antipsychotic treatment (lower NAA with longer duration of treatment) on NAA levels were found (table 4). No effect was found for duration of illness on NAA levels, however. The complete results of the meta-regression are presented as supplemental material (eTable 2).

Outliers and sensitivity analysis

Although there was a high overall degree of consistency between findings, there were a number of outliers which we considered individually.

Frontal Lobe

The study by Wood and colleagues (10), emerged as a significant outlier in the analysis of the frontal lobe in individuals at risk of schizophrenia. The authors note that this increase in NAA/Cr ratio might be due to a reduction in Cr levels, representing hypometabolism, although other groups have not replicated this finding.

The study of FES patients by Yasukawa and colleagues was a significant outlier in frontal lobe NAA measures (89). This particular study reported results two patient

groups: one containing patients diagnosed with Gilbert's syndrome (the outlying result); the other patients who did not have this condition.

In patients with chronic schizophrenia, Sanches and colleagues (71), reported a markedly greater effect size for NAA reduction in frontal lobe in patients, whilst Tebartz van Elst and colleagues, reported a marked increase in NAA in patients in this brain region (80). The reason for these discrepancies is not clear, but Sanches and colleagues employed a ratio to creatine plus choline for their measurement of NAA, a measure rarely used by other groups. The paper by Tebartz van Elst has been criticized for failing to employ adequate quality control of acquired magnetic resonance spectra for the reliable measurement of glutamate (117), and it is possible that this may have contributed to the difference in their reported data.

Temporal lobe

The same group that studied NAA in FES patients with Gilbert's syndrome in frontal lobe reported data from temporal lobe in a separate paper (33). This result was similarly the only outlier for this region and patient group.

For chronic patients, the only outlier in temporal lobe was the left hemisphere subgroup from Maier and colleagues (99). One possible explanation is that the patients and controls in this study were not well matched in terms of age; the patients being significantly older. Age-related reductions in hippocampal NAA levels have been reported in healthy subjects (118-119), and it seems plausible that these should also occur to at least the same degree in patients with schizophrenia. However, it is not clear why this would affect only the left hippocampus.

Other regions

In thalamus, one subgroup of Heimburg and colleagues (32), was identified as an outlier in the chronic group. It is likely that its outlier status is due to its diminutive size – only two patients.

Removal of outliers

Meta-analyses were repeated with outliers excluded. In most cases the result was a slight reduction in the magnitude of the effect size but not to a degree that alters the findings of this study (table 5). The exception to this is for first episode patients in temporal lobe. Here, the result of removing the outlying study was to reduce the effect size to trend level.

Repeating the analyses using a single composite measure for each study yielded no significant differences in outcomes for any region. Likewise, there were no significant differences in effect sizes when the analyses were carried out using a fixed effects model (table 5).

Discussion

This is the first meta-analysis of 1H-MRS data comparing regional findings in patients with chronic, first episode and genetic and clinical risk of schizophrenia. We found that there was little difference in NAA findings in FES and chronic schizophrenia. In both groups, reduced NAA levels compared to controls were found in frontal lobe, temporal lobe and thalamus. The degree of reduction did not differ significantly between patients with FES and chronic schizophrenia, suggesting a lack

of progression. In individuals at risk of schizophrenia, whether due to genetic risk or subthreshold clinical features of schizophrenia, reductions in NAA were not present in frontal lobe. As discussed above, many of these individuals would not go on to develop schizophrenia (3), and so results in this group are likely to be significantly diluted.

The most robust differences in NAA levels in individuals at risk of schizophrenia compared to controls were found in thalamus. Relative NAA reductions in temporal lobe were present only at trend level (although this may have been due to the lower power in the at risk group), and NAA levels in frontal lobe did not differ significantly from controls. Taken together, these findings suggest that NAA reductions in thalamus, and possibly in corpus callosum, may be a trait marker of schizophrenia risk, or, alternatively, may be the first regions to be affected by the illness.

As longitudinal data about which of the at risk individuals went on to develop a first episode of schizophrenia were not reported, it is not possible to determine the reason that reduced NAA levels were not present in frontal lobe, and were present at trend level only in temporal lobe. It is possible to speculate that NAA reductions in these regions might occur only with transition to psychosis, mirroring findings in gray matter change (5). Alternatively, reductions in NAA levels may already have occurred in these regions but only those individuals destined to develop psychosis.

Another possibility for differences in temporal lobe measures is suggested by the meta-regression. The magnitude of the NAA reduction in the temporal lobe for patients with FES was greater in studies using ratio to Cr as an outcome measure than

in those employing voxel brain tissue correction. The same pattern is seen for at-risk individuals. The reason for this finding is not clear, but it is possible temporal lobe creatine levels were increased in these groups. There is some evidence to support increased hippocampal activity as a possible mechanism in the early stages of schizophrenia (121-122), which could conceivably be associated with increased hippocampal creatine levels (a marker of cellular metabolism). Thus, significant reductions in temporal lobe NAA may arise only in the later stages of illness, with increased metabolism, as indicated by increased creatine levels, occurring earlier. There is a need for well-designed longitudinal studies to answer this question.

This study provides the first evidence of a significant correlation between negative symptoms and temporal lobe NAA levels in patients with chronic schizophrenia. Correlations between severity of negative symptoms and NAA levels have been observed before, notably in frontal lobe (78, 88). Given the suggested close relationship between NAA and glutamatergic neurotransmission (123), the current finding fits with previous reports of negative symptoms correlating with measures of abnormal glutamatergic transmission in hippocampus and temporal lobe (124-125).

This study indicates that an earlier age of onset is associated with lower frontal NAA levels in individuals with FES, supporting the hypothesis that an earlier age of onset may be associated with a more severe illness and more marked anatomical changes (126-127). The study also indicates that antipsychotic exposure is associated with reduced frontal NAA levels in FES patients. This finding is in keeping with earlier studies which have reported correlations between duration of treatment with typical antipsychotic medication and low NAA levels in this region (particularly anterior

cingulate cortex), while atypical neuroleptics appear to be associated with less of a reduction and perhaps even an increase in NAA levels (56, 128-130). No significant effect was found for duration of illness, supporting the hypothesis that NAA reductions are not progressive in schizophrenia.

Weaknesses

There are a number of shortcomings and potential weaknesses of this study that we acknowledge. The combination of results from different sub-regions, into a single analysis may have obscured some findings. This was a relatively unavoidable problem, given that different research groups use different a-priori regions of interest. A previous study did not find any significant differences in NAA changes in sub-regions (12), and we attempted to address this issue by analyzing these data using meta-regression. We did not find any evidence of significant differences in findings between different frontal subregions, nor between left and right hemispheres, and so feel that the inclusion of these data in a single analysis was justified. We cannot, however, exclude the possibility that some laterality or subregional effects in NAA levels may exist in the three groups.

Similarly, by including studies reporting different outcome measures in a single analysis, we were potentially obscuring other subtle effects. While meta-regression did not uncover any systematic influence of outcome measure, a near-significant effect was found in temporal lobe for first episode patients. In these groups, significantly lower NAA compared to controls was found only with scaled to metabolite measures. It is possible that this reflects increased temporal lobe creatine levels. It is not known whether or to what extent alterations in creatine levels in other

studies have affected the results.

Conclusions

These data suggest that schizophrenia is associated with reductions in neuronal integrity in frontal and temporal lobe and in the thalamus. Preliminary findings suggest that the first regions to be affected by loss of NAA in psychotic illness may be the thalamus, and possibly the corpus callosum. Further studies examining longitudinal changes in NAA in individuals at risk of schizophrenia are required to investigate this hypothesis.

Acknowledgements and Financial Disclosures

SL received speaker/consultancy/advisory board honoraria from SanofiAventis, BMS, Eli Lilly, Essex Pharma, AstraZeneca, GlaxoSmithKline, Janssen, Johnson and Johnson, Lundbeck and Pfizer. SanofiAventis and Eli Lilly supported research projects by SL. All other authors report no biomedical financial interests or potential conflicts of interest.

References

1. Moffett JR, Ross B, Arun P, Madhavarao CN, Namboodiri AM (2007): N-Acetylaspartate in the CNS: from neurodiagnostics to neurobiology. *Prog Neurobiol.* 81:89-131.
2. Steen RG, Hamer RM, Lieberman JA (2005): Measurement of brain metabolites by 1H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis. *Neuropsychopharmacology.* 30:1949-1962.
3. Yung AR, Yuen HP, Berger G, Francey S, Hung TC, Nelson B, et al. (2007): Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? *Schizophr Bull.* 33:673-681.
4. Borgwardt SJ, Riecher-Rossler A, Dazzan P, Chitnis X, Aston J, Drewe M, et al. (2007): Regional gray matter volume abnormalities in the at risk mental state. *Biological psychiatry.* 61:1148-1156.
5. Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, et al. (2003): Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet.* 361:281-288.
6. Lappin JM, Dazzan P, Morgan K, Morgan C, Chitnis X, Suckling J, et al. (2007): Duration of prodromal phase and severity of volumetric abnormalities in first-episode psychosis. *The British journal of psychiatry.* 51:s123-127.
7. Jessen F, Scherk H, Träber F, Theyson S, Berning J, Tepest R, et al. (2006): Proton magnetic resonance spectroscopy in subjects at risk for schizophrenia. *Schizophrenia research.* 87:81-88.
8. Lewis DA, Glantz LA, Pierri JN, Sweet RA (2003): Altered cortical glutamate neurotransmission in schizophrenia: evidence from morphological studies of pyramidal neurons. *Annals of the New York Academy of Sciences.* 1003:102-112.
9. Stone JM, Day F, Tsagaraki H, Valli I, McLean MA, Lythgoe DJ, et al. (2009): Glutamate dysfunction in people with prodromal symptoms of psychosis: relationship to gray matter volume. *Biological psychiatry.* 66:533-539.
10. Wood SJ, Berger G, Velakoulis D, Phillips LJ, McGorry PD, Yung AR, et al. (2003): Proton Magnetic Resonance Spectroscopy in First Episode Psychosis and Ultra High-Risk Individuals. *Schizophr Bull.* 29:831-843.
11. Venkatraman TN, Hamer RM, Perkins DO, Song AW, Lieberman JA, Steen RG (2006): Single-voxel 1H PRESS at 4.0 T: precision and variability of measurements in anterior cingulate and hippocampus. *NMR Biomed.* 19:484-491.
12. Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA (2006): Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *Br J Psychiatry.* 188:510-518.
13. Abbott C, Bustillo J (2006): What have we learned from proton magnetic resonance spectroscopy about schizophrenia? A critical update. *Current opinion in psychiatry.* 19:135-139.
14. Jansen JF, Backes WH, Nicolay K, Kooi ME (2006): 1H MR spectroscopy of the brain: absolute quantification of metabolites. *Radiology.* 240:318-332.
15. Phillips LJ, Yung AR, McGorry PD (2000): Identification of young people at risk of psychosis: validation of Personal Assessment and Crisis Evaluation Clinic intake criteria. *The Australian and New Zealand journal of psychiatry.* 34 Suppl:S164-169.
16. Ihaka R, Gentleman R (1996): R: a language for data analysis and graphics. *J Comput Graph Stat.* 5:299-314.
17. Ihaka R, Gentleman R (1996): R: a language for data analysis and graphics. *J*

Comput Graph Stat. 5:299-314.

18. DerSimonian R, Laird N (1986): Meta-analysis in clinical trials. *Controlled Clinical Trials.* 7:177-188.
19. Egger M, Smith GD, Schneider M, Minder C (1997): Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 315:629-634.
20. Duval S, Tweedie R (2000): Trim and Fill: A Simple Funnel-Plot Based Method of Testing and Adjusting for Publication Bias in Meta-Analysis. *Biometrics*, pp 455-463.
21. Holm S (1979): A Simple Sequentially Rejective Multiple Test Procedure. *Scandinavian Journal of Statistics.* 6:65-70.
22. Bertolino A, Callicott JH, Elman I, Mattay VS, Tedeschi G, Frank JA, et al. (1998): Regionally Specific Neuronal Pathology in Untreated Patients with Schizophrenia: A Proton Magnetic Resonance Spectroscopic Imaging Study. *Biological Psychiatry.* 43:641-648.
23. Ando K, Takei N, Matsumoto H, Iyo M, Isoda H, Mori N (2002): Neural damage in the lenticular nucleus linked with tardive dyskinesia in schizophrenia: a preliminary study using proton magnetic resonance spectroscopy. *Schizophrenia Research.* 57:273-279.
24. Block W, Bayer TA, Tepest R, Träber F, Rietschel M, Müller DJ, et al. (2000): Decreased frontal lobe ratio of N-acetyl aspartate to choline in familial schizophrenia: a proton magnetic resonance spectroscopy study. *Neuroscience Letters.* 289:147-151.
25. Bustillo JR, Lauriello J, Rowland LM, Jung RE, Petropoulos H, Hart BL, et al. (2001): Effects of chronic haloperidol and clozapine treatments on frontal and caudate neurochemistry in schizophrenia. *Psychiatry Research: Neuroimaging.* 107:135-149.
26. Bustillo JR, Lauriello J, Rowland LM, Thomson LM, Petropoulos H, Hammond R, et al. (2002): Longitudinal follow-up of neurochemical changes during the first year of antipsychotic treatment in schizophrenia patients with minimal previous medication exposure. *Schizophrenia Research.* 58:313-321.
27. Bustillo JR, Rowland LM, Jung R, Brooks WM, Qualls C, Hammond R, et al. (2007): Proton Magnetic Resonance Spectroscopy During Initial Treatment With Antipsychotic Medication in Schizophrenia. *Neuropsychopharmacology.* 33:2456-2466.
28. Ende G, Braus DF, Walter S, Weber-Fahr W, Henn FA (2003): Multiregional 1H-MRSI of the hippocampus, thalamus, and basal ganglia in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience.* 253:9-15.
29. Fannon D, Simmons A, Tennakoon L, O'Céallaigh S, Sumich A, Doku V, et al. (2003): Selective deficit of hippocampal N-acetylaspartate in antipsychotic-naïve patients with schizophrenia. *Biological Psychiatry.* 54:587-598.
30. Fujimoto T, Nakano T, Takano T, Takeuchi K, Yamada K, Fukuzako T, et al. (1996): Proton magnetic resonance spectroscopy of basal ganglia in chronic schizophrenia. *Biological Psychiatry.* 40:14-18.
31. Giménez M, Junqué C, Pérez M, Vendrell P, Baeza I, Salamero M, et al. (2003): Basal ganglia N-acetylaspartate correlates with the performance in the procedural task ['Tower of Hanoi' of neuroleptic-naïve schizophrenic patients. *Neuroscience Letters.* 347:97-100.
32. Heimberg C, Komoroski RA, Lawson WB, Cardwell D, Karson CN (1998): Regional proton magnetic resonance spectroscopy in schizophrenia and exploration of drug effect. *Psychiatry Research.* 83:105-115.
33. Miyaoka T, Yasukawa R, Mizuno S, Sukegawa T, Inagaki T, Horiguchi J, et

- al. (2005): Proton magnetic resonance spectroscopy (1H-MRS) of hippocampus, basal ganglia, and vermis of cerebellum in schizophrenia associated with idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome). *Journal of Psychiatric Research*. 39:29-34.
34. Ohara K, Isoda H, Suzuki Y, Takehara Y, Ochiai M, Takeda H, et al. (2000): Proton magnetic resonance spectroscopy of lenticular nuclei in simple schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 24:507-519.
35. O'Neill J, Levitt J, Caplan R, Asarnow R, McCracken JT, Toga AW, et al. (2004): 1H MRSI evidence of metabolic abnormalities in childhood-onset schizophrenia. *NeuroImage*. 21:1781-1789.
36. Sharma R, Venkatasubramanian PN, Bárány M, Davis JM (1992): Proton magnetic resonance spectroscopy of the brain in schizophrenic and affective patients. *Schizophrenia Research*. 8:43-49.
37. Shioiri T, Hamakaw H, Kato T, Murashita J, Fujii K, Inubushi T, et al. (1996): Proton magnetic resonance spectroscopy of the basal ganglia in patients with schizophrenia: a preliminary report. *Schizophrenia Research*. 22:19-26.
38. Tayoshi SY, Sumitani S, Taniguchi K, Shibuya-Tayoshi S, Numata S, Iga J-i, et al. (2009): Metabolite changes and gender differences in schizophrenia using 3-Tesla proton magnetic resonance spectroscopy (1H-MRS). *Schizophrenia Research*. 108:69-77.
39. Yamasue H, Fukui T, Fukuda R, Kasai K, Iwanami A, Kato N, et al. (2003): Drug-induced parkinsonism in relation to choline-containing compounds measured by 1H-MR spectroscopy in putamen of chronically medicated patients with schizophrenia. *The International Journal of Neuropsychopharmacology*. 6:353-360.
40. Deicken RF, Feiwell R, Schuff N, Soher B (2001): Evidence for altered cerebellar vermis neuronal integrity in schizophrenia. *Psychiatry Research: Neuroimaging*. 107:125-134.
41. Ende G, Hubrich P, Walter S, Weber-Fahr W, Kammerer N, Braus DF, et al. (2005): Further Evidence for Altered Cerebellar Neuronal Integrity in Schizophrenia. *Am J Psychiatry*. 162:790-792.
42. Tibbo P, Hanstock CC, Asghar S, Silverstone P, Allen PS (2000): Proton magnetic resonance spectroscopy (1H-MRS) of the cerebellum in men with schizophrenia. *Journal of Psychiatry & Neuroscience: JPN*. 25:509-512.
43. Bartha R, Williamson PC, Drost DJ, Malla A, Carr TJ, Cortese L, et al. (1997): Measurement of Glutamate and Glutamine in the Medial Prefrontal Cortex of Never-Treated Schizophrenic Patients and Healthy Controls by Proton Magnetic Resonance Spectroscopy. *Arch Gen Psychiatry*. 54:959-965.
44. Bertolino A, Nawroz S, Mattay VS, Barnett AS, Duyn JH, Moonen CT, et al. (1996): Regionally specific pattern of neurochemical pathology in schizophrenia as assessed by multislice proton magnetic resonance spectroscopic imaging. *The American Journal of Psychiatry*. 153:1554-1563.
45. Bertolino A, Esposito G, Callicott JH, Mattay VS, Van Horn JD, Frank JA, et al. (2000): Specific Relationship Between Prefrontal Neuronal N-Acetylaspartate and Activation of the Working Memory Cortical Network in Schizophrenia. *Am J Psychiatry*. 157:26-33.
46. Bertolino A, Breier A, Callicott JH, Adler C, Mattay VS, Shapiro M, et al. (2000): The Relationship between Dorsolateral Prefrontal Neuronal N-Acetylaspartate and Evoked Release of Striatal Dopamine in Schizophrenia. *Neuropsychopharmacology*. 22 125-132.
47. Bertolino A, Sciota D, Brudaglio F, Altamura M, Blasi G, Bellomo A, et al.

- (2003): Working Memory Deficits and Levels of N-Acetylaspartate in Patients With Schizophreniform Disorder. *Am J Psychiatry*. 160:483-489.
48. Brooks WM, Hodde-Vargas J, Vargas LA, Yeo RA, Ford CC, Hendren RL (1998): Frontal lobe of children with schizophrenia spectrum disorders: A proton magnetic resonance spectroscopic study. *Biological Psychiatry*. 43:263-269.
 49. Buckley PF, Moore C, Long H, Larkin C, Thompson P, Mulvany F, et al. (1994): 1H-magnetic resonance spectroscopy of the left temporal and frontal lobes in schizophrenia: clinical, neurodevelopmental, and cognitive correlates. *Biological Psychiatry*. 36:792-800.
 50. Callicott JH, Egan MF, Bertolino A, Mattay VS, Langheim FJP, Frank JA, et al. (1998): Hippocampal N-acetyl aspartate in unaffected siblings of patients with schizophrenia: a possible intermediate neurobiological phenotype. *Biological Psychiatry*. 44:941-950.
 51. Choe BY, Kim KT, Suh TS, Lee C, Paik IH, Bahk YW, et al. (1994): 1H magnetic resonance spectroscopy characterization of neuronal dysfunction in drug-naïve, chronic schizophrenia. *Academic Radiology*. 1:211-216.
 52. Choe B-YP, Suh T-SP, Shinn K-SM, Lee C-WM, Lee CM, Paik I-HM (1996): Observation of Metabolic Changes in Chronic Schizophrenia After Neuroleptic Treatment by In Vivo Hydrogen Magnetic Resonance Spectroscopy. *Investigative Radiology*. 31:345-352.
 53. Deicken R, Zhou L, Corwin F, Vinogradov S, Weiner M (1997): Decreased left frontal lobe N-acetylaspartate in schizophrenia. *Am J Psychiatry*. 154:688-690.
 54. Delamillieure P, Constans JM, Fernandez J, Brazo P, Dollfus S (2000): Proton magnetic resonance spectroscopy (1H-MRS) of the thalamus in schizophrenia. *European Psychiatry*. 15:489-491.
 55. Delamillieure P, Constans JM, Fernandez J, Brazo P, Benali K, Courtheoux P, et al. (2002): Proton Magnetic Resonance Spectroscopy (1H MRS) in Schizophrenia: Investigation of the Right and Left Hippocampus, Thalamus, and Prefrontal Cortex. *Schizophr Bull*. 28:329-339.
 56. Ende G, Braus DF, Walter S, Weber-Fahr W, Soher B, Maudsley AA, et al. (2000): Effects of age, medication, and illness duration on the N-acetyl aspartate signal of the anterior cingulate region in schizophrenia. *Schizophrenia Research*. 41:389-395.
 57. Fukuzako H, Takeuchi K, Hokazono Y, Fukuzako T, Yamada K, Hashiguchi T, et al. (1995): Proton magnetic resonance spectroscopy of the left medial temporal and frontal lobes in chronic schizophrenia: preliminary report. *Psychiatry Research*. 61:193-200.
 58. Galińska B, Szulc A, Tarasów E, Kubas B, Dzienis W, Czernikiewicz A, et al. (2009): Duration of untreated psychosis and proton magnetic resonance spectroscopy (1H-MRS) findings in first-episode schizophrenia. *Med Sci Monit*. 15:CR82-88.
 59. Hagino H, SUZUKI M, MORI K, NOHARA S, YAMASHITA I, TAKAHASHI T, et al. (2002): Proton magnetic resonance spectroscopy of the inferior frontal gyrus and thalamus and its relationship to verbal learning task performance in patients with schizophrenia: A preliminary report. *Psychiatry and Clinical Neurosciences*. 56:499-507.
 60. Lim KO, Adalsteinsson E, Spielman D, Sullivan EV, Rosenbloom MJ, Pfefferbaum A (1998): Proton Magnetic Resonance Spectroscopic Imaging of Cortical Gray and White Matter in Schizophrenia. *Arch Gen Psychiatry*. 55:346-352.
 61. Lutkenhoff ES, van Erp TG, Thomas MA, Therman S, Manninen M, Huttunen MO, et al. (2008): Proton MRS in twin pairs discordant for schizophrenia. *Mol*

Psychiatry.

62. Molina V, Sanz J, Sarramea F, Luque R, Benito C, Palomo T (2006): No Association between Dorsolateral Prefrontal Gray Matter Deficit and N-Acetyl Aspartate Ratios in Schizophrenia. *Neuropsychobiology*. 54:171-178.
63. Ohrmann P, Siegmund A, Suslow T, Spitzberg K, Kersting A, Arolt V, et al. (2005): Evidence for glutamatergic neuronal dysfunction in the prefrontal cortex in chronic but not in first-episode patients with schizophrenia: a proton magnetic resonance spectroscopy study. *Schizophrenia Research*. 73:153-157.
64. Ohrmann P, Siegmund A, Suslow T, Pedersen A, Spitzberg K, Kersting A, et al. (2007): Cognitive impairment and in vivo metabolites in first-episode neuroleptic-naïve and chronic medicated schizophrenic patients: A proton magnetic resonance spectroscopy study. *Journal of Psychiatric Research*. 41:625-634.
65. Ohrmann P, Kugel H, Bauer J, Siegmund A, Kölkebeck K, Suslow T, et al. (2008): Learning potential on the WCST in schizophrenia is related to the neuronal integrity of the anterior cingulate cortex as measured by proton magnetic resonance spectroscopy. *Schizophrenia Research*. 106:156-163.
66. Olbrich HM, Valerius G, Räsch N, Bächert M, Thiel T, Hennig Jr, et al. (2008): Frontolimbic glutamate alterations in first episode schizophrenia: Evidence from a magnetic resonance spectroscopy study. *World Journal of Biological Psychiatry*. 9:59 - 63.
67. Omori M, Murata T, Kimura H, Koshimoto Y, Kado H, Ishimori Y, et al. (2000): Thalamic abnormalities in patients with schizophrenia revealed by proton magnetic resonance spectroscopy. *Psychiatry Research: Neuroimaging*. 98:155-162.
68. Öngür D, Jensen JE, Prescot AP, Stork C, Lundy M, Cohen BM, et al. (2008): Abnormal Glutamatergic Neurotransmission and Neuronal-Glial Interactions in Acute Mania. *Biological Psychiatry*. 64:718-726.
69. Pae CU, Choe BY, Joo RH, Lim HK, Kim TS, Yoo SS, et al. (2004): Neuronal Dysfunction of the Frontal Lobe in Schizophrenia. *Neuropsychobiology*. 50:211-215.
70. Rowland LM, Spieker EA, Francis A, Barker PB, Carpenter WT, Buchanan RW (2009): White Matter Alterations in Deficit Schizophrenia. *Neuropsychopharmacology*. 34:1514-1522.
71. Sanches RF, Crippa JAS, Hallak JEC, de Sousa JPM, Araújo D, Santos AC, et al. (2008): Proton magnetic resonance spectroscopy of the frontal, cingulate and perirolandic cortices and its relationship to skin conductance in patients with schizophrenia. *Brazilian Journal of Medical and Biological Research*. 41:1132-1141.
72. Sarramea Crespo F, Luque R, Prieto D, Sau P, Albert C, Leal I, et al. (2008): Biochemical changes in the cingulum in patients with schizophrenia and chronic bipolar disorder. *European Archives of Psychiatry and Clinical Neuroscience*. 258:394-401.
73. Shimizu E, Hashimoto K, Ochi S, Fukami G, Fujisaki M, Koike K, et al. (2007): Posterior cingulate gyrus metabolic changes in chronic schizophrenia with generalized cognitive deficits. *Journal of Psychiatric Research*. 41:49-56.
74. Sigmundsson T, Maier M, Toone BK, Williams SCR, Simmons A, Greenwood K, et al. (2003): Frontal lobe N-acetylaspartate correlates with psychopathology in schizophrenia: a proton magnetic resonance spectroscopy study. *Schizophrenia Research*. 64:63-71.
75. Stanley JA, Vemulapalli M, Nutche J, Montrose DM, Sweeney JA, Pettegrew JW, et al. (2007): Reduced N-acetyl-aspartate levels in schizophrenia patients with a younger onset age: A single-voxel 1H spectroscopy study. *Schizophrenia Research*.

93:23-32.

76. Steel RM, Bastin ME, McConnell S, Marshall I, Cunningham-Owens DG, Lawrie SM, et al. (2001): Diffusion tensor imaging (DTI) and proton magnetic resonance spectroscopy (1H MRS) in schizophrenic subjects and normal controls. *Psychiatry Research: Neuroimaging*. 106:161-170.
77. Szulc A, Galińska B, Tarasów E, Kubas B, Dzienis W, Konarzewska B, et al. (2007): N-acetylaspartate (NAA) levels in selected areas of the brain in patients with chronic schizophrenia treated with typical and atypical neuroleptics: a proton magnetic resonance spectroscopy (1H MRS) study. *Med Sci Monit*.
78. Tanaka Y, OBATA T, SASSA T, YOSHITOME E, ASAI Y, IKEHIRA H, et al. (2006): Quantitative magnetic resonance spectroscopy of schizophrenia: Relationship between decreased N-acetylaspartate and frontal lobe dysfunction. *Psychiatry and Clinical Neurosciences*. 60:365-372.
79. Tang C, Friedman J, Shungu D, Chang L, Ernst T, Stewart D, et al. (2007): Correlations between Diffusion Tensor Imaging (DTI) and Magnetic Resonance Spectroscopy (1H MRS) in schizophrenic patients and normal controls. *BMC Psychiatry*. 7:25.
80. Tebartz van Elst L, Valerius G, Büchert M, Thiel T, Rüscher N, Bubl E, et al. (2005): Increased Prefrontal and Hippocampal Glutamate Concentration in Schizophrenia: Evidence from a Magnetic Resonance Spectroscopy Study. *Biological Psychiatry*. 58:724-730.
81. Théberge J, Al-Semaan Y, Williamson PC, Menon RS, Neufeld RWJ, Rajakumar N, et al. (2003): Glutamate and Glutamine in the Anterior Cingulate and Thalamus of Medicated Patients With Chronic Schizophrenia and Healthy Comparison Subjects Measured With 4.0-T Proton MRS. *Am J Psychiatry*. 160:2231-2233.
82. Théberge J, Bartha R, Drost DJ, Menon RS, Malla A, Takhar J, et al. (2002): Glutamate and Glutamine Measured With 4.0 T Proton MRS in Never-Treated Patients With Schizophrenia and Healthy Volunteers. *Am J Psychiatry*. 159:1944-1946.
83. Thomas MA, Ke Y, Levitt J, Caplan R, Curran J, Asarnow R, et al. (1998): Preliminary study of frontal lobe 1H MR spectroscopy in childhood-onset schizophrenia. *Journal of Magnetic Resonance Imaging: JMRI*. 8:841-846.
84. Venkatraman TN, Hamer RM, Perkins DO, Song AW, Lieberman JA, Steen RG (2006): Single-voxel 1H PRESS at 4.0 T: precision and variability of measurements in anterior cingulate and hippocampus. *NMR in Biomedicine*. 19:484-491.
85. Tunc-Skarka N, Weber-Fahr W, Hoerst M, Meyer-Lindenberg A, Zink M, Ende G (2009): MR spectroscopic evaluation of N-acetylaspartate's T2 relaxation time and concentration corroborates white matter abnormalities in schizophrenia. *Neuroimage*. 48:525-531.
86. Wobrock T, Kasper T, Roy A, Vogele K, Schneider-Axmann T, Wagner M, et al. (2008): Reduction of the Internal Capsule in Families Affected with Schizophrenia. *Biological Psychiatry*. 63:65-71.
87. Wood SJ, Yücel M, Wellard RM, Harrison BJ, Clarke K, Fornito A, et al. (2007): Evidence for neuronal dysfunction in the anterior cingulate of patients with schizophrenia: A proton magnetic resonance spectroscopy study at 3 T. *Schizophrenia Research*. 94:328-331.
88. Yamasue HC, Fukui T, Fukuda R, Yamada H, Yamasaki S, Kuroki N, et al. (2002): 1H-MR spectroscopy and gray matter volume of the anterior cingulate cortex

in schizophrenia. *Neuroreport*. 13:2133-2137.

89. Yasukawa R, Miyaoka T, Mizuno S, Inagaki T, Horiguchi J, Oda K, et al. (2005): Proton magnetic resonance spectroscopy of the anterior cingulate gyrus, insular cortex and thalamus in schizophrenia associated with idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome). *Journal of Psychiatry & Neuroscience: JPN*. 30:416-422.

90. Zabala A, Sánchez-González J, Parellada M, Moreno DM, Reig S, Burdalo MT, et al. (2007): Findings of proton magnetic resonance spectrometry in the dorsolateral prefrontal cortex in adolescents with first episodes of psychosis. *Psychiatry Research: Neuroimaging*. 156:33-42.

91. Auer DP, Wilke M, Grabner A, Heidenreich JO, Bronisch T, Wetter TC (2001): Reduced NAA in the thalamus and altered membrane and glial metabolism in schizophrenic patients detected by 1H-MRS and tissue segmentation. *Schizophrenia Research*. 52:87-99.

92. Bluml S, Tan J, Harris K, Adatia N, Karme A, Sproull T, et al. (1999): Quantitative Proton-Decoupled 31P MRS of the Schizophrenic Brain In Vivo. *Journal of Computer Assisted Tomography March/April*. 23:272-275.

93. BAŞOĞLU C, ÇETİN M, ÖNER Ö, EBRİNÇ S, SEMİZ ÜB, KANDİLCİOĞLU H, et al. (2006): Comparison of Right Thalamus and Temporal Cortex Metabolite Levels of Drug-Naive First-Episode Psychotic and Chronic Schizophrenia in Patients. *Turkish Journal of Psychiatry*. 17.

94. Bartha R, Al-Semaan YM, Williamson PC, Drost DJ, Malla AK, Carr TJ, et al. (1999): A short echo proton magnetic resonance spectroscopy study of the left mesial-temporal lobe in first-onset schizophrenic patients. *Biological Psychiatry*. 45:1403-1411.

95. Deicken RF, Zhou L, Schuff N, Fein G, Weiner MW (1998): Hippocampal neuronal dysfunction in schizophrenia as measured by proton magnetic resonance spectroscopy. *Biological Psychiatry*. 43:483-488.

96. Fukuzako H, Kodama S, Fukuzako T, Yamada K, Doi W, Sato D, et al. (1999): Subtype-associated metabolite differences in the temporal lobe in schizophrenia detected by proton magnetic resonance spectroscopy. *Psychiatry Research*. 92:45-56.

97. Fukuzako H (2000): Heritability Heightens Brain Metabolite Differences in Schizophrenia. *J Neuropsychiatry Clin Neurosci*. 12:95-97.

98. Kegeles LS, Shungu DC, Anjilvel S, Chan S, Ellis SP, Xanthopoulos E, et al. (2000): Hippocampal pathology in schizophrenia: magnetic resonance imaging and spectroscopy studies. *Psychiatry Research: Neuroimaging*. 98:163-175.

99. Maier M, Ron MA (1996): Hippocampal age-related changes in schizophrenia: a proton magnetic resonance spectroscopy study. *Schizophrenia Research*. 22:5-17.

100. Nasrallah HA, Skinner TE, Schmalbrock P, Robitaille PM (1994): Proton magnetic resonance spectroscopy (1H MRS) of the hippocampal formation in schizophrenia: a pilot study. *The British Journal of Psychiatry: The Journal of Mental Science*. 165:481-485.

101. Scherk H, Backens M, Zill P, Schneider-Axmann T, Wobrock T, Usher J, et al. (2008): SNAP-25 genotype influences NAA/Cho in left hippocampus. *Journal of Neural Transmission*. 115:1513-1518.

102. Weber-Fahr W, Ende G, Braus DF, Bachert P, Soher BJ, Henn FA, et al. (2002): A Fully Automated Method for Tissue Segmentation and CSF-Correction of Proton MRSI Metabolites Corroborates Abnormal Hippocampal NAA in

Schizophrenia. *NeuroImage*. 16:49-60.

103. Wood SJ, Berger GE, Wellard RM, Proffitt T, McConchie M, Velakoulis D, et al. (2008): A 1H-MRS investigation of the medial temporal lobe in antipsychotic-naïve and early-treated first episode psychosis. *Schizophrenia Research*. 102:163-170.
104. Yurgelun-Todd DA, Renshaw PF, Gruber SA, Waternaux C, Cohen BM (1996): Proton magnetic resonance spectroscopy of the temporal lobes in schizophrenics and normal controls. *Schizophrenia Research*. 19:55-59.
105. Delamillieure P, Fernandez J, Constans J-M, Brazo P, Benali K, Abadie P, et al. (2000): Proton Magnetic Resonance Spectroscopy of the Medial Prefrontal Cortex in Patients With Deficit Schizophrenia: Preliminary Report. *Am J Psychiatry*. 157:641-643.
106. Ende G, Braus DF, Walter S, Henn FA (2001): Lower Concentration of Thalamic N-Acetylaspartate in Patients With Schizophrenia: A Replication Study. *Am J Psychiatry*. 158:1314-1316.
107. Jakary A, Vinogradov S, Feiwell R, Deicken RF (2005): N-acetylaspartate reductions in the mediodorsal and anterior thalamus in men with schizophrenia verified by tissue volume corrected proton MRSI. *Schizophrenia Research*. 76:173-185.
108. Martínez-Granados B, Brotons O, Martínez-Bisbal MC, Celda B, Martí-Bonmati L, Aguilar EJ, et al. (2008): Spectroscopic metabolomic abnormalities in the thalamus related to auditory hallucinations in patients with schizophrenia. *Schizophrenia Research*. 104:13-22.
109. Yoo SY, Yeon S, Choi C-H, Kang D-H, Lee J-M, Shin NY, et al. (2009): Proton magnetic resonance spectroscopy in subjects with high genetic risk of schizophrenia: Investigation of anterior cingulate, dorsolateral prefrontal cortex and thalamus. *Schizophrenia Research*.
110. Keshavan MS, Montrose DM, Pierri JN, Dick EL, Rosenberg D, Talagala L, et al. (1997): Magnetic resonance imaging and spectroscopy in offspring at risk for schizophrenia: Preliminary studies. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 21:1285-1295.
111. Purdon SE, Valiakalayil A, Hanstock CC, Seres P, Tibbo P (2008): Elevated 3T proton MRS glutamate levels associated with poor Continuous Performance Test (CPT-0X) scores and genetic risk for schizophrenia. *Schizophrenia Research*. 99:218-224.
112. Tibbo P, Hanstock C, Valiakalayil A, Allen P (2004): 3-T Proton MRS Investigation of Glutamate and Glutamine in Adolescents at High Genetic Risk for Schizophrenia. *Am J Psychiatry*. 161:1116-1118.
113. Aydin K, Ucok A, Cakir S (2007): Quantitative Proton MR Spectroscopy Findings in the Corpus Callosum of Patients with Schizophrenia Suggest Callosal Disconnection. *AJNR Am J Neuroradiol*. 28:1968-1974.
114. Aydin K, Ucok A, Guler J (2008): Altered Metabolic Integrity of Corpus Callosum Among Individuals at Ultra High Risk of Schizophrenia and First-Episode Patients. *Biological Psychiatry*. 64:750-757.
115. Bustillo JR, Rowland LM, Lauriello J, Petropoulos H, Hammond R, Hart B, et al. (2002): High Choline Concentrations in the Caudate Nucleus in Antipsychotic-Naïve Patients With Schizophrenia. *Am J Psychiatry*. 159:130-133.
116. Steen RG, Hamer RM, Lieberman JA (2005): Measurement of Brain Metabolites by 1H Magnetic Resonance Spectroscopy in Patients with Schizophrenia: A Systematic Review and Meta-Analysis. *Neuropsychopharmacology*. 30:1949-1962.
117. Theberge J, Williamson KE, Aoyama N, Drost DJ, Manchanda R, Malla AK,

- et al. (2007): Longitudinal grey-matter and glutamatergic losses in first-episode schizophrenia. *Br J Psychiatry*. 191:325-334.
118. Schuff N, Amend DL, Knowlton R, Norman D, Fein G, Weiner MW (1999): Age-related metabolite changes and volume loss in the hippocampus by magnetic resonance spectroscopy and imaging[small star, filled]. *Neurobiology of Aging*. 20:279-285.
 119. Driscoll I, Hamilton DA, Petropoulos H, Yeo RA, Brooks WM, Baumgartner RN, et al. (2003): The Aging Hippocampus: Cognitive, Biochemical and Structural Findings. *Cereb Cortex*. 13:1344-1351.
 120. Wood SJ, Berger GE, Lambert M, Conus P, Velakoulis D, Stuart GW, et al. (2006): Prediction of Functional Outcome 18 Months After a First Psychotic Episode: A Proton Magnetic Resonance Spectroscopy Study. *Archives of general psychiatry*. 63:969-976.
 121. Lisman JE, Coyle JT, Green RW, Javitt DC, Benes FM, Heckers S, et al. (2008): Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci*. 31:234-242.
 122. Schobel SA, Lewandowski NM, Corcoran CM, Moore H, Brown T, Malaspina D, et al. (2009): Differential targeting of the CA1 subfield of the hippocampal formation by schizophrenia and related psychotic disorders. *Archives of general psychiatry*. 66:938-946.
 123. Reynolds GP, Harte MK (2007): The neuronal pathology of schizophrenia: molecules and mechanisms. *Biochemical Society transactions*. 35:433-436.
 124. Pilowsky LS, Bressan RA, Stone JM, Erlandsson K, Mulligan RS, Krystal JH, et al. (2006): First in vivo evidence of an NMDA receptor deficit in medication-free schizophrenic patients. *Molecular psychiatry*. 11:118-119.
 125. Szulc A, Galinska B, Tarasow E, Dzienis W, Kubas B, Konarzewska B, et al. (2005): The effect of risperidone on metabolite measures in the frontal lobe, temporal lobe, and thalamus in schizophrenic patients. A proton magnetic resonance spectroscopy (1H MRS). *Pharmacopsychiatry*. 38:214-219.
 126. Rajji TK, Ismail Z, Mulsant BH (2009): Age at onset and cognition in schizophrenia: meta-analysis. *Br J Psychiatry*. 195:286-293.
 127. Mehler C, Warnke A (2002): Structural brain abnormalities specific to childhood-onset schizophrenia identified by neuroimaging techniques. *J Neural Transm*. 109:219-234.
 128. Braus DF, Ende G, Weber-Fahr W, Demirakca T, Henn FA (2001): Favorable Effect on Neuronal Viability in the Anterior Cingulate Gyrus due to Long-Term Treatment with Atypical Antipsychotics: An MRSI Study. *Pharmacopsychiatry*. 34:251-253.
 129. Braus DF, Ende G, Weber-Fahr W, Demirakca T, Tost H, Henn FA (2002): Functioning and neuronal viability of the anterior cingulate neurons following antipsychotic treatment: MR-spectroscopic imaging in chronic schizophrenia. *European Neuropsychopharmacology*. 12:145-152.
 130. Bertolino A, Callicott JH, Mattay VS, Weidenhammer KM, Rakow R, Egan MF, et al. (2001): The effect of treatment with antipsychotic drugs on brain N-acetylaspartate measures in patients with schizophrenia. *Biological Psychiatry*. 49:39-46.

Figure 1: Forest plot (random effects meta-analysis) of frontal cortex NAA levels in patients with chronic schizophrenia compared to controls.

Figure 2: Forest plot (random effects meta-analysis) of frontal cortex NAA levels in patients with first episode psychosis compared to controls.

Figure 3: Forest plot (random effects meta-analysis) of frontal cortex NAA levels in individuals at high risk of psychosis compared to controls.

Figure 4: Forest plot (random effects meta-analysis) of temporal cortex NAA levels in patients with chronic schizophrenia compared to controls.

Figure 5: Forest plot (random effects meta-analysis) of temporal cortex NAA levels in patients with first episode psychosis compared to controls.

Figure 6: Forest plot (random effects meta-analysis) of temporal cortex NAA levels in individuals at high risk of psychosis compared to controls.

Figure 7: Forest plot (random effects meta-analysis) of thalamic NAA levels in patients with chronic schizophrenia compared to controls.

Figure 8: Forest plot (random effects meta-analysis) of thalamic NAA levels in patients with first episode psychosis compared to controls.

Table 1: Effect size by region for individuals at risk of psychosis (At risk), patients with first-episode schizophrenia (FES), chronic schizophrenia (Chronic), and for both patient groups combined (All pts). Studies reporting multiple regions or outcome measures were entered as separate datasets, with sample sizes adjusted where necessary to ensure that participants were not double-counted.

Region	Phase	No. Studies	No. Separate Datasets	No. Patients	No. Controls	Effect Size	Effect Size P Value
Frontal	<i>At risk</i>	10	17	212	203	0.05	0.7995
	<i>FES</i>	19	32	376	428	-0.45	< 0.0001
	<i>Chronic</i>	41	71	880	799	-0.45	< 0.0001
	<i>All pts</i>	61*	104*	1279	1256	-0.45	< 0.0001
Temporal	<i>At risk</i>	4	5	82	100	-0.38	0.0703
	<i>FES</i>	11	19	232	189	-0.53	0.0025
	<i>Chronic</i>	22	35	524	530	-0.60	< 0.0001
	<i>All pts</i>	33	54	756	719	-0.58	< 0.0001
Thalamus	<i>At risk</i>	2	3	49	49	-0.72	0.0006
	<i>FES</i>	5	8	102	88	-0.40	0.0203
	<i>Chronic</i>	12	20	291	255	-0.32	0.0041
	<i>All pts</i>	17	28	393	313	-0.34	0.0002
Basal Ganglia	<i>FES</i>	6	9	125	91	-0.09	0.599
	<i>Chronic</i>	11	17	200	181	-0.07	0.4981
	<i>All pts</i>	17	26	325	272	-0.09	0.3195
Cerebellum	<i>All pts</i>	5	6	108	75	-0.50	0.0114
Occipital	<i>All pts</i>	7	11	127	132	0.06	0.6397
Parietal	<i>All pts</i>	5	10	92	83	-0.08	0.6233

Table 2: Differences in regional NAA between illness phase as determined using meta-regression (* $p < 0.05$) for individuals at risk of psychosis (At risk), patients with first-episode schizophrenia (FES), chronic schizophrenia (Chronic).

Region	All phases		At-risk v. FES		At-risk v. Chronic		FES v. Chronic	
	QM(df=1)	P-value	QM(df=1)	P-value	QM(df=1)	P-value	QM(df=1)	P-value
Frontal	4.0544	0.0441*	6.1078	0.0135*	5.4019	0.0201*	0.0028	0.9577
Temporal	1.0072	0.3156						
Thalamus	1.7934	0.1805						
Basal Ganglia	1.1202	0.2899						

Table 3: Measures of heterogeneity (Cochran Q and I^2), and estimates of publication bias (* $p < 0.05$) for individuals at risk of psychosis (At risk), patients with first-episode schizophrenia (FES), chronic schizophrenia (Chronic), and for both patient groups combined (All pts).

Region	Phase	Q	df	Q P Value	I^2 (%)	Publication bias t(df)
Frontal	<i>At risk</i>	50.71	16	< 0.0001	68.4	-0.868(15)
	<i>FES</i>	60.76	31	0.0011	49	-0.531(30)
	<i>Chronic</i>	209.76	70	< 0.0001	66.6	-1.836(69)*
	<i>All pts</i>	271.26	103	< 0.0001	62	-1.709(102)*
Temporal	<i>At risk</i>	7.08	4	0.132	43.5	-0.558(3)
	<i>FES</i>	48.11	18	0.0001	62.6	-0.381(17)
	<i>Chronic</i>	110.73	34	< 0.0001	69.3	0.075(33)
	<i>All pts</i>	159.39	53	< 0.0001	66.7	0.051(52)
Thalamus	<i>At risk</i>	1.83	2	0.3998	0	0.446(1)
	<i>FES</i>	9.05	7	0.2491	22.7	-0.789(6)
	<i>Chronic</i>	25.67	19	0.1398	26	0.801(18)
	<i>All pts</i>	34.89	27	0.1418	22.6	0.405(26)
Basal Ganglia	<i>FES</i>	10.56	8	0.2281	24.2	1.089(7)
	<i>Chronic</i>	13.58	16	0.6301	0	0.858(15)
	<i>All pts</i>	24.18	25	0.509	0	1.305(24)
Cerebellum	<i>All pts</i>	7.72	5	0.1725	35.2	1.011(1)
Occipital	<i>All pts</i>	10.21	10	0.4223	2	1.939(4)
Parietal	<i>All pts</i>	2.83	9	0.9707	0	-0.560(4)

Table 4: Significant modifiers of NAA levels by region and illness phase, as determined using meta-regression. Significance (p) values are presented both as raw values and as values corrected for multiple comparisons (* corrected $p < 0.1$; ** corrected $p < 0.05$).

region	phase	modifier	intercept	co-efficient	P-value	Adjusted P-value (BH)
Frontal	FES	Treatment duration	-0.3261424	-0.656463833	0.000181	0.01269461 **
Frontal	FES	Age of onset	-4.3600038	0.175791899	0.001226	0.02942189 **
Frontal	FES	Overall symptoms (PANSS)	-2.7258645	0.028745427	0.004484	0.08070678 *
Frontal	Chr	Age of onset	-5.4310586	0.22006038	0.021902	0.19711422
Temporal	At risk	Outcome measure	0.6180435	-0.65117903	0.03494	0.23579182
Temporal	FES	Outcome measure	0.7288	-0.7386	0.0064	0.09216 *
Temporal	FES	Age	1.3257	-0.0701	0.012186	0.14622605
Temporal	Chr	Negative symptoms (PANSS)	3.1049593	-0.150365854	0.000353	0.01269461 **
Temporal	Chr	Overall symptoms (PANSS)	3.5703324	-0.050596849	0.020307	0.19711422
Temporal	Chr	Positive Symptoms (PANSS)	4.9573865	-0.359261152	0.030048	0.23579182

Table 5: Comparison of effect size by region and illness phase when combining all data from each paper into one composite measure (“combined”), when using a fixed effects meta-analysis (“fixed”) and when removing outliers (“outliers removed”)

Region	Phase	Combined effect size	Combined effect size P-value	Fixed effect size	Fixed effect size p-value	Outliers removed effect size	Outliers removed effect size p-value
Frontal	At risk	0.12	0.25	0.0495	0.7995	-0.0628	0.6587
	FES	-0.42	< 0.0001	-0.4474	< 0.0001	-0.3883	< 0.0001
	Chronic	-0.39	< 0.0001	-0.4489	< 0.0001	-0.4046	< 0.0001
Temporal	At risk	-0.36	0.02	-0.3816	0.0703		
	FES	-0.46	0.01	-0.5325	0.0025	-0.253	0.0694
	Chronic	-0.61	< 0.0001	-0.6008	< 0.0001	-0.4948	< 0.0001
Thalamus	At risk	-0.72	0.00	-0.7198	0.0006		
	FES	-0.39	0.01	-0.4048	0.0203		
	Chronic	-0.32	0.00	-0.3174	0.0041	-0.3468	0.0002
Basal Ganglia	FES	-0.11	0.45	-0.0884	0.599		
	Chronic	-0.07	0.50	-0.0718	0.4981		
Cerebellum	All pts	-0.49	0.00	-0.4989	0.0114		
Occipital	All pts	0.06	0.65	0.0606	0.6397		
Parietal	All pts	-0.08	0.62	-0.0779	0.6233		