TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

Magnetic resonance spectroscopy

Introduction

Magnetic resonance spectroscopy (MRS) is a specialised nuclear imaging technique that utilises magnetic resonance imaging (MRI) technology to investigate biochemical alterations within tissues of interest. Different biochemicals have distinct peaks along a proton nuclear magnetic resonance (NMR) frequency spectrum and can be used to identify metabolites present in target tissues[1-6].

Two notable methods of MRS are ^{1}H-MRS (proton-MRS) and ^{31}P-MRS (phosphorus-MRS). Each technique is sensitive to different metabolic compounds. ^{1}H-MRS can be used to measure N-acetylaspartate (NAA), an amino acid that is associated with the myelin sheath surrounding neurons, used as a marker of neural viability. Decreased levels of NAA are associated with neuronal death or axonal injury. ^{1}H-MRS is also used to measure Creatine (Cr), a nitrogenous compound involved in energy metabolism; Glutamate (Glu), a neurotransmitter; and Glutamine (Gln), a synaptic metabolite of glutamate[1-3, 6].

Alternatively, ^{31}P-MRS is used to visualise phospholipid levels, such as phospho-monoesters (PME) and phosphodiesters (PDE)[4-6]. These phospholipids provide information about cellular energy metabolism, membrane synthesis, and neurodevelopment.

Research has identified that compounds such as NAA, Glu and phospholipids may be altered in schizophrenia. Functional activity has been investigated in patients with schizophrenia to identify regions of altered metabolic function compared to healthy controls. Reviews included in this table reflect evidence from whole brain investigations into biochemical activity in the frontal lobe, prefrontal cortex, temporal, occipital and parietal lobes, cerebellum, hippocampus, cingulate cortex, thalamus, striatum and basal ganglia, as well as regions containing cerebral white matter.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis[7]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of

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reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[8]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found ten systematic reviews that met our inclusion criteria[1-6, 9-12].

NAA

- Moderate or moderate to high quality evidence suggests NAA levels (measured as both NAA and NAA/Cr) are decreased in people with schizophrenia in the frontal lobe, temporal lobe, thalamus, hippocampus, cerebellum, cingulate cortex.
- Moderate to low quality evidence suggests that NAA may also be decreased in the parietal cortex, basal ganglia and occipital lobe (white matter only). NAA may be increased in the striatum and lenticular nucleus.
- Moderate quality evidence suggests there are NAA reductions in the anterior cingulate and hippocampus of first-degree relatives of people with schizophrenia. People at clinical or genetic high-risk of schizophrenia showed NAA reductions in the thalamus and NAA/Cr ratio reductions in the prefrontal cortex.

Glutamate/glutamine

- Moderate to low quality evidence suggests small to medium-sized reductions in glutamate and increases in glutamine levels in the frontal cortex of people with schizophrenia, which may progress with age. Low quality evidence is unclear about hippocampus and thalamic levels.

Phospholipids

- Moderate quality evidence suggests decreased PME levels and increased PDE levels in the prefrontal cortex and temporal cortex of people with first-episode psychosis.
- Moderate quality evidence suggests decreased prefrontal PME levels in people with schizophrenia.
- Moderate to low quality evidence suggests reduced prefrontal PME levels and increased prefrontal PDE levels in first-degree relatives of people with schizophrenia.

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Abbott C, Bustillo J

What have we learned from proton magnetic resonance spectroscopy about schizophrenia? A critical update

Current Opinion in Psychiatry 2006; 19(2): 135-9

View review abstract online

Comparison	**Comparison of metabolic activity (measured by ^{1}H-MRS) in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Low quality evidence (small sample sizes, direct, unable to assess precision or consistency) is unable to determine metabolic activity levels in people with schizophrenia.**

NAA/Cr

DLPFC

2 studies, N = 115, NAA/Cr levels were decreased in chronic schizophrenia (mean > 6 years)

Posterior cingulate cortex

1 study, N = 37, NAA/Cr levels were decreased in chronic schizophrenia

Medial temporal cortex/hippocampus

1 study, N = 37, no difference in NAA/Cr levels

Hippocampus

1 study, N = 30, NAA/Cr levels were decreased in chronic schizophrenia

Thalamus

1 study, N = 44, NAA/Cr levels were decreased in chronic schizophrenia

Vermis and cerebellar cortex

1 study, N = 28, NAA/Cr levels were decreased in chronic schizophrenia

Glu and Gln

DLPFC

2 studies, N = 102, one study reported decreased Glu/Gln levels in chronic schizophrenia, one study reported increased Glu levels in chronic patients with acute exacerbation.

Anterior cingulate cortex

2 studies, N = 84, one study reported increased Gln levels in antipsychotic-naive patients (mean illness duration 1.7 years), one study reported decreased Gln and Glu levels in chronic

schizophrenia patients. Medial prefrontal cortex 1 study, N = 20, reported increased Glu and Gln levels in adolescents with genetic risk of schizophrenia. Thalamus 2 studies, N = 102, one study reported increased Gln levels in both antipsychotic-naive patients and in chronic schizophrenia patients. Hippocampus 1 study, N = 42, reported increased Glu levels in chronic patients with acute exacerbation.	
Consistency in results‡	No measure of heterogeneity is reported.
Precision in results§	No confidence intervals are reported.
Directness of results‖	Direct measures and comparison of metabolic activity.

Berger GE, Wood SJ, Pantelis C, Velakoulis D, Wellard RM, McGorry PD

Implications of lipid biology for the pathogenesis of schizophrenia

Australian and New Zealand Journal of Psychiatry 2002; 36(3): 355-366

View review abstract online

Comparison	**Comparison of phospholipid metabolites (measured by ^{31}P MRS) in people with schizophrenia at varying illness stages vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (medium to large samples, direct, unable to assess precision, some in consistency) suggests decreased prefrontal PME levels in first-episode psychosis and chronic schizophrenia patients, and increased prefrontal PDE levels in the prefrontal cortex of first-episode psychosis patients only. There is also decreased temporal PME and increased temporal PDE levels in first-episode psychosis patients. Chronic patients show no differences in temporal PME levels, and inconsistent evidence for temporal PDE levels.**
PME and PDE levels	
Prefrontal PME	

Chronic schizophrenia patients; 7 of 11 studies (222/415 patients) reported decreased PME levels *Drug naive first-episode psychosis and newly diagnosed schizophrenia patients;* 3 of 3 studies (N = 78), reported decreased PME levels <u>Prefrontal PDE</u> *Chronic schizophrenia patients;* 3 of 10 studies (87/363 patients) reported increased PDE levels 1 of 10 studies (86/363 patients) reported decreased PDE levels *Drug naive first-episode psychosis and newly diagnosed schizophrenia patients;* 3 of 3 studies (N = 78), reported increased PDE levels <u>Temporal PME</u> *Chronic schizophrenia patients;* 7 studies (N = 246) reported no significant difference in PME levels *Drug naive first-episode psychosis patients;* 3 of 3 studies (N = 84), reported decreased PME levels <u>Temporal PDE</u> *Chronic schizophrenia patients;* 3 of 7 studies (130/246 patients) reported increased PDE levels *Drug naive first-episode psychosis patients;* 3 of 3 studies (N = 84), reported increased PME levels	
Consistency in results	Consistent apart from PDE levels in chronic patients.
Precision in results	No confidence intervals are provided.
Directness of results	Direct measures and comparison of lipid metabolism.

Bruggar S, Davis JM, Leucht S, Stone JM

Proton magnetic resonance spectroscopy and illness stage in schizophrenia – a systematic review and meta-analysis

Biological Psychiatry 2011; 69: 495-503

View review abstract online

Magnetic resonance spectroscopy

Comparison	**Comparison of metabolic N-acetyl aspartate (NAA) activity measured by ^{1}H-MRS in people at high risk of schizophrenia (clinical and genetic), first-episode schiozphrenia, and chronic schizophrenia patients vs. healthy controls.**
Summary of evidence	**Moderate to high quality evidence (mostly consistent, precise where applicable, direct) suggests decreased NAA levels in the frontal and temporal lobes, thalamus and cerebellum of people with first-episode or chronic schizophrenia. People at high-risk of schizophrenia showed NAA reductions only in the thalamus.**
NAA	
Frontal lobe *Significant, medium-sized reductions of NAA in people with chronic schizophrenia;* 41 studies (N = 1679), *d* = -0.45, 95%CI -0.63 to -0.26, *p* < 0.0001, Q = 209.76, *p* < 0.0001, I^2 = 66% *Significant, medium-sized reductions of NAA in people with first-episode schizophrenia;* 19 studies (N = 804), *d* = -0.45, 95%CI -0.67 to -0.23, *p* < 0.0001, Q = 60.76, *p* = 0.001, I^2 = 49% *No differences between people at high-risk of psychosis and controls;* 10 studies (N = 425), *d* = 0.05, 95%CI -0.33 to 0.43, *p* = 0.799, Q = 50.71, *p* < 0.0001, I^2 = 68% Temporal lobe *Significant, large reductions of NAA in people with chronic schizophrenia;* 22 studies (N = 1054), *d* = -0.60, 95%CI -0.85 to -0.35, *p* < 0.0001, Q = 110.73, *p* < 0.0001, I^2 = 69% *Significant, medium-sized reductions of NAA in people with first-episode schizophrenia;* 11 studies (N = 421), *d* = -0.53, 95%CI -0.69 to -0.07, *p* = 0.0025, Q = 48.11, *p* < 0.0001, I^2 = 62% *Trend level, small to medium-sized reduction of NAA in people at high-risk of psychosis;* 4 studies (N = 182), *d* = -0.38, 95%CI -0.79 to 0.03, *p* = 0.07, Q = 7.08, *p* = 0.13, I^2 = 43% Thalamus *Significant, small to medium-sized reductions of NAA in people with chronic schizophrenia;* 12 studies (N = 546), *d* = -0.32, 95%CI -0.53 to -0.10, *p* = 0.004, Q = 25.67, *p* = 0.14, I^2 = 26% *Significant, medium-sized reductions of NAA in people with first-episode schizophrenia;* 5 studies (N = 190), *d* = -0.40, 95%CI -0.70 to -0.06, *p* = 0.02, Q = 9.05, *p* = 0.25, I^2 = 23% *Significant, medium to large reduction of NAA in people at high-risk of psychosis;* 2 studies (N = 98), *d* = -0.72, 95%CI not reported, *p* = 0.0006, Q = 1.83, *p* = 0.39, I^2 = 0%	

Basal ganglia *No difference between people with chronic schizophrenia and controls;* 11 studies (N = 381), *d* = -0.07 95%CI not reported, *p* = 0.498, Q = 13.58, *p* = 0.63, I^2 = 0% *Significant, medium-sized reductions of NAA in people with first-episode schizophrenia;* 6 studies (N = 216), *d* = -0.09, 95%CI not reported, *p* = 0.599, Q = 10.56, *p* = 0.23, I^2 = 24% Cerebellum *Significant, medium-sized reductions of NAA in people with schizophrenia (all patients);* 5 studies (N = 183), *d* = -0.50 95%CI not reported, *p* = 0.01, Q = 7.72, *p* = 0.17, I^2 = 35% Occipital lobe *No difference between people with schizophrenia (all patients) and controls;* 7 studies (N = 259), *d* = 0.06 95%CI not reported, *p* = 0.64, Q = 10.21, *p* = 0.42, I^2 = 2% Parietal lobe *No difference between people with schizophrenia (all patients) and controls;* 5 studies (N = 175) *d* = -0.08 95%CI not reported, *p* = 0.62, Q = 2.83, *p* = 0.97, I^2 = 0%	
Consistency in results	Consistent apart from frontal lobe and temporal lobe data.
Precision in results	Precise where confidence intervals are reported.
Directness of results	Direct

Fenton WS, Hibbeln J, Knable M

Essential Fatty Acids, Lipid Membrane Abnormalities, and the Diagnosis and Treatment of Schizophrenia

Biological Psychiatry 2000; 47:8-21

View review abstract online

Comparison	**Comparison of phospholipid metabolite levels (measured by ^{31}P MRS) in people with schizophrenia at varying illness stages vs. healthy controls.**
Summary of evidence	**Low quality evidence (small sample sizes, direct, unable to assess precision or consistency) is unclear as to any differences in phospholipid levels in people with schizophrenia.**

PME and PDE	
Two studies (N = 43) report reduced PME and increased PDE in drug naive first-episode schizophrenia patients. Four studies (N = 126) report reduced PME in medicated people with schizophrenia, with no difference in PDE. Two studies (N not reported) report correlations between reduced PME and negative symptom profiles, as well as WCST performance.	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct measures and comparison of phospholipid metabolite levels.

Fusar-Poli P, Perez J, Broome M, Borgwardt S, Placentino A, Caverzasi E, Cortesi M, Veggiotti P, Politi P, Barale F, McGuire P

Neurofunctional correlates of vulnerability to psychosis: A systematic review and meta-analysis

Neuroscience & Biobehavioral Reviews 2007; 31(4): 465-484

View review abstract online

Comparison 1	**Whole brain comparison of metabolite levels (measured by ^{1}H-MRS) in first-degree relatives of people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to low quality evidence (medium sample sizes, direct, unable to assess precision or consistency) suggests increased Glu/Gln levels in the frontal lobe, and reduced NAA/Cr in the anterior cingulate cortex and hippocampus in first-degree relatives of people with schizophrenia. The medial temporal lobe shows no reductions in glutamatergic metabolite levels.** **Moderate to low quality evidence (medium sample size, direct, unable to assess precision and inconsistency) suggests reduced prefrontal PME, increased PDE in first-degree relatives of people with schizophrenia.**
Glu/Gln, NAA/Cr	

4 studies, N = 268 Frontal lobe Increased Glu/Gln in relatives Anterior cingulate cortex Reduced NAA/Cr in relatives Hippocampus Reduced NAA/Cr in relatives Medial temporal lobe No differences in glutamatergic metabolite levels
PME and PDE
3 studies, N = 116 Prefrontal cortex Reduced PME levels and reduced phospholipid synthesis in relatives who later developed schizophrenia. Frontal lobe Increased PDE levels relatives, disrupted membrane metabolism, increased phospholipid breakdown.

Consistency in results	No measured of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct measures and comparison of metabolic activity.

Kraguljac NV, Reid M, White D, Jones R, den Hollander J, Lowman D, Lahti AC

Neurometabolites in schizophrenia and bipolar disorder – a systematic review and meta-analysis

Psychiatry Research: Neuroimaging 2012. 203: 111-25

View review abstract online

Comparison	**Whole brain comparison of metabolite levels (measured by ^{1}H-MRS) in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (unclear sample sizes, some**

	inconsistency and imprecision, direct) suggests reduced NAA levels in the frontal lobe and the thalamus, reduced NAA/Cr in the frontal lobe, temporal lobe, thalamus, and the hippocampus. There was a small reducion in Cho/Cr ratio in the hippocampus.
NAA/Cr or Cho/Cr	
Frontal lobe *Significant medium-sized reduction in NAA absolute levels;* 11 studies, *d* = -0.44, 95%CI -0.65 to -0.23, *p* < 0.001, I^2 = 5%, *p* = 0.39 *Significant, small reduction in NAA/Cr ratio;* 16 studies, *d* = -0.22, 95%CI -0.39 to -0.06, *p* < 0.01, I^2 = 0% *There were no differences in;* Cr levels: 10 studies, *d* = 0.06, 95%CI -0.16 to 0.28, *p* = 0.58, I^2 = 11% Cho levels: 10 studies, *d* = -0.06, 95%CI -0.27 to 0.15, *p* = 0.57, I^2 = 0% Cho/Cr ratio: 13 studies, *d* = 0.09, 95%CI -0.24 to 0.41, *p* = 0.61, I^2 = 68% Temporal lobe *Significant, medium-sized reduction in NAA/Cr ratio;* 7 studies, *d* = -0.64, 95%CI -1.09 to -0.19, *p* < 0.01, I^2 = 77% Thalamus *Significant, medium-sized reduction in NAA absolute levels;* 8 studies *d* = -0.62, 95%CI -1.12 to -0.13, *p* = 0.01, Q not reported, *p* = 0.001, I^2 = 73% When first-episode patients (unmedicated) and chronic schizophrenia patients (medicated) were analysed separately, reduced NAA levels were found only for chronic schizophrenia (*d* = -0.77, *p* < 0.01), but not first-episode patients (*d* = -0.13, *p* = 0.86). *Significant, medium-sized reduction in NAA/Cr ratio;* 9 studies, *d* = -0.37, 95%CI -0.58 to -0.17, *p* < 0.01, I^2 = 6% *There were no differences in;* Cr levels: 8 studies, *d* = -0.03, 95%CI -0.29 to 0.23, *p* = 0.81, I^2 = 0% Cho levels: 8 studies, *d* = -0.13, 95%CI -0.41 to 0.16, *p* = 0.38, I^2 = 18% Cho/Cr ratio: 6 studies, *d* = -0.02, 95%CI -0.34 to 0.30, *p* = 0.91, I^2 = 42% Hippocampus *Significant, medium to large reduction in NAA/Cr ratio;* 8 studies, *d* = -0.72, 95%CI -1.20 to -0.25, *p* < 0.01, I^2 = 74% *Signficant, small reduction in Cho/Cr ratio;*	

5 studies, *d* = -0.28, 95%CI -0.54 to -0.02, *p* = 0.03, I^2 = 0% *There were no differences in:* NAA levels: 7 studies, *d* = -0.82, 95%CI -1.69 to 0.05, *p* = 0.06, I^2 = 92% Cr levels: 7 studies, *d* = -0.12, 95%CI -1.22 to 0.99, *p* = 0.84, I^2 = 95% Cho levels: 7 studies, *d* = -0.19, 95%CI -1.09 to 0.71, *p* = 0.68, I^2 = 93% Anterior cingulate cortex *There were no sigificant differences in:* NAA levels: 10 studies, *d* = -0.22, 95%CI -0.81 to 0.38 *p* = 0.48, I^2 = 88% Cr levels: 10 studies, *d* = -0.15, 95%CI -0.41 to 0.10, *p* = 0.23, I^2 = 37% Cho levels: 10 studies, *d* = 0.05, 95%CI -0.15 to 0.24, *p* = 0.64, I^2 = 0% DLPFC *There were no sigificant differences in:* NAA levels: 6 studies, *d* = -0.46, 95%CI -1.09 to 0.17 *p* = 0.15, I^2 = 85% Cr levels: 6 studies, *d* = -0.13, 95%CI -0.10 to 0.36, *p* = 0.26, I^2 = 0% Cho levels: 6 studies, *d* = 0.15, 95%CI -0.44 to 0.74, *p* = 0.62, I^2 = 84% NAA/Cr ratio: 3 studies, *d* = 0.14, 95%CI -0.72 to 1.00, *p* = 0.75, I^2 = 86% Cho/Cr ratio: 2 studies, *d* = -0.15 95%CI -0.73 to 0.42, *p* = 0.60, I^2 = 58% Basal ganglia *There were no sigificant differences in:* NAA levels: 6 studies, *d* = -0.22, 95%CI -0.48 to 0.05 *p* = 0.11, I^2 = 0% Cr levels: 6 studies, *d* = -0.19, 95%CI -0.59 to 0.21, *p* = 0.35, I^2 = 53% Cho levels: 6 studies, *d* = 0.15, 95%CI -0.37 to 0.68, *p* = 0.57, I^2 = 84% NAA/Cr ratio: 8 studies, *d* = -0.16, 95%CI -0.46 to 0.13, *p* = 0.28, I^2 = 32% Cho/Cr ratio: 6 studies, *d* = -0.13, 95%CI -0.22 to 0.48, *p* = 0.47, I^2 = 37%	
Consistency in results	From the significant findings, data are consistent for frontal lobe NAA and NAA/Cr, thalamas NAA/CR, and hippocampus Cho/CR.
Precision in results	From the significant findings, data are precise for frontal lobe NAA and NAA/Cr, temporal lobe NAA/Cr, thalamas NAA/CR, and hippocampus NAA/Cr and Cho/CR.
Directness of results	Direct measures and comparison of metabolic activity.

Marsman A, van den Heuvel MP, Klomp DWJ, Kahn RS, Luijten PR, Hulshoff Pol HE

Glutamate in schizophrenia: a focused review and meta-analysis of ^{1}H-MRS studies

Schizophrenia Bulletin 2013; 39(1): 120-9

View review abstract online

Comparison	**Glutamate, glutamine and N-acetyl aspartate (NAA) levels (measured by ^{1}H-MRS) in the medial frontal cortex, hippocampus and thalamus of schizophrenia patients vs. healthy controls.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, direct, unable to assess precision or consistency) suggests reduced Glu and increased Gln levels in the frontal cortex of people with schizophrenia, with greater reductions associated with age. Low quality evidence is unclear about hippocampus and thalamic levels.**

Glu, gln and NAA

Medial frontal cortex

A significant, small reduction in glutamate level in people with schizophrenia;

9 studies, N = 337, *d* = -0.391, *p* = 0.006

Meta-regression showed a progressive decrease with age in patients compared to controls (*p* = 0.008).

A significant, medium-sized increase in glutamine in people with schizophrenia;

8 studies, N = 275, *d* = 0.403, *p* = 0.045

Meta-regression showed a progressive decrease with age in patients compared to controls (*p* = 0.0005).

No significant difference in total glutamate + glutamine levels between patients and controls;

8 studies, N = 330, *d* = 0.122, *p* = 0.393

No significant difference in glutamate/glutamine ratio levels between patients and controls;

6 studies, N = 228, *d* = 0.308, *p* = 0.062

Meta-regression showed a progressive decrease with age in patients compared to controls (*p* = 0.02).

A significant, small reduction in NAA levels in people with schizophrenia;

19 studies, N = 779, *d* = -0.320, *p* = 0.019

Meta-regression showed a progressive decrease with age in patients compared to controls (p = 0.04). *A significant, small reduction in NAA/glutamate ratio in people with schizophrenia;* 7 studies, N = 247, d = -0.357, p = 0.038 Meta-regression showed a progressive decrease with age in patients compared to controls (p = 0.049). Hippocampus *No significant differencez in total glutamate levels between patients and controls;* 3 studies, N = 107, d = 0.031, p = 0.92 Thalamus *No significant difference in glutamate levels between patients and controls;* 3 studies, N = 128, d = -0.286, p = 0.20	
Consistency in results	Unable to assess
Precision in results	Unable to assess
Directness of results	Direct

Mondino M, Brunelin J, Saoud M

N-acetyl-aspartate level is decreased in the prefrontal cortex in subjects at-risk for schizophrenia

Frontiers in Psychiatry 2013; 4: 99

View review abstract online

Comparison	**Comparison of NAA/Cr ratio (measured by ^{1}H-MRS) in the prefrontal cortex of people at risk of schizophrenia vs. age and sex matched controls.** **Clinical high-risk subjects were people who developed a brief psychotic episode (<7 days) resolved without any intervention or people who exhibited schizotypal traits, i.e., subthreshold non-clinical psychotic symptoms. Genetic high-risk subjects were first or second-degree relatives of patients with schizophrenia, frequently unaffected siblings of patients.**
Summary of evidence	**Moderate quality evidence (large sample, direct, inconsistent, precise) suggests NAA/Cr ratio is reduced in the prefrontal cortex of people at clinical or familial risk of schizophrenia.**

NAA/Cr	
NAA/Cr was significantly lower in the high-risk group; 9 studies, N = 442, *d* = -0.42, 95%CI -0.61 to -0.23, *p* < 0.0001 In the subgroup analysis of age, the effect size was larger in studies with younger samples than in studies with older samples (<40 years, *d* = -0.82, >40 years *d* = 0.11 [NS]).	
Consistency in results	I^2 is not reported. Forest plot appears inconsistent, most likely due to differences in age.
Precision in results	Precise
Directness of results	Direct

Sanches RF, Crippa JA, Hallak JE, Araujo D, Zuardi AW

Proton magnetic resonance spectroscopy of the frontal lobe in schizophrenics: a critical review of the methodology

Revista do Hospital das Clinicas; Faculdade de Medicina Da Universidade de Sao Paulo 2004; 59(3): 145-152

View review abstract online

Comparison	**Comparison of NAA and Cr activity (measured by ^{1}H-MRS) in the frontal lobes of people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample sizes, direct, unable to assess precision or consistency) suggests NAA levels are reduced in the frontal lobe and the cingulate cortex in people with schizophrenia.**
NAA	
Frontal lobe 18/26 studies (N = 781) showed decreased NAA in people with schizophrenia Frontal pole 6/9 studies (N = 252), showed decreased NAA in schizophrenia patients DLPFC 8/12 studies (N = 346), showed decreased NAA in schizophrenia patients	

Cingulate cortex 8/10 studies (N = 301), showed decreased NAA in schizophrenia patients	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct measures and comparison of NAA levels

Steen RG, Hamer RM, Lieberman JA

Measurement of brain metabolites by ^{1}H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis

Neuropsychopharmacology 2005; 30(11): 1949-1962

View review abstract online

Comparison	**Comparison of metabolic NAA activity (measured by ^{1}H-MRS) in the hippocampus of schizophrenia patients vs. healthy controls** **Compares the consistency of measuring NAA as a raw percentage to measuring as a ratio with control data**
Summary of evidence	**Moderate to low quality evidence (sample size unclear, direct inconsistent, unable to assess precision) suggests that NAA may be decreased in the frontal cortex, temporal cortex, hippocampus, anterior cingulate, cerebellum, parietal cortex, thalamus, basal ganglia and occipital lobe white matter. NAA may be increased in the striatum and lenticular nucleus.**
NAA/Cr	
Frontal cortex Grey matter: 25 (N unclear), patient average NAA 94.2% of control levels White matter: 18 (N unclear), patient average NAA 94.8% of control levels Temporal cortex Grey matter: 5 (N unclear), patient average NAA 94.0% of control levels White matter: 8 (N unclear), patient average NAA 87.3% of control levels Hippocampus	

All: 8 studies (N = 305), patient average NAA/Cr 88.8% of control levels All: 5 studies (N = 248), patient average NAA/Cr 85.8% of control levels Grey matter: 17 studies (N unclear), NAA 88.9% of control levels <u>Anterior cingulate gyrus</u> Grey matter: 12 studies (N unclear), patient average NAA 95.9% of control levels <u>Cerebellum</u> Grey matter: 3 studies (N unclear), patient average NAA 92.3% of control levels <u>Parietal cortex</u> Grey matter: 1 study (N unclear), patient average NAA 94.0% of control levels White matter: 2 studies (N unclear), patient average NAA 99.0% of control levels <u>Thalamus</u> Grey matter: 19 studies (N unclear), patient average NAA 96.5% of control levels <u>Basal ganglia</u> Grey matter: 6 studies (N unclear), patient average NAA 98.5% of control levels <u>Occipital cortex</u> White matter: 1 study (N unclear), patient average NAA 96.0% of control levels Grey matter: 8 studies (N unclear), patient average NAA 102.8% of control levels <u>Striatum (caudate + putamen)</u> Grey matter: 1 study (N unclear), patient average NAA 112.6% of control levels <u>Lenticular nucleus (putamen + globus pallidus)</u> Grey matter: 2 studies (N unclear), patient average NAA 104.5% of control levels <u>Posterior cingulate</u> Grey matter: 5 studies (N unclear), patient average NAA 100% of control levels <u>Caudate nucleus</u> Grey matter: 3 studies (N unclear), patient average NAA 100.3% of control levels <u>Putamen</u> Grey matter: 7 studies (N unclear), patient average NAA 100.6% of control levels <u>Centrum semiovale</u> White matter: 5 studies (N unclear), patient average NAA 100.2% of control levels	
Consistency in results	Significant heterogeneity reported, $p < 0.0001$
Precision in results	Precise, CIs reasonably stringent

Magnetic resonance spectroscopy

Directness of results	Direct measures and comparison of NAA levels.

Explanation of acronyms

CI = Confidence Interval, Cr = Creatine amino acid, DLPFC = dorsolateral prefrontal cortex, Gln = glutamine (glutamate synaptic metabolic), Glu = glutamate neurotransmitter, ^{1}H-MRS = Proton Magnetic Resonance Spectroscopy, LS = Least Squares mean, N = number of participants, NAA = N-acetylaspartate amino acid, NAA/Cr = ratio of NAA and Cr, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), ^{31}P-MRS = Phosphorus Magnetic Resonance Spectroscopy, PDE = phosphodiester lipid, PME = phosphomonoester lipid, U = units

Magnetic resonance spectroscopy

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias which involves the selective reporting of results; publication bias - trials which are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small.

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† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[13].

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives), and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[14]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other

independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[15].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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