

Magnetic resonance spectroscopy

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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.

Two notable methods of MRS are ^1H -MRS (proton-MRS) and ^{31}P -MRS (phosphorus-MRS). Each technique is sensitive to different metabolic compounds. ^1H -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. ^1H -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.

Alternatively, ^{31}P -MRS is used to visualise phospholipid levels, such as phosphomonoesters (PME) and phosphodiesteres (PDE). 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 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-analysis¹. 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 reporting bias. It may also be downgraded if

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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)². 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 14 systematic reviews that met our inclusion criteria³⁻¹⁶.

All patients

- Moderate or moderate to high quality evidence suggests NAA levels are decreased in people with schizophrenia in the frontal lobe, temporal lobe, thalamus, hippocampus, cerebellum, cingulate cortex. Moderate to low quality evidence suggests NAA may also be decreased in the parietal cortex, basal ganglia and occipital lobe (white matter only) and increased in the striatum and lenticular nucleus.
- Moderate to low quality evidence finds small to medium-sized reductions in glutamate and increases in glutamine in the frontal cortex of people with schizophrenia.
- Moderate to high quality evidence finds a medium-sized decrease in PME in the frontal lobes and increased PDE in the temporal lobes of people with schizophrenia. There were no differences in frontal PDE or temporal PME levels.
- High quality evidence finds a small decrease in glutathione in the anterior cingulate of people with schizophrenia.

- Moderate quality evidence finds a small reduction in Cho/Cr ratio in the hippocampus of people with schizophrenia.
- High quality evidence finds a small decrease in myo-inositol levels in the medial prefrontal region in people with schizophrenia.
- Moderate quality evidence finds no differences in GABA levels.

Unmedicated patients

- Moderate to high quality evidence finds unmedicated people with schizophrenia have medium-sized decreases in N-acetylaspartate in the thalamus and in frontal white matter (using <3T MRI scanners only), and medium-sized increases in glutamate+glutamine in the medial prefrontal cortex, and in choline in the basal ganglia. There were no differences in glutamate, creatine, or myo-inositol levels.

First-episode psychosis patients

- Moderate quality evidence finds decreased PME levels and increased PDE levels in both the prefrontal cortex and temporal cortex of people with first-episode psychosis.

People at clinical or genetic high risk

- Moderate to low quality evidence finds NAA/Cr 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 reductions in the prefrontal cortex.
- Moderate to low quality evidence finds reduced prefrontal PME levels and increased prefrontal PDE levels in first-degree relatives.
- Moderate to high quality evidence finds a medium-sized decrease in glutamate in the thalamus of people at clinical high risk, and a medium-sized increase in glutamate+glutamine in the frontal lobe of people at genetic high risk. There were no other significant differences in other brain regions (occipital, temporal, hippocampal, striatum, cerebellum, or white matter).

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 ³¹P MRS) in people with schizophrenia at varying illness stages vs. controls.
Summary of evidence	Moderate quality evidence (medium to large samples, unable to assess precision, some inconsistency, direct) 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	
<p style="text-align: center;"><u>Prefrontal PME</u></p> <p style="text-align: center;"><i>Chronic schizophrenia patients;</i></p> <p style="text-align: center;">7 of 11 studies (222/415 patients) reported decreased PME levels</p> <p style="text-align: center;"><i>Drug naive first-episode psychosis and newly diagnosed schizophrenia patients;</i></p> <p style="text-align: center;">3 of 3 studies (N = 78), reported decreased PME levels</p> <p style="text-align: center;"><u>Prefrontal PDE</u></p> <p style="text-align: center;"><i>Chronic schizophrenia patients;</i></p> <p style="text-align: center;">3 of 10 studies (87/363 patients) reported increased PDE levels</p> <p style="text-align: center;">1 of 10 studies (86/363 patients) reported decreased PDE levels</p> <p style="text-align: center;"><i>Drug naive first-episode psychosis and newly diagnosed schizophrenia patients;</i></p> <p style="text-align: center;">3 of 3 studies (N = 78), reported increased PDE levels</p> <p style="text-align: center;"><u>Temporal PME</u></p> <p style="text-align: center;"><i>Chronic schizophrenia patients;</i></p> <p style="text-align: center;">7 studies (N = 246) reported no significant difference in PME levels</p> <p style="text-align: center;"><i>Drug naive first-episode psychosis patients;</i></p>	

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<p>3 of 3 studies (N = 84), reported decreased PME levels</p> <p style="text-align: center;"><u>Temporal PDE</u></p> <p style="text-align: center;"><i>Chronic schizophrenia patients;</i></p> <p>3 of 7 studies (130/246 patients) reported increased PDE levels</p> <p style="text-align: center;"><i>Drug naive first-episode psychosis patients;</i></p> <p>3 of 3 studies (N = 84), reported increased PDE levels</p>	
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.

<p><i>Brugger S, Davis JM, Leucht S, Stone JM</i></p> <p>Proton magnetic resonance spectroscopy and illness stage in schizophrenia – a systematic review and meta-analysis</p> <p>Biological Psychiatry 2011; 69: 495-503</p> <p>View review abstract online</p>	
Comparison	Comparison of metabolic N-acetyl aspartate (NAA) activity measured by ¹H-MRS in people at high risk of schizophrenia (clinical and genetic), first-episode schizophrenia, and chronic schizophrenia patients vs. controls.
Summary of evidence	Moderate to high quality evidence (medium to large samples, 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	
<u>Frontal lobe</u>	
<p style="text-align: center;"><i>Significant, medium-sized reduction of NAA in people with chronic schizophrenia;</i></p> <p>41 studies, N = 1,679, $d = -0.45$, 95%CI -0.63 to -0.26, $p < 0.0001$, $Q = 209.76$, $p < 0.0001$, $I^2 = 66\%$</p> <p style="text-align: center;"><i>Significant, medium-sized reduction of NAA in people with first-episode schizophrenia;</i></p>	



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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 reduction of NAA in people with chronic schizophrenia;

22 studies, N = 1,054, $d = -0.60$, 95%CI -0.85 to -0.35, $p < 0.0001$, $Q = 110.73$, $p < 0.0001$, $I^2 = 69\%$

Significant, medium-sized reduction 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 reduction 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 reduction 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 reduction 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 reduction 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.



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Precision in results	Precise where confidence intervals are reported.
Directness of results	Direct

Das TK, Javadzadeh A, Dey A, Sabesan P, Theberge J, Radua J, Palaniyappan L

Antioxidant defense in schizophrenia and bipolar disorder: A meta-analysis of MRS studies of anterior cingulate glutathione

Progress in Neuro Psychopharmacology and Biological Psychiatry 2018; August

[View online review abstract](#)

Comparison	Glutathione in the anterior cingulate of people with schizophrenia vs. controls.
Summary of evidence	High quality evidence (large sample, consistent, precise, direct) suggests a small decrease in glutathione in the anterior cingulate of people with schizophrenia.
Glutathione	
<p><i>A small, significant decrease in glutathione in the anterior cingulate of people with schizophrenia; 13 studies, N = 726, SMD = 0.26, 95%CI 0.07 to 0.44, p = 0.008, I² = 29%, p = 0.11</i></p> <p>There was a trend-effect finding that studies with longer echo-time of MRS acquisitions were more likely to report reduced glutathione concentrations in patients compared to controls.</p> <p>There were no moderating effects of medication, sex, scanner strength, repetition time, patient age or duration of illness.</p>	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Das TK, Dey A, Sabesan P, Javadzadeh A, Theberge J, Radua J, Palaniyappan L

Putative astroglial dysfunction in schizophrenia: A meta-analysis of H-MRS studies of medial prefrontal myo-inositol



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<p>Frontiers in Psychiatry 2018; 9: September View review abstract online</p>	
Comparison	Medial prefrontal myo-inositol levels measured by ¹H-MRS in people with schizophrenia vs. controls.
Summary of evidence	High quality evidence (large sample, consistent, precise, direct) finds a small decrease in myo-inositol levels in the medial prefrontal region in people with schizophrenia.
Myo-inositol	
<p><u>Medial prefrontal</u></p> <p><i>Significant, small decrease in people with schizophrenia;</i></p> <p>19 studies, N = 1,146, SMD = 0.19, 95%CI 0.05 to 0.32, $p = 0.0067$, $I^2 = 15\%$, $p = 0.09$</p> <p>Studies with more female patients reported greatest reduction in myo-inositol. There were no moderating effects of medication, scanner strength, echo time, repetition time, patient age or duration of illness.</p>	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

<p><i>Egerton A, Modinos G, Ferrera D, McGuire P</i></p> <p>Neuroimaging studies of GABA in schizophrenia: a systematic review with meta-analysis</p> <p>Translational Psychiatry 2017; 7: e1147 View review abstract online</p>	
Comparison	GABA levels measured by ¹H-MRS in people with schizophrenia vs. controls.
Summary of evidence	Moderate quality evidence (medium to large sample, inconsistent, mostly imprecise, direct) finds no differences in GABA levels.
GABA	
<i>No significant differences between groups;</i>	

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Medial frontal cortex

12 studies, N = 904, $g = -0.30$, 95%CI -0.60 to 0.10, $p = 0.10$, $I^2 = 84\%$

There were no moderating effects of diagnosis (first-episode psychosis vs. schizophrenia), medications (adjunctive benzodiazepines/anticonvulsants or antipsychotics vs. no antipsychotics), ¹H-MRS locations (medial prefrontal vs. all medial frontal), gender, age, illness duration, symptom severity, %grey matter or publication date.

Parietal/occipital cortex

6 studies, N = 250, $g = -0.30$, 95%CI -0.90 to 0.03, $p = 0.30$, $I^2 = 80\%$

There were no moderating effects of diagnosis (first-episode psychosis vs. schizophrenia), age, illness duration, symptom severity, %grey matter or publication date.

Striatum

4 studies, N = 219, $g = 0.004$, 95%CI -0.70 to 0.70, $p = 1.00$, $I^2 = 82\%$

There were no moderating effects of age, illness duration, symptom severity, %grey matter or publication date.

Consistency in results	Inconsistent
Precision in results	Precise for medial frontal analysis only.
Directness of results	Direct

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	Whole brain comparison of metabolite levels (measured by ¹H-MRS) in first-degree relatives of people with schizophrenia vs. controls.
Summary of evidence	Moderate to low quality evidence (small to medium-sized samples, unable to assess precision or consistency, direct) suggests increased Glu/Gln ratio 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. There were reduced prefrontal PME, increased PDE in first-degree



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

Haszto CS, Stanley JA, Iyengar S, Prasad KM

Regionally Distinct Alterations in Membrane Phospholipid Metabolism in Schizophrenia: A Meta-analysis of Phosphorus Magnetic Resonance Spectroscopy Studies

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2019; 5: 264–80

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Comparison	Frontal and temporal PME and PDE levels measured by ¹ H-MRS in people with schizophrenia vs. controls.
Summary of evidence	Moderate to high quality evidence (large samples, mostly inconsistent and precise, direct, some publication bias) finds a medium-sized decrease in PME in the frontal lobe and increased PDE in the temporal lobe of people with schizophrenia. There were no differences in frontal PDE or temporal PME levels.
PME and PDE	
<u>Frontal lobe</u>	
<i>A significant, medium-sized effect of lower PME levels in the frontal regions of people with schizophrenia;</i>	
10 studies, N = 744, $g = -0.54$, 95%CI -1.05 to -0.03, $p = 0.0038$, $I^2 = 92\%$	
Authors report possible publication bias.	
<i>There were no differences in PDE levels;</i>	
17 studies, N = 792, $g = 0.23$, 95%CI -0.06 to 0.53, $p = 0.12$, $I^2 = 79\%$	
Authors report possible publication bias.	
<u>Temporal lobe</u>	
<i>A significant, medium-sized effect of increased PDE levels in the temporal regions of people with schizophrenia;</i>	
9 studies, N = 319, $g = 0.55$, 95%CI 0.28 to 0.82, $p < 0.0001$, $I^2 = 68\%$	
Authors report possible publication bias.	
<i>There were no differences in PME levels;</i>	
8 studies, N = 270, $g = -0.08$, 95%CI -0.27 to 0.10, $p = 0.37$, $I^2 = 25\%$	
No publication bias was detected.	
Consistency in results	Inconsistent, apart from temporal lobe PME.
Precision in results	Precise, apart from frontal lobe PME.
Directness of results	Direct

Iwata Y, Nakajima S, Plitman E, Mihashi Y, Caravaggio F, Chung JK, Kim J, Gerretsen P, Mimura M, Remington G, Graff-Guerrero A

Neurometabolite levels in antipsychotic-naive/free patients with



schizophrenia: A systematic review and meta-analysis of ¹H-MRS studies

Progress in Neuro-Psychopharmacology & Biological Psychiatry 2018; 86: 340-52

[View review abstract online](#)

Comparison	Neurometabolite levels measured by ¹ H-MRS in unmedicated people with schizophrenia vs. controls.
Summary of evidence	Moderate to high quality evidence (small to medium-sized samples, consistent, mostly precise, direct) finds unmedicated people with schizophrenia have medium-sized decreases in N-acetylaspartate (NAA) in the thalamus and in frontal white matter (using <3T MRI scanners only), and medium-sized increases in glutamate+glutamine (Glx) in the medial prefrontal cortex, and in choline in the basal ganglia. There were no differences in glutamate, creatine or myo-inositol levels.
NAA	
<p><i>Significant, medium-sized decrease in NAA in the thalamus of unmedicated people with schizophrenia;</i></p> <p>3 studies, N = 174, SMD = -0.56, 95%CI -0.87 to -0.25, <i>p</i> = 0.0005, <i>I</i>² = 0%, <i>p</i> = 0.37</p> <p>Subgroup analysis found lower NAA levels in frontal white matter in studies using <3T MRI scanners (3 studies, N = 167, SMD = -0.63, 95%CI -0.95 to -0.31, <i>p</i> = 0.0001).</p> <p>There were no significant differences in NAA in the medial prefrontal cortex, dorsolateral prefrontal cortex, basal ganglia, hippocampus/medial temporal lobe.</p>	
Glx	
<p><i>A significant, medium-sized increase in Glx in the medial prefrontal cortex of unmedicated people with schizophrenia;</i></p> <p>3 studies, N = 99, SMD = 0.47, 95%CI 0.06 to 0.88, <i>p</i> = 0.03, <i>I</i>² = 0%, <i>p</i> = 0.60</p> <p>There were no significant differences in Glx levels the dorsolateral prefrontal cortex, hippocampus/medial temporal lobe.</p> <p><i>There was no significant difference in glutamine levels in the medial prefrontal cortex;</i></p> <p>3 studies, N = 136, SMD = -0.02, 95%CI -0.36 to 0.39, <i>p</i> = 0.89, <i>I</i>² = 0%, <i>p</i> = 0.52</p>	
Choline	
<p><i>A significant, medium to large increase in choline in the basal ganglia of unmedicated people with schizophrenia;</i></p> <p>3 studies, N = 168, SMD = 0.77, 95%CI 0.24 to 1.31, <i>p</i> = 0.005, <i>I</i>² = 48%, <i>p</i> = 0.15</p> <p>There were no significant differences in choline levels the medial prefrontal cortex, dorsolateral</p>	

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prefrontal cortex, frontal white matter, thalamus, hippocampus/medial temporal lobe.	
Creatine	
<i>There was no significant difference in creatine levels in the medial prefrontal cortex;</i> 3 studies, N = 344, SMD = 0.16, 95%CI -0.24 to 0.57, $p = 0.43$, $I^2 = 51%$, $p = 0.10$ <i>There was no significant difference in creatine in the dorsolateral prefrontal cortex.</i>	
Myo-inositol	
<i>There was no significant difference in myo-inositol levels in the hippocampus/medial temporal lobe;</i> 3 studies, N = 182, SMD = -0.09, 95%CI -0.53 to 0.57, $p = 0.68$, $I^2 = 51%$, $p = 0.10$	
Consistency in results	Consistent
Precision in results	Precise, apart from choline
Directness of results	Direct

<i>Kraguljac NV, Reid M, White D, Jones R, den Hollander J, Lowman D, Lahti AC</i>	
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. 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 reduction in Cho/Cr ratio in the hippocampus.
NAA/Cr or Cho/Cr	
<u>Frontal lobe</u>	
<i>Significant medium-sized reduction in NAA absolute levels;</i> 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, $p < 0.01$, $I^2 = 74\%$

Significant, 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 significant 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, $p = 0.23$, $I^2 = 37\%$



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Cho levels: 10 studies, $d = 0.05$, 95%CI -0.15 to 0.24, $p = 0.64$, $I^2 = 0\%$

DLPFC

There were no significant 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 significant 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

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

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

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

[View review abstract online](#)

Comparison	Glutamate, glutamine and N-acetylaspartate in people with schizophrenia vs. controls.
Summary of evidence	Moderate to low quality evidence (small to medium-sized samples,



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	unable to assess precision or consistency, direct) 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	
<u>Medial frontal cortex</u>	
<i>A significant, small reduction in glutamate level in people with schizophrenia;</i> 9 studies, N = 337, $d = -0.391$, $p = 0.006$ Meta-regression showed a progressive decrease with age in patients compared to controls ($p = 0.008$).	
<i>A significant, medium-sized increase in glutamine in people with schizophrenia;</i> 8 studies, N = 275, $d = 0.403$, $p = 0.045$ Meta-regression showed a progressive decrease with age in patients compared to controls ($p = 0.0005$).	
<i>No significant difference in total glutamate + glutamine levels between patients and controls;</i> 8 studies, N = 330, $d = 0.122$, $p = 0.393$	
<i>No significant difference in glutamate/glutamine ratio levels between patients and controls;</i> 6 studies, N = 228, $d = 0.308$, $p = 0.062$ Meta-regression showed a progressive decrease with age in patients compared to controls ($p = 0.02$).	
<i>A significant, small reduction in NAA levels in people with schizophrenia;</i> 19 studies, N = 779, $d = -0.320$, $p = 0.019$ Meta-regression showed a progressive decrease with age in patients compared to controls ($p = 0.04$).	
<i>A significant, small reduction in NAA/glutamate ratio in people with schizophrenia;</i> 7 studies, N = 247, $d = -0.357$, $p = 0.038$ Meta-regression showed a progressive decrease with age in patients compared to controls ($p = 0.049$).	
<u>Hippocampus</u>	
<i>No significant difference in total glutamate levels between patients and controls;</i> 3 studies, N = 107, $d = 0.031$, $p = 0.92$	
<u>Thalamus</u>	
<i>No significant difference in glutamate levels between patients and controls;</i> 3 studies, N = 128, $d = -0.286$, $p = 0.20$	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.



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Directness of results	Direct
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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	<p>Comparison of NAA/Cr (measured by ¹H-MRS) in the prefrontal cortex of people at risk of schizophrenia vs. controls.</p> <p>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.</p>
Summary of evidence	<p>Moderate quality evidence (medium to large sample, inconsistent, precise, direct) suggests NAA/Cr is reduced in the prefrontal cortex of people at clinical or familial risk of schizophrenia.</p>
NAA/Cr	
<p>NAA/Cr was significantly lower in the high-risk group; 9 studies, N = 442, $d = -0.42$, 95%CI -0.61 to -0.23, $p < 0.0001$</p> <p>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]).</p>	
Consistency in results	<p>I^2 is not reported. Forest plot appears inconsistent, most likely due to differences in age.</p>
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 ¹H-MRS) in the frontal lobes of people with schizophrenia vs. controls.
Summary of evidence	Moderate quality evidence (medium to large samples, unable to assess precision or consistency, direct) suggests NAA levels are reduced in the frontal lobe and the cingulate cortex in people with schizophrenia.
NAA	
<p><u>Frontal lobe</u> 18/26 studies (N = 781) showed decreased NAA in people with schizophrenia</p> <p><u>Frontal pole</u> 6/9 studies (N = 252), showed decreased NAA in schizophrenia patients</p> <p><u>DLPFC</u> 8/12 studies (N = 346), showed decreased NAA in schizophrenia patients</p> <p><u>Cingulate cortex</u> 8/10 studies (N = 301), showed decreased NAA in schizophrenia patients</p>	
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 ¹H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis

Neuropsychopharmacology 2005; 30(11): 1949-1962

[View review abstract online](#)

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<p>Comparison</p>	<p>Comparison of metabolic NAA activity (measured by ¹H-MRS) in people with schizophrenia vs. controls</p> <p>Compares the consistency of measuring NAA as a raw percentage to measuring as a ratio with control data</p>
<p>Summary of evidence</p>	<p>Moderate to low quality evidence (unclear sample size, inconsistent, unable to assess precision, direct) suggests 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.</p>
<p>NAA/Cr</p>	
<p style="text-align: center;"><u>Frontal cortex</u></p> <p>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</p> <p style="text-align: center;"><u>Temporal cortex</u></p> <p>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</p> <p style="text-align: center;"><u>Hippocampus</u></p> <p>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</p> <p style="text-align: center;"><u>Anterior cingulate gyrus</u></p> <p>Grey matter: 12 studies (N unclear), patient average NAA 95.9% of control levels</p> <p style="text-align: center;"><u>Cerebellum</u></p> <p>Grey matter: 3 studies (N unclear), patient average NAA 92.3% of control levels</p> <p style="text-align: center;"><u>Parietal cortex</u></p> <p>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</p> <p style="text-align: center;"><u>Thalamus</u></p> <p>Grey matter: 19 studies (N unclear), patient average NAA 96.5% of control levels</p> <p style="text-align: center;"><u>Basal ganglia</u></p> <p>Grey matter: 6 studies (N unclear), patient average NAA 98.5% of control levels</p> <p style="text-align: center;"><u>Occipital cortex</u></p> <p>White matter: 1 study (N unclear), patient average NAA 96.0% of control levels</p>	

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Grey matter: 8 studies (N unclear), patient average NAA 102.8% of control levels

Striatum (caudate + putamen)

Grey matter: 1 study (N unclear), patient average NAA 112.6% of control levels

Lenticular nucleus (putamen + globus pallidus)

Grey matter: 2 studies (N unclear), patient average NAA 104.5% of control levels

Posterior cingulate

Grey matter: 5 studies (N unclear), patient average NAA 100% of control levels

Caudate nucleus

Grey matter: 3 studies (N unclear), patient average NAA 100.3% of control levels

Putamen

Grey matter: 7 studies (N unclear), patient average NAA 100.6% of control levels

Centrum semiovale

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
Directness of results	Direct measures and comparison of NAA levels.

Wenneberg C, Glenthøj BY, Hjorthøj C, Buchardt Zingenberg FJ, Glenthøj LB, Rostrup E, Broberg BV, Nordentoft M

Cerebral glutamate and GABA levels in high-risk of psychosis states: A focused review and meta-analysis of ¹H-MRS studies

Schizophrenia Research Jan: doi: 10.1016/j.schres.2019.10.050

[View review abstract online](#)

Comparison	Cerebral glutamate and GABA levels measured by ¹ H-MRS in people at high risk of psychosis vs. controls.
Summary of evidence	Moderate to high quality evidence (small to medium-sized samples, consistent, precise, direct) finds a medium-sized decrease in glutamate in the thalamus of people at clinical high risk, and a medium-sized increase in glutamate+glutamine in the frontal lobe of people at genetic high risk. There were no other significant differences in other brain regions (occipital, temporal,



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	hippocampal, striatum, cerebellum, or white matter).
GABA, Glu, Glx	
<u>Thalamus</u>	
<i>A medium-sized effect showed significantly lower glutamate levels in the thalamus of people at clinical high risk;</i>	
3 studies, N = 218, SMD = 0.50, 95%CI 0.23 to 0.78, $p = 0.0003$, $I^2 = 0\%$	
There were no significant differences in other brain regions (frontal, occipital, temporal, hippocampal, striatum, cerebellum, white matter).	
<u>Frontal</u>	
<i>A medium-sized, significant effect showed higher glutamate + glutamine levels in the frontal lobe of people at genetic high risk;</i>	
4 studies, N = 140, SMD = -0.55, 95%CI -0.89 to -0.21, $p = 0.001$, $I^2 = 0\%$	
There were no significant differences in other brain regions (thalamus, occipital, temporal, hippocampal, striatum, cerebellum), and in the analysis of the frontal lobe that combined clinical and genetic high-risk individuals.	
No significant differences were found in GABA levels.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

Cho = choline, CI = confidence interval, Cr = creatine amino acid, DLPFC = dorsolateral prefrontal cortex, GABA = gamma aminobutyric acid, Gln = glutamine, Glu = glutamate, Glx = glutamate + glutamine, ¹H-MRS = Proton Magnetic Resonance Spectroscopy, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), LS = least squares mean, N = number of participants, NAA = N-acetylaspartate amino acid, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), ³¹P-MRS = Phosphorus Magnetic Resonance Spectroscopy, PDE = phosphodiester lipid, PME = phosphomonoester lipid, SMD = standardised mean difference, U = units

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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.

† 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 effect¹⁷.

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 ¹⁸. InOR stands for logarithmic OR where a InOR 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 unforeseen 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

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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 relaxed¹⁹.

|| 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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