TECHNICAL COMMENTARY

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Neurometabolites

Introduction

Products of normal chemical metabolism may be altered in schizophrenia. Changes in metabolite levels may be indicative of altered biochemical activity. Magnetic resonance spectroscopy (MRS) has been used to measure levels of metabolites, such as N-acetylaspartate (NAA), creatine (Cr), trimethylamines/ choline containing compounds (Cho) and glutamine (Gln). These derivatives are indirect indicators of biochemical activity. Alteration in levels of NAA/Cr is associated with the protective myelin sheath surrounding neurons, which is used as a marker of neural cell viability. Decreased levels of NAA are associated with neuron death, or injury to the part of the neuron that connects to other cells, the axon. Gln is a metabolite of the neurotransmitter, glutamate (Glu).

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[1]. 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 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 ten systematic reviews that met our inclusion criteria[3-12].

- High quality evidence finds a small decrease in myo-inositol levels in the medial prefrontal region in people with schizophrenia.
- Moderate or moderate to high quality evidence suggests NAA levels (measured as both NAA and NAA/Cr) are decreased in

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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.
- Moderate quality evidence suggests small to medium-sized reductions in glutamate and increases in glutamine levels in the frontal cortex of people with schizophrenia compared to controls, which may progress with age. Lower quality evidence is unclear about hippocampus and thalamic levels.
- 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 increases in choline in the basal ganglia. There were no changes in glutamate, creatine or myo-inositol levels.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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

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 (medium to large samples, mostly consistent, precise, 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 = 1,679, *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 = 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 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%

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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

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

Frontiers in Psychiatry 2018; 9 (SEP)

View review abstract online

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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Comparison	**Medial prefrontal myo-inositol levels measured by ^{1}H-MRS in people with schizophrenia vs. healthy 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	
Medial prefrontal *Significant, small decrease in people with schizophrenia;* 19 studies, N = 1,146, SMD = 0.19, 95%CI 0.05 to 0.32, p = 0.0067, I^2 = 15%, p = 0.09 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.	
Consistency in results	Consistent
Precision in results	Precise
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 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-sized sample, unable to assess precision or consistency, direct) 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.**

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	
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.

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 ^{1}H-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. healthy 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 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.**

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Neurometabolites

NAA
Significant, medium-sized decrease in NAA in the thalamus of unmedicated people with schizophrenia; 3 studies, N = 174, SMD = -0.56, 95%CI -0.87 to -0.25, *p* = 0.0005, I^2 = 0%, *p* = 0.37 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, *p* = 0.0001). There were no significant differences in NAA in the medial prefrontal cortex, dorsolateral prefrontal cortex, basal ganglia, hippocampus or medial temporal lobe.
Glx/Glu
A significant, medium-sized increase in Glx in the medial prefrontal cortex of unmedicated people with schizophrenia; 3 studies, N = 99, SMD = 0.47, 95%CI 0.06 to 0.88, *p* = 0.03, I^2 = 0%, *p* = 0.60 There were no significant differences in Glx levels the dorsolateral prefrontal cortex, hippocampus or medial temporal lobe. *There was no significant difference in Glu levels in the medial prefrontal cortex;* 3 studies, N =136, SMD = -0.02, 95%CI -0.36 to 0.39, *p* = 0.89, I^2 = 0%, *p* = 0.52
Choline
A significant, medium to large increase in choline in the basal ganglia of unmedicated people with schizophrenia; 3 studies, N = 168, SMD = 0.77, 95%CI 0.24 to 1.31, *p* = 0.005, I^2 = 48%, *p* = 0.15 There were no significant differences in Glx levels the medial prefrontal cortex, dorsolateral prefrontal cortex, frontal white matter, thalamus, hippocampus or medial temporal lobe.
Creatine
There was no significant difference in creatine levels in the medial prefrontal cortex; 3 studies, N = 344, SMD = 0.16, 95%CI -0.24 to 0.57, *p* = 0.43, I^2 = 51%, *p* = 0.10 There was no significant difference in creatine in the dorsolateral prefrontal cortex.
Myo-inositol
There was no significant difference in myo-inositol levels in the hippocampus/medial temporal lobe; 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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Directness of results	Direct

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, 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 significant 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 significant 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 significant 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%

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 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 quality evidence (medium to large samples, 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. Lower quality evidence (small samples) 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). <u>Hippocampus</u> *No significant differencez in total glutamate levels between patients and controls;* 3 studies, N = 107, *d* = 0.031, *p* = 0.92 <u>Thalamus</u> *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; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
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 to high quality evidence (large sample, inconsistent, precise, direct) 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 (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	

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	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct measures and comparison of NAA levels

Spencer AE, Uchida M, Kenworthy T, Keary CJ, Biederman J

Glutamatergic dysregulation in pediatric psychiatric disorders: a systematic review of the magnetic resonance spectroscopy literature

Journal of Clinical Psychiatry 2014; 75(11): 1226-1241

View review abstract online

Comparison	**Glutamatergic metabolite levels (measured by MRS) in children or youth with schizophrenia or with parent with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess precision or consistency, direct) is uncertain of glutamateric metabolite levels in children or youth with schizophrenia or with parent with schizophrenia.**
Glutamatergic metabolites	
1 study (N = 42) reported increased glutamate+glutamine/creatine ratio in the right medial frontal lobe of youth (mean age 16.4 years) with a parent with schizophrenia. Increased ratio levels correlated with poorer functioning levels assessed by the Global Assessment of Functioning scale. There were no differences in NAA/creatine, inosital-containing compounds/creatine or choline compounds/creatine. 1 study (N = 86) reported increased glutamate+glutamine in the inferior paritetal/occipital cortex of youth (mean age 15.6 years) with a parent with schizophrenia or schizoaffective disorder. Glutamate+glutamine levels correlated negatively in high-risk youth (older age = lower levels), and	

positively in controls (older age = increased levels). No differences were found in glutamate+glutamine levels the caudate, prefrontal white matter, anterior cingulate cortex, superior temporal region, or posterior white matter. There were also decreased NAA, choline compounds, creatine and phosphocreatine levels in the caudate and increased NAA in prefrontal white matter in a subgroup of youth at at-risk for schizophrenia that were without psychopathology. There were no differences in NAA, choline compounds, creatine or phosphocreatine levels in the anterior cingulate cortex, thalamus, inferior paritetal/occipital cortex, or superior temporal region. 1 study (N = 47) reported increased glutamate+glutamine and decreased NAA in the left and right thalamus and caudate of youth with a parent with schizophrenia (mean age 15.9 years). Positive correlations between these increases and attenuated psychotic symptoms (increased metabolites = increased symptoms), and perseverative errors on the Wisconsin Card Sorting Test were reported. Reduced NAA and increased choline compounds were found in the anterior cingulate cortex. 1 study (N = 25) found decreased glutamate+glutamine/creatine ratio in in occipital and frontal lobes (trend effect for frontal lobes) of children with schizophrenia (mean age 14 years). There was also reduced NAA/creatine in the frontal lobes, and no differences in NAA/creatine in the occipital lobes. There were no differences in choline compounds/creatine or mlno/creatine. 1 study (N = 41) found no differences in glutamatergic metabolites in the inferior and middle frontal and superior temporal gyri between children with schizophrenia (mean age 14 years) and controls (mean age 11.5 years).

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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 (mostly unclear samples size, inconsistent, unable to assess precision, direct) 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 studies, patient average NAA 94.2% of control levels White matter: 18 studies, patient average NAA 94.8% of control levels Temporal cortex Grey matter: 5 studies, patient average NAA 94.0% of control levels White matter: 8 studies, 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, NAA 88.9% of control levels Anterior cingulate gyrus Grey matter: 12 studies, patient average NAA 95.9% of control levels Cerebellum Grey matter: 3 studies, patient average NAA 92.3% of control levels Parietal cortex Grey matter: 1 study, patient average NAA 94.0% of control levels White matter: 2 studies, patient average NAA 99.0% of control levels Thalamus Grey matter: 19 studies, patient average NAA 96.5% of control levels Basal ganglia Grey matter: 6 studies, patient average NAA 98.5% of control levels Occipital cortex White matter: 1 study, patient average NAA 96.0% of control levels Grey matter: 8 studies, patient average NAA 102.8% of control levels Striatum (caudate + putamen) Grey matter: 1 study, patient average NAA 112.6% of control levels Lenticular nucleus (putamen + globus pallidus) Grey matter: 2 studies, patient average NAA 104.5% of control levels Posterior cingulate	

Neurometabolites

Grey matter: 5 studies, patient average NAA 100% of control levels Caudate nucleus Grey matter: 3 studies, patient average NAA 100.3% of control levels Putamen Grey matter: 7 studies, patient average NAA 100.6% of control levels Centrum semiovale White matter: 5 studies, 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.

Explanation of acronyms

CI = confidence interval, Cr = creatine amino acid, DLPFC = dorsolateral prefrontal cortex, Gln = glutamine (glutamate synaptic metabolic), Glu = glutamate neurotransmitter, Glx = glutamate+glutamine, ^{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, vs. = versus

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias that involves the selective reporting of results; publication bias - trials that 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 randomized 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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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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