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

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Abstract

This meta-analysis evaluates alterations of neurometabolites in schizophrenia and bipolar disorder. PubMed was searched to find controlled studies evaluating N-acetylaspartate (NAA), Choline (Cho) and Creatine (Cr) assessed with ^{1}H-MRS (proton magnetic resonance spectroscopy) in patients with schizophrenia and bipolar disorder up to September 2010. Random effects meta-analyses were conducted to estimate pooled standardized mean differences. I^2 statistic was used to quantify inconsistencies. Subgroup analyses were conducted to explore potential explanations for inconsistencies. 146 studies with 5643 participants were included in the systematic review. NAA levels were affected in schizophrenia and bipolar disorder. Decreased levels in the basal ganglia and frontal lobe were the most consistent findings in schizophrenia, decreased levels in the basal ganglia were the most consistent findings in bipolar disorder. Cho and Cr levels were not altered in either disorder. Findings for Cr were most consistent in the thalamus, frontal lobe and dorsolateral prefrontal cortex in schizophrenia and the basal ganglia and frontal lobe in bipolar disorder. Findings for Cho were most consistent in the thalamus, frontal lobe and anterior cingulate cortex in schizophrenia and basal ganglia in bipolar disorder. Large, carefully designed studies are needed to better estimate the extent of alterations in neurometabolites.

Keywords

Magnetic resonance spectroscopy (MRS); N-acetylaspartate; Creatine (Cr); Choline (Cho)

1. INTRODUCTION

Emil Kraepelin was the first to establish dementia praecox and manic-depressive insanity as dichotomous model, which has been utilized in conceptualization of schizophrenia and

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bipolar disorder ever since (Crow, 1990a; Heckers, 2008). However, emerging data suggest a relationship between schizophrenia and bipolar disorder, even a conceptualization of these disorders as polar ends of a continuum of the same mental illness is proposed (Crow, 1990b).

Family studies and twin studies have shown co-aggregation between schizophrenia and bipolar disorder. Shared genetic susceptibility has been reported in both candidate gene studies and whole-genome linkage analyses (Dalby et al. 1986; Bramon and Sham, 2001; Craddock and Owen, 2005; Lichtenstein et al., 2009; Purcell et al., 2009; Van Snellenberg and de Candia, 2009). A meta-analysis in magnetic resonance imaging (MRI) studies suggested gray matter reductions in paralimbic structures implicated in emotional processing in bipolar disorder, with a more extensive reduction in schizophrenia, not only affecting paralimbic structures, but also limbic and neocortical structures (Ellison-Wright and Bullmore, 2010).

Magnetic Resonance Spectroscopy (MRS) is increasingly being applied to characterize tissue-based chemical or metabolic abnormalities in psychiatric disorders. It is a non-invasive technique that measures chemical composition of tissues, energy metabolism, neurotransmitter levels, and neuronal integrity *in vivo*. It detects magnetic resonance signals produced by atomic nuclei located within molecules in living tissue. Quantification of MRS signal amplitude can provide an estimate for concentrations of signal generating molecules. (Kreis et al., 1993; Dager et al., 2008; Alger, 2010). The peak integral is proportional to the number of resonating nuclei. However, metabolite quantification is affected by high variability as the signal has low sensibility and multiple processing steps are performed. To take these variations in account, a reference signal is obtained. The reference signal is generally generated by a metabolite, water or a chemical compound in a phantom object. The reference signal often is classified as either “internal” or “external”, with internal meaning that the reference signal is generated by a metabolite or by water within the brain, and external meaning that the reference signal is generated by a phantom that is outside the brain. Resulting metabolite levels are then reported in two different ways. The first method is to report metabolite ratios, referring to Creatine (Cr) (e.g. NAA/Cr); the second method is to report absolute concentrations. These absolute concentrations are referenced to either brain water content or an external metabolic phantom with known metabolite concentrations and usually reported as mmol/l or institutional units (i.u.) (reviewed in Bagory et al., 2007).

^{1}H-MRS (proton magnetic resonance spectroscopy) is the most widely applied technique studying alterations of neurometabolites in psychiatric disorders. Metabolites measured with ^{1}H-MRS include N-acetyl aspartate (NAA), a metabolite that is thought to reflect neuronal integrity and is exclusively found in the brain; Cr, a putative marker of phosphate metabolism; Trimethylamines/ choline containing compounds (Cho), indicating breakdown of cell membranes and cellular turnover; and neurotransmitters such as Gamma-aminobutyric acid, glutamine, glutamate, with glutamate being the most abundant amino acid and excitatory neurotransmitter in the brain (Miller, 1991; Keshavan et al. 2000).

Abnormalities of neurometabolites in various regions of the brain have been implicated in the pathophysiology of both schizophrenia and bipolar disorder. Meta-analytic evidence in schizophrenia suggests that NAA may be reduced in the hippocampus and the frontal lobe (grey and white matter). Similar findings were reported in a systematic review performed in bipolar disorder, showing decreased NAA levels in euthymic bipolar patients in the hippocampus and frontal lobe as well. (Steen et al., 2005; Yildiz-Yesiloglu and Ankerst, 2006). Decrease of NAA is thought reflect neuronal or axonal loss or mitochondrial dysfunction (Meyerhoff et al., 1993; Sager et al., 2001), implying structural abnormalities on a molecular/neuronal level in both disorders. Cr has long thought to be a stable

neurometabolite, and has been widely used as internal reference in MRS studies. However, several studies found reduced Cr levels in the dorsolateral prefrontal cortex, hippocampus and basal ganglia in both bipolar disorder and schizophrenia (Deicken et al., 2003; Ohrmann et al. 2005; Frey et al., 2007; Ruesch et al., 2008). These reports not only suggest alterations in the cellular energy metabolism but also question the validity of using Cr as internal reference. Conflictive results are also found for Cho; levels have been reported to be decreased in some studies in the basal ganglia, hippocampus and DLPFC in schizophrenia while others report an increase (Maier et al., 1996; Stanley et al. 1996; Bustillo et al., 2002; Ohrmann et al., 2005; Bustillo et al., 2008; Ruesch et al., 2008). In bipolar disorder, different studies suggest an increase, decrease or no change in Cho levels in the DLPFC, increased and decreased levels in the hippocampus and increased or unchanged levels in the ACC (Deicken et al., 2003; Michael et al., 2003; Brambilla et al., 2005; Frye et al., 2007a; Iosifescu et al. 2009; Colla et al., 2009).

We sought to systematically review all controlled studies of brain metabolite levels measured by ^{1}H-MRS, to estimate the extent to which NAA, Cr, and Cho are altered in schizophrenia and bipolar disorder, to seek explanations (other than chance) by which studies in this field have yielded inconsistent results, and to examine if data supports the conception of a continuum or a dichotomy of bipolar disorder and schizophrenia.

2. METHODS

2.1 Eligibility Criteria

Eligible studies were clinical trials evaluating brain metabolites with ^{1}H-MRS in patients with schizophrenia, schizoaffective disorder, schizophreniform disorder, or bipolar disorder according to DSM-III, DSM-III-R, or DSM-IV criteria.

Studies published in languages other than English, reported neurometabolites other than NAA, Cho or Cr, did not include a healthy control group, postmortem studies and studies enrolling adolescent subjects (younger than age 18) or geriatric subjects (older than 65) were excluded.

2.2 Literature Search

NVK and MAR performed a literature search in PubMed for ^{1}H-MRS studies in schizophrenia and bipolar disorder for the timeframe up to September 2010 using the following key words: “Schizophrenia”, “Bipolar Disorder”, “Manic depressive disorder”, and “Magnetic Resonance Spectroscopy (MRS)”. The reference lists of included studies were inspected for additional eligible studies.

2.3 Study Selection

NVK and MAR reviewed titles and abstracts retrieved from the search and selected potentially eligible studies for full text review. Full text articles were then requested and assessed for eligibility. Figure 1 describes the outcomes at each level of our study identification process.

2.4. Author Contact

If relevant data were not reported in the article, we attempted to contact authors via e-mail to obtain this information. If no initial response was received, a second e-mail was sent two weeks later. If we did not receive a response then, the study was excluded from the meta-analysis. We contacted 76 authors for additional information. We received information from 13% of the authors. A total of 146 studies were included in the systematic review.

2.5. Data Extraction

We extracted the following data from each study: year of publication, number of participants (patients and healthy controls), illness duration (first episode vs. chronic illness), mood state (manic, depressed, euthymic), use of psychotropic medication (currently on medication vs. off medication vs. never treated and or minimally treated), MRS data acquisition parameters (MRSI vs. single-voxel (SV), field strength, location of voxel placement, use of a internal or external reference), absolute metabolite levels (mM or institutional units), and metabolite ratios.

2.6. Outcome Measures

Our primary outcome variables were absolute metabolite levels reported as mmol/l or i.u. (NAA, Cr, and Cho) as well as metabolite ratios (NAA/Cr and Cho/Cr) in the following regions of the brain: frontal lobe (given that the frontal lobe is a large and functionally complex region, we decided to analyze the ACC and DLPFC separately when authors specified that they studied these specific regions), parietal lobe, temporal lobe, occipital lobe, hippocampus, thalamus, basal ganglia, and cerebellum.

2.7. Statistical Analyses

2.7.1. Meta-analyses—We conducted meta-analyses for studies including subjects with bipolar disorder and schizophrenia meeting criteria as outlined above across all mentioned regions of the brain; however, not all regions had adequate number of studies to conduct a formal meta-analysis. If individual study results were reported separately for the left and right hemisphere, the left hemisphere data was included in the analysis, as it is the dominant hemisphere in most subjects. (Analyses were then re-run with right hemisphere data and compared with the initial analysis, given there was no significant difference between results of left and right hemisphere, this data is not shown).

To avoid double counting of the control group we only included subjects with chronic schizophrenia and not first episode psychosis when results were reported separately for both groups, but only one control group was reported. Chronic schizophrenia subjects were included because diagnostic stability likely is higher in this group.

To limit heterogeneity, eight studies that reported values (either in the original publication or via author contact) were excluded from analysis with absolute metabolite data, because they reported peak areas and did not report a internal water reference or external phantom of metabolites for spectra obtained (Buckley et al., 1994; Nasrallah et al., 1994; Shioiri et al., 1996; Kegeles et al., 2000; Ohara et al., 2000; Delamillieure et al., 2002; Szulc et al., 2007; Tang et al., 2007). One study was excluded because it reported relaxation times as opposed to concentrations (Ongur et al., 2010a). Eight studies were excluded because they reported the same subjects, or clearly had high overlap in subjects that have been published in other studies already included in the meta-analysis (Maier et al., 1995; Deicken et al., 1999; Deicken et al., 2000; van Elst et al., 2005; Ohrmann et al., 2007; Theberge et al., 2007; Ongur et al., 2008; Wood et al., 2009).

Data were analyzed with Review Manager 5.0.25 (Collaboration, 2008). We expected a high level of heterogeneity in the studies included in this meta-analysis; therefore, we conducted meta-analyses using the DerSimonian and Laird random-effects model to estimate effect sizes as standardized mean difference and its 95% confidence interval (CI) (DerSimonian and Laird, 1986).

We further quantified the extent to which observed inconsistency corresponded to between-study differences using the I^2 statistic which measures the percentage of total variation

across studies due to methodological or treatment heterogeneity rather than chance. Inconsistency is low when I^2 is less than 25%, moderate when I^2 is between 25% and 75%, and high when I^2 is greater than 75% (Higgins et al., 2003).

2.7.2. Quantitative comparison of schizophrenia and bipolar disorder—We performed secondary meta-analyses, grouping both studies conducted in bipolar disorder and schizophrenia together in the same analysis. To assess differences in metabolite levels based on diagnosis, we then did a subgroup analysis with subgroups being defined as bipolar disorder and schizophrenia.

2.7.3. Subgroup analyses—*A priori* hypotheses examining potential heterogeneity across studies included differences in magnetic resonance field strength (low field strength: 1.5T and 2T vs. high field strenght: 3T and 4T), duration of illness (first episode vs. chronic disease), mood state (manic vs. depressed vs. euthymic), and medication status (current treatment vs. off medication vs. never/minimal treatment). A subgroup analysis performs separate meta-analyses in each subgroup. SMD in each subgroup is obtained, I^2 statistics are performed to assess heterogeneity within the subgroup and χ^2 statistics are done to explore differences between subgroups. Subgroup analyses were performed if inconsistency was moderate to high, and if there were at least two studies to include in each subgroup.

2.7.4. Assessment of publication bias—We planned to conduct a funnel plot to explore publication bias, but did not have an adequate number of studies to perform analysis. When only a limited number of studies are included, accurate identification of publication bias is practically due to chance. Resulting problems are subjectivity in the visual interpretation of the results, technical feasibility, and remaining uncertainty (Lau et al., 2006).

3. RESULTS

3.1. Study Characteristics

Table 1a and 1b give the characteristics of the studies. A total of 4182 subjects (2067 patients and 2115 healthy controls) were included in the 103 studies conducted in patients with schizophrenia, with a median study size of 36 participants (range: 13–115). In the 43 studies with bipolar disorder, 1461 subjects (738 patients and 721 healthy controls) were included, with a median study size of 34 participants (range: 13–64).

84% of studies investigating schizophrenia included chronically ill patients, with 80% of studies including patients currently on antipsychotic medications. 33% of studies researching bipolar disorder included subjects in various mood states, 45% included euthymic patients only, three studies depressed patients only, and five studies included exclusively manic subjects. 45% of studies were conducted in patients currently on psychotropic medications.

A total of 104 studies used MRS with 1.5T field strength, eight studies with 2T, 21 studies with 3T, and 13 studies with 4T field strength.

3.2. Meta-Analyses

In schizophrenia, available data allowed conducting meta-analyses of absolute metabolite levels (NAA, Cr, and Cho) in the following regions of the brain: frontal lobe (n= 11) (separate analyses shown for ACC (n= 10) and DLPFC (n= 6)), hippocampus (n= 7), thalamus (n= 8), and basal ganglia (n= 6). Data were insufficient to perform analyses in both temporal lobe and cerebellum.

Meta-analyses for NAA/Cr ratios were performed in the hippocampus (n= 8), thalamus (n= 9), basal ganglia (n= 8), frontal lobe (n= 16), and temporal lobe (n= 7). Analyses for Cho/Cr ratios were performed in all the aforementioned regions except temporal lobe, due to lack of sufficient number of studies to include. There were not a sufficient number of studies to conduct meta-analysis in the ACC.

In bipolar disorder, sufficient data were available to conduct meta-analyses of absolute metabolite levels (NAA, Cr, and Cho) in the frontal lobe (n= 7) (separate analyses shown for ACC (n= 5) and DLPFC (n= 5)), hippocampus (n= 4), and basal ganglia (n= 4). Data were insufficient to perform analyses in the temporal lobe and thalamus.

Meta-analyses for NAA/Cr were conducted in the hippocampus (n= 4), basal ganglia (n= 7), ACC (n= 5), and DLPFC (n= 6). For Cho/Cr ratios analyses were conducted in the hippocampus (n= 3), basal ganglia (n= 6), ACC (n= 6), and DLPFC (n= 5). There were not sufficient numbers of studies to conduct meta-analyses in the thalamus, frontal lobe, and temporal lobe.

3.2.1. Absolute metabolite value data—Results in schizophrenia demonstrated significantly decreased levels of NAA in the thalamus [SMD = −0.62 (CI −1.12 to −0.13); p= 0.01], and frontal lobe [SMD = −0.44 (CI −0.65 to −0.23); p< 0.001]. Cr and Cho levels did not differ in any of the regions investigated (Figure 2a). NAA data were consistent over studies in basal ganglia and the frontal lobe. Cr data were consistent in frontal lobe, DLPFC and thalamus. Cho data were consistent in the thalamus, frontal lobe and ACC. Inconsistency was moderate to high in all metabolite levels in the hippocampus. Inconsistencies were evident also in thalamus (NAA), basal ganglia (Cr, Cho), ACC (NAA, Cr) and DLPFC (NAA, Cho).

In bipolar disorder (Figure 2b), results showed significantly decreased levels of NAA in the basal ganglia compared to healthy controls [SMD = −0.44 (CI −0.83 to −0.06); p= 0.02]. Increased NAA levels approached significance in the DLPFC [SMD = 0.24 (CI 0.00 to 0.49); p= 0.05]. Cr and Cho levels did not differ in any of the regions investigated (Figure 2b). Results were consistent over studies in the basal ganglia for all metabolites and in the frontal lobe for Cr levels. Results showed moderate to high inconsistency in all metabolite levels in hippocampus, ACC, and DLPFC. Inconsistency for Cho in the frontal lobe was moderate.

3.2.2. Metabolite ratio data—Results in schizophrenia demonstrated lower levels of NAA/Cr in the hippocampus (p< 0.01), thalamus (p< 0.01), frontal lobe (p< 0.01), and temporal lobe (p< 0.01), but not in the basal ganglia or the DLPFC. Cho/Cr was significantly lower in the hippocampus (p= 0.03). No differences were found in any other region. Inconsistency between studies was low for NAA/Cr in the thalamus and frontal lobe and for Cho/Cr in the hippocampus. However, results for ratio data were moderately inconsistent in the hippocampus and basal ganglia, and highly inconsistent in the temporal lobe (Table 2a).

In bipolar disorder, significantly lower NAA/Cr ratios were seen in the hippocampus (p< 0.01). Inconsistency was low for Cho/Cr only in the hippocampus and DLPFC (Table 2b).

3.2.3. Absolute versus ratio data—In schizophrenia, data for NAA levels and NAA/Cr ratios were relatively consistent in areas examined. Absolute Cho levels were not affected in patients with schizophrenia, but Cho/Cr levels in the hippocampus were significantly lower in schizophrenia compared to healthy controls.

In bipolar disorder, absolute NAA levels were found to be significantly decreased in the basal ganglia, but these findings could not be confirmed with NAA/Cr ratio data. NAA/Cr ratios were only decreased in the hippocampus, while absolute NAA levels were not decreased in the hippocampus.

3.2.4. Quantitative comparison of schizophrenia and bipolar disorder—We found significant lower NAA levels in the hippocampus (χ^2= 21.96; df= 1; p< 0.001) and DLPFC (χ^2= 11.84; df= 1; p< 0.001) in subjects with schizophrenia compared to subjects with bipolar disorder. Cho levels in the hippocampus (χ^2= 10.17; df= 1; p< 0.001) and Cr levels in the ACC (χ^2= 7.35; df= 1; p< 0.001) were also significantly lower in schizophrenia than in bipolar disorder. No significant differences in metabolite levels between the disorders were found in any other region studied.

3.2.5. Subgroup analyses

3.2.5.1. First episode vs. chronic schizophrenia: In schizophrenia, all studies that were conducted in first episode subjects enrolled them while off medication. Further, all studies that were conducted in subjects with chronic schizophrenia enrolled subjects currently treated with medication. We were therefore unable to attribute differences between subgroups to either duration of illness or medication status alone.

While initial analyses in schizophrenia showed a significant decrease of NAA in the thalamus with moderate inconsistency, subgroup analyses demonstrated that the decrease was attributable to studies conducted in chronic schizophrenia/subjects on medication [SMD= −0.77, p<0.01]. In first episode psychosis/subjects of medication, there was no significant decrease of NAA compared to healthy controls [SMD= −0.13; p= 0.86]. Differences between subgroups were significant [χ^2= 10.90; p< 0.01]. Inconsistencies found in the basal ganglia and DLPFC could not be explained by difference in illness duration. Data were not sufficient to conduct subgroup analyses in the hippocampus and ACC.

3.2.5.2. Manic vs depressive episode vs euthymic mood state: Data were insufficient to perform subgroup analyses based on mood states.

3.2.5.3. Medication status: For studies conducted in subjects with schizophrenia, results are as described above. Data was insufficient to perform subgroup analyses based on medication status in bipolar disorder.

3.2.5.4. Field strength: In the thalamus, studies conducted with low field strength demonstrated significant decrease of absolute NAA concentrations in schizophrenia (SMD= −0.89, p< 0.01) with inconsistencies across studies remaining moderate, while studies conducted with high field strength did not show any difference compared to healthy controls, with low inconsistency (SMD= −0.17, p= 0.86). There was a significant difference between studies conducted with low vs. high field strength [χ^2= 11.03; p< 0.01]. This means that studies conducted with high field strength did not find differences, and these findings were consistent across studies. Findings with low field strength did show decrease in NAA but inconsistency was higher between studies. Inconsistencies in hippocampus and ACC could not be explained by differences in field strength, SMDs between studies conducted with high vs. low field strength did not significantly differ, heterogeneity between studies in subgroups remained high. Data was not sufficient to perform subgroup analyses in basal ganglia and DLPFC.

While none of the subgroups significantly differed in from healthy controls, there was a significant difference between studies conducted with low vs high field strength in the ACC

in bipolar disorder. (NAA (absolute values): χ^2= 5.82; p= 0.02, Cr (absolute values): χ^2= 16.02; p< 0.01]. When only studies with low field strength vs studies with high field strength were grouped together, inconsistency between studies was low. This means that inconsistencies between groups can be explained by differences in field strength. Inconsistencies in the frontal lobe in both absolute and ratio data could not be explained by differences in field strength. Data was not sufficient to perform subgroup analyses in the hippocampus and DLPFC.

4. DISCUSSION

4.1. Findings

While our meta-analysis failed to reveal significant abnormalities in either Cr or Cho levels, we found several abnormalities in NAA levels in schizophrenia and bipolar disorder.

NAA levels appear to be globally decreased (hippocampus, thalamus, frontal and temporal lobe) in patients with schizophrenia compared with healthy controls, which is consistent with previous reports of a subtle decrease of NAA of about 5% overall (Steen, et al., 2005). Brugger previously suggested decreased NAA levels in the thalamus as trait marker of schizophrenia, as he did not find any significant difference between first episode psychosis and chronic schizophrenia (Brugger et al., 2011). However, our analysis suggests that NAA levels in the thalamus are only decreased in chronic schizophrenia but not first episode patients. These differences in results may be partly accounted for by inclusion of a study in pediatric population (O'Neill et al., 2004) and a study published in Turkish language (Basoglu et al., 2006) by Brugger, but at this time it is unclear if findings can be generalized to first episode patients.

NAA levels in bipolar disorder appear to be decreased in the basal ganglia. Data for the DLPFC show that NAA levels in bipolar disorder are increased compared to healthy controls. While the finding of an increase in NAA appears counterintuitive, a recent study suggests a close correlation between NAA and glutamate levels in healthy subjects (Waddell et al., 2011). Glutamate levels are consistently found to be elevated in bipolar disorder (Yuksel and Ongur, 2010), which could imply that the increase of NAA may be related to an increase of glutamate levels. Our understanding of the physiology/ pathophysiology of NAA remains limited, relationships between and interactions with other neurometabolites and resulting pathological implications are poorly researched. In conclusion, alterations of NAA levels may reflect a much more complex underlying process than simply neuronal viability.

In a comparison of effect sizes of alterations in metabolite levels we found significant differences in NAA in the DLPFC between schizophrenia and bipolar disorder. While levels in bipolar disorder were significantly increased compared to healthy controls, decrease in NAA did not reach significance in schizophrenia. However, a bidirectional effect appears to be emerging. While not as clear, a similar pattern is noticeable in NAA and Cho in the hippocampus. No statistically significant increase in NAA in the hippocampus in bipolar disorder was found, but levels were decreased at a trend level in schizophrenia; results differed significantly between the two groups. Cho in the hippocampus and Cr in the ACC did not significantly differ from healthy controls in schizophrenia and bipolar disorder. However, Cho in the hippocampus and Cr in the ACC were significantly lower in schizophrenia and bipolar disorder. It appears that, although alterations in neurometabolites share several commonalities, there appear to be several differences, which stands in contrast to the conceptualization of schizophrenia and bipolar disorder as a continuum of the same disorder. However, the validity of these findings is limited, as there was no direct comparison in metabolite levels. Also, the total number of subjects reported in studies conducted in schizophrenia (1329 patients and 1394 healthy controls in 103 studies) differs

from the ones conducted bipolar disorder (738 patients and 721 healthy controls in 43 studies). While this may be affecting outcomes, subgroup analysis compares effect sizes between groups. Effect size calculations take into account the number of subjects included in the analysis. Many studies did not specify that they have matched their samples for age and gender, which may have confounded results. To date, only a few studies have directly examined neurometabolite level differences between the disorders. Ongur did not find differences in Cr between subjects with schizophrenia and bipolar disorder (Ongur et al., 2009). In the ACC, NAA/Cr was found to be lower in schizophrenia and Cho/Cr was higher when compared to bipolar disorder (Sarramea et al., 2000); others reported decrease in NAA that were similar in both disorders (Molina et al., 2007). More data needs to become available before firm conclusions can be drawn.

4.2. Limitations

The evidence of alterations in brain metabolite levels consists of small studies in different regions of the brain with different patient populations receiving different or no treatment for their disorder. To detect a 10% change in NAA levels with 80% power, a sample size of 39 subjects and 39 controls was suggested; assuming these parameters, no studies conducted in bipolar disorder and only five studies in schizophrenia were adequately powered (Steen et al., 2005). While we attempted to ameliorate the effect of publication and outcome reporting bias by contacting authors, but only 13% provided requested data.

To avoid double counting effects, we excluded studies that included subjects reported elsewhere from analysis. However, it is possible that data remains in analyses that have been published in two sources. For the same reason, we decided to only include one reported dataset when two different sets of schizophrenic/bipolar subjects (e.g. first episode and chronic schizophrenia, manic and euthymic subjects) but only one healthy control group were included in a study. While this approach may lead to decreased power in overall analysis, we believe it is crucial to do so in order to avoid an overstating of the precision of results (Senn, 2009).

To reduce inconsistencies we excluded studies from data analysis if no internal or external concentration reference was used in data acquisition.

We have not attempted to weigh studies by methodological quality, as there is no objective way to assess this from published study methodology descriptions. However, it should be noted that studies conducted with magnets with high field strength that have a priori defined measures of spectral quality, spectral fitting and partial volume correction and include subjects that are not on medications with healthy controls that are matched by age, gender and socioeconomic status are considered to be of highest methodological quality.

We only examined NAA, Cr, and Cho in our systematic review. Since high field strength magnets are available, glutamate, glutamine, and GABA have become metabolites of interest. These metabolites have been implicated in the pathophysiology of both schizophrenia and bipolar disorder (Ongur, et al., 2008; Bustillo et al., 2010; Ongur et al., 2010b; Reid et al., 2010). Given the limited number of studies conducted examining glutamate, we decided that a meta-analytical approach would be premature and not include glutamate, glutamine and GABA in our analysis.

High remaining inconsistency in different areas of the brain makes results harder to interpret as factors that have not been controlled for could have a significant influence on the results. Further data will need to be obtained to clarify these findings, and other potential confounding factors need to be explored. Inconsistencies may be partly attributable to a number of variables that differ in the populations studied.

One of the variables that differ between populations and potentially confounds results is medication status. Many studies enrolled subjects currently treated with antipsychotic or moodstabilizers, potentially confounding our results. 80% of all studies conducted in schizophrenia included subjects on medication, while only 45% of subjects in bipolar trials were currently treated. Modulation of neurometabolite levels with both classes of drugs were demonstrated in the rat model. A consistent upregulation of NAA, with distinct regional patterns of activation depending on the agent given was the most robust finding (McLoughlin et al., 2009). In humans, antipsychotic medications are reported to increase NAA levels, even after a short period of treatment (Bertolino et al., 2001; Szulc et al., 2005). While some studies reported fewer effects on NAA levels in typical antipsychotics than atypical antipsychotics, others were unable to replicate these findings (Braus et al., 2001; Braus et al., 2002; Szulc, et al., 2007; Bustillo et al., 2008). Valproic acid was found to increase NAA/Cr in bipolar patients; lithium, but not valproic acid, was reported to increase NAA in euthymic bipolar patients (Silverstone et al., 2003; Atmaca et al., 2007). We were unable to draw conclusions on the influence of psychotropic medication on neurometabolites as data was not sufficient to do subgroup analyses.

Another potentially confounding clinical factor is mood state of subjects included. A small study suggested that Cr in the frontal lobe was decreased when the same subjects were in a depressed state compared to euthymia Hamkawa et al., 1999). Severity of depression was positively correlated with elevation of Cho levels in the cingulate, suggesting a mood state dependent alteration (Moore et al., 2000) A recent systematic review found alteration of glutamate levels in bipolar disorder are increased independent of mood state (Yuksel and Ongur, 2010). Our analysis did not allow drawing conclusions about mood state dependent alterations of neurometabolites, as not enough data was available to conduct subgroup analysis.

Several technical variations that may contribute to remaining inconsistencies. Differences in voxel size and voxel placement as well as grey and white matter contributions to selected voxels across studies may have contributed to inconsistencies. Studies used various definitions for areas of interest. Especially in studies with voxel placement within the frontal lobe, authors often identified their area of interest globally as “frontal lobe”. Others placed and defined their area of interest specifically within the ACC or DLPFC, both located within the frontal lobe. Where areas of interest within the frontal lobe were identified, we decided to analyze them separately, in an attempt to avoid overgeneralization of results in this functionally complex region. However, a potential limitation is that studies that actually did place their voxel completely or partly in one of these areas but did not state this in their method section were included in the general frontal lobe analysis which may have skewed the results. Further, MRS quantification is affected by signal to noise ratio (SNR), the quality of spectra form some regions is higher than others. Results show the moderate to high inconsistency in all metabolite levels in hippocampus, inconsistencies were evident also in thalamus, which may be attributable to lower SNR. T1/T2 is different at different field strength and affects metabolite quantification, it has also been demonstrated that T2 changes are associated with psychotic disorders, which may affect outcomes (Ongur et al. 2010a).

Some studies acquired single-voxel MRS while others used MRSI. Single-voxel MRS benefits from ease of implementation and quantitation, with only a single spectrum to process. MRSI has the advantage of acquiring data from multiple voxels in a single measurement, allowing investigation of different brain regions and tissue types. However, the spectrum at a given voxel will have contributions from neighboring voxels, and it is difficult to get a good shim and water suppression over a larger volume.

^{1}H-MRS studies generally report a combined NAA and N-acetylaspartyl-glutamate (NAAG) peak, this peak is composed of approximately 90% NAA and 10% NAAG (Pouwels et al., 1997; Edden et al., 2007). NAAG is a peptide that is synthesized from NAA and glutamate and abundant in the nervous system, NAAG has been implied to be altered in both schizophrenia and bipolar disorder. It is possible that some of the alterations in NAA levels can be contributed to actual abnormalities of NAAG.

Use of a concentration reference is necessary to account for spatial field inhomogeneities as well as field variations across scanning sessions. Metabolite ratios provide a measure of relative concentrations and are easy to obtain, many studies used Cr as an internal reference. However, this method has the disadvantage of not definitively distinguishing between the numerator and denominator metabolite changes. To calculate metabolite concentrations, an internal or external reference is needed. Some studies used an unsuppressed internal water reference spectrum. Another approach is the use of an external reference solution, but this method is sensitive to inhomogeneities because the reference solution is separated from the volume of interest in the brain.

4.3. Research implications

We found a global decrease of NAA levels in schizophrenia. Of the regions studied, altered NAA levels in bipolar disorder seem to be limited to the basal ganglia and frontal lobe, with decreased levels in the ACC and increased levels in the DLPFC. Cr and Cho levels do not appear to be significantly affected any of the studied areas in either schizophrenia or bipolar disorder. While absolute metabolite levels and ratio data appeared to be consistent in schizophrenia, data were more conflictive in bipolar disorder.

Heterogeneity of data remains large in both schizophrenia and bipolar disorder. We were able to explain some of the inconsistencies. Specifically, high field strength magnets appear to detect more subtle alterations in metabolite levels, but factors that have not been controlled for are probably accounting for the majority of inconsistent findings. Likely confounding factors are not only variability in the patient populations studied but also data acquisition parameters.

Large, carefully designed studies are needed to better estimate the extent of alterations in brain metabolite levels in patient and to determine if MRS could be established as a tool to help differentiate schizophrenia from bipolar disorder.

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DISCLOSURE/ CONFLICT OF INTEREST

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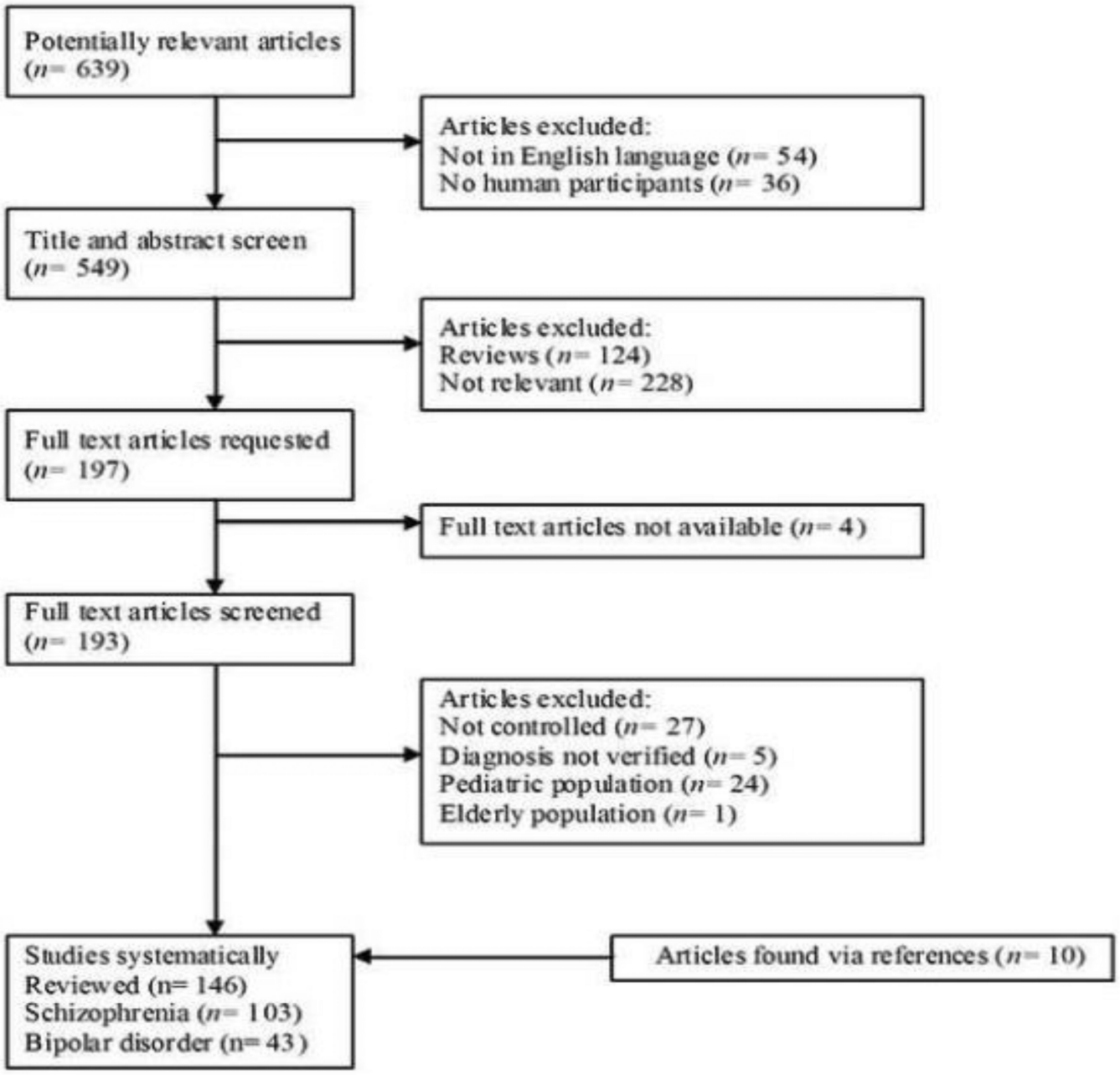
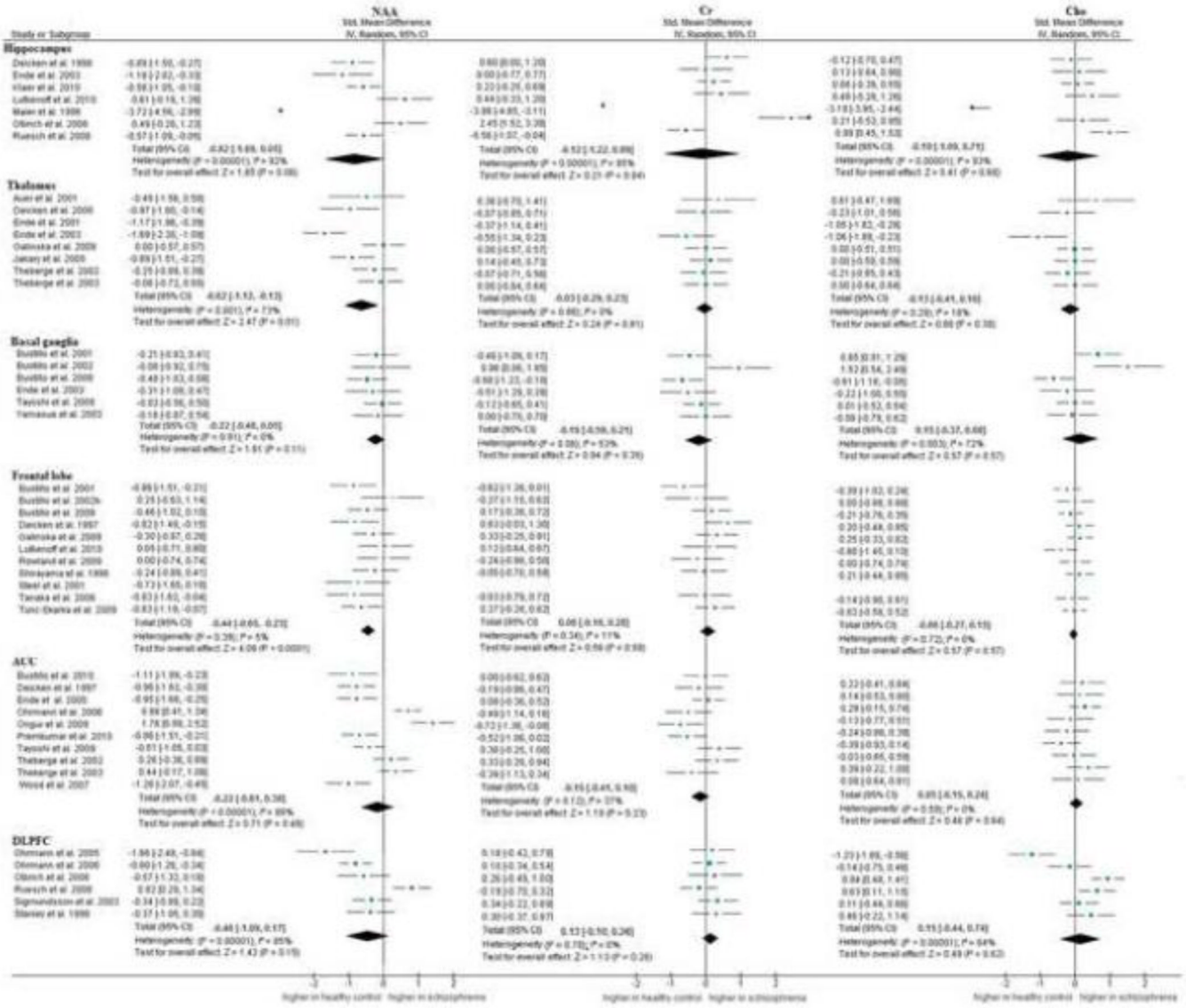


Fig. 1.



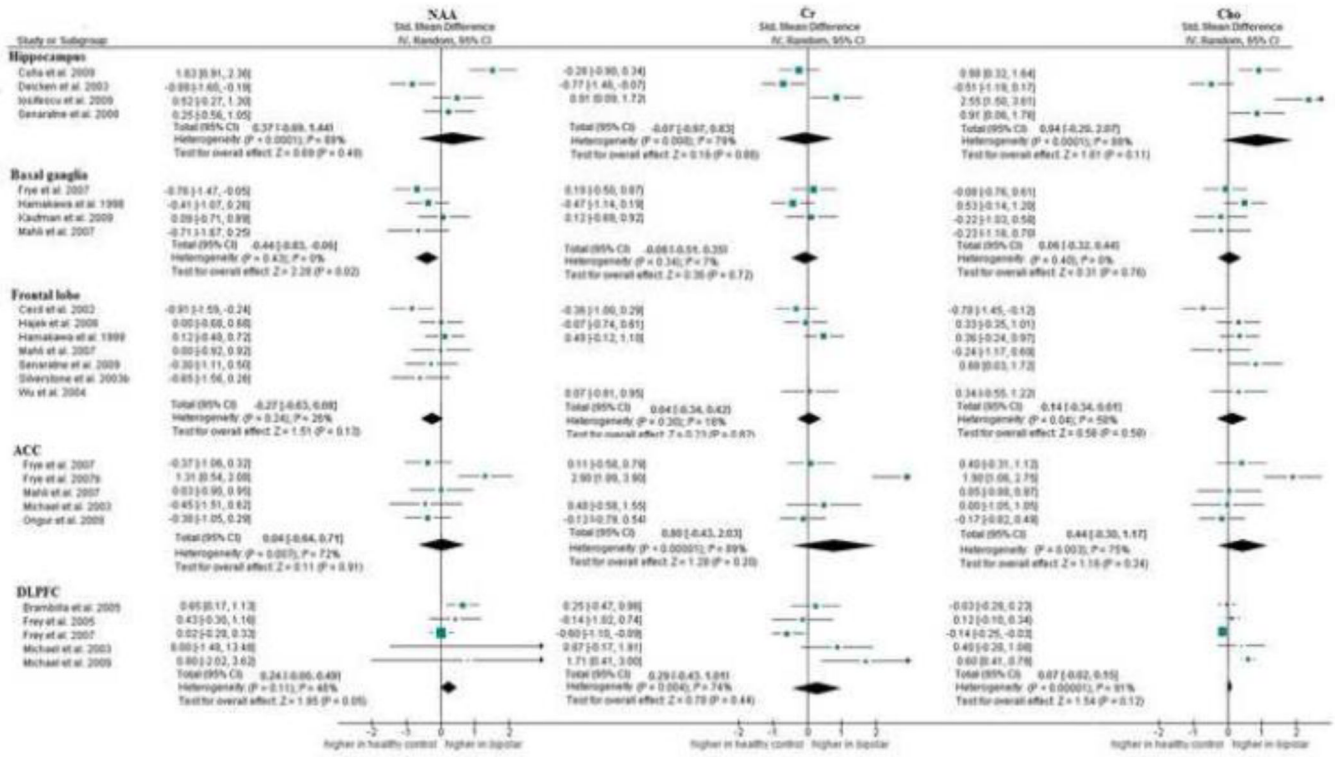


Fig. 2.

Table 1

a: Studies included in systematic review, schizophrenia

Author	Year	n sz/hc	Illness duration	Antipsychotic treatment	MRS	Tesla	Data processing	use of reference	Region studied	Absolute value data available	Ratio data available
Ando et al.	2002	7/7	chronic	current	SV	1.5	peak area		lenticular nucleus		incomplete *
Auer et al.	2001	32/17	chronic	current	SV	1.5	institutional units	internal water	thalamus, parietal white matter	X	
Aydin et al.	2007	28/28	chronic	current	SV	1.5	concentration	Internal water	cingulate gyrus	X	
Aydin et al.	2008	14/30	first episode	never	SV	1.5	concentration	internal water	whole brain	X	
Bartha et al.	1997	10/10	first episode	never	SV	1.5	concentration	internal water	medial prefrontal cortex, ACC		
Bartha et al.	1999	11/11	first episode	never/minimal	SV	1.5	concentration	internal water	left mesial temporal lobe	incomplete	
Bertolino et al.	1996	10/10	chronic	current	MRSI	1.5	peak area		hippocampus, DLPFC, thalamus, putamen, superior temporal gyrus, orbitofrontal cortex, posterior cingulate, ACC, occipital cortex, centrum semiovale, prefrontal white matter		incomplete
Bertolino et al.	2000a	13/13	chronic	varies	MRSI	1.5	peak area		DLPFC		
Bertolino et al.	2000b	9/7	chronic	never/off	MRSI	1.5	peak area		DLPFC		
Bertolino et al.	2003b	24/24	first episode	minimal	MRSI	1.5	peak area		hippocampus, DLPFC		incomplete
Block et al.	2000	25/19	chronic	current	SV	1.5	peak area		frontal lobe, BG		X
Buckley et al.	1994	28/20	varies	varies	SV	1.5	?concentration		frontal lobe, temporal lobe	X	
Bustillo et al.	2001	19/21	chronic	current	SV	1.5	concentration	internal water	frontal lobe, caudate nucleus	X	
Bustillo et al.	2002a	11/11	first episode	never	SV	1.5	concentration	internal water	frontal lobe, occipital lobe	X	
Bustillo et al.	2002b	10/10	first episode	never/minimal	SV	1.5	concentration	Internal water	caudate nucleus	X	
Bustillo et al.	2008	32/21	early	never/minimal	SV	1.5	concentration	internal water	frontal obe, occipital lobe, cerebellum, caudate nucleus	X	
Bustillo et al.	2010	14/10	early	never/minimal	SV	4	concentration	internal water	frontal white matter, thalamus, ACC	incomplete	
Callicott et al.	1998	47/66	chronic	current	MRSI	1.5	peak area		mesial temporal cortex, hippocampus		
Callicott et al.	2000a	13/18	chronic	unclear	MRSI	1.5	peak area		superior temporal gyrus, DLPFC, ACC, posterior cingulate, occipital cortex, frontal white matter,		

a: Studies included in systematic review, schizophrenia

Author	Year	n sz/hc	Illness duration	Antipsychotic treatment	MRS	Tesla	Data processing	use of reference	Region studied	Absolute value data available	Ratio data available
									putamen, hippocampus, thalamus		
Callicott et al.	2000b	36/73	chronic	varies	MRSI	1.5	peak area		DLPFC, hippocampus		
Choe et al.	1994	23/10	chronic	never	SV	1.5	peak area		prefrontal white matter		incomplete
Choe et al.	1996	55/20	chronic	off	SV	1.5	peak area		prefrontal cortex		incomplete
Cecil et al.	1999	8/14	first episode	never	SV	1.5	peak area		DLPFC, temporal lobe		
Deicken et al.	1997a	24/15	chronic	current	MRSI	1.5	concentration	internal water	frontal lobe	X	
Deicken et al.	1997b	26/16	chronic	varies	MRSI	1.5	concentration	internal water	ACC	X	
Deicken et al.	1998	30/18	chronic	varies	MRSI	1.5	concentration	internal water	hippocampus	X	X
Deicken et al.	1999	23/18	chronic	current	MRSI	1.5	concentration	internal water	hippocampus	X	
Deicken et al.	2000	17/10	chronic	current	MRSI	1.5	concentration	internal water	thalamus	X	incomplete
Deicken et al.	2001	20/15	chronic	current	MRSI	1.5	concentration	internal water	cerebellum	X	
Delamillieure et al.	2000a	27/24	unclear	unclear	SV	1.5	peak area		thalamus		incomplete
Delamillieure et al.	2000b	17/21	chronic	current	SV	1.5	peak area		medial prefrontal cortex		incomplete
Delamillieure et al.	2002	17/14	chronic	current	SV	1.5	peak area		prefrontal cortex, thalamus, hippocampus	X*	X*
Eluri et al.	1998	12/8	chronic	current	SV	1.5	peak area		cerebellum, pons		incomplete
Ende et al.	2000	19/16	chronic	current	MRSI	1.5	absolute integral values		ACC	X	
Ende et al.	2001	15/15	chronic	current	MRSI	1.5	absolute integral values		thalamus	X	
Ende et al.	2003	13/13	chronic	current	MRSI	1.5	absolute integral values		thalamus, hippocampus, BG	X	incomplete
Ende et al.	2005	13/14	chronic	unclear	MRSI	1.5	?concentration	internal water	cerebellum, dentate nucleus		
Fannon et al.	2003	11/25	first episode	off	SV	1.5		internal water	prefrontal cortex, hippocampus, BG		incomplete
Fujimoto et al	1996	14/12	chronic	current	SV	2	peak area		BG		X
Fukuzako et al.	1995	15/15	chronic	current	SV	2	peak area		frontal lobe, medial temporal lobe		X
Fukuzako et al.	1999	40/40	chronic	current	SV	2	peak area		medial temporal lobe		incomplete
Fukuzako et al.	2000	64/51	chronic	current	SV	2	peak area		hippocampus		incomplete
Galinska et al.	2009	30/19	first episode	never	SV	1.5	?concentration	internal water	frontal lobe, temporal lobe, thalamus	X*	incomplete
Gimenez et al.	2003	11/11	first episode	never	SV	1.5	peak area		striatum		

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a: Studies included in systematic review, schizophrenia

Author	Year	n sz/hc	Illness duration	Antipsychotic treatment	MRS	Tesla	Data processing	use of reference	Region studied	Absolute value data available	Ratio data available
Goto et al.	2009	18/18	unclear	current	SV	3			frontal lobe, BG, parieto-occipital lobe		incomplete *
Hagino et al.	2002	13/13	chronic	current	SV	1.5	peak area		inferior frontal cortex, thalamus		X
Heimberg et al.	1998	24/39	chronic	varies	SV	1.5	peak area	internal water	BG, frontal cortex, temporal cortex, thalamus		incomplete
Jakary et al.	2005	22/22	chronic	current	MRSI	1.5	concentration	internal water	thalamus	X	
Klaer et al.	2010	29/44	chronic	current	SV	3	concentration	Internal water	hippocampus	X	
Kegeles et al.	2000	10/10	chronic	varies	SV	1.5	peak area		hippocampus	X *	X
Lim et al.	1998	10/9	chronic	current	MRSI	1.5	concentration	AA, Cho and Cr	grey matter, white matter	X	incomplete
Lutkenhoff et al.	2010	14/13	chronic	unclear	SV	3	concentration	internal water	mesial prefrontal cortex, prefrontal white matter, hippocampus	X	
Maier et al.	1995	25/32	chronic	unclear	SV	1.5	concentration	internal water	hippocampus	X *	
Maier et al.	1996	26/38	chronic	current	SV	1.5	concentration	internal water	hippocampus	X	
Martinez-Granados et al.	2008	49/37	chronic	current	MRSI	1.5	peak area		thalamus		X
Molina et al.	2005	17/15	chronic	current	SV	1.5	peak area		DLPFC		X *
Molina et al.	2006	34/20	chronic	current	SV	1.5	peak area		DLPFC		X *
Molina et al	2007	11/10	chronic	current	SV	1.5	peak area		DLPFC		X *
Moore et al.	2002	20/20	chronic	current	SV	1.5	peak area		mesial temporal lobe		incomplete
Nasrallah et al.	1994	11/11	chronic	current	SV	1.5	peak area		hippocampus	incomplete	
Ohara et al.	2000	10/10	chronic	varies	SV	1.5	peak area		lenticular nucleus		X
Ohrmann et al.	2005	21/21	chronic	current	SV	1.5	concentration	internal water	DLPFC	X	
Ohrmann et al.	2007	20/20	chronic	current	SV	1.5	concentration	internal water	DLPFC	X	
Ohrmann et al.	2008	43/37	chronic	current	SV	1.5	concentration	internal water	ACC, DLPFC	X	
Olbrich et al.	2008	9/32	first episode	naive	SV	2	concentration	internal water	DLPFC, hippocampus	X	
Omori et al.	2000	20/16	chronic	varies	SV	1.5	peak area		thalamus, frontal lobe		incomplete
Ongur et al.	2010b	21/19	chronic	current	SV	4	concentration	internal water	ACC, parieto-occipital cortex	X	
Ongur et al.	2009	15/22	chronic	current	SV	4	institutional units	internal water	ACC, parieto-occipital cortex	incomplete	
Pae et al.	2004	24/20	varies	naïve/off	SV	1.5	peak area		frontal lobe		incomplete

a: Studies included in systematic review, schizophrenia

Author	Year	n sz/hc	Illness duration	Antipsychotic treatment	MRS	Tesla	Data processing	use of reference	Region studied	Absolute value data available	Ratio data available
Pajonk et al.	2010	8/8	chronic	current	SV	1.5	peak area		hippocampus		incomplete
Premkumar et al.	2010	30/15	chronic	current	SV	1.5	concentration	internal water	ACC	X	
Reid et al.	2010	26/23	chronic	current	SV	3			ACC		X*
Rowland et al.	2009	20/11	chronic	current	SV	3	concentration	internal water	frontal lobe, inferior parietal lobe	X	
Ruesch et al.	2008	29/31	chronic	current	SV	2	concentration	internal water	hippocampus, DLPFC	X*	X*
Sanches et al.	2008	38/38	chronic	current	SV	1.5	peak area		frontal lobe, ACC, perirolandic fissure		
Sarramea et al.	2008	14/15	chronic	current	SV	1.5	peak area		cingulate gyrus		X
Sharma et al.	1992	4/9	chronic	current	SV	1.5	peak area		basal ganglia, occipital cortex		incomplete
Shimizu et al.	2007	19/18	chronic	current	SV	1.5	peak area		posterior cingulate gyrus		incomplete
Shirayama et al.	2010	19/18	chronic	current	SV	3	concentration	internal water	medial prefrontal cortex	X	X
Shioiri et al.	1996	21/21	chronic	current	SV	1.5	peak area		BG	X	X
Sigmundsson et al.	2003	25/26	chronic	current	SV	1.5	concentration	internal water	DLPFC	X	
Stanley et al.	1996	13/25	first episode	never	SV	1.5	concentration	internal water	DLPFC	X*	X*
Steel et al.	2001	10/10	chronic	current	SV	2	institutional units	internal water	frontal lobe	incomplete	
Szulc et al.	2007	58/21	chronic	current	SV	1.5	?concentration	internal water	frontal lobe, temporal lobe, thalamus	X	incomplete
Tanaka et al.	2006	14/13	chronic	current	SV	1.5	concentration	NAA phantom	frontal lobe	X	incomplete
Tang et al.	2007	40/42	chronic	varies	SV	3	peak area		DLPFC, medial temporal cortex, occipital cortex	incomplete	incomplete
Tayoshi et al.	2009	30/25	chronic	current	SV	3	concentration	internal water	ACC, BG	incomplete*	X*
Theberge et al.	2002	21/21	first episode	never	SV	4	concentration	internal water	ACC, thalamus	X*	X*
Theberge et al.	2003	21/21	chronic	current	SV	4	concentration	internal water	ACC, thalamus	X*	X*
Theberge et al.	2004a	9/8	chronic	current	SV	4	concentration	internal water	ACC, thalamus		
Theberge et al.	2004b	18/18	first episode	never	SV	4	concentration	internal water	ACC, thalamus	incomplete*	incomplete*
Theberge et al.	2007	13/16	first episode	never	SV	4	concentration	internal water	ACC, thalamus	X*	X*
Tibbo et al.	2000	12/12	chronic	current	SV	3	peak area		cerebellum		incomplete
Tunc-Skarka et al.	2009	23/29	chronic	varies	SV	3	concentration	internal water	frontal white matter	X	X*

a: Studies included in systematic review, schizophrenia

Author	Year	n sz/hc	Illness duration	Antipsychotic treatment	MRS	Tesla	Data processing	use of reference	Region studied	Absolute value data available	Ratio data available
van Elst et al.	2005	21/32	chronic	current	SV	2	concentration	internal water	DLPFC, hippocampus	X	
Weber-Fahr et al.	2002	15/15	chronic	current	MRSI	1.5	concentration	internal water	hippocampus		
Wobrock et al.	2008	14/24	chronic	current	SV	1.5	relative concentration		internal capsule		X
Wood et al.	2003	56/21	first episode	current	SV	1.5	peak area		temporal lobe, DLPFC		X
Wood et al.	2007	15/14	chronic	current	SV	3	concentration	internal water	ACC	X*	
Wood et al.	2008	19/19	chronic	current	SV	3	concentration	internal water	temporal lobe	X*	
Wood et al.	2009	30/18	first episode	never/minimal	SV	3	concentration	internal water	temporal lobe	X*	
Yamasue et al.	2003	16/15	chronic	current	SV	1.5	concentration	in vitro spectra	putamen	X	X*
Yurgelun-Todd et al.	1996	16/14	chronic	current	SV	1.5	peak area		mesial temporal lobe		incomplete

b: Studies included in systematic review, bipolar disorder

Author	Year	n bp/hc	Mood state	Mood stabilizing treatment	MRS	Tesla	Data processing	use of reference	Region studied	Absolute value data available	Ratio data available
Amaral et al.	2006	13/15	euthymic	current	SV	1.5	ratio		ACC		incomplete
Atmaca et al.	2006	12/12	unclear	unclear	MRSI	1.5	ratio		hippocampus		X
Atmaca et al.	2007	30/10	varies	varies	MRSI	1.5	ratio		hippocampus		X
Bertolino et al.	2003a	17/17	varies	varies	MRSI	1.5	ratio		Thalamus, putamen, hippocampus, inferior frontal gyrus, DLPFC, ACC, posterior cingulated, centrum semiovale, prefrontal white matter, superior temporal gyrus		incomplete
Bhagwagar et al.	2007	16/18	euthymic	off meds	SV	3	ratio		parieto-occipital cortex		incomplete
Brambilla et al.	2005	10/32	unclear	varies	SV	1.5	concentration	internal water	DLPFC	X	X
Cecil et al.	2002	17/21	Manic/mixed	varies	SV	1.5	concentration	internal water	frontal lobe grey and white matter	X	
Colla et al.	2009	21/19	Manic/mixed	current	SV	3	concentration	internal water	hippocampus	X	
Dager et al.	2004	32/26	depressed/ mixed	off meds	MRSI	1.5	concentration	internal water	thalamus, putamen, cingulate gyrus, caudate nucleus, frontal white matter, parietal white matter, occipital lobe		
Deicken et al.	2001	15/15	euthymic	varies	MRSI	1.5	institutional units	internal water	thalamus	X	
Deicken et al.	2003	15/20	euthymic	varies	SV	1.5	institutional units	internal water	hippocampus	X	
Frey et al.	2005	10/10	manic/mixed	varies	SV	1.5	concentration	internal water	DLPFC	X	

b: Studies included in systematic review, bipolar disorder

Author	Year	n bp/hc	Mood state	Mood stabilizing treatment	MRS	Tesla	Data processing	use of reference	Region studied	Absolute value data available	Ratio data available
Frey et al.	2007	32/32	varies	off meds	SV	1.5	concentration	internal water	DLPFC	X	
Friedman et al.	2004	21/12	varies	off meds	MRSI	1.5	concentration	internal water	grey matter, white matter		
Frye et al.	2007a	16/17	manic	current	SV	3	concentration	internal water	ACC, basal ganglia, occipito-parietal white matter	X	incomplete
Frye et al.	2007b	23/12	depressed	varies	SV	1.5	concentration	internal water	ACC	X	incomplete
Hamakawa et al.	1998	18/20	varies	varies	SV	1.5	concentration	external phantom	basal ganglia	X	X
Hamakawa et al.	1999	23/20	varies	varies	SV	1.5	concentration	external phantom	frontal lobe	X	
Hajek et al.	2008	14/21	unclear	unclear	SV	1.5	concentration	internal water	dorsal frontal lobe	X	
Iosifescu et al.	2009	18/10	euthymic	current	SV	4	institutional units	internal water	hippocampus	X	
Kato et al.	1996	19/19	euthymic	varies	SV	1.5	ratio		basal ganglia		incomplete
Kaufman et al.	2009	13/11	varies	current	MRSI	4	concentration	internal water	basal ganglia, whole brain	X	
Michael et al.	2003	8/8	manic	unclear	SV	1.5	concentration	internal water	ACC, DLPFC	X*	
Michael et al.	2009	6/8	varies	current	SV	1.5	concentration	internal water	DLPFC	X	
Mahli et al.	2007	9/9	hypomanic/euthymic	current	SV	1.5	concentration	internal water	ACC, basal ganglia, frontal white matter	incomplete	
Molina et al.	2007	13/10	euthymic	current	SV	1.5	ratio		DLPFC		X*
Moore et al.	2000	12/9	depressed	off meds	SV	1.5	arbitrary units	internal water	frontal lobe, parietal lobe, occipital lobe, temporal lobe		
Moore et al.	2000b	9/14	depressed	current	MRSI	1.5	ratio		ACC		
Ohara et al.	1998	10/10	euthymic	varies	SV	1.5	ratio		basal ganglia		X
Ongur et al.	2008	15/22	manic	current	SV	4	arbitrary units	internal water	ACC, parieto-occipital cortex	X	
Ongur et al.	2009	15/22	manic	current	SV	4	arbitrary units	internal water	ACC, parieto-occipital cortex		
Ongur et al.	2010a	15/20	manic	varies	SV	4	relaxation times	internal water	ACC, parieto-occipital cortex	X	
Port et al.	2008	21/21	varies	off meds	MRSI	3	concentration	internal water	basal ganglia		
Sarramea et al.	2008	15/17	euthymic	varies	SV	1.5	ratio		cingulum		X
Scherk et al.	2008	13/13	euthymic	varies	SV	1.5	ratio		hippocampus, thalamus, putamen		X
Scherk et al.	2009a	30/16	euthymic	current	SV	1.5	ratio		putamen		X
Scherk et al.	2009b	33/29	euthymic	current	SV	1.5	ratio		ACC, DLPFC		X
Senaratne et al.	2009	12/12	euthymic	current	SV	3	concentration	internal water	hippocampus, orbitofrontal lobe, occipital lobe	incomplete	
Sharma et al.	1992	4/9	manic	current	SV	1.5	ratio		basal ganglia, occipital cortex		X
Silverstone et al.	2002	14/18	euthymic	current	SV	3	ratio	external standard	temporal lobe		incomplete

b: Studies included in systematic review, bipolar disorder

Author	Year	n bp/hc	Mood state	Mood stabilizing treatment	MRS	Tesla	Data processing	use of reference	Region studied	Absolute value data available	Ratio data available
Silverstone et al.	2003	25/18	euthymic	current	SV	3	ratio		frontal lobe, temporal lobe		incomplete
Silverstone et al.	2003	9/11	euthymic	current	SV	3	concentration	internal water	frontal lobe, temporal lobe	incomplete	
Winsberg et al.	2000	20/20	euthymic	off meds	SV	1.5	ratio		DLPFC		X
Wu et al.	2004	25/18	euthymic	current	SV	3	concentration	internal water	frontal lobe, temporal lobe	incomplete	

* data obtained from author directly

X: data is available and included in meta-analysis. Studies with no X have not reported actual values

Incomplete: only some data available

Table 2

a: Meta-analysis with ratio data, schizophrenia					
Region	**number of studies**	**Metabolite**	**SMD [95% CI]**	**p value**	**Heterogeneity (I^2)**
Hippocampus	8	NAA/Cr	−0.72 [−1.20, −0.25]	***<0 .01***	74%
	5	Cho/Cr	−0.28 [−0.54, −0.02]	***0.03***	0%
Thalamus	9	NAA/Cr	−037 [−0.58, −0.17]	***<0 .01***	6%
	6	Cho/Cr	−0.02 [−0.34, 0.30]	0.91	42%
Basal ganglia	8	NAA/Cr	−0.16 [−0.46, 0.13]	0.28	32%
	6	Cho/Cr	0.13 [−0.22, 0.48]	0.47	37%
Frontal lobe	16	NAA/Cr	−0.22 [−0.39, −0.06]	***< 0.01***	0%
	13	Cho/Cr	0.09 [−0.24, 0.41]	0.61	68%
DLPFC	3	NAA/Cr	0.14 [−0.72, 1.00]	0.75	86%
	2	Cho/Cr	−0.15 [−0.73, 0.42]	0.60	58%
Temporal lobe	7	NAA/Cr	−0.64 [−1.09, −0.19]	***<0 .01***	77%

b: Meta-analysis with ratio data, bipolar disorder					
Region	**number of studies**	**Metabolite**	**SMD [95% CI]**	**p value**	**Heterogeneity (I^2)**
Hippocampus	4	NAA/Cr	−0.96 [−1.37, −0.55]	***<0.01***	0%
	3	Cho/Cr	−0.37 [−0.84, 0.11]	0.13	0%
Basal ganglia	7	NAA/Cr	−0.02 [−0.55, 0.51]	0.95	69%
	6	Cho/Cr	−0.04 [−0.62, 0.54]	0.89	70%
ACC	5	NAA/Cr	−0.59 [−1.18, 0.01]	0.06	75%
	6	Cho/Cr	0.00 [−0.00, 0.01]	0.52	43%
DLPFC	6	NAA/Cr	−0.03 [−0.42, 0.36]	0.88	49%
	5	Cho/Cr	0.05 [−0.23, 0.33]	0.74	6%