TECHNICAL COMMENTARY

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NMDA receptor function

Introduction

An N-methyl-d-aspartate (NMDA) receptor consists of several subunits; the NR1 subunits that bind coagonists glycine and d-serine, the NR2 subunits that bind the neurotransmitter glutamate, and the NR3 subunits that bind glycine. The NMDA receptor is activated by binding glutamate and a coagonist.

Glutamate is the major excitatory neurotransmitter in the brain and is crucial to normal brain function. In bipolar disorder, there may be changes in levels of glutamate and its metabolites, and changes in levels or activity of mechanical components of the NMDA receptor system, such as the receptors that 'receive' glutamate, or the transporters that 'remove' it.

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 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, only the most recent and comprehensive 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 that describes a preferred way to present a meta-analysis. Reviews were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. Reviews rated as having less than 50% of items checked have now 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)[1]. 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 two systematic reviews that met our inclusion criteria[2, 3].

- Moderate to low quality evidence suggests significant effects of medium to large increased glutamate+glutamine levels in people with bipolar disorder in all brain regions combined, and in the analysis of frontal brain regions. Non-significant trend effects were found for increased glutamate, and glutamate+glutamine/creatine ratio levels in people with bipolar disorder in all brain regions combined, but no differences were found in frontal regions. There were no differences in glutamate/creatine ratio levels, nor in the analyses contained to children and adolescents.

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- Moderate quality evidence suggests people with bipolar depression showed a medium-sized, trend effect of higher glutamate+glutamine in the anterior cingulate cortex than controls, while people with unipolar depression showed a large, significant effect of lower glutamate+glutamine in the anterior cingulate cortex than controls.

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Gigante AD, Bond DJ, Lafer B, Lam RW, Young L, Yatham LN

Brain glutamate levels measured by magnetic resonance spectroscopy in patients with bipolar disorder: A meta-analysis

Bipolar Disorders 2012; 14: 478-87

View online review abstract

Comparison	**Glutamate levels in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, inconsistent, imprecise, direct) suggests medium to large effects of increased glutamate + glutamine levels in people with bipolar disorder in all brain regions combined, and in the analysis of frontal brain regions.** **Medium to large trend effects were found for increased glutamate, and glutamate + glutamine/creatine ratio levels in people with bipolar disorder in all brain regions combined, but no significant differences were found in the frontal region analysis.** **There were no significant differences in glutamate/creatine ratio levels or in the analyses contained to children and adolescents.**

Glutamate (Glu)

Medium to large, non-significant trends for increased Glu levels in people with bipolar disorder;

All patients, all brain regions: 7 studies, N = 363, SMD = 0.71, 95%CI 0.11 to 1.52, $p = 0.09$, $I^2 = 92\%$, $p < 0.00001$

Adult patients, all brain regions: 4 studies, N = 220, SMD = 1.41, 95%CI 0.06 to 2.87, $p = 0.06$

No significant differences in frontal regions;

All patients, frontal regions: 6 studies, N = 322, SMD = 0.37, 95%CI 0.33 to 1.08, $p = 0.30$

No significant differences in children or adolescents with bipolar disorder;

Children/adolescents, all brain regions: 3 studies, N = 143, SMD = 0.11, 95%CI 0.62 to 0.39, $p = 0.67$

Glutamate + glutamine (Glx)

Significant, medium to large effects of increased Glx levels in people with bipolar disorder;

All patients, all brain regions: 9 studies, N = 327, SMD = 0.72, 95%CI 0.17 to 1.27, $p = 0.01$, $I^2 = 80\%$, $p < 0.00001$

Adult patients, all brain regions: 7 studies, N = 258, SMD = 0.89, 95%CI 0.22 to 1.57, $p = 0.010$

All patients, frontal region: 8 studies, N = 269, SMD = 0.74, 95%CI 0.09 to 1.39, $p = 0.03$, $I^2 = 82\%$,

$p < 0.00001$ Adult patients, frontal regions: 6 studies, N = 200, SMD = 0.96, 95%CI 0.09 to 1.82, $p = 0.03$ *No significant differences were found in children or adolescents with bipolar disorder;* Children/adolescents, frontal regions: 2 studies, N = 69, SMD = 0.19, 95%CI 0.66 to 1.05, $p = 0.66$ Subgroup analyses found a large, significant effect in non-medicated patients (SMD = 1.91; $p = 0.03$), and a small to medium-sized effect in medicated patients (SMD = 0.31, $p = 0.03$).
Glutamate + glutamine / creatine ratio (Glx/Cr)
Medium to large, non-significant trends for increased Glx/Cr levels in people with bipolar disorder; All patients, all brain regions: 6 studies, N = 184, SMD = 0.63, 95%CI 0.10 to 1.36, $p = 0.09$, $I^2 = 81\%$, $p < 0.0001$ *No significant differences in frontal regions;* All patients, frontal region: 5 studies, N = 150, SMD = 0.63, 95%CI 0.21 to 1.47, $p = 0.14$ Adult patients, frontal regions: 3 studies, N = 102, SMD = 0.96, 95%CI 0.37 to 2.30, $p = 0.16$ *No significant differences were found in children or adolescents with bipolar disorder;* Children/adolescents, all brain regions: 3 studies, N = 82, SMD = 0.28, 95%CI 0.45 to 1.01, $p = 0.45$
Glutamate / creatine ratio (Glu/Cr)
No significant differences between groups; All patients, all brain regions: 3 studies, N = 99, SMD = 0.44, 95%CI 0.89 to 1.76, $p = 0.52$, $I^2 = 89\%$, $p < 0.0001$ Adult patients, all brain regions: 2 studies, N = 83, SMD = 0.65, 95%CI 0.47 to 1.77, $p = 0.26$

Consistency in results‡	Inconsistent where reported
Precision in results§	Imprecise
Directness of results‖	Direct

Taylor MJ

Could glutamate spectroscopy differentiate bipolar depression from unipolar?

Journal of Affective Disorders 2014; 167: 80-4

View review abstract online

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Comparison	**Glutamatergic levels in the anterior cingulate cortex of people with bipolar disorder or unipolar depression vs. controls.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, some inconsistency, precise, direct) suggests people with bipolar depression showed a medium-sized, trend effect of higher glutamate + glutamine levels in the anterior cingulate cortex than controls, while people with unipolar depression showed a large, significant effect of lower levels of glutamate + glutamine in the anterior cingulate cortex than controls.**
Glutamate + glutamine (Glx)	
People with bipolar depression showed a medium-sized trend effect of higher Glx than controls, while people with unipolar depression showed a large, significant effect of lower levels of Glx than controls; Bipolar disorder: 4 studies, N = 166, SMD = 0.40, 95%CI -0.04 to 0.85, p = 0.05, I^2 = 44%, p = 0.1492 Unipolar depression: 8 studies, N = 240, SMD = -1.05, 95%CI -0.58 to -1.53, $p < 0.05$, I^2 = 63.5%, p = 0.0077 The difference in effect sizes was significant ($p < 0.0001$)	
Consistency in results	Consistent for bipolar disorder, inconsistent for unipolar depression.
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), SMD = standardised mean difference, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – 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[4].

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† Different effect measures are reported by different reviews.

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.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that 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 treatment effect[4].

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, an 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. An 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[5]. 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

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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 dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of 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 substantial heterogeneity and 75% to 100%: 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, these criteria should be relaxed[6].

‖ 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 that 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 and is therefore 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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