TECHNICAL COMMENTARY

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S100 proteins

Introduction

S100 proteins are a subgroup of proteins which regulate intracellular processes such as cell growth and motility, cell cycle regulation, transcription and differentiation. They are characterised by two calcium binding sites of the helix-loop-helix conformation, and at least 21 members have been identified so far. S100B is one member of this subgroup that is primarily found in the cytoplasm of astrocytes. It regulates cell shape, energy metabolism, and intracellular signal transduction. Serum S100B has been used as a marker for CNS damage, particularly in astrocytes, as well as a marker of blood-brain-barrier disruption.

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 four systematic reviews that met our inclusion criteria[2-5].

- Moderate quality evidence suggests a large effect of increased serum S100B in people with bipolar disorder compared to controls. This was found regardless of age, gender, current mood state (depression, hypo/mania, mixed, or euthymic), illness duration, or measure (serum or plasma).
- Moderate quality evidence finds similar effects of increased serum S100B in people with bipolar disorder or major depression, but the effect was larger in people with schizophrenia compared to controls.

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Bartoli F, Misiak B, Crocamo C, Carra G

Glial and neuronal markers in bipolar disorder: A meta-analysis testing S100B and NSE peripheral blood levels

Progress in Neuro-Psychopharmacology and Biological Psychiatry 2020; 101: 109922

View online review abstract

Comparison	**S100B in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a large effect of increased serum S100B in people with bipolar disorder during mania compared to controls.**
S100B	
A large, significant effect of increased S100B in people with bipolar disorder; 8 studies, N = 581, SMD = 0.81, 95%CI 0.36 to 1.26, $p < 0.001$, $I^2 = 82\%$ Results were not moderated by age, gender, current mood state (depression, hypo/mania, mixed, or euthymic), or illness duration. There were no differences in neuron-specific enolase.	
Consistency in results‡	Inconsistent
Precision in results§	Precise
Directness of results‖	Direct

da Rosa MI, Simon C, Grande AJ, Barichello T, Oses JP, Quevedo J

Serum S100B in manic bipolar disorder patients: Systematic review and meta-analysis

Journal of Affective Disorders 2016; 206: 210-5

View online review abstract

Comparison	**S100B in people with bipolar disorder during a mania phase vs. controls.**

Summary of evidence	**Moderate quality evidence (small sample, consistent, precise, direct) suggests a large increase in serum S100B in people with bipolar disorder during mania compared to controls.**
S100B	
A large, significant effect of increased S100B in people with bipolar disorder; 2 studies, N = 104, SMD = 0.80, 95%CI 0.39 to 1.20, $p < 0.001$, $I^2 = 0\%$	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Futtrup J, Margolinsky R, Benros ME, Moos T, Routhe LJ, Rungby J, Krogh, J.

Blood-brain barrier pathology in patients with severe mental disorders: a systematic review and meta-analysis of biomarkers in case-control studies

Brain, Behavior, and Immunity - Health 2020; 6: 100102

View online review abstract

Comparison	**S100B in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (small sample, consistent, precise, direct) finds a medium-sized increase in S100B levels in people with bipolar disorder compared to controls. This effect size was similar in the comparison between controls and major depression, but smaller than in the comparison between controls and schizophrenia. The effect estimates were similar when S100B was measured in plasma or serum.**
S100B	
A medium-sized, significant effect of increased S100B in people with bipolar disorder; 4 studies, N = 142, SMD = 0.55, 95%CI 0.16 to 0.94, $p < 0.05$, $I^2 = 48\%$, $p = 0.013$ This effect size was similar in the comparison between controls and major depression (SMD = 0.57), but smaller than in the comparison between controls and schizophrenia (SMD = 0.82). Subgroup analysis showed the effect estimates were similar when S100B was measured in plasma or serum.	

Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Schroeter ML, Steiner J, Mueller K

Glial pathology is modified by age in mood disorders - A systematic meta-analysis of serum S100B in vivo studies

Journal of Affective Disorders 2011; 134: 32-38

View online review abstract

Comparison	**Serum S100B in people with bipolar disorder or major depression vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess consistency or precision, direct) suggests similar, large increases in serum S100B in people with bipolar disorder or major depression compared to controls.**

S100B

Both disorders showed large effect sizes vs. controls, with no significant differences in the effect sizes;

Bipolar disorder vs. controls: 4 studies, N = 117, g = 0.85, SD = 0.19

Major depression vs. controls: 4 studies, N = 159, g = 0.95, SD = 0.45

Between group test: p = 0.74

There was a significant relationship between increasing age and increasing effect sizes, with no effects of illness duration or age at onset.

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

Explanation of acronyms

CI = confidence interval, *g* = Hedges *g* standardised mean difference, 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[6].

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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[6].

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[7]. 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 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[8].

‖ 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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