TECHNICAL COMMENTARY

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Neurotrophins

Introduction

Neurotrophins, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), regulate neuronal survival and growth during development. Effects of neurotrophins on neuronal transmission in the hippocampus, cortex, cerebellum, and basal forebrain are important for learning and memory processes. Reduced neurotrophins may affect synaptic efficiency and connectivity in schizophrenia that is hypothesised to underpin signs and symptoms of the disorder.

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 given priority 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 or if there is a dose dependent response. We have also taken into account sample size and whether results are 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 six reviews that met our inclusion criteria[3-8].

- Moderate to high quality evidence suggests reduced blood BDNF levels in people with schizophrenia compared to controls, regardless of symptom severity, medication dose, age, BMI, sample size, or study quality. First-episode or drug-free patients showed a larger reduction in BDNF levels compared to controls than other patients. This may be explained by medication status, as blood BDNF levels increased after treatment with antipsychotics, although this effect was found only in plasma and not serum studies.
- Moderate quality evidence suggests a small association between increased BDNF levels

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

following non-pharmaceutical, non-exercise interventions.

- High quality evidence suggests a small association between increased BDNF levels and increased performance on reasoning and problem -solving, verbal memory, working memory, processing speed and verbal fluency tasks.
- Moderate to high quality evidence suggests a medium-sized reduction in blood NGF levels in people with schizophrenia compared to controls, regardless of medication status. More severe symptoms were related to greater NGF reductions.

Ahmed AO, Mantini AM, Fridberg DJ, Buckley PF

Brain-derived neurotrophic factor (BDNF) and neurocognitive deficits in people with schizophrenia: A meta-analysis

Psychiatry Research 2015; 226: 1-13

View review abstract online

Comparison	**Association between BDNF levels and cognition in people with schizophrenia.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests a small association between increased BDNF levels and increased performance on reasoning and problem-solving tasks.**
BDNF levels	
Small, significant associations between increased BDNF levels and increased reasoning and problem-solving scores. No association with attention; Reasoning & problem solving: 4 studies, N = 478, *r* = 0.19, 95%CI 0.09 to 0.29, *p* = 0.0003, Q = 11.01, *p* = 0.28 Attention: 4 studies, N = 1,757, *r* = 0.04, 95%CI 0.21 to 0.12, *p* = 0.60, Q = 13.5, *p* = 0.02	
Consistency in results‡	Consistent for reasoning and problem solving, inconsistent for attention.
Precision in results§	Precise
Directness of results‖	Direct

Bora E

Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: A meta-analysis

Psychological Medicine 2019; 49: 1971-9

View review abstract online

Comparison	**Association between BDNF levels and cognition in people with schizophrenia.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests a small association between increased BDNF levels and increased performance on cognitive tasks involving verbal**

	memory, working memory, processing speed and verbal fluency.
BDNF levels	
A small association was found between increased BDNF levels and better cognitive functioning; 12 studies, N = 972, r = 0.12, 95%CI 0.04 to 0.19, $p < 0.05$, I^2 = 0% Subgroup analysis showed increased BDNF levels were significantly associated with better verbal memory (r = 0.16), working memory (r = 0.14), processing speed (r = 0.18) and verbal fluency (r = 0.09). There was no association with executive functioning speed. Subgroup analysis suggested that the relationship between cognitive and BDNF was more pronounced in chronic samples. There were no moderating effects of stable vs. non-stable patients, age, sex, and quality score.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Fernandes BS, Steiner J, Berk M, Molendijk ML, Gonzalez-Pinto A, Turck CW, Nardin P, Gonçalves CA

Peripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: meta-analysis and implications

Molecular Psychiatry 2015; 20: 1108-1119

View review abstract online

Comparison	**Serum and plasma BDNF levels in people with schizophrenia compared to controls, and the long-term effects of medication on BDNF levels in patients.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests reduced blood BDNF levels in people with schizophrenia compared to controls, regardless of symptom severity, medication dose, age, BMI, sample size, or study quality. First-episode or drug-free patients showed a larger reduction in BDNF levels compared to controls than other patients. This may be explained by medication status, as blood BDNF levels increased after treatment with antipsychotics, although this effect was found only in plasma and not serum studies.**
BDNF levels and effects of medication	

BDNF levels

A significant, medium-sized effect of reduced BDNF levels in patients compared to controls;

39 studies, N = 5,247, *g* = -0.70, 95%CI -0.94 to -0.45, *p* < 0.0001, I^2 = 93.59%, *p* < 0.0001

A larger effect was found in first-episode patients than in chronic patients;

First-episode vs. controls: 17 studies, N = 1,560, *g* = -0.87, 95%CI -1.23 to -0.51, *p* < 0.0001, I^2 = 89.59%, *p* < 0.0001

Other patients vs. controls: 22 studies, N = 3,687, *g* = -0.56, 95%CI -0.90 to 0.22, *p* = 0.0002, I^2 = 95.22%, *p* < 0.0001

A larger effect was found in drug-naive or drug-free patients than in medicated patients;

Drug-naïve/free vs. controls: 21 studies, N = 1,881, *g* = -0.84, 95%CI -1.17 to -0.51, *p* < 0.0001, I^2 = 90.14%, *p* < 0.0001

Medicated vs. controls: 18 studies, N = 3,366, *g* = -0.53, 95%CI -0.92 to -0.15, *p* = 0.0007, I^2 = 95.62%, *p* < 0.0001

A larger effect was found in studies assessing BDNF in plasma than in serum:

Plasma: 11 studies, N = 1,426, *g* = -0.97, 95%CI -1.50 to -0.44, *p* = 0.0007, I^2 = 94.52%, *p* < 0.0001

Serum: 28 studies, N = 3,821, *g* = -0.60, 95%CI -0.88 to -0.31, *p* = 0.0007, I^2 = 93.07%, *p* < 0.0001

Effects of medication on BDNF levels

A significant, small effect of increased serum and plasma BDNF levels after treatment with antipsychotic medication (for 4-52 weeks);

14 studies, N = 463, *g* = 0.26, 95%CI 0.12 to 0.44, *p* < 0.0001, I^2 = 62.33%, *p* = 0.001

Increased BDNF levels after treatment were apparent in both responders and non-responders to medication (measured as an improvement of at least 40% on PANSS total or positive scores);

Responders: 6 studies, N = 145, *g* = 0.23, 95%CI 0.04 to 0.41, *p* = 0.015, I^2 = 17.19%, *p* = 0.30

Non-responders: 8 studies, N = 318, *g* = 0.31, 95%CI 0.08 to 0.55, *p* = 0.008, I^2 = 75.04%, *p* < 0.0001

Increased BDNF levels after treatment were apparent in plasma but not serum studies;

Plasma: 8 studies, N = 283, *g* = 0.37, 95%CI 0.15 to 0.59, *p* = 0.001, I^2 = 69.15%, *p* = 0.002

Serum: 6 studies, N = 170, *g* = 0.15, 95%CI -0.04 to 0.34, *p* = 0.19, ^{2} = 34.10%, *p* = 0.18

Investigating sources of heterogeneity

Patients with a longer length of illness showed greater reduction in BDNF levels than patients with a shorter length of illness. Greater length of follow-up was related to greater increase in BDNF levels during the course of treatment in plasma but not serum studies.

Removal of each study, symptom severity, antipsychotic dose, age, BMI, sample size or study quality did not explain the heterogeneity in the between-group meta-analysis.

Authors report no evidence of publication bias.

Consistency in results	Inconsistent, apart from responders and serum subgroup analyses

	in the effects of medication meta-analysis.
Precision in results	Precise
Directness of results	Direct

Lin PY

Increase in brain-derived neurotrophic factor in patients with schizophrenia treated with olanzapine: a systematic review and meta-analysis

Journal of Experimental and Clinical Medicine 2012; 4(2): 119-124

View review abstract online

Comparison	**BDNF levels in people with schizophrenia before and after treatment with antipsychotics.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests a medium-sized increase in blood BDNF levels in patients following treatment with olanzapine. Other antipsychotics were not associated with a similar increase.**

BDNF levels

Results showed a significant, small increase in blood BDNF levels in schizophrenia patients following treatment with antipsychotics;

10 studies, N = 399, g = 0.171, 95%CI 0.008 to 0.334, p = 0.04, Q = 11.69, p = 0.232, I^2 = 23%

Meta-regression showed that this effect was not moderated by patient age (p = 0.59), gender (p = 0.815), duration of illness (p = 0.509), time of treatment (p = 0.326), or source of sample (p = 0.759)

Subgroup analyses stratified by type of antipsychotic medication found a medium-sized, significant increase in BDNF levels only following olanzapine treatment;

Olanzapine: 6 studies, g = 0.635, 95%CI 0.323 to 0.948, p = 0.0001

Risperidone: 7 studies, g = 0.005, 95%CI -0.176 to 0.185, p = 0.612

No difference in BDNF levels were found following treatment with amisulpride (1 study), aripiprazole (1 study), clozapine (2 studies), haloperidol (2 studies), or quetiapine (1 study)

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

Qin XY, Wu HT, Cao C, Loh YP, Cheng Y

A meta-analysis of peripheral blood nerve growth factor levels in patients with schizophrenia

Molecular Psychiatry 2017; 22: 1306-12

View review abstract online

Comparison	**Blood NGF levels in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds a medium-sized reduction in NGF levels in people with schizophrenia compared to controls, regardless of medication status. More severe symptoms were related to greater blood NGF reductions.**

Blood NGF levels

People with schizophrenia showed a medium-sized reduction in NGF;

13 studies, N = 1,693, g = -0.63, 95%CI -0.95 to -0.32, $p < 0.001$, $I^2 = 88\%$, $p < 0.001$

Unmedicated and medicated patients both showed medium-sized reductions in NGF;

Unmedicated: 6 studies, g = -0.67, 95%CI -1.12 to -0.22, $p = 0.003$, $I^2 = 84\%$, $p < 0.001$

Medicated: 9 studies, g = -0.36, 95%CI -0.59 to -0.12, $p = 0.003$, $I^2 = 71\%$, $p = 0.001$

More severe symptoms were related to greater blood NGF reductions.

There were no moderating effects of measure (serum vs. plasma), age, gender, or sample size.

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

Sanada K, Zorrilla I, Iwata Y, Bermudez-Ampudia C, Graff-Guerrero A, Martinez-Cengotitabengoa M, Gonzalez-Pinto A

The Efficacy of Non-Pharmacological Interventions on Brain-Derived Neurotrophic Factor in Schizophrenia: A Systematic Review and Meta-Analysis

International Journal of Molecular Sciences 2016; 17: 24

View review abstract online

Comparison	**BDNF levels after non-pharmaceutical treatments (exercise, diet, or cognitive training) in people with schizophrenia vs. mixed comparisons.**
Summary of evidence	**Moderate quality evidence (consistent, precise, indirect, medium-sized samples) suggests a small association between increased BDNF levels following non-pharmaceutical, non-exercise interventions.**
BDNF levels	
A large, significant increase in BDNF levels in people with schizophrenia following non-pharmaceutical treatments; 6 RCTs, N = 263, SMD = 0.95, 95%CI 0.07 to 1.83, $p = 0.03$, $I^2 = 90\%$, $p = 0.00001$ *The effect size was reduced to small, but still significant, with one outlier removed;* 5 RCTs, N = 227, SMD = 0.31, 95%CI 0.04 to 0.58, $p = 0.02$, $I^2 = 0\%$, $p < 0.05$ Subgroup analysis of intervention type (exercise/non-exercise) showed a significant effect of non-exercise interventions (probiotic supplementation, l-theanine supplementation or auditory training), but not exercise interventions, on increased BDNF levels. There were no significant effects when studies with active control groups or passive control groups were analysed separately. Meta-regression showed that higher completion rates increased effect sizes.	
Consistency in results	Consistent for the analysis with the outlier removed.
Precision in results	Precise for the analysis with the outlier removed.
Directness of results	Indirect comparisons; mixed intervention and control conditions.

Explanation of acronyms

b = correlation coefficient, BDNF = Brain derived neurotrophic factor, CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect size), 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), PANSS = Positive and Negative Syndrome Scale, Q = Q statistic for the test of heterogeneity, Q_w = test for within group differences (heterogeneity in study results within a group of studies – measure of study consistency), Q_B = test for between group differences (heterogeneity between groups of studies for an outcome of interest), *r* = regression coefficient, RCT = randomised controlled trial, 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 – 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[9].

† 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.

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).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[9].

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[10]. 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 can provide an

indirect 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 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 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[9];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ 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[11].

‖ 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 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.

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

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