TECHNICAL COMMENTARY

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 bipolar disorder 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 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, the most recent and/or comprehensive review 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]. These are presented below in alphabetical order.

- High quality evidence suggests a small increase in blood nerve growth factor levels in unmedicated people with bipolar disorder compared to controls.
- Moderate quality evidence suggests a medium-sized increase in blood neurotrophin-3 and 4/5 levels in people with bipolar disorder (compared to controls) during a depressive state, but not during a manic or euthymia state.
- Moderate quality evidence suggests an overall small decrease in blood BDNF levels in people with bipolar disorder compared to controls. This effect is medium-sized when patients are in a manic state, and large in a depressive state, with no effect during euthymia. The effects increase with

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increased symptom severity and decrease with longer duration of illness.

- There was a small increase in blood BDNF levels with pharmacological treatment for mania but not for depression, and a medium-sized increase in blood BDNF levels after treatment with ECT.

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Brunoni AR, Baeken C, Machado-Vieira R, Gattaz WF, Vanderhasselt MA

BDNF blood levels after electroconvulsive therapy in patients with mood disorders: A systematic review and meta-analysis

World Journal of Biological Psychiatry 2014; 15: 411-8

View review abstract online

Comparison	**Change in BDNF levels following electroconvulsive (ECT) treatment (6-12 sessions, unilateral or bilateral) in people with bipolar disorder.** **Note; the sample also included people with unipolar depression (some also had psychotic features).**
Summary of evidence	**Moderate quality evidence (inconsistent, precise, direct, medium-sized sample) suggests a medium-sized effect of increased BDNF levels after treatment with ECT. There was also a large improvement in depression symptoms.**

Blood BDNF levels following ECT

A medium-sized, significant effect of increased BDNF levels post-treatment with ECT;

11 studies, N = 221, g = 0.376, 95%CI 0.076 to 0.676, $p < 0.05$, I^2 = 54%, p = 0.01

There was also a large effect of improved depressive symptoms post-treatment;

g = 3.10, 95%CI 2.50 to 3.60, p = 0.03, I^2 = 0%, p = 0.967

Meta-regression showed no influence on the effect size according to; diagnosis, mean study age, sex, type of blood measurement, or time period between BDNF assessments.

Authors report no evidence of publication bias.

Consistency in results	Inconsistent
Precision in results	Precise for BDNF levels, imprecise for depression
Directness of results	Direct

Fernandes BS, Molendijk ML, Kohler CA, Soares JC, Leite CM, Machado-Vieira R, Ribeiro TL, Silva JC, Sales PM, Quevedo J, Oertel-Knochel V, Vieta E, Gonzalez-Pinto A, Berk M, Carvalho AF

Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies

BMC Medicine 2015; 13: 289 View review abstract online	
Comparison	**BDNF levels in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (inconsistent, precise, direct, large samples, possible publication bias) suggests a medium-sized effect of decreased BDNF in people with bipolar disorder during a manic state, and a large effect during a depressive state, with the effect increasing with more severe symptoms. There were no significant differences during a normal (euthymic) mood state, or during a mixed mania/depressive state.** **There was a small effect of increased BDNF with treatment for mania but not for depression.**
Blood BDNF levels	

During a depressive state (mostly measured on the Hamilton Depression Rating Scale)

A significant, large effect of decreased BDNF levels in people with bipolar disorder compared to controls;

15 studies, N = 1,074, g = -0.93, 95%CI -1.37 to -0.50, p = 0.001, I^2 = 88%, p = 0.001

The effect sizes were similar in the subgroup analyses of medication status, measurement source, matching, and in studies that included only bipolar disorder 1 patients (bipolar disorder 1 = the most severe type of the disorder).

Meta-regressions showed that the effect size was greater in studies of patients with more severe depressive symptoms. There were no effects of age, sex (% female) or sample size.

There were no significant changes in BDNF levels post-treatment with valproate, ketamine, mifepristone or atypical antipsychotics;

8 studies, N = 184, g = 0.05, 95%CI -0.18 to 0.49, p = 0.364, I^2 = 73%, p = 0.001

The effect sizes were also not significant in the subgroup analyses of measurement source (plasma/serum), and treatment response.

During a manic state (mostly measured on the Young Mania Rating Scale)

A significant, medium-sized effect of decreased BDNF levels in people with bipolar disorder compared to controls;

19 studies, N = 1,397, g = -0.57, 95%CI -0.99 to -0.14, p = 0.010, I^2 = 92%, p = 0.001

Subgroup analyses showed similar medium-sized effects for medication status (unmedicated/medicated, trend effect for medicated); measurement source (serum/plasma, with one outlier removed from the plasma analysis); and matching (not matched/matched, trend effect for matched).

Meta-regressions showed that the effect size was greater in studies of patients with more severe manic symptoms, and in studies of older patients. There were no effects of duration of illness, sex (%

female), or sample size.

A significant, small effect of increased BDNF levels post-treatment with lithium, valproate, or atypical antipsychotics;

13 studies, N = 556, *g* = 0.26, 95%CI 0.09 to 0.45, *p* = 0.003, I^2 = 70%, *p* = 0.001

The effect sizes were similar in the subgroup analyses of measurement source (plasma/serum, trend effect for serum).

Meta-regression showed less increase in BDNF levels in patients over time (measured by year of publication). There were no significant effects according to age, sex (% female), baseline symptoms, or duration of follow-up.

<u>During an euthymia state</u>

There were no significant differences in BDNF levels between patients and controls;

24 studies, N = 3,057, *g* = 0.05, 95%CI -0.13 to 0.24, *p* = 0.569, I^2 = 82%, *p* = 0.001

The effect sizes were similar in the subgroup analyses of measurement source, matching, and bipolar disorder type (bipolar disorder 1 vs. 11, with less severe manic symptoms in bipolar disorder 11 than bipolar disorder 1).

Meta-regressions showed no effects of age, sex (% female), illness duration, number of mood episodes. or sample size.

<u>During a mixed manic/depressive state</u>

There were no significant differences in BDNF levels between patients and controls;

3 studies, N = 213, *g* = 0.09, 95%CI -0.57 to 0.75, *p* = 0.787, I^2 = 69%, *p* = 0.039

Authors report that the median effect sizes were significantly different across the three mood states;

58 studies, N = 5,528, *p* = 0.002

Depression: -0.86, IQR -1.91 to -0.13

Mania: -0.67, IQR -1.09 to 0.06

Euthymia: -0.03, IQR -0.24 to 0.31

Post-hoc analyses revealed no significant difference between mania and depression, but significant differences between euthymia and mania and depression.

Authors report possible publication bias.

Consistency in results	Inconsistent
Precision in results	Precise, apart from the mixed state analysis.
Directness of results	Direct

Munkholm K, Vinberg M, Kessing LV

Peripheral blood brain-derived neurotrophic factor in bipolar disorder: a comprehensive systematic review and meta-analysis

Molecular Psychiatry 2016; 21: 216-28

View review abstract online

Comparison	**BDNF levels in people with bipolar disorders vs. controls.**
Summary of evidence	**Moderate quality evidence (inconsistent, precise, direct, large samples, possible publication bias) suggests an overall small effect of decreased BDNF levels in people with bipolar disorder compared to controls.** **Moderate to low quality evidence (imprecise) suggests the effect size was large during a depressive state and medium-sized during a manic state (with one outlier removed from the analysis), with no differences during an euthymic state. Increased severity of symptoms was related to increased effect sizes, and increased duration of illness was related to decreased effect sizes.**

Blood BDNF levels

Overall

A significant, small effect of decreased BDNF levels in people with bipolar disorder compared to controls;

34 studies, N = 3,538, g = -0.28, 95%CI -0.51 to -0.04, p = 0.02, I^2 = 90%, p < 0.0001

Removing one study resulted in a trend effect;

33 studies, N = 3,468, g = -0.21, 95%CI -0.44 to 0.01, p = 0.06, I^2 > 88%, p < 0.0001

Subgroup analysis of serum studies gave a medium-sized effect;

22 studies, N = 2,059, g = -0.46, 95%CI -0.76 to -0.16, p = 0.002, I^2 > 88%, p < 0.0001

There were no significant differences in the plasma subgroup, or in medication subgroups (unmedicated/medicated).

Meta-regressions showed significant correlations between decreasing effect sizes in more recent studies, in better quality studies, and in studies of patients with a longer duration of illness. There were no significant associations with sex (% male), or sample size.

Authors report possible publication bias.

During a depressive state

A significant, large effect of decreased BDNF levels in people with bipolar disorder compared to controls;

12 studies, N = 914, g = -0.73, 95%CI -1.21 to -0.24, p = 0.003, I^2 = 90%, p < 0.0001

Subgroup analysis of serum studies gave a large effect;

10 studies, N = 631, *g* = -0.87, 95%CI -1.42 to -0.32, *p* = 0.002, I^2 > 88%, *p* < 0.0001

Subgroup analysis of medication status (unmedicated/medicated) found significant decreases in BDNF levels in patients in the medicated subgroup only.

Meta-regressions showed significant correlations between increasing study effect sizes and increasing manic and depressive symptom severity, and decreasing study effect sizes and increasing age/longer duration of illness. There were no significant associations between effect sizes and sex (% male), publication year, study quality or sample size.

Authors report possible publication bias.

<u>During a manic state</u>

There were no significant differences in BDNF levels between patients and controls;

14 studies, N = 882, *g* = -0.38, 95%CI -0.93 to 0.16, *p* = 0.16, I^2 = 92%, *p* < 0.0001

Removing one study gave a medium-sized significant effect;

13 studies, N = 810, *g* = -0.53, 95%CI -1.04 to -0.02, *p* = 0.04, I^2 > 88%, *p* = 0.0001

Subgroup analysis of serum studies gave a large, significant effect;

9 studies, N = 511, *g* = -0.77, 95%CI -1.36 to -0.18, *p* = 0.01, I^2 > 88%, *p* = 0.0001

Subgroup analysis of plasma studies found no significant differences between groups. Subgroup analyses also showed no differences in BDNF levels between patients and controls according to medication status.

Meta-regressions showed correlations between increasing study effect sizes and increasing manic symptom severity, and between decreasing study effect sizes and longer duration of illness, better study quality, and larger samples.

There were no significant differences in BDNF levels pre- vs. post-treatment, apart from the analysis of patients with manic state showing a small to medium-sized increase in BDNF levels post-treatment;

6 studies, N = 236, *g* = 0.38, 95%CI 0.03 to 0.73, *p* = 0.03

<u>During an euthymia state</u>

There were no significant differences in BDNF levels between patients and controls;

18 studies, N = 1,475, *g* = 0.02, 95%CI -0.30 to 0.34, *p* = 0.92, I^2 = 90%, *p* < 0.0001

Subgroup analysis of plasma studies found no significant differences between groups. Subgroup analyses also showed no differences in BDNF levels between patients and controls according to medication status.

Meta-regressions showed correlations between increasing study effect sizes and increasing manic symptom severity.

Consistency in results	Inconsistent
Precision in results	Precise for the overall and euthymia analyses only.

Directness of results	Direct

Polyakova M, Stuke K, Schuemberg K, Mueller K, Schoenknecht P, Schroeter ML

BDNF as a biomarker for successful treatment of mood disorders: a systematic & quantitative meta-analysis

Journal of Affective Disorders 2015; 174: 432-40

View review abstract online

Comparison	**BDNF levels in people with bipolar disorders vs. controls.**
Summary of evidence	**Moderate to low quality evidence (inconsistent, imprecise, direct, small samples) suggests a large effect of reduced BDNF levels during a depressive state, and moderate quality evidence (precise) shows a medium-sized effect during a manic state (with one outlier removed from the analysis). There was no effect during euthymia.**

Blood BDNF levels

During a depressive state

A significant, large effect of decreased BDNF levels in people with bipolar disorder compared to controls;

6 studies, N = 117, d = -1.16, 95%CI -1.79 to -0.54, $p < 0.05$, I^2 = 83%

During a manic state

A significant, medium-sized effect of decreased BDNF levels in people with bipolar disorder compared to controls;

With one outlier removed: 8 studies, N = 156, d = -0.77, 95%CI -1.10 to -0.44, $p < 0.05$, I^2 = 50%

During an euthymia state

There were no significant differences in BDNF levels between patients and controls;

9 studies, N = 426, d = 0.05, 95%CI -0.42 to 0.43, p = 0.098, I^2 = 88%

BDNF levels in the depression and mania groups were significantly lower than in the euthymic group.

There were no differences in effect size according to source (serum vs. plasma), age, sex (% males), duration of illness and study quality.

Consistency in results	Inconsistent

Precision in results	Precise for the manic and euthymia analyses only.
Directness of results	Direct

Rao S, Martinez-Cengotitabengoa M, Yao Y, Guo Z, Xu Q, Li S, Zhou, X, Zhang F

Peripheral blood nerve growth factor levels in major psychiatric disorders

Journal of Psychiatric Research 2017; 86: 39-45

View review abstract online

Comparison	**NGF levels in people with bipolar disorder vs. controls.**
Summary of evidence	**High quality evidence (consistent, precise, direct, large samples) suggests a small effect of increased NGF levels in unmedicated people with bipolar disorder compared to controls.**

NGF levels

There were no significant differences in NGF levels between people with bipolar disorders and controls;

5 studies, N = 624, SMD = 0.13, 95%CI -0.03 to 0.29, $p = 0.105$, $I^2 = 0\%$, $p = 0.454$

Subgroup analysis of studies of unmedicated patients showed a small effect of increased NGF in people with bipolar disorders;

4 studies, N = 539, SMD = 0.19, 95%CI 0.02 to 0.36, $p = 0.03$, $I^2 = 0\%$, $p = 0.967$

Authors report no evidence of publication bias.

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

Tseng PT, Chen YW, Tu KY, Wang HY, Chung W, Wu CK, Hsu SP, Kuo HC, Lin PY

State-dependent increase in the levels of neurotrophin-3 and neurotrophin-4/5 in patients with bipolar disorder: A meta-analysis

Journal of Psychiatric Research 2016; 79: 86-92

View review abstract online

Comparison	**Neurotrophin-3 and 4/5 levels in people with bipolar disorders vs. controls.**
Summary of evidence	**Moderate quality evidence (inconsistent, precise, direct, medium-large samples, possible publication bias) suggests a medium-sized effect of increased neurotrophin-3 and 4/5 levels in people with bipolar disorder during a depressive state, but not during a manic or euthymia state.**

Blood neurotrophin-3 levels

Overall

A significant, medium-sized effect of increased neurotrophin-3 levels in people with bipolar disorder compared to controls;

6 studies, N = 533, g = 0.38, 95%CI 0.12 to 0.64, p = 0.0046, I^2 = 75%, p < 0.0001

Meta-regression showed that the effect size decreased as duration of illness increased, and the effect size increased as depressive symptom severity increased. There were no associations with age, sex, or mania symptom severity.

Authors report possible publication bias.

During a depressive state

A significant, medium-sized effect of increased neurotrophin-3 levels in people with bipolar disorder compared to controls;

5 studies, N = 357, g = 0.664, 95%CI 0.215 to 1.112, p = 0.0038

During a manic state

There were no significant differences in neueotrophin-3 levels between patients and controls;

5 studies, N = 365, g = 0.218, 95%CI -0.311 to 0.787, p = 0.4185

During an euthymia state

There were no significant differences in neurotrophin-3 levels between patients and controls;

4 studies, N = 330, g = 0.241, 95%CI -0.168 to 0.649, p = 0.2488

Blood neurotrophin 4/5 levels

Overall

A significant, medium-sized effect of increased neurotrophin-4/5 levels in people with bipolar disorder compared to controls;

4 studies, N = 401, g = 0.53, 95%CI 0.25 to 0.82, p = 0.0003, I^2 = 77%, p = 0.0002

Meta-regression showed that the effect size decreased as duration of illness increased, and the effect size increased as depressive symptom severity increased. There were no associations with

age or sex. Authors report no publication bias. During a depressive state *A significant, medium-sized effect of increased neurotrophin-4/5 levels in people with bipolar disorder compared to controls;* 2 studies, N = 142, *g* = 0.696, 95%CI 0.347 to 1.044, *p* = 0.0001 During a manic state *There were no significant differences in neurotrophin-4/5 levels between patients and controls;* 2 studies, N = 131, *g* = -0.017, 95%CI -1.277 to 1.244, *p* = 0.9794 During an euthymia state *There were no significant differences in neurotrophin-4/5 levels between patients and controls;* 3 studies, N = 213, *g* = 0.212, 95%CI -0.349 to 0.774, *p* = 0.4583

Consistency in results	Inconsistent
Precision in results	Precise for the overall and depressive state analyses, and for euthymia neurotrophin-3.
Directness of results	Direct

Explanation of acronyms

BDNF = Brain derived neurotrophic factor, CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), IQR = interquartile range, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), SMD = standardised mean difference, vs = versus

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].

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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.

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.

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‡ 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];

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

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§ 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 ENREF 9[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.

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