Neuroscience and Biobehavioral Reviews 149 (2023) 105159

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

The role of BDNF in major depressive disorder, related clinical features, and antidepressant treatment: Insight from meta-analyses

Daniele Cavaleri [a], Federico Moretti [a], Alessandra Bartoccetti [a], Stefano Mauro [a], Cristina Crocamo [a], Giuseppe Carrà [a,b], Francesco Bartoli [a,*]

[a] Department of Medicine and Surgery, University of Milano-Bicocca, via Cadore 48, 20900 Monza, Italy
[b] Division of Psychiatry, University College London, Maple House 149, London W1T 7BN, United Kingdom

ARTICLE INFO

Keywords:
Brain-derived neurotrophic factor
Biomarker
Major depressive disorder
Antidepressants
Treatment
Meta-analysis

ABSTRACT

The brain-derived neurotrophic factor (BDNF) has received considerable attention as a potential biomarker of major depressive disorder (MDD) and antidepressant response. We conducted an overview of meta-analyses investigating the relationship of BDNF with MDD, related clinical features, and antidepressant treatment. Based on a systematic screening on main electronic databases, 11 systematic reviews with meta-analyses were included. Available evidence suggests that people with MDD have peripheral and central BDNF levels lower than non-depressed individuals. A negative correlation between blood BDNF and symptom severity emerged, while no association with suicidality was detected. Moreover, an increase in blood BDNF levels after antidepressant treatment, proportional to symptom improvement, was reported. BDNF levels seem to be increased in both treatment responders and remitters, remaining stable in non-responders. Conversely, no variations of BDNF concentrations after non-pharmacological interventions (electroconvulsive therapy, repetitive transcranial magnetic stimulation, and physical activity) were found. The findings of this overview appear consistent with the neurotrophic hypothesis of depression, suggesting that BDNF may play a role in both MDD pathophysiology and pharmacological treatment response.

1. Introduction

The brain-derived neurotrophic factor (BDNF) is an extracellular signalling protein belonging to the family of neurotrophins, which are molecules that promote the development, health, and survival of neurons (Zuccato and Cattaneo, 2009). It is the most widespread neurotrophin in the central nervous system (CNS) and is largely expressed in crucial regions such as hippocampus, amygdala, hypothalamus, neocortex, and cerebellum (Tsai, 2018; Zhao et al., 2018; Binder and Scharfman, 2004). BDNF is encoded (as pro-BDNF) by a gene of which several variants exist – with the single-nucleotide Val66Met polymorphism being the most common (Tsai, 2018; Egan et al., 2003) – and mainly exerts its effects by binding and activating the tropomyosin-related kinase B (TrkB) receptors. These are located on both presynaptic and postsynaptic membranes and are coupled to the activation of several transmission pathways (Gelle et al., 2021; Cattaneo et al., 2016; Leal et al., 2014). BDNF is thus involved in a wide range of key neural mechanisms – such as neuronal growth, differentiation, and survival, synaptic plasticity, neurotransmission, and resistance to neuronal stress (Marosi and Mattson, 2014; Zuccato and Cattaneo, 2009; Binder and Scharfman, 2004) – that might play a role in the pathophysiology of several psychiatric conditions (Cattaneo et al., 2016; Zuccato and Cattaneo, 2009). These certainly include major depressive disorder (MDD) (Gelle et al., 2021), in which functional and structural disruptions of neural circuits might underlie individual variations in mood and behaviour (Duman et al., 2016; Kuhn et al., 2014). In particular, a growing number of primary studies in the last two decades investigated BDNF as a possible biomarker of MDD and antidepressant response (Cattaneo et al., 2016; Molendijk et al., 2014; Shimizu et al., 2003). This large bulk of data has been synthesized in several meta-analyses (Gelle et al., 2021), generating sometimes conflicting and inconsistent evidence. A preliminary overview of meta-analyses highlighted that blood BDNF levels variations in MDD might be correlated with antidepressant treatment, while its role as a potential biomarker of MDD was less clear (Kishi et al., 2018). However, recent data pose a challenge in the interpretation of the link between BDNF and both

* Corresponding author.
E-mail address: francesco.bartoli@unimib.it (F. Bartoli).

https://doi.org/10.1016/j.neubiorev.2023.105159
Received 14 January 2023; Received in revised form 10 March 2023; Accepted 2 April 2023
Available online 3 April 2023

pathophysiology and treatment of MDD (Arosio et al., 2021). In particular, additional insight on the role that both central and peripheral BDNF concentrations might play in MDD, as well as their correlation with specific clinical features and antidepressant treatment, can be derived by several recently published meta-analyses (e.g., Mousten et al., 2022; Çakici et al., 2021; Fusar-Poli et al., 2021). In this work, we thus summarised evidence emerging from meta-analyses investigating the relationship of BDNF with MDD, related clinical features, and antidepressant treatment.

2. Materials and methods

The current work was performed following standard recommendations for conducting narrative reviews of the literature (Baethge et al., 2019). We summarised evidence from meta-analyses exploring BDNF cerebrospinal fluid (CSF) or blood (serum or plasma) concentrations in people with MDD. More specifically, we included meta-analyses that: i) compared BDNF concentrations between people suffering from MDD and healthy controls (HCs); ii) explored possible correlations between BDNF levels and specific clinical features of MDD; iii) investigated BDNF levels as a possible predictor of treatment response; iv) explored BDNF variations after pharmacological or non-pharmacological treatment in people with MDD. In case of overlapping data from meta-analyses investigating the same outcome, we selected the one including the largest number of studies and/or the most complete findings. In order to improve consistency and comparability of data, we excluded meta-analyses i) involving people with bipolar depression or depressive episodes in other psychiatric disorders (e.g., schizophrenia, post-traumatic stress disorder, obsessive-compulsive disorder); ii) focusing on special populations, such as people suffering from organic diseases.

Systematic searches of Embase, MEDLINE, and PsycInfo databases (via Ovid), as well as of the Cochrane Database of Systematic Reviews, were performed for meta-analyses published up to 13 November 2022. The search phrase used was: *(brain-derived neurotrophic factor OR BDNF) AND (depression OR depressive OR depressed) AND (meta-analys* OR metaanalys* OR metanalys*).mp* as a multiple purpose search of title, abstract, heading words, and keywords. No language or publication date restrictions were applied. Grey literature, conference abstracts, and all publications not having undergone peer-review were excluded. After a preliminary screening based on titles and abstracts, studies were retrieved and read in full text by four authors (DC, FM, AB, and SM). Any potential disagreement was resolved by discussion with other authors. We then extracted key information from the eligible articles – including number of included studies (k), total (N) and subgroup (n) sample sizes, diagnosis and main characteristics of participants, as well as outcomes with related measures of the effects, heterogeneity, and information on publication bias. The magnitude of the effects was classified according to conventional cut-offs (Schünemann et al., 2022; Olivier and Bell, 2013; Rosenthal, 1996; Cohen, 1988), and statistical heterogeneity was categorised according to the reported I^2 value as low (25%), moderate (50%), or high (75%) (Higgins et al., 2003).

3. Results

Our systematic search generated 483 records via Ovid (317 from Embase, 97 from MEDLINE, and 69 from PsycInfo), reduced to 333 unique articles after deduplication, and 17 systematic reviews from the Cochrane Database of Systematic Reviews. Eleven systematic reviews with meta-analyses met the eligibility criteria and were included in this overview (Mousten et al., 2022; Pelosof et al., 2022; Çakici et al., 2021; Fusar-Poli et al., 2021; Çakici et al., 2020; Shi et al., 2020; Dinoff et al., 2018; Zhou et al., 2017; Brunoni et al., 2015; Polyakova et al., 2015; Molendijk et al., 2014). Fig. 1 shows the flow chart with reasons of inclusion and exclusion.

The included meta-analyses were all in English and published between 2014 (Molendijk et al., 2014) and 2022 (Mousten et al., 2022; Pelosof et al., 2022).

Three meta-analyses compared BDNF concentrations between people with MDD and healthy controls (Mousten et al., 2022; Çakici et al., 2020; Shi et al., 2020), two reported data on the correlation between BDNF concentrations and clinical features of MDD (Fusar-Poli et al.,

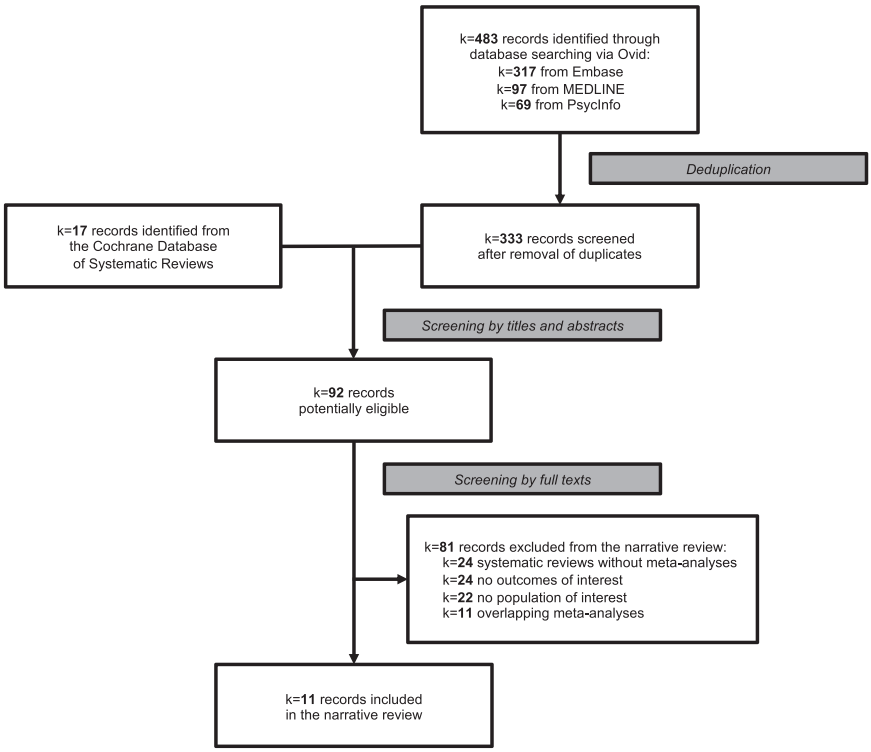

Fig. 1. Flow chart of the study selection process.

2021; Molendijk et al., 2014), and seven explored the influence of treatment on BDNF concentrations (Pelosof et al., 2022; Çakici et al., 2021; Dinoff et al., 2018; Zhou et al., 2017; Brunoni et al., 2015; Polyakova et al., 2015; Molendijk et al., 2014).

3.1. BDNF concentrations in major depressive disorder

A meta-analysis of 97 studies compared blood BDNF concentrations between treated and untreated people with MDD (n = 7117) and HCs (n = 7075) (Shi et al., 2020). People with MDD showed significantly lower peripheral BDNF levels, with a medium-to-large effect size (SMD = −0.64; 95% CI: −0.77 to –0.50, $p < 0.001$). These findings were inconsistent ($I^2 = 92\%$) and affected by a likely risk of publication bias (Egger's test p = 0.003) which could not be addressed even with the trim-and-fill method.

With regard to central levels of BDNF, Mousten and colleagues meta-analysed three studies reporting that BDNF concentrations in CSF were lower in antidepressant-free people with MDD as compared with HCs, with a medium effect size (N = 108; SMD = −0.58, 95% CI: −0.97 to −0.19, p = 0.004; $I^2 = 0\%$) (Mousten et al., 2022).

One meta-analysis provided specific data on never-medicated MDD. Data pooling results from 10 studies including 373 antidepressant-naïve people with first-episode MDD and 456 HCs did not find any statistically significant difference between the two groups (SMD = −0.47, 95% CI: −1.18 to 0.24, p = 0.19; $I^2 = 95\%$), without evidence of publication bias (Egger's test p = 0.37) (Çakici et al., 2020).

3.2. BDNF concentrations and clinical features of major depressive disorder

Two meta-analyses provided data on the relationship between BDNF and specific clinical features of MDD (Fusar-Poli et al., 2021; Molendijk et al., 2014). Molendijk and colleagues showed that serum BDNF concentrations negatively correlated with symptom severity of MDD in drug-free people (k = 30, n = 1807; Pearson's r = –0.19, 95% CI: –0.28 to –0.10, $p < 0.001$) but not in antidepressant-treated participants (k = 20, n = 1820; Pearson's r = –0.02, p = 0.36) (Molendijk et al., 2014). Fusar-Poli et al. investigated suicidality in people with MDD (mostly unmedicated), comparing the peripheral BDNF levels of participants who attempted suicide to those of subjects without a history of suicide attempts. However, they did not find statistically significant differences between the two groups (k = 7, N = 502; SMD = –0.33, 95% CI: –0.70 to 0.03; $I^2 = 74\%$) (Fusar-Poli et al., 2021).

The characteristics of the included meta-analyses on BDNF concentrations in people with MDD are displayed in Table 1.

3.3. BDNF concentrations and treatment

3.3.1. Antidepressant drug treatment

Molendijk and colleagues estimated that, among people with MDD, antidepressant-free subjects had lower serum BDNF concentrations than individuals treated with antidepressants (k = 28, N = 4204; SMD = –0.56, 95% CI: –0.77 to –0.35, $p < 0.001$; $I^2 = 84\%$), although with a high probability of publication bias (Egger's test $p < 0.05$). When considering studies that reported pre- and post-treatment BDNF concentrations only, the resulting pooled effect size was even larger (k = 23, N = 711; SMD = –0.74, 95% CI: –1.04 to –0.45, $p < 0.001$; $I^2 = 84\%$). Both analyses showed evidence of publication bias, which was addressed using the trim-and-fill method, confirming previous results, though with smaller effect sizes (SMD = –0.54 and SMD = –0.34, respectively). Additionally, over the course of antidepressant treatment, a larger decrease in symptom severity significantly correlated with a larger increase in serum BDNF concentrations (Pearson's r = –0.48, p = 0.01) (Molendijk et al., 2014).

Moreover, BDNF levels in people with MDD seemed to increase upon drug treatment in remitters (k = 7, N = 116; SMD = 0.85, 95% CI: 0.39 to 1.29) and in responders (k = 11, N = 252; SMD = 1.33, 95% CI: 0.69 to 1.97), with large-to-very large effect sizes. Conversely, BDNF levels in the non-responder group remained stable (k = 7, N = 118; SMD = 0.15, 95% CI: –0.33 to 0.63). Meta-analyses on serum BDNF levels in responders and non-responders showed a likely risk of publication bias, though the trim-and-fill method confirmed the overall findings. Tests for subgroup differences confirmed that serum BDNF changes in remitters and responders were significantly larger than those in non-responders (p = 0.036 and p = 0.012, respectively) (Polyakova et al., 2015).

Stratifying by antidepressant drug class, treatments with selective serotonin reuptake inhibitors (SSRIs) (k = 12, N = 270; SMD = 0.68, 95% CI: 0.27 to 1.10, p = 0.001; $I^2 = 80\%$) and with serotonin and norepinephrine reuptake inhibitors (SNRIs) (k = 7, N = 154; SMD = 0.92, 95% CI: 0.07 to 1.77, p = 0.03; $I^2 = 91\%$) both led to a significant increase in BDNF concentrations in people with MDD, with medium-to-large and large effect sizes respectively, whereas no meta-analytic data were available regarding other antidepressants. Meta-analyses on single antidepressant agents, though limited by small sample sizes, showed that sertraline significantly increased BDNF levels from pre- to post-treatment (k = 4, N = 111; SMD = 0.53, 95% CI: 0.13 to 0.93, p = 0.009; $I^2 = 34\%$), while estimates for escitalopram, paroxetine, and venlafaxine were not statistically significant (Zhou et al., 2017).

Furthermore, Çakici et al. specifically focused on the effects of antidepressant drugs in previously antidepressant-naïve people with first-episode MDD. They showed that BDNF concentrations in antidepressant-naïve MDD increased following first antidepressant treatment (k = 7, N = 188; SMD = 0.51, 95% CI: 0.06 to 0.96, p = 0.027; $I^2 = 76\%$), with a medium effect size, with age (p = 0.14), sex (p = 0.54), and treatment duration (p = 0.61) not significantly influencing the results (Çakici et al.,

Table 1
Characteristics of the included meta-analyses on BDNF concentrations in people with major depressive disorder.

Authors, year	Condition	k	N	n cases	n controls	Biological sample	Outcome
Çakici et al. (2020)	First-episode MDD (antidepressant-naïve)	10	829	373	456	Blood (serum/ plasma)	Blood BDNF concentrations in antidepressant-naïve first-episode MDD vs. HCs
Fusar-Poli et al. (2021)	MDD (mostly unmedicated)	7	502	N/R	N/R	Blood (serum/ plasma)	Blood BDNF concentrations in people with MDD who attempted suicide vs. people with MDD without a history of suicide attempts
Molendijk et al. (2014)	MDD	30	1807	1807	–	Serum	Correlation between serum BDNF concentrations and symptom severity in drug-free people with MDD
		20	1820	1820	–		Correlation between serum BDNF concentrations and symptom severity in antidepressant-treated people with MDD
Mousten et al. (2022)	MDD (antidepressant-free)	3	108	46	62	CSF	CSF BDNF concentrations in MDD vs. HCs
Shi et al. (2020)	MDD (treated or untreated)	97	14192	7117	7075	Blood (serum/ plasma)	Blood BDNF concentrations in MDD vs. HCs

BDNF = brain-derived neurotrophic factor; CSF = cerebrospinal fluid; HCs = healthy controls; MDD = major depressive disorder; N/R = not reported.

2021).

3.3.2. Electroconvulsive therapy (ECT)

Meta-analysing 12 studies with both medicated and unmedicated participants (N = 376), Pelosof et al. did not find a significant increase in BDNF concentrations in people with MDD after a course of electroconvulsive therapy (ECT) (SMD = 0.35, 95% CI: –0.02 to 0.71; I^2 = 80%) (Pelosof et al., 2022).

3.3.3. Repetitive transcranial magnetic stimulation (rTMS)

Brunoni et al. performed a meta-analysis addressing the effects of repetitive transcranial magnetic stimulation (rTMS) on blood BDNF levels in people with treatment-resistant MDD. Participants were continuously medicated with antidepressant drugs for at least 3 weeks before rTMS was initiated. Blood BDNF levels did not change after a course of rTMS (k = 4, N = 74; SMD = 0.05, 95% CI: –0.30 to 0.39; I^2 = 11%) (Brunoni et al., 2015).

3.3.4. Physical activity

A meta-analysis of six studies, including 176 participants with MDD (mostly under concomitant antidepressant drug treatment), investigated the effect of 3–12 weeks of aerobic exercise on blood BDNF concentrations. However, resting concentrations of blood BDNF were not likely to increase after the physical activity period (SMD = 0.43, 95% CI: −0.06 to 0.92, p = 0.09; I^2 = 76%). This result was confirmed by a sensitivity analysis including studies of high quality only (SMD = 0.24, 95% CI: −0.06 to 0.53, p = 0.12). Meta-regression analyses, though underpowered, showed that age (p = 0.72), sex (p = 0.40), mean baseline BMI (p = 0.90), antidepressant use (p = 0.52), duration of exercise intervention (p = 0.86), and exercise intensity (p = 0.24) did not seem to moderate the effect (Dinoff et al., 2018).

The characteristics of the included meta-analyses on the relationship between blood BDNF concentrations and treatment in MDD are reported in Table 2.

A summary of the findings of the included meta-analyses is shown in Table 3.

Table 2
Characteristics of the included meta-analyses on blood (serum/plasma) BDNF concentrations and treatment of major depressive disorder.

Authors, year	Condition	Treatment	k	N	Outcome
Brunoni et al. (2015)	Treatment-resistant MDD	rTMS	4	74	Blood BDNF concentrations pre- vs. post-rTMS
Çakici et al. (2021)	Antidepressant-naïve first-episode MDD	Drug treatment	7	188	Blood BDNF concentrations pre- vs. post-drug treatment
Dinoff et al. (2018)	MDD	Aerobic physical exercise	6	176	Blood BDNF concentrations pre- vs. post-physical exercise
Molendijk et al. (2014)	MDD	Drug treatment	28	4204	Serum BDNF concentrations in antidepressant-free vs. antidepressant-treated MDD
			23	711	Serum BDNF concentrations pre- vs. post-drug treatment
Pelosof et al. (2022)	MDD	ECT	12	376	Blood BDNF concentrations pre- vs. post-ECT
Polyakova et al. (2015)	MDD	Drug treatment	7	116	Blood BDNF concentrations pre- vs. post-drug treatment in remitters
			11	252	Blood BDNF concentrations pre- vs. post-drug treatment in responders
			7	118	Blood BDNF concentrations pre- vs. post-drug treatment in non-responders
Zhou et al. (2017)	MDD	SSRIs	12	270	Blood BDNF concentrations pre- vs. post-treatment with SSRIs
		SNRIs	7	154	Blood BDNF concentrations pre- vs. post-treatment with SNRIs
		Sertraline	4	111	Blood BDNF concentrations pre- vs. post-treatment with sertraline

BDNF = brain-derived neurotrophic factor; ECT = electroconvulsive therapy; MDD = major depressive disorder; rTMS = repetitive transcranial magnetic stimulation; SNRIs = serotonin and norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.

4. Discussion

4.1. Summary of findings

In this overview, we synthesised the evidence reported by 11 meta-analyses exploring the role of BDNF in MDD, showing a meaningful influence of both MDD clinical features and treatments on BDNF levels. The available meta-analytic evidence suggests that people with MDD are likely to have peripheral and central BDNF levels lower than non-depressed individuals. The medium-to-large magnitude of the estimated effects makes these findings robust. Conversely, the substantial between-study heterogeneity and the high risk of publication bias detected from the meta-analysis on BDNF blood concentrations (Shi et al., 2020), as well as the limited sample size of the meta-analysis on BDNF CSF levels (Mousten et al., 2022), preclude full confidence in these results. Moreover, in terms of clinical features, while a negative correlation between serum BDNF and depressive symptom severity was uncovered (Molendijk et al., 2014), suicidality did not seem to correlate with BDNF levels in MDD (Fusar-Poli et al., 2021).

With regard to the treatment of MDD, although there seem to be no variations in BDNF levels in first-episode antidepressant-naïve individuals (Çakici et al., 2020), a pooled effect of medium magnitude (though with evidence of publication bias) suggests that antidepressant drug treatment may be correlated with higher serum BDNF concentrations (Molendijk et al., 2014). Pre-/post- treatment studies strengthen this assumption, showing an increase in BDNF in blood after both SSRI (especially sertraline) and SNRI administration (Çakici et al., 2021; Zhou et al., 2017; Molendijk et al., 2014). Interestingly, available meta-analytic evidence also suggests a relationship between the improvement of depressive symptoms and the increase in serum BDNF concentrations after antidepressant drug treatment (Molendijk et al., 2014). Consistently, BDNF levels seem to increase in both treatment responders and remitters though remaining stable in non-responders (Polyakova et al., 2015).

Finally, evidence concerning the effect of non-pharmacological interventions on BDNF is less clear. Although a previous meta-analysis on ECT had shown that blood BDNF concentrations increased after a full treatment course (Rocha et al., 2016), more recent data did not confirm this effect (Pelosof et al., 2022). Similarly, no variations of BDNF after rTMS were found (Brunoni et al., 2015). Moreover, physical activity

Table 3
Summary of findings.

Study	Finding	Effect size	Heterogeneity (I^2)	Risk of publication bias
BDNF concentrations in MDD				
Çakici et al. (2020)	No significant differences in blood BDNF levels between antidepressant-naïve people with first-episode MDD and HCs	SMD = −0.47 (95% CI: −1.18 to 0.24) p = 0.19	High (I^2 = 95%)	Low
Mousten et al. (2022)	Significantly lower CSF BDNF levels in people with MDD compared to HCs	SMD = −0.58 (95% CI: −0.97 to −0.19) p = 0.004	Low (I^2 = 0%)	–
Shi et al. (2020)	Significantly lower blood BDNF levels in people with MDD compared to HCs	SMD = −0.64 (95% CI: −0.77 to –0.50) p < 0.001	High (I^2 = 92%)	High
BDNF concentrations and clinical features of MDD				
Fusar-Poli et al. (2021)	No significant differences between people with MDD who attempted suicide and people with MDD who never attempted suicide	SMD = –0.33 (95% CI: –0.70 to 0.03)	High (I^2 = 74%)	–
Molendijk et al. (2014)	Negative correlation between depressive symptom severity and serum BDNF levels in drug-free people with MDD	Pearson's r = –0.19 (95% CI: –0.28 to –0.10) p < 0.001	–	–
	No significant correlation between depressive symptom severity and serum BDNF levels in antidepressant-treated people with MDD	Pearson's r = –0.02 p = 0.36	–	–
BDNF concentrations and treatment				
Brunoni et al. (2015)	No significant change in blood BDNF levels after a rTMS course	SMD = 0.05 (95% CI: –0.30 to 0.39)	Low (I^2 = 11%)	–
Çakici et al. (2021)	Significant increase in blood BDNF concentrations in antidepressant-naïve people treated after antidepressant drug treatment	SMD = 0.51 (95% CI: 0.06–0.96) p = 0.027	High (I^2 = 76%)	–
Dinoff et al. (2018)	No significant change in blood BDNF levels after a physical exercise course	SMD = 0.43 (95% CI: −0.06 to 0.92) p = 0.09	High (I^2 = 76%)	–
Molendijk et al. (2014)	Significantly lower serum BDNF levels in antidepressant-treated people compared to antidepressant-free people	SMD = –0.56 (95% CI: –0.77 to –0.35) p < 0.001	High (I^2 = 84%)	High[a]
	Significantly lower serum BDNF levels in antidepressant-treated people compared to antidepressant-free people in pre- vs. post-treatment comparisons	SMD = –0.74 (95% CI: –1.04 to –0.45) p < 0.001	High (I^2 = 84%)	High[a]
	Significant negative correlation between decrease in symptom severity and increase in serum BDNF levels	Pearson's r = –0.48 p = 0.01	–	–
Pelosof et al. (2022)	No significant differences in blood BDNF levels after an ECT course	SMD = 0.35 (95% CI: –0.02 to 0.71)	High (I^2 = 80%)	–
Polyakova et al. (2015)	Significant increase in blood BDNF levels in drug treatment remitters	SMD = 0.85 (95% CI: 0.39 to 1.29)	–	Low
	Significant increase in blood BDNF levels in drug treatment responders	SMD = 1.33 (95% CI: 0.69 to 1.97)	–	High[a]
	No significant change in blood BDNF levels in drug treatment non-responders	SMD = 0.15 (95% CI: –0.33 to 0.63)	–	High[a]
Zhou et al. (2017)	Significant increase in blood BDNF concentrations in people treated with SSRIs	SMD = 0.68 (95% CI: 0.27 to 1.10) p = 0.001	High (I^2 = 80%)	–
	Significant increase in blood BDNF concentrations in people treated with SNRIs	SMD = 0.92 (95% CI: 0.07 to 1.77) p = 0.03	High (I^2 = 91%)	–

95% CI = 95% confidence interval; BDNF = brain-derived neurotrophic factor; CSF = cerebrospinal fluid; ECT = electroconvulsive therapy; HCs = healthy controls; MDD = major depressive disorder; rTMS = repetitive transcranial magnetic stimulation; SMD = standardized mean difference; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

[a] the application of the trim-and-fill method did not change the results, which remained significant.

does not seem to significantly increase blood BDNF in MDD (Dinoff et al., 2018).

4.2. Interpretation of findings

Notwithstanding the significant heterogeneity and the possible risk of publication bias, some relevant neurobiological implications can be derived according to the evidence emerging from available meta-analyses. The reduced levels of BDNF in people with MDD are consistent with the "neurotrophic hypothesis" of depression (Duman and Monteggia, 2006; Duman et al., 1997). Indeed, it has been hypothesised that depressive states may be related to an aberrant neurogenesis caused by a decreased expression of BDNF in brain regions regulating higher functions, such as emotion and memory (Molendijk et al., 2014; Duman and Monteggia, 2006). The functional significance of BDNF in depression has been highlighted by preclinical research showing limited neurogenesis in vivo: a decrease in BDNF in key limbic regions correlated with mood, such as hippocampus, amygdala, and prefrontal cortex, may lead to reduced neuronal growth, worse synapse formation and plasticity, and increased apoptosis (Taliaz et al., 2010; Heldt et al., 2007; Duman and Monteggia, 2006).

It is also worth mentioning that BDNF production is not limited to the brain but occurs in several peripheral tissues, including vascular smooth muscle cells, activated macrophages, lymphocytes, muscle, heart, and liver, with platelets storing most of the BDNF secreted by non-neural tissues and releasing it during clotting (Kronenberg et al., 2021; Serra-Millàs, 2016; Bus et al., 2011; Karege et al., 2005). Considering the putative BDNF storage stability of platelets (Polyakova et al., 2017), serum is considered a source of information on peripheral BDNF levels more reliable than plasma (Shi et al., 2020). However, serum BDNF measurement is influenced by platelet concentration and activation: this issue, albeit often overlooked, should be carefully taken into account, also because of the possible mediating role of platelet activation across the link between BDNF abnormalities and MDD (Gejl et al., 2019; Naegelin et al., 2018; Serra-Millàs, 2016). Moreover, several other characteristics, including body weight, lifestyle factors (dietary patterns, alcohol consumption, cigarette smoking), and somatic disorders – may putatively influence peripheral BDNF levels (Bus et al., 2011; Ziegenhorn et al., 2007; Lommatzsch et al., 2005). In addition, inconsistency in storage and measurement methods, with enzyme-linked immunosorbent assay (ELISA) seemingly associated with higher inconsistency (Shi et al., 2020), should be considered (Polyakova et al., 2017; Polacchini et al., 2015).

Moreover, preclinical evidence has shown that BDNF seems able to cross the blood-brain barrier in both directions through an active transport system. Thus, while the relevance of findings on CSF levels of BDNF might look questionable, the relationship between peripheral and central BDNF concentrations supports the assumption that blood BDNF levels may represent an appropriate enough proxy of BDNF concentrations in the brain (Gejl et al., 2019; Klein et al., 2011; Gass and Hellweg, 2010).

Recent evidence by functional magnetic resonance investigations in human subjects indicated that serum BDNF concentrations are associated with the integrity of the cerebral cortex, which is involved in the pathophysiology of mood disorders (Lang et al., 2007). Consistently, findings of this review have shown consistent decreases of both peripheral and central BDNF levels in MDD.

The "neurotrophic hypothesis" of depression seems further supported by the relationship between blood BDNF and treatment of MDD. Meta-analytic evidence shows that an increase in BDNF concentrations occurs after most antidepressant drug treatments (Çakici et al., 2021; Zhou et al., 2017; Molendijk et al., 2014). This effect may not be limited to SSRIs and SNRIs: indeed, other antidepressant agents belonging to different classes such as amitriptyline (Hellweg et al., 2008) and mirtazapine (Deuschle et al., 2013) have also been shown to increase serum BDNF. Moreover, increased BDNF concentrations have been found in treatment responders and remitters but not in non-responders (Polyakova et al., 2015) and depressive symptoms improvement correlated with serum BDNF after antidepressant drug treatment (Molendijk et al., 2014). Different neurobiological mechanisms have been hypothesised to explain BDNF-related antidepressant effects. BDNF seems to be a key transducer of antidepressant-like response, involving specific areas of the CNS (Björkholm and Monteggia, 2016). In particular, previous research has focused on the possible antidepressant mechanisms related to BDNF-TrkB signalling in the hippocampus (Castrén and Monteggia, 2021; Björkholm and Monteggia, 2016; Li et al., 2008). Moreover, BDNF seems an important regulator of neuronal plasticity in the CNS, supporting the existence of a strict relationship between neurotrophic factors and neuronal plasticity in depressive disorders, also sustaining antidepressant response (Castrén and Monteggia, 2021). These hypotheses are further supported by preclinical studies in which BDNF was directly administered in the cerebral ventricles or hippocampus of animal models of depression, restoring synaptic plasticity and producing behaviours similar to those induced by antidepressant drugs (Ye et al., 2011; Schmidt and Duman, 2010; Hoshaw et al., 2005). Nonetheless, it is likely that the neurobiological underpinnings of the possible antidepressant effects of BDNF might be more complex, involving different brain regions and circuits. Indeed, it has been recently highlighted that BDNF, despite an antidepressant effect in the prefrontal cortex and hippocampus, would play an opposite role in the mesolimbic circuit (Cubillos et al., 2022). In addition, preclinical research has shown that abnormalities in BDNF gene expression might be associated with a higher vulnerability to depression due to an enhanced neuroinflammatory response, possibly mediated by the kynurenine pathway (Parrott et al., 2021), in turn involved in the pathophysiology of mood disorders (Bartoli et al., 2022; Bartoli et al., 2021). Interestingly, the role of polymorphisms in the BDNF gene seems correlated with the clinical response to antidepressant treatment rather than with the individual vulnerability to MDD (Kishi et al., 2018). Moreover, different factors such as nutrition, life events, and ageing all have been proposed as possible moderators of the BDNF-related antidepressant response, influencing BDNF gene expression (Cubillos et al., 2022).

4.3. Limitations

Although we were able to examine a large amount of meta-analytic evidence, the findings of our overview should be interpreted with caution in view of some limitations. First, due to the narrative approach of our synthesis, we did not conduct a critical appraisal of the included meta-analyses nor a formal grading of the emerging evidence, even though our systematic search allowed us to identify and include the most recent or comprehensive meta-analysis available on each relevant outcome. However, while all but one (Shi et al., 2020) of systematic reviews included used a comprehensive search strategy across at least three databases, as recommended (Lemeshow et al., 2005), we cannot exclude that some eligible primary study was missed out. Second, substantial heterogeneity was present in most analyses. This was possibly due to both the large variability across primary studies in participants characteristics and methods used to store and process biological samples (Polyakova et al., 2017; Polacchini et al., 2015) and the limited comparability between serum and plasma studies (Shi et al., 2020; Polyakova et al., 2017; Molendijk et al., 2014). Besides, the high risk of publication bias emerging from some meta-analyses limits the confidence in the available evidence. Third, the possible selective reporting of outcomes from the included meta-analyses could have biased our findings towards positive results. Moreover, evidence on BDNF concentrations in CSF is very limited (Mousten et al., 2022), preventing us from making deeper considerations regarding the role of BDNF distribution in the CNS and its relationship with peripheral levels. Finally, we could not consider evidence from single studies not included in our pool of meta-analyses.

5. Conclusions

BDNF seems to have a considerable role in the pathophysiology of MDD: BDNF levels are lower in people with MDD, may correlate negatively with depressive symptom severity, and seem to increase after psychopharmacological treatment. This seems consistent with the neurotrophic hypothesis of depression, suggesting that BDNF may underlie the disruption of neural circuits that characterise MDD and mediate the improvement of neurogenesis and neurotransmission in response to antidepressant drug treatment. Additional investigations, taking into account variables putatively influencing BDNF concentrations and favouring the standardization of laboratory techniques to increase consistency and reproducibility of measurements, may further shed light on the complex relationship between BDNF and MDD.

Role of the funding source

None.

Declarations of interest

None.

References

Arosio, B., Guerini, F.R., Voshaar, R.C.O., Aprahamian, I., 2021. Blood brain-derived neurotrophic factor (BDNF) and major depression: do we have a translational perspective? Front. Behav. Neurosci. 15, 626906 https://doi.org/10.3389/fnbeh.2021.626906.

Baethge, C., Goldbeck-Wood, S., Mertens, S., 2019. SANRA-a scale for the quality assessment of narrative review articles. Res. Integr. Peer Rev. 4, 5. https://doi.org/10.1186/s41073-019-0064-8.

Bartoli, F., Cioni, R.M., Callovini, T., Cavaleri, D., Crocamo, C., Carrà, G., 2021. The kynurenine pathway in schizophrenia and other mental disorders: Insight from meta-analyses on the peripheral blood levels of tryptophan and related metabolites. Schizophr. Res. 232, 61–62. https://doi.org/10.1016/j.schres.2021.04.008.

Bartoli, F., Cioni, R.M., Cavaleri, D., Callovini, T., Crocamo, C., Misiak, B., Savitz, J.B., Carrà, G., 2022. The association of kynurenine pathway metabolites with symptom severity and clinical features of bipolar disorder: an overview. Eur. Psychiatry 65, e82. https://doi.org/10.1192/j.eurpsy.2022.2340.

Binder, D.K., Scharfman, H.E., 2004. Brain-derived neurotrophic factor. Growth Factors 22, 123–131. https://doi.org/10.1080/08977190410001723308.

Björkholm, C., Monteggia, L.M., 2016. BDNF - a key transducer of antidepressant effects. Neuropharmacology 102, 72–79. https://doi.org/10.1016/j.neuropharm.2015.10.034.

Brunoni, A.R., Baeken, C., Machado-Vieira, R., Gattaz, W.F., Vanderhasselt, M.A., 2015. BDNF blood levels after non-invasive brain stimulation interventions in major depressive disorder: a systematic review and meta-analysis. World J. Biol. Psychiatry 16, 114–122. https://doi.org/10.3109/15622975.2014.958101.

Bus, B.A., Molendijk, M.L., Penninx, B.J., Buitelaar, J.K., Kenis, G., Prickaerts, J., Elzinga, B.M., Voshaar, R.C., 2011. Determinants of serum brain-derived neurotrophic factor. Psychoneuroendocrinology 36, 228–239. https://doi.org/10.1016/j.psyneuen.2010.07.013.

Çakici, N., Sutterland, A.L., Penninx, B.W.J.H., Dalm, V.A., de Haan, L., van Beveren, N.J.M., 2020. Altered peripheral blood compounds in drug-naïve first-episode patients with either schizophrenia or major depressive disorder: a meta-analysis. Brain Behav. Immun. 88, 547–558. https://doi.org/10.1016/j.bbi.2020.04.039.

Çakici, N., Sutterland, A.L., Penninx, B.W.J.H., de Haan, L., van Beveren, N.J.M., 2021. Changes in peripheral blood compounds following psychopharmacological treatment in drug-naïve first-episode patients with either schizophrenia or major depressive disorder: a meta-analysis. Psychol. Med. 51, 538–549. https://doi.org/10.1017/S0033291721000155.

Castrén, E., Monteggia, L.M., 2021. Brain-derived neurotrophic factor signaling in depression and antidepressant action. Biol. Psychiatry 90, 128–136. https://doi.org/10.1016/j.biopsych.2021.05.008.

Cattaneo, A., Cattane, N., Begni, V., Pariante, C.M., Riva, M.A., 2016. The human BDNF gene: peripheral gene expression and protein levels as biomarkers for psychiatric disorders. Transl. Psychiatry 6, e958. https://doi.org/10.1038/tp.2016.214.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Lawrence Erlbaum Associates, Hillsdale, NJ, USA.

Cubillos, S., Engmann, O., Brancato, A., 2022. BDNF as a mediator of antidepressant response: recent advances and lifestyle interactions. Int. J. Mol. Sci. 23, 14445. https://doi.org/10.3390/ijms232214445.

Deuschle, M., Gilles, M., Scharnholz, B., Lederbogen, F., Lang, U.E., Hellweg, R., 2013. Changes of serum concentrations of brain-derived neurotrophic factor (BDNF) during treatment with venlafaxine and mirtazapine: role of medication and response to treatment. Pharmacopsychiatry 46, 54–58. https://doi.org/10.1055/s-0032-1321908.

Dinoff, A., Herrmann, N., Swardfager, W., Gallagher, D., Lanctôt, K.L., 2018. The effect of exercise on resting concentrations of peripheral brain-derived neurotrophic factor (BDNF) in major depressive disorder: a meta-analysis. J. Psychiatr. Res. 105, 123–131. https://doi.org/10.1016/j.jpsychires.2018.08.021.

Duman, R.S., Monteggia, L.M., 2006. A neurotrophic model for stress-related mood disorders. Biol. Psychiatry 59, 1116–1127. https://doi.org/10.1016/j.biopsych.2006.02.013.

Duman, R.S., Heninger, G.R., Nestler, E.J., 1997. A molecular and cellular theory of depression. Arch. Gen. Psychiatry 54, 597–606. https://doi.org/10.1001/archpsyc.1997.01830190015002.

Duman, R.S., Aghajanian, G.K., Sanacora, G., Krystal, J.H., 2016. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nat. Med. 22, 238–249. https://doi.org/10.1038/nm.4050.

Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., Weinberger, D.R., 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112, 257–269. https://doi.org/10.1016/S0092-8674(03)00035-7.

Fusar-Poli, L., Aguglia, A., Amerio, A., Orsolini, L., Salvi, V., Serafini, G., Volpe, U., Amore, M., Aguglia, E., 2021. Peripheral BDNF levels in psychiatric patients with and without a history of suicide attempt: a systematic review and meta-analysis. Prog. Neuropsychopharmacol. Biol. Psychiatry 111, 110342. https://doi.org/10.1016/j.pnpbp.2021.110342.

Gass, P., Hellweg, R., 2010. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker for affective disorders? Int. J. Neuropsychopharmacol. 13, 1–4. https://doi.org/10.1017/S1461145709991039.

Gejl, A.K., Enevold, C., Bugge, A., Andersen, M.S., Nielsen, C.H., Andersen, L.B., 2019. Associations between serum and plasma brain-derived neurotrophic factor and influence of storage time and centrifugation strategy. Sci. Rep. 9, 9655. https://doi.org/10.1038/s41598-019-45976-5.

Gelle, T., Samey, R.A., Plansont, B., Bessette, B., Jauberteau-Marchan, M.O., Lalloué, F., Girard, M., 2021. BDNF and pro-BDNF in serum and exosomes in major depression: Evolution after antidepressant treatment. Prog. Neuropsychopharmacol. Biol. Psychiatry 13, 110229. https://doi.org/10.1016/j.pnpbp.2020.110229.

Heldt, S.A., Stanek, L., Chhatwal, J.P., Ressler, K.J., 2007. Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. Mol. Psychiatry 12, 656–670. https://doi.org/10.1038/sj.mp.4001957.

Hellweg, R., Ziegenhorn, A., Heuser, I., Deuschle, M., 2008. Serum concentrations of nerve growth factor and brain-derived neurotrophic factor in depressed patients before and after antidepressant treatment. Pharmacopsychiatry 41, 66–71. https://doi.org/10.1055/s-2007-1004594.

Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560. https://doi.org/10.1136/bmj.327.7414.557.

Hoshaw, B.A., Malberg, J.E., Lucki, I., 2005. Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects. Brain Res. 1037, 204–208. https://doi.org/10.1016/j.brainres.2005.01.007.

Karege, F., Bondolfi, G., Gervasoni, N., Schwald, M., Aubry, J.M., Bertschy, G., 2005. Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol. Psychiatry 57, 1068–1072. https://doi.org/10.1016/j.biopsych.2005.01.008.

Kishi, T., Yoshimura, R., Ikuta, T., Iwata, N., 2018. Brain-derived neurotrophic factor and major depressive disorder: evidence from meta-analyses. Front. Psychiatry 8, 308. https://doi.org/10.3389/fpsyt.2017.00308.

Klein, A.B., Williamson, R., Santini, M.A., Clemmensen, C., Ettrup, A., Rios, M., Knudsen, G.M., Aznar, S., 2011. Blood BDNF concentrations reflect brain-tissue BDNF levels across species. Int. J. Neuropsychopharmacol. 14, 347–353. https://doi.org/10.1017/S1461145710000738.

Kronenberg, G., Gertz, K., Schöner, J., Bertram, L., Liman, T., Steinhagen-Thiessen, E., Demuth, I., Endres, M., Hellweg, R., 2021. BDNF serum concentrations in 2053 participants of the Berlin Aging Study II. Neurobiol. Aging 101, 221–223. https://doi.org/10.1016/j.neurobiolaging.2021.01.020.

Kuhn, M., Höger, N., Feige, B., Blechert, J., Normann, C., Nissen, C., 2014. Fear extinction as a model for synaptic plasticity in major depressive disorder. PLoS One 9, e115280. https://doi.org/10.1371/journal.pone.0115280.e115280.

Lang, U.E., Hellweg, R., Seifert, F., Schubert, F., Gallinat, J., 2007. Correlation between serum brain-derived neurotrophic factor level and an in vivo marker of cortical integrity. Biol. Psychiatry 62, 530–535. https://doi.org/10.1016/j.biopsych.2007.01.002.

Leal, G., Comprido, D., Duarte, C.B., 2014. BDNF-induced local protein synthesis and synaptic plasticity. Neuropharmacology 76, 639–656. https://doi.org/10.1016/j.neuropharm.2013.04.005.

Lemeshow, A.R., Blum, R.E., Berlin, J.A., Stoto, M.A., Colditz, G.A., 2005. Searching one or two databases was insufficient for meta-analysis of observational studies. J. Clin. Epidemiol. 58, 867–873. https://doi.org/10.1016/j.jclinepi.2005.03.004.

Li, Y., Luikart, B.W., Birnbaum, S., Chen, J., Kwon, C.H., Kernie, S.G., Bassel-Duby, R., Parada, L.F., 2008. TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. Neuron 59, 399–412. https://doi.org/10.1016/j.neuron.2008.06.023.

Lommatzsch, M., Zingler, D., Schuhbaeck, K., Schloetcke, K., Zingler, C., Schuff-Werner, P., Virchow, J.C., 2005. The impact of age, weight and gender on BDNF levels in human platelets and plasma. Neurobiol. Aging 26, 115–123. https://doi.org/10.1016/j.neurobiolaging.2004.03.002.

Marosi, K., Mattson, M.P., 2014. BDNF mediates adaptive brain and body responses to energetic challenges. Trends Endocrinol. Metab. 25, 89–98. https://doi.org/10.1016/j.tem.2013.10.006.

Molendijk, M.L., Spinhoven, P., Polak, M., Bus, B.A., Penninx, B.W., Elzinga, B.M., 2014. Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N=9484. Mol. Psychiatry 19, 791–800. https://doi.org/10.1038/mp.2013.105.

Mousten, I.V., Sørensen, N.V., Christensen, R.H.B., Benros, M.E., 2022. Cerebrospinal fluid biomarkers in patients with unipolar depression compared with healthy control individuals: a systematic review and meta-analysis. JAMA Psychiatry 79, 571–581. https://doi.org/10.1001/jamapsychiatry.2022.0645.

Naegelin, Y., Dingsdale, H., Säuberli, K., Schädelin, S., Kappos, L., Barde, Y.A., 2018. Measuring and validating the levels of brain-derived neurotrophic factor in human serum. eNeuro 2018. https://doi.org/10.1523/ENEURO.0419-17.2018, 5, ENEURO.0419–17.

Olivier, J., Bell, M.L., 2013. Effect sizes for 2×2 contingency tables. PLoS One 8, e58777. https://doi.org/10.1371/journal.pone.0058777.

Parrott, J.M., Porter, G.A., Redus, L., O'Connor, J.C., 2021. Brain derived neurotrophic factor deficiency exacerbates inflammation-induced anhedonia in mice. Psychoneuroendocrinology 134, 105404. https://doi.org/10.1016/j.psyneuen.2021.105404 (Epub ahead of print).

Pelosof, R., Santos, L.A.D., Farhat, L.C., Gattaz, W.F., Talib, L., Brunoni, A.R., 2022. BDNF blood levels after electroconvulsive therapy in patients with mood disorders: An updated systematic review and meta-analysis. World J. Biol. Psychiatry 21, 1–10. https://doi.org/10.1080/15622975.2022.2058083.

Polacchini, A., Metelli, G., Francavilla, R., Baj, G., Florean, M., Mascaretti, L.G., Tongiorgi, E., 2015. A method for reproducible measurements of serum BDNF: comparison of the performance of six commercial assays. Sci. Rep. 5, 17989. https://doi.org/10.1038/srep17989.

Polyakova, M., Stuke, K., Schuemberg, K., Mueller, K., Schoenknecht, P., Schroeter, M.L., 2015. BDNF as a biomarker for successful treatment of mood disorders: a systematic & quantitative meta-analysis. J. Affect. Disord. 174, 432–440. https://doi.org/10.1016/j.jad.2014.11.044.

Polyakova, M., Schlögl, H., Sacher, J., Schmidt-Kassow, M., Kaiser, J., Stumvoll, M., Kratzsch, J., Schroeter, M.L., 2017. Stability of BDNF in human samples stored up to 6 months and correlations of serum and EDTA-plasma concentrations. Int. J. Mol. Sci. 18, 1189. https://doi.org/10.3390/ijms18061189.

Rocha, R.B., Dondossola, E.R., Grande, A.J., Colonetti, T., Ceretta, L.B., Passos, I.C., Quevedo, J., da Rosa, M.I., 2016. Increased BDNF levels after electroconvulsive therapy in patients with major depressive disorder: a meta-analysis study. J. Psychiatr. Res. 83, 47–53. https://doi.org/10.1016/j.jpsychires.2016.08.004.

Rosenthal, J.A., 1996. Qualitative descriptors of strength of association and effect size. J. Soc. Serv. Res. 21, 37–59. https://doi.org/10.1300/J079v21n04_02.

Schmidt, H.D., Duman, R.S., 2010. Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models. Neuropsychopharmacol 35, 2378–2391. https://doi.org/10.1038/npp.2010.114.

Schünemann, H.J., Higgins, J.P.T., Vist, G.E., Glasziou, P., Akl, E.A., Skoetz, N., Guyatt, G.H., 2022. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In Cochrane Handbook for Systematic Reviews of Interventions, version 6.3 (updated February 2022), Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., Welch, V.A., Eds., Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Serra-Millàs, M., 2016. Are the changes in the peripheral brain-derived neurotrophic factor levels due to platelet activation? World J. Psychiatry 6, 84–101. https://doi.org/10.5498/wjp.v6.i1.84.

Shi, Y., Luan, D., Song, R., Zhang, Z., 2020. Value of peripheral neurotrophin levels for the diagnosis of depression and response to treatment: a systematic review and meta-analysis. Eur. Neuropsychopharmacol. 41, 40–51. https://doi.org/10.1016/j.euroneuro.2020.09.633.

Shimizu, E., Hashimoto, K., Okamura, N., Koike, K., Komatsu, N., Kumakiri, C., Nakazato, M., Watanabe, H., Shinoda, N., Okada, S., Iyo, M., 2003. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol. Psychiatry 54, 70–75. https://doi.org/10.1016/s0006-3223(03)00181-1.

Taliaz, D., Stall, N., Dar, D.E., Zangen, A., 2010. Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. Mol. Psychiatry 15, 80–92. https://doi.org/10.1038/mp.2009.67.

Tsai, S.J., 2018. Critical issues in BDNF Val66Met genetic studies of neuropsychiatric disorders. Front. Mol. Neurosci. 11, 156. https://doi.org/10.3389/fnmol.2018.00156.

Ye, Y., Wang, G., Wang, H., Wang, X., 2011. Brain-derived neurotrophic factor (BDNF) infusion restored astrocytic plasticity in the hippocampus of a rat model of depression. Neurosci. Lett. 503, 15–19. https://doi.org/10.1016/j.neulet.2011.07.055.

Zhao, M., Chen, L., Yang, J., Han, D., Fang, D., Qiu, X., Yang, X., Qiao, Z., Ma, J., Wang, L., Jiang, S., Song, X., Zhou, J., Zhang, J., Chen, M., Qi, D., Yang, Y., Pan, H., 2018. BDNF Val66Met polymorphism, life stress and depression: a meta-analysis of gene-environment interaction. J. Affect. Disord. 227, 226–235. https://doi.org/10.1016/j.jad.2017.10.024.

Zhou, C., Zhong, J., Zou, B., Fang, L., Chen, J., Deng, X., Zhang, L., Zhao, X., Qu, Z., Lei, Y., Lei, T., 2017. Meta-analyses of comparative efficacy of antidepressant medications on peripheral BDNF concentration in patients with depression. PLoS One 12, e0172270. https://doi.org/10.1371/journal.pone.0172270.

Ziegenhorn, A.A., Schulte-Herbrüggen, O., Danker-Hopfe, H., Malbranc, M., Hartung, H. D., Anders, D., Lang, U.E., Steinhagen-Thiessen, E., Schaub, R.T., Hellweg, R., 2007. Serum neurotrophins–a study on the time course and influencing factors in a large old age sample. Neurobiol. Aging 28, 1436–1445. https://doi.org/10.1016/j.neurobiolaging.2006.06.011.

Zuccato, C., Cattaneo, E., 2009. Brain-derived neurotrophic factor in neurodegenerative diseases. Nat. Rev. Neurol. 5, 311–322. https://doi.org/10.1038/nrneurol.2009.54.