International Journal of Neuropsychopharmacology (2008), 11, 1169–1180. Copyright © 2008 CINP
doi:10.1017/S1461145708009309

REVIEW

CINP

A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression

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Abstract

Several clinical studies on major depressive disorder (MDD) have shown that blood brain-derived neurotrophic factor (BDNF) – a factor used to index neuroplasticity – is associated with depression response; however, the results are mixed. The purpose of our study was to evaluate whether BDNF levels are correlated with improvement of depression. We performed a systematic review and meta-analysis of the literature, searching Medline, Cochrane Central, SciELO databases and reference lists from retrieved articles for clinical studies comparing mean BDNF blood levels in depressed patients pre- and post-antidepressant treatments or comparing depressed patients with healthy controls. Two reviewers independently searched for eligible studies and extracted outcome data using a structured form previously elaborated. Twenty articles, including 1504 subjects, met our inclusion criteria. The results showed that BDNF levels increased significantly after antidepressant treatment (effect size 0.62, 95% CI 0.36–0.88, random effects model). In addition, there was a significant correlation between changes in BDNF level and depression scores changes ($p=0.02$). Moreover, the results were robust according to the sensitivity analysis and Begg's funnel plot results did not suggest publication bias. Finally, there was a difference between pre-treatment patients and healthy controls (effect size 0.91, 95% CI 0.70–1.11) and a small but significant difference between treated patients and healthy controls (effect size 0.34, 95% CI 0.02–0.66). Our results show that BDNF levels are associated with clinical changes in depression; supporting the notion that depression improvement is associated with neuroplastic changes.

Received 18 March 2008; Reviewed 28 May 2008; Revised 15 July 2008; Accepted 22 July 2008; First published online 28 August 2008

Key words: Blood levels, brain-derived neurotrophic factor, major depressive disorder, meta-analysis, neuroplasticity.

Introduction

Brain-derived neurotrophic factor (BDNF) is a neurotrophin related to neuronal survival, synaptic signalling and synaptic consolidation (Allen and Dawbarn, 2006). In neuropsychiatry, it has been associated with several disorders, such as substance-related disorders, eating disorders, mood disorders, schizophrenia, pain modulation and epilepsy (Gratacos et al., 2007; Koyama and Ikegaya, 2005; Ren and Dubner, 2007). Furthermore, several studies have been performed assessing BDNF levels in major depressive disorder (MDD) and showing important correlations between MDD and BDNF levels. Karege et al. (2002a) were the first to demonstrate that BDNF serum levels are lower in MDD patients compared to healthy controls. Subsequently, Aydemir et al. (2005) showed that BDNF levels increase after antidepressant treatment. Although most of the studies to date show that BNDF levels increase after antidepressant treatment, the results are mixed. One important question is whether changes in BDNF levels are specific to certain types of antidepressant treatments or whether BDNF levels are associated with general depression improvement. Therefore we aimed to systematically review the studies on BDNF and major depression to

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quantitatively analyse whether BDNF levels are associated with depression symptoms changes and whether they are different when comparing depressed vs. healthy subjects.

This study is important in addressing the relationship between BDNF levels and clinical changes in depression and therefore in assessing the mechanisms of action of antidepressant treatment, as BDNF is associated with neuroplastic changes (Duman and Monteggia, 2006).

We performed a systematic review and meta-analysis of BDNF studies to compare BDNF blood levels between depressed patients pre- and post-antidepressant treatment. We also performed comparisons between patients pre- and post-treatment vs. healthy subjects and we tried to identify, using meta-regression, the influence of other variables such as demographic and clinical factors.

Material and methods

Literature review

The first step was a literature search of the following databases: Medline, Cochrane and SciELO. In addition, we examined reference lists in retrieved papers, searched conference abstracts, and talked to clinical experts. To check for unpublished trials, we contacted experts in the field, consulted the CRISP database, and searched for abstracts. Two authors independently searched from the first date available up to 1 February 2008; we used the key search terms: 'depression' or 'depressive disorder' or 'depressed' vs. 'BDNF' or 'brain-derived neurotrophic factor', obtaining 461 articles; and also searched for the MESH terms 'depressive disorder' or 'depression' or 'depressive disorder, major' vs. 'brain-derived neurotrophic factor', obtaining 165 articles. Subsequently, we checked each article according to our inclusion criteria.

Selection criteria

We included prospective studies that evaluated BDNF blood levels in patients with major depression. We adopted the following inclusion criteria: (1) written in English; (2) studies that reported BDNF mean and standard deviation; (3) BDNF measurement in either serum or plasma; (4) clinical trials or case-control studies; (5) studies that compared BDNF blood levels across several groups were included whether two of them included either control or MDD patients pre- or post-treatment. We excluded series of cases and case reports.

Data extraction

For each study, data were extracted independently by two authors (A.R.B. and M.L), using a structured form. The discrepancies were resolved by consensus and the third author (F.F) consulted if needed. The following variables were extracted: (1) mean and standard deviation of the BDNF levels for each group; (2) demographic, clinical and treatment characteristics (e.g. number of patients, age, gender, previous use of medications, body mass index (BMI), scores in MDD scales, type of antidepressant treatment, duration of treatment); (3) characteristics of measurement (ELISA kit utilized); (4) study design (case-control vs. clinical trial).

When a study measured BDNF blood levels in two different time-points (Bocchio-Chiavetto et al., 2006; Piccinni et al., 2008; Yoshimura et al., 2007), we used the BDNF values after the longest time period. An exception occurred in the study of Piccinni et al. (2008), which had measured BDNF at 1, 3, 6 and 12 months after treatment, and we used only BDNF values measured at the first month, since we were interested in short-time response to treatment. Two studies of Deveci et al. (2007a,b) and one study of Aydemir et al. (2007) used the same study population, therefore only one article was included.

When the study did not report the mean and standard deviation of the BDNF levels, we deduced them from other parameters (Bocchio-Chiavetto et al., 2006; Yoshimura et al., 2007). We asked the groups of Monteleone et al. (2008) and Marano et al. (2007) for these BDNF values, since they were only reported in a graph. We also asked Marano et al. (2007) to exclude patients with bipolar disorder. Finally, we asked the group of Huang et al. (2008) how many weeks the patients were drug-free. We received the required responses in all cases. Moreover, all included articles were written in English. In fact we did not find studies in other languages. Ziegenhorn et al.'s (2007) study was not included in our meta-analysis, because, as stated by the authors, antidepressant medication was not reliably evaluated in the study, therefore it was not possible to differentiate between treated vs. untreated MDD patients.

Quality assessment

We performed individual and comprehensive quality assessment for each study, since most of them were non-controlled studies in which BDNF measurement was performed before and after a therapeutic intervention, without a placebo or sham arm; or case-control studies in which BDNF measurement was

performed in two independent samples (control group and depression group). (1) To assess for selection bias, we observed whether selected studies described selection criteria for healthy subjects and patients with depression and whether the case-control matching was described; (2) to assess for attrition bias, we looked for evidence of intention-to-treat analysis; and (3) we also assessed sources of heterogeneity across studies, and features contributing to between-study heterogeneity were further evaluated in our analysis. However, we observed that major features that contributed to heterogeneity were already expected a priori, and were related to previous antidepressant use and time period for second BDNF assessment, rather than clinical or demographic variables.

Quantitative analysis

All of our analyses were performed using Stata statistical software, version 9.0 (StataCorp, College Station, TX, USA). We initially calculated the standardized mean difference and the pooled standard deviation for each comparison. We used Cohen's d as a measure of the effect size. Then, we measured the pooled weighted effect size (weighted by the inverse variance of each study) using the random- and fixed-effects models. Heterogeneity was evaluated with χ^2 test. We also performed sensitivity analysis, cumulative regression and assessed publication bias using Begg-modified funnel plot and Egger's test (Egger et al., 1997).

Meta-regression was performed using the random-effects model modified by Knapp and Hartung (2003) and τ^2 variance was calculated by the method of the residual maximum likelihood. We tested the following variables: age and gender – treated as continuous variables; treatment administered – dichotomized as drug treatment and non-drug treatment; ELISA kit – dichotomized as Promega and R&D Systems (other kits were not evaluated); previous use of antidepressant drug was dichotomized in two different variables: variable 1 (drug-naive or drug-free for >4 wk and drug-free for <4 wk and using drugs) and variable 2 (drug-naive or drug-free for >2 wk and drug-free for <2 wk or using drugs); and baseline depression – dichotomized as mild/moderate and severe. For the classification of baseline depression, we used the cut-off points of Hamilton Depression Rating Scale and Montgomery–Asberg Depression Rating Scale standardized by the Clinical Global Impression, as proposed by Muller et al. (2003). Finally, we were not able to meta-regress BMI, depressive disorder duration, and previous number of depressive episodes because only a small number of studies reported these. We meta-regressed just one variable at a time.

We also performed two additional analyses, in which we compared depressed patients pre-treatment vs. healthy subjects and depressed patients post-treatment vs. healthy subjects using the same model that was previously described.

Results

Nineteen references met the inclusion criteria – out of 461 citations obtained in our initial search. Our subsequent search identified 17 references (out of 165); however, all of them had been previously identified. References were excluded mainly because of: (1) reviews; (2) studies assessing BDNF polymorphisms; (3) studies in animals; (4) studies measuring BDNF levels in other diseases or conditions; and (5) other topics. Some articles reported two datasets such as Yoshimura et al. (2007) and Lang et al. (2006); and Karege et al. (2005) and Piccinni et al. (2008) measured BDNF on both serum and plasma. Therefore 23 studies were included. Figure 1 shows the QUOROM diagram flow and details used to identify studies in our meta-analysis.

The clinical characteristics of the included studies are summarized in Table 1. Most of them used Promega ELISA kit (65%) for serum measurement (73%). There was also a balance between case-control and clinical trial studies (43% vs. 57%, respectively) and drug vs. non-drug therapies (58% vs. 42%, respectively). Mean and standard deviation of BDNF serum levels were 19.59 (6.92) in depressed patients pre-treatment, 25.78 (8.67) in patients post-treatment and 27.75 (8.8) in healthy subjects. Regarding previous antidepressant drug use before treatment, nine studies measured BDNF in drug-naive or drug-free (for >4 wk) subjects, whereas five studies measured subjects using drugs or who had stopped for <2 wk. Nine studies evaluated patients who had interrupted the use of drugs for >2 wk but <4 wk.

Comparison between MDD patients pre- and post-treatment

Characteristics of each study included in this main analysis are summarized in Table 2, showing that most of the studies used small samples of depressed subjects (median 21 patients; interquartile range 14–28), except for the studies of Huang et al. (2008) and Lee et al. (2007) that included 79 and 77 depressed patients, respectively. The pooled effect size comparing BDNF levels in MDD patients pre- and post-treatment using

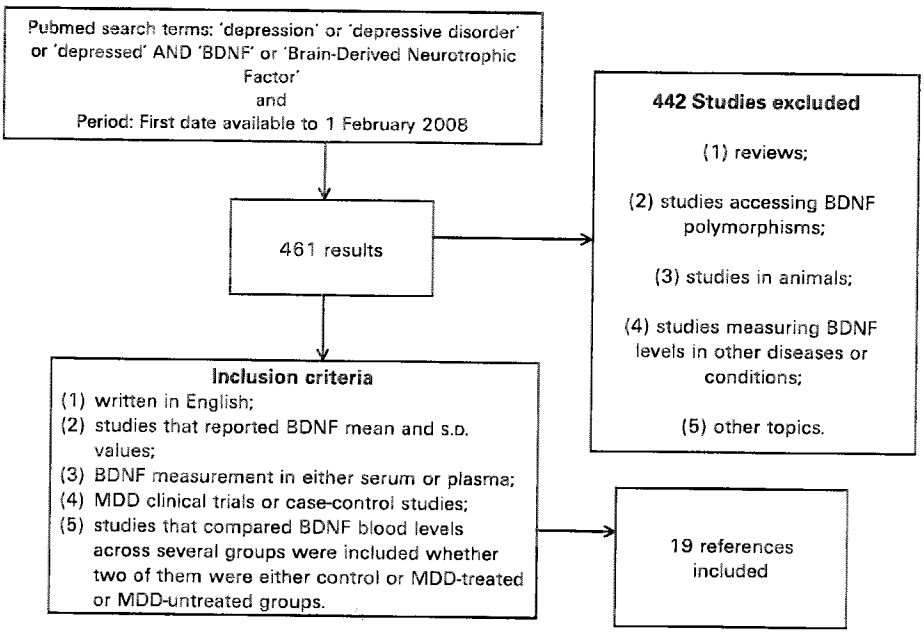

Figure 1. QUOROM trial flow used to identify studies for detailed analysis.

Table 1. Summary of all studies included in the analysis

	MDD		
	Pre-treatment	Post-treatment	Control group
Number of studies	23	17	17
Number of patients	553	335	549
Gender (M/F) (%)	35/65	35/65	38/62
Age, yr (mean ± s.d.)	42.88 (7.35)	44.64 (7.31)	37.5 (4.74)
BDNF (serum) (number of studies)	17	14	13
BDNF (serum) (mean ± s.d.)	19.59 (6.92)	25.78 (8.67)	27.75 (8.8)
BDNF (plasma) (number of studies)	6	3	4
BDNF (plasma) (mean ± s.d.)	1444 (1117)	2633 (2206)	2318 (2145)

BDNF, Brain-derived neurotrophic factor; MDD, major depressive disorder.

the fixed- and random-effects model were 0.54 (95% CI 0.39–0.70) and 0.62 (95% CI 0.36–0.88), respectively; however, since the test for heterogeneity was significant ($\chi^2 = 41.01$, $p = 0.01$) we used only the random-effects model in subsequent analyses. The Forest plot for this analysis is shown in Figure 2.

We performed a sensitivity analysis (Figure 3) in which one study is omitted at a time, showing that the results did not change significantly after the exclusion of any of them. The exclusion of the study of Gonul et al. (2005) would decrease the pooled effect size to 0.55 (95% CI 0.31–0.79), whereas the exclusion of the rTMS trial of Lang et al. (2006) would increase the pooled effect size to 0.67 (95% CI 0.42–0.92). A cumulative meta-analysis in which the cumulative pooled effect size at the time each study was published is calculated was performed – this analysis is interesting in analysing whether the initial studies overestimated the magnitude of the effect. The results of this analysis showed that the pooled effect size of earlier studies was significantly larger compared to recent studies. Indeed, after Yoshimura et al.'s (2007) study, the results became stable (see Figure S1, in online Supplementary material).

To assess publication bias, we performed the funnel plot (Figure 4) and Egger's test. As visually assessed, the 17 studies are symmetrically distributed in the funnel plot, according to sample size and effect size. Moreover, the p value for Egger's test was not significant ($p = 0.10$), supporting the view that the results of our meta-analysis are not likely to be a result of publication bias.

Table 3 shows the results of the meta-regression analysis of our main pairwise comparison (pre- and post-antidepressant treatment). Explanatory variables such as gender, baseline depression, case-control vs. clinical trials studies, ELISA kit utilized for blood measurement were not associated with the outcome.

We observed a trend for association between BDNF levels vs. age ($p=0.12$) and vs. antidepressant treatment ($p=0.08$). A significant association was observed between BDNF levels vs. (i) depression symptoms change ($p=0.02$); (ii) period of treatment ($p=0.01$); (iii) drug use with a 2-wk cut-off ($p=0.004$); and (iv) drug use with a 4-wk cut-off ($p=0.02$). We performed subgroup analyses comparing drug treatment vs. non-drug treatment studies and previous drug use at 2-wk and 4-wk cut-offs (online Figures S2 and S3 respectively). The association between BDNF change vs. depression change and vs. days of treatment are shown in Figure 5.

Other comparisons

The three pairwise comparisons of our meta-analysis are shown in Figure 6. We found that the pooled effect sizes from the random-effects model were 0.62 (95% CI 0.36–0.88) for patients with depression pre- and post-treatment; 0.91 (95% CI 0.70–1.11) for patients with depression pre-treatment vs. healthy subjects; and 0.34 (95% CI 0.02–0.66) for MDD patients post-treatment vs. healthy subjects. We also performed exploratory meta-regressions using the same explanatory variables previously mentioned for these last two comparisons; results are shown in Table S1 (online).

Discussion

The present study includes data from 10 case-control and 13 clinical trial studies, assessing 1504 subjects. Its main finding is that BDNF blood levels increase as depression is treated. In addition, BDNF levels are lower in patients with MDD pre-treatment than in controls, and BDNF levels are higher in MDD patients post-treatment than in healthy controls. The meta-regression reveals that BDNF levels are correlated with depression symptoms change, period of treatment and previous antidepressant use. Taken together, these results lend support to the concept that MDD treatment is associated with neuroplasticity, since BDNF is correlated with neuroplasticity (Ventimiglia et al., 1995). We further discuss these results based on some factors such as type of antidepressant treatment, method of assessment of BDNF levels and age.

An important consideration is the antidepressant treatment. Some studies tested non-pharmacological therapies such as repetitive transcranial magnetic stimulation (rTMS) (Lang et al., 2006; Yukimasa et al., 2006; Zanardini et al., 2006). Although it appears that pharmacological treatments induce greater changes in BDNF levels compared to non-pharmacological studies, when adjusting the main analysis for type of treatment (pharmacological vs. non-pharmacological treatment), the result of meta-regression was not significant ($p=0.08$). However, it is possible that this analysis was underpowered. There are some reasons that might explain this potential difference, since non-drug clinical trials were generally conducted in patients on pharmacological antidepressant treatment and the subsequent BDNF dosage was usually performed only 2–4 wk after treatment – a period that might be insufficient to detect BDNF changes; whereas pharmacological clinical trials generally enrolled patients who were not using antidepressants for at least 4 wk before the trial and assessed post-treatment BDNF levels during the period of 4–8 wk after treatment. Since these variables (previous use of medication and treatment interval) are correlated with change in BDNF levels, they might have played a significant role on this observed difference. Last, these studies used different types of antidepressant drugs and because the present study has no power to perform subgroup analyses on those, it is conceivable that antidepressant type is associated with the magnitude of induced neuroplastic changes and therefore contributes to the heterogeneity observed in this meta-analysis.

Given that there is a paucity of studies evaluating BDNF levels in plasma, we were not able to determine the optimal method for BDNF assessment in blood when we compared subjects pre- and post-treatment Some authors propose that *plasmatic* BDNF returns to basal levels when depressive symptoms remit, while, in contrast, *serum* BDNF levels increase, but do not reach baseline levels, when depression symptoms are remitted (Piccinni et al., 2008). In fact, Marano et al. (2007) showed a significant increase (up to 153%) in plasmatic BDNF levels after 7–22 d of electroconvulsive therapy (ECT), while Bocchio-Chiavetto et al. (2006) did not observe an increase in BDNF serum levels after 14 d ECT. Conversely, a study with 206 healthy subjects showed that BDNF serum levels tend to decrease when blood samples are stored for >6 months (Trajkovska et al., 2007). Along these lines, our meta-analysis, which included studies mainly assessing serum BDNF levels, showed that healthy individuals might have higher BDNF levels than depression-treated patients – although this difference is small. Further studies are necessary to evaluate whether BDNF plasma levels are more sensitive to acute or subacute depression symptoms change (compared to serum BDNF levels) or whether they are related to methodological issues.

Table 2. Characteristics of each study included in the main meta-analysis

First-named author (year)	Serum/ plasma	Age, yr (mean)	Gender (% male)	Sample size	Drug-free period (wk)	Treatment	BDNF pre-treatment, mean (S.D.)	BDNF post-treatment, mean (S.D.)	BDNF controls, mean (S.D.)
Shimizu (2003)	Serum	40.8	75%	16/17[a]	>4	AD drugs (various)	17.9 (9.6)	30.6 (12.3)	27.7 (11.4)
Aydemir (2005)	Serum	31.8	20%	10	>4	Venlafaxine (75–225 mg/d)	17.9 (9.1)	34.6 (7.1)	31.6 (8.6)
Gervasoni (2005)	Serum	40.5	42%	26	>4	AD drugs (various)	22.6 (3.6)	24.4 (3)	26.4 (3.6)
Gonul (2005)	Serum	35.5	25%	28	>4	AD drugs (various)	20.8 (6.7)	33.3 (9.89)	26.8 (9.3)
Aydemir (2006)	Serum	35.5	0%	20	>4	Escitalopram (10 mg/d)	27.68 (13.74)	38.57 (15.3)	41.16 (15.14)
Bocchio-Chiavetto (2006)	Serum	53	30%	23	<2	ECT	27.64 (9.13)	32.3 (7.76)	n.a.
Lang (2006) rTMS	Serum	46.2	n.a.	14	2–4[d]	rTMS	13.04 (3.9)	11.2 (5.8)	n.a.
Lang (2006) VNS	Serum	36.2	n.a.	10	<2	VNS	23.2 (5.8)	24.5 (4.5)	n.a.
Zanardini (2006)	Serum	55.94	31%	16	<2	rTMS	29.7 (8)	32.6 (7.6)	n.a.
Yukimasa (2006)	Plasma	52.9	42%	26	<2	rTMS	2530 (2010)	3110 (2000)	n.a.
Marano (2007)	Plasma	50	68%	10	<2	ECT	94.6 (68.5)	227.4 (207.6)	n.a.
Huang (2008)	Serum	37.3	23%	79	<2	AD drugs (various)	10.7 (7.3)	12 (8.9)	14.1 (7)
Yoshimura (2007) Paroxetine	Serum	48	38%	21	2–4	Paroxetine (20–40 mg/d)	9.1 (7.7)	19.3 (7.9)	23.4 (10.1)
Yoshimura (2007) Milnacipran	Serum	44	38%	21	2–4	Milnacipran (50–150 mg/d)	9.9 (9)	16.1 (8.2)	23.4 (10.1)
Piccinni (2008)	Serum	47	13%	15/9[b]	2–4	AD drugs (various)	19.3 (8.8)	22.1 (8.3)	33.6 (8.6)
Piccinni (2008)	Plasma	47	13%	15/9[b]	2–4	AD drugs (various)	2900 (1900)	4448 (2095)	5400 (2300)
Monteleone (2008)	Serum	45.7	18%	11/24[b]	2–4[c]	AD drugs (various)	29 (15.9)	29.4 (11.9)	42.5 (12.5)

AD, Antidepressant; ECT, electroconvulsive therapy; BDNF, brain-derived neurotrophic factor; MDD, major depressive disorder; rTMS, repetitive transcranial magnetic stimulation; VNS, vagal nerve stimulation.

[a] Case-control studies.

[b] Six patients dropped-out in the second assessment.

[c] Four patients were drug-treated and seven were drug-free.

[d] Seven patients were drug-treated and seven were drug-free.

The following studies were not included in this table because they did not assess patients with depression before and after treatment: Karege et al. (2002a, 2005), Aydemir et al. (2007), Lee et al. (2007) and Kim et al. (2007).

A trend for a differential effect was also observed for age ($p=0.12$). Lommatzsch et al. (2005) observed a small correlation ($r=-0.20$) between age and BDNF in a cohort of 140 healthy subjects, while Ziegenhorn et al. (2007) also observed a similar correlation ($r=-0.15$) in a cohort of 250 elderly (>70 yr) individuals, whereas Trajkovska et al. (2007) did not observe a correlation of age in their sample, which was not composed of elderly people. Supposedly, brain BDNF expression decreases in specific brain regions during the normal ageing process (Lommatzsch et al., 2005). It is possible that the lack of significance in the correlation between changes in BDNF levels and age in our study is because our analysis was underpowered.

Limitations

Although the clinical characteristics of the patients were fairly similar regarding age, gender and baseline

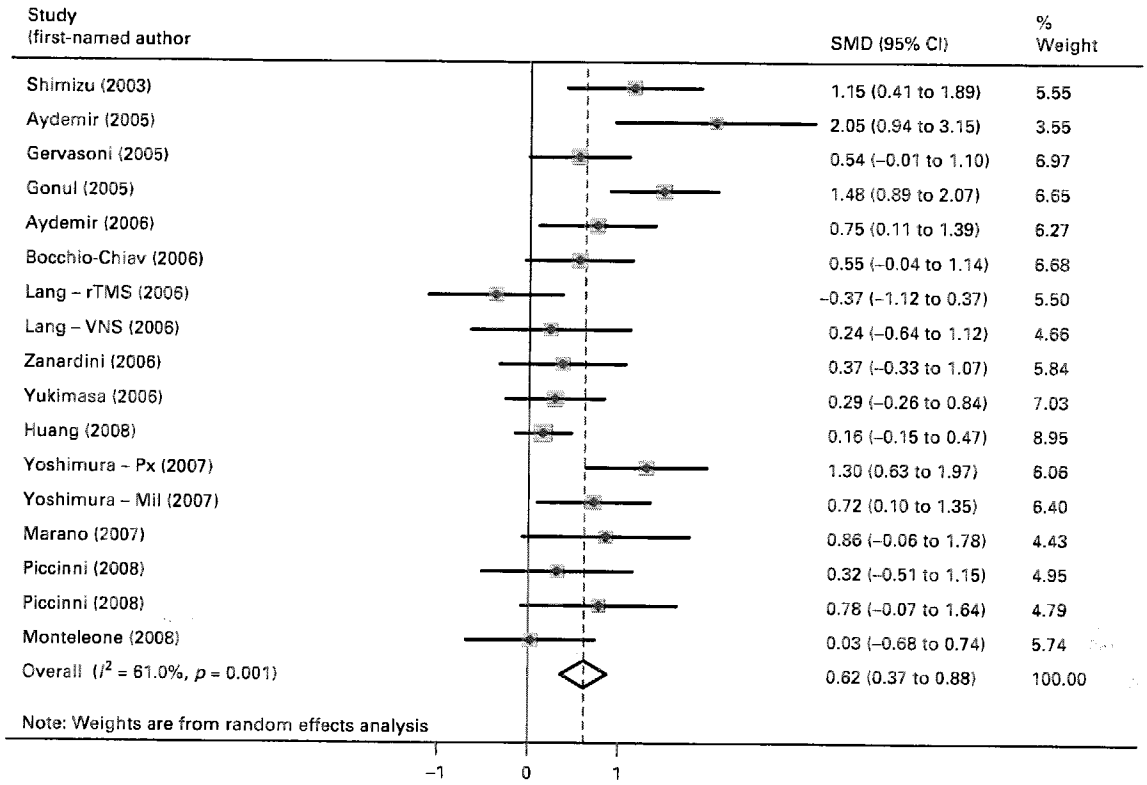

Figure 2. Forest plot showing effect sizes from the random effects model. A negative effect indicates BDNF blood levels after treatment are lower than before. Effect sizes are Cohen's *d* (standardized mean difference), error bars represent the 95% confidence interval. Px, Paroxetine; Mil, milnacipran.

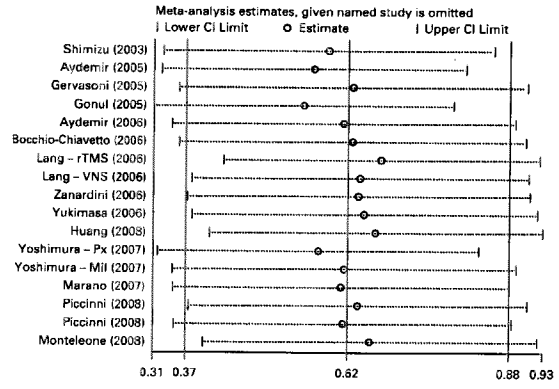

Figure 3. Assessment of the individual influence of each study. The change in the overall effect size and 95% confidence interval for the meta-analysis after eliminating the indicated study is shown. Effect size are Cohen's *d* (standardized mean difference), error bars represent the 95% confidence interval. Px, Paroxetine; Mil, milnacipran.

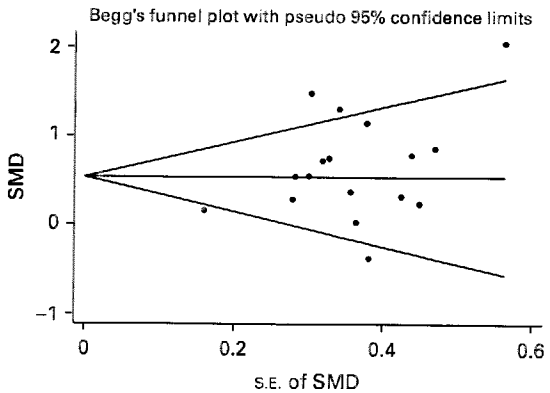

Figure 4. Funnel plot (publication bias assessment) of the effect size (Cohen's *d*) according to their standard errors. The horizontal solid line is drawn at the pooled effect size, and angled lines represent the expected 95% confidence interval for a given standard error, assuming no between-study heterogeneity. SMD, standardized mean difference.

depression, the majority of studies enrolled a small number of subjects, used different ELISA kits to measure BDNF, different depression scales, included patients using various drugs [selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants]

Table 3. Meta-regression results in which several explanatory variables were analysed through simple linear regressions, which allows comparison of the relative strengths of each variable

Explanatory variables	Variable model	d.f.	Coef. *B* unstandardized	95% CI of unstandardized *B*	Coef. *B* standardized	*p*
ELISA kit	Categorical (PROMEGA vs. R&D Systems)[a]	13	−0.07	−0.92 to 0.76	−0.08	0.84
Blood measurement	Categorical (serum vs. plasma)	15	−0.3	−0.83 to 0.76	−0.01	0.92
Study design	Categorical (case-control vs. clinical trial)	15	0.05	−0.88 to 0.98	0.04	0.91
Age	Continuous (yr)	15	−0.03	−0.07 to 0.01	−0.49	0.12
Gender	Continuous (% males)	13	0.47	−1.11 to 2.05	0.13	0.53
Baseline depression	Categorical (moderate vs. severe)	15	−0.08	−0.67 to 0.51	−0.12	0.77
Drug-free period[b]	Ordinal (>4 wk vs. <4 wk)	12	0.85	0.18 to 1.52	0.66	**0.02**
Drug-free period[b]	Ordinal (>2 wk vs. <2 wk)	12	0.80	−1.22 to -0.37	−0.69	**<0.01**
Depression response[b]	Continuous (Cohen's *d*)	12	0.23	0.04 to 0.41	0.65	**0.02**
Period of treatment[b]	Continuous (d)	12	0.02	0.01 to 0.03	0.52	**0.01**
Antidepressant treatment[b]	Categorical (drug vs. non-drug)	12	0.54	−0.08 to 1.16	0.65	0.08

D.f., Degrees of freedom; Coef. *B* unstandardized, the non-standardized regression coefficient of each linear regression, representing the slope of each model; 95% CI, the confidence interval for the β coefficient; Coef. *B* standardized, the regression coefficients standardized by z scores, which allows comparison of the relative strengths of each variable.
Bold values represent significant results at $p<0.05$.
[a] Other kits were not included.
[b] Meta-regression performed in clinical trials studies.

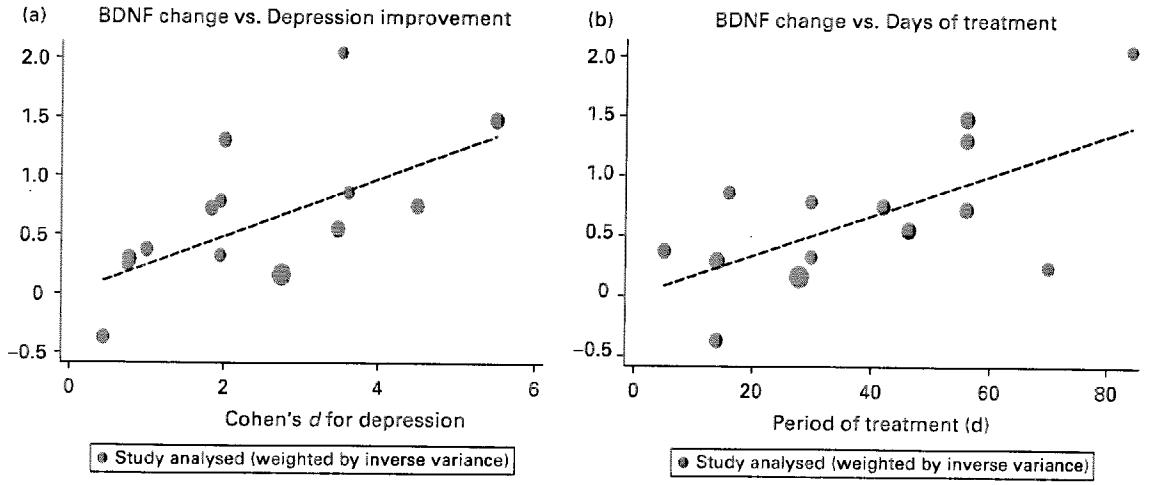

Figure 5. (a) BDNF change (effect size, Cohen's *d*) compared to depression change (effect size, Cohen's *d*). (b) BDNF change compared to days of treatment. Constant is supressed because there is neither BDNF change nor depression change at the begining of treatment.

and studies using different non-pharmacological interventions (ECT, rTMS, vagal nerve stimulation) therapies. Therefore, an important limitation of this meta-analysis is that the heterogeneity test that addresses whether effect sizes from different studies are estimates from the same population was significant.

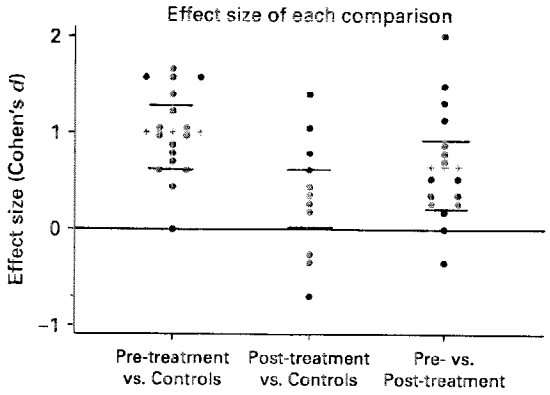

Figure 6. The effect size of each comparison performed is summarized in this table. Grey, small dots represent each comparison effect size, grey pluses are the pooled effect size, and lines represent 95% Confidence Interval. Effect sizes are Cohen's d (standardized mean difference).

To deal with this, we used a random-effects model to calculate the pooled effect size, which is used when heterogeneity is significant. Moreover, sensitivity analysis did not show that our results were driven by a particular study as the exclusion of any of them would not change the results. Further, Begg's funnel plot did not detect a publication bias and showed a fairly symmetrical distribution. Finally, we explored heterogeneity through meta-regression on variables such as antidepressant treatment and ELISA kits that could be responsible for heterogeneity.

MDD, neuroplasticity and BDNF

The understanding of MDD has constantly changed. The observation that tricyclic antidepressants and, later, SSRI drugs can treat depression and increase catecholamines at the synaptic site gave rise to the monoamine hypothesis of depression, a notion where MDD is related to serotonin, norepinephrine and/or dopamine deficiencies and its restitution to normal levels would be associated with alleviation of depression symptoms (Leonard, 2000). Although the monoamine hypothesis was the main hypothesis for depression in the 1980s and mid 1990s, subsequent studies demonstrated that depletion of serotonin and norepinephrine precursors did not decrease mood in healthy subjects, however, a decrease in mood was observed in patients with MDD in remission (Delgado, 2000). In fact, a meta-analysis of monoamine depletion studies showed that monoamines alone are not sufficient to cause depression, and that depression does not have a direct causal relation with monoamine depletion (Ruhe et al., 2007). Conversely, the observation that antidepressants have a time lag for therapeutic action suggests that changes in synaptic connectivity might be required, since three meta-analyses of neuroimaging studies showed that amygdala in patients with MDD present volume loss that increases after antidepressant treatment (Hamilton et al., 2008) as well as lower hippocampal volume that is associated with depression (Campbell et al., 2004; Videbech and Ravnkilde, 2004) – moreover, hippocampal and hypothalamic–pituitary–adrenal axis dysfunction is associated with significant depressive symptoms, such as memory deficit and cognitive impairment (Duman and Monteggia, 2006).

Preclinical studies show that antidepressant increases BDNF expression in rats and cell cultures (Alme et al., 2007; Balu et al., 2008; Henkel et al., 2008). The clinical studies included in our meta-analysis also showed an increase in BDNF blood levels due to MDD treatment. Because BDNF is related to neuroplasticity, our findings give additional support to the critical role of neuroplasticity on the pathophysiology of major depression. In fact, decreased BDNF expression is associated with reduced synaptic plasticity and neuronal atrophy (Kuipers et al., 2003) while increased BDNF expression is associated with neuronal survival and differentiation (Ventimiglia et al., 1995). In addition, BDNF is particularly associated with the late phases of long-term potentiation (LTP), the property of neurons in increasing synaptic strength (Gartner and Staiger, 2002), which evolves protein synthesis and de-novo gene expression (Bramham and Messaoudi, 2005). Therefore, in the neurotrophin hypothesis of depression, MDD leads to atrophy of specific brain areas, such as amygdala and hippocampus, that is reversed after antidepressant treatment – hence, neuroplasticity should occur in these sites. The bridging link between pharmacological (and non-pharmacological) treatments and neurogenesis is seen by the actions of neurotrophins such as BDNF, which might be a 'final common pathway' for several types of antidepressant treatment (Kempermann and Kronenberg, 2003). Our results showing that BDNF levels increase in MDD patients during antidepressant treatment are in line with the neurotrophin hypothesis, as an increase in BDNF levels indicates increased neuronal survival and differentiation, therefore, reversing, at least partially, the reduced synaptic plasticity associated with major depression.

An important issue of clinical studies is whether BDNF blood levels are related to BDNF brain levels; i.e. whether BDNF can cross the blood–brain barrier (BBB). Pan et al. (1998) demonstrated that peripheral BDNF crosses the BBB by a transport system, whereas

Karege et al. (2002b) showed a positive correlation between serum and cortical levels in rats. However, other studies suggest that BDNF crossover of the BBB is minimal if not conjugated to specific vectors (Wu, 2005). Moreover, blood BDNF is stored in platelets, and lower serum BDNF levels in depressed patients might be related to lowered platelet release (Karege et al., 2005). Therefore, further studies are warranted to investigate whether BDNF blood levels directly reflect BDNF brain metabolism.

Clinical and research implications

Our study suggests there is an increase in neuroplasticity induced by antidepressant treatment that is indexed to BDNF blood levels. Neuroimaging studies in MDD patients directly relating change in BDNF blood levels to an increase in the volume of hippocampus and amygdala would support the idea that BDNF blood levels reflect brain activity. Further, in clinical research, BDNF could be used together with depression rating scales to address the efficacy of an antidepressant therapy.

Our study also shows preliminary findings regarding the optimum parameters to assess BDNF levels. It appears that its accuracy is maximized in patients who are antidepressant drug-free for >2 wk and, ideally, for >4 wk. In addition, optimum results might be obtained when post-treatment BDNF levels are assessed 4–8 wk after treatment onset. However, other important parameters in BDNF measurement, such as menstrual cycle and physical activity, (Begliuomini et al., 2007; Winter et al., 2007), were not assessed in our meta-analysis.

Conclusions

The present meta-analysis supports the neurotrophin hypothesis of depression suggesting that MDD improvement is associated with neuroplasticity. Our findings showing that different antidepressant treatments are associated with an increase in BDNF suggest that this neuropeptide might be a 'final common pathway' in MDD treatment and encourage further BDNF studies on major depression to explore its role in neurogenesis and neuroplasticity.

Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org).

Acknowledgements

None.

Statement of Interest

None.

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