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ORIGINAL ARTICLE

Chronic depression is associated with a pronounced decrease in serum brain-derived neurotrophic factor over time

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One of the leading neurobiological hypotheses on depression states that decreased expression of brain-derived neurotrophic factor (BDNF) contributes to depression. This is supported by consistent findings of low serum BDNF levels in depressed patients compared with non-depressed controls. Whereas it has been generally assumed that this is a state characteristic of depression, strong inferences about state or trait effects require a longitudinal study design. To investigate the longitudinal association between serum BDNF and depression, we measured serum BDNF, (current and past) depression status, use of antidepressants, and all potential covariates at baseline and after 2 years in 1751 individuals, consisting of patients with an incident ($n = 153$), remitted ($n = 420$) and persistent depression ($n = 310$) and non-depressed controls ($n = 868$). We analyzed change/differences in serum BDNF across these four groups with analyses of covariance adjusted for covariates and baseline BDNF value, together with the effects of starting and stopping antidepressant treatment. Our analyses revealed a significant difference for the depression course groups ($P = 0.007$). Compared with non-depressed controls, persistently depressed and remitted patients had a steeper decrease of BDNF levels over time (−1.33 ($P = 0.001$) and − 0.97 ng ml^{-1} ($P = 0.011$), respectively), whereas BDNF reductions in patients with incident depression were similar to those in healthy controls. Initiation or discontinuation of antidepressants was not associated with BDNF change ($P = 0.72$). These findings suggest that BDNF not only contributes to depression, but that depression in turn may also contribute to low BDNF.

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INTRODUCTION

According to the neurotrophic hypothesis of depression, stress leads to a lack of neurotrophic support, which insufficiency increases the vulnerability to depression.[1] Depression often presents with a chronic or intermittent course.[2,3] Each recurrence seems to increase the likelihood of further recurrences,[4] implicating that eventually even small stressors can elicit a new episode. Stress-related neurobiological changes may be underlying this 'kindling' effect,[5] so that long-term changes in the stress response of depressed patients can be notably different from the state-related changes early in the course of depression. Despite a multitude of papers on the aversive effects of stress on neurotrophy, studies on chronic recurrent depression are underrepresented even though long-term changes in the stress response of depressed patients can be notably different from the state-related changes early in the course of depression. For instance, there are indications that the higher HPA-axis response in depressed patients eventually shifts toward a blunted response in chronically depressed patients.[6] Studies comparing first versus recurrent episodes of depression are underrepresented in the literature on the neurotrophic hypothesis, however, and it is hence relevant to extend with longer-term studies of chronic depression.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors and is involved in the plasticity of neurons in several brain regions. The neurotrophic hypothesis is supported by consistent findings of lower serum BDNF concentrations in depressed patients compared with non-depressed controls.[7] Recently, we addressed the question whether low BDNF is a state or a trait characteristic and showed that BDNF was lower in currently depressed patients compared with patients with a remitted depression.[8] On the basis of this result, we tentatively concluded that low serum BDNF levels are a state characteristic of depression. Nevertheless, it remains unknown whether these lower values occurred before the onset of depression, as the neurotrophic hypothesis implies, or become lower during the depressed state. In the current study, we extend our findings with longitudinal data, allowing a comparison of serum BDNF levels of in patients with persistent, remitted and incident depression. Longitudinal serum-BDNF studies largely consist of open-label medication trials with a 12-week pre-post design, mainly confirming that low BDNF is a state rather than a trait characteristic of depression.[7] These designs, however, cannot disentangle effects of medication and course. To our knowledge, only one study examined fluctuations in serum BDNF levels during the natural course of depression, with results showing that BDNF increased with remission and decreased again with the recurrence of depression, confirming the hypothesis that low BDNF is a state effect.[9] As that study only included 20 participants who were

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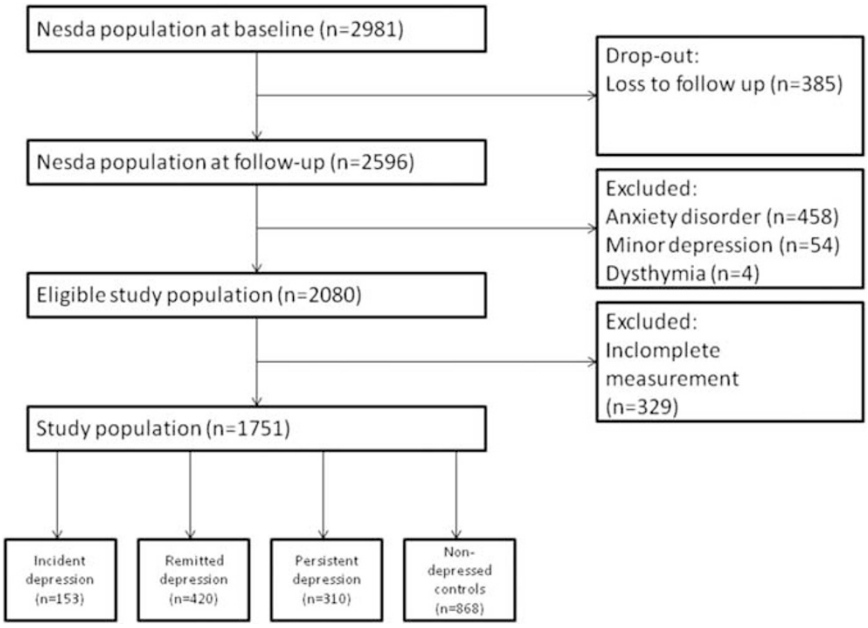

Figure 1. Flowchart of selection process of study population.

selected from a larger study based on their clinical course (depressed, remitted and relapsed), replication with more patients and different courses is warranted.

In the current study, we therefore investigate the longitudinal association between serum BDNF and depression in a large cohort ($n = 1751$). On the basis of the emerging evidence regarding state-linked BDNF in depression, we hypothesize that BDNF levels will decrease when non-depressed individuals go into depression and that levels will increase when depressed patients go into remission. Notwithstanding that we are the first to compare longitudinal data of persistently depressed patients with data of individuals in a non-depressed state, our logical expectations would be that BDNF would further decrease in persistently depressed patients.

MATERIALS AND METHODS

Patients and sample collection

Patient data were obtained from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study on the long-term course and consequences of depression and anxiety. Full details on NESDA's rationale, objectives and protocol are described by Penninx *et al.*[10] In brief, NESDA is a multi-site naturalistic prospective cohort study ($N = 2981$) aimed at describing the 8-year course and consequences of depressive and anxiety disorders and to integrate biological and research paradigms within an epidemiological approach. Study participants were recruited from mental health care, primary care and the general population to secure different stages of psychopathology, that is, patients with a current or remitted depressive and/or anxiety disorder (78%), and healthy controls (22%). Exclusion criteria were insufficient command of the Dutch language or having a primary other psychiatric disorder (e.g., psychotic, bipolar, obsessive compulsive or severe alcohol use disorder). Current or remitted depressive and anxiety states were established at baseline and at a 2-year follow-up using the Composite International Diagnostic Interview (CIDI; version 2.1). Collected by specially trained researchers, the data cover a wide range of domains, among which are demographics, psychopathology, public health consequences of mental disorders, and biological and genetic measures. The study was approved by the Ethical Review Boards of all participating centers. All participants provided written informed consent.

The present study drew on the NESDA baseline and 2-year follow-up data of 1751 participants who had completed both measurements and fulfilled our criteria (see Figure 1 for details on the selection process), that is, the presence of a major depressive disorder (MDD) at baseline or follow-up. Participant data were divided into four groups (see Results for numbers), with the first, the *incident depression* group, consisting of patients with a 6-month diagnosis of MDD at follow-up, but not at baseline. The second, the *remitted depression* group, included patients with a 6-month diagnosis of MDD at baseline but not at follow-up. The third, *the persistent depression* group, incorporated patients with a 6-month MDD diagnosis at both baseline and follow-up, while the final group comprised *non-depressed controls,* that is,. individuals who had (i) no diagnosis of MDD at baseline or follow-up, (ii) no current anxiety disorder 6 months preceding baseline or follow-up, and (iii) no minor depressive episode/dysthymia based on the CIDI interview at baseline and follow-up.

Antidepressant use

Use of antidepressants was by self-report and checked through container observation. We defined antidepressant use as the minimal daily dose as recommended by the World Health Organization of selective serotonin reuptake inhibitors (ATC code N06AB), tricyclic antidepressants (ATC code N06AA) and serotonergic and noradrenergic reuptake inhibitors (ATC code N06AF/AX).

The effect of antidepressants on BDNF levels was estimated by creating four groups similar to the depression groups, that is, *ex-users* (antidepressant at baseline, not at follow-up, $n = 128$), *new users* (antidepressant at follow-up, not at baseline, $n = 78$), *persistent users* (antidepressants at baseline and follow-up, $n = 244$) and *persistent non-users* (no antidepressants at either baseline or follow-up, $n = 1265$).

Post-hoc, we extended this categorization by including information on the change in (type of) antidepressant usage in terms of continued (non) use, initiation or discontinuation of selective serotonin reuptake inhibitors, serotonergic and noradrenergic reuptake inhibitors, and tricyclic antidepressants, and all possible drug switches.

Clinical features

Phenotypic characteristics-Depression symptom severity was determined using the Inventory of Depressive Symptoms.[11] Age of depression onset was established with the CIDI. Additionally, we assessed depression duration, expressed as a percentage of the total time 'of being depressed,' between the first and the second measurement using the life chart method.[12] The insomnia rating scale was used as a reliable indicator of sleep disturbances.[13] On the basis of the CIDI 2.1 interview, comorbid anxiety was considered present when there was a confirmed diagnosis in the last 6 months of a generalized anxiety disorder, a panic disorder (with or without agoraphobia) or a social phobia.

Psychological stressors

Childhood abuse was assessed retrospectively using a semi-structured childhood trauma interview, previously used in the Netherlands Mental Health Survey and Incidence study.[14] As a measure for the amount of stress between baseline and follow-up, the occurrence of 12 stressful life events was assessed using the List of Threatening Events Questionnaire, which has a good test-retest reliability and a high agreement with interview-based ratings.[15,16] Stressful events were divided into positive and negative experiences (e.g., marriage and death of a relative, respectively). Answers were coded as the total number of life events.

BDNF assessment

Blood (50 ml) was extracted from the brachial vein in the morning after an overnight fast, processed within an hour and consequently stored at − 85 °C. After the assessment waves were finalized, both baseline and follow-up samples were measured at the same location that is, the Department of Psychiatry and Neuropsychology at Maastricht University Hospital (the Netherlands) using the same assay (Emax ImmunoAssay system (Promega, Madison, WI, USA)) according to the manufacturer's protocol on both occasions (for details, also *see Bus et al.*[17,18]). Greiner Bio-One (Alphen a/d Rijn, The Netherlands) high affinity 96-well plates were used and the resulting absorbance was read in duplicate at 450 nm using a Bio-Rad Benchmark microplate reader (Veenendaal, The Netherlands) for baseline samples and a Perkin Elmer 2030 Multireader Victor X3 (Waltham, MA, USA) for the follow-up. All baseline and follow-up samples were measured in duplicate with another duplicate containing only buffer on each plate to assess the unspecific absorption binding, that is, background. The (mean) background value was subtracted from all measured values on each plate. The background was maximally 50% of the measured absorption of the minimum amount of BDNF of the standard curve containing 7.8 pg ml^{-1}. The assay sensitivity threshold was ascertained at 1.56 ng ml^{-1} reflecting the minimum level of BDNF in the serum that could be reliably determined. The inter-assay coefficients of variance were determined to range from 0.2 to 9.6% at this follow-up compared with 2.9 to 8.1% at baseline. Measures of the intra-assay variance in the present follow-up study resulted in coefficients of variance of 0.53–7.5% and 0.0–3.1% at baseline. Of note, this is well below the maximum intra-assay variance of 8.8% as specified by the manufacturer.

In order to investigate the change in BDNF levels, a variable was created by subtracting the baseline from the follow-up value, with a positive resultant value reflecting an increase and a negative value a decrease in BDNF.

Covariates

On the basis of previous research of the baseline sample, potential variance due to comorbid anxiety, age, gender, sample storage time, time of sampling, fasting status at time of measurement, smoking behavior and drinking behavior was taken into account.[17,18] Age and gender were entered into the analyses without further changes, but for other covariates, we created variables that coded for change. A covariate was included for fasting behavior indicating whether a participant had adhered to the pretest fasting protocol. Smoking behavior was coded as smokers versus non-smokers. The frequency of alcohol use was evaluated by the Alcohol Use Identification Test,[19] with problematic alcohol use being coded as present when more than 13 (female participants) or 15 units (male participants) of alcohol a week were consumed.

Statistical analysis

BDNF levels were normally distributed, but both the baseline ($n = 15$) and the follow-up measurement ($n = 9$) contained several outliers, that is, levels three standard deviations (s.ds.) above the mean. To prevent results from being driven by these potentially influential cases, all BDNF levels exceeding three s.ds. of the respective mean were trimmed to the +3 s. d. value. Values below the sensitivity threshold (baseline: $n = 4$; follow-up: $n = 58$) were recoded to the 1.56 ng ml^{-1} level as they are likely to reflect a 'true' low level with the exact value remaining indeterminable.

Analyses of variance and χ^2 tests were used to evaluate group differences on demographic variables and the covariates. The within-subject correlation between the baseline and follow-up BDNF measures was determined by calculating the Pearson coefficient.

To determine whether a different course of depression would coincide with a difference in change in BDNF, analyses of covariance were used with the change in BDNF levels as the dependent variable in the four depression categories and the change in antidepressant use as independent variables. Contrasts were calculated for the three depression groups and the non-depressed controls. The baseline BDNF value was added as a covariate to correct for the potential occurrence of regression to the mean, with all analyses being fully corrected for all previously mentioned covariates. As covariates can change within individuals in the course of 2 years and because these changes may influence BDNF, we took possible changes in covariates into account by using change variables; for continuous variables, we subtracted the baseline from the follow-up value and for categorical variables we entered a variable that indicated whether participants had moved from one category to another.

The same model was repeated by replacing the antidepressant variable with an extended version in which we coded all possible longitudinal changes in antidepressant classes.

Using several multiple linear regression analyses, we further explored the impact of phenotypic clinical characteristics and psychosocial stressors on the course of BDNF in patient groups where the course of serum BDNF level over the 2-year period significantly differed from that obtained for the non-depressed controls. In these models, we used change in BDNF as the dependent variable. The baseline BDNF value, age, gender, smoking behavior and alcohol use were entered as covariates. For the inventory of depressive symptom and insomnia rating scale sum scores, a change variable (follow-up value minus baseline value) was used. Dummy variables were created to analyze the change in comorbid anxiety. For each clinical characteristic under study, a separate model was calculated. Hence a total of 16 multiple linear regression analyses were performed. Correcting for multiple comparisons is controversial, with some arguing against such procedures because they increase the risk of type II errors.[20] However, we have also indicated in the table the *P*-values that remained significant ($P = 0.0031$; i.e. 0.05/16) following Bonferoni correction for multiple testing.[21]

All computations were performed with SPSS version 20 (IBM, Chicago, IL, USA). A two-tailed α level of 0.05 was used to determine statistical significance.

RESULTS

Study sample

Of the 1751 participants, 153 were categorized in the incident depression group, 420 in the remitted depression group and 310 in the persistent depression group, whereas 868 were classified as non-depressed controls. Of the total sample, 1137 (64.9%) participants were women and the mean age was 44.4 (s.d. 13.3) years. A more detailed overview of our study population and depression course group differences in demographics are given in Table 1. Overall, mean serum BDNF levels were lower at follow-up than at baseline (mean 9.0 ng ml^{-1} (s.d. 3.3 ng ml^{-1}) versus 7.9 ng ml^{-1} (s.d. 5.1 ng ml^{-1})). Statistically, baseline and follow-up BDNF values did not correlate significantly ($r = -0.04$; $P = 0.10$).

Course of depression and effect of antidepressant change

Longitudinal analyses of covariance, fully adjusted for covariates and regression to mean, revealed a significant group difference in the change in BDNF levels ($F = 4.097$; df(3); $P = 0.007$) for the different courses of depression.

Post hoc contrast estimates revealed that BDNF had decreased during the 2-year interval in all groups. Compared with the non-depressed controls, the chronically depressed patients and the remitted patients showed a steeper decrease in BDNF concentrations over time (−1.33 ($P = 0.001$) and − 0.97 ng ml^{-1} ($P = 0.011$), respectively). Comparison of the incident depression group and the non-depressed controls ($P = 0.60$) did not yield a significant difference. The results are illustrated in Figure 2.

No significant differences were found in BDNF changes and (changes in) antidepressant use ($F = 0.441$; df(3); $P = 0.72$). A further exploration of the effect of the various classes of antidepressants on BDNF change revealed that there was no significant group effect ($F = 0.426$; df(11); $P = 0.95$). When contrasts were calculated comparing each of the possible switches between types of

Table 1. Demographic and clinical characteristics

	Incident depression (n = *153*)	*Remitted depression* (n = *420*)	*Persistent depression* (n = *310*)	*Non-depressed controls* (n = *868*)	P
Demographics and covariates					
Age (s.d.)	44.1 (12.9)	42.9 (12.5)	44.9 (11.9)	44.9 (14.2)	0.17
% female (*n*)	75.2 (115)	64.3 (270)	65.2 (202)	63.4 (550)	0.05
BDNF ng ml^{-1}—*baseline* (s.d.)	8.85 (3.59)	8.89 (3.25)	9.45 (3.63)	9.02 (3.14)	0.11
BDNF ng ml^{-1}—*follow-up* (s.d.)	8.31 (5.59)	7.49 (5.26)	6.98 (4.04)	8.35 (5.19)	< 0.001
% with comorbid anxiety—*baseline* (*n*)	47.7 (73)	59.8 (251)	67.1 (208)	NA	< 0.001[a]
% with comorbid anxiety—*follow-up* (*n*)	55.6 (85)	30.5 (128)	57.4 (178)	NA	< 0.001[a]
Days of sample storage—*baseline* (s.d.)	1333 (228)	1274 (223)	1268 (220)	1293 (222)	0.01
Days of sample storage—*follow-up* (s.d.)	1289 (224)	1241 (226)	1236 (220)	1262 (223)	0.07
Time of sampling (minutes after 6am)—*baseline* (s.d.)	165 (15)	166 (16)	167 (21)	167 (15)	0.72
Time of sampling (minutes after 6am)—*follow-up* (s.d.)	171 (22)	173 (28)	176 (33)	171 (31)	0.08
% adhered to fasting protocol—*baseline* (*n*)	99.3 (152)	97.6 (410)	95.5 (296)	96.8 (840)	0.16
% adhered to fasting protocol—*follow-up* (*n*)	94.8 (145)	92.9 (390)	92.6 (287)	94.4 (819)	0.65
% smokers—*baseline* (*n*)	40.5 (62)	38.8 (163)	43.5 (135)	29.8 (259)	< 0.001
% smokers—*follow-up* (*n*)	33.3 (51)	33.6 (141)	40.6 (126)	24.1 (209)	< 0.001
% with problematic alcohol use—*baseline* (*n*)	5.2 (8)	7.2 (30)	10.0 (31)	3.2 (28)	< 0.001
% with problematic alcohol use—*follow-up* (*n*)	6.5 (10)	5.5 (23)	10.6 (33)	3.8 (33)	< 0.001
% duration of depressive complaints between baseline and follow-up (s.d.)	43.1 (31.3)	28.7 (34.1)	54.7 (31.4)	0 (0)	< 0.001
IDS sum score—*baseline* (s.d.)	21.5 (10.1)	28.9 (12.0)	35.1 (12.3)	9.8 (7.8)	< 0.001
IDS sum score—*follow-up* (s.d.)	23.7 (11.4)	17.0 (10.9)	28.5 (12.9)	8.0 (6.7)	< 0.001
Use of antidepressants					
% taking an antidepressant—*baseline* (*n*)	21.6 (33)	42.1 (177)	46.5 (144)	4.7 (41)	< 0.001
% taking an antidepressant—*follow-up* (*n*)	30.1 (46)	29.8 (125)	42.9 (133)	4.8 (42)	< 0.001
% taking an SSRI—*baseline* (*n*)	15.7 (24)	29.0 (122)	30.6 (95)	3.6 (31)	< 0.001
% taking an SSRI—*follow-up* (*n*)	21.6 (33)	19.0 (80)	20.6 (64)	3.8 (33)	< 0.001
% taking an SNRI—*baseline* (*n*)	4.6 (7)	7.6 (32)	17.1 (53)	0.6 (5)	< 0.001
% taking an SNRI—*follow-up* (*n*)	3.9 (6)	10.0 (42)	12.3 (38)	0.3 (3)	< 0.001
% taking a TCA—*baseline* (*n*)	2.0 (3)	4.5 (19)	3.9 (12)	0.8 (7)	< 0.001
% taking a TCA—*follow-up* (*n*)	3.9 (6)	4.1 (17)	5.8 (18)	0.6 (5)	< 0.001

Abbreviations: BDNF, brain-derived neurotrophic factor; IDS, inventory of depressive symptoms; NA, not applicable; s.d., standard deviation; SNRI, serotonergic and noradrenergic reuptake inhibitor; SSRI, selective serotonergic reuptake inhibitor; TCA, tricyclic antidepressant. [a]Calculated with the exclusion of the non-depressed control group.

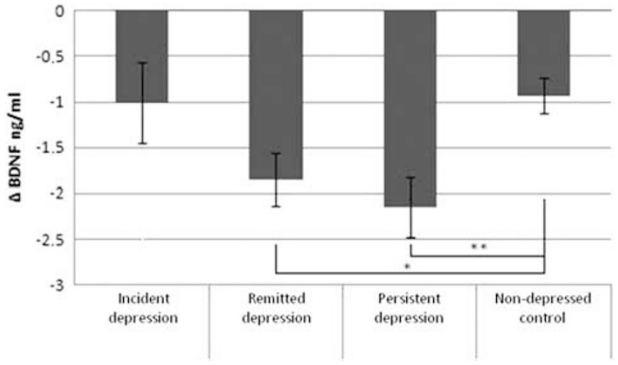

Figure 2. Mean adjusted (for course of depression, gender, age, smoking, alcohol consumption, comorbid anxiety, adherence to the pretest fasting protocol, time of blood withdrawal and storage time) changes in serum brain-derived neurotrophic factor (BDNF) levels from baseline to follow-up for the four courses of depression. *Denotes a statistical significance at $P = 0.011$; **Denotes a statistical significance at $P = 0.001$; Whiskers reflect ± 1 s.e.

antidepressants with subjects who did not use an antidepressant at both measurements, no significant results were found either. Selective serotonin reuptake inhibitors were the most frequently used antidepressants in our study and were significantly associated with BDNF in the baseline measurement.[8] Therefore, we also looked at switches to and from selective serotonin reuptake inhibitors specifically, but found no significant group effect ($F = 0.531$; df(5); $P = 0.75$).

Clinical features and psychological stressors

Within the persistent depression group, the BDNF decrease, the steepest of all patient groups, was inversely associated with the number of negative life events ($\beta = -0.10$; $P = 0.03$): those patients who had experienced more negative life events showed a sharper decrease in their serum BDNF levels. Within the same group, patients without a comorbid anxiety disorder at baseline and follow-up had a significantly sharper decrease in BDNF than their peers who had reported an anxiety disorder at follow-up ($\beta = 0.13$; $P = 0.03$ for incident anxiety and $\beta = 0.16$; $P = 0.002$ for persistent anxiety). The other clinical features for this group and all features of the remitted patient group yielded non-significant results. Results are shown in Table 2.

DISCUSSION

Main finding

We found the 2-year decrease in serum BDNF levels to be more profound in the patients with persistent and remitted depression than in the non-depressed controls, whereas the incident depression group did not differ significantly from the non-depressed controls. Changes in the use of antidepressants had not led to significant changes in BDNF levels. The occurrence of negative life events was found to be associated

Table 2. Depression characteristics and psychological stressors in participants with a persistent and remitted depression as a function of the 2-year change in serum BDNF

	Persistent depression (n = 310)					*Remitted depression (n = 420)*				
	Mean (s.d.)[a]	% (n)[b]	B	β	P[c]	Mean (s.d.)[a]	% (n)[b]	B	β	P[c]
Phenotypic depression characteristic										
Comorbid anxiety disorder										
Dummy no comorbid anxiety versus incident anxiety	N/A	11.1 (34)	2.64	0.16	0.002[d]	N/A	4.1 (17)	1.77	0.06	0.20
Dummy no comorbid anxiety versus remitted anxiety	N/A	21.0 (64)	0.62	0.05	0.38	N/A	34.0 (140)	−0.18	−0.01	0.78
Dummy no comorbid anxiety versus persistent anxiety	N/A	47.2 (144)	1.35	0.13	0.03	N/A	26.9 (111)	−0.02	> −0.01	0.98
Change IRS sum score[e]	−0.93 (4.9)	N/A	0.03	0.02	0.61	−1.91 (4.8)	N/A	−0.02	−0.01	0.78
Change in IDS sum score[e]	−6.57 (12.0)	N/A	0.30	0.07	0.11	−11.84 (12.1)	N/A	0.02	0.03	0.41
Age of onset of depression	35.6 (13.3)	N/A	−0.01	−0.01	0.85	30.7 (12.5)	N/A	< 0.01	< 0.01	0.96
% duration of depressive symptoms between baseline and follow-up	54.6 (31.4)	N/A	−1.17	−0.07	0.11	28.7 (34.1)	N/A	−0.19	−0.01	0.84
Psychological stressors										
Number of negative life events between baseline and follow-up	2.26 (1.7)	N/A	−0.30	−0.10	0.028	1.82 (1.4)	N/A	−0.04	−0.01	0.85
Number of positive life events between baseline and follow-up	2.3 (1.4)	N/A	−0.16	−0.04	0.39	2.67 (1.3)	N/A	0.19	0.04	0.36
Childhood abuse (yes/no)	N/A	67.3 (208)	−0.38	−0.04	0.44	N/A	54.5 (228)	0.66	0.05	0.21

Abbreviations: IDS, inventory of depressive symptoms; IRS, insomnia rating scale; N/A, not applicable; s.d., standard deviation. [a]Mean calculated within respective depression groups for numerical variable (Standard deviation in parenthesis). [b]For comorbid anxiety disorder the total percentage within respective depression groups of having an incident, remitted and persistent comorbid anxiety disorder is depicted (n in parenthesis); for childhood abuse the total percentage of participants within respective depression groups scoring 'yes' is depicted (n in parenthesis). [c]Fully corrected for covariates: age, gender, alcohol use, smoking and baseline BDNF. [d]value remains significant following Bonferroni correction for multiple testing (i.e., P = 0.05/16). [e]A change variable was created by subtracting the baseline value from the follow-up value.

with a sharper decrease in BDNF in the patients with a persistent depression.

Effect of psychopathology

Previous findings of our group suggested that reduced serum BDNF might be a state rather than a trait characteristic.[8] On the basis of our current results, it seems difficult to maintain that hypothesis. If BDNF expression indeed reflects state levels of depression, one would expect to find a decrease in BDNF concentrations with transitions from a healthy or remitted state to a depressive state and an increase when depression goes into remission. Yet, we did not find that pattern. Hence, we propose the hypothesis that low BDNF is characteristic for episodic depression, particularly occurring some time after the onset of depression and that in persistently depressed subjects, BDNF levels may even decrease further. This premise corresponds with findings from neuroimaging studies. In episodic depression lower volumes of the hippocampus, a brain region directly influenced by neurotrophic support, are seen. This reduction in volume is more pronounced in depressed patients with a longer duration of disease.[22] In addition, we found similar reductions in BDNF in *remitted* patients, which is in line with previous findings that being in the early remission phase of depression (1–6 months) versus having a current episode is associated with lower serum BDNF levels.[8] Taken together, these findings suggest that depression episodes may contribute to decreases in BDNF rather than low BDNF contributing to depression. However, we do want to point out that, unlike our current design, a prospective cohort with participants without a history of depression at baseline would be required to truly disentangle the state-trait issues.

We found chronically depressed patients to exhibit the steepest decline in serum BDNF over the course of 2 years. Exploring potential factors that might have contributed to these results, we found a significant association between the number of negative life events and reduced BDNF. As this correlation was not seen in the remitted patients, it seems specific for persistent depression. Chronic stress is known to downregulate BDNF expression in the brain,[1] which in turn renders the brain vulnerable to depression. Conversely, BDNF is known to exert an antidepressant effect,[23] even when administered peripherally.[24] Additionally, an early change in peripheral BDNF levels predicts a favorable outcome in depression patients.[25–27]

The largest decrease in BDNF was found in persistently depressed patients who had no comorbid anxiety disorder. Previous cross-sectional studies reported reduced serum BDNF for patients who suffered from an anxiety disorder only[28] but not for depressed patients with a comorbid anxiety disorder,[8] which suggest that the strongest effects are found in non comorbid disorders.

In summary, based on our results, it seems plausible to suggest that a persistent decrease in serum BDNF, or a deficient upregulation during a depressive episode, underlies the chronicity of the disorder. However, because of the naturalistic nature of our data, no inferences can be made about causality or the direction of the association. Hence, the alternative hypothesis that persistent depression causes a depletion of available BDNF may also hold true.

Effect of medication

The BDNF-inducing effect of antidepressants has been extensively investigated and described.[7,8,27] Collectively, the studies suggest an upregulation of peripheral BDNF levels by antidepressants. Although some of our subgroup analyses may have been underpowered, even our strongest powered results did not show any significant antidepressant-related differences in BDNF levels over the course of 2 years.

Considering that selection in cross-sectional studies may be confounded by indication and open-label treatment studies to date only included short-term follow-up data, our study extends

previous findings and, by examining antidepressant use to correct for different courses in an observational design, we have limited the influence of bias by indication as much as possible.

The rise in BDNF that in the previous studies is often ascribed to the use of antidepressants co-occurs with remission of the depressive episode.[7] Yet, our stratified analyses did not reveal any significant effects of changes in the type or use of antidepressants, not even in the remitted patient group. We accordingly conclude that the effects seen in the short-term after starting antidepressant treatment cannot be extrapolated to the longer term. This may potentially be attributable to the development of tolerance to the effect of antidepressants on neuroplasticity. Medication trials have shown that antidepressants, although effective in the short-term, might be less effective as a maintenance drug.[29] Along these lines, a translation of our results to clinical practice would then imply that the beneficial effect of antidepressants on elevated neuroplasticity may be reduced with long-term administration.

Limitations

For a proper interpretation of our results, some limitations should be addressed. First, one should bear in mind that the correlations between baseline and follow-up BDNF levels were low, pointing to high between-subjects variability of change in serum BDNF over time, with the existence of comorbid anxiety and negative life events possibly contributing to this variation to a certain extent. Additionally or alternatively, in light of the small effect sizes, the high inter-individual variation may also point to the existence of other relevant subgroups than those we investigated. Moreover, BDNF was measured with a 2-year interval, which limited the possibility to pick up transient changes of BDNF during that interval. Similarly, by restricting our study to depression status at the time of measurement, we do not know whether patients classified as having a persistent depression might have achieved remission followed by a recurrence. Information on the patients' depression status in the intermediary period could only be determined retrospectively, which we considered to be too imprecise. Rather than rendering our current claims on the 2-year changes unreliable, we feel these imperfections merely prevented us from interpreting what may have happened in between. Furthermore, one should note that, because of the storage of BDNF in platelets[30–32] and the association between antidepressant use and platelet count,[33] the number of platelets could influence the serum concentration of BDNF. Yet, even though a platelet count was not present in this study, our results can be reliably interpreted in the light of previous findings because the majority of studies on this subject did not include platelet count as a confounder.

CONCLUSION

With our naturalistic cohort study, we are the first to show that a persistent and a remitted MDD is associated with a substantial decline in serum BDNF: the decrease in BDNF levels was significantly more pronounced in these groups of patients than it was in non-depressed controls. Taken together, these findings suggest that depression episodes may contribute to decreases in BDNF rather than low BDNF contributing to depression.

CONFLICT OF INTEREST

The authors declare noconflict of interest.

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