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Prognostic effect of serum BDNF levels in late-life depression: Moderated by childhood trauma and SSRI usage?

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ABSTRACT

Background: Brain-derived neurotrophic factor (BDNF) levels decline during depression and normalise after remission, although studies in older patient samples are inconsistent. Whether BDNF serum levels predict depression remission is unclear. We hypothesize that the predictive value of serum BDNF levels in late-life depression is moderated by selective serotonin reuptake inhibitors (SSRI) usage and early traumatization.

Methods: Our study sample was a subset of the Netherlands Study of Depression in Older persons (NESDO), a prospective cohort study. It consisted of 267 older persons with a diagnosis of depression, for which follow-up data were available. Depression diagnosis was assessed at baseline and follow up using a structured diagnostic interview (Composite International Diagnostic Interview (CIDI), volume2.1). Logistic regression was performed (adjusted for covariates) with remission of depression after two years as the dependent variable and baseline BDNF serum levels, childhood traumatization and SSRI use as independent variables. *Results* - The mean age of the subjects was 70.7 years, 65.6% of them were female, their mean BDNF level was 7.7 ng/ml, 80 (30.0%) of them were traumatised in their childhood,71 (26.6%) used SSRIs and 136 (50.9%) no longer had a depressive disorder at the two year follow up. The predictive value of BDNF serum levels was conditional on traumatization and SSRI usage (threeway interaction p = .010). Higher BDNF serum levels predicted remission in traumatized depressed patients without SSRI usage (OR = 1.17, 95% C.I.: 1.00–1.36; p = .048) and in non-traumatized depressed patients who used SSRIs (OR = 1.17, 95% C.I.: 1.00–1.36; p = .052), but not in the other two subgroups.

Conclusion: The association between BDNF serum levels and the course of late-life depression seems to depend on SSRI use and childhood trauma. Based on these results, we hypothesize that childhood trauma may permanently reduce ('blunt') the responsiveness of the neurotrophic system to SSRI usage, and that this responsiveness might be more important for depression course than the actual BDNF serum levels.

1. Introduction

The neurotrophic hypothesis of depression postulates that a stress-induced reduction of neurotrophic support, predisposes an individual to depression (Duman et al., 1997). The hypothesis expands further, by assigning the therapeutic effects of antidepressant medications to their potency to increase the levels of neurotrophic factors in the brain. One of the most extensively researched neurotrophins is brain-derived neurotrophic factor (BDNF) and meta-analyses have indeed shown lowered serum BDNF-levels in adult depressed patients compared to non-depressed controls (Bocchio-Chiavetto et al., 2010; Molendijk et al., 2014; Sen et al., 2008). To our knowledge, five studies have been confined to late life depression; three of them found signifficantly decreased serum BDNF levels (one found decreased plasma BDNF levels) in depressed patients compared to non-depressed controls, (Chu et al., 2012; Diniz et al., 2010; Laske et al., 2010; Shi et al., 2010), whereas the fifth study did not (van der Meij et al., 2014)

Whether BDNF serum levels predict depression remission is still unclear. A few studies have so far shown that BDNF serum levels are associated with depression remission (Freire et al., 2016; Karege et al., 2002a; Shimizu et al., 2003; Yoshimura et al., 2010b). However, meta-analyses concluded that these results need further replication in studies with larger patient samples (Molendijk et al., 2014; Polyakova et al., 2015), and that BDNF serum levels may not be sufficient to predict depression remission. We hypothesize that the impact of BDNF on the course of depression is moderated by selective serotonin reuptake

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inhibitors (SSRI) usage and by early traumatization, as outlined below.

Within the Netherlands Study of Depression and Anxiety (NESDA), patients with depressive disorders had significantly lower BDNF serum levels compared to non-depressed controls and to remitted patients, and within the depressed patients, those not using an SSRI had lower BDNF levels than those using an SSRI (Bus et al., 2015; Molendijk et al., 2014). Interestingly, nearly all animal studies on BDNF upregulation have been conducted with SSRIs (Ibrahim et al., 2016; O'Leary et al., 2009) and in humans, treatment with an SSRI has been found to be a consistent determinant of depression remission (Cipriani et al., 2018), also among depressed older patients (Kok et al., 2012; Nelson et al., 2008; Thorlund et al., 2015). However, in the Netherlands Study of Depression in Older persons (NESDO), we did not find any difference in serum BDNF levels between depressed patients and non-depressed controls (van der Meij et al., 2014), but the depressed patients who were treated with an SSRI did have significantly higher serum BDNF levels compared to patients using other or no antidepressants (van der Meij et al., 2014). Furthermore, post-hoc analyses of this SSRI effect showed that its association was moderated by the presence of childhood trauma. Increased BDNF serum levels were only found in non-traumatized depressed older patients using an SSRI, and not in traumatized patients (van der Meij et al., 2014). Based on these findings, one may hypothesize that BDNF levels increase by SSRI usage, but that early traumatization results in a permanent blunting of this responsiveness of the neurotrophic system across the lifespan. This hypothesis would offer a biological explanation of why early trauma is consistently associated with non-remission of depressed patients (Nanni et al., 2012).

The present study aims to examine the predictive value of serum BDNF levels in late life depression. We hypothesize that: 1) Lower baseline BDNF serum levels are associated with lower chance of achieving remission of late-life depression at two-year follow-up, and 2)This effect is moderated by SSRI usage and early traumatization, and is most pronounced in patients who use an SSRI and did not experience a childhood trauma.

2. Methods

The present study was performed with data collected for the Netherlands Study of Depression in Older persons (NESDO). NESDO is a prospective cohort study with the aim of examining depression in old age. It specifically looks into the course of late life depression, its determinants and the impact that late life depression has on the life of the older individual. The study is approved by the ethical review boards of the participating institutes. Further details about the NESDO study can be found in (Comijs et al., 2011).

2.1. Sample

The subjects were between 60 to 93 years of age and were recruited from mental health institutions and general practitioners in the Netherlands. A total of 510 older adults were recruited, of which 378 had a depressive disorder during the 6 months before assessment and 132 were non-depressed comparison subjects.

2.2. Inclusion and exclusion criteria

Inclusion criteria for depressed patients were an age of 60 years or older, a primary diagnosis of a major depressive disorder, dysthymia or minor depression according to DSM-IV criteria (American Psychiatric Association, 2000), and being mentally able to give written informed consent after having received verbal and written information about NESDO. Persons who had a primary diagnosis of dementia, were suspected for dementia according to the clinician, or had a Mini Mental State Examination-score (MMSE, Folstein et al., 1975) under 18 (out of 30 points) were excluded. Patients with another primary psychiatric disease such as bipolar disorder or psychosis were also excluded, as were, persons with insufficient command of the Dutch language. In- and exclusion criteria for the non-depressed comparison group were similar, except that these persons had no lifetime diagnosis of any depressive disorder.

For the present study, we selected all 378 participants with a depressive disorder in the 6 months before the baseline assessment. From this group, 111 (29%) patients had to be excluded because they dropped out before the two-year follow-up interview (n = 93, 24.6%), or had missing data on BDNF at baseline (n = 15, 4.0%), or on childhood trauma (n = 2, 0.5%) or on SSRI usage (n = 1, 0.3%). This resulted in a final dataset of 267 patients with complete data on the main determinants and outcomes. The 111 excluded patients did not differ from the 267 included patients with respect to any of the primary variables of interest, i.e. BDNF serum levels at baseline (7.8 (SD = 4.5) versus 7.7 (SD = 4.2), p = .870), childhood traumatization (35% versus 30%, p = .353), or SSRI usage (31% versus 27%, p = .395).

2.3. Data collection

Information was gathered from the participants, regarding their demographics, mental health outcomes and other physiological and cognitive characteristics which may influence the course of depression (see covariates section). Assessments at baseline and two-year follow-up included a face-to-face interview, medical examinations, written questionnaires, cognitive tests and (on baseline only) collection of fasted blood samples in the morning. All interviews were performed by well-trained research assistants and were regularly audiotaped for quality control.

2.4. Primary outcome measure

Depression was assessed using the Composite International Diagnostic Interview (CIDI; WHO version2.1) at baseline and at two-year follow-up. The CIDI is a fully structured diagnostic interview which is designed to assess diagnosis of depression and dysthymia in a research setting, based on the DSM-IV-TR criteria (Wittchen et al., 1991). It has a high validity for depressive disorders. Additional questions were added to the interview to be able to also diagnose minor depression according to the research criteria of the DSM-IV-TR (Comijs et al., 2011). At baseline, we also assessed the lifetime prevalence of a depressive diagnosis with the CIDI.

The presence of a depression diagnosis was defined as major depressive disorder (MDD, n = 252) or dysthymia in the past 6 months (n = 72) or minor depression in the last month (n = 16). Note that the numbers do not add up to 267 as some patients suffer from more than one depressive disorder.

Furthermore, 47 of the patients with an MDD or dysthymia in the past 6 months before baseline, did not meet the full criteria for a DSM-IV defined depressive disorder anymore in the last month before baseline. Since BDNF serum levels were assessed at baseline and these levels have been shown to correlate with depression severity (Bus et al., 2012) and treatment response (Yoshimura et al., 2007), we will perform sensitivity analyses to check whether the results of our analyses change when we restrict our sample to the 220 patients whose depressive disorder persisted until the last month before baseline. Our primary outcome of depression remission was determined from the CIDI at the two-year follow up assessment, and was defined as the absence of depression, i.e. of an MDD or dysthymia over the past 6 months and of a minor depression over the last month (Comijs et al., 2015).

The dichotomous "remission of depression" variable was determined by assigning the value "0″ to the patients who still suffered from depression during follow-up, and the value "1″ to the patients who no longer suffered from depression during follow-up.

2.5. Predictor variables

2.5.1. BDNF

BDNF was assessed in serum taken at the baseline assessment. BDNF serum levels have been used as a marker for BDNF levels in the human brain, based on the facts that circulating BDNF can cross the blood brain barrier and strong correlations between serum and brain levels of BDNF have been found in rats (Karege et al., 2002b). Blood was withdrawn into vacuum tubes between 07.30 h and 09.30 h after an overnight fast. No restrictions were enforced on patients with respect to their medication use before blood withdrawal. Following collection, the blood was stored at -80 ° Celsius until it was assayed. The Emax Immuno Assay system was used according to its manufacturer's protocol, by one technician who was blind to the diagnoses and took place in one laboratory. The assay sensitivity threshold was ascertained at 1.56 ng/ml (ng/ml), reflecting the minimum level of BDNF in the serum that could be reliably determined.

2.5.2. Early childhood trauma

Childhood trauma was assessed using a structured inventory previously used in the Netherlands Mental Health Survey and Incidence Study (de Graaf et al., 2010) and the Netherlands Study of Depression and Anxiety (Penninx et al., 2008). In this inventory participants are asked whether they experienced abuse before the age of 16. As report of childhood abuse might be prone for recall bias with increasing age as well as in patients experiencing a depression, we specifically looked at the presence or absence of physical and/or sexual abuse in line with a previous cross-sectional report on this topic (van der Meij et al., 2014). Physical and sexual abuse were found to be consistently reported over time in patients with personality disorders (Spinhoven et al., 2012) and meta-analyses have shown that 45–60% of depressed patients meet the criteria for any personality disorder (Friborg et al., 2014). Physical abuse included being kicked, hit with or without an object and any other physical harm. Sexual abuse was defined as being sexually touched against one's will or being forced to touch someone sexually. After an affirmative answer, a question was asked about the frequency of these events, which was recorded as: Never, once, sometimes, regularly, often or very often. A dichotomous variable was constructed indicating the presence of either physical or sexual abuse with patients reporting either physical or sexual abuse, once or more often.

2.5.3. SSRI usage

Data on medication use were obtained by registration of the medications the participants brought with them to the interviews. Medications were registered by name, dosage and frequency of use, and Anatomical Therapeutical Chemical (ATC) codes were added later. Antidepressant drugs were classified in three categories, i.e. selective serotonin reuptake inhibitors (SSRIs; including N06AB), tricyclic antidepressants (TCAs; including N06AA), and other antidepressants (serotonin-norepinephrine reuptake inhibitors (SNRI; including N06AX16, N06AX21), tetracyclic antidepressants (TeCA; including N06AX03, N06AX05, and N06AX11).

2.6. Covariates

All characteristics that have been reported previously as potentially associated with serum BDNF levels were considered as potential confounders in the present study and thus included as covariates (Bus et al., 2011; Molendijk et al., 2014). We considered age, sex, and educational level (years of education) as potentially important socio-demographic characteristics.

Additionally, we considered the global level of cognitive functioning (MMSE; Folstein et al., 1975), the number of chronic somatic diseases based on self-report and drug use (Kriegsman et al., 1996), season of blood withdrawal, fasten blood withdrawal (yes/no) and life-style characteristics like use of alcohol (assessed with Alcohol Use Disorder Identification Test; AUDIT; Bohn et al., 1995), smoking (yes/ no), physical activity (minutes based on the International Physical Activity Questionnaire; IPAQ; CRAIG et al., 2003), and body mass index (kg/m2), since these characteristics are associated with BDNF and mood (Bus et al., 2011; Molendijk et al., 2011a).

2.7. Statistical analyses

First, baseline characteristics were described for the sample, stratified by the presence of childhood trauma as well as SSRI usage. For variables that were normally distributed we used the Student *t*-test to compare groups and for non-normally distributed variables the Mann Whitney U test. Categorical variables were compared with the chi-square test.

Logistic regression was performed, with remission of depressive disorders at two-year follow-up (yes/no) as the dependent variable and the three predictor variables as independent variables (i.e. BDNF serum levels, childhood traumatization, SSRI usage). Each potential confounder (see above) was tested on its association with the primary outcome variable (remitted depression) by logistic regression analysis with the potential confounder as single independent variable. Variables associated with the outcome at the 10% level ($p < .10$) were included in the final multivariate model. The hypothesized moderating effects of childhood traumatization and SSRI usage were examined by adding the three-way interaction term of BDNF by childhood traumatization by SSRI usage to the model, which also included their respective two-way interaction terms and main effects. In case of significance of the three-way interaction, odds ratios for the effect of BDNF on remission were calculated stratified for the presence of childhood traumatization and SSRI usage.

P-values < 0.05 were considered significant. All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 24.0.

3. Results

3.1. Population characteristics

The mean age of the included 267 depressed patients was 70.7 years (SD 7.5 years) and 176 were female (65.9%). The BDNF variable was approximately normally distributed (Skewness: 0.59, Kurtosis: 0.28). The mean BDNF blood serum level was 7.7 ng/ml (SD 4.2 ng/ml). Out of the 267 patients, 80 (30.0%) reported a history of physical or sexual childhood abuse. A total of 71 patients (27%) used SSRIs, whereas of the 196 non-SSRI users, 68 used a TCA, 49 another antidepressant, 4 a combination of a TCA and another antidepressant, and 75 used no antidepressants.

Table 1 presents all the characteristics of the study sample at baseline, stratified by the presence of childhood trauma as well as stratified by the presence of SSRI-usage. Patients who used an SSRI had a significantly higher IDS baseline sum score, indicating a more severe depression, than patients not using an SSRI. These patients also had higher BDNF levels at baseline than non-SSRI users, and somewhat lower MMSE scores, indicating more cognitive problems. Traumatized patients also had higher IDS scores at baseline than non-traumatized patients, were somewhat younger and had more physical problems, as indicated by more chronic somatic diseases and a higher body mass index.

3.2. Primary outcome

After 2 years of follow-up, out of the 267 depressed patients at baseline, 136 (50.9%) had a remission of their depression while 131 (49.1%) were still suffering from a depressive disorder.

The unadjusted analyses showed that serum BDNF levels (OR = 1.03; 95% CI: 0.97–1.09; p = .400) as well as SSRI usage

Table 1
Baseline characteristics of study sample stratified by childhood traumatization and by SSRI usage.

	Childhood trauma			SSRI usage		
Characteristics	No (n = 187)	Yes (n = 80)	p-value	No (n = 196)	Yes (n = 71)	p-value
Demographics:						
- Age, years, mean (SD)	71.6 (7.6)	68.9 (7.0)	.007	70.8 (7.7)	70.7 (7.1)	.975
- Female sex, n (%)	121 (64.7)	54 (67.5)	.660	125 (63.8)	50 (70.4)	.313
- Education, years, mean (SD)	10.6 (3.4)	10.4 (3.6)	.769	10.6 (3.4)	10.2 (3.6)	.426
Psychopathology:						
- Depression severity (IDS score), mean (SD)	28.1 (12.7)	33.0 (12.8)	.004	28.4 (13.0)	33.0 (11.9)	.009
- Cognitive functioning (MMSE score), mean (SD)	27.8 (1.8)	28.0 (1.7)	.404	28.0 (1.8)	27.5 (1.9)	.037
- Use of SSRI, n (%)	50 (26.7)	21 (26.3)	.934	–	–	
- Childhood traumatization, n (%)	–	–		59 (30.1)	21 (29.6)	.934
Blood withdrawal parameters:						
- BDNF serum level, mean (SD)	7.7 (4.2)	7.7 (4.1)	.937	7.3 (4.2)	8.9 (4.1)	.007
- Fasten blood withdrawal, n (%)	180 (96.8)	75 (97.4)	.787	185 (96.4)	70 (98.6)	.348
- Season of blood withdrawal, n (%)			.826			.324
Autumn	39 (20.9)	16 (20.3)		40 (20.5)	15 (21.2)	
Winter	37 (19.8)	12 (15.2)		31 (15.9)	18 (25.4)	
Spring	55 (29.4)	25 (31.6)		62 (31.8)	18 (25.4)	
Summer	56 (29.9)	26 (32.9)		62 (31.8)	20 (28.2)	
Lifestyle characteristics:						
- Current smoker, n (%)	44 (23.5)	22 (27.5)	.491	47 (24.0)	19 (26.8)	.642
- Alcohol use (AUDIT score), mean (SD)	2.3 (3.1)	3.2 (4.4)	.052	2.6 (3.5)	2.5 (3.5)	.739
- Physical activity (IPAQ MET-minutes), mean (SD)	2587 (2450)	2572 (2407)	.964	2696 (2501)	2260 (2209)	.208
Physical functioning						
- No. chronic diseases, mean (SD)	1.9 (1.4)	2.5 (1.7)	.002	2.1 (1.5)	2.2 (1.6)	.762
- Body Mass Index, kg/m^2, mean (SD)	25.6 (3.8)	27.2 (5.3)	.006	26.3 (4.3)	25.3 (4.3)	.087

Abbreviations: BDNFbrain derived neurotrophin factor; IDSinventory of depressive symptomatology; SSRIselective serotonin re-uptake inhibitor; MMSEmini mental state examination; SDstandard deviation.

Table 2
Association of baseline characteristics with remission of depression at two-year follow-up.

Co-variates	OR	[95% CI]	p-value
Demographics:			
- Age (years)	0.99	[0.96 - 1.02]	.454
- Female sex	0.93	[0.56 - 1.55]	.791
- Years of education	1.02	[0.95 - 1.09]	.666
Psychopathology:			
- Depression severity (IDS score)	0.95	[0.93 - 0.97]	< .001
- Cognitive functioning (MMSE score)	1.11	[0.97 - 1.27]	.138
Blood withdrawal parameters:			
- Season of blood withdrawal (summer = reference)			.556
Autumn	1.61	[0.74 – 3.52]	.226
Winter	1.01	[0.51 – 2.01]	.979
Spring	1.23	[0.62 – 2.44]	.553
- Fasten blood withdrawal	1.57	[0.37 - 6.69]	.545
Lifestyle characteristics:			
- Smoker	0.64	[0.36 - 1.11]	.112
- Physical activity (IPAQ MET-minutes)	1.00	[1.00 - 1.00]	.202
- Alcohol use (AUDIT sum score)	1.02	[0.96 - 1.10]	.513
Physical functioning:			
- Number of chronic diseases	0.73	[0.61 - 0.87]	< .001
- Body Mass Index	0.92	[0.87 - 0.98]	.009

Abbreviations: OR, Odds ratio; CI, confidence interval; IDS, inventory of depressive symptomatology; SSRI, selective serotonin re-uptake inhibitor.

(OR = 0.91; 95% CI: 0.53–1.57; p = .747) were not associated with remission at follow-up, whereas a history of physical and/or sexual childhood abuse was related to a lower odds of achieving remission (OR = 0.39; 95% CI: 0.23 – 0.68; p = .001). As shown in Table 2, only three of the confounders studied were significantly associated with remission at two-year follow-up at the 10% significance level. These were: severity of depressive symptoms at baseline (IDS sum score), body mass index (BMI), and number of chronic diseases. These three variables were included as covariates in the multivariate analyses.

In the adjusted analyses - without interaction terms for BDNF, childhood trauma, and SSRI - BDNF serum levels did not significantly predict depression remission at two-year follow-up (OR = 1.03; 95% CI: 0.97–1.10; p = .346). SSRI usage also did not significantly predict depression remission (OR = 1.02; 95% CI: 0.55–1.88; p = .956). The presence of childhood traumatization, however, did significantly predict depression remission (OR = 0.53; 95% CI: 0.29 – 0.95; p = .032).

In the model including interaction terms, the three-way interaction of BDNF serum level by childhood traumatization by SSRI usage was found to be statistically significant in both the unadjusted (p = .014) as well as the adjusted (p = .010) analyses. Therefore, analyses were

Table 3
Predictive value of BDNF for depression remission stratified by childhood traumatization and SSRI usage.

If		N	Unadjusted			Adjusted*		
Trauma	SSRI		OR	[95% CI]	p-value	OR	[95% CI]	p-value
No	No	137	0.97	[0.89 – 1.05]	.393	0.97	[0.89 – 1.06]	.465
No	Yes	50	1.16	[1.00 – 1.35]	.056	1.17	[1.00 – 1.36]	.052
Yes	No	59	1.15	[1.00 – 1.31]	.053	1.17	[1.00 – 1.36]	.048
Yes	Yes	21	0.91	[0.71 – 1.17]	.448	0.90	[0.70 – 1.17]	.435

Abbreviations: BDNF, brain-derived neurotrophic factor; SSRI, selective serotonin reuptake inhibitor; OR, odds ratio; CI, confidence interval.

* Adjusted for Body Mass Index, Depression severity (IDS sum score), and number of chronic somatic diseases (i.e. only the covariates associated with the primary outcome at the 10% level).

stratified by childhood traumatization as well as SSRI usage (see Table 3).

Higher serum BDNF levels were found to predict remission of depression at two-year follow-up with an OR of 1.17 (95% C.I.: 1.00–1.36; p = .052) among non-traumatized patients using an SSRI and with an OR of 1.17 (95% C.I.: 1.00–1.36; p = .048) among traumatized patients not using an SSRI, both after adjustment for covariates (see Table 3). No relationship between serum BDNF levels and depression remission was found in non-traumatized patients not using an SSRI or in traumatized patients using an SSRI.

The sensitivity analyses in the 220 patients whose depressive disorder persisted until the last-month before baseline, showed similar results as for the whole sample. The three-way interaction of BDNF serum level by childhood traumatization by SSRI usage was again found to be statistically significant in both the unadjusted (p = .041) as well as the adjusted (p = .023) analyses. The strength of the association between serum BDNF and depression remission in the adjusted analyses did not reduce for the non-traumatized patients using an SSRI (OR = 1.18; 95%CI: 1.01–1.39; p = .044) or the traumatized patients not using an SSRI (OR = 1.17; 95%CI: 0.95–1.35; p = .166). Although it did no longer reach statistical significance for the latter group, because of the reduction in size of this group (from n = 59 to n = 48). Again, no relationship between serum BDNF levels and depression remission was found for non-traumatized patients not using an SSRI or for traumatized patients using an SSRI (OR = 0.99; 95%CI: 0.90–1.09; p = .831, and OR = 0.90; 95%CI: 0.70–1.17; p = .440, respectively).

4. Discussion

4.1. Main findings

In contrast to our first hypothesis, higher BDNF serum levels at baseline were not overall associated with remission of late-life depression at two-year follow-up. We found that the impact of BDNF serum levels on remission of late-life depression was moderated by the combination of the presence of early childhood traumatization and SSRI usage. Higher BDNF serum levels at baseline were associated with a higher odds on achieving remission at two-year follow-up among two specific subgroups, i.e. non-traumatized depressed older patients using SSRIs and traumatized, depressed older patients not using SSRIs. The first subgroup was the group in which we expected the strongest relationship between baseline BDNF serum levels and depression remission, based on the reasoning outlined in the Introduction. The positive finding in the second subgroup was unanticipated. To understand these findings, we will first discuss how we hypothesize that BDNF, childhood traumatization and SSRI usage affect human brain functioning.

4.2. Hypothesized pathophysiological mechanisms

In the adult human brain, neurotrophic factors such as BDNF promote neuronal survival, induce synaptic plasticity, and modulate the formation of long-term memories. Animal studies show that early traumatization may have a long-lasting negative effect on the responsiveness of the neurotrophic system (Kuma et al., 2004; Roceri et al., 2004, 2002; Russo-Neustadt et al., 2001). SSRI usage, on the other hand, may be thought of as a more contemporary influence on the neurotrophic system (Balu et al., 2008; Bus et al., 2011; Molendijk et al., 2011a; van der Meij et al., 2014). SSRI usage generally stimulates BDNF expression, but the responsiveness of BDNF to SSRI usage might be permanently reduced -'blunted' one could say- in traumatized patients (van der Meij et al., 2014). The interaction between these two mechanisms may explain our findings, as will be discussed in more detail below.

In our stratified analyses, higher BDNF serum levels were found to be associated with remission of late-life depression among patients with no childhood trauma history who use an SSRI. Randomized controlled studies have shown the efficacy of SSRIs in predicting depression remission (Cipriani et al., 2009; Darby-Stewart et al., 2010). We may hypothesize that BDNF could play a role in the pathway towards depression remission for the following reasons. First, a growing body of literature shows that SSRIs usage is associated with increased levels of serum BDNF in depressed individuals, while other types of anti-depressants do not have such a pronounced effect on BDNF (Molendijk et al., 2011b; Zhou et al., 2017). Secondly, higher baseline serum BDNF levels in depressed adult patients have been found to be associated with remission at follow-up as well as with a decrease in depressive symptom severity (Karege et al., 2002a; Shimizu et al., 2003; Yoshimura et al., 2010a), although negative findings have also been reported (Bus et al., 2015). Finally, one clinical study of 42 depressed patients observed a significant increase in serum BDNF from baseline to after 8 weeks of treatment in patients who responded to treatment, but not in non-responders (Yoshimura et al., 2007). However, it is important to state that all the studies hitherto who reported differences in serum BDNF levels between depressive patients and patients who achieved remission, had small sample sizes (range 19 through 83 patients) and are based on relatively young patients (mean age of 45 years). Moreover, these studies did not take childhood traumatization into account. Our findings suggest that successful treatment with SSRIs might depend on its ability to achieve higher BDNF levels, and that this ability is lost or significantly reduced in traumatized patients.

We also found that, higher baseline BDNF serum levels are associated with remission at two-year follow-up in traumatized depressed older patients not using an SSRI. Animal studies have consistently shown that childhood trauma not only reduces hippocampal BDNF expression acutely (Kuma et al., 2004; Roceri et al., 2004, 2002) but also chronically (Russo-Neustadt et al., 2001). Although it still remains debated whether serum BDNF levels correspond to hippocampal BDNF-expression, studies in rats have shown very high correlations between both measures (Karege et al., 2002b). Whether the above findings can be extended to humans, remains unclear. The general consensus, however, appears to be that BDNF levels are also reduced in human adults subjected to early life stressors (Daskalakis et al., 2015). Recently, our group showed that among depressed older patients elevated BDNF levels were only found among depressed SSRI-users who were not traumatized during their childhood (van der Meij et al., 2014). This finding fits with animal research, which shows that serum BDNF levels do not respond to SSRIs in traumatized animals (Carboni et al., 2010; Chourbaji et al., 2011a).

To our knowledge, no studies have examined the impact of early childhood trauma on BDNF levels in older persons. We hypothesize that in depressed traumatized patients, serum BDNF levels indicate the magnitude of the effect of the childhood trauma on the individual, in the sense that lower BDNF levels represent a more severe effect of the

trauma on the older individual and that this reduces their chance to achieve depression remission. Our finding that higher baseline BDNF serum levels in traumatized depressed older patients not using an SSRI are associated with remission at two-year follow-up, may therefore indicate that the childhood trauma had a less severe impact on the lives of these older patients than for those who had lower BDNF levels. Not finding this effect in traumatized patients using an SSRI might result from the opposing effect of SSRI usage on BDNF levels, which neutralizes the negative effect of childhood traumatization on BDNF expression.

The fact that serum BDNF levels are not associated with remitted depression in the largest subgroup, i.e. non-traumatized patients not using an SSRI, is also of interest. While BDNF is thought to be a stress-related, and potentially causative factor regarding the onset of depression (Chourbaji et al., 2011b; Shadrina et al., 2018), this does not necessarily imply that BDNF serum levels is a factor strong enough to influence the course of depression. In line with our own findings, external stimulation of BDNF expression (by SSRI usage for instance) might be necessary for it to have an impact on the course of depression.

4.3. Methodological considerations

For proper interpretation, some limitations of the present study should be acknowledged. Firstly, BDNF levels were only assessed at baseline. Therefore, we do not have data on changes in serum BDNF levels during follow-up. Nonetheless, a study among younger chronically depressed patients using a similar design showed only minor variations in BDNF over a two-year follow-up period (Bus et al., 2015). Secondly, it is also important to mention that data on early childhood traumatization of the patients were obtained in a retrospective manner. Arguably it is hard to tell whether this has led to under reporting events due to memory problems associated with depression (Hickie et al., 2005) or unwillingness to report embarrassing events(Comijs et al., 2013) or whether this has led to over reporting due to a cognitive bias associated with a negative mood (Gerlsma et al., 1990). Two reviews and one recent study have shown that the impact of these factors is quite limited (Brewin et al., 1993; Hardt and Rutter, 2004; Mesquita and Maia, 2018). Moreover, to increase the reliability of our measure of childhood traumatization, we only included physical or sexual abuse which we assume to be less susceptible to distorted recall than psychological abuse and emotional neglect. Thirdly, we only studied the influence of presence or absence of a childhood traumatization, but repetitive or continuous traumatization may affect brain neurotrophic functioning more than a trauma single incident. Fourthly, we did not have data on the treatment regiments of each patient. Duration of therapy with a specific drug, reasons for discontinuation (if any) or maintaining treatment during the follow-up period are unknown. Finally, as already mentioned above, we would like to emphasize that although the interaction term tested was statistically significant, in one of the subgroups the effect of interest did not reach statistical significance at the 5% level (with a p-value of .052). This may be due to the relatively small size of this subgroup (n = 50), as some of the other subgroups. More in general, we can not exclude chance findings, especially false negative findings (i.e. Type II errors), due to limited statistical power in some of the subgroups. Replication studies in larger samples are therefore needed to check our findings.

5. Conclusion

The association between BDNF serum levels and the course of late-life depression might be better understood by a complex interaction between enduring effects of early-life traumatization and current SSRI usage on BDNF serum levels. Based on our results, we hypothesize that childhood trauma may affect the responsiveness of the neurotrophic system with respect to SSRI usage. If true, this implies that the responsiveness of the neurotrophic system is more important than actual BDNF serum levels. Therefore, we recommend developing paradigms measuring the responsiveness of the neurotrophic system directly and implementing these responsiveness measures as mediating mechanisms into randomized controlled trials on the effectiveness of antidepressants, especially SSRIs.

Declarations of interest

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CRediT authorship contribution statement

M. Dimitriadis: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Writing - review & editing, Project administration. **R.H.S. van den Brink:** Methodology, Software, Formal analysis, Writing - review & editing, Supervision. **H.C. Comijs:** Investigation, Resources, Data curation, Writing - review & editing, Supervision, Funding acquisition. **R.C Oude Voshaar:** Supervision.

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