Distinct association of plasma BDNF concentration and cognitive function in depressed patients treated with vortioxetine or escitalopram

Šagud, Marina; Nikolac Perković, Matea; Dvojković, Anja; Jakšić, Nenad; Vuksan-Ćusa, Bjanka; Živković, Maja; Kušević, Zorana; Mihaljević-Peleš, Alma; Pivac, Nela

Distinct association of plasma BDNF concentration and cognitive function in depressed patients treated with vortioxetine or escitalopram

Marina Sagud[1,2], Matea Nikolac Perkovic[3], Anja Dvojkovic[4], Nenad Jaksic[1], Bjanka Vuksan-Cusa[1,2], Maja Zivkovic[1,2], Zorana Kusevic[1,2], Alma Mihaljevic-Peles[1,2], Nela Pivac[3,*]

[1] Department of Psychiatry and Psychological Medicine, University Hospital Centre Zagreb, Kispaticeva 12, 10000 Zagreb, Croatia

[2] School of Medicine, University of Zagreb, Salata 3, 10000 Zagreb, Croatia

[3] Rudjer Boskovic Institute, Bijenicka cesta 54, 10000 Zagreb, Croatia

[4] University Psychiatric Hospital Vrapce, Bolnicka cesta 32, 10090 Zagreb, Croatia

*Communicating author:
Rudjer Boskovic Institute, Bijenicka cesta 54, 10000 Zagreb, Croatia
E-mail: npivac@irb.hr
Phone: +385 1 457 1207

Funding

This study was funded by the project “The influence of religiosity on treatment outcome in depression: clinical and biochemical parameters”, sponsored by University of Zagreb, BM126, led by Marina Sagud; and by the project No. 098-0982522-2455 "Molecular basis and treatment of psychiatric and stress-related disorders" funded by the Ministry of Sciences, Education and Sports of Croatia, led by Nela Pivac.

Abstract

Rationale Cognitive dysfunction is frequent in major depressive disorder (MDD), and brain-derived neurotrophic factor (BDNF) is involved both in regulation of cognition and in therapeutic response in MDD.

Objectives The aim of this study was to determine if baseline plasma BDNF might predict change in cognitive function in MDD patients treated with vortioxetine or escitalopram, and whether the alterations in BDNF levels correlate with changes in cognitive performance during treatment.

Methods Drug-naive or drug-free patients with MDD (N=121) were sampled and evaluated at baseline and 4 weeks after treatment initiation with vortioxetine or escitalopram. Cognitive function was evaluated using the F-A-S test, Digit Span test, and Digit Symbol Coding Test. Plasma BDNF was determined using ELISA.

Results The results of the study indicate that both vortioxetine (V) and escitalopram (E) improved cognitive functions evaluated with F-A-S test (V: $p<0.001$; $r=-0.427$, E: $p<0.001$; $r=-0.370$), Digit Symbol Coding test (V: $p<0.001$; $r=-0.706$, E: $p<0.001$; $r=-0.435$) and Digit Span test - backward span (V: $p=0.001$; $r=-0.311$, E: $p=0.042$; $r=-0.185$), while only vortioxetine ($p<0.001$; $r=-0.325$) improved cognition evaluated with the Digit Span test - forward span. A moderate positive correlation between pretreatment plasma BDNF levels and improvement in cognitive performance was only detected in patients treated with vortioxetine (delta F-A-S test: $p=0.011$; $r=0.325$, delta Digit Span Test - forward span: $p=0.010$, $r=0.326$).

Conclusions These results suggest that higher baseline plasma BDNF levels might be associated with improvements in verbal fluency and working memory in vortioxetine, but not escitalopram treated patients. Vortioxetine treatment was superior in simple attention efficiency.

Keywords: vortioxetine, escitalopram, cognition, memory, executive function, BDNF, depression, MDD

Introduction

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, is essential for neuronal maintenance and plasticity. The alterations in BDNF function have long been implicated in the pathophysiology of major depressive disorder (MDD) (Nedic Erjavec et al. 2020). Cognitive dysfunction has increasingly been recognized as one of the core features of MDD (Semkovska et al. 2019).

There is compelling evidence on the involvement of BDNF in both depression and cognitive deficits in preclinical and clinical studies. In a rat model of post-operative cognitive dysfunction, reversible memory and learning difficulties were associated with transient reduction in hippocampal BDNF levels (Zhang et al. 2014), whereas a negative correlation between hippocampal BDNF mRNA levels and recognition memory was found in rats chronically exposed to alcohol (Silva-Peña et al. 2018). In animal models of depression, such as learned helplessness or chronic mild stress, the reduction of hippocampal mRNA BDNF expression and cognitive deficits were detected, which were improved by antidepressants (Song et al. 2006). Strikingly, intranasal BDNF administration induced strong memory improvement in mice with induced neurodegeneration (Brachi et al. 2020).

In clinical studies, the relationship between BDNF and cognition was investigated mostly in healthy individuals during different exercise protocols, elderly population with or without cognitive impairments, and in patients with schizophrenia. Studies in older population, without severe cognitive decline, reported no relationships between plasma BDNF concentration and mean cognitive scores on several prospective visits during 9 years, and plasma BDNF levels did not predict the rates of change with age in performance on any of the cognitive domains (Driscoll et al. 2012), whereas serum BDNF was associated with a decline in story memory and digit symbol substitution test scores, but not with the word-list memory, or figure selection (Shimada et al. 2014). However, there is strong evidence on the involvement of BDNF in cognitive dysfunction in participants with neurodegenerative disorders, particularly Alzheimer's disease. Lower cerebrospinal fluid (Forlenza et al. 2015a) and serum BDNF (Forlenza et al. 2015b) levels were associated with progression from minimal cognitive impairment to Alzheimer's disease. Likewise, plasma BDNF level displayed high sensitivity and moderate specificity to discriminate patients with mild neurocognitive disorders due to Alzheimer's disease, in which it correlated with the severity of memory impairment (Levada et

al. 2016). Similarly, in patients with schizophrenia, a meta-analysis reported the correlation between reduced BDNF levels and cognitive dysfunction, which was relatively more pronounced for verbal memory, processing speed and working memory (Bora et al. 2019). It is possible that plasma BDNF had no relationship with cognitive performance in relatively cognitively intact adults, which might be altered in conditions characterized by the cognitive dysfunction. Interventions might also influence these connections. For example, serum BDNF levels correlated with the improvement in Stroop test performance after sprint interval exercise in healthy young males (Kijach et al. 2019).

Despite the reported data on the peripheral BDNF and cognitive indices in different illnesses or non-clinical samples, surprisingly little is known about this relationship in MDD patients. Actually, we detected only three studies addressing this issue. Elderly, drug-free patients with both MDD and cognitive difficulties had lower cerebrospinal fluid BDNF levels than those without cognitive decline, despite similar levels of neurodegenerative biomarkers, and lower BDNF levels also correlated with worse cognitive performance (Diniz et al. 2014). The second cross-sectional trial found no correlation between serum BDNF levels and cognition, assessed only by the Hamilton Depression Scale (HAM-D) subscale "cognitive disturbance" (Sotamura et al. 2011), which does not cover specific cognitive domains, but rather typical symptoms of depression. All participants in the latter trial were on antidepressants (Sotamura et al. 2011). The third trial enrolled exclusively MDD patients who suffered from executive dysfunction, and investigated whether its normalization was related to baseline plasma BDNF, or its changes during treatment with antidepressants (Wagner et al. 2019). Therefore, the relationship between circulatory BDNF and cognitive dysfunction in drug-free, non-elderly depressed patients, and the dynamics of this ratio during antidepressant treatment, was not investigated.

Vortioxetine recently appeared on the market, and is the only antidepressant, as far as we know, that improved cognitive dysfunction on the Digit Symbol Substitution Test (Baune et al. 2018). It was also shown to increase BDNF levels in the plasma (Sagud et al. 2016; Dvojkovic et al. 2020) and serum (Yan et al. 2019). Given the large amount of data on the cognitive dysfunction in MDD, and the involvement of BDNF in both cognition and depression, the aim of the present trial was to determine if baseline plasma BDNF might predict change in cognitive function in MDD patients treated with vortioxetine or escitalopram, and whether the alterations in BDNF levels correlate with changes in cognitive performance during treatment with these two antidepressants.

Materials and methods

Study design and participants

We used data from our previous trial (Dvojkovic et al. 2020), to conduct the separate analysis on the association of baseline plasma BDNF levels and cognition in MDD patients, and their changes during vortioxetine or escitalopram treatment. Thus, several of the methods presented here have been previously described (Dvojkovic et al. 2020). Briefly, included were 121 drug-naive or drug-free patients for at least 4 weeks (except low-dose benzodiazepines given on "as-needed" basis), diagnosed with MDD with a structured clinical interview (First et al. 1995), who had HAMD-17 (Hamilton 1960) score ≥ 15. Key exclusion criteria were other major psychiatric disorders, recent alcohol or substance dependence, neurodegenerative and severe somatic illnesses, the presence of psychotic features and/or treatment resistance to previous antidepressants, intellectual disability or any other condition known to compromise cognitive abilities.

Procedures and instruments

Depression severity was assessed by the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979) and HAMD-17. Cognitive function was evaluated by the tests presented in detail in Table 1.

---- Table 1 ----

Administration of tests and BDNF sampling were carried out at baseline and 4 weeks after treatment initiation. After baseline assessment, patients were randomized at 1:1 ratio, to vortioxetine or escitalopram, during 4 weeks. Starting doses were 10 mg once daily for both drugs. At the discretion of the psychiatrist-investigator, antidepressants might have been decreased to 5 mg daily, or increased up to the maximum of 20 mg daily. Only low-dose benzodiazepines (up to 10 mg diazepam equivalent on "as needed" basis) were allowed during the entire study period.

Blood sampling

Blood specimen were taken in 8.5 ml yellow-top Vacutainer tubes with 1.5 ml of acid citrate dextrose anticoagulant, after the overnight fast, at 8 a.m. Platelet-poor plasma was obtained from whole blood samples by a series of centrifugation. Aliquots of platelet-poor plasma were stored at −20°C for BDNF concentration analysis. To decrease possible variability, all samples were processed within 1 h of being collected.

Plasma BDNF concentration

BDNF concentration in platelet-poor plasma was determined using a commercial enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Quantikine ELISA, R&D Systems, Minneapolis, USA). All plasma samples were diluted (1:2) using the diluent provided by the manufacturer and added, with standards and blanks, to the 96-well plate pre-coated with the monoclonal antibody specific for human BDNF. The plate was incubated for 2 hours at RT and, afterwards, a solution containing monoclonal antibodies conjugated to horseradish peroxidase was added to each well. After incubation (1 h) at RT, the plate was washed with washing buffer to remove any unbound antibodies and a substrate solution was added. After 30 min of incubation in the dark at RT, the reaction was terminated using 2N sulfuric acid. A microplate reader was used to measure the absorbance of each sample, using a wavelength of 450 nm and corrected by absorbance at 570 nm. The intra- and inter-assay coefficients of variations were less than 10 %. The concentrations of each sample were calculated based on a standard curve. All samples were determined in duplicates.

Statistical analysis

Data were evaluated with Sigma Stat 3.5 (Jandel Scientific Corp., San Jose, California, USA) with the level of significance α set to 0.05. The Kolmogorov-Smirnov test was used to test the normality of all analyzed parameters, including demographic parameters, clinical parameters, and plasma BDNF concentration. Due to the deviation of the mentioned parameters from the normal distribution, appropriate non-parametric statistical test, the Mann-Whitney U test, was used to compare the results between two groups of patients, while the Wilcoxon signed-rank test was used to compare the two dependent data sets. Categorical data was analyzed using a chi^2 (χ^2) test. Multiple linear regression analysis was performed to eliminate the possible effects of age, sex and smoking on plasma BDNF concentration, using BDNF plasma concentration as a dependent variable, and age, sex and smoking as independent variables. Correlation between

plasma BDNF levels and specific cognitive test scores was assessed using Spearman's rank-order correlation.

G*Power 3 Software was used to determine a priori sample size and actual power. For the Mann-Whitney U test (with $\alpha = 0.050$; power $(1 - \beta) = 0.80$; effect size $d = 0.50$), total desired sample size was 43 per group, for the χ^2 test (with $\alpha = 0.050$; power $(1 - \beta) = 0.80$; effect size $\omega = 0.50$) total desired sample size was 32, and for testing the correlation (with $\alpha = 0.050$; power $(1 - \beta) = 0.80$; effect size $d = 0.50$) total desired sample size was 53 per group, while the actual sample size was 60 in escitalopram group and 61 for the group treated with vortioxetine. Therefore, we had the appropriate sample size and statistical power to detect significant differences in the studied groups.

Results

Both escitalopram- and vortioxetine-treated patients (Table 2) had similar age (p=0.164), proportion of smokers (p=0.752) and number of life-time suicide attempts (p=0.395). However, group treated with escitalopram had a higher proportion of female subjects (p=0.015), more participants with a first depressive episode (p=0.009), and a family history of depression (p=0.017), a shorter illness duration (p=0.019), a lower number of depressive episodes (p=0.017) and a lower baseline HAMD-17 (p=0.022) and MADRS (p=0.006) scores. The Mann-Whitney U test revealed no significant differences in cognitive functions between the two groups of patients, both before and after 4 weeks of treatment (Table 2).

---- Table 2 ----

Related-Samples Wilcoxon Signed-Rank test was used to evaluate the effect of antidepressant treatment on the patients' cognitive functions. In vortioxetine-treated patients (Figure 1), significant differences were revealed between baseline and week-4 scores in F-A-S test (Z=-4.70; p<0.001; r=-0.427), Digit Span test - forward span (Z=-3.57; p<0.001; r=-0.325), Digit Span test - backward span (Z=-3.42; p=0.001; r=-0.311), and Digit Symbol Coding test (Z=-7.77; p<0.001; r=-0.706). Likewise, escitalopram-treated patients (Figure 1) had significantly different baseline and week-4 scores in F-A-S test (Z=-4.07; p<0.001; r=-0.370), Digit Span test - backward span (Z=-2.03; p=0.042; r=-0.185), and Digit Symbol Coding test

(Z=-4.78; p<0.001; r=-0.435), but a similar score in Digit Span test - forward span (Z=-1.61; p=0.108; r=-0.146).

---- Figure 1 ----

Figure 1. Effect of vortioxetine and escitalopram treatment on the patients' cognitive functions evaluated with F-A-S test (A), Digit Span test - forward span (B), Digit Span test - backward span (C), and Digit Symbol Coding test (D).

As reported previously (Dvojkovic et al. 2020), both HAMD-17 and MADRS scores significantly decreased after 4 weeks of treatment with vortioxetine (HAMD-17: Z=-6.65; p<0.001; r=-0.605, MADRS: Z=-6.48; p<0.001; r=-0.589) or escitalopram (HAMD-17: Z=-6.62; p<0.001; r=-0.602, MADRS: Z=-6.52; p<0.001; r=-0.593). Plasma BDNF concentration was significantly (Z=-2.37; p=0.018; r=-0.215) increased in the vortioxetine group, but it did not differ significantly (Z=-0.88; p=0.379, r=-0.080) within patients before and after treatment with escitalopram (Dvojkovic et al. 2020).

To eliminate the possible effects of age, gender and smoking on plasma BDNF concentration, multiple linear regression analysis was performed, using baseline and post-treatment BDNF as dependent, and age, gender, and smoking as independent variables, respectively. Analyses involving the group of patients who were prescribed vortioxetine therapy showed no significant effect of age (p=0.05), gender (p=0.451), and smoking (p=0.482) on baseline BDNF plasma concentration (F(3,57)=1.87; p=0.145; R_{adj}^2=0.042). This lack of significant effect of age (p=0.272), gender (p=0.937), and smoking (p=0.042) on BDNF concentration was also detected after treatment with vortioxetine (F(3,57)=2.89; p=0.043; R_{adj}^2=0.086). In the group of patients who were prescribed escitalopram therapy, multiple linear regression analysis yielded a non-significant model (F(3,56)=0.91; p=0.441; R_{adj}^2=-0.004) due to the lack of significant effects of age (p=0.278), gender (p=0.172), and smoking (p=0.996) on baseline plasma BDNF concentration. The model was not significant for post-treatment plasma BDNF concentration (F(3,56)=2.67; p=0.056; R_{adj}^2=0.078) as a result of the non-significant effects of age (p=0.138), gender (p=0.061), and smoking (p=0.132) after treatment with escitalopram.

We observed a significant positive correlation between pretreatment plasma BDNF and delta F-A-S test (p=0.011) scores in the group of patients treated with vortioxetine. Likewise,

positive correlation was observed for delta Digit Span Test - forward span score (p=0.010) in the group of patients treated with vortioxetine (Table 3). Both these correlation coefficients represent medium effect sizes, as suggested by Cohen et al. (2003). Additionally, when combining the two groups of patients together (Table 3), we detected positive correlation (p=0.040) between delta Digit Symbol Coding test scores and delta BDNF level, as well as between delta F-A-S test and baseline plasma BDNF (p=0.043). However, we did not observe significant correlation between pretreatment or delta BDNF levels and any specific clinical measurements in the group of patients treated with escitalopram (Table 3).

---- Table 3 ---

Discussion

The main results of the study were that both vortioxetine and escitalopram significantly improved cognitive functions evaluated with F-A-S test, Digit Symbol Coding test and Digit Span test - backward span. However, when cognitive functions were evaluated with Digit Span test - forward span, only vortioxetine treated patients showed significant cognitive improvement. Also, as reported previously (Dvojkovic et al. 2020), both antidepressants led to significant clinical improvement assessed with MADRS and HAMD-17. Our results suggest a significant positive correlation between pretreatment plasma BDNF levels and delta F-A-S test scores and delta Digit Span Test - forward span scores in the group of patients treated with vortioxetine. In contrast, no significant correlation between pretreatment BDNF levels and specific clinical measurements of cognitive functions in the group of patients treated with escitalopram was detected.

The findings of similar effects of vortioxetine and escitalopram on cognitive function in MDD patients is in accordance with results from the study of Vieta et al. (2018). However, our results do not agree with superior vortioxetine efficacy on some tested cognitive parameters in comparison to escitalopram (Levada and Troyan 2019), and with the meta-analytic evidence on the superior effects of vortioxetine versus escitalopram on the Digit Symbol Substitution Test (Baune et al. 2018). The discrepancies might be attributed to different number of participants,

treatment duration and cognitive tests. For example, Levada and Troyan (2019), included overall 53 participants, while the present study had more than twice larger sample size. Unlike in our present and previous (Dvojkovic et al. 2020) study, vortioxetine led to the greater antidepressant efficacy compared to escitalopram (Levada and Troyan 2019). Differences between vortioxetine and escitalopram on Rey Auditory Verbal Learning Test (RAVLT), which assesses acquisition and recall, but similar effects of both antidepressants on the Trail Making Test B (TMT-B), which assesses processing speed, executive function, i.e., set shifting; and on the Digit Symbol Substitution Test (DSST), which assesses processing speed, executive function, learning, memory, and attention, were reported (Levada and Troyan 2019). The meta-analysis on vortioxetine efficacy on cognitive dysfunction in MDD patients included only one study with 54 escitalopram-treated patients during 8 weeks on Digit Symbol Substitution Test scores (Dube et al. 2010). The more recent study, however, reported no differences in the effects of vortioxetine and escitalopram on the Digit Symbol Substitution Test, as well as on the University of San Diego Performance-based Skills Assessment - Brief (UPSA-B) performance after 8 weeks of treatment (Vieta et al. 2018). However, subtle difference between two antidepressants was detected, given that vortioxetine was superior with regard to simple attention efficiency.

Our results suggest that the association between baseline plasma BDNF level and changes in cognitive test scores is medication- and test- specific, given the significant association between baseline BDNF and post-treatment delta F-A-S test and delta Digit Span test (forward span) scores, but only in vortioxetine-treated individuals. These findings suggest distinct relationship between baseline plasma BDNF and changes in cognitive ratings induced by the two antidepressants, with otherwise similar effects on cognitive performance. In other words, in vortioxetine-treated patients, pretreatment plasma BDNF levels predicted change (improvement) in executive functions and attention, but not in information processing speed.

To the best of our knowledge, only one study so far prospectively evaluated the relationship between circulatory BDNF and cognition in MDD patients (Wagner et al. 2019). In line with our findings, participants with normalized verbal fluency dysfunction during 8-week treatment had higher baseline plasma BDNF, compared to those with persistent dysfunction, which was not observed for dysfunction measured by the Trail making test (Wagner et al. 2019). Moreover, all patients who demonstrated normalization on the verbal fluency tests had very high baseline plasma BDNF levels. These findings, together with our results, support the hypothesis that peripheral BDNF levels might indicate some aspects of the cognitive functions dynamic in MDD patients, and, more specifically, that baseline plasma

BDNF levels were higher in patients with more pronounced improvement in verbal fluency. Furthermore, early changes in plasma BDNF levels (2 weeks) did not enhance the likelihood for the executive test results normalization (Wagner et al. 2019), which agrees with our findings of no correlations between plasma BDNF dynamics and cognitive scale changes during treatment with either antidepressant, although plasma BDNF in our trial was determined at week 4. This implicates that pretreatment BDNF level, but not its change, correlates with the treatment-emergent improvement in certain cognitive scales in MDD patients. However, in the latter study, patients were treated with different medications (escitalopram, venlafaxine or venlafaxine plus lithium) (Wagner et al. 2019), while we observed this finding only in patients on vortioxetine monotherapy. The difference might arise from the distinct mechanism of action between vortioxetine and escitalopram, primarily from the specific partial 5HT1A agonism of vortioxetine. In the preclinical studies, the 5-HT1A receptor agonist NLX-101, but not escitalopram, increased the BDNF protein levels in prefrontal cortex of mice model of cerebral ishemia (Aguiar et al. 2020). Therefore, the magnitude of improvement of both fonemic fluency and executive functions in vortioxetine-treated patients may be partially related to pre-treatment plasma BDNF levels, while escitalopram-induced cognitive improvement could include other mechanisms, at least during the short-time treatment.

Longitudinal studies on the relationship between circulatory BDNF and changes in cognition in non-MDD samples, and interventions other than antidepressants, yielded inconsistent findings. In agreement with our results, breast cancer patients with higher baseline plasma BDNF levels had lower odds of developing persistent subjective cancer-related cognitive impairment at the end of chemotherapy (Yap et al. 2020). Likewise, in healthy older adults, greater increase of plasma BDNF immediately after physical exercise was associated with greater cognitive training gains, but only if such increases preceded cognitive training (Nilsson et al. 2020). These results suggest that, after plasma BDNF was first elevated by exercise, consequent cognitive training resulted in better cognitive training gains, or post-exercise increases in plasma BDNF were related to subsequent better cognitive outcome in older adults (Nilsson et al. 2020). Moreover, a shorter completion time in Trail making tests was correlated with an increase in serum BDNF immediately after single high intensity aerobic exercise in healthy young adults (Hwang et al. 2016). In patients with schizophrenia, the change in plasma BDNF levels correlated with the attention score improvement (digit span and coding) after 12-week olanzapine treatment (Zhang et al. 2018). Likewise, in patients with vascular dementia, the increase in serum BDNF level correlated with the increase in MMSE scores after 12 weeks of fluoxetine treatment (Liu et al. 2014), though the cognitive deterioration in

dementia is of much higher magnitude than in MDD patients. A change in plasma BDNF levels was also associated with self-perceived concentration deficit in a longitudinal study in chemotherapy-receiving early-stage breast cancer patients without psychiatric disorder (Ng et al. 2017). On the contrary, no associations were found between changes in the symbol search cognitive test or semantic and verbal fluency measured by Montreal Cognition Scale (MoCA), and changes in serum BDNF (although the trend was positive), in elderly participants from long-term nursing facilities after 3 months of physical, dual-task, or cognitive training interventions (Rezola-Pardo et al. 2020).

In contrast, our results do not agree with the findings that low blood levels of BDNF were predictive of an improvement in alternating letter verbal fluency (Kalbe et al. 2018). Similarly, higher levels of serum BDNF at baseline assessment were associated with smaller changes from pre- to post-intervention on memory tests in fibromyalgia patients treated with transcranial direct current stimulation combined with a working memory training (Santos et al. 2018). The differences among studies are in the assessment of the effects of combined cognitive and physical interventions in healthy older adults without any past or present psychiatric disorder (Kalbe et al. 2018), or in the evaluation of the transcranial direct current stimulation combined with a working memory training in fibromyalgia patients (Kalbe et al. 2018) as opposed to our individuals with MDD. The results are difficult to compare due to different populations, diagnoses, cognitive tests, and interventions. Notwithstanding those differences, peripheral BDNF may be a potential, and easy-to-obtain marker for predicting improvement in cognitive dysfunction in several clinical populations, such as during physical activity in healthy people, patients with dementia or schizophrenia. Our findings broaden this knowledge to MDD patients, in which pretreatment BDNF levels appear worth being the candidate marker for future studies of pro-cognitive effects of antidepressants.

Our findings implicate the involvement of peripheral BDNF levels in the cognitive effects of vortioxetine, but not escitalopram, although the debate continues whether peripheral BDNF is a reliable marker of central BDNF (Giacobbo et al. 2019), and which blood compartment is the most reliable source for measuring BDNF. However, positive correlations were demonstrated between plasma and serum BDNF in healthy volunteers (Polyakova et al. 2017) and in drug-free schizophrenia patients with acute exacerbation (Kudlek Mikulic et al. 2017).

This study is burdened by several limitations. Sampling in women was taken irrespective on the menstrual cycle. Plasma BDNF levels are influenced by hormonal status, and its modifications during the menstrual cycle might have influenced the results, at least in

premenopausal women (Begliuomini et al. 2007). The duration and intensity of physical activity, which might influence both plasma BDNF levels and cognition, was not recorded. For example, plasma BDNF was reported to increase more than 300% following physical exercise (Nilssen et al. 2020). The differences in physical activity prior to inclusion might have influenced plasma BDNF and consequent better cognitive test results in a subgroup of vortioxetine-treated patients. However, baseline plasma BDNF levels were similar across both groups. Like in most similar studies carried out in clinical/psychiatric samples, we cannot rule out at least some effects of practice, i.e., improvements in cognitive test performance due to repeated exposure to the test materials (Duff et al. 2007). Similarly, without a corresponding placebo group, vortioxetine- and escitalopram-specific effects could not be confirmed, although the obtained cognition-related differences are suggestive of some unique properties of these two drugs. Finally, the patients were randomized in terms of their initial appointments and allocation to one of the groups, but they were not appropriately stratified by duration of depression as well as gender. This is partly in line with depression occurring more often in women than in men (Ma et al. 2019). However, the two groups were similar in age and performance on cognitive tests, which is of vital importance given the fact that the main goal of our research was to examine possible pro-cognitive effects of the two drugs and the relation of these effects to the plasma BDNF.

Conclusion

Vortioxetine and escitalopram displayed almost identical effects on cognitive functions in MDD patients, with vortioxetine being superior only with regard to simple attention efficiency. Neither baseline plasma BDNF levels nor its levels after 4 weeks of escitalopram treatment were related to the change of any of the cognitive test scores. On the contrary, in patients on vortioxetine, higher baseline plasma BDNF levels were associated with the improvement in verbal fluency and working memory, while the magnitude of change in BDNF levels did not correlate with the change in any cognitive measure in either group. If confirmed in larger patient samples, higher baseline plasma BDNF levels might be associated with improvement in some aspects of cognition in vortioxetine-, but not escitalopram-treated patients. Given the importance of targeting cognitive symptoms in MDD patients, strategies that might increase peripheral BDNF levels, such as physical activity (Nilsson et al. 2020) or psychotherapy, might

further contribute to the cognitive improvement, at least in MDD patients treated by vortioxetine. Namely, vortioxetine combined with cognitive behavioral therapy resulted in a higher improvement in both cognitive function and serum BDNF levels than vortioxetine treatment alone (Yan et al. 2019).

Vortioxetine was previously reported to produce some additional effects on cognition, compared to other antidepressants (Bennabi et al. 2019). Our results extend those findings, suggesting that the medication-free MDD patients with higher baseline plasma BDNF levels may have greater benefits on executive functions and attention, during treatment with vortioxetine, but not with escitalopram, at least for first four weeks. Given the importance of cognition on functional outcomes in MDD, plasma BDNF level appears to be a promising candidate for future studies on biomarkers of pro-cognitive effects of vortioxetine. Despite having similar antidepressant activities, vortioxetine and escitalopram are distinct antidepressants. Therefore, establishing patient-related factors which would make them more likely to respond to either of those drugs, would lead to the optimal use of those two otherwise effective, safe, and widely-prescribed antidepressants.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

Aguiar RP, Soares LM, Meyer E, da Silveira FC, Milani H, Newman-Tancredi A, Varney M, Prickaerts J, Oliveira RMW (2020) Activation of 5-HT1A postsynaptic receptors by NLX-101 results in functional recovery and an increase in neuroplasticity in mice with brain ischemia. Prog Neuropsychopharmacol Biol Psychiatry 99:109832

Baune BT, Brignone M, Larsen KG (2018) A Network Meta-Analysis Comparing Effects of Various Antidepressant Classes on the Digit Symbol Substitution Test (DSST) as a Measure of Cognitive Dysfunction in Patients with Major Depressive Disorder. Int J Neuropsychopharmacol 21(2):97-107

Begliuomini S, Casarosa E, Pluchino N et al (2007) Influence of endogenous and exogenous sex hormones on plasma brain-derived neurotrophic factor. Hum Reprod 22(4):995-1002

Bennabi D, Haffen E, Van Waes V (2019) Vortioxetine for Cognitive Enhancement in Major Depression: From Animal Models to Clinical Research. Front Psychiatry 10:771

Bora E (2019) Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: a meta-analysis. Psychol Med 49(12):1971-1979

Braschi C, Capsoni S, Narducci R et al (2020) Intranasal delivery of BDNF rescues memory deficits in AD11 mice and reduces brain microgliosis. Aging Clin Exp Res. https://doi.org/10.1007/s40520-020-01646-5

Cohen J, Cohen P, West SG, Aiken LS (2003) Applied multiple regression/correlation analysis for the behavioral sciences (3rd edition). Lawrence Erlbaum Associates, Mahwah, NJ

Diniz BS, Teixeira AL, Machado-Vieira R, Talib LL, Radanovic M, Gattaz WF, Forlenza OV (2014) Reduced cerebrospinal fluid levels of brain-derived neurotrophic factor is associated with cognitive impairment in late-life major depression. J Gerontol B Psychol Sci Soc Sci 69(6):845-51

Driscoll I, Martin B, An Y, Maudsley S, Ferrucci L, Mattson MP, Resnick SM (2012) Plasma BDNF is associated with age-related white matter atrophy but not with cognitive function in older, non-demented adults. PLoS One 7(4):e35217

Dubé S, Dellva MA, Jones M et al (2010) A study of the effects of LY2216684, a selective norepinephrine reuptake inhibitor, in the treatment of major depression. J Psychiatr Res 44(6):356-363

Duff K, Beglinger LJ, Schultz SK et al (2007) Practice effects in the prediction of long-term cognitive outcome in three patient samples: a novel prognostic index. Arch Clin Neuropsychol 22(1):15-24

Dvojkovic A, Nikolac Perkovic M, Sagud M, Nedic Erjavec G, Mihaljevic Peles A, Svob Strac D, Vuksan Cusa B, Tudor L, Kusevic Z, Konjevod M, Zivkovic M, Jevtovic S, Pivac N (2020) Effect of vortioxetine vs. escitalopram on plasma BDNF and platelet serotonin in depressed patients. Prog Neuropsychopharmacol Biol Psychiatry. https:// doi.org/10.1016/j.pnpbp.2020.110016

First MB, Spitzer RL, Gibbon M, Williams JBW (1995) Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). American Psychiatric Press, Inc., Washington, DC

Forlenza OV, Diniz BS, Teixeira AL et al (2015a) Lower Cerebrospinal Fluid Concentration of Brain-Derived Neurotrophic Factor Predicts Progression from Mild Cognitive Impairment to Alzheimer's Disease. Neuromolecular Med 17(3):326-332

Forlenza OV, Miranda AS, Guimar I et al (2015b) Decreased Neurotrophic Support is Associated with Cognitive Decline in Non-Demented Subjects. J Alzheimers Dis 46(2):423-429.

Giacobbo BL, de Freitas BS, Vedovelli K et al (2019) Long-term environmental modifications affect BDNF concentrations in rat hippocampus, but not in serum. Behav Brain Res 372:111965

Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62

Hwang J, Brothers RM, Castelli DM et al (2016) Acute high-intensity exercise-induced cognitive enhancement and brain-derived neurotrophic factor in young, healthy adults. Neurosci Lett 630:247-253

Jaeger J (2018) Digit Symbol Substitution Test: The Case for Sensitivity Over Specificity in Neuropsychological Testing. J Clin Psychopharmacol 38(5):513-519

Kalbe E, Roheger M, Paluszak K, Meyer J, Becker J, Fink GR, Kukolja J, Rahn A, Szabados F, Wirth B, Kessler J (2018) Effects of a cognitive training with and without additional physical activity in healthy older adults: A follow-up 1 year after a randomized controlled trial. Front Aging Neurosci 10:407

Kudlek Mikulić S, Mihaljević-Peleš A, Šagud M, Bajs Janović M, Ganoci L, Grubišin J, Kuzman Rojnić M, Vuksan Ćusa B, Bradaš Z, Božina N (2017) Brain-derived neurotrophic factor serum and plasma levels in the treatment of acute schizophrenia with olanzapine or risperidone: 6-week prospective study. Nord J Psychiatry 71(7):513-520

Kujach S, Olek RA, Byun K, Suwabe K, Sitek EJ, Ziemann E, Laskowski R, Soya H (2020) Acute Sprint Interval Exercise Increases Both Cognitive Functions and Peripheral Neurotrophic Factors in Humans: The Possible Involvement of Lactate. Front Neurosci 13:1455

Levada OA, Cherednichenko NV, Trailin AV, Troyan AS (2016) Plasma Brain-Derived Neurotrophic Factor as a Biomarker for the Main Types of Mild Neurocognitive Disorders and Treatment Efficacy: A Preliminary Study. Dis Markers 2016:4095723.

Levada OA, Troyan AS (2019) Cognitive-functional relationships in major depressive disorder: Crucial data from a Ukrainian open-label study of vortioxetine versus escitalopram. J Affect Disord 250:114-122

Liu X, Zhang J, Sun D, Fan Y, Zhou H, Fu B (2014) Effects of fluoxetine on brain-derived neurotrophic factor serum concentration and cognition in patients with vascular dementia. Clin Interv Aging 9:411-418

Ma L, Xu Y, Wang G, Li R (2019) What do we know about sex differences in depression: A review of animal models and potential mechanisms. Prog Neuropsychopharmacol Biol Psychiatry 89:48-56

Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382-9

Nedic Erjavec G, Sagud M, Nikolac Perkovic M, Svob Strac D, Konjevod M, Tudor L, Uzun S, Pivac N (2021) Depression: Biological markers and treatment. Prog Neuropsychopharmacol Biol Psychiatry 105:110139

Ng T, Lee YY, Chae JW, Yeo AHL, Shwe M, Gan YX, Ng RCH, Chu PPY, Khor CC, Ho HK, Chan A (2017) Evaluation of plasma brain-derived neurotrophic factor levels and self-perceived cognitive impairment post-chemotherapy: a longitudinal study. BMC Cancer 17(1):867

Nilsson J, Ekblom Ö, Ekblom M, Lebedev A, Tarassova O, Moberg M, Lövdén M (2020) Acute increases in brain-derived neurotrophic factor in plasma following physical exercise relates to subsequent learning in older adults. Sci Rep 10(1):4395

Polyakova M, Schlögl H, Sacher J, Schmidt-Kassow M, Kaiser J, Stumvoll M, Kratzsch J, Schroeter ML (2017) Stability of BDNF in Human Samples Stored Up to 6 Months and Correlations of Serum and EDTA-Plasma Concentrations. Int J Mol Sci 18(6):1189

Respino M, Hoptman MJ, Victoria LW et al (2020) Cognitive Control Network Homogeneity and Executive Functions in Late-Life Depression. Biol Psychiatry Cogn Neurosci Neuroimaging 5(2):213-221

Rezola-Pardo C, Hervás G, Arrieta H et al (2020) Physical exercise interventions have no effect on serum BDNF concentration in older adults living in long-term nursing homes. Exp Gerontol 139:111024

Sagud M, Nikolac Perkovic M, Vuksan-Cusa B, Maravic A, Svob Strac D, Mihaljevic Peles A, Zivkovic M, Kusevic Z, Pivac N (2016) A prospective, longitudinal study of platelet serotonin and plasma brain-derived neurotrophic factor concentrations in major depression: effects of vortioxetine treatment. Psychopharmacology 233(17):3259-67

Santos VSDSD, Zortea M, Alves RL, Naziazeno CCDS, Saldanha JS, Carvalho SDCR, Leite AJDC, Torres ILDS, Souza A, Calvetti PÜ, Fregni F, Caumo W (2018) Cognitive effects of transcranial direct current stimulation combined with working memory training in fibromyalgia: a randomized clinical trial. Sci Rep 8(1):12477

Satomura E, Baba H, Nakano Y, Maeshima H, Suzuki T, Arai H (2011) Correlations between brain-derived neurotrophic factor and clinical symptoms in medicated patients with major depression. J Affect Disord 135(1-3):332-335

Semkovska M, Quinlivan L, O'Grady T, Johnson R, Collins A, O'Connor J, Knittle H, Ahern E, Gload T (2019)Cognitive function following a major depressive episode: a systematic review and meta-analysis. Lancet Psychiatry 6(10):851-861

Shimada H, Makizako H, Doi T, Yoshida D, Tsutsumimoto K, Anan Y, Uemura K, Lee S, Park H, Suzuki T (2014) A large, cross-sectional observational study of serum BDNF, cognitive function, and mild cognitive impairment in the elderly. Front Aging Neurosci 6:69

Silva-Peña D, García-Marchena N, Alén F et al (2019) Alcohol-induced cognitive deficits are associated with decreased circulating levels of the neurotrophin BDNF in humans and rats. Addict Biol 24(5):1019-1033

Song L, Che W, Min-Wei W, Murakami Y, Matsumoto K (2006) Impairment of the spatial learning and memory induced by learned helplessness and chronic mild stress. Pharmacol Biochem Behav 83(2):186-193

Spreen O, Benton AL (1977) Neurosensory Center Comprehensive Examination for Aphasia. University of Victoria, Neuropsychology Laboratory, Victoria, BC

Trapp W, Dotterweich S, Hintner L, Wollny H, Lautenbacher S, Hajak G (2017) Speed and capacity of working memory and executive function in schizophrenia compared to unipolar depression. Schizophr Res Cogn 10:1-6

Vieta E, Sluth LB, Olsen CK (2018) The effects of vortioxetine on cognitive dysfunction in patients with inadequate response to current antidepressants in major depressive disorder: A short-term, randomized, double-blind, exploratory study versus escitalopram [published correction appears in J Affect Disord 2018;15;236:319]. J Affect Disord 227:803-809

Wagner S, Kayser S, Engelmann J et al (2019) Plasma brain-derived neurotrophic factor (plasma BDNF) and executive dysfunctions in patients with major depressive disorder. World J Biol Psychiatry 20(7):519-530

Walsh K, Darby D (1999) Neuropsychology: A clinical approach (4th edition). Churchill Livingston, Edinburgh

Wechsler D (2010) WAIS-IV UK. Administration and Scoring Manual. Pearson, London

Yan G, Zhang M, Liu Y, Yin M (2019) Efficacy of vortioxetine combined cognitive behaviour intervention therapy on brain-derived neurotrophic factor level on depressive patients. Psychogeriatrics 19(5):475-481

Yap NY, Tan NYT, Tan CJ, Loh KW, Ng RCH, Ho HK, Chan A (2020) Associations of plasma brain-derived neurotrophic factor (BDNF) and Val66Met polymorphism (rs6265) with long-term cancer-related cognitive impairment in survivors of breast cancer. Breast Cancer Res Treat 183(3):683-696

Zhang Y, Fang X, Fan W, Tang W, Cai J, Song L, Zhang C (2018) Brain-derived neurotrophic factor as a biomarker for cognitive recovery in acute schizophrenia: 12-week results from a prospective longitudinal study. Psychopharmacology 235(4):1191-1198

Zhou C, Zhong J, Zou B, Fang L, Chen J, Deng X, Zhang L, Zhao X, Qu Z, Lei Y, Lei T (2017) Meta-analyses of comparative efficacy of antidepressant medications on peripheral BDNF concentration in patients with depression. PLoS One 12(2):e0172270

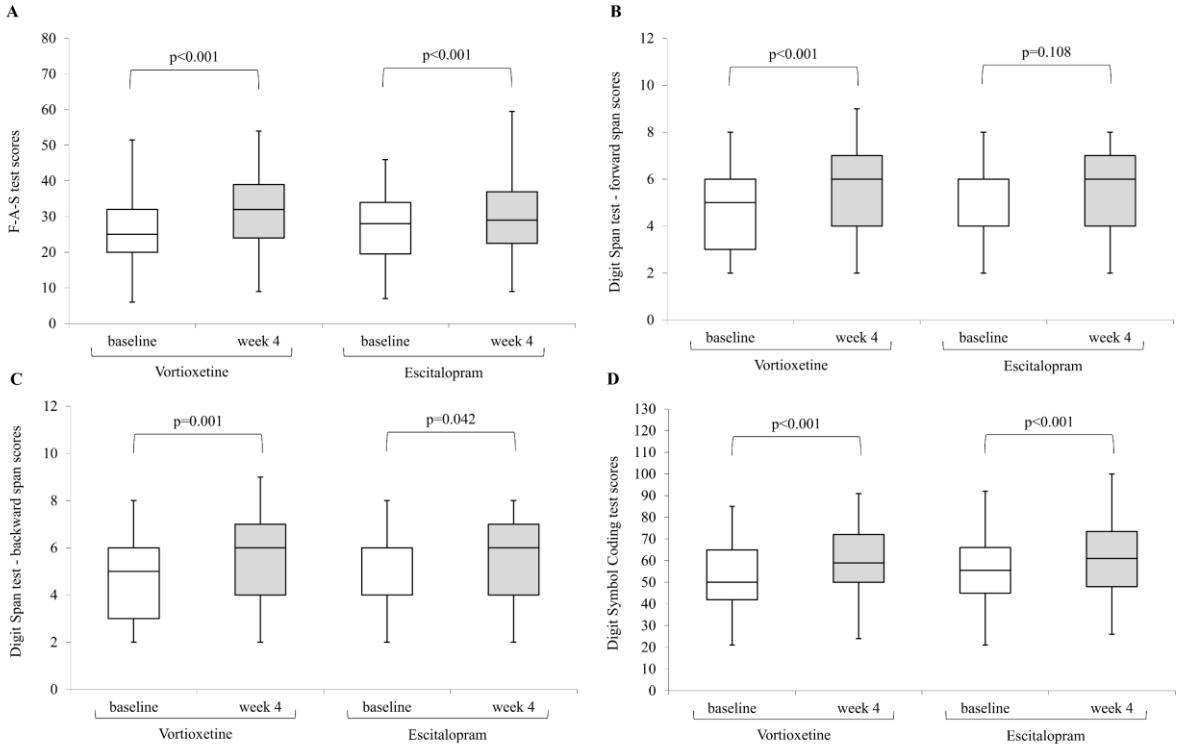
A
F-A-S test scores
p<0.001
p<0.001
baseline
week 4
baseline
week 4
Vortioxetine
Escitalopram
B
Digit Span test - forward span scores
p<0.001
p=0.108
baseline
week 4
baseline
week 4
Vortioxetine
Escitalopram
C
Digit Span test - backward span scores
p=0.001
p=0.042
baseline
week 4
baseline
week 4
Vortioxetine
Escitalopram
D
Digit Symbol Coding test scores
p<0.001
p<0.001
baseline
week 4
baseline
week 4
Vortioxetine
Escitalopram

Table 1 Assessment of cognitive functions in the present study

Test	Cognitive domain	Description
The F-A-S test A subtest of the *Neurosensory Center Comprehensive Examination for Aphasia* (NCCEA; Spreen and Benton 1977)	It measures phonemic word fluency, which is a type of verbal fluency, and facilitates information retrieval from memory. It requires executive control over cognitive process such as selective attention, mental set shifting, internal response generation, and self-monitoring. Verbal fluency tests, and in particular initial letter fluency, are widely used as tests of *executive dysfunction* (Walsh and Darby 1999).	It assesses phonemic fluency by requesting an individual to orally produce as many words as possible that begin with the letters F, A, and S, under time constraints, normally 60 seconds per letter. Phonemic fluency tests are most often scored summing the total words produced over three letters.
The Digit Span test A subtest of both the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Memory Scales) (WMS) (Wechsler 2010)	Generally, this test is routinely used as a measure of *verbal working memory* in psychiatric populations (Trapp et al. 2017; Respino et al. 2020). It is divided into 1) Forward span, which captures *attention efficiency* and 2) Backward span, that is an executive task particularly dependent on *working memory*.	Respondents read a sequence of numbers and are asked to repeat the same sequence back to the examiner in order (forward span) or in reverse order (backward span). It can be scored as one summary value, or separately for forwards and backwards performance.
The Digit Symbol Coding Test A subtest of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler 2010)	It is perhaps the most commonly used test in neuropsychology, owing to its brevity, reliability, and the minimal impact of language, culture and education on test performance (Jaeger 2018). In practice, it is frequently used as an indicator of *information processing speed* (Jaeger 2018).	A paper-and-pencil test is conducted on a sheet of paper, and the subject is instructed to match symbols to numbers, according to a certain key. The number of correct symbols within the allowed time, usually 120 seconds, constitutes the score.

Table 2 Comparison of demographic and clinical data of patients with major depressive disorder treated with vortioxetine or escitalopram

Demographic and clinical parameters		Vortioxetine N=61	Escitalopram N=60	Test statistics
Sex (male/female)		27/34	14/46	χ^2=5.91; p=**0.015**
Smoking (yes/no)		22/39	20/40	χ^2=0.10; p=0.752
Depressive episode (first or single/recurrent)		33/28	46/14	χ^2=6.80; p=**0.009**
Family history of depression (yes/no)		12/48	24/36	χ^2=5.71; p=**0.017**
Number of suicide attempts		0 (0-2)	0 (0-1)	U=1803.0; p=0.395
Age (years)		52 (18-78)	45.5 (19-67)	U=1562.0; p=0.164
Duration of illness (months)		0 (0-420)	0 (0-192)	U=1397.5; p=**0.019**
Number of depressive episodes		0 (0-10)	0 (0-10)	U=1372.0; p=**0.017**
HAMD-17 score	At baseline	23 (17-36)	21 (17-37)	U=1388.5; p=**0.022**
	After treatment	10 (1-26)	8.5 (1-34)	U=1806.5; p=0.903
MADRS score	At baseline	27 (16-51)	24 (17-41)	U=1288.5; p=**0.006**
	After treatment	11 (0-35)	10 (1-46)	U=1737.5; p=0.631
F-A-S test	At baseline	25 (6-57)	28 (7-46)	U=1902.5; p=0.707
	After treatment	32 (9-54)	29 (9-71)	U=1623.5; p=0.284
Digit Span test - forward span	At baseline	7 (3-9)	8 (5-9)	U=2061.0; p=0.219
	After treatment	8 (4-9)	8 (4-9)	U=2001.0; p=0.356
Digit Span test - backward span	At baseline	5 (2-8)	6 (2-8)	U=2085.5; p=0.178
	After treatment	6 (2-9)	6 (2-8)	U=1896.0; p=0.729
Digit Symbol Coding test	At baseline	51.0 (21-85)	55 (21-92)	U=2083.5; p=0.189
	After treatment	59 (24-91)	61 (26-100)	U=1913.0; p=0.667
plasma BDNF (ng/ml)	At baseline	0.326 (0.028-1.103)	0.342 (0.026-1.574)	U=1839.0; p=0.963
	After treatment	0.445 (0.054-3.196)	0.330 (0.067-1.392)	U=1531.0; p=0.121

Categorical data was analyzed with χ^2 test (df=1). Numerical data was analyzed with Mann-Whitney U test and shown as median (range). Significant p values are highlighted in bold. *HAMD-17*, The Hamilton Depression Rating Scale-17; *MADRS*, Montgomery-Åsberg Depression Rating Scale; *BDNF*, brain-derived neurotrophic factor; *N*, number of subjects

Table 3 Correlations of plasma BDNF levels (at baseline, after treatment, and delta BDNF) with specific clinical parameters

Clinical parameters	Spearman's rank correlation	All subjects N=121		Vortioxetine N=61		Escitalopram N=60	
		plasma BDNF (ng/ml)		plasma BDNF (ng/ml)		plasma BDNF (ng/ml)	
		At baseline	Delta (Δ)	At baseline	Delta (Δ)	At baseline	Delta (Δ)
HAMD-17 score	r_s	-0.103	-0.008	-0.177	0.007	-0.023	0.024
Delta (Δ)	p	0.260	0.930	0.173	0.954	0.862	0.853
MADRS score	r_s	-0.060	-0.007	-0.079	0.008	-0.022	-0.019
Delta (Δ)	p	0.511	0.943	0.543	0.952	0.865	0.883
F-A-S test	r_s	0.184	0.004	0.325	-0.003	0.081	-0.077
Delta (Δ)	p	**0.043**	0.963	**0.011**	0.982	0.537	0.556
Digit Span test - forward span	r_s	0.068	-0.061	0.326	-0.225	-0.178	-0.035
Delta (Δ)	p	0.460	0.509	**0.010**	0.081	0.174	0.788
Digit Span test - backward span	r_s	0.001	0.084	0.086	0.028	-0.130	0.050
Delta (Δ)	p	0.989	0.359	0.508	0.829	0.321	0.702
Digit Symbol Coding test	r_s	0.034	0.187	0.149	0.071	-0.045	0.171
Delta (Δ)	p	0.708	**0.040**	0.252	0.584	0.732	0.190

Significant p values are highlighted in bold; *HAMD-17*, The Hamilton Depression Rating Scale-17; *MADRS*, Montgomery-Åsberg Depression Rating Scale; *N*, number of subjects; *Delta (Δ)*, the percentage of change relative to the initial value.