Reduced Cerebrospinal Fluid Levels of Brain-Derived Neurotrophic Factor Is Associated With Cognitive Impairment in Late-Life Major Depression

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Objectives. Late-life depression (LLD) is associated with reduced neurotrophic support and abnormalities in neurodegenerative cascades. The aim of the present study is to determine the concentrations of brain-derived neurotrophic factor (BDNF), amyloid-β1–42, total Tau, and phosphorylated Tau in the cerebrospinal fluid (CSF) of patients with LLD and cognitive impairment compared to healthy older adults.

Method. We included 25 antidepressant-free patients with LLD (10 with mild cognitive impairment [LLD + MCI] and 15 with no cognitive decline [LLD + NCD]) and 25 healthy older adults as a comparison group. Depressive symptoms were assessed by the 21-item Hamilton Depression Rating Scale (HDRS-21) and cognitive performance by a comprehensive cognitive battery.

Results. Patients with LLD + MCI showed significantly lower CSF BDNF levels compared to LLD + NCD and healthy controls (p = .003). There were no significant differences in Alzheimer’s disease–related CSF biomarkers between groups. CSF BDNF concentrations were positively correlated with Cambridge Cognitive Test (CAMCOG) scores (r = .36, p = .02).

Discussion. The present study adds to the growing body of evidence that abnormalities in the BDNF system are involved in the pathophysiology of LLD. The reduction of the availability of BDNF in the central nervous system may indicate increased vulnerability to the development of several age-related neuropsychiatric disorders as well as to adverse cognitive outcomes.

Key Words: Alzheimer’s disease—Amyloid-β1–42—BDNF—Cerebrospinal fluid—Cognition—Late-life depression.

Cognitive impairment is common among older adults with late-life depression (LLD) and may be associated with higher risk of Alzheimer’s disease (AD) and vascular dementia (Butters et al., 2004; Diniz, Butters, Albert, Dew, & Reynolds, 2013). The neurobiological links between LLD, cognitive impairment, and dementia may involve abnormalities in neurotrophic, vascular, inflammatory, and neurodegenerative cascades (Naismith, Norrie, Mowszowski, & Hickie, 2012). A recent study reported that older adults with remitted major depression and persistent cognitive impairment showed a significant decline in plasma brain-derived neurotrophic factor (BDNF) levels over 2 years of follow-up in contrast to older adults with remitted major depression and no evidence of cognitive impairment and never-depressed elderly controls (Diniz et al., 2014). In addition, increased levels of the proapoptotic protein GSK-3β activity and increased inflammatory status correlated with worse cognitive performance (Diniz et al., 2010a; 2011).

Recent studies in LLD focused on the determination of neurodegenerative (AD-related) biomarkers, yielding contradictory results. Gudmundsson and coworkers (2007) found increased concentrations of the amyloid-beta peptide (Aβ1–42) in the cerebrospinal fluid (CSF) of LLD patients. More recently, Pomara and coworkers (2012) presented opposite findings (i.e., decreased CSF levels of Aβ1–42), whereas Reis, Brandão, Freire Coutinho, Engelhardt, and Laks (2012) did not find significant differences of CSF concentrations of Aβ1–42 in LLD patients as compared to controls. Molecular neuroimaging studies showed higher β-amyloid load in older adults with LLD compared to elderly controls (Butters et al., 2008; Kumar et al., 2011). Nonetheless, none of the previous studies specifically addressed whether cognitive impairment in older adults with LLD related to abnormalities in CSF biomarkers related to AD (i.e., Aβ1–42 total Tau, and phosphorylated Tau1–31) or other biomarkers. Abnormalities in these CSF biomarkers have been linked to higher risk of AD in subjects with mild cognitive
improvement (MCI) (Hansson et al., 2006). To understand how changes in biomarkers relate to cognitive impairment in LLD is of utmost importance given the higher risk of dementia in these subjects (Diniz, Butters, et al., 2013).

Therefore, this study aims to evaluate CSF concentrations of AD-related biomarkers (Aβ42, total Tau, and phosphorylated Tau181), and BDNF in elderly individuals with major depression and MCI compared to healthy older adults. We hypothesize that older adults with LLD and MCI have reduced CSF BDNF levels and changes in AD-related CSF biomarkers (i.e., lower Aβ42 levels and higher total and phosphorylated Tau protein) compared to elderly individuals with major depression and no cognitive decline (NCD), and healthy older adults.

**METHOD**

**Participants and Setting**

The present study was conducted at a university-based psychogeriatric clinic (Institute of Psychiatry, University of Sao Paulo, Brazil), and participants were community-dwelling older adults from the hospital catchment area. The local ethics committee approved all procedures and the study was conducted under the tenets of the Declaration of Helsinki.

Fifty older adults were included in this study (25 older adults with LLD and 25 healthy older adults, as a comparison group). Patients with LLD were not under antidepressant treatment for at least 1 month prior to enrollment. Eleven LLD subjects had recurrent early-onset depression (EOD) (i.e., the first depressive episode took place before 60 years old, EOD) and 14 had first episode, late-onset depression (LOD) (first depressive episode took place after 60 year old, LOD). Subjects in the comparison group were recruited from a prospective cohort study on cognitive aging in course at this institution, and had no evidence of past or present major psychiatric disorders or signs of cognitive impairment (Forlenza et al., 2010a). All participants were assessed by the Structured Clinical Interview for DSM-IV disorders (SCID) (First, Spitzer, Gibbon, & Williams, 2002), and the diagnosis of major depression episode was made according to the DSM-IV-TR criteria (American Psychiatric Association, 2000). The severity of the current depressive episode was determined with the 21-item Hamilton Depression Rating Scale (HDRS-21) (Hamilton, 1960). All participants underwent a comprehensive clinical evaluation for the assessment of concurrent clinical comorbidities and neuroimaging assessments (magnetic resonance) to exclude for major cerebrovascular lesions when clinically indicated.

All subjects underwent a comprehensive cognitive assessment. The assessment battery included the Cambridge Cognitive Test (CAMCOG) (Roth et al., 1986), the Mini-Mental State Examination (MMSE) (M. F. Folstein, S. E. Folstein, & McHugh, 1975), the Rivermead Behavioral Memory Test (RBMT), Short Cognitive Test (SKT), semantic verbal fluency (animal category), Trail Making Test A (TMT-A), and Trail Making Test B (TMT-B). Cognitive status was adjudicated at consensus meeting with psychiatrists and neuropsychologists experienced in the diagnosis and management of cognitive disorders in the elderly. The performance on the cognitive tests was adjusted for age and educational status according to local norms. Older adults with LLD were classified as MCI (i.e., LLD + MCI) according to the Mayo Clinic criteria (Petersen et al., 2001) (n = 10); otherwise, they were classified as having NCD (i.e., LLD + NCD) (n = 15).

**CSF Sampling and Analysis**

Patients consented to undergo lumbar puncture for CSF sampling and biomarker analysis. CSF samples were taken by lumbar puncture in the L3/L4 or L4/L5 intervertebral space, with a 23-gauge needle and using polypropylene tubes, in the morning. A total of 12–15 ml of CSF was collected and, then, centrifuged at 3200 g for 10 min at 4 °C. After centrifugation, the samples were separated in 0.5 ml aliquots, and immediately frozen at −80 °C until analysis.

The determination of CSF concentrations of AD-related biomarkers, that is, total Tau (T-Tau), phosphorylated Tau181 (P-Tau), and amyloid-β (Aβ42), was done in duplicate with the INNo-Bia AlzBio3 assay (Innogenetics, Ghent, Belgium), a multiplex microsphere-based Luminex (xMAP) platform that allows the simultaneous analysis of these biomarkers. After pre-wetting the filter plate with a wash buffer, a suspension of microsphere carrying the corresponding capturing antibodies (AT120, AT270, and 4D7A3 for T-Tau, phosphorylated Tau181, P-Tau, and amyloid-β (Aβ42), respectively) was added to the plate. A mixture of biotinylated monoclonal antibodies, designed to detect specifically one of the capturing antibodies (HT7 for T-Tau and P-Tau, and 3D6 for Aβ42), and 75 µl of CSF or standards were added to the plate and incubated overnight in the dark. Next, the plate was washed and a detection conjugate (phycoerythrin-labeled streptavidin) was added and incubated for 1 hr at room temperature. The plate was washed and after the addition of a reading solution (phosphate buffer saline), the assay was analyzed on a Luminex 100 IS platform (Luminex, Austin, TX). Standard curves were constructed for each biomarker using a sigmoidal curve-fitting method, and the mean fluorescence values for the duplicate CSF samples were used to determine the concentration of T-Tau, P-Tau, and Aβ42.

CSF levels of BDNF were measured by enzyme-linked immunosorbent assay according to the procedures supplied by the manufacturer (DuoSet, R&D Systems, Minneapolis, MN). In brief, the capture antibody (concentration provided by the manufacturer) was diluted in phosphate-buffered saline (PBS), added to each well and left overnight at 4 °C. The plate was washed four times in PBS with 0.05% Tween 20 (Sigma, St Louis, MO). The plate was blocked with 1% bovine serum albumin and incubated for 1 hr at room temperature before washing four times with PBS and
0.05% Tween 20. The samples and standards were added and the plate incubated overnight at 4 °C. After washing the plate, detection antibody (concentration provided by the manufacturer) diluted in PBS was added. The plate was incubated for 2 hs at room temperature. After washing the plate, streptavidin (DuoSet, R&D Systems) was added and the plate incubated for 30 min. At last, a color reagent o-phenylenediamine (Sigma) was added to each well and the reaction was allowed to develop in the dark for 15 min. The reaction was stopped with the addition of 1 M H₂SO₄ to each well. The absorbance was read on a plate reader at 492 nm wave length (Emax; Molecular Devices, Minneapolis, MN). All samples were assayed in duplicate. The detection limits for the BDNF assays were 5 pg/ml.

Statistical Analysis
Because the concentrations of CSF biomarkers did not show a normal distribution, they were log-transformed prior to statistical analysis. Student’s t-tests and analysis of variances were used to examine differences in the mean values of continuous variables (demographic, clinical, and CSF biomarker levels). Pearson’s chi-squared tests were used to examine differences in categorical variables (e.g., gender distribution). Pearson’s correlation analyses were carried out to determine the correlation between demographic, clinical, and biological variables.

Results
There were no significant differences in age, educational level, and gender distribution between LLD and controls. Individuals in the LLD group had significantly higher HDRS-21 scores and worse cognitive performance (Supplementary Table 1). The most common comorbid clinical conditions either in patients or controls were hypertension and dyslipidemia; there were no significant differences in the frequency of clinical comorbidity between the two groups (data not shown). We found no significant differences in CSF concentrations of AD-related biomarkers between individuals in the LLD and control groups (Aβ₄₂: LLD, 462.10±208.0 pg/ml vs. controls, 465.0±166.5 pg/ml, t(48) = 0.54, p = .9; T-Tau: LLD, 55.5±36.6 pg/ml vs. controls, 49.0±33.9 pg/ml, t(48) = 0.64, p = .5; P-Tau_181: LLD, 73.6±49.2 pg/ml vs. control, 68.4±54.1 pg/ml, t(48) = 0.35, p = .7). Nonetheless, participants with LLD had a significantly lower CSF BDNF levels compared to controls (LLD, 39.9±31.8 pg/ml vs. controls, 98.1±83.99 pg/ml, t(48) = 3.2, p = .002).

Age of onset of depressive disorder did not significantly influence CSF Aβ₄₂ (EOD: 503.7±205.6 pg/ml vs. LOD: 429.4±211.6 pg/ml, df = 23, t = 0.88, p = .38), total Tau protein (EOD: 74.1±40.6 pg/ml vs. LOD: 73.1±46.6 pg/ml, df = 23, t = 0.05, p = .96), phosphorylated Tau protein (EOD: 52.5±41.67 pg/ml vs. LOD: 57.8±33.5 pg/ml, df = 23, t = 0.35, p = .73). There was no significant differences in CSF BDNF level between EOD and LOD (EOD: 45.92±41.7 pg/ml vs. LOD: 35.23±20.67 pg/ml, df = 23, t = 0.84, p = .4).

After dividing the participants in the LLD group according to the cognitive status, individuals with LLD + MCI had significantly fewer years of education and significantly higher HDRS-21 scores compared to LLD + NCD and controls. There were no significant differences in age or gender distribution among groups (Table 1). We found no significant differences on AD-related biomarkers among groups (Table 2). We found a significant difference in CSF BDNF levels across the three groups, with individuals in the LLD + MCI group having the lower CSF BDNF levels compared to LLD + NCD and controls. There were no significant differences in age or gender distribution among groups (Table 1). We found no significant differences on AD-related biomarkers among groups (Table 2). We found a significant difference in CSF BDNF levels across the three groups, with individuals in the LLD + MCI group having the lower CSF BDNF levels compared to LLD + NCD and controls. There were no significant differences in age or gender distribution among groups (Table 1). We found no significant differences on AD-related biomarkers among groups (Table 2). We found a significant difference in CSF BDNF levels across the three groups, with individuals in the LLD + MCI group having the lower CSF BDNF levels compared to LLD + NCD and controls. There were no significant differences in age or gender distribution among groups (Table 1). We found no significant differences on AD-related biomarkers among groups (Table 2).

| Notes. Data (except Gender) represent mean values (±SD), CAMCOG = Cambridge Cognitive Test; HDRS-21 = 21-item Hamilton Depression Rating Scale; LLD = late-life depression; M = Men; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NCD = no cognitive decline; SKT = Short Cognitive Test; W = women. |

Table 1. Demographic and Clinical Variables According to the Presence of Cognitive Impairment in LLD Subjects

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control (n = 25)</th>
<th>LLD + NCD (n = 15)</th>
<th>LLD + MCI (n = 10)</th>
<th>Statistics</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (W/M)</td>
<td>17/8</td>
<td>9/6</td>
<td>7/3</td>
<td>χ² = 0.62</td>
<td>2</td>
<td>.7</td>
</tr>
<tr>
<td>Age</td>
<td>71.0±3.7</td>
<td>69.5±5.4</td>
<td>68.7±5.9</td>
<td>F = 1.03</td>
<td>2.97</td>
<td>.36</td>
</tr>
<tr>
<td>Years of education</td>
<td>13.2±5.5</td>
<td>12.6±5.6</td>
<td>7.9±6.7</td>
<td>F = 2.93</td>
<td>2.47</td>
<td>.04</td>
</tr>
<tr>
<td>CAMCOG</td>
<td>98.4±2.3</td>
<td>89.3±24.2</td>
<td>75.1±8.4</td>
<td>F = 9.07</td>
<td>2.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.1±1.2</td>
<td>28.3±1.3</td>
<td>22.3±2.4</td>
<td>F = 65.9</td>
<td>2.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDRS-21</td>
<td>1.2±1.9</td>
<td>13.3±6.4</td>
<td>20.3±8.3</td>
<td>F = 55.4</td>
<td>2.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RBMT screening score</td>
<td>10.4±1.5</td>
<td>8.2±2.4</td>
<td>4.4±2.8</td>
<td>F = 22.5</td>
<td>2.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RBMT profile score</td>
<td>22.01±1.9</td>
<td>19.5±3.2</td>
<td>10.8±5.5</td>
<td>F = 33.0</td>
<td>2.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>20.3±5.4</td>
<td>16.3±5.7</td>
<td>13.1±2.6</td>
<td>F = 44.6</td>
<td>2.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TMT-A</td>
<td>51.1±14.6</td>
<td>77.2±42.6</td>
<td>130.2±78.6</td>
<td>F = 9.9</td>
<td>2.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TMT-B</td>
<td>113.3±49.1</td>
<td>196.8±177.2</td>
<td>343.0±147.6</td>
<td>F = 9.9</td>
<td>2.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SKT</td>
<td>2.8±2.9</td>
<td>6.1±3.5</td>
<td>12.7±4.8</td>
<td>F = 20.2</td>
<td>2.47</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Notes: Data (except Gender) represent mean values (±SD), CAMCOG = Cambridge Cognitive Test; HDRS-21 = 21-item Hamilton Depression Rating Scale; LLD = late-life depression; M = Men; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NCD = no cognitive decline; SKT = Short Cognitive Test; W = women.
Table 2. Concentrations of CSF Biomarkers in According to the Presence of Cognitive Impairment in Subjects With LLD and Healthy Older Adults

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 25)</th>
<th>LLD + NCD (n = 16)</th>
<th>LLD + MCI (n = 9)</th>
<th>F</th>
<th>df</th>
<th>p</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDNF (pg/ml)</td>
<td>98.14 ± 84.00</td>
<td>46.99 ± 37.73</td>
<td>27.40 ± 2.96</td>
<td>6.58</td>
<td>2,47</td>
<td>.003</td>
<td>0.22</td>
</tr>
<tr>
<td>Aβ42 (pg/ml)</td>
<td>464.97 ± 166.48</td>
<td>480.12 ± 232.29</td>
<td>429.99 ± 163.92</td>
<td>0.117</td>
<td>2,47</td>
<td>.89</td>
<td>0.005</td>
</tr>
<tr>
<td>P-Tau181 (pg/ml)</td>
<td>49.04 ± 33.90</td>
<td>58.20 ± 41.76</td>
<td>50.56 ± 26.66</td>
<td>0.38</td>
<td>2,47</td>
<td>.69</td>
<td>0.016</td>
</tr>
<tr>
<td>T-Tau (pg/ml)</td>
<td>68.41 ± 54.07</td>
<td>64.83 ± 41.62</td>
<td>89.15 ± 60.02</td>
<td>0.51</td>
<td>2,47</td>
<td>.6</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Notes. Data represent mean ± SD; all biomarkers values are shown as raw values (prior to log transformation). Aβ42 = amyloid-β; BDNF = brain-derived neurotrophic factor; CSF = cerebrospinal fluid; LLD = late-life depression; MCI = mild cognitive impairment; NCD = no cognitive decline; P-Tau181 = phosphorylated Tau181; T-Tau = total Tau.

levels compared to LLD + NCD (p = .03) and controls (p = .002); participants in the LLD + NCD group had significantly lower BDNF levels compared to controls (p = .04) (Figure 1).

Pearson correlation analyses showed that CSF BDNF levels were significantly correlated with the scores on the CAMCOG (r = .33, p = .02), trail making test B (r = .35, p = .02), STK (r = .36, p = .01), and the HDRS-21 (r = −.38, p = .006). CSF BDNF levels were not significantly correlated with other demographic variables, scores on other tests, or CSF AD-related biomarkers. It is noteworthy that AD-related CSF biomarkers were not significantly correlated with any demographic or clinical data in these subjects (Supplementary Table 2).

**DISCUSSION**

In the present study, we found that elderly patients with major depression had significantly lower CSF concentrations of BDNF compared to healthy older adults. After dividing the LLD participants according to the cognitive status, those with MCI had the lowest BDNF, compared to LLD + NCD and controls. In addition, lower CSF BDNF levels correlated with the more severe depressive symptoms and with worse cognitive performance. To the best of our knowledge, this is the first study to report a significant reduction in BDNF levels in the CSF in LLD, in particular in LLD subjects with MCI. On the other hand, we did not find significant differences in AD-related biomarkers nor a significant correlation between BDNF and these biomarkers. Thus, the present study confirms previous studies that LLD is associated with significant reduction in BDNF levels. Furthermore, we provide evidences that cognitive impairment in LLD may not be related to AD neuropathology, but to abnormalities in other biological cascades, like the neurotrophic cascade, as demonstrated by the lowest BDNF levels found in LLD + MCI participants in this study.

Most of the evidence linking abnormalities in BDNF and depression in humans derived from studies based on peripheral sources of BDNF, such as plasma or serum. In the present work, we addressed BDNF in the CSF, which is considered a reliable source for biomarker assessment and discovery for brain disorders (Reiber, 2001). Due to the intimate contact of the CSF with brain tissue, changes in the latter may be readily detected in the CSF. Our findings are in line with the available literature on peripheral sources of BDNF and provide strong evidence that down-regulation of the BDNF system is an important feature of the pathophysiology of depression and cognitive impairment in the elderly.

Previous studies from our group and others showed that patients with LLD are systemically depleted of several neurotrophins, such as BDNF, nerve growth factor, and Glial cell–derived neurotrophic factor (Diniz et al., 2010b; 2012; Diniz, Teixeira, et al., 2013). In a recent study, we found that among older adults with remitted major depression and on antidepressant maintenance treatment, those with persistent cognitive showed a greater decline in BDNF levels, over 2 years of follow-up, compared to subjects with LLD and NCD and healthy elderly controls (Diniz et al., 2014). Altogether, these findings reinforce the association between decreased neurotrophic support in brain aging and the emergence of depressive and cognitive symptoms in the elderly (McKinney & Siblee, 2013; Siblee, 2013).

Depression in the elderly is associated with increased risk for cognitive decline and dementia, particularly in the presence of cognitive impairment (Diniz, Butters, et al., 2013; Modrego & Ferrández, 2004). Abnormalities in the BDNF system have also been found in other neuropsychiatric disorders, including MCI and AD (Forlenza et al., 2010b). During a major depressive episode in late life, decreased availability of BDNF may potentiate other coexisting abnormalities that take place throughout the aging process, and eventually exert a negative impact on brain aging. In the presence of other pathological events associated with neurodegeneration (e.g., increased brain amyloid deposition and Tau protein phosphorylation), decreased neurotrophic support may hasten the rate of cognitive decline and progression to AD or other dementia syndrome (Diniz et al., 2014). Therefore, LLD may lead to increased risk of dementia not by increasing neurodegenerative changes in the brain (Tsopelas et al., 2011), but by rendering the brain more vulnerable to insults, that is, by reducing brain reserve against neurotoxic insults.

We did not find significant differences in elderly depressed patients, even after splitting the sample according to cognitive status, compared to healthy elders in the CSF biomarkers related to AD pathophysiology. Our findings are in agreement with those presented by Reis and coworkers (2012) in...
a relatively similar sample. Nonetheless, previous studies also reported reduced CSF amyloid-β_{42} levels and increased brain amyloid burden in older adults with major depression (Butters et al., 2008; Pomara et al., 2012). These contradictory findings point to the highly heterogeneous nature of the pathophysiological changes in LLD as previously observed in neuropathological studies (Tsopelas et al., 2011).

The main limitation of the present study is the relatively small sample, limiting the generalizability of the results. Older adults with depression may not readily consent to undergo lumbar puncture due to its invasive nature and this may limit the recruitment of larger samples. On the other hand, this sample is very homogeneous with respect to socio-demographic characteristics and all patients were antidepressant free for at least 1 month prior to lumbar puncture, clinical, and cognitive assessments. Thus, the current results are less likely to be biased by the effect of antidepressants on BDNF levels and on cognitive status. We did not include subjects with MCI and no depression or with AD as additional comparison groups. The inclusion of these subjects would support the current findings that lower BDNF and not the presence of neurodegenerative markers is one of the drivers of cognitive impairment in LLD.

Reduced BDNF levels can also be found in younger adults with major depression and with bipolar disorder (Brunoni, Lopes, & Fregni, 2008; Fernandes et al., 2011). Therefore, reduced BDNF levels are not a specific marker of depression in older adults and may be a state marker of current affective episode across lifespan. However, the comorbid cognitive impairment in LLD may indicate the presence of more severe neurobiological abnormalities in these subjects that is specifically reflected in a more significant reduction of BDNF in LLD and cognitive impairment (Diniz et al., 2014). Additional studies are needed to confirm the present findings, with larger sample sizes and preferentially including community-based subjects. Ideally, repeated determinations of BDNF and other biomarkers should be performed at baseline and longitudinally, in order to ascertain the effect of antidepressant treatment on BDNF homeostasis.

In conclusion, the present study adds to the growing body of evidence that abnormalities in the BDNF system are involved in the pathophysiology of depression, and more specifically, to the emergence of cognitive impairment in these subjects. The reduction of the availability of BDNF in the central nervous system, as shown by significantly lower concentrations in the CSF, may indicate increased

Figure 1. BDNF levels in the cerebrospinal fluid according to cognitive status.
vulnerability to the development of several age-related neuropsychiatric disorders as well as to negative cognitive outcomes. Pharmacological and non-pharmacological interventions aiming not only the remission of depressive symptoms, but also being able to restore BDNF system homeostasis, may help, at least in part, to prevent cognitive decline and the increased risk of dementia observed in older adults with major depression.

SUPPLEMENTARY MATERIAL
Supplementary material can be found at: http://psychsocgerontology.oxfordjournals.org/

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CONFLICT OF INTEREST
The authors do not have any conflict of interest to report regarding this manuscript.

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