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Brain-derived neurotrophic factor levels in late-life depression and comorbid mild cognitive impairment: A longitudinal study

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ABSTRACT

Changes in brain-derived neurotrophic factor (BDNF) level are implicated in the pathophysiology of cognitive decline in depression and neurodegenerative disorders in older adults. We aimed to evaluate the longitudinal association over two years between BDNF and persistent cognitive decline in individuals with remitted late-life depression and Mild Cognitive Impairment (LLD + MCI) compared to either individuals with remitted LLD and no cognitive decline (LLD + NCD) or never-depressed, cognitively normal, elderly control participants. We additionally evaluated the effect of double-blind, placebo-controlled donepezil treatment on BDNF levels in all of the remitted LLD participants (across the levels of cognitive function). We included 160 elderly participants in this study (72 LLD + NCD, 55 LLD + MCI and 33 never-depressed cognitively normal elderly participants). At the same visits, cognitive assessments were conducted and blood sampling to determine serum BDNF levels were collected at baseline assessment and after one and two years of follow-up. We utilized repeated measure, mixed effect models to assess: (1) the effects of diagnosis (LLD + MCI, LLD + NCD, and controls), time, and their interaction on BDNF levels; and (2) the effects of donepezil treatment (donepezil vs. placebo), time, baseline diagnosis (LLD + MCI vs. LLD + NCD), and interactions between these contrasts on BDNF levels. We found a significant effect of time on BDNF level ($p = 0.02$) and a significant decline in BDNF levels over 2 years of follow-up in participants with LLD + MCI ($p = 0.004$) and controls ($p = 0.04$). We found no effect of donepezil treatment on BDNF level. The present results suggest that aging is an important factor related to decline in BDNF level.

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1. Introduction

Late-life depression (LLD) is a common psychiatric disorder in older adults. It is associated with significant functional and cognitive impairment and is an important risk factor for dementia, in particular Alzheimer's disease (AD) and Vascular Dementia (VaD) (Diniz et al., 2013). Persistent cognitive impairment is common even after successful antidepressant treatment and may be a marker of risk for progression to dementia (Bhalla et al., 2009; Lee et al., 2007). In a recent double-blind randomized clinical trial, our group evaluated whether long-term donepezil treatment was associated with cognitive improvement in patients with LLD (Reynolds et al., 2011). We found that patients with remitted LLD and MCI who were treated with donepezil showed significant improvement on memory performance and reduced risk of Dementia/AD over two years compared with patients on placebo. Similar findings have been reported by others, suggesting that donepezil treatment can have a protective effect against cognitive impairment and progression to dementia in LLD (Lu et al., 2009).

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The pathophysiologic mechanisms of cognitive impairment in LLD are not clear, but may involve cerebrovascular burden, dysfunction of the Hypothalamus-Pituitary-Adrenal (HPA) axis, inflammatory status, and decreased neurotrophic support (Butters et al., 2008; Caraci et al., 2010). BDNF is the most abundant neurotrophic factor in the brain. It is involved in several functions including the maintenance of neuronal homeostasis, synapse development and strengthening via glutamate activity-dependent pathways, cell proliferation, memory consolidation and resilience against insults (Tapia-Aranciba et al., 2008). BDNF is also found in the periphery (e.g. serum and platelets) and can be assessed in relation to psychiatric disorders and brain function (Teixeira et al., 2010). Serum BDNF levels can be modulated by antidepressant pharmacotherapies (Sen et al., 2008). Treatment with cholinesterase inhibitors (e.g. donepezil), which are approved for the treatment of AD, can also modulate peripheral BDNF levels. In a preliminary, open study, including a small sample of 19 subjects diagnosed with AD and treated with 10 mg of Donepezil over 15 months, Leyhe et al. (2008) showed a significant increase in serum BDNF levels after donepezil treatment. The results suggest increasing increments in BDNF levels as a possible mechanism of action of donepezil (Leyhe et al., 2008).

Changes in the BDNF system has been associated with LLD. The presence of the Met allele in position 66 of the BDNF gene confers an increased risk of LLD, and is associated with greater whiter matter hyperintensity lesion burden in these individuals (Taylor et al., 2008; Pei et al., 2012). Reduced BDNF levels may be a putative mechanism of cognitive decline in LLD, as a similar pattern of changes in BDNF levels is observed among LLD, MCI and AD patients (Diniz et al., 2010; Diniz and Teixeira, 2011). In addition, there is evidence that BDNF is negatively correlated with age-related reduction in hippocampal volume (Erickson et al., 2010). Nonetheless, the cross-sectional design of these studies limits the ability to interpret the effect of LLD, cognitive impairment, and aging on BDNF levels. To date no study has evaluated whether persistent cognitive impairment in individuals with remitted LLD is associated with lower BDNF levels, or whether BDNF continues to decline over time. A better understanding of the relationship between changes in BDNF and cognitive function in LLD is important to develop more specific treatments for these associated conditions.

We aimed therefore to evaluate the association between BDNF and persistent cognitive decline in participants with remitted LLD (LLD + MCI) compared to either participants with remitted LLD and no cognitive decline (LLD + NCD) and to healthy control subjects over two years of follow-up. We further evaluated the impact of long-term donepezil treatment on BDNF levels in these patients. We hypothesized that BDNF would be reduced in subjects with LLD + MCI and would decline faster in these subjects compared to LLD + NCD and to healthy controls. Additionally, we hypothesized, based on prior preliminary data (Leyhe et al., 2008), that long-term donepezil treatment would significantly increase BDNF levels in everyone.

2. Methods

This study is based upon a previously published double-blind, randomized, placebo-controlled clinical trial to evaluate the effect of donepezil on cognitive performance, instrumental activities of daily living and prevention of depressive episode recurrence in patients with recently remitted LLD. Patients' recruitment, methodology, and primary outcomes of this clinical trial have been reported by Reynolds et al. (2011).

In brief, a total of 299 older adults were initially screened for this study. Two hundred twenty qualified for participation and provided consent, 158 responded to open antidepressant pharmacotherapy and completed assessment for the randomized controlled trial, and of these, 130 eligible participants agreed to randomization to receive donepezil or placebo in addition to continuing two years of maintenance antidepressant medication after remission of the index depressive episode. Following antidepressant response during the first phase, participants had baseline neuropsychological and cognitive instrumental activities of daily living (C-IADL) assessment (baseline assessment) and independent ascertainment of cognitive status (normal, MCI, dementia) by the University of Pittsburgh Alzheimer's Disease Research Center (ADRC).

At baseline, 73 of 130 LLD participants who had responded to antidepressant treatment were cognitively normal and 57 were found to have MCI. The participants were then randomized to receive placebo or donepezil treatment and had repeated neuropsychological and C-IADL assessment 12 and 24 months later. Donepezil/placebo treatment was provided throughout the 24 month duration of the trial. Of note, the randomization process was stratified by cognitive status (No Cognitive Disorder vs. Mild Cognitive Impairment); thus, the placebo and donepezil treatment arms were balanced in the proportion of participants with and without cognitive impairment at baseline.

In order to provide a benchmark to assess change over time in depressed participants, 36 older adults with no evidence of lifetime cognitive or psychiatric disorders were included in a control group. They had the same clinical and neuropsychological and C-IADL evaluations as participants with depression in the clinical trial at 12 and 24 month follow-up.

2.1. Blood sampling and BDNF analysis

Blood samples from depressed and control subjects were drawn in the morning at baseline (and prior to randomization in the case of LLD participants), 12 and 24 month assessments. Serum was separated by centrifugation and serum aliquots were frozen and stored at −80 °C until analysis. Serum BDNF levels were measured using a high-sensitivity quantitative enzyme immunoassay (ELISA) (R&D Systems, Minneapolis, MN). All samples were measured in duplicate and the average intra-assay and inter-assay coefficients of variation were 6.2% and 11.3%, respectively.

2.2. Statistical analysis

We followed the intention-to-treat principle for all analyses. Thus, all randomized LLD participants and control subjects were considered in the analyses if they had at least one BDNF measurement available and were analyzed according to the intervention group that the subjects were assigned at the time of randomization (e.g. maintenance phase of the trial (in the case of LLD participants). Therefore, the analysis focused on data from the 160 participants who had a BDNF measurement (72 LLD + NCD, 55 LLD + MCI and 33 controls). There were no differences in sociodemographic and clinical variables between participants with and without baseline BDNF levels (*data not shown*). For all analyses, we utilized a repeated measure, mixed model analysis with an unstructured covariance structure (Laird and Ware, 1982). The mixed model analysis allows for missing data and the modeling uses all available data for the estimates. Linear contrasts were used to examine patterns of change over time.

In the first set of analyses, we evaluated the association between persistent cognitive impairment and changes in BDNF level over two years of follow-up. We tested the main effect of baseline diagnosis (LLD + MCI, LLD + NCD, controls) and time (baseline, 12 months and 24 months of follow-up), and diagnosis × time interaction on BDNF levels. We carried out an additional exploratory analysis to evaluate the pattern of change on BDNF levels on the

Table 1
Baseline socio-demographic and cognitive performance according to diagnostic groups.

	Controls ($N = 33$)	LLD + NCD ($N = 72$)	LLD + MCI ($N = 55$)	Test statistics	df	P	Effect size[a]
Gender (% Women)	73%	78%	76%	$\chi^2 = 0.32$	2	0.85	0.05
Race (% Whites)*	88%	93%	86%	$\chi^2 = 2.00$	2	0.37	0.11
Age (years)**	74.1 ± 5.1	72.0 ± 5.9	75.5 ± 6.1	$F = 5.96$	2157	0.003	0.07
Education (years)**	14.3 ± 2.1	14.1 ± 2.7	12.9 ± 2.1	$F = 5.04$	2157	0.008	0.06
Baseline HDRS**	2.6 ± 1.9	6.1 ± 3.1	7.2 ± 3.1	$F = 27.30$	2157	<0.001	0.26
DRS**	137.4 ± 3.9	138.3 ± 3.8	132.7 ± 5.6	$F = 25.44$	2157	<0.001	0.25
MMSE**	28.8 ± 1.0	28.9 ± 1.1	27.8 ± 1.5	$F = 14.75$	2157	<0.001	0.16
BDNF (pg/ml)[b]	18.3 ± 7.3	16.2 ± 6.0	15.5 ± 6.1	$F = 1.64$	2146	0.20	0.02

HDRS: Hamilton Depression Rating Scale; DRS: Dementia Rating Scale; MMSE: Mini-Mental State Examination.
Baseline HDRS: HDRS scores after the remission of the index depressive episode, prior to randomization to Donepezil or placebo (Reynolds et al., 2011).
*Vs. non-Whites.
**Data shown as mean ± standard deviation.
[a] Effect size: Cramer's V for categorical and eta-square for continuous.
[b] Data shown as mean ± standard error (analysis controlled for baseline age and HDRS scores, eta squared: 0.03 and 0.0003 respectively).

subjects whose cognitive diagnosis did not change during course of follow-up.

In the second set of analyses, we evaluated the effect of long-term donepezil treatment on BDNF in participants with remitted LDD. We tested the main effect of treatment (donepezil vs. placebo), time (baseline, 12 months and 24 months of follow-up), and cognitive status at baseline (LLD + MCI, LLD + NCD), and all interactions between these contrasts. For this analysis, we included only the LLD participants (LLD + NCD, 72 subjects; LLD + MCI, 55 subjects).

We used the SPSS v. 14 for Windows (SPSS, Chicago, IL) and SAS version 9.3 statistical software (SAS Institute, Inc, Cary, North Carolina) for all analysis. Statistical significance was set at $\alpha < 0.05$.

3. Results

Table 1 shows baseline (that is, following remission of depression, at the point of randomization to donepezil or placebo) socio-demographic, depressive symptoms and cognitive performance according to diagnostic groups. As expected, participants with LLD + MCI had significantly worse scores on the Mini-Mental State Examination (MMSE) and the Dementia Rating Scale (DRS) with less years of education than both LLD + NCD and controls. Both LLD groups had higher depressive scores than the control subjects at time of baseline BDNF measurement with LLD + MCI having highest scores. LLD + NCD were younger than the LLD + MCI and controls.

Baseline BDNF levels did not differ among diagnostic groups both looking at unadjusted and adjusted models controlling for baseline age and HDRS scores given that participants differed in age and HDRS scores at baseline ($F(2,148) = 1.97$, $p = 0.14$, and $F(2,146) = 1.64$, $p = 0.20$ respectively). Repeated measure, mixed model analyses were run using baseline age and HDRS scores as covariates (Table 2, model 1). Neither age nor HDRS scores were significant covariates. We found a main effect for time on BDNF level; but no significant effect of diagnosis, or interaction between diagnosis and time. Fig. 1A shows the BDNF level over time for each of the 3 groups.

As the diagnosis of MCI may change over a short period of time, with some participants resuming normal cognitive performance, while others with no evidence of cognitive impairment showing cognitive decline (Diniz et al., 2009), we focused the analysis only on participants who retained the same diagnosis at all observable time points. These analyses showed that mean BDNF levels decreased in LLD + MCI participants between baseline and 24 months of follow-up (estimated difference = −6.04(se = 2.06), $t(114) = 2.93$, $p = 0.004$), and in healthy controls (estimated difference = 3.77 (se = 1.82), $t(114) = 2.07$, $p = 0.04$). We did not find a significant change in mean BDNF level in LLD + NCD between baseline and 24 months of follow-up (estimated difference = 0.15 (se = 1.25), $t(114) = -0.12$, $p = 0.90$). Interaction between diagnosis and time was not significant $F(4,114) = 1.99$, $p = 0.10$.(Fig. 1B). We did additional analyses in the whole sample examining whether an individual's trajectory of BDNF change correlated with his/her trajectory of cognitive change. We did not find a significant correlation

Table 2
Repeated measure mixed model analyses.

Main effect	Beta (se)	df	F	p
Model 1: Effect of diagnosis (LLD + MCI, LLD + NCD, controls), time, and the interaction between diagnosis and time on BDNF levels using baseline age and HDRS as covariates.**				
Intercept	27.81 (5.82)			
Age*	−0.13 (0.08)	1155	2.71	0.10
HRSD scores*	0.02 (0.16)	1155	0.02	0.90
Diagnosis		2155	1.89	0.16
LLD + MCI	−2.73 (1.59)			
LLD + NCD	−2.58 (1.47)			
Time		2155	4.32	0.02
1 year	−1.87 (1.63)			
2 year	−3.50 (1.64)			
Diagnosis × Time		4155	0.97	0.42
LLD + MCI: 1 year	−0.12 (2.11)			
LLD + MCI: 2 year	0.26 (2.25)			
LLD + NCD: 1 year	1.80 (2.00)			
LLD + NCD: 2 year	3.08 (1.98)			
Model 2: effects of Treatment (Donepezil vs. Placebo), time, baseline diagnosis (LLD + MCI vs. LLD + NCD) on BDNF levels using baseline age and HDRS as covariates.***				
Intercept	23.97 (6.17)			
Age*	−0.11 (0.08)	1121	1.84	0.18
HRSD scores*	0.04 (0.16)	1121	0.06	0.80
Treatment (Donepezil)	0.41 (1.46)	1121	0.38	0.54
Time		2121	1.85	0.16
1 year	1.08 (1.63)	1121	1.92	0.17
2 year	−0.19 (1.42)			
Diagnosis (MCI)	−0.84 (1.66)			
Treatment × Diagnosis (MCI*Donepezil)	1.05 (2.21)	1121	1.25	0.27
Time × Treatment		2121	0.07	0.94
1 year: Donepezil	−2.52 (2.36)			
2 year: Donepezil	−0.39 (2.03)			
Time × Diagnosis		2121	1.10	0.34
1 year: MCI	−3.85 (2.39)			
2 year: MCI	−2.28 (2.45)			
Time × Treatment × Diagnosis		2121	1.04	0.36
1 year: Donepezil: MCI	4.85 (3.64)			
2 year: Donepezil: MCI	−0.47 (3.50)			

BDNF: Brain-Derived Neurotrophic Factor; LLD + NCD: late-life depression and no cognitive decline; LLD + MCI: late-life depression and mild cognitive impairment. HDRS: Hamilton Depression Rating Scale-17 items.
*Baseline age and HDRS scores.
**References controls and baseline.
***References: LLD + NCD, baseline and placebo.

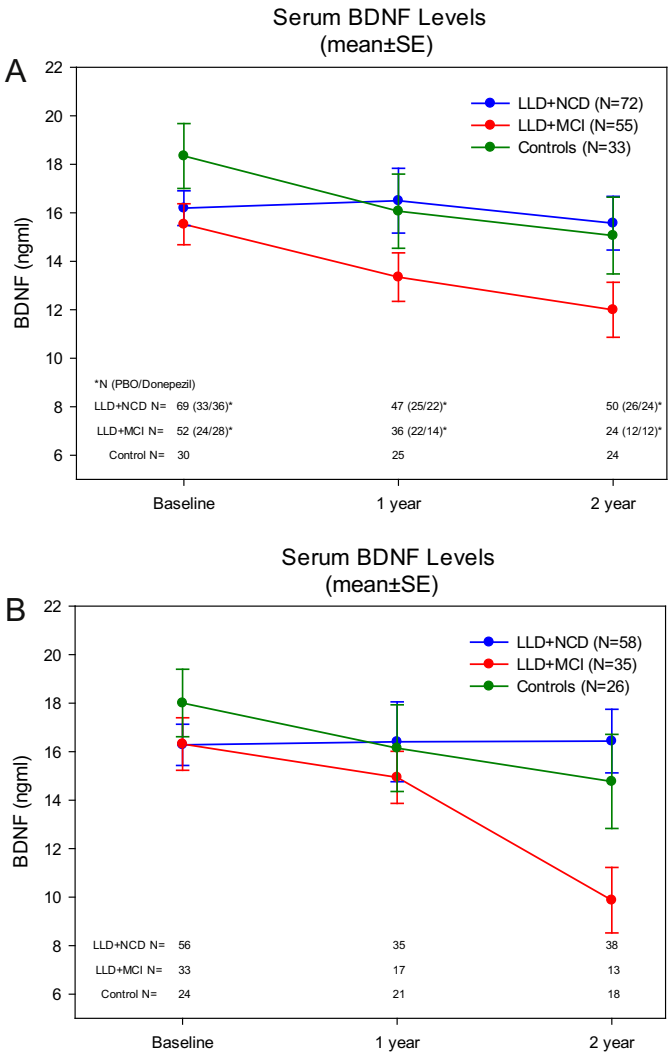

Fig. 1. A – Longitudinal pattern of changes in BDNF levels according to baseline diagnosis. B – Longitudinal pattern of changes in BDNF levels according to baseline diagnosis in subjects whose cognitive diagnosis did not change during course of follow-up. BDNF: Brain-Derived Neurotrophic Factor; LLD + NCD: late-life depression and no cognitive decline; LLD + MCI: late-life depression and mild cognitive impairment.

between individual changes in BDNF and cognitive changes over one year (rho = 0.07, $p = 0.48$, $n = 100$) nor over two years of follow-up (rho = 0.13, $p = 0.24$, $n = 89$).

3.1. Effect of donepezil treatment on BDNF level in remitted LLD participants

In the parent study, participants with remitted LLD participated in a double-blind placebo controlled clinical trial to evaluate whether donepezil treatment improves cognitive performance and reduces progression to dementia. Mixed model analysis for repeated measures tested for the main effects of donepezil treatment (donepezil vs. placebo), time, baseline diagnosis (LLD + MCI vs. LLD + NCD), and the interactions between these terms on BDNF levels. We also included baseline age and HDRS scores as covariates in this analysis. Neither age nor HDRS scores were significant covariates. There were no significant main effects of treatment, time, baseline diagnosis or interactions on BDNF levels (Table 2, model 2).

4. Discussion

This is the first study to describe longitudinal changes in serum BDNF levels in both older adults with LLD and healthy control subjects. We found that BDNF levels significantly decline over 2 years of follow-up in the whole sample. Exploratory analyses showed that the decline in BDNF levels was largely driven by participants with LLD + MCI and controls. On the other hand, we did not find a significant effect on BDNF levels after long-term donepezil treatment. Overall, the present findings suggest that aging is an important factor related to the decline of BDNF levels.

Cross-sectional studies suggest that BDNF levels are negatively correlated with age-related hippocampal volume changes and cognitive impairment (Erickson et al., 2010; Lee et al., 2007). Previous studies have consistently shown a significant reduction of BDNF levels in subjects with neurodegenerative disorders, such as Alzheimer's disease and amnestic mild cognitive impairment (Forlenza et al., 2010; Lee et al., 2009). Recent studies suggest that the molecular changes associated with depression may lead to accelerated brain aging and changes in the expression of the BDNF gene might play an important role in this process (McKinney and Sibille, 2013). In a recent *post-mortem* study, Douillard-Guilloux et al. (2013) found that the expression of BDNF mRNA was negatively correlated with age; moreover, the mean reduction was significantly higher in participants with history of major depression. In addition, lower BDNF expression is found in the brain of subjects with Alzheimer's disease, in particular in areas with high Tau protein levels (Murer et al., 1999).

BDNF significantly declined over time in healthy controls and did so with higher intensity in participants with LLD + MCI. Such declines may suggest that changes in the neurotrophic system are related to the aging process, but may be accelerated or intensified in subjects with LLD and persistent cognitive impairment, possibly indicating the emergence of neurodegenerative changes in the latter group.

In addition, we evaluated the effect of long-term donepezil treatment on BDNF levels in participants with LLD. Contrary to our hypothesis, we observed no long-term donepezil treatment effect on serum BDNF levels. In the primary analysis of this clinical trial, patients with LLD and comorbid MCI showed a significant improvement on memory performance over two years (Reynolds et al., 2011). In the light of the present results, we hypothesize that memory improvement after donepezil treatment is not due to changes in BDNF. Nonetheless, donepezil can modulate BDNF-related cascades by mechanisms other than by directly increasing serum BDNF levels. For example, donepezil can rapidly induce the phosphorylation of the neurotrophin receptors TrkA and TrkB and increase the phosphorylation of transcription factor CREB in mature mouse hippocampal neurons; these effects are independent of the increased synthesis and release of BDNF (Autio et al., 2011). The activation of TrkB and CREB, by phosphorylation, acts as the main down-stream effector of BDNF functions in neurons. Therefore, donepezil treatment can significantly modulate BDNF-related cascades without directly affecting BDNF protein synthesis and release. On the other hand, the present results are consistent with the evidence that donepezil and other acetylcholinesterase inhibitors mainly have effects on symptomatic, cognitive, and behavioral expression of dementia (both vascular and AD) and MCI (Doody et al., 2001; Erkinjuntti et al., 2002; Petersen et al., 2005).

The pathophysiology of cognitive impairment may involve changes in several biologic cascades other than BDNF and changes in individual cascades may have small overall effects on cognitive impairment in LLD (Butters et al., 2008; Caraci et al., 2010). Thus, the positive effect of donepezil on memory and global cognitive performance reported in the primary analysis of this clinical trial

(Reynolds et al., 2011) may be secondary to the effects of this drug on biologic cascades other than BDNF. Additional studies are needed to disentangle the biologic mechanisms by which donepezil improves cognitive performance in patients with LLD and cognitive impairment.

The present study has several limitations. The original trial was not designed to evaluate the effects of donepezil on serum BDNF levels, and thus the present findings should be considered more exploratory or hypothesis-generating than confirmatory or hypothesis-testing. We also observed a high dropout rate in the LLD + MCI group that might have influenced the present results. Furthermore, given the large number of tests, there is a high chance of false positive findings. In addition, we did not evaluate BDNF levels prior to antidepressant treatment. Thus, we cannot reliably state that individuals with LLD and cognitive impairment after depressive episode remission had lower BDNF levels compared to patients with LLD and no cognitive impairment. Finally, some studies have failed to show a significant correlation between BDNF levels in the CNS and in the periphery in older individuals (Laske et al., 2007). Hence, we need to be cautious about interpreting the extent to which changes in serum BDNF may reflect changes in brain levels of BDNF. Nonetheless, the positive correlations observed between serum BDNF levels and both cognitive and depressive symptoms in the elderly are in line with other research using BDNF serum as a marker of brain integrity (Erickson et al., 2010). The large sample size, the longitudinal measures of BDNF levels, and the inclusion of healthy controls in the analysis are major strengths of the present study.

In conclusion, serum BDNF levels significantly decline over time in healthy controls and in participants with LLD and persistent cognitive impairment, though the intensity of decline in greater in the latter group. Additionally, we did not find a significant effect of long term donepezil treatment on serum BDNF concentration, suggesting that the benefit of donepezil on memory and cognitive performance is not secondary to the modulation of BDNF in these individuals. Further studies are necessary to disentangle the biologic mechanisms by which donepezil improves cognitive performance in patients with LLD, with the aim of discovering new biologic targets for the treatment of cognitive impairment in individuals with LLD.

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Oscar Lopez: Dr Lopez served as consultant for Lilly, Baxter, Grifols, and Cognoptix.

Contributions

Breno Satler Diniz: Study design, data analysis, interpretation of results and drafting the manuscript.

Charles F. Reynolds III: Study design, interpretation of results and drafting the manuscript.

Mary Amanda Dew: Interpretation of results and drafting the manuscript.

Stewart Anderson: Data analysis, interpretation of results and drafting the manuscript.

Amy Begley: Data analysis, interpretation of results and drafting the manuscript.

Francis Lotrich: Data analysis, interpretation of results and drafting the manuscript.

Oscar Lopez: Study design, interpretation of results.

Ettienne, Ettienne L. Sibille: Study design, interpretation of results.

Howard Aisenstein: Study design, interpretation of results.

Kirk I. Erickson: Interpretation of results and drafting the manuscript.

Meryl, Meryl A. Butters: Study design, interpretation of results and drafting the manuscript.

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