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Serum Brain-Derived Neurotrophic Factor Levels Are Specifically Associated with Memory Performance among Alzheimer's Disease Cases

Sid E. O'Bryant[a, b] Valerie L. Hobson[d] James R. Hall[e] Robert C. Barber[f] Song Zhang[g] Leigh Johnson[c] Ramon Diaz-Arrastia[h] for the Texas Alzheimer's Research Consortium

[a]Department of Neurology and [b]F. Marie Hall Institute for Rural and Community Health, and [c]Department of Family and Community Medicine, Laura W. Bush Institute for Women's Health, Texas Tech University Health Sciences Center, and [d]Department of Psychology, Texas Tech University, Lubbock, Tex., Departments of [e]Psychiatry and [f]Pharmacology and Neuroscience, University of North Texas Health Science Center, Forth Worth, Tex., and Departments of [g]Clinical Sciences and [h]Neurology, University of Texas Southwestern Medical Center, Dallas, Tex., USA

Key Words
Alzheimer's disease · Biomarkers · Brain-derived neurotrophic factor · Cognition · Neuropsychology · Aging

Abstract
Aims: Our purpose was to study the link between serum brain-derived neurotrophic factor (BDNF) levels and neuropsychological functioning through the Texas Alzheimer's Research Consortium cohort. ***Methods:*** A total of 399 participants [probable Alzheimer's disease (AD) n = 198, controls n = 201] were available for analysis. The BDNF levels were assayed via multiplex immunoassay. Regression analyses were utilized to examine the relation between BDNF levels and neuropsychological functioning. ***Results:*** There were no significant mean differences in BDNF levels between cases and controls. In the AD group, the BDNF levels were significantly negatively associated with the scores on immediate [B = –0.07 (0.02), t = –3.55, p = 0.001] and delayed [B = –0.05 (0.02), t = –2.79, p = 0.01] verbal memory and immediate [B = –0.12 (0.05), t = –2.70, p = 0.01] visual memory. No other neuropsychological variables were significantly related to the BDNF levels. The BDNF levels were not significantly related to the neuropsychological test scores in the control group. ***Conclusions:*** Increased serum BDNF levels were associated with poorer visual and verbal memory, but only among AD cases. The current findings point toward an upregulation of serum BDNF as one possible mechanism linked to memory disturbances in AD though it does not appear to be linked to disease severity.

Investigators from the Texas Alzheimer's Research Consortium: Baylor College of Medicine: Rachelle Doody, Violeta Capriles, Eveleen Darby, Kinga Szigeti; Texas Tech University Health Science Center: Paula Grammas, Benjamin Williams, Gregory Schrimsher, Andrew Dentino, Larry Hill; University of North Texas Health Science Center: Thomas Fairchild, Janice Knebl, Douglas Mains, Lisa Alvarez; University of Texas Southwestern Medical Center: Perrie Adams, Roger Rosenberg, Joan Reisch, Doris Svetlik, Janet Smith.

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Sid E. O'Bryant, PhD
Department of Neurology
Texas Tech University Health Sciences Center
3601 4th Street STOP 8321, Lubbock, TX 79430 (USA)
Tel. +1 806 743 4999, ext. 270, Fax +1 806 743 1147, E-Mail sid.obryant@ttuhsc.edu

Introduction

Neurotrophic factors (NTFs) [1] are a family of regulatory proteins that have been given a great deal of attention in Alzheimer's disease (AD) research. NTFs are small proteins that play essential roles in cell morphology, axonal guidance, neuronal survival, as well as memory formation and cognition [2]. Given that (1) NTFs are oftentimes synthesized in areas impacted by AD neuropathology early in the course of the disease [3], axonal transport is essential for NTF signaling, and (2) axonal transport failures are oftentimes associated with neurodegenerative dementias [2], dysregulation of the NTF system can be expected to be associated with AD.

Brain-derived neurotrophic factor (BDNF) is an NTF that has been widely studied in AD. Autopsy studies have found decreased BDNF, pro-BDNF and BDNF mRNA levels in brains of patients with AD and mild cognitive impairment [4–6]. There is less consensus regarding the serum levels of BDNF in AD, as reports of increase [7], decrease [8] and no difference [9] as compared to elder controls have been published. In terms of cognitive functioning, Peng et al. [4] analyzed autopsy data available on 54 participants (control n = 20, mild cognitive impairment n = 17, AD n = 17) of the Religious Orders Study and found that pro-BDNF and mature BDNF levels were positively associated with Mini-Mental State Examination (MMSE) and Global Cognitive scores (a composite score of 19 neuropsychological tests administered as part of the Religious Orders Study protocol). Analyzing data from 27 AD patients and 28 age-matched controls, Laske et al. [7] found no significant relation between serum BDNF levels and MMSE scores, which was consistent with an independent investigation including 60 AD patients and 33 controls [10]. Analyzing data from the 198 participants (99 AD and 99 elder controls) from the Texas Alzheimer's Research Consortium (TARC), O'Bryant et al. [9] failed to demonstrate any significant relation between serum BDNF levels and MMSE or Clinical Dementia Rating (CDR) scores. However, each of the previously mentioned studies reported data on only global estimates of cognition rather than detailed neuropsychological test findings of specific cognitive domains. Gunstad et al. [11] recruited 35 older adults (age = 60–85 years) who were screened for current significant medical, neurological or psychiatric conditions in order to evaluate the relation between serum BDNF levels and neuropsychological functioning among healthy older adults. These authors found a significant positive association between serum BDNF levels and scores of global cognition (MMSE) and confrontation naming [Boston Naming Test (BNT) – short form] with BDNF accounting for 13 and 15% of the variance in obtained scores, respectively. There was, however, no significant association between serum BDNF levels and measures of learning and memory, attention and information processing speed, working memory, executive functioning or verbal fluency, which may have been due to low power from the small sample size. Komulainen et al. [12] analyzed data from 1,389 participants of the DR's EXTRA project and found decreased levels of plasma BDNF significantly associated with poorer CERAD scores of confrontation naming, list learning, list recall, list recognition and list savings for women, but not for men.

The current study sought to examine the link between serum BDNF levels and neuropsychological functioning among a sample of patients diagnosed as having probable AD primarily in the early stage of their disease and normal controls from the TARC Longitudinal Research Cohort. Based on the previous human and animal literature linking BDNF to learning and memory [12–16], it was hypothesized that the serum BDNF levels would be significantly associated with measures of immediate and delayed memory scores.

Subjects and Methods

Participants

The participants included 399 individuals (198 diagnosed as having probable AD and 201 controls) enrolled in the TARC Longitudinal Research Cohort. The methodology of the TARC project has been described in detail elsewhere [17]. Briefly, each participant completes an annual examination consisting of a medical examination, interview, blood draw and neuropsychological testing at 1 of the 5 TARC sites. These data are reviewed by each site consensus committee and diagnosis is assigned according to NINCDS-ADRDA criteria [18] with only those meeting criteria for probable AD included into the study. Controls were judged to be within normal limits on consensus review. Participants with AD were studied at a relatively early stage of the disease. The breakdown of numbers of CDR global scores for the AD patients was as follows: 0.5 = 69, 1 = 79, 2 = 41, 3 = 7 (2 AD cases were missing CDR scores). The TARC project received institutional review board approval and all participants and/or caregivers signed written informed consent documents. A subset of this sample (AD n = 98, controls n = 98) was published previously in a study examining the potential of BDNF in distinguishing between case and control status [9].

Measures

The TARC neuropsychology core battery consists of common instruments administered as part of the established AD

clinical/research platforms at each participating institution and includes digit span (WAIS-R, WAIS-III, WMS-R), Trail Making Test, WMS Logical Memory and Visual Reproduction (WMS-R and WMS-III), BNT (30- and 60-item versions), verbal fluency (FAS), Clock Drawing Test, the American National Adult Reading Test, the Geriatric Depression Scale, MMSE [19], and ratings on the CRD scale [20]. In order to equate scores from digit span and story memory scales, all raw scores were converted to scale scores based on previously published normative data [21–23]. For the BNT, the current group recently published an independent study demonstrating the psychometric utility of an estimated 60-item BNT score that can be calculated from 30-item versions [24]; this estimated 60-item score was used for all 30-item administrations. Adjusted scale scores were utilized as dependent variables in the analyses.

Assays

Nonfasting samples were collected in serum-separating tubes during clinical evaluations, allowed to clot at room temperature for 1 h, centrifuged, aliquoted and stored at –80°C in plastic vials. Samples were sent frozen in a single batch to Rules Based Medicine (www.rulesbasedmedicine.com, Austin, Tex., USA), where they were thawed for assay without additional freeze-thaw cycles. Rules Based Medicine conducted multiplexed immunoassay via their human Multi-Analyte Profile (human MAP). Multiple proteins, including BDNF, were quantified though multiplex fluorescent immunoassay utilizing colored microspheres with protein-specific antibodies. For BDNF, the least detectable dose was 0.029 ng/ml, the interrun coefficient of variation was ≤7%, the dynamic range was 0.0028–14 ng/ml, the overall spiked standard recovery was 95%, and the crossreactivity with other human MAP analytes was <5%. Assays conducted by this company utilizing this platform, including TARC data, have been published elsewhere [9, 25].

Analyses

Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Inc., Cary, N.C., USA). In order to determine if the serum BDNF levels were significantly predictive of neuropsychological scores, linear regression models were created using serum BDNF as the predictor variable and neuropsychological scores as the outcome variable. Statistical significance was declared for p values <0.05.

Results

The average age and education of the control group was 70.4 (SD = 8.9) and 15.5 (SD = 2.7) years, respectively, while the average age and education of the AD group was 76.6 (SD = 8.3) and 14.2 (SD = 3.4) years, respectively. The sample was 95% Caucasian and there were slightly more females than males, though the gender distribution was not significantly different between the groups. As expected, the AD patients obtained significantly lower MMSE scores (mean = 20.9, SD = 5.6) than the controls (mean = 29.4, SD = 0.9) as well as higher CDR sum of boxes scores (AD mean = 6.3, SD = 3.8; controls mean = 0.005, SD = 0.05). As in our prior report on a subset of this cohort, there was no difference in serum BDNF levels between the control and AD groups. Demographic characteristics of the study population are shown in table 1.

Table 1. Baseline demographic characteristics

	AD	Control	p value
Subjects	198	201	
Sex (female)	130 (65.7)	137 (68.2)	0.60
Age, years			
Mean ± SD	76.63 ± 8.33	70.42 ± 8.86	<0.01
Range	56–93	52–90	
Race/ethnicity (Caucasian)	190 (96.5)	188 (93.5)	0.18
Education, years			
Mean ± SD	14.20 ± 3.40	15.52 ± 2.72	<0.01
Range	0–22	10–25	
MMSE			
Mean ± SD	20.93 ± 5.56	29.42 ± 0.85	<0.01
Range	4–30	26–30	
CDR sum of Boxes			
Mean ± SD	6.35 ± 3.82	0.005 ± 0.05	<0.01
Range	0.5–17.0	0.0–0.5	
BDNF			
Mean ± SD	31.46 ± 9.10	30.96 ± 8.82	0.57
Range	6.40–43.0	2.10–43.0	

Figures in parentheses are percentages.

The mean serum BDNF levels were not significantly different between AD cases and normal controls ($p > 0.05$). The BDNF levels did not significantly predict any neuropsychological scores among the control group. In the AD group, however, the BDNF levels were significantly negatively associated with the scores on immediate ($B = –0.07$, $SE = 0.02$, $t = –3.55$, $p = 0.001$) and delayed ($B = –0.05$, $SE = 0.02$, $t = –2.79$, $p = 0.01$) verbal memory (WMS Logical Memory immediate and delayed indices) and immediate ($B = –0.12$, $SE = 0.05$, $t = –2.70$, $p = 0.01$) visual memory (WMS Visual Reproduction immediate index). No other neuropsychological variables were significantly related with the BDNF levels.

Next we split the AD cases into early AD (CDR Global Score = 0.5–1; n = 99) versus late AD (CDR Global Score = 2–3; n = 47) to determine if the findings above were moderated by disease severity. The BDNF levels were no longer significantly related to the memory scores, suggesting that this effect is across the AD disease spec-

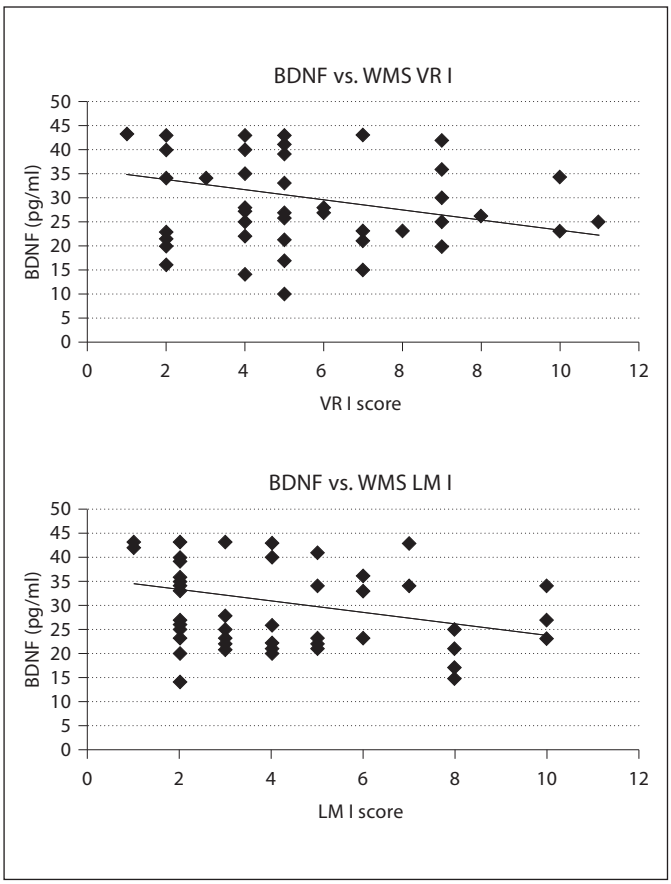

Fig. 1. Relation between serum BDNF levels and WMS Logical Memory I and Visual Reproduction I scores.

trum. To further delve into this, we then split the file by APOE4 status (present versus absent). Among the AD cases without any missing data, there were 52 cases who were APOE4 negative and 84 who were APOE positive. BDNF was a significant predictor of immediate memory scores (WMS Logical Memory I B = –0.96, SE = 0.04, t = –2.43, p = 0.02; WMS Visual Reproduction I B = –0.95, SE = 0.04, t = –2.22, p = 0.03) among the APOE4-negative AD cases, whereas BDNF was not significantly related to any memory measures among the APOE4-positive cases (fig. 1).

Discussion

In the current study, the serum BDNF levels were not significantly different between AD cases and controls, which is consistent with our previously published findings [9] and suggests that serum BDNF is not a useful marker for disease status. However, the BDNF levels were found to be significantly negatively associated with measures of immediate and delayed verbal memory as well as immediate visual memory among the AD patients, whereas the serum BDNF levels were not associated with any neuropsychological test scores among the nondemented controls. These findings are consistent with those of Laske et al. [8], who evaluated a sample of 30 patients diagnosed as having AD (15 'early' and 15 'late') along with 10 controls and found that the serum BDNF levels were increased in early AD cases relative to controls and late AD cases, which were not significantly different from one another. The mean serum BDNF level in that study was comparable to our AD sample though the level among their late AD cases was much lower, which is consistent with prior work [10]. Our study is different from that of Laske et al. [8] in that we examined a much larger sample of cases and controls, our AD cases were at a predominantly early stage of their disease, and more detailed neuropsychological testing was available in our study. Our study is also unique from other prior work in this same respect given the relatively larger sample size along with neuropsychological, rather than global cognitive screening, outcomes.

The finding of a negative association between serum BDNF levels and performance on measures of visual and verbal memory suggest the possibility that upregulation of BDNF is a compensatory mechanism in patients with AD. Such compensatory mechanisms have been identified in those at risk for developing AD (e.g. mild cognitive impairment patients, APOE4, family history) in previous investigations through neuropathological analysis [26] as well as neuroimaging [27]. In terms of BDNF, Christensen et al. [28] recently examined the link between intrahippocampal aggregated $A\beta_{1-42}$ injections (1 μg/μl) and cortical and serum BDNF as well as cortical 5-HT_{2A} levels among rats. These authors found that the $A\beta_{1-42}$-injected animals performed significantly poorer on a memory task than the control group at 2- and 6-week assessment periods. Additionally, over time, the vehicle-injected animals had significantly higher serum BDNF levels than the control group, which was due to a continuous rise in BDNF levels throughout the course of the experiment. However, the BDNF levels in the frontal cortex were found to be significantly lower among the vehicle-injected rats than the controls though no difference was noted in the hippocampal cortex between groups. These findings point to the possibility of a link between Aβ

and BDNF as well as the possibility of an upregulation of serum BDNF levels with early accumulation of Aβ in the cerebral cortex. It is also noteworthy that the serum BDNF concentrations increase during treatment with donepezil, suggesting that this is one possible mechanism for efficacy of this drug with AD patients [7].

In order to determine if this potential compensatory mechanism was specific to early AD cases, we reran our analyses by early versus late AD. These analyses did not support the notion of disease severity as a potential moderator of this finding. Additional analyses by APOE4 status were conducted and showed that higher BDNF levels were related to poorer memory scores only among APOE4-negative cases (there was no link between BDNF and memory measures among controls regardless of APOE4 status). These data point to the possibility of a neurotrophic-related endophenotype of AD that is specific to APOE4-negative cases. However, the sample size for these analyses was small and requires further inquiry. It is possible that targeted therapeutics may offer additional relief (or slowed progression) of some cases, whereas others (i.e. those with significantly upregulated BDNF) would likely not benefit from this additional treatment.

The current findings are limited by the cross-sectional nature of the analyses. However, the TARC cohort is being evaluated annually and follow-up analyses examining the link between serum BDNF levels and progression of cognitive dysfunction and/or dementia are underway as well as inclusion of relevant genetic polymorphisms. The current findings point toward an upregulation of serum BDNF as one possible mechanism linked to memory disturbances in AD though it does not appear linked to disease severity in our cohort, possibly due to the predominance of individuals with early stage disease. Additionally, this link was restricted to learning measures (visual and verbal) among cases who were APOE4 negative. It is likely that the restriction of range among delayed memory scores played a significant role in those analyses. These findings may be indicative of an additional AD-specific endophenotype that is related to BDNF and APOE genotype.

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References

1 Tapia-Arancibia L, et al: New insights into brain BDNF function in normal aging and Alzheimer disease. Brain Res Rev 2008;59:201–220.
2 Schindowski K, Belarbi K, Buee L: Neurotrophic factors in Alzheimer's disease: role of axonal transport. Genes Brain Behav 2008;1:43–56.
3 Kukull WA, et al: Dementia and Alzheimer disease incidence: a prospective cohort study. Arch Neurol 2002;59:1737–1746.
4 Peng S, et al: Precursor form of brain-derived neurotrophic factor and mature brain-derived neurotrophic factor are decreased in the pre-clinical stages of Alzheimer's disease. J Neurochem 2005;93:1412–1421.
5 Holsinger RM, et al: Quantitation of BDNF mRNA in human parietal cortex by competitive reverse transcription-polymerase chain reaction: decreased levels in Alzheimer's disease. Brain Res Mol Brain Res 2000;76:347–354.
6 Connor B, et al: Brain-derived neurotrophic factor is reduced in Alzheimer's disease. Brain Res Mol Brain Res 1997;49:71–81.
7 Leyhe T, et al: Increase of BDNF serum concentration during donepezil treatment of patients with early Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci 2008;258:124–128.
8 Laske C, et al: Stage-dependent BDNF serum concentrations in Alzheimer's disease. J Neural Transm 2006;113:1217–1224.
9 O'Bryant SE, et al: Brain-derived neurotrophic factor levels in Alzheimer's disease. J Alzheimer Dis 2009;17:337–341.
10 Yasutake C, et al: Serum BDNF, TNF-α and IL-1β levels in dementia patients: comparison between Alzheimer's disease and vascular dementia. Eur Arch Psychiatry Clin Neurosci 2006;256:402–406.
11 Gunstad J, Benitez A, Smith J, Glickman E, Spitznagel MB, Alexander T, Juvancic-Heltzel J, Murray L: Serum brain-derived neurotrophic factor is associated with cognitive function in healthy older adults. J Geriatr Psychiatry Neurol 2008;21:166–170.
12 Komulainen P, et al: BDNF is a novel marker of cognitive function in ageing women: the DR's EXTRA Study. Neurobiol Learn Mem 2008;90:596–603.
13 Egan MF, et al: The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 2003;112:257–269.
14 Gorski JA, et al: Learning deficits in forebrain-restricted brain-derived neurotrophic factor mutant mice. Neuroscience 2003;121:341–354.
15 Harris SE, et al: The brain-derived neurotrophic factor Val66Met polymorphism is associated with age-related change in reasoning skills. Mol Psychiatry 2006;11:505–513.
16 Monteggia LM, et al: Essential role of brain-derived neurotrophic factor in adult hippocampal function. Proc Natl Acad Sci USA 2004;101:10827–10832.
17 Waring S, O'Bryant SE, Reisch JS, Diaz-Arrastia R, Knebl J, Doody R; Texas Alzheimer's Research Consortium: The Texas Alzheimer's Research Consortium longitudinal research cohort: study design and baseline characteristics. Texas Public Health J 2008;60:9–13.

18 McKhann D, Drachman D, Folstein M, et al: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group. Neurology 1984;34:939–944.
19 Folstein MF, Folstein SE, McHugh PR: Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
20 Morris JC: Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 1997;1:173–176.
21 Ivnik R, Malec JF, Smith GE, Tangalos EG, Petersen RC, Kokmen E, Kurkland LT: Mayo's Older Americans Normative Studies: WAIS-R norms for age 56 to 97. Clin Neuropsychologist 1992;6:1–30.
22 Ivnik RJ, Malec JF, Smith GE, Tangalos EG, Petersen RC: Neuropsychological tests' norms above age 55: COWAT, BNT, MAE token, WRAT-R reading, AMNART, STROOP, TMT and JLO. Clin Neuropsychologist 1996; 10:262–278.
23 Psychological Corporation: WAIS-III – WMS-III Technical Manual. San Antonio, Psyhcological Corporation, 1997.
24 Hobson V, Hall JR, Harvey M, Cullum CM, Lacritz L, Massman PJ, Waring SC, O'Bryant SE: An examination of the Boston Naming Test: calculation of an 'estimated' 60-item score from 30- and 15-item scores in a cognitively impaired population. Int J Geriatr Psychiatry, Epub ahead of print.
25 O'Bryant SE, et al: Decreased C-reactive protein levels in Alzheimer disease. J Geriatr Psychiatry Neurol 2010;23:49–53.
26 DeKosky ST, et al: Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment. Ann Neurol 2002;51:145–155.
27 Fleisher AS, et al: Identification of Alzheimer disease risk by functional magnetic resonance imaging. Arch Neurol 2005;62: 1881–1888.
28 Christensen R, et al: $A\beta_{1-42}$ injection causes memory impairment, lowered cortical and serum BDNF levels, and decreased hippocampal 5-HT_{2A} levels. Exp Neurol 2008;210: 164–171.