that plasma levels of BDNF were decreased in participants with type 2 diabetes independent of obesity (Krabbe et al., 2007). Plasma BDNF was inversely associated with fasting plasma glucose, but not with insulin. When plasma insulin was increased while maintaining normal blood glucose, the cerebral output of BDNF was not inhibited, indicating that high levels of glucose, but not insulin, inhibit the output of BDNF from the human brain. They concluded that the cerebral output of BDNF, which is negatively related to high plasma glucose levels and decreased BDNF, may be a pathogenetic factor involved not only in dementia, but also in type 2 diabetes. The results of our cohort support previous findings. Smoking was associated with higher BDNF levels; this finding is consistent with several studies. In animal studies, regional brain BDNF expression was altered by exposure to or withdrawal from nicotine (Kenny et al., 2000). In some human studies, smoking cessation increased BDNF serum levels over the span of several months (Kim et al., 2007; Bhang et al., 2010). A recent epidemiological study of 1168 subjects aged 18–65 years also reported an independent relationship between smoking and serum BDNF levels, with higher BDNF in former and current smokers compared to subjects who never smoked (Bus et al., 2011). The results of our study confirm this relationship between BDNF and smoking in adults 65 years of age and older. Nicotine has induced SH-SY5Y neuroblastoma cell proliferation through BDNF and its receptor, TrkB. The activation of nicotinic receptors has effects upon the BDNF–TrkB pathway, inducing cell proliferation by promoting the release of BDNF, which in turn activates TrkB receptors (Serres and Carney, 2006). Moreover, the beta-arrestin-2 protein is important in induction and expression of nicotine sensitization as well as nicotine's effects on accumbal BDNF (Correll et al., 2009).

Brain-derived neurotrophic factor is highly concentrated in the hippocampus (Phillips et al., 1990; Wetmore et al., 1990). A single nucleotide polymorphism in the BDNF gene affects the regulated secretion of BDNF in the hippocampus (Egan et al., 2003) and has been related to lower serum levels of BDNF (Ozan et al., 2010) and smaller hippocampal volumes (Pezawas et al., 2004; Szeszko et al., 2005), which can lead to deficits in executive function (Frodl et al., 2006) and memory function (Erickson et al., 2009). The hippocampus–orbitomedial prefrontal circuit integrates cognition, emotion, and behavior, thereby influencing working memory and executive functions (Wall and Messier, 2001). The observed relationship between lower serum BDNF and impaired memory and processing speed is consistent with previous studies. However, the relationships between serum BDNF and executive function, the Trail Making Test – Part B, did not reach significance ($P = 0.09$). Further studies will be needed to establish the relationships between serum BDNF and executive function in the elderly adults.

Serum BDNF values 1.5 SD lower than the age- and sex-adjusted mean were associated with MCI, whereas serum BDNF levels lower than 1.0 SD from age- and sex-adjusted mean serum BDNF values were not. These results suggest that the participants who had 1.5 SD lower than the mean age- and sex-adjusted BDNF values may pose a risk of cognitive impairment. BDNF supports cholinergic, dopaminergic, serotonergic, and neuropeptide-containing neurons (Hyman et al., 1991; Knusel et al., 1991; Mamounas et al., 1995) and may play an important role in AD-related pathophysiology. Animal studies found that Aβ disrupts BDNF signaling and that BDNF protects against Aβ toxicity via TrkB signaling (Tapia-Arancibia et al., 2008). Lower levels of both BDNF and TrkB have been found in postmortem brains of individuals with AD (Murer et al., 2001). BDNF levels are significantly reduced in the hippocampus and parietal cortex and BDNF/neurotrophin 3 ratios are lower in frontal and parietal cortices in patients with AD compared with age-matched controls (Hock et al., 2000). Higher serum levels of BDNF in individuals with AD are predictive of slower rates of decline (Laske et al., 2011). Peng et al. (2005) reported strong relationships between MMSE and Global Cognitive Score results and proBDNF and mature BDNF levels. Decreased serum BDNF in the preclinical stages of AD further suggests that BDNF and proBDNF deficiency play a pivotal role in cell atrophy, cell loss, and synaptic dysfunction, with a lack of trophic support contributing to the degeneration of specific neuronal subpopulations in the AD-affected brain (Hock et al., 2000; Laske et al., 2007).

Other studies have shown that BDNF serum levels increase in MCI and AD patients (Angelucci et al., 2010). This increase may reflect a compensatory repair mechanism in early and late neurodegeneration that is protective by contributing to Aβ degradation. Laske et al. (2006) found that patients in the early stages of probable AD with MMSE scores ≥ 21 (mean of 25.5) had significantly higher serum BDNF levels compared to patients in late-stage AD with MMSE scores <21 (mean of 13.3) and age-matched healthy controls. The study also showed a tendency toward lower BDNF levels in patients with late-stage AD and progressive dementia (mean MMSE: 13.3; range: 6–20). The mean MMSE scores of our MCI participants was 26.6 (range: 24–30), higher than that of patients in the early stages of probable AD in the Laske et al. (2006) study. Our MCI participants may have been at a stage earlier than the point at which the BDNF compensatory repair mechanism is triggered in early neurodegeneration.

The strengths of the present study include the large sample size and comprehensive measurement of cognitive function, which correlates closely with dementia. One limitation of the study is that the analysis is based on cross-sectional data. Although our study was population-based, further prospective investigations are needed to validate using 1.5 SD serum BDNF levels for discriminating the risk of cognitive decline and MCI in older people. Sensitivity of the 1.5 SD serum BDNF levels to discriminate MCI and healthy participants showed a very low value (6.4%). The result suggests that it is necessary to review the discrimination point to screen MCI in the community with high sensitivity. BDNF is reduced in elderly individuals with major depression and bipolar disorder, with distinct dynamics according to the disease stages, treatment, or the presence of cognitive impairment (Molendijk et al., 2011; McKinney and Sibille, 2013; Sibille, 2013). In a recently published study, Diniz et al. (2014) showed a significant decline in serum BDNF level over 2 years of follow-up only in those individuals with persistent cognitive decline (Diniz et al., 2014). Therefore, BDNF seems to be a non-specific marker for many neuropsychiatric disorders, thus, reducing its discriminative power to identify individuals with MCI. Our study also excluded older adults with neurological disorders and those adults who were certified for long-term care insurance due to functional

decline. Therefore, the study findings may not be generalized to these patient groups. It is likely that several clinical and etiological heterogeneities exist between subtypes of MCI (Petersen, 2004). Although amnestic MCI appears to be most closely linked with AD, there are many concomitant pathologic abnormalities, including argyrophilic grain disease, hippocampal sclerosis, and vascular lesions (Petersen et al., 2006). The findings of the study about the relationships between serum BDNF and MCI may change in further analyses of each subtype of MCI.

In conclusion, we provide preliminary evidence that serum BDNF can be associated with lower cognitive test scores in older people. In our cohort, serum BDNF was marginally associated with the presence of MCI when BDNF was 1.5 SD lower than the mean age- and sex-adjusted values. Future prospective studies should establish the discriminative value of serum BDNF for a risk of MCI and its validity as a screening test for this population.

AUTHOR CONTRIBUTIONS

Study concept and design: Hiroyuki Shimada, Takao Suzuki; acquisition of data: Hyuma Makizako, Takehiko Doi, Daisuke Yoshida, Kota Tsutsumimoto, Yuya Anan, Kazuki Uemura; analysis and interpretation of data: Sangyoon Lee; critical revision of the manuscript: Hyuma Makizako, Hyuntae Park; statistical analysis: Hyuntae Park; drafting of the manuscript: Hiroyuki Shimada; obtaining funding: Hiroyuki Shimada, Takao Suzuki, Hyuma Makizako; study supervision: Takao Suzuki.

ACKNOWLEDGMENTS

We would like to thank the Obu city office for the help provided with participant recruitment. This work was supported by a Health Labour Sciences Research Grant (23-001) from the Japanese Ministry of Health, Labour and Welfare and by Research Funding for Longevity Sciences (22-16) from the National Center for Geriatrics and Gerontology (NCGG), Japan. Additional support was provided by a Grant-in-Aid for Scientific Research (B) to Hiroyuki Shimada and a Grant-in-Aid for JSPS Fellows from the Japan Society for the Promotion of Science to Hyuma Makizako. The funding source played no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

REFERENCES

Angelucci, F., Spalletta, G., Di Iulio, F., Ciaramella, A., Salani, F., Colantoni, L., et al. (2010). Alzheimer's disease (AD) and mild cognitive impairment (MCI) patients are characterized by increased BDNF serum levels. *Curr. Alzheimer Res.* 7, 15–20. doi:10.2174/156720510790274473

Anthony, J. C., Leresche, L., Niaz, U., Von Korff, M. R., and Folstein, M. F. (1982). Limits of the 'mini-mental state' as a screening test for dementia and delirium among hospital patients. *Psychol. Med.* 12, 397–408. doi:10.1017/S0033291700046730

Bhang, S. Y., Choi, S. W., and Ahn, J. H. (2010). Changes in plasma brain-derived neurotrophic factor levels in smokers after smoking cessation. *Neurosci. Lett.* 468, 7–11. doi:10.1016/j.neulet.2009.10.046

Bus, B. A., Molendijk, M. L., Penninx, B. J., Buitelaar, J. K., Kenis, G., Prickaerts, J., et al. (2011). Determinants of serum brain-derived neurotrophic factor. *Psychoneuroendocrinology* 36, 228–239. doi:10.1016/j.psyneuen.2010.07.013

Bus, B. A., Tendolkar, I., Franke, B., De Graaf, J., Heijer, M. D., Buitelaar, J. K., et al. (2012). Serum brain-derived neurotrophic factor: determinants and relationship with depressive symptoms in a community population of middle-aged and elderly people. *World J. Biol. Psychiatry* 13, 39–47. doi:10.3109/15622975.2010.545187

Correll, J. A., Noel, D. M., Sheppard, A. B., Thompson, K. N., Li, Y., Yin, D., et al. (2009). Nicotine sensitization and analysis of brain-derived neurotrophic factor in adolescent beta-arrestin-2 knockout mice. *Synapse* 63, 510–519. doi:10.1002/syn.20625

Cunha, A. B., Frey, B. N., Andreazza, A. C., Goi, J. D., Rosa, A. R., Goncalves, C. A., et al. (2006). Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. *Neurosci. Lett.* 398, 215–219. doi:10.1016/j.neulet.2005.12.085

Diniz, B. S., Reynolds, C. F. III, Begley, A., Dew, M. A., Anderson, S. J., Lotrich, F., et al. (2014). Brain-derived neurotrophic factor levels in late-life depression and comorbid mild cognitive impairment: a longitudinal study. *J. Psychiatr. Res.* 49, 96–101. doi:10.1016/j.jpsychires.2013.11.004

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., et al. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 112, 257–269. doi:10.1016/S0092-8674(03)00035-7

Elliott, E., Atlas, R., Lange, A., and Ginzburg, I. (2005). Brain-derived neurotrophic factor induces a rapid dephosphorylation of tau protein through a PI-3 kinase signalling mechanism. *Eur. J. Neurosci.* 22, 1081–1089. doi:10.1111/j.1460-9568.2005.04290.x

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Hu, L., Morris, K. S., et al. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus* 19, 1030–1039. doi:10.1002/hipo.20547

Figurov, A., Pozzo-Miller, L. D., Olafsson, P., Wang, T., and Lu, B. (1996). Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. *Nature* 381, 706–709. doi:10.1038/381706a0

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi:10.1016/0022-3956(75)90026-6

Frodl, T., Schaub, A., Banac, S., Charypar, M., Jager, M., Kummler, P., et al. (2006). Reduced hippocampal volume correlates with executive dysfunctioning in major depression. *J. Psychiatry Neurosci.* 31, 316–323.

Gezen-Ak, D., Dursun, E., Hanagasi, H., Bilgic, B., Lohman, E., Araz, O. S., et al. (2013). BDNF, TNFalpha, HSP90, CFH, and IL-10 serum levels in patients with early or late onsetalzheimer's disease or mild cognitive impairment. *J. Alzheimers Dis.* 37, 185–195. doi:10.3233/JAD-130497

Hanninen, T., Hallikainen, M., Tuomainen, S., Vanhanen, M., and Soininen, H. (2002). Prevalence of mild cognitive impairment: a population-based study in elderly subjects. *Acta Neurol. Scand.* 106, 148–154. doi:10.1034/j.1600-0404.2002.01225.x

Hock, C., Heese, K., Hulette, C., Rosenberg, C., and Otten, U. (2000). Region-specific neurotrophin imbalances in Alzheimer disease: decreased levels of brain-derived neurotrophic factor and increased levels of nerve growth factor in hippocampus and cortical areas. *Arch. Neurol.* 57, 846–851. doi:10.1001/archneur.57.6.846

Hyman, C., Hofer, M., Barde, Y. A., Juhasz, M., Yancopoulos, G. D., Squinto, S. P., et al. (1991). BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. *Nature* 350, 230–232. doi:10.1038/350230a0

Iacono, D., Markesbery, W. R., Gross, M., Pletnikova, O., Rudow, G., Zandi, P., et al. (2009). The nun study: clinically silent AD, neuronal hypertrophy, and linguistic skills in early life. *Neurology* 73, 665–673. doi:10.1212/WNL.0b013e3181b01077

Iacono, D., O'Brien, R., Resnick, S. M., Zonderman, A. B., Pletnikova, O., Rudow, G., et al. (2008). Neuronal hypertrophy in asymptomatic Alzheimer disease. *J. Neuropathol. Exp. Neurol.* 67, 578–589. doi:10.1097/NEN.0b013e3181772794

Jungwirth, S., Weissgram, S., Zehetmayer, S., Tragl, K. H., and Fischer, P. (2005). VITA: subtypes of mild cognitive impairment in a community-based cohort at the age of 75 years. *Int. J. Geriatr. Psychiatry* 20, 452–458. doi:10.1002/gps.1311

Kang, H., and Schuman, E. M. (1995). Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus. *Science* 267, 1658–1662. doi:10.1126/science.7886457

Karege, F., Perret, G., Bondolfi, G., Schwald, M., Bertschy, G., and Aubry, J. M. (2002). Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Res.* 109, 143–148. doi:10.1016/S0165-1781(02)00005-7

Kenny, P. J., File, S. E., and Rattray, M. (2000). Acute nicotine decreases, and chronic nicotine increases the expression of brain-derived neurotrophic factor mRNA in rat hippocampus. *Brain Res. Mol. Brain Res.* 85, 234–238. doi:10.1016/S0169-328X(00)00246-1

Kim, T. S., Kim, D. J., Lee, H., and Kim, Y. K. (2007). Increased plasma brain-derived neurotrophic factor levels in chronic smokers following unaided smoking cessation. *Neurosci. Lett.* 423, 53–57. doi:10.1016/j.neulet.2007.05.064

Knaepen, K., Goekint, M., Heyman, E. M., and Meeusen, R. (2010). Neuroplasticity – exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. *Sports Med.* 40, 765–801. doi:10.2165/11534530-000000000-00000

Knusel, B., Winslow, J. W., Rosenthal, A., Burton, L. E., Seid, D. P., Nikolics, K., et al. (1991). Promotion of central cholinergic and dopaminergic neuron differentiation by brain-derived neurotrophic factor but not neurotrophin 3. *Proc. Natl. Acad. Sci. U.S.A.* 88, 961–965. doi:10.1073/pnas.88.3.961

Krabbe, K. S., Nielsen, A. R., Krogh-Madsen, R., Plomgaard, P., Rasmussen, P., Erikstrup, C., et al. (2007). Brain-derived neurotrophic factor (BDNF) and type 2 diabetes. *Diabetologia* 50, 431–438. doi:10.1007/s00125-006-0537-4

Lang, U. E., Hellweg, R., and Gallinat, J. (2004). BDNF serum concentrations in healthy volunteers are associated with depression-related personality traits. *Neuropsychopharmacology* 29, 795–798. doi:10.1038/sj.npp.1300382

Laske, C., Stellos, K., Hoffmann, N., Stransky, E., Straten, G., Eschweiler, G. W., et al. (2011). Higher BDNF serum levels predict slower cognitive decline in Alzheimer's disease patients. *Int. J. Neuropsychopharmacol.* 14, 399–404. doi:10.1017/S1461145710001008

Laske, C., Stransky, E., Leyhe, T., Eschweiler, G. W., Maetzler, W., Wittorf, A., et al. (2007). BDNF serum and CSF concentrations in Alzheimer's disease, normal pressure hydrocephalus and healthy controls. *J. Psychiatr. Res.* 41, 387–394. doi:10.1016/j.jpsychires.2006.01.014

Laske, C., Stransky, E., Leyhe, T., Eschweiler, G. W., Wittorf, A., Richartz, E., et al. (2006). Stage-dependent BDNF serum concentrations in Alzheimer's disease. *J. Neural Transm.* 113, 1217–1224. doi:10.1007/s00702-005-0397-y

Makizako, H., Shimada, H., Park, H., Doi, T., Yoshida, D., Uemura, K., et al. (2012). Evaluation of multidimensional neurocognitive function using a tablet personal computer: test-retest reliability and validity in community-dwelling older adults. *Geriatr. Gerontol. Int.* 13, 860–866. doi:10.1111/ggi.12014

Mamounas, L. A., Blue, M. E., Siuciak, J. A., and Altar, C. A. (1995). Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. *J. Neurosci.* 15, 7929–7939.

McKinney, B. C., and Sibille, E. (2013). The age-by-disease interaction hypothesis of late-life depression. *Am. J. Geriatr. Psychiatry* 21, 418–432. doi:10.1016/j.jagp.2013.01.053

Molendijk, M. L., Bus, B. A., Spinhoven, P., Penninx, B. W., Kenis, G., Prickaerts, J., et al. (2011). Serum levels of brain-derived neurotrophic factor in major depressive disorder: state-trait issues, clinical features and pharmacological treatment. *Mol. Psychiatry* 16, 1088–1095. doi:10.1038/mp.2010.98

Murer, M. G., Yan, Q., and Raisman-Vozari, R. (2001). Brain-derived neurotrophic factor in the control human brain, and in Alzheimer's disease and Parkinson's disease. *Prog. Neurobiol.* 63, 71–124. doi:10.1016/S0301-0082(00)00014-9

Ozan, E., Okur, H., Eker, C., Eker, O. D., Gonul, A. S., and Akarsu, N. (2010). The effect of depression, BDNF gene val66met polymorphism and gender on serum BDNF levels. *Brain Res. Bull.* 81, 61–65. doi:10.1016/j.brainresbull.2009.06.022

Peng, S., Wuu, J., Mufson, E. J., and Fahnestock, M. (2005). 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.* 93, 1412–1421. doi:10.1111/j.1471-4159.2005.03135.x

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *J. Intern. Med.* 256, 183–194. doi:10.1111/j.1365-2796.2004.01388.x

Petersen, R. C., Parisi, J. E., Dickson, D. W., Johnson, K. A., Knopman, D. S., Boeve, B. F., et al. (2006). Neuropathologic features of amnestic mild cognitive impairment. *Arch. Neurol.* 63, 665–672. doi:10.1001/archneur.63.5.665

Pezawas, L., Verchinski, B. A., Mattay, V. S., Callicott, J. H., Kolachana, B. S., Straub, R. E., et al. (2004). The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *J. Neurosci.* 24, 10099–10102. doi:10.1523/JNEUROSCI.2680-04.2004

Phillips, H. S., Hains, J. M., Laramee, G. R., Rosenthal, A., and Winslow, J. W. (1990). Widespread expression of BDNF but not NT3 by target areas of basal forebrain cholinergic neurons. *Science* 250, 290–294. doi:10.1126/science.1688328

Plassman, B. L., Williams, J. W. Jr., Burke, J. R., Holsinger, T., and Benjamin, S. (2010). Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. *Ann. Inter. Med.* 153, 182–193. doi:10.1059/0003-4819-153-3-201008030-00258

Riudavets, M. A., Iacono, D., Resnick, S. M., O'Brien, R., Zonderman, A. B., Martin, L. J., et al. (2007). Resistance to Alzheimer's pathology is associated with nuclear hypertrophy in neurons. *Neurobiol. Aging* 28, 1484–1492. doi:10.1016/j.neurobiolaging.2007.05.005

Scharfman, H. E., and MacLusky, N. J. (2006). Estrogen and brain-derived neurotrophic factor (BDNF) in hippocampus: complexity of steroid hormone-growth factor interactions in the adult CNS. *Front. Neuroendocrinol.* 27:415–435. doi:10.1016/j.yfrne.2006.09.004

Schindowski, K., Belarbi, K., and Buee, L. (2008). Neurotrophic factors in Alzheimer's disease: role of axonal transport. *Genes Brain Behav.* 7(Suppl. 1), 43–56. doi:10.1111/j.1601-183X.2007.00378.x

Schneider, J. A., Arvanitakis, Z., Leurgans, S. E., and Bennett, D. A. (2009). The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann. Neurol.* 66, 200–208. doi:10.1002/ana.21706

Serres, F., and Carney, S. L. (2006). Nicotine regulates SH-SY5Y neuroblastoma cell proliferation through the release of brain-derived neurotrophic factor. *Brain Res. 1101*, 36–42. doi:10.1016/j.brainres.2006.05.023

Shimizu, E., Hashimoto, K., Okamura, N., Koike, K., Komatsu, N., Kumakiri, C., et al. (2003). Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biol. Psychiatry* 54, 70–75. doi:10.1016/S0006-3223(03)00181-1

Sibille, E. (2013). Molecular aging of the brain, neuroplasticity, and vulnerability to depression and other brain-related disorders. *Dialogues Clin. Neurosci.* 15, 53–65.

Szeszko, P. R., Lipsky, R., Mentschel, C., Robinson, D., Gunduz-Bruce, H., Sevy, S., et al. (2005). Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation. *Mol. Psychiatry* 10, 631–636. doi:10.1038/sj.mp.4001656

Takahashi, J., Palmer, T. D., and Gage, F. H. (1999). Retinoic acid and neurotrophins collaborate to regulate neurogenesis in adult-derived neural stem cell cultures. *J. Neurobiol.* 38, 65–81. doi:10.1002/(SICI)1097-4695(199901)38:1<65::AID-NEU5>3.3.CO;2-H

Tapia-Arancibia, L., Aliaga, E., Silhol, M., and Arancibia, S. (2008). New insights into brain BDNF function in normal aging and Alzheimer disease. *Brain Res. Rev.* 59, 201–220. doi:10.1016/j.brainresrev.2008.07.007

Terracciano, A., Lobina, M., Piras, M. G., Mulas, A., Cannas, A., Meirelles, O., et al. (2011). Neuroticism, depressive symptoms, and serum BDNF. *Psychosom. Med.* 73, 638–642. doi:10.1097/PSY.0b013e3182306a4f

Tong, L., Balazs, R., Thornton, P. L., and Cotman, C. W. (2004). Beta-amyloid peptide at sublethal concentrations downregulates brain-derived neurotrophic factor functions in cultured cortical neurons. *J. Neurosci.* 24, 6799–6809. doi:10.1523/JNEUROSCI.5463-03.2004

Trajkovska, V., Marcussen, A. B., Vinberg, M., Hartvig, P., Aznar, S., and Knudsen, G. M. (2007). Measurements of brain-derived neurotrophic factor: methodological aspects and demographical data. *Brain Res. Bull.* 73, 143–149. doi:10.1016/j.brainresbull.2007.03.009

Wall, P. M., and Messier, C. (2001). The hippocampal formation – orbitomedial prefrontal cortex circuit in the attentional control of active memory. *Behav. Brain Res.* 127, 99–117. doi:10.1016/S0166-4328(01)00355-2

Wang, D. C., Chen, S. S., Lee, Y. C., and Chen, T. J. (2006). Amyloid-beta at sublethal level impairs BDNF-induced arc expression in cortical neurons. *Neurosci. Lett.* 398, 78–82. doi:10.1016/j.neulet.2005.12.057

Wetmore, C., Ernfors, P., Persson, H., and Olson, L. (1990). Localization of brain-derived neurotrophic factor mRNA to neurons in the brain by *in situ* hybridization. *Exp. Neurol.* 109, 141–152. doi:10.1016/0014-4886(90)90068-4

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., et al. (2004). Mild cognitive impairment – beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. *J. Intern. Med.* 256, 240–246. doi:10.1111/j.1365-2796.2004.01380.x

Yaffe, K., Middleton, L. E., Lui, L. Y., Spira, A. P., Stone, K., Racine, C., et al. (2011). Mild cognitive impairment, dementia, and their subtypes in oldest old women. *Arch. Neurol.* 68, 631–636. doi:10.1001/archneurol.2011.82

Yu, H., Zhang, Z., Shi, Y., Bai, F., Xie, C., Qian, Y., et al. (2008). Association study of the decreased serum BDNF concentrations in amnestic mild cognitive impairment and the Val66Met polymorphism in Chinese Han. *J. Clin. Psychiatry* 69, 1104–1111. doi:10.4088/JCP.v69n0710

Ziegenhorn, A. A., Schulte-Herbruggen, O., Danker-Hopfe, H., Malbranc, M., Hartung, H. D., Anders, D., et al. (2007). Serum neurotrophins – a study on the time

course and influencing factors in a large old age sample. *Neurobiol. Aging* 28, 1436–1445. doi:10.1016/j.neurobiolaging.2006.06.011

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 20 January 2014; accepted: 28 March 2014; published online: 15 April 2014.
Citation: Shimada H, Makizako H, Doi T, Yoshida D, Tsutsumimoto K, Anan Y, Uemura K, Lee S, Park H and 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. doi: 10.3389/fnagi.2014.00069
This article was submitted to the journal Frontiers in Aging Neuroscience.

Journal of Psychiatric Research 57 (2014) 149–156

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Depressive symptoms and cognitive performance in older adults

Hiroyuki Shimada [a, *], Hyuntae Park [b], Hyuma Makizako [a], Takehiko Doi [a], Sangyoon Lee [a], Takao Suzuki [b]

[a] Department of Functioning Activation, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-machi, Obu, Aichi 474-8511, Japan
[b] Research Institute, National Center for Geriatrics and Gerontology, Obu, Japan

ARTICLE INFO

Article history:
Received 2 January 2014
Received in revised form
21 May 2014
Accepted 6 June 2014

Keywords:
Cognitive test
BDNF
Brain atrophy
Hippocampus
Geriatric depression scale
Elderly

ABSTRACT

Many longitudinal studies have found that older adults with depressive symptoms or depression have increased risk of cognitive impairment. We investigated the relationships between depressive symptoms or depression, cognitive function, serum brain-derived neurotrophic factor (BDNF), and volumetric MRI measurements in older adults. A total of 4352 individuals aged 65 years or older (mean age 72 years) participated in the study. We investigated medical history and geriatric depression scale-15 (GDS-15) items to determine depression and depressive symptoms. Cognitive tests included the mini-mental state examination (MMSE), story memory, word list memory, trail-making tests, and the symbol digit substitution task. Of the 4352 participants, 570 (13%) fulfilled the criteria for depressive symptoms (GDS-15: 6 + points) and 87 (2%) were diagnosed with depression. All cognitive tests showed significant differences between the 'no depressive symptoms', 'depressive symptoms', and 'depression' groups. The 'depressive symptoms' and 'depression' groups showed lower serum BDNF ($p < 0.001$) concentrations than the 'no depressive symptoms' group. The 'depressive symptoms' group exhibited greater atrophy of the right medial temporal lobe than did the 'no depressive symptoms' group ($p = 0.023$). These results suggest that memory, executive function, and processing speed examinations are useful to identify cognitive decline in older adults who have depressive symptoms and depression. Serum BDNF concentration and atrophy of the right medial temporal lobe may in part mediate the relationships between depressive symptoms and cognitive decline.

1. Introduction

An epidemiological study estimated that up to half of Alzheimer's disease (AD) cases worldwide (17.2 million) might be attributable to potentially modifiable risk factors. If the prevalence of all these risk factors were 10% lower, it is estimated that there would be as many as 1.1 million fewer AD cases worldwide; if risk factor prevalence were 25% lower, AD prevalence could potentially be reduced by over 3.0 million cases worldwide (Barnes and Yaffe, 2011).

Persons with cognitive decline are at increased risk for progressing to mild cognitive impairment (MCI) and dementia. Findings from numerous epidemiologic and clinical studies suggest that multiple biological, behavioral, psychosocial, and environmental factors may contribute to the risk of cognitive decline (Plassman et al., 2010). Also, many longitudinal studies have found that older persons with depressive symptoms or depression have an increased risk of cognitive decline, MCI, and dementia (Barnes et al., 2006; Berger et al., 1999; Devanand et al., 1996; Geerlings et al., 2000; Green et al., 2003; Verdelho et al., 2013; Wilson et al., 2002; Yaffe et al., 1999). In fact, depressive symptoms are common in dementia patients, with a prevalence of approximately 30% in people with dementia (Lyketsos et al., 2002). It is important to clarify which cognitive domains are associated with depressive symptoms or depression and to identify potential mediators between depression and cognitive decline to design strategies for the prevention of dementia in older adults.

Previous studies have reported that serum brain-derived neurotrophic factor (BDNF) levels are reduced in major depressive disorder and depressive symptoms (Cunha et al., 2006; Karege et al., 2002; Shimizu et al., 2003; Terracciano et al., 2011). BDNF has neurotrophic and neuroprotective properties (Barde, 1994; Lindvall et al., 1994) and can affect functions that underlie brain plasticity (Altar and DiStefano, 1998; Lu and Chow, 1999; McAllister

* Corresponding author. Tel.: +81 562 44 5651x5254; fax: +81 562 46 8294.
E-mail address: shimada@ncgg.go.jp (H. Shimada).

http://dx.doi.org/10.1016/j.jpsychires.2014.06.004
0022-3956/

et al., 1999; Schinder and Poo, 2000). The neurotrophin hypothesis of depression is based on these functions of BDNF and postulates that depression results from stress-induced decreases in BDNF expression (Duman et al., 1997; Duman, Malberg, Nakagawa, & D'Sa, 2000). However, the majority of these studies have a small sample size or the design compares patients with major depression with healthy people. Extensive research is needed to determine the exact relationships between depressive symptoms and serum BDNF levels adjusted or controlled for potential confounders using large samples to examine the prevention strategies of depression in later life.

Another key factor that might affect the relationship between depression and cognition is age-related brain structural changes, especially hippocampal volume loss. Previous research has demonstrated reduced right hippocampal volume in older adults with depression (Bell-McGinty et al., 2002); moreover, depressed older adults with hippocampal volume loss were at greater risk of cognitive decline (Steffens et al., 2011). In addition, BDNF plays a role in regulating hippocampal plasticity: BDNF is presumed to be important for the integrity of the hippocampus and the maintenance of cognition. Normal aging appears to be associated with decreased BDNF signaling capacity in the brain. BDNF levels are decreased in hippocampal pyramidal neurons and dentate granule cells during aging in monkeys (Hayashi et al., 2001). These evidences suggest that a loss of BDNF plays a major role in the pathophysiology of depression, and that the neurotrophin hypothesis of depression appears to be valid especially when considered with relation to hippocampal function. However, it is not clear which cognitive categories are altered in patients with depressive symptoms and how BDNF levels might be associated to these and to hippocampal volume changes. The primary objective of this study was to examine which cognitive domains are associated with depressive symptoms and whether serum BDNF and brain atrophy are potential mediators between depression and cognitive decline in older adults.

2. Methods and materials

2.1. Participants

Our study assessed 5104 individuals who were enrolled in the Obu Study of Health Promotion for the Elderly (OSHPE) (Shimada et al., 2013). Each individual was recruited from Obu, Japan, which is a residential suburb of Nagoya. Each participant was 65 years or older at the time of examination (2011 or 2012), resided in Obu city, and had not participated in another study. We excluded participants who had been diagnosed with stroke ($n = 280$), Parkinson's disease ($n = 22$), or AD ($n = 8$); we also excluded those who had certified long-term care insurance needs ($n = 119$), functional decline in activities of daily living ($n = 11$), severe cognitive decline, i.e., mini-mental state examination (MMSE) 20 points or fewer ($n = 121$), or missing BDNF data or characteristics ($n = 191$). Ultimately, 752 of the 5104 participants were excluded and 4352 older adults (mean age 71.7 ± 5.3 years, range 65–97 years, 2085 men, 2267 women) were included in this study. Informed consent was obtained from all participants prior to their inclusion in the study, and the Ethics Committee of the National Center for Geriatrics and Gerontology approved the study protocol.

2.2. Measurements: depressive symptoms and depression

The self-report screening instruments available to detect depression were deemed suitable for use in this community-based study. The 15-item version of the geriatric depression scale (GDS-15) has been validated as a screening tool for depressive symptoms in older people (Sheikh and Yesavage, 1986). A cut-off point of ≥5 on the GDS-15 has a pooled sensitivity of 88% and specificity 64%, and a cut-off point of ≥6 has a pooled sensitivity of 79% and specificity of 77% for diagnosing depression in older people (Dennis et al., 2012). A recent longitudinal study, which used GDS-15 and a cut-off score of 6, identified that MCI and subjective memory impairment were associated with incident depression (Weyerer et al., 2013). Participants were screened for depressive symptoms using the GDS-15 and a cut-off value of ≥6 to indicate clinically critical depressive symptoms. All participants completed a face-to-face interview including medical history by licensed and well-trained nurses. Depression was defined as follows: diagnosed as having depressive disorder by a family doctor and having received medication for depression.

2.3. Measurements: cognitive performance

Well-trained study assistants conducted assessments of cognitive functions. Prior to commencing the study, all staff received training from the authors in the correct protocols for administering the assessment measures. Cognitive tests were conducted using the MMSE (Folstein et al., 1975) and the National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT) (Makizako et al., 2013; Shimada et al., 2013). The computerized multidimensional neurocognitive task battery, the NCGG-FAT, comprises several cognitive domains: story memory (delayed recognition), word list memory (delayed recall), attention and executive function (tablet version of trail-making test, parts A and B), and processing speed (tablet version of symbol digit substitution task). In story memory, the participants heard a short story (approximately 1 min in length) through an auditory system using headphones. They were instructed to remember the details of a story, and then select the correct answer that described the details of the story from four choices after 20–30 min. All 10 questions in each task were shown and we calculated the total number of correct answers. Word list memory involved delayed recall of a 10-word target list. The participants were instructed to recall the 10 target words after approximately 20 min. The tablet version of trail-making test consists of part A and B, as well as the original written version of trail-making test. We recorded the time (in seconds) taken to complete each task, within a maximum period of 90 s in the tablet version of symbol digit substitution task, nine pairs of numbers and symbols were provided at the top of the display. A target symbol was shown at the center of the display. Participants then chose a number corresponding to a target symbol at the bottom of the display as rapidly as possible. The score was the number of correct numbers chosen within 90 s. One point was given for each correctly chosen number completed within the time limit. High test–retest reliability and moderate-to-high validity were confirmed in community-dwelling older adults for all task components of the NCGG-FAT (Makizako et al., 2013).

2.4. Measurements: potential correlates

With reference to the review articles by Cole and Dendukuri (2003) and Plassman et al. (2010), we selected four demographic variables, three physiological variables, two health status indicators, two blood biomarkers, and four behavioral variables as possible confounding factors of depressive symptoms and depression and cognitive decline (Table 1) (Cole and Dendukuri, 2003; Plassman et al., 2010). We selected four demographic variables—age, sex, educational level, and living alone—as possible correlates in determining the association between depressive syndromes and cognitive decline.

Table 1
Comparisons of potential confounders between the three groups.

	'No depressive symptoms' ($n = 3695$)		'Depressive symptoms' ($n = 570$)		'Depression' ($n = 87$)		Statistics	
	Mean	SD	Mean	SD	Mean	SD	ANOVA F	P
Age (years)	71.5	5.2	73.2	6.1	71.1	4.0	27.46	<0.001
Body mass index	23.4	3.1	23.2	3.1	23	2.9	2.65	0.071
Body fat (%)	28.2	7.9	28.5	7.5	29.6	7.7	1.48	0.227
Walking speed (m/s)	1.2	0.2	1.1	0.2	1.2	0.2	62.54	<0.001
Triglyceride (mg/dl)	152.9	93.1	155.3	103.5	155.5	85.7	0.19	0.831
HbA1c (%)	5.5	0.7	5.5	0.6	5.5	0.7	0.52	0.597
Frequency of going outdoors (times/week)	1.6	1.8	1.2	1.6	1.4	1.6	15.01	<0.001
Sleep time (min)	460.8	69.9	469.8	95.6	468.9	72.5	4.00	0.018
	%		%		%		Chi square	P
Sex (female)	52.0		50.9		63.2		4.66	0.097
Education (<10 years)	33.3		45.4		39.1		32.54	<0.001
Living alone (yes)	8.5		15.1		12.6		26.42	<0.001
Frailty (yes)	6.9		27.7		12.6		244.23	<0.001
Self-rated health (not well)	10.0		34.0		35.6		278.72	<0.001
Current smoking (yes)	10.0		8.8		13.8		2.35	0.309
Habitual exercise (no)	36.0		46.7		32.2		24.93	<0.001

The physiological variables were body mass index, percentage body fat, and walking speed. A multi-frequency bioelectrical impedance analyzer (MC-980A, Tanita Corp., Tokyo, Japan) was used to measure percentage body fat. This instrument uses six frequencies (1, 5, 50, 250, 500, and 1000 kHz) and the percentage body fat is calculated by multi-frequency bioelectrical impedance. Walking speed was measured on a flat and straight surface at a comfortable walking speed. Two markers were used to indicate the start and end of a 2.4-m walk path, with a 2-m section to be traversed before passing the start marker so that participants were walking at a comfortable pace by the time they reached the timed path. Participants were asked to continue walking for an additional 2 m past the end of the path to ensure a consistent walking pace while on the timed path.

Frailty and self-rated health were assessed as health status indicators. We considered the frailty phenotype to be characterized by limitations in three or more of the following five domains: mobility, strength, endurance, physical activity, and nutrition (Fried et al., 2001). We defined "good self-rated health" to be ratings of either "excellent" or "good" self-rated health, and we defined "poor self-rated health" to be ratings of either "not very good" or "poor" self-rated health.

Diabetes and hyperlipidemia are associated with cognitive decline, and we therefore measured HbA1c and triglyceride levels.

Behavioral factors, including current smoking, regular exercise, frequency of going outdoors, and sleep time were identified during the interview. Participants were asked whether they currently smoked or exercised regularly: responses were "yes" or "no". Participants were asked how often they traveled to places outside their town during a week and how long they slept during the day.

2.5. Measurements: potential mediators

Serum BDNF and brain volume were measured as potential mediators. All participants underwent BDNF measurement and 618 participants underwent brain volume assessments. Whole blood samples were collected from each participant by venipuncture. To obtain serum, the whole blood samples were allowed to coagulate at room temperature for 30 min and then centrifuged at room temperature for 15 min at 1000 × g. The collected serum was stored in polypropylene tubes at −80 °C until assayed. BDNF concentrations were quantitatively determined by enzyme-linked immunosorbent assay using the DuoSet ELISA Development Kit from R&D Systems (Minneapolis, MN). Assays were performed using a specific human BDNF antibody; no significant cross reactivity or interference was observed. Serum samples were diluted 1:50. Sample BDNF concentrations were then determined by nonlinear regression from the standard curves. Measurements were performed in duplicate and averaged to give a value in pg/ml, which was then expressed in ng/ml after correcting for sample dilution. "Low" and "high" concentration quality control pools were prepared by adding 10 or 100 ng to 5 ml portions of human serum (Innovative Research, Novi, MI), giving nominal concentrations of 2 and 20 ng/ml, respectively. The assays were performed by SRL Inc. (Tokyo, Japan).

Magnetic resonance imaging (MRI) was performed on a 3-T system (TIM Trio, Siemens, Germany) in a portion of the participants without diagnosis of depression ($n = 618$). Most participants who underwent an MRI had frailty ($n = 108$) or MCI ($n = 400$) who were not treated. Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (inversion time [TI], 800 ms; echo time (TE)/repetition time (TR), 1.98 ms/1800 ms; 1.1-mm slice thickness). Axial T2-weighted spin-echo images (TR, 4200 ms; TE, 89.0 ms; 5-mm slice thickness) and axial fluid-attenuated inversion recovery images (TR, 9000 ms; TE, 100 ms; TI, 2500 ms; 5-mm slice thickness) were obtained. We used voxel-based morphometry, an automatic whole-brain MRI analysis technique, to calculate the volume of the bilateral medial temporal lobe including the entorhinal cortex, head to tail of the hippocampus, and amygdala. (Matsuda et al., 2012). The stand-alone software program running on Windows for voxel-based morphometry analysis by statistical parametric mapping 8 (SPM8; Wellcome Department of Imaging Neuroscience, London, UK) and the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL; Wellcome Department of Imaging Neuroscience) (Ashburner, 2007) were developed to differentiate patients with AD from healthy controls based on MRI data. First, MRI images were spatially normalized with only a 12-parameter affine transformation to the SPM template to correct for differences in brain size. These linearly transformed images were nonlinearly transformed and then modulated to the customized template for DARTEL, followed by smoothing using an 8-mm full width at half maximum Gaussian kernel. Each

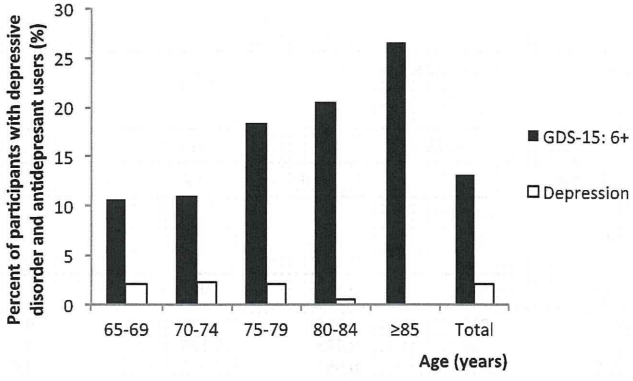

Fig. 1. Proportion of participants with depressive symptoms and depression.

participant's processed gray matter image was compared with the mean and SD of gray matter images of the 58 healthy volunteers chosen in the group comparison, using voxel-by-voxel z-score analysis with and without voxel normalization to global mean intensities (global normalization): Z-score = ([control mean] − [individual value])/(control SD). These Z-score maps were displayed by overlay on tomographic sections and surface rendering of the standardized brain (Matsuda et al., 2012).

2.6. Statistical analysis

Participants were divided into three groups: the 'no depressive symptoms' group (GDS-15 ≤ 5), the 'depressive symptoms' group (GDS-15 6+), and the 'depression' (depressive disorder) group. Analysis of variance (ANOVA) was used to compare potential correlates and GDS-15 scores among the three groups. ANOVA and analysis of covariance (ANCOVA) were used to determine the intergroup differences for the cognitive tests and BDNF measurements. Post-hoc analyses in ANCOVA were conducted using Bonferroni comparisons to compare cognitive tests among the groups. MRI measurements were compared using *t*-tests and ANCOVA. Ordinal logistic regression was used to study associations between the categories of depressive state ('no depressive symptoms', 'depressive symptoms', and 'depression') and cognitive performances, and serum BDNF. This analysis was not an analysis of risk factors since the data were collected in a cross-sectional fashion. Simple binary logistic regression was used to study associations the depressive symptoms ('depressive symptoms' versus 'no depressive symptoms') and brain volumes. Covariates such as significant variables of the potential correlates were included in the multivariate model. All statistical comparisons were made at the 0.05 level of significance, and all data management and statistical computations were performed using the IBM SPSS Statistics 20.0 software package (SPSS Inc., Chicago, IL, USA).

3. Results

Of the 4352 participants who completed all the assessments except the MRI scan, 3695 (85%) were defined as having 'no depressive symptoms' (GDS-15: ≤5 points), 570 (13%) fulfilled the criteria for 'depressive symptoms' (GDS-15: 6 + points), and 87 (2%) were diagnosed with depression. The proportion of participants with depressive symptoms increased with age: from 10.6% between the ages of 65 and 69 to 26.5% for subjects 85 years and older (Fig. 1). The mean GDS-15 scores in the 'no depressive symptoms', 'depressive symptoms', and 'depression' groups were 2.0 (SD = 1.5), 7.6 (SD = 1.81), and 4.2 (SD = 3.6), respectively ($p < 0.001$). There was a significant difference in age among the three groups ($p < 0.001$) (Table 1).

In comparisons with potential confounders, there were significant differences in education level ($p < 0.001$), living alone status ($p < 0.001$), walking speed ($p < 0.001$), frailty ($p < 0.001$), self-rated health ($p < 0.001$), regular exercise ($p < 0.001$), frequency of going outdoors ($p < 0.001$), and sleep time ($p = 0.018$) among the 'no depressive symptoms', 'depressive symptoms' and 'depression' groups (Table 1).

All cognitive performance measures including general function, memory, attention and executive function, and processing speed showed significant differences among the 'no depressive symptoms', 'depressive symptoms' and 'depression' groups by ANOVA. In multivariate analyses adjusted for significant correlates including age, education level, living alone status, walking speed, frailty, self-rated health, regular exercise, frequency of going outdoors, and sleep time, significant effects were maintained in all cognitive tests except for the MMSE (Table 2). Post-hoc analyses revealed that the 'no depressive symptoms' group scored significantly better than the 'depressive symptoms' group in the word recall test and trail-making test part B. The story memory and symbol digit substitution tasks were scored higher by the 'no depressive symptoms' group compared with the 'depression' group (Table 2).

The mean BDNF concentrations were 21.2 ± 5.3 ng/ml in the 'no depressive symptoms' group, 20.2 ± 5.0 ng/ml in the 'depressive symptoms' group, and 20.3 ± 5.4 ng/ml in the 'depression' group ($p < 0.001$). The significant difference disappeared in multivariate analyses adjusted for the correlates.

Of the 618 participants who underwent an MRI scan, 544 (88%) were in the 'no depressive symptoms' group and 74 (12%) were in the 'depressive symptoms' group. The 'depressive symptoms' group

Table 2
Comparisons of cognitive performance among the groups.

	'No depressive symptoms' ($n = 3695$)		'Depressive symptoms' ($n = 570$)		'Depression' ($n = 87$)		Statistics				
	Mean	SD	Mean	SD	Mean	SD	ANOVA *F*	*P*	ANCOVA *F*	*P*	Post hoc in ANCOVA
MMSE	26.5	2.4	26.1	2.5	26.6	2.6	10.285	<0.001	0.723	0.485	
Word recall	3.9	1.9	3.3	1.9	3.5	1.9	31.835	<0.001	9.901	<0.001	a
Story memory	6.9	1.8	6.4	1.9	6.4	1.9	20.134	<0.001	4.871	0.008	b
Trail-making test part A (s)	20.6	5.8	22.6	8.3	22.2	7.7	27.497	<0.001	3.424	0.033	
Trail-making test part B (s)	41.5	16.4	48.0	19.8	43.9	17.1	36.688	<0.001	5.600	0.004	a
Symbol digit substitution task	39.0	7.9	36.0	8.7	36.9	7.4	37.456	<0.001	4.252	0.014	b

a: $p < 0.05$ for comparison between the 'no depressive symptoms' and 'depressive symptoms' groups.
b: $p < 0.05$ for comparison between the 'no depressive symptoms' and 'depression' groups.
MMSE: mini-mental state examination. Age, education level, living alone status, walking speed, frailty, self-rated health, regular exercise, frequency of going outdoors, and sleep time were included as covariates in ANCOVA.

Table 3
Comparisons of BDNF level, and hippocampal and whole gray matter atrophy.

	'No depressive symptoms' ($n = 3695$)		'Depressive symptoms' ($n = 570$)		'Depression' ($n = 87$)		Statistics			
	Mean	SD	Mean	SD	Mean	SD	ANOVA F	P	ANCOVA F	P
BDNF (ng/ml)	21.2	5.3	20.2	5.0	20.3	5.4	8.098	<0.001	2.738	0.065

	'No depressive symptoms' ($n = 544$)		'Depressive symptoms' ($n = 74$)		Statistics			
	Mean	SD	Mean	SD	t-test t	P	ANCOVA F	P
Bilateral MTL atrophy	0.7	0.5	0.8	0.6	1.753	0.083	3.197	0.074
Right MTL atrophy	0.7	0.6	0.9	0.7	2.229	0.028	5.169	0.023
Left MTL atrophy	0.6	0.5	0.7	0.5	0.054	0.957	0.007	0.933
Whole gray matter atrophy	2.0	1.4	2.2	1.2	1.530	0.126	0.999	0.318

BDNF: brain-derived neurotrophic factor, MTL: medial temporal lobe, Age, education level, living alone status, walking speed, frailty, self-rated health, regular exercise, frequency of going outdoors, and sleep time were included as covariates in ANCOVA.

exhibited greater atrophy in right medial temporal lobe upon multivariate analyses ($p = 0.023$), although there were no significant differences in bilateral and left medial temporal lobe and whole gray matter atrophy (Table 3, Fig. 2).

The ordinal and binary logistic analyses examined the factors associated with being in 1 of 3 categories of depressive state ('depressive symptoms' vs. 'no depressive symptoms' and 'depression' vs. 'no depressive symptoms'). The likelihood of having the 'depressive symptoms' increased having low performances in word recall, story memory, and trail-making test part A and B, being low serum BDNF, and having high bilateral and right MTL atrophy. The correlates with 'depressive symptoms' that remained significant after adjustment were word recall, story memory, trail-making test part B, and right MTL atrophy (Table 4). The likelihood of having 'depression' increased having low performances in all cognitive tests, and being low serum BDNF. The correlates with 'depression' that remained significant after adjustment were word recall, story memory, trail-making test part A, and symbol digit substitution task (Table 4).

4. Discussion

The present study showed that depressive symptoms in older participants were associated with worse overall performance in tests of general cognitive function, memory, attention and executive functions, and processing speed. Similar results were observed when the data were controlled for socio-demographic, physiological, health, and behavioral variables.

Many studies have reported a relationship between depressive symptoms or major depression and cognitive dysfunction in older adults (Barnes et al., 2006; Berger et al., 1999; Devanand et al., 1996; Geerlings et al., 2000; Green et al., 2003; Verdelho et al., 2013; Wilson et al., 2002; Yaffe et al., 1999). The strengths of our study include a large sample size of rigorously assessed older people, and the potential to control for many variables implicated in cognition (age, education, marital status, health status, physical performance, and health-related behaviors). A new finding of our study was that, in the word recall test, story memory, and the trail-making tests, older adults with depressive symptoms achieved lower scores and took longer to complete the task than did people without depressive symptoms. In addition, word recall test, story memory, the trail-making test, and symbol digit substitution task scores were decreased in the depression group. These results suggest that memory, executive function, and processing speed examinations are useful to identify cognitive decline in older adults who have depressive symptoms or depression.

We found that BDNF levels were significantly lower in the 'depressive symptoms' and 'depression' group than in the 'no depressive symptoms' group. Recently, Chu et al. compared the differences in BDNF levels among 167 Chinese older adults with

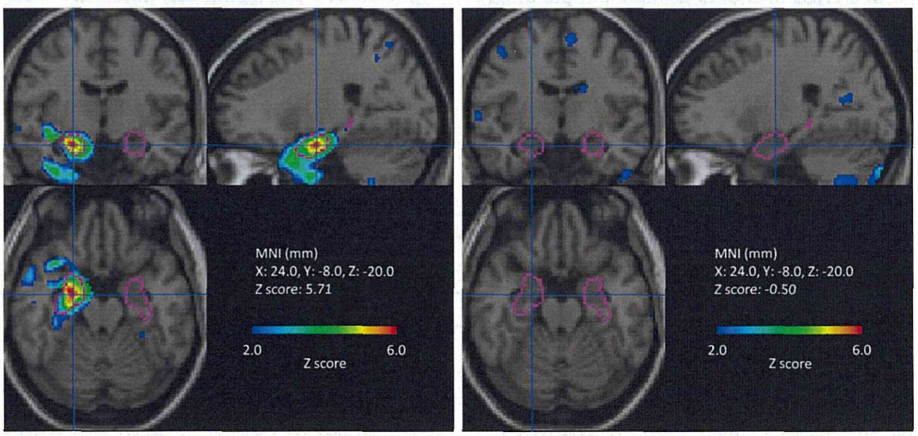

Fig. 2. Atrophy of the medial temporal lobe in participants with and without depressive symptoms. The panels show typical images, indicating regions of atrophy, in participants with and without depressive symptoms. The left panel shows whole brain cortical atrophy in a man (65 years old) with depressive symptoms. The Z-score of right medial temporal lobe atrophy was 3.8 in this depressive participant, who scored low on word recall (3 points) and had low serum BDNF levels (16.6 ng/ml). The right panel shows fusion images in a man (65 years old) without depressive symptoms. The Z-score of right medial temporal lobe atrophy was 0.2 in this non-depressive participant, who had a high word recall test score (5 points) and high serum BDNF levels (23.9 ng/ml).

Table 4
Relationships between 'Depressive symptoms' and 'Depression' and measurements.

	'Depressive symptoms' vs. 'No depressive symptoms'						'Depression' vs. 'No depressive symptoms'					
	Crude model			Adjusted model			Crude model			Adjusted model		
	Beta	*P*	OR (95% CI)	Beta	*P*	OR (95% CI)	Beta	*P*	OR (95% CI)	Beta	*P*	OR (95% CI)
MMSE	0.314	0.518	0.92 (0.89–0.95)	−0.024	0.244	0.98 (0.94–1.02)	−3.892	0.001	1.01 (0.92–1.10)	0.021	0.670	1.02 (0.93–1.12)
Word recall	−1.212	<0.001	0.83 (0.8–0.87)	−0.108	<0.001	0.90 (0.85–0.95)	−3.304	<0.001	0.89 (0.79–0.99)	−0.143	0.021	0.87 (0.77–0.98)
Story memory	−0.922	<0.001	0.87 (0.83–0.91)	−0.056	0.046	0.95 (0.90–1.00)	−2.913	<0.001	0.88 (0.79–0.99)	−0.150	0.018	0.86 (0.76–0.97)
Trail-making test part A	−2.778	<0.001	1.04 (1.03–1.06)	0.011	0.139	1.01 (1.0 0–1.03)	−4.518	<0.001	1.04 (1.01–1.07)	0.034	0.024	1.03 (1.00–1.07)
Trail-making test part B	−2.743	<0.001	1.02 (1.02–1.03)	0.009	0.004	1.01 (1.00–1.01)	−4.102	<0.001	1.01 (1.00–1.02)	0.009	0.194	1.01 (1.00–1.02)
Symbol digit substitution task	−0.131	0.53	0.96 (0.94–0.97)	−0.012	0.102	0.99 (0.97–1.00)	−2.495	<0.001	0.97 (0.94–0.99)	−0.042	0.011	0.96 (0.93–0.99)
BDNF	−1.184	<0.001	0.97 (0.95–0.98)	−0.018	0.043	0.98 (0.96–1.00)	−3.124	<0.001	0.97 (0.93–1.01)	−0.025	0.236	0.98 (0.94–1.02)
Bilateral MTL atrophy	0.442	0.036	1.56 (1.03–2.35)	0.480	0.069	1.62 (0.96–2.71)						
Right MTL atrophy	0.448	0.01	1.57 (1.11–2.20)	0.481	0.025	1.62 (1.06–2.47)						
Left MTL atrophy	0.014	0.957	1.01 (0.61–1.69)	0.067	0.829	1.07 (0.58–1.96)						
Whole gray matter atrophy	0.118	0.129	1.13 (0.97–1.31)	0.095	0.327	1.10 (0.91–1.33)						

Age, education level, living alone status, walking speed, frailty, self-rated health, regular exercise, frequency of going outdoors, and sleep time were included as covariates in the adjusted models.

major depression and those in a non-depressed control group. They found a significant negative association between age and BDNF levels and noted that BDNF was significantly lower in the major depression group than in the non-depressed control group (Chu et al., 2012). In a systematic review including 19 studies, BDNF levels were significantly higher in healthy people than in patients with depression (Brunoni et al., 2008). In addition, meta-regression found significant associations between BDNF levels and depression score changes (Brunoni et al., 2008). Our findings were similar to those of previous studies that found a negative association between BDNF levels and depression. Moreover, adjusted logistic model showed marginal significance in the relationship between serum BDNF and 'depressive symptoms' even though 'depression' was not associated with BDNF. It is possible that the small sample size in the 'depression' group, effects of antidepressant, (Nibuya et al., 1995) and multiple control variables in this study contributed to the non-significant results.

Atrophy of the right medial temporal lobe in the 'depressive symptoms' group was higher than that in the 'no depressive symptoms' group even in multivariate analyses. BDNF supports cholinergic, dopaminergic, serotonergic, and neuropeptide-containing neurons (Hyman et al., 1991; Knusel et al., 1991; Mamounas et al., 1995) and may play an important role in AD and depression-related pathophysiology. Several studies have shown that serum BDNF levels are reduced in depressed patients and can be normalized by treatment (Karege et al., 2005; Monteleone et al., 2008; Sen et al., 2008). Erickson and colleagues reviewed the interactions between exercise, depression, and hippocampal function including memory and atrophy and concluded that there was mounting evidence that BDNF expression plays an important role in age-related hippocampal atrophy and that geriatric depression magnifies hippocampal atrophy (Erickson et al., 2012). BDNF is highly concentrated in the hippocampus (Phillips et al., 1990; Wetmore et al., 1990), promoting cell proliferation and signaling through several pathways. A single nucleotide polymorphism in the *BDNF* gene causes a valine (val) to methionine (met) substitution at codon 66 in the prodomain (Egan et al., 2003). BDNF val66met affects the regulated secretion of BDNF in the hippocampus (Egan et al., 2003) and has been related to lower serum levels of BDNF (Ozan et al., 2010) and smaller hippocampal volumes (Pezawas et al., 2004; Szeszko et al., 2005), which can lead to deficits in executive function (Frodl et al., 2006) and memory function (Erickson et al., 2009). Moreover, hippocampal volume is consistently reduced in BDNF met carriers compared with BDNF val/val patients with major depressive disorder (Frodl et al., 2007). The memory task engaged the right hippocampal region when the memory task was compared with either the baseline or the priming condition (Squire et al., 1992). The relationships between cognitive decline, low BDNF, and atrophy of the right medial temporal lobe were confirmed in this study, in accordance with previous studies.

Although this study is a large population-based sample of older adults, causation cannot be inferred from a cross-sectional study. Further prospective investigations are needed to validate the causal relationships between cognitive decline and depressive symptoms in older people. Moreover, our study excluded individuals with neurological disorders such as stroke and Parkinson's disease and those who were certified to have long-term care insurance needs because of functional decline. Hence, our findings may not be generalizable to these patient populations.

Nevertheless, this study provides promising preliminary evidence that memory, executive function, and cognitive speed examinations are useful to identify cognitive decline in older adults who have depressive symptoms or depression. Serum BDNF concentration and atrophy of the right medial temporal lobe may play a role as mediators. Further investigation is needed, and future research should include a prospective measurement of cognitive decline to establish the validity of these preliminary results.

Contributors

Author contributions were as follows: Hiroyuki Shimada, Takao Suzuki: study concept and design and data analysis or interpretation; Hiroyuki Shimada, Hyuntae Park, Hyuma Makizako, Takehiko Doi, Sangyoon Lee, Takao Suzuki: drafting or revising the manuscript for important intellectual content. All authors contributed to and have approved the final manuscript.

Role of the funding source

The funding source played no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.