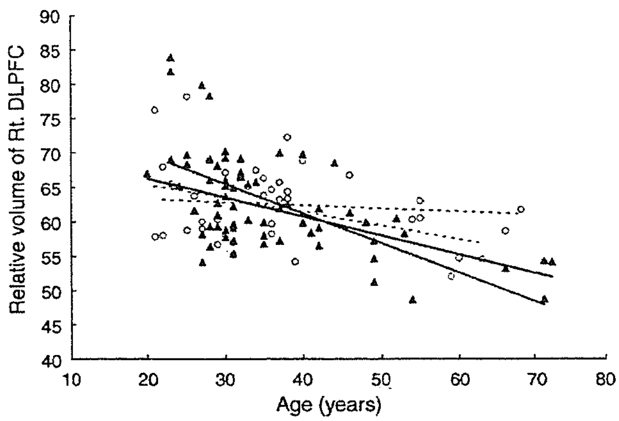

Fig. 3. Scatter plot of relative gray matter volume of the right DLPFC against age in each genomic group. The Met-BDNF carriers showed more significant volume reduction with normal aging compared to homozygous Val-BDNF subjects in the bilateral DLPFC in each gender (right: male Met-BDNF carriers: $y=-0.27x+71.8$, $r=-0.71$, $p<0.0001$, male homozygous Val-BDNF subjects: $y=-0.046x+64.2$, $r=-0.12$, $p=0.67$, female Met-BDNF carriers: $y=-0.43x+78.4$, $r=-0.56$, $p<0.001$, female homozygous Val-BDNF subjects: $y=-0.20x+69.5$, $r=-0.41$, $p=0.03$; left: male Met-BDNF carriers: $y=-0.20x+67.2$, $r=-0.53$, $p=0.01$, male homozygous Val-BDNF: $y=-0.11x+65.3$, $r=-0.25$, $p=0.367$, female Met-BDNF carriers: $y=-0.48x+77.0$, $r=-0.71$, $p<0.0001$, female homozygous Val-BDNF: $y=-0.14x+65.3$, $r=-0.27$, $p=0.18$). Due to limitations of space, only the plot at the right DLPFC in each gender is shown. Blue stands for male subjects and red stands for female subjects. Open circle: homozygous Val-BDNF; closed triangle: Met-BDNF carrier. Dotted lines are the regression line of homozygous Val-BDNF, whereas solid lines are those of Met-BDNF carrier.

reduction in the right inferior parietal lobules (BA40, t-value: 3.86, Talairach coordinates: 40, −43, 53). We found a significant interaction effect (male: $p=0.003$, female: $p<0.0001$) between the aging effect and the genotype on the gray matter volume in the DLPFC in each gender. (right: male Met-BDNF carriers: $r=-0.71, p<0.001$, male homozygous Val-BDNF subjects: $r=-0.12, p=0.67$; female Met-BDNF carriers: $r=-0.56$, $p<0.001$, female homozygous Val-BDNF subjects: $r=-0.41$, $p=0.03$; left: male Met-BDNF carriers: $r=-0.53$, $p=0.01$, male homozygous Val-BDNF subjects: $r=-0.25$, $p=0.367$, female Met-BDNF carriers: $r=-0.71$, $p<0.0001$, female homozygous Val-BDNF subjects: $r=-0.27, p=0.18$) (Fig. 3).

This is the first study which investigated the impacts of BDNF Val66Met polymorphism on age-associated brain morphological changes in normal individuals. We found an exaggerated age-related volume reduction of the DLPFC in the Met-BDNF carriers.

Several studies demonstrated morphological changes associated with normal aging in the STG, insula, inferior parietal lobules, motor cortex, ACC, and DLPFC [10,24]. In consistent with previous studies, our data also showed age-related volume reduction in similar regions in all subjects' analysis of each gender. Further analysis revealed that the Met-BDNF carriers showed a stronger negative correlation between age and gray matter volume in the DLPFC and right precentral gyrus when compared to individuals with homozygous Val-BDNF. Though the mechanisms underlying the predilection of the prefrontal cortex for age-related volume reduction are still unclear, the prefrontal cortex exhibits the greatest age-related alteration of GABA and glutamate [11], and glucose metabolism and age-related declines in regional cerebral blood flow [4]. Though there has been no study investigating the relationship between Val66Met SNP and vulnerability to age-related changes, BDNF protein itself is reported to be associated with aging. Amounts of BDNF protein in hippocampal pyramidal neurons and dentate granule cells are decreased during aging in monkeys [14]. Further, several studies demonstrated neuroprotective effects of BDNF [3,29]. Our data suggest that the Met-BDNF carriers, particularly females carrying Met-BDNF allele, may be more vulnerable to aging than individuals with homozygous Val-BDNF. Considering the fact that prefrontal cortex is one of the regions in which BDNF is expressed abundantly [25], we suggest that the Val66Met polymorphism may be associated with functional variances of neuroprotective and stress resistant effects of BDNF, which results in different effects on age-related morphological changes. Furthermore, we found a reduction of the striatal volumes in met-BDNF carriers as compared to individuals with homozygous Val-BDNF. It has been postulated that enhancement of BDNF in the cortex may be involved in protection of striatal neurons against damage via anterograde transport because BDNF exerts neuroprotective effects against excitoxicity in the striatum [1,16]. The result, reduced volumes in the striatum in met-BDNF carriers, may again suggest the reduced neuroprotective effects of met-BDNF. Since there has been no direct evidence of differential regulation of vulnerability to neurodegenerative process by BDNF Val66Met polymorphism, further study such as investigating how Val66Met SNP affects cell survival in a cellular model is required to clarify our speculation.

Although we could not replicate results of the previous studies, the smaller hippocampus in the Met-BDNF carriers [23,28], our data also suggest that BDNF polymorphism should have impacts on brain morphology associated with episodic memory. The discrepancy between our results and those of the previous studies could be partially explained by the racial difference. Binding its receptor TrkB, BDNF activates several pathways including the PI3-kinase/Akt, the mitogen-activated protein kinase, and PLC-gamma1 pathway [15]. These signals are known to be critical for survival of neuron, suggesting that not only Val66Met polymorphism of BDNF, but also interaction of polymorphism of each signal or molecule has effects on brain morphology. Racial differences might be related to such interactions, resulting in the different findings. This may partially contribute to the discrepancy in associations between BDNF polymorphism and the prevalence of neuropsychiatric diseases in Asian and Caucasian populations [17,27].

Finally, we mention a limitation of this study. To explore the association between aging effects on the brain morphology and the Val66Met polymorphism, we performed a cross-sectional study. There is a secular bias, which can be resolved by a longitudinal study. In this context, our data may be considered preliminary rather than conclusive. However, a recent longitudinal MR study of normal aging demonstrated that cross-sectional and longitudinal estimates of atrophy rates were similar [26].

In conclusion, we found that Val66Met polymorphism of BDNF had impacts on age-associated morphological changes in Japanese subjects. Our data suggest that Val66Met polymorphism of BDNF may play important roles for vulnerability to age-related morphological changes as well as the efficiency of plasticity, especially in DLPFC. Furthermore, we suggest that genotype effects of the BDNF gene on brain morphology might differ in female from in male.

Acknowledgements

The authors thank Ms. Tomoko Shizuno and Ms. Keiko Okada for technical assistance. This work was supported in part by Grants-in-Aid from the Japanese Ministry of Health, Labor and Welfare (H17-kokoro-007 and H16-kokoro-002), the Japanese Ministry of Education, Culture, Sports, Science and Technology, Core research for Evolutional Science and Technology (CREST) of Japan Science and Technology Agency (JST), Japan Foundation for Neuroscience and Mental Health, and the Program for Promotion of Fundamental Studies in Health Science of the Organization for Pharmaceuticals and Medical Devices Agency (PMDA).

References

[1] C.A. Altar, N. Cai, T. Bliven, M. Juhasz, J.M. Conner, A.L. Acheson, R.M. Lindsay, S.J. Wiegand, Anterograde transport of brain-derived neurotrophic factor and its role in the brain, Nature 389 (1997) 856–860.
[2] J. Ashburner, K.J. Friston, Voxel-based morphometry—the methods, Neuroimage 11 (2000) 805–821.
[3] Z.C. Baquet, J.A. Gorski, K.R. Jones, Early striatal dendrite deficits followed by neuron loss with advanced age in the absence of anterograde cortical brain-derived neurotrophic factor, J. Neurosci. 24 (2004) 4250–4258.
[4] M. Bentourkia, A. Bol, A. Ivanoiu, D. Labar, M. Sibomana, A. Coppens, C. Michel, G. Cosnard, A.G. De Volder, Comparison of regional cerebral blood flow and glucose metabolism in the normal brain: effect of aging, J. Neurol. Sci. 181 (2000) 19–28.
[5] C. Buchel, R.J. Wise, C.J. Mummery, J.B. Poline, K.J. Friston, Nonlinear regression in parametric activation studies, Neuroimage 4 (1996) 60–66.
[6] Z.Y. Chen, P.D. Patel, G. Sant, C.X. Meng, K.K. Teng, B.L. Hempstead, F.S. Lee, Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons, J. Neurosci. 24 (2004) 4401–4411.
[7] C.E. Coffey, J.F. Lucke, J.A. Saxton, G. Ratcliff, L.J. Unitas, B. Billig, R.N. Bryan, Sex differences in brain aging: a quantitative magnetic resonance imaging study, Arch. Neurol. 55 (1998) 169–179.
[8] M.F. Egan, M. Kojima, J.H. Callicott, T.E. Goldberg, B.S. Kolachana, A. Bertolino, E. Zaitsev, B. Gold, D. Goldman, M. Dean, B. Lu, D.R. Weinberger, The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function, Cell 112 (2003) 257–269.
[9] C.R. Genovese, N.A. Lazar, T. Nichols, Thresholding of statistical maps in functional neuroimaging using the false discovery rate, Neuroimage 15 (2002) 870–878.
[10] C.D. Good, I.S. Johnsrude, J. Ashburner, R.N. Henson, K.J. Friston, R.S. Frackowiak, A voxel-based morphometric study of ageing in 465 normal adult human brains, Neuroimage 14 (2001) 21–36.
[11] I.D. Grachev, A. Swarnkar, N.M. Szeverenyi, T.S. Ramachandran, A.V. Apkarian, Aging alters the multichemical networking profile of the human brain: an in vivo (1)H-MRS study of young versus middle-aged subjects, J. Neurochem. 77 (2001) 292–303.
[12] A.R. Hariri, T.E. Goldberg, V.S. Mattay, B.S. Kolachana, J.H. Callicott, M.F. Egan, D.R. Weinberger, Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance, J. Neurosci. 23 (2003) 6690–6694.
[13] R. Hashimoto, T. Okada, T. Kato, A. Kosuga, M. Tatsumi, K. Kamijima, H. Kunugi, The breakpoint cluster region gene on chromosome 22q11 is associated with bipolar disorder, Biol. Psychiatry 57 (2005) 1097–1102.
[14] M. Hayashi, F. Mistunaga, K. Ohira, K. Shimizu, Changes in BDNF-immunoreactive structures in the hippocampal formation of the aged macaque monkey, Brain Res. 918 (2001) 191–196.
[15] E.J. Huang, L.F. Reichardt, Neurotrophins: roles in neuronal development and function, Annu. Rev. Neurosci. 24 (2001) 677–736.
[16] Z. Kokaia, G. Andsberg, Q. Yan, O. Lindvall, Rapid alterations of BDNF protein levels in the rat brain after focal ischemia: evidence for increased synthesis and anterograde axonal transport, Exp. Neurol. 154 (1998) 289–301.
[17] H. Kunugi, Y. Iijima, M. Tatsumi, M. Yoshida, R. Hashimoto, T. Kato, K. Sakamoto, T. Fukunaga, T. Inada, T. Suzuki, N. Iwata, N. Ozaki, K. Yamada, T. Yoshikawa, No association between the Val66Met polymorphism of the brain-derived neurotrophic factor gene and bipolar disorder in a Japanese population: a multicenter study, Biol. Psychiatry 56 (2004) 376–378.
[18] E.A. Maguire, D.G. Gadian, I.S. Johnsrude, C.D. Good, J. Ashburner, R.S. Frackowiak, C.D. Frith, Navigation-related structural change in the hippocampi of taxi drivers, Proc. Natl. Acad. Sci. (2000) 4398–4403.
[19] J.A. Maldjian, P.J. Laurienti, R.A. Kraft, J.H. Burdette, An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets, Neuroimage 19 (2003) 1233–1239.
[20] K. Matsuoka, Y. Kim, H. Hiro, Y. Miyamoto, K. Fujita, K. Tanaka, K. Koyama, N. Kazuki, Development of Japanese Adult Reading Test (JART) for Predicting Premorbid IQ in Mild Dementia, Seishinigaku 44 (2002) 503–511.
[21] J.K. Morse, S.J. Wiegand, K. Anderson, Y. You, N. Cai, J. Carnahan, J. Miller, P.S. DiStefano, C.A. Altar, R.M. Lindsay, Brain-derived neurotrophic factor (BDNF) prevents the degeneration of medial septal cholinergic neurons following fimbria transection, J. Neurosci. 13 (1993) 4146–4156.
[22] H.E. Nelson, A. O'Connell, Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test, Cortex 14 (1974) 234–244.
[23] L. Pezawas, B.A. Verchinski, V.S. Mattay, J.H. Callicott, B.S. Kolachana, R.E. Straub, M.F. Egan, A. Meyer-Lindenberg, D.R. Weinberger, The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology, J. Neurosci. 24 (2004) 10099–10102.
[24] N. Raz, F. Gunning-Dixon, D. Head, K.M. Rodrigue, A. Williamson, J.D. Acker, Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume, Neurobiol. Aging 25 (2004) 377–396.
[25] M. Sandrini, S.F. Cappa, S. Rossi, P.M. Rossini, C. Miniussi, The role of prefrontal cortex in verbal episodic memory: rTMS evidence, J. Cogn. Neurosci. 15 (2003) 855–861.
[26] R.I. Scahill, C. Frost, R. Jenkins, J.L. Whitwell, M.N. Rossor, N.C. Fox, A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging, Arch. Neurol. 60 (2003) 989–994.
[27] P. Sklar, S.B. Gabriel, M.G. McInnis, P. Bennett, Y.M. Lim, G. Tsan, S. Schaffner, G. Kirov, I. Jones, M. Owen, N. Craddock, J.R. DePaulo, E.S. Lander, Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. Brain-derived neutrophic factor, Mol. Psychiatry 7 (2002) 579–593.
[28] P.R. Szeszko, R. Lipsky, C. Mentschel, D. Robinson, H. Gunduz-Bruce, S. Sevy, M. Ashtari, B. Napolitano, R.M. Bilder, J.M. Kane, D. Goldman, A.K. Malhotra, Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation, Mol. Psychiatry 10 (2005) 631–636.
[29] H. Yanamoto, I. Nagata, M. Sakata, Z. Zhang, N. Tohnai, H. Sakai, H. Kikuchi, Infarct tolerance induced by intra-cerebral infusion of recombinant brain-derived neurotrophic factor, Brain Res. 859 (2000) 240–248.