Effects of BDNF Val66Met polymorphism on brain metabolism in Alzheimer's disease

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Earlier studies showed that the Val66Met polymorphisms of the brain-derived neurotrophic factor differentially affect gray matter volume and brain region activities. This study used resting positron emission tomography to investigate the relationship between the polymorphisms of Val66Met and the regional cerebral metabolic rate in the brain. We analyzed the positron emission tomography images of 215 patients from the Alzheimer's Disease Neuroimaging Initiative and found significant differences in the parahippocampal gyrus, superior temporal gyrus, prefrontal cortex, and inferior parietal lobule when comparing Met carriers with noncarriers among both the normal controls and those with mild cognitive impairment. For those with Alzheimer's disease, we also found additional differences in the bilateral insula between the carriers and noncarriers. *NeuroReport* 21:802–807 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Alzheimer's disease is a neurodegenerative disorder characterized by severe cognitive impairment and neurofibrillary tangles [1], and shows disrupted functional neuronal metabolic activity in specific brain regions [2–4]. Several neuroimaging studies have reported that patients with Alzheimer's disease have lower cerebral metabolism in the bilateral posterior cingulated cortex, precuneus, and temporal–parietal cortex [3] and in the temporal, parietal, and prefrontal lobes [4], compared with clinically normal controls.

Brain-derived neurotrophic factor (BDNF) is a member of the 'neurotrophin' family of growth factors related to the nerve growth factor, which is critical for the survival and maintenance of sympathetic and sensory neurons [5]. Without the nerve growth factor, the sympathetic and sensory neurons will undergo apoptosis. In the BDNF gene, which is located on chromosome 11p14, the Val66Met allele is another candidate for a common single nucleotide polymorphism, which affects Alzheimer's disease [6,7]. The BDNF Met allele has been reported to be related to cognitive function [8], human memory function, [9] and anxiety-related behavior [10]. A functional MRI study on adolescents experiencing anxiety and depression reported that Met carriers showed greater activation in the hippocampus and the amygdala in response to emotional stimuli than was observed for noncarriers [11].

In brain morphology studies, the hippocampus and the temporal cortex exhibited a progressive loss in gray matter from the effect of the BDNF Met allele according to an Alzheimer's disease study [12]. Moreover, the BDNF Met allele is associated with reduced volumes in the prefrontal cortex, hippocampus, parahippocampal gyrus, and amygdala in normal individuals and patients with schizophrenia and major depression [13]. It has been already shown that the effect of the Val66Met polymorphism on reduced gray matter occurs in some specific regions, such as the prefrontal lobe [14] and the hippocampus [15].

All of the above reports pointed out that each specific BDNF Val66Met polymorphism causes different effects in the development of Alzheimer's disease. Although these inferences are helpful, glucose metabolism in the brain, as measured by PET technology, is what has typically been used to assess the severity of brain disease; so establishing glucose metabolism alterations would yield more specific information connecting Alzheimer's disease with genetic differences. However, the effects of

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BDNF polymorphisms on glucose uptake in the brain remain unknown. Therefore, the purpose of this study is to explore what effects the Val66Met polymorphism has on abnormal glucose consumption in Alzheimer's disease, mild cognitive impairment, and normal control participants.

Materials and methods

Participants

The data used in this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (*www.loni.ucla.edu/ADNI*). The initial goal of the ADNI was to recruit 800 adults, aged 55–90 years, to participate in the research; approximately 200 cognitively normal older individuals were to be followed for 3 years, 400 people with mild cognitive impairment to be followed for 3 years, and 200 people with early Alzheimer's disease to be followed for 2 years. See *www.adni-info.org* for up-to-date information.

All PET data were acquired using standardized approaches: the participant lay quietly in a dimly lit room with their eyes open and with minimal sensory stimulation. A 30-min dynamic emission scan, consisting of six 5-min frames, was acquired starting 30 min after an intravenous injection of 5.0 ± 0.5 mCi of [^{18}F] fluorodeoxyglucose. The original data were processed with a reconstructing algorithm. To eliminate the effect of multiple centers and different tracers, we used the [^{18}F] 2-fluoro-2-deoxy-D-glucose image data only. A total of 268 participants had their fluorodeoxyglucose (FDG)-PET data recorded as a baseline scan. After combining our dataset with blood genotype data and discarding some improperly processed images, we had 215 participants who corresponded with the BDNF dataset. Details are as below: we studied 68 patients with Alzheimer's disease, [Mini-mental state examination (MMSE) score between 20 and 25], 85 with mild cognitive impairment (MMSE score above 24), and 62 normal controls (MMSE score above 24) (Table 1).

Of course, BDNF has three subtypes, namely Val/Val, Val/Met, and Met/Met. Therefore, we divided each clinical group into two subgroups: the Met/Met and Val/Met carriers that were combined as the first subgroup because the number of Met/Met individuals was much smaller than that of the other two groups. Thus, the second subgroup was composed of the Val/Val individuals. Therefore, we had six different groups as follows: normal control Met carriers and noncarriers, mild cognitive impairment Met carriers and noncarriers, and Alzheimer's disease Met carriers and noncarriers. Their demographical characteristics are summarized in Table 1.

Data processing

Preprocessing

All the baseline data we used were downloaded from the Laboratory for Neuro Imaging website of ADNI and processed using the Statistical Parametric Mapping [Wellcome Department of Cognitive Neurology, University College London, London, UK (*http://www.fil.ion.ucl.ac.uk/spm/software*)], which is a toolbox based on Matlab 7.0.1 [The MathWorks Inc., Massachusetts, USA (*http://www.mathworks.com/products/*)]. The preprocessing steps were as follows: (i) realignment and co-registration: we realigned the other five frames to the first frame using the anterior cingulated, posterior cingulated theory to eliminate head rotation, and co-registered each PET image to its own structural magnetization prepared rapid gradient echo for the exact location of metabolism; (ii) standardization: each participant's six 5-min images were averaged into a single file, and then each voxel was divided by the average value of the entire image; (iii) normalization and smoothing: each FDG-PET image was linearly and nonlinearly deformed to the Montreal Neurological Imaging template, spatially normalized into a $3 \times 3 \times 3$ mm voxel size, and smoothed to a spatial resolution of 8 mm full-width at half-maximum using a Gaussian Kernel.

Statistics

We used the analysis of variance to test the differences in age and sex in all the groups. Student *t*-tests were used to test the FDG-uptake differences between the clinical Alzheimer's disease and normal control groups and those between the mild cognitive impairment and normal control groups on a voxel-by-voxel basis, generating

Table 1 PET data characteristics

	AD ($n=68$)			MCI ($n=85$)			Normal controls ($n=62$)		
	Met carriers ($n=21$)	Met noncarriers ($n=47$)	*P* value	Met carriers ($n=31$)	Met noncarriers ($n=54$)	*P* value	Met Carriers ($n=21$)	Met noncarriers ($n=41$)	*P* value
Age (years)	78.2 ± 5.4	75.8 ± 7.7	0.87[a]	75.5 ± 6.5	75.3 ± 7.3	0.86[a]	75.9 ± 5.5	76.1 ± 5.3	0.19[a]
Sex (male)	12 (57.1%)	27 (47.3%)	0.97[b]	25 (80.6%)	40 (74.1%)	0.49[b]	14 (66.7%)	19 (46.3%)	0.13[b]
APOE (ε4)	13 (61.9%)	28 (59.6%)	0.86[b]	15 (48.4%)	24 (44.4%)	0.73[b]	8 (38.1%)	9 (22.0%)	0.18[b]

Values are expressed as mean (SD).
(ε4) means the numbers of participants who carry APOE ε4 allele.
AD, Alzheimer's disease; APOE, apolipoprotein E; MCI, mild cognitive impairment.
[a]The *P* value was obtained by using analysis of variance.
[b]The *P* value was obtained by using Pearson's χ^2 test.

statistical parametric maps of group-related reductions in the regional-whole brain cerebral metabolic rate for glucose (CMRglu). The effects of age and apolipoprotein E ε4 (APOE ε4) are remarkable in Alzheimer's disease [16], so we set APOE ε4 and age as covariates in addition to sex. In addition, we applied an analysis of covariance to check the differences in FDG uptake using the clinical groups and the Val66Met genotypes as fixed factors with age and sex as covariates. A False Discovery Rate-corrected approach was used for multiple comparison corrections, and clusters with fewer than 30 voxels were discarded to reduce the possible influences of noise.

Results

We found no significant difference between Met carriers and Met noncarriers in the participants' ages, sex, or APOE ε4 for the three clinical groups (Table 1).

The effects of Val66Met on the regional uptake within each group

In the normal control group, Met carriers had a lower CMRglu in the right parahippocampal gyrus and the superior temporal gyrus than the noncarriers, and a higher CMRglu in the superior and middle frontal gyrus (prefrontal cortex) ($P < 0.005$, uncorrected) (Fig. 1a). The findings in the mild cognitive impairment group showed a similar metabolism pattern, but with a small difference from those in the normal control group; glucose consumptions in the right parahippocampal gyrus, right insula, and right inferior temporal gyrus were lower in Met carriers than in noncarriers. Moreover, a higher metabolism appeared primarily in the middle occipital gyrus and inferior parietal lobule (BA40) when comparing Met carriers with noncarriers ($P < 0.005$, uncorrected) (Fig. 1b). In addition, the Met carriers' metabolism was lower in the bilateral insula compared with the noncarriers ($P < 0.005$, uncorrected) in the Alzheimer's disease group, as shown in Fig. 1c.

Discussion

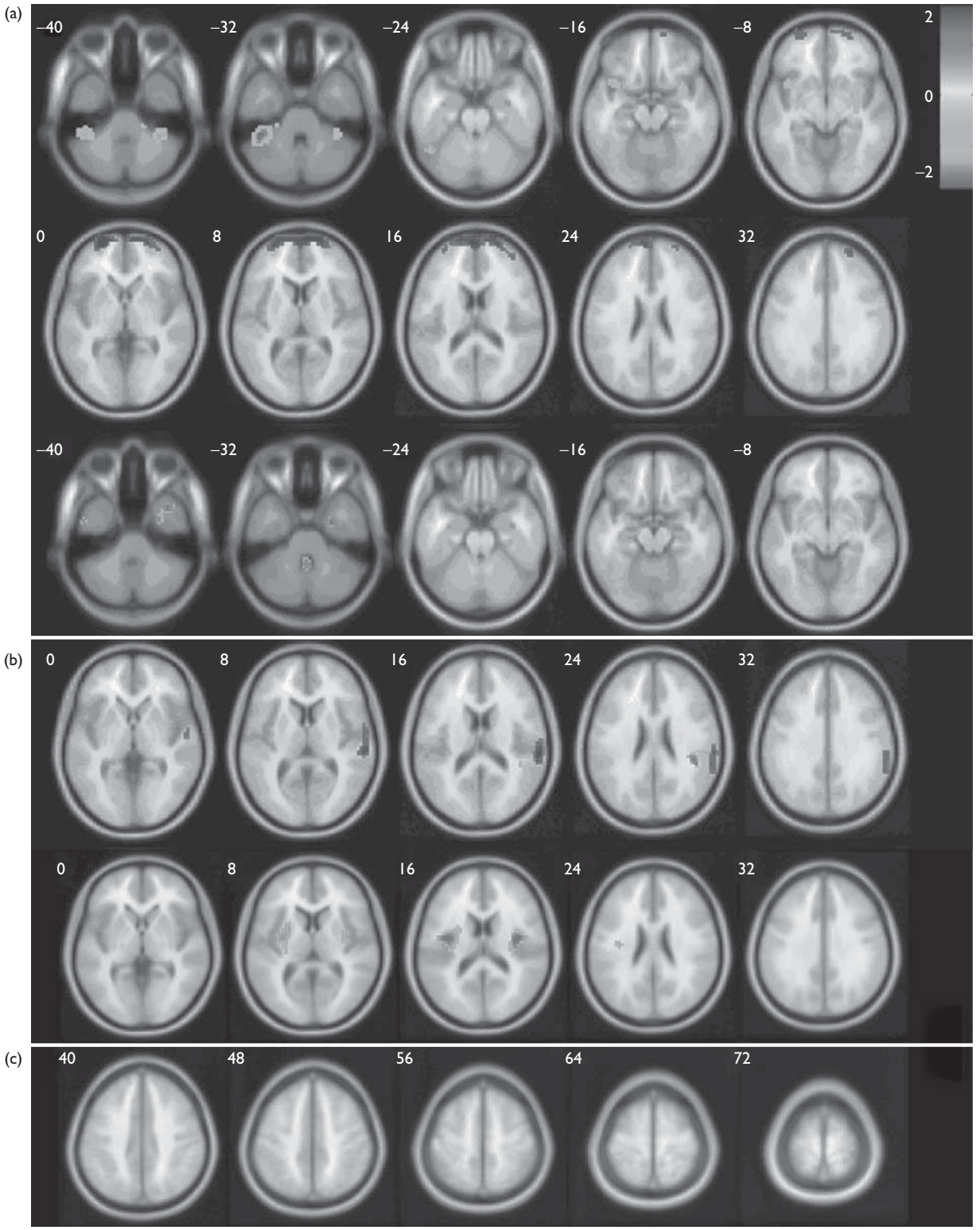
We comprehensively investigated the effects of the Val66Met polymorphism on brain function in Alzheimer's disease, mild cognitive impairment, and normal control using FDG-PET. Our findings indicated that the BDNF Met allele affects glucose metabolism in some specific regions, such as the memory-related regions, including the temporal, parietal, and occipital cortices and the hippocampus, and emotion-related insula. To our knowledge, this study is the first to find an effect of this polymorphism of the BDNF gene on the CMRglu in Alzheimer's disease, mild cognitive impairment, and normal control.

Hypermetabolism was found in Met carriers compared with noncarriers both in the normal control and the mild cognitive impairment group in regions including the superior and middle frontal gyrus cortex in the normal control group, and the temporal-parietal, inferior parietal lobule, and middle occipital gyrus in the mild cognitive impairment group. These findings are in accordance with several related studies. One study reported hyperactivity in the frontal and posterior parietal cortexes in healthy Met carriers during a spatial working memory task [17]. Another Alzheimer's disease-related study reported that the Met allele could contribute to atrophy in the prefrontal cortex [18]. A morphological study on healthy adults suggested that a decrease in the gray matter occurs in the right inferior parietal lobule in Met carriers [19]. Moreover, dysfunction [3] and atrophy [20] in the prefrontal cortex and in the inferior parietal lobule have been observed in Alzheimer's disease. Our findings suggest that the functional abnormalities observed in the PET may emerge before structural degeneration and that the dysfunction is derived from damage to the brain structure, which could in turn exacerbate its structural deterioration. The hypermetabolisms found in our study could possibly be compensatory activities to offset the dysfunction resulting from damage to the brain structure.

In addition, Met carriers showed a reduced uptake of glucose compared with noncarriers in the normal control and mild cognitive impairment groups, and the reductions were primarily in the right hippocampal gyrus and the left temporal cortex. The hippocampus, which is considered to be a memory-related region, shows atrophy in patients with Alzheimer's disease [21]. Our findings indicated that these uptake reductions could be a functional reflection of structural deterioration in mild cognitive impairment individuals. A recent study suggested a reduced activation in Met carriers in the bilateral hippocampus and parahippocampal gyrus during a memory-related task [22]. Some other studies have also found that Met carriers had gray matter atrophy in the hippocampal cortex and parahippocampal gyrus compared with noncarriers [13,15]. This atrophy may result from disrupted activation in these regions. The above studies support our findings of reduced CMRglu in these regions. We found a lower CMRglu in Met carriers than in noncarriers in the bilateral insula in the mild cognitive impairment and Alzheimer's disease groups. The insula, a relay area for multiple neurocognitive systems [23], plays important roles in interoception, emotion, and risky decision-making [24]. The reduced uptake in the insula indicates that the Met allele may affect the emotions and perceptions of Alzheimer's disease patients.

Our findings show a similar uptake pattern between the normal control and mild cognitive impairment groups in the parahippocampal gyrus and temporal cortex, and for the mild cognitive impairment and Alzheimer's disease groups in the insula. A possible explanation is that mild cognitive impairment is considered to be a transitional stage between normal control and Alzheimer's disease and has some clinical manifestations of both normal

Fig. 1



The effect of Val66Met polymorphism in clinical disease and normal controls. (a) In the normal control group, reduced cerebral metabolic rate for glucose (CMRglu) was found in the parahippocampal gyrus (right), and the superior temporal gyrus (left) in the Met carriers compared with the noncarriers; in contrast, hyperCMRglu in the superior and prefrontal cortex was found in the Met carriers. (b) In the mild cognitive impairment group, reduced CMRglu in the parahippocampal gyrus (right), insula (right) and superior temporal gyrus (left) was found in the Met carriers; in contrast, hyperCMRglu was found in the middle occipital gyrus (right) and inferior parietal lobule (right) (BA40) in the Met carriers. (c) In the Alzheimer's disease group, only reduced CMRglu was found in the bilateral insula in the Met carriers compared with the noncarriers.

control and Alzheimer's disease, suggesting that the patterns of effects of the BDNF Val/Met are sensitive to the pathological progression. Most importantly, in our findings, regions such as the frontal and temporal cortices and the parahippocampal gyrus that showed abnormal metabolism as evidenced by CMRglu are the core regions of the default-mode network, which has been found to be damaged in the early stages of Alzheimer's disease [25]. Therefore, our studies on the regional metabolic differences caused by the effect of the BDNF polymorphisms could provide valuable evidence in support to the earlier findings. More importantly, our understanding of the pathophysiologic mechanisms of Alzheimer's disease and mild cognitive impairment will be greatly helped by seeing them from a functional imaging perspective and by using the FDG-PET approach.

Conclusion

In conclusion, we have provided new evidence in favor of an association between a specific polymorphism of the BDNF gene and Alzheimer's disease using FDG-PET. Our study suggests that the polymorphism of the BDNF gene could be a putative candidate genetic factor that affects the CMRglu in the prefrontal cortex, inferior parietal lobule, parahippocampal gyrus, temporal cortex, and insula.

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