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Brain Metabolism of Less-Educated Patients With Alzheimer Dementia Studied by Positron Emission Tomography

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Abstract: Alzheimer dementia (AD) is the commonest form of dementia. Although illiteracy is associated with high prevalence of dementia of the Alzheimer type (DAT), their relationship is still unclear. Nevertheless, mild DAT in illiterate participants seems to be due to brain atrophy.

In this study, we compared the impact of brain metabolism efficiency in healthy participants and less-educated patients with mild DAT using 2-fluoro-2-deoxy-D-glucose (^{18}F-FDG-PET) positron emission tomography (^{18}F-FDG-PET). Out of 43 eligible less-educated participants with dementia, only 23 (14 women and 9 men) met Diagnostic and Statistical Manual (DSM)-III-R or DSM-IV criteria for DAT and AD and were included. Participants with intracranial insults were excluded by brain magnetic resonance imaging and participants with metabolic or systemic conditions were excluded by blood sampling. In addition, 16 cognitively normal elderly (age >70 years), including 7 women and 9 men, were enrolled in the sham group. The PET imaging data were analyzed using statistical parametric mapping (SPM8) to determine reliability and specificity.

Glucose metabolic rate was low in the DAT group, especially in the middle temporal gyrus, middle frontal gyrus, superior frontal gyrus, inferior frontal gyrus, posterior cingulate gyrus, angular gyrus, parahippocampal gyrus, middle occipital gyrus, rectal gyrus, and lingual gyrus.

Our results showed that DAT patients with less education not only have prominent clinical signs and symptoms related to dementia but also decreased gray matter metabolism.

(*Medicine* 94(30):e1252)

Abbreviations: ^{18}F-FDG-PET = 2-fluoro-2-deoxy-D-glucose positron emission tomography, AD = Alzheimer dementia, DAT = dementia of the Alzheimer type, MMSE = minimental statement examination.

INTRODUCTION

Alzheimer dementia (AD) is a progressive degenerative disorder characterized by a gradual decline in cognition, decrease in ability to perform activities of daily living, and, often, neuropsychiatric/behavioral problems.[1,2] As life expectancy increases worldwide, the issue of dementia is becoming more important. Ferri et al[3] reported the current prevalence of dementia as 24.3 million people, with 4.6 million new cases of dementia per year and doubling of the prevalence every 20 years to reach 81.1 million cases by 2040. However, dementia prevalence is forecast to increase by 100% in developed countries between 2001 and 2040 and by >300% in India, China, and their south Asian and western Pacific neighbors. In Taiwan,[4] 14% of the population will be aged by 2025. According to the Health Economics Research Centre, University of Oxford, the cost of dementia in the United Kingdom was £23 billion in terms of health and social care, informal care, and productivity losses in 2008.[5] Evidence demonstrates that elderly people without clinical evidence of dementia and only mild memory complaints can have neurofibrillary tangles and neuritic plaques (pathological markers of AD)[5,6] causing cognitive impairment that may surreptitiously progress to dementia.[7] This can also occur in less-educated people with mild cognitive impairment and mild dementia. Thus, early diagnosis and intervention are important strategies to decrease the rate of progression from mild cognitive dementia (MCI) to dementia of the Alzheimer type (DAT).[8] From previous experiments, we know that 2-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG-PET)[1] is sensitive to mild, early brain changes and can be used to monitor the gradual progression of the disease.[8–10] Similarly, FDG-PET can be used to identify patients with AD or other neurodegenerative disease with high sensitivity and specificity (94% and ca. 73%–78%, respectively).[9,10] Consequently, we used ^{18}F-FDG-PET, the minimental statement examination (MMSE) score, and clinical dementia

Editor: Michael Masoomi.
Received: March 27, 2015; revised: July 7, 2015; accepted: July 8, 2015.
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Author contributions: Conceived and designed the experiments—YCH, CHK. Performed the experiments—All authors. Analyzed the data—All authors. Contributed reagents/materials/analysis tools—CHK. Wrote the manuscript—All authors. Approval of the manuscript—All authors.

This study is supported in part by the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212-113002); China Medical University Hospital, Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM104010092); NRPB Stroke Clinical Trial Consortium (MOST 103-2325-B-039-006); Tseng-Lien Lin Foundation, Taichung, Taiwan; Taiwan Brain Disease Foundation, Taipei, Taiwan; Katsuzo and Kiyo Aoshima Memorial Funds, Japan; and CMU under the Aim for Top University Plan of the Ministry of Education, Taiwan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study.

The authors have no conflicts of interest to disclose, both collectively and individually.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001252

rating (CDR) to investigate the difference in brain metabolism between dementia patients with more than a 12th grade education and dementia patients with less than a ninth grade education. All the studies were carried out in Chang Bing Show Chwan Memorial Hospital and China Medical University Hospital, Taiwan.

MATERIALS AND METHODS

Subjects

In this study, the diagnosis in all included participants fulfilled Diagnostic and Statistical Manual (DSM)-III-R or DSM-IV criteria. All nonselected participants were recruited after agreeing to join this clinical study. Initially, 43 of the less-educated (less than a ninth grade education) participants were included, but only 23 of these participants completed this study. The mean MMSE score of these 23 participants was <25. Patients with intracranial insults and metabolic or systemic conditions were excluded by brain magnetic resonance imaging (MRI) and blood testing, respectively. In addition, MMSE score and CDR were used to evaluate and monitor cognitive function. In the sham group, 51 patients (aged ≥ 70 years) who were fully educated (more than a 12th grade education) were recruited from the general health practice of China Medical University Hospital. Only 16 of these participants (7 women and 9 men; mean age, 75.06 ± 4.73 years [range 70–87]) were finally enrolled. They had normal physical and cognitive function according to the private customer (VIP) health examination records, no history of mental decline or strokes, a mean MMSE score of 29, and 12 years of compulsory education. All participants gave their informed consent after receiving a full explanation of the study and its objectives.

Informed Consent

The procedures in this study followed the ethical guidelines on human experimentation of the institutional review board of Chang Bing Show Chwan Memorial Hospital and the principles of the Helsinki Declaration of 1975, as revised in 2004. Signed informed consents were obtained from patients or family members.

Imaging Protocol

Then, PET was performed. Signal intensity on PET indicates the level of glucose consumption in brain tissue, and signal intensity on computed tomography (CT) indicates the level of x-ray radiation absorption by brain tissue.[11] The image processing steps aim to mitigate noise and normalize brain shape discrepancies so that the brain image of each participant can be clearly analyzed on a basis of signal quality. This process in statistical parametric mapping (SPM) is called voxel-based morphometry (VBM).[12] In VBM, the image of each participant is first smoothed with a 8-mm Gaussian kernel to mitigate noise; the size of the kernel depends on image quality. In the second step, image processing and statistics modules are used to resample the images and register the data to the same coordinate system, so each voxel in an image is aligned and voxels can be compared. Medical imaging is a combination of electronic signals absorbed by brain tissue and environmental ambient signals (noise). Both types of signals are obtained from PET/CT systems.

The PET images of 16 normal control participants were obtained using a GE Discovery Advance scanner, and PET images of the 23 patients were obtained using a GE Discovery ST scanner. All patients fasted at least 6 hours. In a dark and quiet room, the patients were asked to lie down on a comfortable bed and then intravenously injected with 10 mCi of FDG. Imaging was performed 60 minutes after FDG injection. The image acquisition protocols were the same for both PET scanners, with a matrix of 128×128, pixel space of 1.95×1.95 mm, and slice thickness of 3.75 mm. All images were acquired in the digital imaging and communications in medicine format and analyzed by SPM software (SPM8; University College London, Queen Square, London, UK). SPM is specifically used by neuroscience researchers to analyze images of the brain.[13,14]

PET images of all 39 participants were processed by SPM8. The PET and VBM modules were used, and 2-sample *t* tests were performed. The parameters of age, MMSE score, and years of education of participants were taken as covariates. Each covariate was evaluated for all 38 cases. The image analysis steps were as follows. The 8-mm Gaussian blur filter was first applied to reduce noise and improve statistical stability. Then, spatial normalization using affine transformation with 12 degrees of freedom was used to realign participant maps to the Talairach space. In this study, we were also interested in examining the effects of different combinations of parameters. We repeated this imaging study by alternating parameters to see whether discrepancies significantly altered the analysis. Five settings were used in this study: FDG-PET images only (denoted by ''img''), images and age (''img-age''), images with MMSE score (''img-mmse''), images with years of education (''img-edu''), and images with all 3 parameters (''img-all'').

Statistical Analysis

The significance of differences between brain anatomical regions was statistically analyzed. Paired *t* tests were used to determine the significance of difference in voxel intensity between the patient and control groups. Significant differences demonstrated in FDG uptake represented differences in metabolic rate; the greater the difference in uptake, the more significant the difference in metabolic rates between the regions.

RESULTS

There were 23 participants (14 women, 9 men; mean age $\pm$ standard deviation [SD], 75.39 ± 8.42 years [range 52–90]; mean MMSE score 15.78 ± 6.03; Table 1) in the dementia group and only 16 participants (7 women, 9 men; age mean age $\pm$ SD, 75.06 ± 4.73 years [range 70–87]) in the normal control group. The study population is shown with the design matrix in Figure 1. In Figure 2, the darker areas indicate lower rates of glucose metabolism.[15] Areas are significantly brighter in group 1 than group 2, indicating the brain is more active in educated participants (group 1). The gray shades in different areas represent atrophy, and the level of gray intensity indicates the degree of atrophy. Our analysis shows a significantly lower

TABLE 1. Characteristics of the Participants

	AD Participants	Control Participants
Age	75.39 ± 8.42	75.06 ± 4.73
Sex	7 women; 9 men	14 women; 9 men
MMSE score	15.78 ± 6.03	29

MMSE = minimental statement examination score.

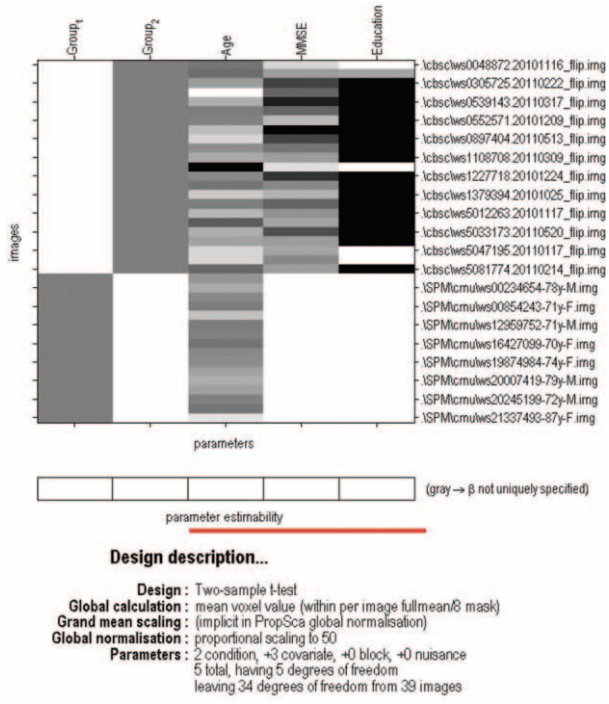

FIGURE 1. The design matrix. Groups 1 and 2 are Alzheimer dementia and normal control participants, respectively. The right 3 columns represent the covariance vector of age, minimental statement examination score, and years of education, respectively. The signal intensity of each entry in the matrix represents the magnitude of the covariance.

glucose metabolic rate in the following brain areas of the less-educated dementia group: middle temporal gyrus, middle frontal gyrus, superior frontal gyrus, inferior frontal gyrus, posterior cingulate gyrus, angular gyrus, parahippocampal gyrus, middle occipital gyrus, rectal gyrus, and lingual gyrus (Table 2). For clarification, the data in Figure 2 are summarized in Table 2.

DISCUSSION

Illiteracy has been associated with high prevalence of DAT,[4,16] and advanced studies imply that early-life education has a negative association with Alzheimer disease pathology hypothesis, which implies that people with higher education have a greater reserve capacity,[17] although this relationship is still not completely understood. In our study, using a combination data of Mini Mental Statement Examination (MMSE) studies, Clinical Dementia Rating (CDR) studies, and ^{18}F-FDG-PET studies, we found decreased brain metabolism especially in illiterate or less educated dementia patients; which also found in previous study point out the undeniable fact that reduced amyloid pathology in highly educated and cognitively normal participants. Which suggesting that education may have an inhibitory effect on AD pathology.[17]

As we know, ^{18}F-FDG-PET can be used to measure the local cerebral metabolic rate of glucose (CMRglc).[18–20] From a previous pilot study, longitudinal FDG-PET examinations demonstrated progressive reduction in CMRglc in advance of the appearance of DAT symptoms in a cohort of patients with pathologically verified disease, and provided temporal and topographical information on the progressive involvement of different brain regions during AD development.[21] Therefore, in patients presenting with cognitive symptoms of dementia, the change in regional brain metabolism is a sensitive indicator of the development of AD and of neurodegenerative disease, in general. The human brain is incredibly adaptive and has an astonishingly large capacity to process widely varied information and complex new experiences in ever-changing ways.[20] Subtle differences in the resting status of the brain are difficult to detect with current imaging technologies, even functional MRI. However, ^{18}F-FDG-PET can be used to detect changes in the metabolism of many brain cortex areas.[21,22]

A comparison of FDG-PET, Single Photon Emission Computed Tomography (SPECT), and structural MRI (to predict conversion to AD in patients with MCI) showed that FDG-PET was somewhat better able to predict rapid conversion to AD.[22] Moreover, the study of Silverman et al[23] found that a positive PET scan could indicate AD and any neurodegenerative disease with a sensitivity of 94% and specificities of 73% and 78%, respectively, and a negative PET scan could indicate the improbability of pathologic progression of cognitive impairment during a mean 3-year follow-up period. In fact, FDG-PET imaging has been approved in the United States as a routine examination tool for the early detection and differential diagnosis of AD.[24] In guidelines used for AD diagnosis in Europe, FDG-PET is also used to differentiate AD from other dementias with a specificity >95% in early-onset cases.[25]

Interestingly in our study, brain glucose metabolic rate significantly differed in the following gray matter areas in less-educated dementia patients when compared with normal participants: middle temporal gyrus, middle frontal gyrus, superior frontal gyrus, inferior frontal gyrus, posterior cingulate gyrus, angular gyrus, parahippocampal gyrus, middle occipital gyrus, rectal gyrus, and lingual gyrus. Previous studies also demonstrated reduced regional cerebral glucose rate in the left inferior parietal cortex, left temporal gyrus, posterior cingulate cortex, and temporoparietal cortex of patients with mild cognitive impairment and mild dementia.[7,26] In fact, ^{18}F-FDG-PET studies seem to indicate a strong relationship between lower brain region metabolism and prominent gyrus atrophy in less-educated patients with dementia[27] and greater and more rapid functional decline in this group.

However, one of the limitations of this study is that it is hospital based and has a small sample-cross sectional design. In addition, SPM was used for voxel-by-voxel analysis. To reduce the number of possible artifacts caused by SPM, NEUROSTAT was used as an alternate tool for anatomical normalization and registration. It detects brain atrophy more accurately than SPM. In addition, it is a deciding element of PET studies using the appropriate sample size, let alone that the primary criterion for assessing sample size is replicable. The traditional method for determining sample size is challenged by the complexities of PET data analysis, which was developing hypothesis-testing approaches for power calculations to determine sample size. This method was using exploratory analysis strategies, search for multiple correlated nodes on interlinked networks, and analysis of large numbers of pixels that may have correlated values due to both anatomical and functional dependence.[28 28, p. 303] We repeated to examine the effects of variable sample size in a study of human memory, comparing different size samples, and the results revealed that the large sample analyses are terrifically assumed to be the ''gold standard.'' This method was applying a hierarchically ordered group of parameters: the first level using pattern of peaks, the second level using location of peaks, followed number of peaks, then size (volume) of

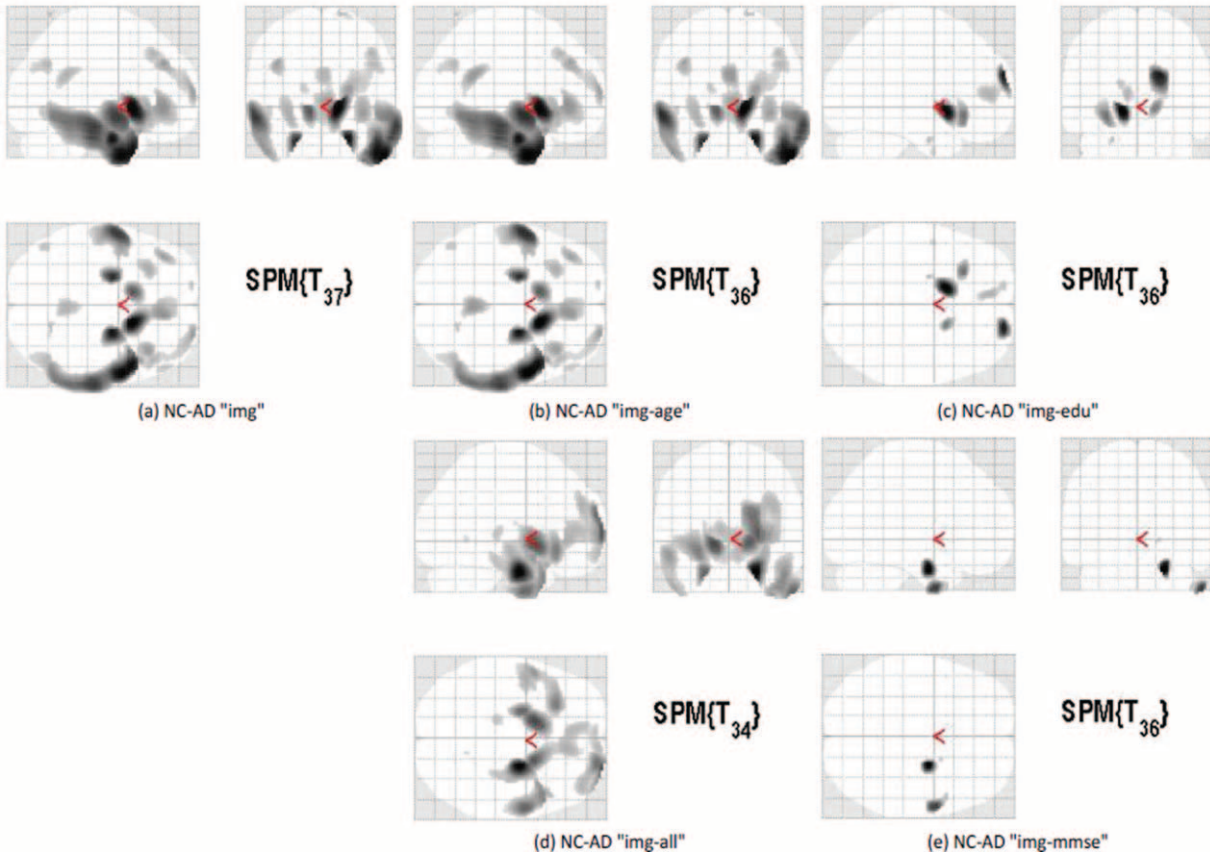

FIGURE 2. Voxel-based morphometry showing the difference between normal control (NC) participants and less-educated Alzheimer dementia (AD) participants. The results are expressed in the form of Talairach coordinates (A)–(E) under 5 different conditions: FDG-PET images only (denoted as ''img''), images and age (''img-age''), images with minimental statement examination score (''img-mmse''), images with years of education (''img-edu''), and images with all 3 parameters (''img-all'').

TABLE 2. Brain Metabolic Rates Compared Between DAT Patients and Normal Participants

	''img''	''img-age''	''img-mmse''	''img-edu''	''img-all''
Lentiform nucleus	○		○	○	○
Uncus	○	○		○	
Middle temporal gyrus	○				
Middle frontal gyrus	○	○		○	
Superior frontal gyrus	○	○			
Inferior frontal gyrus	○	○			
Posterior cingulate	○	○			
Angular gyrus	○	○			
Middle occipital gyrus	○	○			○
Superior frontal gyrus	○	○		○	
Inferior frontal gyrus	○	○		○	
Middle temporal gyrus	○	○			
Rectal gyrus	○				
Extranuclear regions		○		○	
Parahippocampal gyrus			○		○
Thalamus					○
Lingual gyrus					○

○ indicates the brain area with significantly lower metabolic rate in the DAT patient group. DAT = dementia of the Alzheimer type.

peaks, and the last using intensity of the associated *t* (or *z*) statistic. The increasing false negatives with the sample size decreasing are pertinent to some loss of pattern of peaks and number of peaks detection. There is no corresponding increase in false positives to date. The algorithm suggest that good replicability occurs with a sample size of 10 to 20 participants in studies of human cognition that use paired subtraction comparisons of single experimental/baseline conditions with even very low blood flow degree.

Based on these results, a proper therapy program can be designed in advance for patients who need earlier intervention. From the improvement of PET detection of preclinical and mild cognitive impairment by ^{18}F-FDG-PET imaging, we can rationally expect the modifies advanced image used in the clinic, in the future, for the purpose of early detect disease to get early intervention, therefore it can decrease the prevalence of dementia and improve the quality of life of the aged.

CONCLUSION

From this study, it was shown that education level in older adults is an important factor influencing dementia development. Besides, using brain metabolism assessed by ^{18}F-FDG-PET as a marker of dementia development, DAT progression can be detected in the preclinical stage. Thus, physicians can use ^{18}F-FDG-PET as a tool to monitor cognitive decline.

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