Characterizing the normative profile of ^{18}F -FDG PET brain imaging: Sex difference, aging effect, and cognitive reserve [☆]

Hiroshi Yoshizawa ^{a,*}, Yunglin Gazes ^b, Yaakov Stern ^b, Yoko Miyata ^c, Shinichiro Uchiyama ^a

^a Department of Neurology, Neurological Institute, Tokyo Women's Medical University, 8-1, Kawadacho, Shinjuku, Tokyo 162-8666, Japan

^b Cognitive Neuroscience Division, Department of Neurology and Taub Institute, Columbia University College of Physicians and Surgeons, New York, NY, USA

^c Department of Diagnostic Imaging and Nuclear Medicine, Tokyo Women's Medical University, Shinjuku, Tokyo, Japan

ARTICLE INFO

Article history:

Received 8 March 2013

Received in revised form

14 July 2013

Accepted 25 October 2013

Available online 31 October 2013

Keywords:

^{18}F -Fluorodeoxyglucose

Positron emission tomography

Normal brain

Gender differences

Aging

Cognitive brain reserve

ABSTRACT

The aim of this study was to investigate findings of positron emission tomography with ^{18}F -fluorodeoxyglucose (^{18}F -FDG PET) in normal subjects to clarify the effects of sex differences, aging, and cognitive reserve on cerebral glucose metabolism. Participants comprised 123 normal adults who underwent ^{18}F -FDG PET and a neuropsychological battery. We used statistical parametric mapping (SPM8) to investigate sex differences, and aging effects. The effects of cognitive reserve on ^{18}F -FDG uptake were investigated using years of education as a proxy. Finally, we studied the effect of cognitive reserve on the recruitment of glucose metabolism in a memory task by dichotomizing the data according to educational level. Our results showed that the overall cerebral glucose metabolism in females was higher than that in males, whereas male participants had higher glucose metabolism in the bilateral inferior temporal gyri and cerebellum than females. Age-related hypometabolism was found in anterior regions, including the anterior cingulate gyrus. These areas are part of the attentional system, which may decline with aging even in healthy elderly individuals. Highly educated subjects revealed focal hypermetabolism in the right hemisphere and lower recruitment of glucose metabolism in memory tasks. This phenomenon is likely a candidate for a neural substrate of cognitive reserve.

© 2013 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

With today's increasing life expectancy, precise diagnosis of neurodegenerative disorders has become important. Imaging of cerebral glucose metabolism with ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET) has been increasingly applied to aid in the clinical diagnosis of Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD), and dementia with Lewy bodies (DLB) (Bohnen et al., 2012). Voxel-based statistical image analyses such as three-dimensional stereotactic surface projection (3D-SSP) (Minoshima et al., 1995) and statistical parametric mapping (SPM) (Friston, 1997) have been reported to improve diagnostic accuracy compared with conventional images. In these analyses, a precise understanding of the profile of a normative reference image (normative database) is essential for an accurate diagnosis. However, there remains debate with respect to the effects of sex, aging, and educational attainment on cerebral glucose metabolism.

First, findings of sex effects on normal cerebral glucose metabolism have been inconsistent (Andreason et al., 1994; Loessner et al.,

1995; Kawachi et al., 2002; Willis et al., 2002; Fujimoto et al., 2008; Iseki et al., 2010; Chen et al., 2011). Accurate characterization of sex differences in normal cerebral glucose metabolism would aid in arriving at a precise diagnosis, in predicting disease progression, and elucidating underlying disease mechanisms. Second, despite the general consensus that reduction in brain metabolism with age tends to occur in the anterior part of the brain (Kuhl et al., 1982; Ivancević et al., 2000; Newberg and Alavi, 2010), it is unclear whether there are sex differences in the effects of aging on brain glucose metabolism. The trajectory of the neuropsychological profile with aging varies according to sex (Bleecker et al., 1988; Tisserand and Jolles, 2003); thus, sex-specific aging effects on brain metabolism may also exist. Finally, the effects of educational level on ^{18}F -FDG uptake during the resting state and in tasks investigating memory function have not yet been fully investigated. Education, occupational experience, and leisure activities are thought to improve "cognitive reserve", which may render individuals relatively resistant to brain damage before functional deficits emerge (Stern, 2009). Although the mechanistic underpinnings of cognitive reserve remain to be elucidated, past reports have indicated that educational level plays a pivotal role in cognitive reserve. Investigating educational effects on brain activity would contribute to further understanding of cognitive reserve.

In the present study, we used a voxel-based analytic approach implemented in SPM to study the effects of sex, age, and education on brain glucose metabolism measured with ^{18}F -FDG PET.

[☆] Financial support provided by Ministry of Education, Culture, Sports, Science and Technology, Japan.

* Corresponding author. Tel.: +81 3 3353 8111; fax: +81 3 5269 7324.

E-mail address: hyoshizaw@nij.twmu.ac.jp (H. Yoshizawa).

Furthermore, the brain regions positively correlated to memory function were analyzed separately by subgroups divided according to their educational levels. Through this analysis, we investigated whether educational attainment is a moderating factor in brain–behavior correlations.

2. Methods

2.1. Subjects

Participants were selected from 164 consecutive volunteers (91 males, 73 females) who were recruited to the current study at the PET Unit of Tokyo Women's Medical University Hospital in response to bulletin board advertisements. Each participant underwent an extensive neuropsychological examination, computed tomography (CT), and ^{18}F -FDG PET imaging. Participants were carefully screened by a neurologist for previous neurological disorders, psychiatric disorders, alcohol/substance abuse, and head trauma. Exclusion criteria included diabetes mellitus, uncontrollable hypertension, systemic malignancy, CT abnormalities, or use of medications known to affect brain metabolism or brain perfusion, such as anti-psychotic drugs, anti-anxiety drugs, or acetylcholinesterase inhibitors. Participants did not meet the Petersen criteria for mild cognitive impairment (MCI) (Petersen et al., 1999), and their performance on all neuropsychological tests described below was required to be normal (not more than 1.5 SD below age-adjusted norms). Finally, 123 participants (33–78 years old, mean $\pm$ SD: 57.6 ± 10.3 ; 67 males, 56 females) met the inclusion criteria. Table 1 shows the subject characteristics. Written informed consent was obtained from each subject after a written explanation of the study design. The institutional review board approved the study.

2.2. Neuropsychological assessment

All of the participants underwent clinical and cognitive evaluations by a neurologist and a neuropsychologist on the day of PET scanning. Neuropsychological testing included the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964), and the Rey–Osterrieth Complex Figure Test (ROCF) (Rey, 1941; Osterrieth, 1944). First, baseline intellectual ability was assessed by the MMSE, on which a total score ≥ 27 out of 30 was required with delayed memory recall ≥ 2 out of 3 objects. Second, episodic memory was evaluated by the total score on all five immediate recall trials (learning phase) of a 15-word list of the RAVLT (RAVLT total score). The cut-off for RAVLT total score was 27 for subjects who were 70 years old or higher, 31 for subjects between 60 and 69 years old, and 36 for subjects who were 59 or younger according to the norm in our institute. The RAVLT was adopted for screening because the word list learning tests are considered to be adequate predictors of progression from normal or mild cognitive impairment (MCI) to AD (Blacker et al., 2007). Finally, we applied the copy trial of the ROCF, which evaluates visual perception, constructional praxis, and problem-solving strategies (Knight and Kaplan, 2003). These abilities are affected in early stages of AD, DLB, and FTLD. The cut-off point of the copy trial of the ROCF was set to 33 according to our institutional norm. Additional recall trials of the ROCF were performed 30 min after the copy task, although the results were not used for inclusion criteria.

2.3. PET imaging of cerebral glucose metabolism

Subjects fasted for at least 4 h before the injection of ^{18}F -FDG and remained supine on a bed with eyes closed, covered with a mask, and ears unplugged in a

dark, quiet room for 30 min before intravenous (i.v.) administration of 3.7 MBq/kg of ^{18}F -FDG. Acquisition started 40 min after the injection. PET images were acquired with an ECAT ACCEL PET scanner (Siemens Japan K.K., Tokyo, resolution, 6.0 mm in full width at half maximum [FWHM]) with 10-min emission scans and 5-min transmission scans by a rotating ^{68}Ge source for attenuation correction. Images were reconstructed using a standard two-dimensional filtered back-projection method.

2.4. Data analysis

Baseline demographic characteristics were compared between male and female participants, using Pearson χ^2 tests for nominal data. Sex differences in the MMSE, RAVLT total score, ROCF copy, and ROCF delayed recall were examined by analysis of variance (ANOVA). Statistical analysis of the demographic data was performed using IBM SPSS Statistics version 19 (IBM Corporation, New York, NY).

^{18}F -FDG PET data were preprocessed using Statistical Parametric Mapping (SPM8) (Wellcome Department of Cognitive Neurology, London, UK) based on Matlab 7.9 (The MathWorks, Inc., Natick, MA, USA). The data were normalized to the in-house ^{18}F -FDG template with normal subjects who were not included in this study and then smoothed with a FWHM 12-mm Gaussian kernel. Individual global counts were normalized by proportional scaling to a mean value of 50 mg/100 ml/min.

Sex differences in brain glucose metabolism were investigated by an analysis of covariance (ANCOVA) adjusting for age, years of education, and MMSE score. To investigate the relationship between aging and relative regional ^{18}F -FDG activity, voxelwise correlational analyses were performed on the ^{18}F -FDG activity with age as a regressor and years of education and MMSE score as nuisance variables. The age by sex interaction was analyzed with the contrast female vs. male difference in the slope of the correlation between age and ^{18}F -FDG activity. The correlation of years of education with ^{18}F -FDG activity was investigated adjusting for sex, age, and MMSE score. Finally, to examine the effect of education on memory, we studied the difference in correlated areas of ^{18}F -FDG activity with the RAVLT total score for high (years of education ≥ 16 ; bachelor's degree or higher) vs. low levels of education (years of education < 16 ; less than a bachelor's degree) after controlling for age, sex, and MMSE score. The RAVLT total score by education interaction was analyzed with the contrast high-education-group vs. low-education-group difference in RAVLT score. Regression analysis was performed using brain glucose metabolism as the independent variable and RAVLT total score as the dependent variable at the position of the most significant cluster.

The results were considered significant at $P < 0.05$ corrected for multiple comparisons across the whole brain using the Bonferroni correction for the number of resolution elements (Worsley et al., 1996), and extent threshold was set to 100 voxels. Effect size was calculated in Cohen's d . The Montreal Neurological Institute (MNI) coordinates of the local maxima of each cluster were converted into Talairach–Tournoux coordinates (Talairach and Tournoux, 1988).

3. Results

3.1. Demographics and neuropsychological profiles

Table 1 shows the demographic and clinical data of the participants. Male and female subgroups did not differ significantly on any of the demographic features except for years of education, which was higher in the male than the female group. Neuropsychological testing revealed that the male group had higher scores on the recall subtest of the ROCF and lower RAVLT total scores compared with the female subgroup (ROCF, $F(1, 120) = 5.04$, $P = 0.02$; RAVLT total score, $F(1, 121) = 17.96$, $P < 0.001$). There were no group differences with regard to scores on the MMSE and the copy subtest of the ROCF.

3.2. Sex differences in cerebral glucose metabolism

We confirmed a difference in cerebral glucose metabolism between the male and the female subgroups after adjusting for age, years of education, and MMSE score. Fig. 1A and Table 2 show that the females had significantly higher glucose metabolism in the bilateral inferior parietal lobule, bilateral medial frontal lobes, posterior cingulate gyrus, and right middle frontal gyrus compared with males. Conversely, the regions showing a significantly higher glucose metabolism in males than in females were detected in the bilateral inferior temporal gyri, bilateral middle temporal gyri, left middle frontal gyrus, right precentral gyrus, and cerebellum (Fig. 1B; Table 2).

Table 1
Characteristics of subjects.

	Male	Female	Statistics	P
n	67	56		
Age (years)	58.3 ± 9.7	56.8 ± 11.1	$t(121) = 0.78$	0.44
Education (years)	15.1 ± 2.1	14.2 ± 2.2	$U = 1434.50$	0.02
MMSE	29.3 ± 0.93	29.1 ± 0.96	$F(1, 121) = 1.10$	0.30
RAVLT total score	45.2 ± 7.7	51.2 ± 8.2	$F(1, 121) = 17.96$	< 0.001
ROCF copy	35.6 ± 0.83	35.6 ± 0.85	$F(1, 121) = 0.12$	0.73
ROCF recall ^a	21.4 ± 6.0	19.0 ± 5.8	$F(1, 120) = 5.04$	0.02

Mean $\pm$ S.D. Significant P -values ($P < 0.05$) are written in bold.

MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey–Osterrieth Complex Figure Test.

^a $n = 122$, one female refused the ROCF recall task.

Fig. 1. Sex difference in ^{18}F -FDG PET. Figure shows spatial distribution of hypermetabolic (A) and hypometabolic areas (B) in females (F) compared with males (M). Significant clusters are presented on axial (left panel), coronal (right upper panel), and sagittal (right lower panel) templates. These images were obtained using SPM analysis at cluster level, with a threshold of $P < 0.05$ corrected for multiple comparison with extent threshold of 100 voxels. White numbers indicate Talairach z coordinate. Left hemisphere is on the left-side.

Table 2
Clusters of hypo- and hyper-metabolic region in female and male.

Anatomical regions	BA	Coordinates			T-value	k
		x	y	z		
<i>Female > Male</i>						
R inferior parietal lobule	7	36	−60	44	6.14	757
L cingulate gyrus	31	−4	−23	40	5.53	637
RL medial frontal gyrus	10	0	53	10	5.31	1743
L inferior parietal lobule	40	−46	−58	45	4.99	461
L thalamus		−2	−19	6	4.66	492
R middle frontal gyrus	9	40	29	39	4.49	220
<i>Male > Female</i>						
L inferior temporal gyrus	20	−26	−4	−38	7.17	418
R inferior temporal gyrus	20	28	−6	−37	6.34	534
L cerebellum		−20	−44	−28	5.70	4034
R precentral gyrus	4	22	−19	45	5.08	209
L middle frontal gyrus	11	−20	51	−21	4.71	194
R middle temporal gyrus	21	46	−3	−15	4.63	208
L middle temporal gyrus	21	−48	−3	−13	4.29	100

Coordinates represent the local maxima in each cluster.
BA=Brodman area; k=cluster size; L=left; R=right.

3.3. Aging effects on cerebral glucose metabolism

Regions in which cerebral metabolism negatively correlated with age (i.e., reduction in ^{18}F -FDG activity with age) consisted of

the bilateral medial frontal lobes, left dominant bilateral dorso-lateral frontal region, and bilateral inferior parietal lobule (Fig. 2; Table 3). Analysis of the aging effect on cerebral metabolism associated with sex showed no interaction between age and sex, suggesting no significant sex differences in age-related decline of cerebral glucose metabolism (Cohen's $d=0.671$). We also showed no interaction between age and years of education in a similar fashion (Cohen's $d=0.671$).

3.4. Effects of education on cerebral glucose metabolism

Multiple linear regression analysis between years of education and cerebral glucose uptake showed a significant relationship between years of education and higher uptake in the medial frontal lobe and temporal lobe in the right hemisphere, but no significant correlation was detected in the left hemisphere (Fig. 3; Table 4). The analysis of educational effects on cerebral metabolism associated with sex showed no interaction between years of education and sex, suggesting no significant sex differences in educational attainment on cerebral glucose metabolism (Cohen's $d=0.670$).

3.5. Educational effects on the neural substrates of memory

Subjects were dichotomized based on education in a high education subgroup (years of education ≥ 16 ; $N=71$) and a low education subgroup (years of education < 16 ; $N=52$). The

Fig. 2. The aging effect on ^{18}F -FDG PET. Figure shows spatial distribution of glucose metabolism negatively correlated with age, after adjusting for years of education and MMSE score. Images were thresholded at $P < 0.05$ corrected for multiple comparison with extent threshold of 100 voxels. Left hemisphere is on the left side.

Table 3
Clusters of negative correlation between brain metabolism and age.

Anatomical regions	BA	Coordinates			T-value	k
		x	y	z		
R caudate nucleus	10	8	11	8.09	15,726	
R superior temporal gyrus	38	50	11	–7	6.67	2469
L inferior parietal lobule	40	–51	–39	44	6.01	1251
R inferior parietal lobule	40	36	–56	54	5.91	933
R middle frontal gyrus	10	32	59	12	4.76	152
R middle frontal gyrus	8	28	35	39	4.58	232

Coordinates represent the local maxima in each cluster.
BA=Brodman area; k=cluster size; L=left; R=right.

subgroups did not differ significantly on age ($t(121)=0.126$, $P=0.900$) but did differ in sex composition ($\chi^2=7.21$, $P=0.006$), with more males in the high education subgroup and more females in the low education subgroup. There was no difference with regard to any neuropsychological variables.

Compared with the high education subgroup, subjects in the low education subgroup showed a higher correlation between brain metabolism and the RAVLT total score in the right inferior and middle frontal gyrus, and the left superior frontal gyrus, after adjustment for age, sex, and MMSE score (Fig. 4; Table 5). However, subjects in the high education subgroup did not show any regions with a greater correlation between brain metabolism and the RAVLT total score as compared with subjects in the low education subgroup. Fig. 5 illustrates the relationship between brain metabolism and RAVLT total score for subjects in the low education (A) and high education (B) subgroups; a linear trend is observed in the low education subgroup but not in the high education subgroup. Additional analysis of the correlation between RAVLT score and cerebral metabolism associated with sex showed no interaction between RAVLT score and sex (Cohen's $d=0.670$).

4. Discussion

The current study investigated the profile of cerebral glucose metabolism in normal healthy subjects, demonstrating sex

differences, aging effects, and educational effects on cerebral glucose metabolism. Furthermore, we studied the effect of education on the relationship between brain glucose metabolism and memory scores.

First, our results demonstrated that levels of glucose metabolism in the medial frontal lobe, inferior parietal lobule, and posterior cingulate gyrus were significantly higher in females than males, whereas levels in the bilateral inferior temporal lobes and the cerebellum were significantly higher in males than females. To date, findings regarding cerebral glucose metabolism in males vs. females have been inconsistent. Some researchers showed that sex differences in ^{18}F -FDG activity were either statistically non-significant or minimal (Loessner et al., 1995; Fujimoto et al., 2008; Iseki et al., 2010; Chen et al., 2011). However, other studies reported relatively widespread decreases in cortical glucose metabolism in males compared with females during the resting state (Andreason et al., 1994; Willis et al., 2002). Our results are consistent with the studies showing higher cerebral metabolism in females than males. On the other hand, Ragland et al. (2000) reported that females have better verbal memory and higher rates of resting regional cerebral blood flow (rCBF) bilaterally in the temporal lobe. Some other authors have found higher metabolism in the parietal cortex in males than in females, whereas our study showed higher metabolism in the parietal cortex in females than in males. The contradictory findings are difficult to explain. The inconsistency may reflect multiple factors such as study conditions, sample characteristics, and analytic methods.

The difference in ^{18}F -FDG uptake shown here is also consistent with sex differences in the neuropsychological profile. Our cognitive data indicate that males performed better than females on visuospatial memory tests, whereas females were superior to males on verbal learning tests. These behavioral data are also consistent with past neuropsychological studies showing that females are superior to males on language and verbal learning tasks, whereas males perform better than females on spatial and motor tasks (Maccoby and Jacklin, 1974; Ragland et al., 2000). As found in recent imaging studies of AD, the neural substrates of visuospatial function include the parieto-temporal association area and the cerebellum (Jacobs et al., 2012), and substrates of memory list learning performance reportedly reside in the anterior part of the brain including the cingulate cortex, frontal cortex, and temporal cortex (Nobili et al., 2007). Thus, the different

Fig. 3. The educational effect on ^{18}F -FDG PET. Figure shows spatial distribution of glucose metabolism positively correlated with years of education, after adjusting for age, sex, and MMSE score. Significant clusters are in the medial frontal lobes, superior frontal gyrus, precentral gyrus, and temporal lobe in the right hemisphere. Images were thresholded at $P < 0.05$ corrected for multiple comparison with extent threshold of 100 voxels. Left hemisphere is on the left side.

Table 4
Clusters of positive correlation of brain metabolism with year of education.

Anatomical regions	BA	Coordinates			T-value	k
		x	y	z		
R medial frontal gyrus	6	28	−4	44	4.94	435
R middle temporal gyrus	37	55	−60	7	4.44	333
R superior frontal gyrus	6	16	15	62	4.33	132
R precentral gyrus	6	63	0	30	4.12	102
R superior temporal gyrus	22	51	−6	4	4.08	150
R middle temporal gyrus	21	51	2	−32	4.05	223

Coordinates represent the local maxima in each cluster.
BA=Brodmann area; k=cluster size; L=left; R=right.

patterns of cerebral glucose metabolism may reflect the distinct nature of the behavioral profiles between sexes. However, it is still unclear whether the differences between sexes in the normal database will be related to diagnoses in a clinical setting. Thus, further study examining the diagnostic applicability to patients of this database would be needed to clarify whether separate normal databases for males and females should be provided.

Second, the analysis of aging effects showed age-associated decreases of glucose metabolism mainly in the frontal lobe, anterior cingulate gyrus, and inferior parietal lobule. Multiple investigators have confirmed age-dependent decline in glucose metabolism especially in the frontal region including the bilateral perisylvian areas, insular region, frontal lobes, and anterior cingulate gyrus (Kuhl et al., 1982; Petit-Taboué et al., 1998; Ivančević et al., 2000; Pardo et al., 2007; Fujimoto et al., 2008; Kim et al., 2009; Hazlett et al., 2010; Iseki et al., 2010; Newberg and Alavi, 2010). The frontal aging hypothesis (Tisserand and Jolles, 2003) suggests that hypometabolism in anterior regions including the anterior cingulate gyrus and frontal lobe is related to executive function and attentional performance, which may decline even in the healthy elderly. Our results, coupled with past studies, support the frontal aging hypothesis.

In addition, we showed no significant sex differences in the age-dependent decline of glucose metabolism. Some studies reported discrete age-related patterns according to sex (Hazlett et al., 2010), while others failed to show any significant age by sex interaction (Willis et al., 2002). Although the absence of a statistically significant difference in the present study should not be taken to mean

that the trajectory of aging between males and females is identical, the difference in the age effect on glucose uptake is most likely minimal if it exists at all.

Third, our investigation of educational effects demonstrated a positive correlation between cerebral glucose metabolism and years of education. Many studies have identified the protective effect of education against developing dementia such as AD (Richards and Sacker, 2003; Stern, 2009). This phenomenon supports the brain-cognitive reserve hypothesis, in which more education provides greater brain capacity to compensate for damage by disease. Findings from the Nun Study showed that higher education and larger head size may reduce the risk of dementia in late life, suggesting that a larger brain represents brain reserve (Mortimer et al., 2003). Our findings showed higher resting state activity in the right temporo-parietal region in better educated subjects, suggesting that these areas may be part of the neural substrates for cognitive reserve.

Fourth, we demonstrated a positive correlation between glucose metabolism in the frontal lobe and RAVLT score only in the low education subgroup, although behavioral data showed no educational effect on memory scores. This suggests that educational attainment might protect against the tight relationship between brain metabolism and memory function. In addition to memory storage, successful encoding of the RAVLT word lists requires attention and executive control. These functions may depend on recruitment in the prefrontal cortex (Smith and Jonides, 1999). We posit that the reduced dependence of memory performance on glucose metabolism in the frontal lobes in the high education subgroup may be attributed to greater neural efficiency associated with higher cognitive reserve (Stern, 2009).

As shown in previous studies, persons with higher reserve require fewer cerebral resources to perform the same cognitive tasks compared with persons with less reserve, who have to use additional alternate networks (Stern et al., 2005; Zarahn et al., 2007; Sumowski et al., 2009). Structural magnetic resonance imaging (MRI) studies in patients with multiple sclerosis have revealed that the negative effect of brain atrophy on cognitive tasks (the positive correlation between brain volume and cognitive task performance) was attenuated at higher levels of reserve, suggesting that a compensation phenomenon exists in the low reserve subgroup more than in the high reserve subgroup (Sumowski et al., 2009). The Nun Study showed that head size did not make a difference in lowering the risk of dementia for the

Fig. 4. The educational effect on the correlation between ^{18}F -FDG PET and RAVLT total score. Figure shows FDG uptake correlation with RAVLT total score in the low education group compared to the high education group. Significant clusters are shown in the right middle frontal gyrus, right inferior frontal gyrus, and left superior frontal gyrus after adjusting for age, sex, and MMSE score. Height threshold was set at $P < 0.05$ corrected for multiple comparison with extent threshold of 100 voxels. Left hemisphere is on the left side.

Table 5

Clusters of positive correlation of brain metabolism with RAVLT total score.

Anatomical regions	BA	Coordinates			T-value	k
		x	y	z		
<i>High education > Low education</i>						
No suprathreshold clusters						
<i>Low education > High education</i>						
L superior frontal gyrus	10	−12	61	15	5.15	247
R middle frontal gyrus	9	42	49	18	4.80	549
R inferior frontal gyrus	45	40	20	10	4.12	123

Coordinates represent the local maxima in each cluster.

BA=Brodmann area; k=cluster size; L=left; R=right; RAVLT=Rey Auditory Verbal Learning Test.

Fig. 5. Scatter plots of RAVLT total score vs. glucose metabolism in arbitrary units at the position of the most significant cluster [−12, 61, 15]. Panels show positive correlation in the low education subgroup (A) and no apparent trend in the high education subgroup (B). RAVLT=Rey Auditory Verbal Learning Test.

higher educated people, but in the lower educated group those with higher head size had lower risk of dementia (Mortimer et al., 2003). Although the above-referenced investigations were performed

using structural MRI or head size, the results are in line with our resting state ^{18}F -FDG PET data. We showed that the negative effect of hypometabolism in the frontal lobes on a memory task (the positive

correlation between cerebral metabolism and memory performance) was clearly observed in the low education subgroup. However, this effect diminished in the high education subgroup. These findings suggest that educational attainment could be related to the degree of cerebral recruitment in the prefrontal cortex on memory tasks.

The cognitive reserve hypothesis emphasizes that intellectual enrichment is associated with cerebral efficiency, maintained by the greater preservation of activity within the brain's default/resting network and less recruitment of additional cortical regions during cognitive tasks (Sumowski et al., 2009). Because past reports and our results were based on the assumption that proxy for cognitive reserve is correlated with brain static image such as MRI or resting PET, the possibility that there could be other influences on the results has to be mentioned. However, earlier results, coupled with our findings, as shown in Figs. 3 and 4, may support the cognitive reserve hypothesis in normal subjects.

There are some limitations of this study including the absence of partial-volume correction of the PET images. The hypoconcentration measured by PET might be, thus, the combination of the effect of intrinsic glucose hypometabolism and the effect of a partial volume effect of focal cerebral atrophy. Therefore, further analyses including MRI-coregistered partial volume correction are needed (Yanase et al., 2005). The second limitation is that enrolled subjects were all ethnically Japanese with a relatively high educational background. Thus, the participants may not be representative of the general population. In addition, because the Edinburgh Handedness Inventory was not used to assess cerebral dominance in each subject, our sample comprised participants whose handedness was right, corrected-right, or left. The third limitation is that we do not have clinical follow-up on these subjects to determine if and when their cognition will deteriorate in the future. A past report showed that 22 out of the 77 normal subjects in a PET database developed MCI during a 4-year follow-up (Mosconi et al., 2007). That result suggests a longitudinal follow-up of the subjects is necessary. However, we endeavored to carefully screen our subjects to rule out the possibilities that they were in early stages of dementia such as AD, DLB, FTD, and vascular dementia, so we are confident that we have isolated as pure an aging process as possible. Fourth, in this study, level of education (years of education) was treated as a proxy for cognitive reserve. Because years of education is merely one of many indexes, further analyses should use other indexes such as occupational attainment, leisure activities, or IQ measured by neuropsychological tests.

In conclusion, our analysis demonstrated sex differences in cerebral glucose metabolism, which may explain sex differences in cognitive functions. We also confirmed aging effects on ^{18}F -FDG uptake, which are consistent with age-related cognitive decline. Finally, our results demonstrated educational effects on the resting state ^{18}F -FDG uptake and on the memory-specific recruitment of glucose metabolism, consistent with high cognitive reserve in highly educated subjects.

Acknowledgments

The authors thank Professor Makoto Iwata, Professor Kiyoko Kusakabe, Dr. Chisato Kondo, and Dr. Mitsuru Momose (Tokyo Women's Medical University) for their continuous assistance and helpful suggestions. This work was supported by the International Research and Educational Institute for Integrated Medical Sciences, Tokyo Women's Medical University which is supported by the Program for Promoting the Establishment of Strategic Research Centers, Special Coordination Funds for Promoting Science and Technology, Ministry of Education, Culture, Sports, Science and Technology, Japan. No other potential conflict of interest relevant to this article is reported.

References

- Andreason, P.J., Zametkin, A.J., Guo, A.C., Baldwin, P., Cohen, R.M., 1994. Gender-related differences in regional cerebral glucose metabolism in normal volunteers. *Psychiatry Research: Neuroimaging* 51, 175–183.
- Black, D., Lee, H., Muzikansky, A., Martin, E., Tanzi, R., McArdle, J., Moss, M., Albert, M., 2007. Neuropsychological measures in normal individuals that predict subsequent cognitive decline. *Archives of Neurology* 64, 862–871.
- Bleeker, M.L., Bolla-Wilson, K., Agnew, J., Meyers, D.A., 1988. Age-related sex differences in verbal memory. *Journal of Clinical Psychology* 44, 403–411.
- Bohnen, N.I., Djang, D.S., Herholz, K., Anzai, Y., Minoshima, S., 2012. Effectiveness and safety of ^{18}F -FDG PET in the evaluation of dementia: a review of the recent literature. *Journal of Nuclear Medicine* 53, 59–71.
- Chen, W.P., Samuraki, M., Shima, K., Yanase, D., Takeda, N., Miyazaki, Y., Ono, K., Yoshita, M., Nishimura, S., Yamada, M., Matsunari, I., 2011. Effect of an age-mismatched and sex-mismatched normal database on the diagnostic performance of ^{18}F -FDG PET for Alzheimer's disease: the Ishikawa Brain Imaging Study. *Nuclear Medicine Communications* 32, 1128–1133.
- Folstein, M., Folstein, S., McHugh, P., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 12, 189–198.
- Friston, K., 1997. Analyzing brain images: principles and overview. In: Frackowiak, R., Friston, K., Frith, C., Dolan, R., Mazziotta, J. (Eds.), *Human Brain Function*. Academic Press, San Diego, pp. 25–41.
- Fujimoto, T., Matsumoto, T., Fujita, S., Takeuchi, K., Nakamura, K., Mitsuyama, Y., Kato, N., 2008. Changes in glucose metabolism due to aging and gender-related differences in the healthy human brain. *Psychiatry Research: Neuroimaging* 164, 58–72.
- Hazlett, E.A., Byne, W., Brickman, A.M., Mitsis, E.M., Newmark, R., Haznedar, M.M., Knatz, D.T., Chen, A.D., Buchsbaum, M.S., 2010. Effects of sex and normal aging on regional brain activation during verbal memory performance. *Neurobiology of Aging* 31, 826–838.
- Iseki, E., Murayama, N., Yamamoto, R., Fujishiro, H., Suzuki, M., Kawano, M., Miki, S., Sato, K., 2010. Construction of a (^{18}F -FDG PET normative database of Japanese healthy elderly subjects and its application to demented and mild cognitive impairment patients. *International Journal of Geriatric Psychiatry* 25, 352–361.
- Ivančević, V., Alavi, A., Souder, E., Mozley, P.D., Gur, R.E., Bénard, F., Munz, D.L., 2000. Regional cerebral glucose metabolism in healthy volunteers determined by fluorodeoxyglucose positron emission tomography: appearance and variance in the transaxial, coronal, and sagittal planes. *Clinical Nuclear Medicine* 25, 596–602.
- Jacobs, H.I., Van Bortel, M.P., Heinecke, A., Gronenschild, E.H., Backes, W.H., Ramakers, I.H., Jolles, J., Verhey, F.R., 2012. Functional integration of parietal lobe activity in early Alzheimer disease. *Neurology* 78, 352–360.
- Kawachi, T., Ishii, K., Sakamoto, S., Matsui, M., Mori, T., Sasaki, M., 2002. Gender differences in cerebral glucose metabolism: a PET study. *Journal of the Neurological Sciences* 199, 79–83.
- Kim, I.J., Kim, S.J., Kim, Y.K., 2009. Age- and sex-associated changes in cerebral glucose metabolism in normal healthy subjects: statistical parametric mapping analysis of F-18 fluorodeoxyglucose brain positron emission tomography. *Acta Radiologica* 50, 1169–1174.
- Knight, J., Kaplan, E., 2003. *Handbook of Rey-Osterrieth Complex Figure Usage: Clinical and Research Applications*. Psychological Assessment Resources, Odessa, FL.
- Kuhl, D.E., Metter, E.J., Riege, W.H., Phelps, M.E., 1982. Effects of human aging on patterns of local cerebral glucose utilization determined by the [^{18}F]fluorodeoxyglucose method. *Journal of Cerebral Blood Flow & Metabolism* 2, 163–171.
- Loessner, A., Alavi, A., Lewandrowski, K.U., Mozley, D., Souder, E., Gur, R.E., 1995. Regional cerebral function determined by FDG-PET in healthy volunteers: normal patterns and changes with age. *Journal of Nuclear Medicine* 36, 1141–1149.
- Maccoby, E.E., Jacklin, C.N., 1974. *The Psychology of Sex Differences*. Stanford University Press, Stanford, CA.
- Minoshima, S., Frey, K.A., Koeppe, R.A., Foster, N.L., Kuhl, D.E., 1995. A diagnostic approach in Alzheimer's disease using three-dimensional stereotactic surface projections of fluorine-18-FDG PET. *Journal of Nuclear Medicine* 36, 1238–1248.
- Mortimer, J.A., Snowdon, D.A., Markesbery, W.R., 2003. Head circumference, education and risk of dementia: findings from the Nun Study. *Journal of Clinical and Experimental Neuropsychology* 25, 671–679.
- Mosconi, L., Tsui, W., Pupi, A., De Santi, S., Drzezga, A., Minoshima, S., de Leon, M., 2007. (^{18}F -FDG PET database of longitudinally confirmed healthy elderly individuals improves detection of mild cognitive impairment and Alzheimer's disease. *Journal of Nuclear Medicine* 48, 1129–1134.
- Newberg, A.B., Alavi, A., 2010. Normal patterns and variants in PET brain imaging. In: Newberg, A.B., Alavi, A. (Eds.), *PET in the Aging Brain*. W.B. Saunders Company, Philadelphia, pp. 1–13.
- Nobili, F., Koulibaly, P., Rodriguez, G., Benoit, M., Girtler, N., Robert, P., Brugnolo, A., Darcourt, J., 2007. $^{99\text{m}}\text{Tc}$ -HMPAO and $^{99\text{m}}\text{Tc}$ -ECD brain uptake correlates of verbal memory in Alzheimer's disease. *The Quarterly Journal of Nuclear Medicine and Molecular Imaging* 51, 357–363.
- Osterrieth, P.A., 1944. Le test de copie d'une figure complexe. *Archives de Psychologie* 30, 206–256.
- Pardo, J., Lee, J., Sheikh, S., Sururus-Johnson, C., Shah, H., Munch, K., Carls, J., Lewis, S., Kuskowski, M., Dysken, M., 2007. Where the brain grows old: decline in anterior cingulate and medial prefrontal function with normal aging. *NeuroImage* 35, 1231–1237.
- Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E., 1999. Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology* 56, 303–308.

- Petit-Taboué, M.C., Landeau, B., Desson, J.F., Desgranges, B., Baron, J.C., 1998. Effects of healthy aging on the regional cerebral metabolic rate of glucose assessed with statistical parametric mapping. *NeuroImage* 7, 176–184.
- Ragland, J.D., Coleman, A.R., Gur, R.C., Glahn, D.C., Gur, R.E., 2000. Sex differences in brain-behavior relationships between verbal episodic memory and resting regional cerebral blood flow. *Neuropsychologia* 38, 451–461.
- Rey, A., 1941. L'examen psychologique dans les cas d'encephalopathie traumatique. *Archives de Psychologie* 28, 286–340.
- Rey, A., 1964. *L'Examen Clinique en Psychologie*. Presses Universitaires de France, Paris.
- Richards, M., Sacker, A., 2003. Lifetime antecedents of cognitive reserve. *Journal of Clinical and Experimental Neuropsychology* 25, 614–624.
- Smith, E.E., Jonides, J., 1999. Storage and executive processes in the frontal lobes. *Science* 283, 1657–1661.
- Stern, Y., 2009. Cognitive reserve. *Neuropsychologia* 47, 2015–2028.
- Stern, Y., Habeck, C., Moeller, J., Scarmeas, N., Anderson, K.E., Hilton, H.J., Flynn, J., Sackeim, H., van Heertum, R., 2005. Brain networks associated with cognitive reserve in healthy young and old adults. *Cerebral Cortex* 15, 394–402.
- Sumowski, J.F., Chiaravalloti, N., Wylie, G., Deluca, J., 2009. Cognitive reserve moderates the negative effect of brain atrophy on cognitive efficiency in multiple sclerosis. *Journal of the International Neuropsychological Society* 15, 606–612.
- Talairach, J., Tournoux, P., 1988. *Co-planar Stereotactical Atlas of the Human Brain: Three-dimensional Proportional System—An Approach to Cerebral Imaging*. Thieme Medical Publishers, New York.
- Tisserand, D.J., Jolles, J., 2003. On the involvement of prefrontal networks in cognitive ageing. *Cortex* 39, 1107–1128.
- Willis, M.W., Ketter, T.A., Kimbrell, T.A., George, M.S., Herscovitch, P., Danielson, A.L., Benson, B.E., Post, R.M., 2002. Age, sex and laterality effects on cerebral glucose metabolism in healthy adults. *Psychiatry Research: Neuroimaging* 114, 23–37.
- Worsley, K.J., Marrett, S., Neelin, P., Vandal, A.C., Friston, K.J., Evans, A.C., 1996. A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping*, 4, pp. 58–73.
- Yanase, D., Matsunari, I., Yajima, K., Chen, W., Fujikawa, A., Nishimura, S., Matsuda, H., Yamada, M., 2005. Brain FDG PET study of normal aging in Japanese: effect of atrophy correction. *European Journal of Nuclear Medicine and Molecular Imaging* 32, 794–805.
- Zarahn, E., Rakitin, B., Abela, D., Flynn, J., Stern, Y., 2007. Age-related changes in brain activation during a delayed item recognition task. *Neurobiology of Aging* 28, 784–798.