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Voxel-based morphometric difference in metabolic activity of 50 to 73 years old healthy adult brain: A PET/CT study

Siti Aishah Abdul Aziz[1,4], Mohd Hafrizal Azmi[1], Abdul Jalil Nordin[3], Fathinul Fikri Ahmad Saad[2], Normala Ibrahim[3], Wan Azizun Wan Adnan[1], M. Iqbal Saripan[1]

ABSTRACT

Healthy adult exhibits variants of ^{18}F-FDG distribution of cerebral glucose metabolism associated with age. This study was conducted to investigate the hypometabolism and hypermetabolism as a function of gender in healthy adults unrelated to dementia. The subjects consisted of 21 males aged 51 to 66 (mean + SD = 57.81 + 4.792) and 15 females aged 50 to 73 (mean + SD = 62.8 + 5.906). Six data of equal gender were randomly chosen from the subjects to investigate the difference in metabolic activity. The result showed that hypometabolismwas detected at cerebrum, cerebellum, parahippocampalgyrus, superior frontal gyrus, superior temporal gyrus, frontal lobe and posterior lobe that were not exclusively showing dementia-related diseases but only a sign of mild cognitive decline with increased age. In healthy elderly, hypometabolismwas also seen in the anterior regions of the brain that related to executive function and performance of attention. Preserved glucose consumptionwas seen as both hypo- and hypermetabolized in the cerebrum and cerebellum region. This finding was supported by previous studies that a normal daily function of an AD patient was preserved even with evidence of cognitive decline. Nevertheless, there were gender effect differences in metabolic activity between male and female healthy adults. Hypometabolism was significant in right cerebrum, right cerebellum and left cerebellum for male but hypermetabolic in female at left cerebrum region. On the other hand, only female subject showed a hypometabolic area in thalamus and parahippocampalgyrus due to effect of estrogen where older female aged 50 and above were in menopausal condition unless HRT were taken.

***Keywords**:* voxel-based morphometry; healthy adult; hypometabolism; hypermetabolism; gender effect

1. INTRODUCTION

Positron emission tomography (PET) is an established clinical tool use in neurodegenerative disorders. Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) is used to measure cerebral metabolic rates of glucose (CMRglc), an index of brain synaptic activity and density. Longitudinal studies in Alzheimer's disease (AD) patients have demonstrated that CMRglc reductions in AD-related regions worsen along with dementia progression, with an average decline of 16–19% over a three-year period[1] In this study, the oncology patients diagnosed with cancer in other parts of the body other than their brain were define as having a healthy brain without any cognitive impairments. The pattern and area of the hypometabolism may be used as an indicator for a specific disease. However, the declination is not necessarily representing the sign of dementia-related diseases but a normal gradual decline of certain cognitive function due to aging. Previous study on relationship between brain metabolic activity and age were sometime conflicting. For example, hypometabolic area

[1] Department of Computer and Communication Systems Engineering, Faculty of Engineering, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia, *Email: iqbal@upm.edu.my*

[2] Centre for Diagnostic Nuclear Imaging, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia, *Email: ahmadsaadff@gmail.com*

[3] Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia, *Email: normala_ib@upm.edu.my*

[4] School of Health Sciences, UniversitiSains Malaysia 16150 KubangKerian, Kelantan, Malaysia, *Email: ishah@usm.m*

were detected in thalamus[2], whilst others reported it as hypermetabolic area [3] [4]. Shen et al. found that middle frontal gyrus and superior temporal gyrus were hypometabolic in both male and female healthy adult brain whereas middle frontal gyrus in male showed as hypermetabolic at the same time [4]. On the other hand, Newberg et al. reported AD patients maintained its metabolic activity in the cerebellum region [5]. Cerebellum and cerebrum regions were also highly metabolic in healthy adult. It was found that these region might represent a compensatory mechanism involved in cognitive decline [6]. The thought of cerebellum not to be abnormal in assessment of AD patients may develop a focus on this region as another evaluation for AD patients in future. Other regions considered to be hypometabolic in healthy adults for both genders were found in frontal lobe and temporal lobe that were associated with prominent atrophy in prefrontal cortex and cortical thinning in the temporal cortex [7]. Superior temporal gyrus and frontal lobe were also detected as hypometabolic in both gender[4] [6]. Due to these reasons, we aimed to investigate the hypometabolism and hypermetabolism areas in male and female healthy adult brain for age related brain glucose consumption in clusters of voxels.

2. MATERIALS AND METHODS

2.1. Subjects

We studied on thirty-six consecutive subjects from the PET/CT clinical database who underwent whole-body scanning which extended to brain scan for the purpose of this study. No written consent pertaining to this study was given to the subject as they were patients of Centre for Diagnostic Nuclear Imaging (CDNI), UPM. The subject consisted of 21 males aged 51 to 66 (mean + SD ~ 57.81 + 4.792) and 15 females aged 50 to 73 (mean + SD ~ 62.8 + 5.906). Subjects deemed as 'healthy adults' were selected based on these criteria: patients diagnosed with cancer in other parts of the body other than brain, no history of brain injury and negative reports on cognitive decline beyond the normal aging expected. Exclusion criteria included diabetes mellitus, uncontrollable hypertension, 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.

2.2. Data acquisition

^{18}F-FDG PET/CT images of subjects were collected from CDNI, UPM. The images were acquired using Siemens TruepointBiograph 64 PET/CT scanner which produced functional and structural information of the region scanned. Subjects were required to fast for at least 6 hours before the PET/CT examination procedure. After a standard registration protocol, a fasting blood sugar level (FBS) were measured, only subjects with FBS less than 8mmol/L were allowed for ^{18}F-FDG injection. 8mCi of ^{18}F-FDG was injected into the right arm or forearm venous access of the subject. 1000 ml of normal saline was slowly infused over the resting uptake period of at least 45 minutes. After the resting period, the subject was brought to the PET/CT room for scanning.

The scanning procedure consists of three protocols performed consecutively. The first scanning protocol was the 10-minutes brain imaging, followed by the 20-minutes whole-body scanning. Lastly, the multipoint brain scanning was performed with two sets of 5-minutes brain scan performed consecutively. Brain PET/CT scan was performed placing patient's head in a dedicated support before whole body PET/CT examination. A 40 mA and 120 kV CT scan of the head with attenuation correction was performed before PET image acquisition.

2.3. Image processing

A reference database was built from 30 healthy adults aged 50 to 73 years old. 50 years old was the threshold age for a progressive cognitive decline in AD patients confirmed by previous researchers [2] [8]. The

images were normalized and smoothed into the MNI space (Montreal Neurological Institute, McGill University, Montreal, Canada) using the Statistical Parametric Mapping (version SPM8) software (Wellcome Trust Centre for Neuroimaging, London, 18 U.K.) and Matlab version 8.1 (The Mathworks Inc., MA, USA). A voxel-by-voxel statistical analysis was requested to detect the hypo- or hypermetabolism by comparing one patient's scan to a group of controlled scans. The default setting were set at nonlinear basis function: 7 × 8 × 9; number of iterations: 16; bounding box: -78 80, -112 82, -100 90; regularization: medium; voxel sizes 2 × 2 × 2 mm^3. The smoothed and warped image were done by adding a Gaussian filter of 12 mm FWHM.

2.4. Data analysis

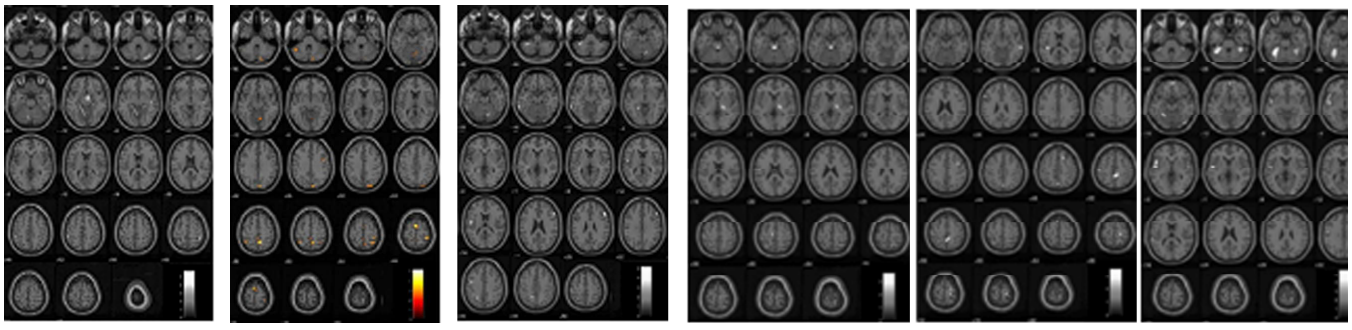
Six subjects were chosen from the clinical database of CDNI to investigate the hypo- and hypermetabolic region. They were three male subjects age 63, 60 and 59 (mean + SD = 60.66 + 2.082) and three female subjects age 71 and 61 (mean + SD = 64.33 + 5.773). (Data analysis was done in SPM8 and Matlab through voxel-based morphometric using general linear model (GLM). The age and gender were the covariates to study the relationship between glucose uptake, age and gender effect. T-map calculations were performed on voxel-wise basis of a single subject analysis of a normal healthy adult to the reference database. Misclassified individuals were considered when cluster of voxels were present in the SPM-t with a minimum extent of 10 voxels and surviving at $p < 0.01$ FWE-corrected threshold at a voxel level.

A single patient vs. healthy adult SPM analysis was performed for all 6 considered ^{18}F-FDG PET patient scans. Each single-patient image was tested for relative hypometabolism and hypermetabolism by comparison with the reference database on a voxel-by-voxel basis using the one sample t-test. Age and gender were included as covariates. Global normalization of voxel values used proportional scaling to a mean voxel value of 50 mg/100 mL/min. The grey matter threshold was left at the default 0.8 value (the mean brain intensity was computed from only those voxels with intensity above 0.8 of the mean over the whole scan). The significant areas were overlaid on a T1-weighted MRI image slice by slice for standard image co-registration. The MNI coordinate were converted to the Thalairach coordinates using the Talairach Client software.

3. RESULTS

3.1. Hypometabolism

Results for the six patients were illustrated in Figure3.1 and Table 3.1



(a) (b) (c) (d) (e) (f)

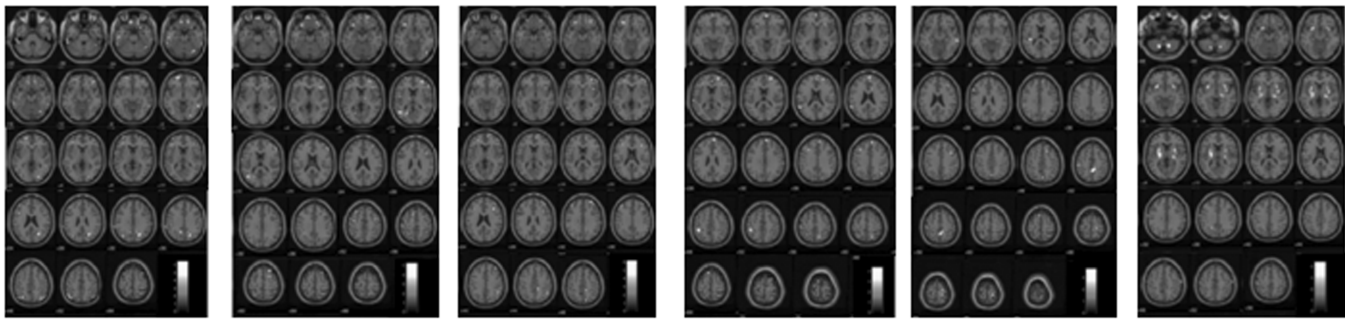
Figure 1: A single patient SPM metabolic map showing hypometabolic activity overlaid on T1-weighted MRI included in SPM8. All six (a) to (f) subjects showed signs of local maxima peak values (T-value) of cluster voxels.

Table 1
Clusters ofhypometabolism of all six subjects (a) to (f).

Subject (gender, age)	*Anatomical region*	*T-value*	k_E *(No. of voxels)*	*BA (Broadmann Area)*	*Coordinates*		
					x	*y*	*z*
a (male, 63)	R cerebrum	5.70	442	2	8	-10	-14
	L cerebrum	4.13	442	4	-2	-8	-14
	R cerebellum	3.80	228		28	-86	-30
	L cerebellum	3.43	406	19	-12	-44	-10
	R parahippocampalgyrus	4.55	442	34	12	0	-14
	R posterior lobe	3.79			38	-78	-30
b (male, 60)	R cerebrum	5.11	151	7	8	-54	54
	Superior frontal gyrus	4.94	111	6	-2	0	70
	R precuneus	3.88	100	18	8	-86	34
c (female, 61)	Inferior frontal gyrus	3.86	92	46	52	26	28
d (female, 71)	R cerebrum	3.89	116	5	4	-30	-20
	R thalamus	3.16	119		20	-16	6
e (female, 61)	L cerebrum	3.05		13	-48	-14	-6
	L parahippocampalgyrus	4.15	316	34	-14	0	-14
	Medial frontal gyrus	3.23		25	-6	12	-18
	Inferior temporal gyrus	3.54	262	20	-44	-12	-14
	Superior temporal gyrus	3.22		22	-58	-36	4
	Inferior frontal gyrus	3.49	157	11	12	18	-16
f (male, 59)	L cerebellum	5.71	989		-28	-42	-24
	R cerebellum	3.16			28	-48	-22
	R cerebrum	3.10		11	16	62	-12
	L cerebrum	4.23	442	21	38	-42	-30
	Culmen	5.37			-34	-48	-26
	Anterior lobe	4.49			-24	-52	-18
	Posterior lobe	3.56		2	42	-84	-16
	Frontal lobe	3.06		47	48	20	-6
	Superior temporal gyrus	4.91	665	22	-48	12	0
	Precentralgyrus	4.84		43	-48	-4	6
	Medial frontralgyrus	4.21	248	11	4	60	-18
	Middle occipital gyrus	3.66	523	18	22	-98	8
	Inferior occipital gyrus	3.28		18	38	-90	-4

3.2. Hypermetabolism

Result for the six single patients were illustrated in Figure3.2 and Table 3.2



(a) **(b)** **(c)** **(d)** **(e)** **(f)**

Figure3.2: A single patient SPM metabolic map showing hypometabolic activity overlaid on T1-weighted MRI included in SPM8. All six (a) to (f) subjects showed signs of local maxima peak values (T-value) of cluster voxels.

Table 3.2
Clusters of hypermetabolismof all six subjects (a) to (f).

Subject (gender, age)	*Anatomical region*	*T-value*	k_E *(No. of voxels)*	*BA (Broadmann Area)*	*Coordinates*		
					x	*y*	*z*
a (male, 63)	L cerebrum	6.20	1799	13	-38	22	18
	Frontal lobe	5.83		13	-18	56	-4
	Temporal lobe	4.31	675	20	-56	-30	-30
	Inferior frontal gyrus	4.89		45	-32	62	8
	Middle temporal gyrus	3.94		21	-60	-40	-16
	Fusiform gyrus	4.25		20	-50	-18	-22
b (male, 60)	R cerebrum	5.24	195	10	32	50	12
	L cerebrum	2.86		39	-36	-72	14
	Frontal lobe	3.82	192	11	-6	54	-22
	Superior frontal gyrus	3.27		10	36	46	22
	Middle frontal gyrus	5.04	159	10	24	26	62
	Middle temporal gyrus	4.05	177	19	-42	-62	14
c (female, 61)	R cerebrum	4.54	639	46	50	46	2
	L cerebrum	4.67	271	39	-30	34	-12
	Middle temporal gyrus	3.42		19	-24	46	28
	Middle frontal gyrus	4.28		46	32	52	32
	Inferior frontal gyrus	3.58	319	10	22	66	8
	Anterior cingulate	3.41			12	48	14
d (female, 71)	R cerebrum	3.91	141	10	26	52	16
	Middle frontal gyrus	3.59	362	10	6	56	32
	Superior frontal gyrus	3.26		9	6	48	42
e (female, 61)	R cerebrum	3.74		7	10	-42	52
	L cerebrum	3.75	153	7	0	-48	54
	Paracentral lobule	2.86		5	8	-28	52
f (male, 59)	R cerebrum	4.06	408	10	36	-6	0
	L cerebrum	4.05	869	13	-28	12	-8
	Lentiform nucleus	3.53			28	4	8
	Putamen	3.48			30	14	-2
	Temporal lobe	3.72		47	-22	-14	12
	Inferior frontal gyrus	3.47		13	-28	8	6

4. DISCUSSIONS

Our investigation in healthy adult patients of old age demonstrated the age effect on hypo- and hypermetabolism of brain. Firstly,hypometabolism were detected at cerebrum, cerebellum, parahippocampalgyrus, superior frontal gyrus, superior temporal gyrus, frontal lobe and posterior lobe showed in Figure 3.1. There was no hypometabolic region at temporal lobe for both male and female but our study contradicted from Shen et al.[4]where we detected hypermetabolic area in this region in two of the female subject as shown in Table 3.1. There was a study reported that females have better verbal memory and higher rates of resting regional cerebral blood flow (rCBF) bilaterally in the temporal lobe [4]. Some other authors have found higher metabolism in the temporal lobe in males than in females, whereas our study showed higher metabolism in the frontal gyrus in females than in males [9][10]. The contradictory findings are difficult to explain. The inconsistency may reflect multiple factors such as study conditions, sample size, subject characteristics and analytic methods.

From Figure 3.1, hypometabolism in anterior regions especially frontal lobe was related to executive function and attentional performance, which may decline even in the healthy elderly. Our results, coupled with pasts studies, supported the frontal aging hypothesis [8]. It was clearly shown from Table 3.1 and

Table 3.2 that cerebrum and cerebellum region were both hypo- and hypermetabolized during the scanning time. This pattern proved that there were preserved glucose consumption in both area. This finding was supported by studies showing FDG-PET brain scan in AD patients may contributed to cognitive decline but not apparent in the daily function of the patient [5].

Secondly, gender effect on hypometabolism and hypermetabolism showed different activated region in cerebrum and cerebellum. Male subjects had low metabolic activity mostly in right cerebrum, right cerebellum and left cerebellum. However, female subjects showed hypermetabolic region in left cerebrum. The specific pattern of activated cerebrum and cerebellum between male and female was not yet known scientifically but it was found that these region might represent a compensatory mechanism involved in cognitive decline[6]. The middle frontal gyrus and superior temporal gyrus were hypometabolic in both male and female healthy adult brain whereas middle frontal gyrus in male showed as hypermetabolic at the same time. The areas mentioned were matched with studies done by Shen et al. and Newberg et al. [4][5]. On the other hand, only female subject showed a hypometabolic area in thalamus and parahippocampalgyrus. This result had contradicted the report by Hsieh et al. that right and left thalamus were hypermetabolic due to the effect of estrogen[11]. We do not support this report due to inconsistency from our knowledge that older females aged 50 and above were in menopausal condition unless HRT (hormone replacement therapy) were taken.

From Figure3.2 and Table 3.2, hypermetabolism in superior frontal gyrus, middle frontal gyrus, and middle temporal gyruswere both present in male and female subjects which also supported the study previously but not in female group as in Shen et al.[4]. The phenomenon can be explained for an increased in activity at these regions were to compensate for other regions of neuron dysfunction or loss. This also proved that difference in metabolic activity in normal aging was always a compensatory for other regions decline to cope with the decrease of brain function in a memory condition [6].

There are some limitations of this study including the absence of partial-volume correction of the PET images. Some studies found that a decline glucose uptake with normal aging becomes significant after taking the partial-volume effects into account [12][13]. Our small sample size also affects the consistency of the result with previous studies. Six subjects who were randomly chosen for a single subject analysiswere also not conclusive enough for the anatomical region comparisons. In addition, since all of the data derived from clinical database, we were unable to take the neuropsychological test such as the Mini Mental State Examination (MMSE) for each subject at this stage because we had assumed earlier that the subjects had fulfilled all the criteria of a 'healthy adult' mention earlier without any signs of AD. All of the limitations mentioned above will be considered in our future work.

5. CONCLUSIONS

Our study disclosed similar decreased brain metabolism in cerebrum, cerebellum, parahippocampalgyrus, superior frontal gyrus, superior temporal gyrus, frontal lobe and posterior lobe that were not exclusively showing dementia-related diseases but only a sign of mild cognitive decline with increased age. Nevertheless, there were gender effect differences in metabolic activity between male and female healthy adults. Hypometabolism was significant in right cerebrum, right cerebellum and left cerebellum for male but hypermetabolic in female at left cerebrum region. On the other hand, only female subject showed a hypometabolic area in thalamus and parahippocampalgyrus due to effect of estrogen where older female aged 50 and above were in menopausal condition unless HRT were taken.

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