Normal patterns of regional brain ^{18}F-FDG uptake in normal aging

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Abstract

Objective: Normal aging alters the brain function even in the absence of recognizable structural changes, which can be detected using modern in vivo functional imaging modalities such as fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) scan. It is highly important to recognize normal age-dependent changes in order to correctly diagnose pathologic states. The goal of the current study was to evaluate the age-related changes in regional brain ^{18}F-FDG uptake in normal healthy population. **Subjects and Methods:** This study was part of the cardiovascular molecular calcification assessed by ^{18}F-sodium fluoride (NaF) (CAMONA) PET/computed tomography (CT) study. This study was approved by the Danish National Committee on Health Research Ethics registered at ClinicalTrials.gov (NCT01724749). Forty normal healthy subjects were prospectively recruited in group A (22-32 years) and B (56-75 years) and underwent ^{18}F-FDG PET/CT. Static images were obtained 180 minutes following ^{18}F-FDG injection. Supratentorial (including individual measurements for frontal, parieto-occipital and temporal lobes) and cerebellar ^{18}F-FDG uptakes were measured by manual placement of region of interest (ROI) over these regions based on predefined criteria for each and standardized uptake value (SUVmean) values were calculated using OsiriX software. **Results:** The mean ages of the patients in group A was 26.1±3.4 versus 61±4.4 for group B. There were 10 females in group A and 10 females in group B. Mean SUV of cerebellum was 6.80±1.21 for the young subjects compared to 6.08±0.7 among old subjects (independent t-test, P= 0.028). Mean SUV of supratentorial brain was 9.14±1.83 for the young subjects compared to 6.92±072 among old subjects (P<0.001). Mean SUV of frontal (9.72±1.97 vs. 7.03±0.69), temporal (7.37±1.52 vs. 5.65±0.68) and parieto-occipital region (10.7±2.28 vs. 7.41±0.79) was higher among young patients (P< 0.001). More interestingly, SUVmean of supratentorial brain was significantly higher among female healthy volunteers in both groups (P= 0.025 and 0.047 for group A and B, respectively). **Conclusion:** In conclusion, these findings confirm a significant age dependent reduction of supratentorial ^{18}F-FDG uptake among healthy individuals. However, cerebellum ^{18}F-FDG uptake reduction was not so redundant. Fluorine-18-FDG uptake of all cerebral lobes including frontal, parieto-occipital and temporal decreases with normal aging in a same fashion. Interestingly, among both young and old female subjects, higher uptake was seen in supratentorial brain.

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Introduction

Knowledge about the time course of normal aging in healthy human brain has become increasingly important in recent years. All humans develop some degree of cognitive decline as they age, usually including forgetfulness, decreased ability to maintain focus, and decreased problem-solving capacity. Normal aging of the brain may result in the development of mild cognitive impairment (MCI), which is considered a transitional state between normal aging and dementia [1]. Mild cognitive impairment may represent as a risk factor of progression to more serious conditions such as Alzheimer's disease (AD) [2-4]. Early identification of cognitive deficits may benefit patients with prophylactic treatment to slow the progression to AD [5].

Age related changes are attributed to a number of structural and functional alterations in the absence of clinically significant impairment [6-9]. For structural changes, neuroimaging techniques play an important role in detecting specific brain regions affected by aging and measuring their global volumes. Magnetic resonance imaging (MRI) was one of the methods used to investigate the progressive alterations to brain tissue that accompany physiological aging [10, 11]. It has been shown that the brain shrinks globally and regionally in volume and the ventricular system increases in size during healthy aging [9]. Although prior studies investigating the patterns of brain structural changes as a result of normal aging have shown heterogeneous findings most have

demonstrated the largest changes occur in the frontal and temporal cortex as loss of cortical thickness and subcortical volume as well as putamen, thalamus and accumbens [9, 10, 12, 13].

By using only structural imaging techniques such as MRI, it is difficult to describe the relative proportion of age related alterations in different locations of brain. Molecular imaging has an important role in neuroimaging and allows scientists to measure the brain function. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) is the most commonly used molecular imaging technique for evaluating brain metabolism and function. Fluorine-18-FDG-PET imaging has an important role in managing patients with MCI to predict the likelihood of transitioning to AD dementia based on metabolic alterations in brain [14], and outpreforms structural MRI [15]. The goal of current study was to evaluate the age-related changes in regional brain ^{18}F-FDG uptake in normal elderly population compared to that in normal young population to better delineate age-related alterations in brain ^{18}F-FDG uptake and glucose.

Subjects and Methods

This study was completed as part of the Cardiovascular Molecular Calcification Assessed by ^{18}F-sodium fluoride (NaF) (CAMONA) PET/computed tomography (CT) study. This study was approved by the Danish National Committee on Health Research Ethics, registered at ClinicalTrials.gov (NCT-01724749), and conducted in accordance with the Declaration of Helsinki. The project was a single center prospective observational study comprising two study cohorts and two types of imaging (^{18}F-FDG and ^{18}F-NaF PET/CT imaging).

Study subjects

The study cohorts comprised of 90 healthy normal control subjects and 50 patients referred to the department of Cardiology for chest pain suggesting stable angina pectoris. The subjects were recruited by decade from 21-80 years old. It provided a broad population of normal healthy aging subjects. The current study was performed in 40 healthy control subjects selected among subjects included in the CAMONA study using the following method: A random sample of healthy subjects from the general population was invited to participate. These subjects were recruited from the Blood Bank of Odense University Hospital. Before examination, the participants filled out a questionnaire in regards to medical conditions, current medications, smoking habits and family history of cerebrovascular disease. Medical history was then complemented by a personal interview on the day of examination. Inclusion criteria was age 21-80 years; no history or symptoms of CVD; blood pressure <140/90mmHg, total cholesterol <7.8mmol/L, fasting p-glucose <7.0 mmol/L, no history of malignant neoplasm within previous 5 years, no known immunodeficiency state including treatment with immunosuppressive drugs, no history of alcohol abuse, illicit drug use or significant mental illness. Exclusion criteria were autoimmune disease during the course of the study, any other clinically significant medical condition that in the opinion of the investigator could have impacted the patient's ability to successfully complete the trial. Forty normal healthy subjects were selected from the normal healthy controls recruited in CAMONA study and assigned to one of the two groups based on age (Group A (Age: 22-32 years) and Group B (Age: 56-75 years)).

Methods

All subjects underwent dual time point ^{18}F-FDG PET/CT imaging studies and scanners (GE Discovery 690, VCT, RX, and STE) with comparable spatial resolution. All the subjects had fasted for at least 6 hours prior to the study and their blood glucose, height and body weight were measured. Whole body imaging was performed 60±5 and 180±5 minu-

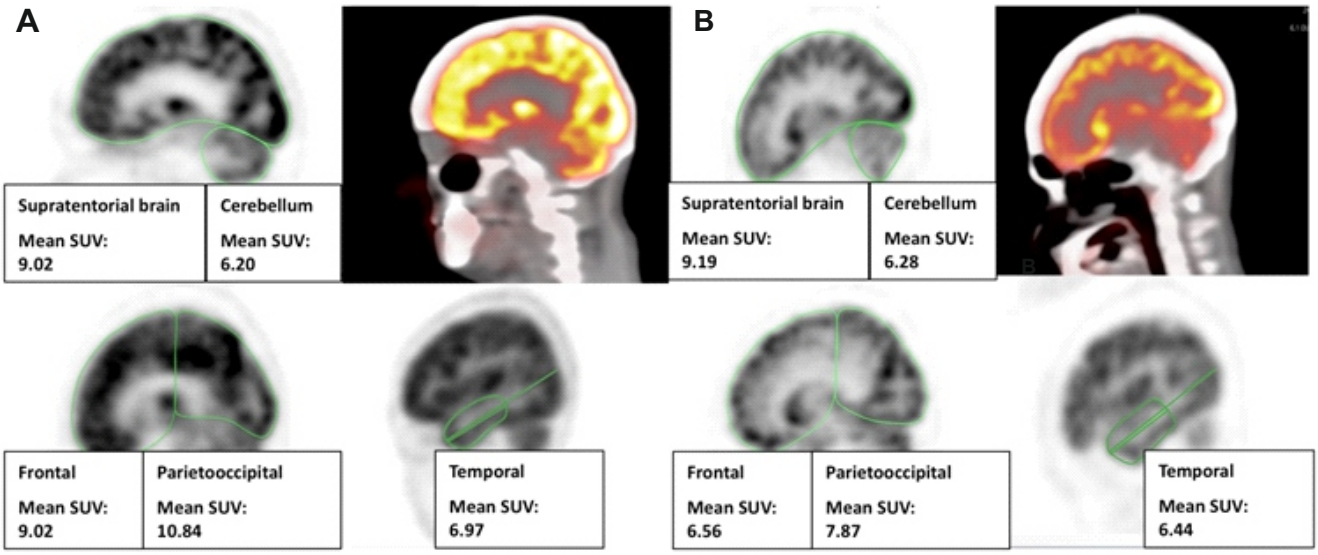

Figure 1. Sample of manual placement of ROI in sagittal plane in young (panel A) and old (panel B) participants by using Osirix software.

tes following administration of 4.0MBq of ^{18}F-FDG per kilogram of body weight. For the current study acquisitions at 180 minutes were used. Positron emission tomography/CT imaging was performed with 40% reduction CT radiation dose and increased timing resolution of 550ps for the PET portion. Computed tomography scans were acquired during inspiratory breath hold phase. A nuclear medicine physician at University of Pennsylvania analyzed whole body PET images using OsiriX software (Pixmeo, Bemex, Switzerland). Supratentorial and cerebellar ^{18}F-FDG uptake was measured by manual placement of region of interest (ROI). Subtle anatomical features such as the preoccipital notch and the parieto-occipital sulcus are not easily visible. Therefore, strict guidelines were followed. Regions of interest were manually placed over the frontal, and temporal lobes as well as the parieto-occipital region using the following method. For placement of ROI over the frontal lobe, the rostral boundary of the superior frontal gyrus was defined as the rostral extent of the superior frontal sulcus, and the caudal boundary was the paracentral sulcus [16]. For the parieto-occipital region, the rostral extent was the central sulcus and the caudal extent was the superior portion of the cerebellum, respectively. The medial and lateral boundaries were the lateral bank of the precentral gyrus and the lateral fissure and/or the medial bank of the superior parietal gyrus, respectively. For the temporal lobe, the posterior boundary was defined as the midpoint between the most anterior tip of the temporal pole and most posterior tip of the occipital pole [17]. Figure 1 shows sample of placement of ROIs in different regions of the brain in both age groups.

The SUVmean across all slices was then calculated for each lobe and region. Mean standardized uptake value (SUVmean) was recorded in all cases. Statistical analysis was performed using SPSS Statistics version 20 (IBM corp, NY, USA). Student t-test and chi-square were used to compare the two groups and statistical significance was defined as P values less than 0.05.

Results

The mean age of the subjects of Group A was 26.1±3.4 (range 22-32 years), and the mean age of subjects of Group B was 61.1±4.4 (range 55-75 years). There were 10 women and 10 men among Group A and 10 women and 10 men among Group B (Chi-square test, P-value=1). All the participants were healthy and had no clinical history of cerebrovascular or cardiovascular diseases, hypertension, or diabetes. Four subjects (two in each group) had family history of cerebrovascular disease. One subject in Group A and four subjects in Group B have had mild hypercholesterolemia. Two subjects of Group A and nine subjects of Group B had a history of smoking with 0.52±0.22 and 8.64± 11.69 pack-years (20 cigarettes/day*years smoked) (P=0.003), respectively. The patient characteristics are shown in Table 1.

The mean SUV of cerebellum was 6.80±1.21 for the young subjects compared to 6.08±0.7 for old subjects (Student t-test, P-value=0.028). The mean SUV of supratentorial brain was 9.14±1.83 for the young subjects compared to 6.92± 0.72 for old subjects (Student's t-test, P-value<0.001) (Figure 2). When comparing the groups' frontal and temporal lobes as well as parieto-occipital region, higher uptake was seen in all three areas among young subjects (Group A) (Figure 3). The ^{18}F-FDG uptake values for all measured regions are shown in Table 2.

Table 1. *Baseline characteristics of the patients. Data is presented as mean±SD.*

	Group A (n=20)	Group B (n=20)	P-value
Age (years)	26.1± 3.4	61.1± 4.47	<0.001*
Sex	10 women 10 men	10 women 10 men	1.0
Smoking history	18 Never 2 quit smoking -	11 Never 8 quit smoking 1 active smoker	0.043*
Pack-years (20 cigarettes/day * years smoked)	0.52± 0.22	8.64± 11.69	0.003*
Alcohol history (positive (%))	18 Active 2 Ever	19 Active 1 Ever	0.54
Alcohol years	10.91± 3.64	35.29± 11.12	<0.001*
Average Systolic Blood Pressure (mm Hg)	120.92± 11.1	138.35± 21.52	0.003*
Total Cholesterol (mmol/L)	4.7±0.96	5.22±0.75	0.09*
HbA1c	31.5± 1.87	35.5± 2.7	<0.001*
History of Hypercholesterolemia (positive (%))	1	4	0.15
Family history of cerebrovascular disease	2	2	1.0

**Statistically significant difference*

We looked at mean SUV of each age group based on gender. Among Group A, mean SUV of supratentorial brain ^{18}F-FDG uptake for female and male subjects were 9.94±1.89 and 8.33±1.44, respectively (Student's t-test, P-value=0.047)

and mean SUV of cerebellum for female and male subjects were 7.32±1.11 and 6.28±1.14, respectively (Student's t-test, P-value=0.054). However, among Group B, mean SUV of supratentorial brain ^{18}F-FDG uptake for female and male subjects were 7.27±0.54 and 6.57±0.72, respectively (Student's t-test, P-value=0.025), and mean SUV of cerebellum for female and male subjects were 6.23±0.69 and 5.93±0.71, respectively (Student's t-test, P-value=0.36). Also among the cerebral lobes, mean SUV of parieto-occipital region for female subjects was higher compared to male subjects with Group A (11.75±2.39 compared to 9.65±1.7, P-value=0.037). Among Group B, mean SUV of frontal and parieto-occipital was higher for female than men (7.38±0.53 vs. 6.68±0.68 for frontal lobe (P-value=0.021) and 7.81±0.68 vs. 7.01±0.71 for parieto-occipital region (P-value=0.019). Table 3 displays the mean SUV of both groups for different sex groups.

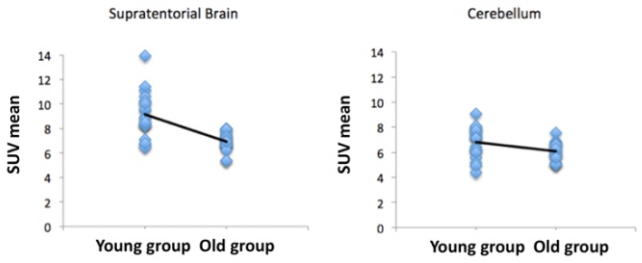

Figure 2. Mean SUV in supratentorial brain was significantly reduced in older participants compared to the young group; however, the reduction in ^{18}F-FDG uptake was much less prominent in the cerebellum.

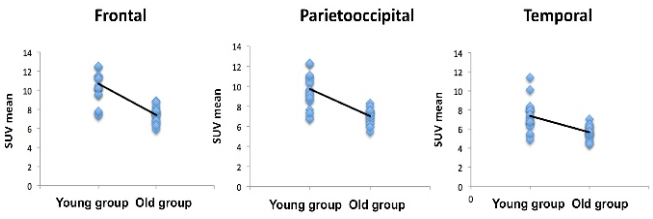

Figure 3. The frontal, parieto-occipital and temporal lobes of the brain showed reduction of ^{18}F-FDG uptake.

Table 2. *Baseline characteristics of the patients. Data is presented as mean±SD.*

	Young group	Old group	P-value
Supratentorial brain	9.14±1.83	6.92±0.72	<0.001*
Frontal lobe	9.72±1.97	7.03 ±0.69	<0.001*
Parieto-occipital	10.7±2.28	7.41±0.79	<0.001*
Temporal lobe	7.37±1.52	5.65±0.68	<0.001*
Cerebellum	6.8±1.12	6.08±0.7	0.028*

**Statistically significant difference*

Discussion

The aim of this study was to explore the age-related differences in brain ^{18}F-FDG uptake. We observed ^{18}F-FDG uptake decreases in both supratentorial and infratentorial regions with normal aging, with supratentorial brain showing the greater reduction, while metabolic activity of the cerebellum remained about the same. These findings are consistent with previous studies showing that cerebral metabolic activity decreases gradually with normal aging and primarily affects frontal lobes bilaterally while sparing the cerebellum of older healthy individuals [18, 19]. In a prior study, Nugent et al. (2014) demonstrated localized glucose hypometabolism in superior frontal cortex, caudal middle frontal cortex and caudate of elderly subjects with normal cognition. They also suggested that decreased regional brain glucose metabolism may not be a definite result of neurodegenerative disease but it could be assumed as a risk factor for subsequent age-dependent cognitive disorder and AD [20].

Aging is the most important risk factor for developing neurodegenerative diseases such as AD. Decline in total brain weight, cortical thinning and gyral atrophy are expected age-related anatomical alterations of the brain. Many studies have showed cerebral volume decreases with age. Jernigan TL et al. (2001) has estimated a volume loss of about 14% in cerebral cortex between the ages of 30 to 90, which is particularly pronounced in the frontal cortex [21]. They showed that the rate of decline in frontal cortex volume is faster than the decline in other regions. Description of anatomical changes provides important information to visualize regional and global atrophy and has implications for diagnosis of cognitive disorders [22]. However, several anatomical changes such as regional cortical atrophy and cortical thinning can occur in brains of normal old adults, who do not show any cognitive deficit [20].

Changes related to aging are not limited to anatomical changes of the brain; functional changes occur at the same time and may even precede anatomical changes. Fluorine-18-FDG PET is an important tool to demonstrate the functional changes of the brain with normal aging and diagnosis of the neurodegenerative diseases. Glucose is the main energy source for the brain. By normal aging, glucose metabolism of the brain decreases and this could be related to early development of neurodegenerative processes. Determining the degree of brain glucose hypometabolism in cognitively normal old adults can be a predictive factor for age-related cognitive disorders, which can be evaluated using ^{18}F-FDG PET. Like anatomical changes, which can occur in brain of cognitively normal old adults, regional brain glucose hypometabolism could be present in cognitively normal adults [20]. Early detection of cognitive impairment increases the chances for planning of treatment and prevents progression to more severe conditions such as neurodegenerative diseases.

In our study, different lobes showed similar rate of glucose metabolism reduction in older subjects. In a study conduc-

Table 3. Comparison of mean SUV values in different brain regions for different sex groups (Data is presented as mean±SD).

	Young group			Old group		
	Female	Male	P-value	Female	Male	P-value
Supratentorial	9.94±1.89	8.33±1.44	0.047*	7.27±0.54	6.57±0.72	0.025*
Frontal	10.45±2.01	8.99±1.73	0.1	7.38±0.53	6.68±0.68	0.021*
Parieto-occipital	11.75±2.39	9.65±1.7	0.037*	7.81±0.68	7.01±0.71	0.019*
Temporal	7.89±1.53	6.85±1.41	0.13	5.83±0.6	5.47±0.73	0.25
Cerebellum	7.32±1.11	6.28±1.14	0.054	6.23±0.69	5.93± 0.71	0.36

**Statistically significant difference*

ted by Tumeh et al. (2007), the investigators reported 42% reduction of frontal lobe metabolism, which was higher than our findings but this may be due to differences between the study populations [23]. In line with other studies, we observed age-dependent differences in alterations of glucose metabolism during normal aging of the brain. Similary, we observed that there is difference in ^{18}F-FDG uptake among men and women, where the effects of aging on ^{18}F-FDG uptake is more pronounced in men, which is consistent with previous studies. [24-26]. Yoschizawa et al. (2014) showed overall metabolic activity of the brain in females was higher compared to males and more accentuated in the medial frontal lobe, inferior parietal lobe and posterior cingulate gyrus [24]. Similarly, Yuxaio Hu et al. (2013) studied 400 healthy (mean age 40.9±3.9 years) subjects and reported females have higher brain metabolism in posterior part of the brain including posterior parietal lobes, bilateral occipital lobes, bilateral thalami and hypothalami compared to males [27].

Our study has some limitations: first, we had small sample sizes in each study group and larger sample sizes are needed for further studies. Second, although the subjects from both groups (young and old) had no clinical history of heart disease, hypertension, diabetes mellitus or hypercholesterolemia, there are some factors, such as smoking, years of alcohol consumption, and average systolic blood pressure that could affect the health of the elderly group more than the young group.

In conclusion, these findings confirm a significant age dependent reduction of supratentorial ^{18}F-FDG uptake among healthy individuals. In addition, the overall supratentorial ^{18}F-FDG uptake was significantly higher among female healthy volunteers in both young and old groups.

The authors declare that they have no conflicts of interest

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