

## Variation in FDG uptakes in different regions in normal human brain as a function of the time (30 and 60 minutes) after injection of FDG

Kazunari ISHII,\* Setsu SAKAMOTO,\* Kayo HOSAKA,\*\* Tetsuya MORI\* and Masahiro SASAKI\*

\*Division of Imaging Research, Hyogo Institute for Aging Brain and Cognitive Disorders

\*\*Department of Radiology, Kobe University School of Medicine

**Objective:** The authors' goal was to determine whether FDG uptakes in various regions of the brain are different for early and late scanning time in positron emission tomography (PET). **Method:** F-18 fluorodeoxyglucose (FDG) PET was performed on 15 healthy normal subjects to obtain early and late acquisition glucose metabolic images (30 and 60 min after FDG injection), respectively. The two sets of images were compared in a voxel-by-voxel analysis. **Results:** In the bilateral posterior cingulate gyrus, parietal and frontal association cortices, and subcallosal cortices, the FDG uptakes were larger on the late scan image than on the early scan image, and the FDG uptakes were larger in the cerebellar hemisphere, vermis and frontal basis on the early scan image than on the late scan image. **Conclusions:** These results suggest that there are different regional FDG uptakes depending on the scanning time after FDG injection and we must be careful in replacing conventional FDG PET scanning with early scanning in FDG PET study.

**Key words:** positron emission tomography (PET), F-18 fluorodeoxyglucose (FDG), normal human brain

### INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) with 2-[F-18]fluoro-2-deoxy-D-glucose (FDG) has been widely used to measure cerebral glucose metabolism in the human brain. In most FDG PET studies, scanning is started 45 to 60 minutes after FDG injection.

Kumar et al. reported that there are no significant differences between 30 and 45 min scans after intravenous injection of FDG<sup>1</sup> in the analysis of region of interest (ROI) studies, although their study did not cover the whole brain.

The present study was started to determine whether there are any regional differences between FDG uptake in early and late scans in the normal human brain in voxel-by-voxel analysis with statistical parametric mapping (SPM). If there is no difference in regional uptake of FDG

in the human brain, beginning data collection earlier in PET studies may be an advantage because some subjects, such as demented patients, are unable to stay in the scanner for prolonged periods.

### METHODS

#### *Subjects*

We studied 15 healthy normal subjects (4 men and 11 women), who volunteered for this study. They showed no clinical evidence of cognitive deficits or neurological disease and were not taking any acute or chronic medications at the time of the scan. They had no abnormal findings on magnetic resonance (MR) images. All the subjects were right handed. Average age  $\pm$  SD was 62.5  $\pm$  6.9 years (range; 55–77 years). This study was approved by the internal ethics committee of our institute. Written informed consent was obtained from each subject.

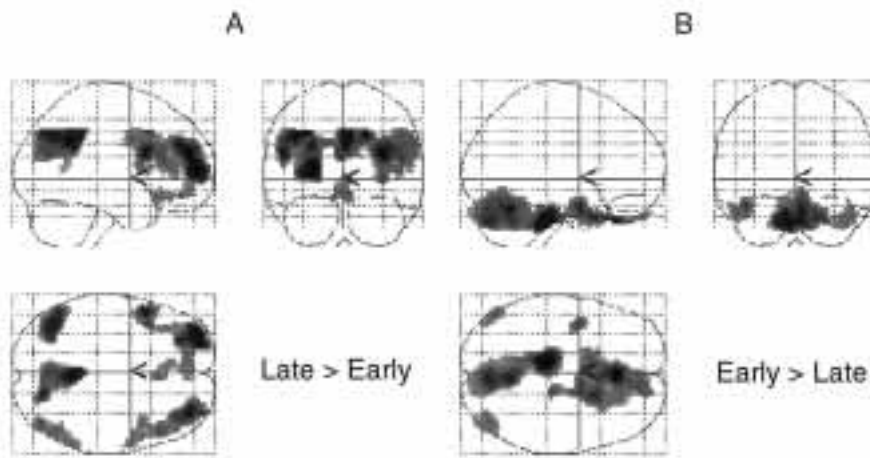
#### *PET Procedure*

Before the PET scans, MR images were obtained for all the subjects for anatomical reference, for PET positioning and to confirm that they had no abnormal conditions. MR

Received January 24, 2002, revision accepted April 1, 2002.

For reprint contact: Kazunari Ishii, M.D., Department of Radiology, Hyogo Brain and Heart Center, 520 Saisho-Ko, Himeji, Hyogo 670-0981, JAPAN.

E-mail: ishii@hiabcd.go.jp



**Fig. 1** Comparison of regional cerebral metabolic rate for glucose (CMR<sub>glc</sub>) reductions shown by statistical parametric mappings (SPM) in normal subjects obtained with early (30 min) and late (60 min) uptake scans. A: Regional FDG uptakes of the late scan are relatively larger than those of the early scan in the bilateral parietal and frontal association cortices, and posterior cingulate gyrus. B: In the bilateral lateral upper part of the cerebellar hemisphere, vermis and the frontal basis, regional FDG uptakes of the early scan were larger than those of the late scan.

and PET were performed as described previously.<sup>2,3</sup> Immediately before the PET examination, sagittal gradient-echo images were obtained to determine the coordinates for positioning of the head on the PET table. PET was performed with a PET scanner Headtome IV (Shimadzu Corp., Kyoto, Japan), which had four rings and yielded a transverse resolution of 4.5 mm full-width-half-maximum (FWHM).<sup>4</sup> The slice thickness was 11 mm and the slice interval was 13 mm. The gantry and scanner table were adjusted according to the coordinates determined by MR imaging so that scans were taken parallel to the AC-PC plane from 32.5 mm below to 52.0 mm above the AC-PC plane. The scans were taken parallel to the anterior commissure-posterior commissure (AC-PC) plane by using the MR markings. A transmission scan was performed with a <sup>68</sup>Ga/<sup>68</sup>Ge pin source for absorption correction after each subject was positioned. PET studies were performed under resting conditions with the subject's eyes closed and ears unplugged. All subjects had fasted for at least 4 hours before PET scanning. A dynamic sequence was performed for 48 min after administration of 185–346 MBq of FDG. The scan protocol was scheduled to take 2 min × 16 images and 4 min × 4 images. Static scanning started at 60 min after the injection and emission data were collected for 12 min.

#### Data Analysis

The data sets were directly transmitted to a workstation (Indigo<sup>2</sup> High Impact, Silicon Graphics, Mountain View, CA, USA) from the PET units, and converted to an Analyze format.

For the early scan (30 min) image, three consecutive dynamic images 32 min after injection (from 32 min to 44 min) were summed, and for the late scan image the static

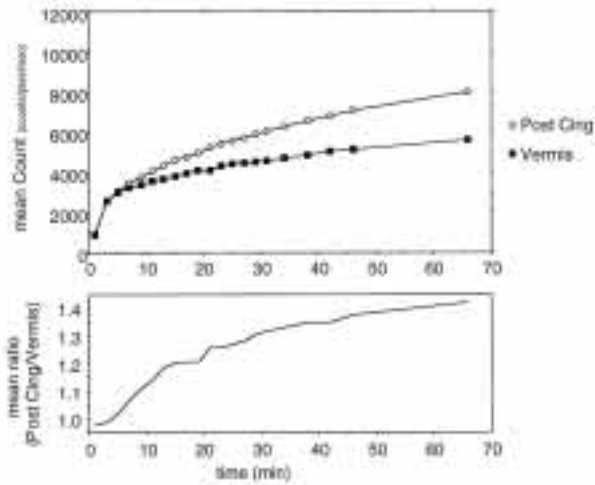
image was used. To evaluate the regional differences between the early and late scans, statistical processing was performed with statistical parametric mapping (SPM) 96 software (Wellcome Department of Cognitive Neurology, London, United Kingdom). Calculations and image matrix manipulations were performed in MATLAB (Mathworks Inc., Natick, MA, USA). All the individual scans were transformed into a standard stereotactic anatomical space. All images were smoothed with a 16 mm isotropic Gaussian kernel to increase the signal-to-noise ratio and to compensate for the differences between individuals in gyral anatomy. Individual FDG images were adjusted by using proportional scaling to compare the effects of the early and late scans. Significance was accepted if the voxels survived an uncorrected threshold of  $p < 0.001$ .

We set regions of interest (ROI; 18 mm diameter) on the areas in which the two scan images appeared to have significantly different FDG uptakes.

## RESULTS

In the bilateral posterior cingulate gyrus, parietal and frontal association cortices, and subcallosal cortices, the FDG uptakes were larger on the late scan image than on the early scan image ( $p < 0.001$ , Fig. 1a), and the FDG uptakes were larger in the frontal basis and cerebellar hemisphere and vermis on the early scan image than on the late scan image ( $p < 0.001$ , Fig. 1b).

According to the analysis with SPM96, we placed the ROIs on the posterior cingulate gyrus and the cerebellum. As shown in Figure 2, the difference in FDG uptakes increased with time and the uptake ratio (posterior cingulate/cerebellum) also increased with time.



**Fig. 2** Upper: Time activity curves of mean count in the posterior cingulate (Post Cing) and vermis (Vermis). Lower: The line shows the mean ratio of posterior cingulate count to vermis count. The ratio increases with time.

## DISCUSSION

Our study showed that FDG uptake is not consistent and there are regional uptake differences between early and late scans after intravenous injection of FDG. This means that there is an intrasubject regional variation in cerebral glucose metabolism. Kumar et al. previously reported that under stable experimental conditions, potential errors in rate constants, which are functions of time, do not significantly influence estimations of the cerebral metabolic rate for glucose (CMR<sub>glc</sub>), so that FDG PET scans can be reliably performed 30 min after intravenous injection of FDG.<sup>1</sup> Nevertheless, this study was analyzed by only the ROI method. Setting ROIs in particular regions on particular slices overlooks the remaining brain regions, and so the values of such regions are not included in the statistics. On the contrary, our present study used a voxel-by-voxel analysis, which covered all of the regions and made it possible to demonstrate regional differences between the two scans. The cause of the regional glucose difference between the two sets of scans remains unknown. The difference may be due to a regional difference in any regional rate constants such as K<sub>1</sub>, which is an indication of FDG transportation rate from plasma to tissue, and k<sub>3</sub>, which is an indication of the phosphorylation of glucose. And k<sub>4</sub> cannot be assumed to be zero after a long period of injection time.<sup>5</sup> But previous studies, which were based on an ROI analysis rather than a voxel-by-voxel analysis, did not demonstrate significant regional differences in rate constants in such regions in normal human brains<sup>6,7</sup> but showed a tendency for K<sub>1</sub> to be higher and k<sub>3</sub> lower in the cerebellum than in the

cerebrum. We suppose this slight difference caused the regional FDG uptake difference shown in Figure 2. Soon after injection, a precursor pool may influence the FDG uptake as in the cerebellum. Further analyses such as parametric images and CMR<sub>glc</sub> images obtained with arterial input functions should be done in future.

An interesting finding of our study is that the regions where uptake is higher in the late scan almost matches the regions where glucose metabolism is affected in patients with Alzheimer's disease.<sup>8,9</sup> Because in Alzheimer's disease k<sub>3</sub> is the parameter that is most affected in the parietotemporal region, our results suggest that the parietal and frontal association cortices and posterior cingulate gyrus are not so resistant to degeneration due to their different FDG uptakes. In future studies, we intend to investigate the regional difference between the early and late FDG uptakes in patients with Alzheimer's disease in order to determine whether these regions also have regional differences.

## REFERENCES

1. Kumar A, Braun A, Schapiro M, Grady C, Carson R, Herscovitch P. Cerebral glucose metabolic rates after 30 and 45 minute acquisitions: a comparative study. *J Nucl Med* 1992; 33: 2103–2105.
2. Ishii K, Sasaki M, Kitagaki H, Sakamoto S, Yamaji S, Maeda K. Regional difference of cerebral blood flow and oxidative metabolism in human cortex. *J Nucl Med* 1996; 37: 1086–1088.
3. Ishii K, Sasaki M, Kitagaki H, Yamaji S, Sakamoto S, Mori E. Reduction of cerebellar glucose metabolism in advanced Alzheimer's disease. *J Nucl Med* 1997; 38: 925–928.
4. Iida H, Miura S, Kanno I, Murakami M, Takahashi K, Uemura K, et al. Design of evaluation of Headtome IV: a whole body positron emission tomograph. *IEEE Trans Nucl Sci* 1989; NS-37: 1006–1010.
5. Reivich M, Alavi A, Wolf A, Fowler J, Russell J, Arnett C, et al. Glucose metabolic rate kinetic model parameter determination in humans: The lumped constants and rate constants for [<sup>18</sup>F] fluorodeoxyglucose and [<sup>11</sup>C] deoxyglucose. *J Cereb Blood Flow Metab* 1985; 5: 179–192.
6. Sasaki H, Kanno I, Murakami M, Shishido F, Uemura K. Tomographic mapping of kinetic rate constants in the fluorodeoxyglucose model using dynamic positron emission tomography. *J Cereb Blood Flow Metab* 1986; 6: 447–454.
7. Sakamoto S, Ishii K. Low cerebral glucose extraction rates in the human medial temporal cortex and cerebellum. *J Neurol Sci* 2000; 172: 41–48.
8. Fukuyama H, Kameyama M, Harada K, Nishizawa S, Senda M, Mukai T, et al. Glucose metabolism and rate constants in Alzheimer's disease examined with dynamic positron emission tomography scan. *Acta Neurol Scand* 1989; 80: 307–313.
9. Minoshima S, Foster NL, Kuhl DE. Posterior cingulate cortex in Alzheimer's disease. *Lancet* 1994; 344: 895.