Correlation of FDG Accumulation in the Frontal Cortex with Fractional Anisotropy in the Corpus Callosum

VIII. 1. Correlation of FDG Accumulation in the Frontal Cortex with Fractional Anisotropy in the Corpus Callosum.

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Introduction

The aging process is thought to result in changes in synaptic activity, reflecting both functional and structural cell derangement. Positron emission tomography and ^{18}F-fluoro-D-deoxyglucose (^{18}F-FDG) has been used to measure glucose utilization of the brain, which reflect activity of neural cells. Several PET studies of brain glucose metabolism have reported regional and global declines[1,2], whereas a recent study has suggested the declines might reflect brain atrophy[3].

Neural function of signaling is carried out by interconnection of neurons via neuronal fibers. For examinations of the integrity of the microstructure of cerebral white matter, diffusion-tensor imaging (DTI) is recently becoming an established technique that provides information on tissue microstructure and architecture for each voxel[4-6]. Among several quantitative measures provided by DTI, fractional anisotropy (FA)[7] is an index of the orientational coherence of water diffusion, and higher in regularly organized tissues, such as the corpus callosum and pyramidal tract, whereas lower in tissues where fiber orientations are more inhomogeneous such as crossing fibers and degenerated fibers, and much lower in more isotropic regions such as in gray matter and in cerebrospinal fluid (CSF) space[8-12]. Several studies focusing on normal aging have reported significant reduction in FA of the whole brain[13], of the corpus callosum and the centrum semiovale[14], as well as of the deep white matter regions[8,10]. Some studies have also demonstrated an anterior-posterior gradient in the effect of normal aging in the white matter and the corpus callosum[8,10,15]. The decline of FA of the white matter with aging has been considered to reflect loss of nerve fibers and degeneration of myelin[16].

In the present study, we aimed to examine whether degradation of microstructure of

fiber tracts was associated with change in the glucose metabolism in the brain evaluated by ^{18}F-FDG-PET in the normal elderly subjects. For the aim of this study, we measured FA of the genu and splenium of the corpus callosum and deep white matter of the frontal and occipitoparietal lobe bilaterally to examine association with microstructure of the fiber tract with regional ^{18}F-FDG accumulation in the brain. We also examined whether there was correlation between FA with gray matter (GM) atrophy measured by using voxel based morphometry (VBM)[17,18] that may cause apparent correlations between FA with ^{18}F-FDG accumulation by partial volume effects.

Methods

Subjects

Nineteen healthy elder volunteers (11 males, 8 females, mean age 73.3±2.5 yr, range 70-78 yr) participated. They were recruited from participants in a research program on brain aging in city dwellers conducted by the Tohoku University. Only those who did not have a history of a major medical, neurological, or psychiatric disease, and had normal T1- and T2- weighted MR brain images, or minor hyperintensities on a T2-weighted image in deep white matter or periventricular white matter, were recruited for the present study. Written informed consent was obtained from all the subjects after a proper explanation of the study being conducted, according to guidelines approved by Tohoku University and the Code of Ethics of the World Medical Association (Declaration of Helsinki).

PET

All subjects fasted for at least 5 hours before injection of ^{18}F-FDG of approximately 214 MBq. The blood glucose level was measured before an injection, which were 99±13 mg/dl. PET scans were obtained using a SET2400W scanner (Shimadzu Inc., Kyoto, Japan), which acquired 63 planes simultaneously over a 200-mm axial field of view (FOV) with a spatial resolution of 4.5 mm at full width at half maximum (FWHM)[19]. An emission scan was obtained for 10 min, beginning 45 min after the injection. Subjects were instructed to stay quietly on a sofa with their eyes closed in a dimly lit room from the injection to the scan. A transmission scan was obtained for 7-10 min with ^{68}Ge/^{68}Ga rod source for attenuation correction after the tracer injection. PET images were reconstructed by filtered back projection using Butterworth-ramp filter (order 2, cutoff frequency 8 mm) with measured attenuation, dead time, and decay correction factors.

MR

All MR imaging studies were performed using a Symphony 1.5-Tesla system (Siemens, Erlangen, Germany). A three-dimensional volumetric T1-weighted image (T1WI) was obtained as a gapless series of thin transverse sections using a MPRAGE sequence (TE/TR, 5.5/2180 ms; flip angle, 30°; 25-cm FOV; acquisition matrix, 256×256; slice thickness, 1.5 mm). DTI was acquired using a single-shot diffusion-weighted spin-echo echo planar imaging (TE/TR, 115/5600; NEX , 4; acquisition matrix, 128×128; 25 cm FOV, and 30 5.0 mm thick contiguous axial slices with 0.5 mm interslice gap). The diffusion tensor was acquired for each slice with six sets involving diffusion gradients placed along non-collinear directions (b = 1000 seconds/mm^2): (x,y,z) = [(1,1,0), (0,1,1), (1,0,1), (-1,1,0), (0,-1,1), (1,0,-1)], and an individual set without diffusion weighting (b = 0 seconds/mm^2; b0 image)[20]. DTIs were processed offline using a Dr. View/LINUX software (Asahi Kasei Information Systems Co., Ltd., Tokyo, Japan) to create a FA image[7].

Image processing

Image processing for PET image and T1WI were performed using SPM2 software (http://www.fil.ion.ucl.ac.uk/spm/). Each PET image was co-registered to a corresponding T1WI image. Linear and non-linear parameters for anatomical normalization to the ICBM 152 template T1WI (Montreal Neurological Institute) were estimated for each T1WI, and applied to anatomical normalization of both PET image and T1WI[21]. A T1WI was then segmented into an image of GM, white matter and CSF. PET images were smoothed using a Gaussian kernel of 16mm full-width at half maximum (FWHM) to compensate individual anatomical differences. GM images were smoothed using a Gaussian kernel of 12mm for further VBM analysis.

ROI measurement of FA.

For each subject, six regions of interest (ROIs) were drawn on each b0 image using 3D ROI function of the MRIcro software (v. 1.38)[22]. ROIs were placed on the splenium (SCC) and genu (GCC) of the corpus callosum and the deep white matter in the frontal (F-DWM) and occipitoparietal (OP-DWM) lobe bilaterally (Fig. 1) using the b0 image, and overlaid on the FA image.

Analysis

Counts of PET images were globally normalized using proportional scaling.

Statistical analysis was performed using "single subject and covariate only" model of SPM2, with FA values for each ROI as a covariate. Statistical threshold was set at $P < 0.05$ (false discovery rate corrected for multiple comparisons)[23].

We also performed VBM of GM[17,18] to examine if there was correlation of GM concentration with FA that would be associated with correlation of FDG accumulation with FA using the same statistical model mentioned above.

Results

FA of each ROI was 0.64±0.07 for the GCC, 0.73±0.07 for the SCC, 0.24±0.03 and 0.27±0.03 for the right and left F-DWM, 0.36±0.05 and 0.33±0.06 for the right and left OP-DWM, respectively. We found statistically significant positive correlation with FA in the GCC and regional FDG accumulation in the posterolateral frontal cortex bilaterally, and the anterior part of the left superior frontal gyrus (SFG) (Fig. 2, Table 1). We found no statistically significant correlation with FA in other ROIs. We did not find statistically significant correlation of the GM concentration with FA.

Discussion

In the present study, we measured FA of white matter fiber in the corpus callosum and DWM in the frontal and occipitoparietal lobe, and compared with FDG accumulation in the brain. We found that the FDG accumulation in the posterior lateral prefrontal cortex bilaterally and the anterior prefrontal cortex in the left hemisphere was positively correlated with FA in the GCC, i.e., the regional FDG accumulation was decreased in subjects who has lower FA of the GCC. Several studies have shown that apparent regional decrease in brain FDG uptake or cerebral blood flow could be resulted from partial volume averaging due to the brain atrophy[3,26]. The decreases in the FDG accumulation observed in the present study, however, was not resulted from partial volume effects, because we found no statistically significant GM atrophy which was correlated with FA. The GCC consist of fibers that connecting the lateral and medial surfaces of the frontal lobes[27]. The deterioration in fibers of the GCC would result to compromise in neural signaling between the frontal cortical regions of the each hemisphere connected via the GCC, and to decrease in neural activities in those regions. Among the cortical regions in which we detected decreases in FDG accumulation, the anterior SFG might send fibers to the GCC. The homotopic regions of the posterior prefrontal cortex where we found statistically significant correlation, however, have been considered to send fibers to the body of the corpus

callosum, not to the GCC[27,28]. The present findings could reflect indirect functional connections between the posterior and anterior prefrontal cortex, which sends fibers to the GCC. In the present study, subjects stayed in a resting state with their eyes closed without any control of subject's mental activity. Functional relationships of frontal cortices and mental activity of the subjects were, therefore, difficult to make straightforward interpretation. In conclusion, the present study demonstrated that deterioration in microstructure of the white matter fibers are associated with metabolic changes in the cerebral cortex without significant GM atrophy in the healthy elderly subjects.

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Table 1. Regions where the peak of t values were observed.

Region	x	y	z	t
Lt. inferior frontal gyrus	-52	10	36	7.8
Lt. superior frontal gyrus	-28	52	32	5.9
Rt. middle frontal gyrus	48	4	38	6.3

(x, y, z): coordinates of standard space (Montreal Neurological Institute).

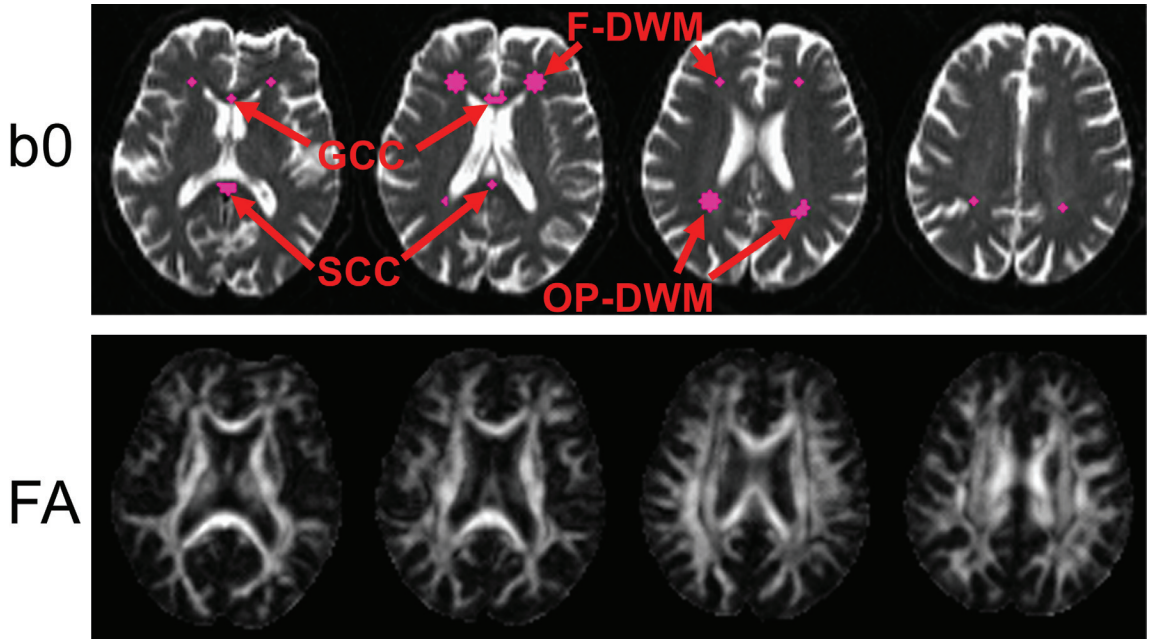

Figure 1. Regions of interest (ROIs) : placed for each subject's b0 image on the genu (GCC) and splenium (SCC) of the corpus callosum, deep white matter of the frontal (F-DWM) and occipitoparietal (OP-DWM) lobe. The ROIs were overlaid on the FA image for each subject.

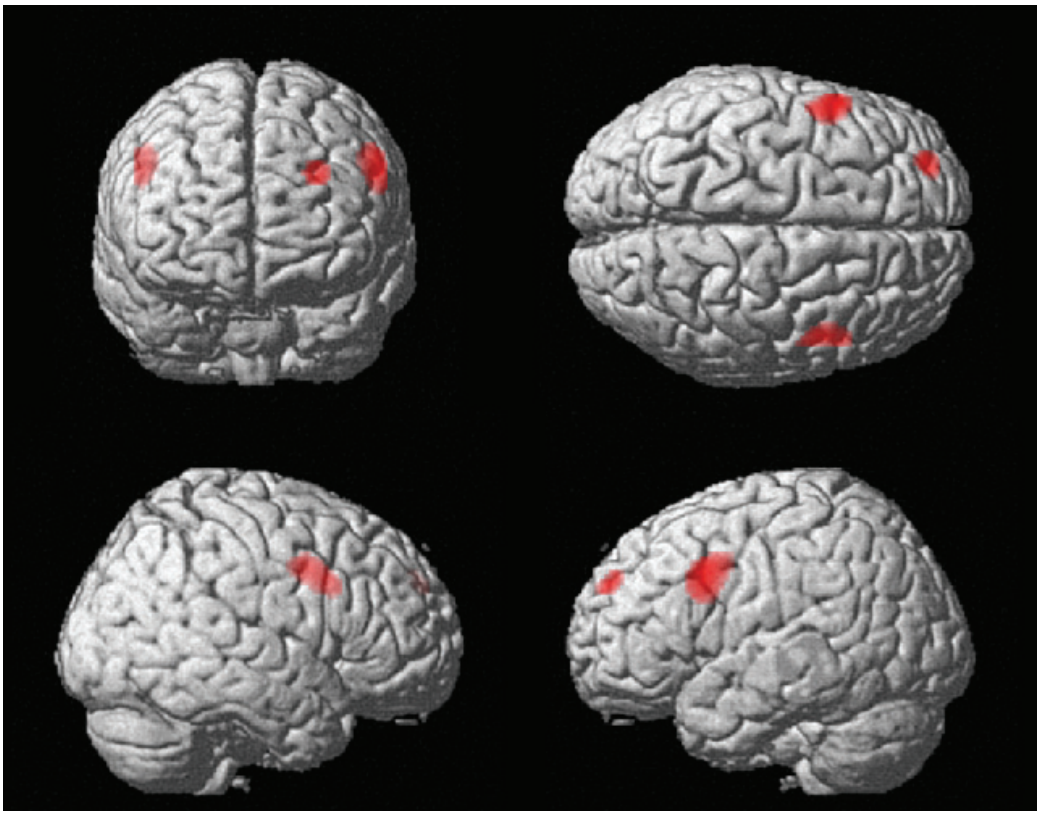

Figure 2. ^{18}F-FDG accumulation in the lateral prefrontal cortex showed statistically significant positive correlation with FA in the GCC ($P < 0.05$, corrected for multiple comparison).