Age-Related Microstructural Changes in Subcortical White Matter During Postadolescent Periods in Men Revealed by Diffusion-Weighted MR Imaging

Takashi Yoshiura,^{1*} Tomoyuki Noguchi,¹ Akio Hiwatashi,¹ Osamu Togao,¹ Koji Yamashita,¹ Tomohiro Nakao,² Eiki Nagao,¹ Seiji Kumazawa,³ Hidetaka Arimura,³ and Hiroshi Honda¹

¹Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka 812-8582, Japan

²Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka 812-8582, Japan

³Department of Health Sciences, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka 812-8582, Japan

Abstract: Continuous maturation of cerebral white matter (WM) in the postadolescent period is not fully understood. To elucidate the time course and location of possible postadolescent maturational changes in cerebral WM, we studied 60 healthy male subjects who were in their second to seventh decade using diffusion-weighted imaging. Mean diffusivity (MD) in subcortical WM was measured in 78 cortical regions in each subject's brain using an automated method. Regression analysis was used to model the age-related change in MD by either a linear or a quadratic function in each region. Age-related changes in subcortical MD were best modeled by either a linear function or a quadratic function in 27 regions including language-related regions, visual or multimodal areas in the bilateral occipital and temporal lobes, limbic areas including the bilateral parahippocampal gyri, and the bilateral postcentral and left precentral gyri. In these regions, the MD rapidly decreased until middle age and thereafter reached a plateau. Our results revealed microstructural changes in local subcortical WM and suggests a continuing maturational process in postadolescent periods. *Hum Brain Mapp* 30:3142–3150, 2009. © 2009 Wiley-Liss, Inc.

Key words: brain; maturation; white matter; magnetic resonance imaging; diffusion-weighted imaging

INTRODUCTION

Contract grant sponsor: Japan Society for the Promotion of Science; Contract grant numbers: 1859351.

*Correspondence to: Takashi Yoshiura, Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. E-mail: tyoshiu@med.kyushu-u.ac.jp

Received for publication 1 July 2008; Revised 14 December 2008; Accepted 17 December 2008

DOI: 10.1002/hbm.20738

Published online 13 February 2009 in Wiley InterScience (www.interscience.wiley.com).

Numerous imaging studies have been reported regarding age-related structural changes in the human brain. In these previous studies, magnetic resonance (MR) imaging has been most commonly used because of its noninvasiveness and multi-parametric capability. MR imaging allows for gross morphological analysis based on high-resolution T1-weighted (T1W) images, evaluation of myelination based on measurement of T1 and T2 relaxation times, magnetization transfer (MT) measurement, and more recently, evaluation of microstructural changes using diffusion-weighted (DW)

imaging and diffusion-tensor (DT) imaging [Basser and Pierpaoli, 1996; Pierpaoli et al., 1996]. Most previous research has focused on maturational changes in the early period of life. From the neonatal to the childhood period, rapid development of white matter (WM) myelination has been consistently observed using T1, T2, DWI, and DTI methods [Barkovich et al., 1988; Holland et al., 1986; Mukherjee et al., 2002; Provenzale et al., 2007]. More recently, several imaging reports have suggested that these maturational changes continue into adolescence [Barnea-Goraly et al., 2005; Giedd et al., 1999; Paus et al., 1999; Schmithorst et al., 2002], and even into early adulthood [Gogtay et al., 2004]. Other investigational efforts have focused on understanding the degenerative process occurring with aging, finding a monotonic loss of cerebral gray matter (GM) volume [Good et al., 2001; Pfefferbaum et al., 1994], and WM microstructural integrity with age [Abe et al., 2002; Pfefferbaum et al., 2000; Rovaris et al., 2003] throughout adulthood. However, the results of recent imaging studies have suggested that the maturational process in the cerebral WM may continue longer than previously thought. For example, gross-morphological studies based on high-resolution T1W imaging have shown that the volume of the cerebral WM continues to grow until middle age [Bartzokis et al., 2001; Ge et al., 2002a]. Moreover, similar temporal patterns of WM maturation have been reported based on T2 relaxometry [Bartzokis et al., 2003] and MT measurement [Ge et al., 2002b]. These new findings suggest that maturation of the cerebral WM may continue well beyond childhood and adolescence, and perhaps into late adulthood. There is also some pathological evidence for progressive myelination in adulthood [Benes et al., 1994; Yakovlev and Lecours, 1967].

In this study, we used DW imaging in order to elucidate possible age-related microstructural changes in the cerebral subcortical WM in the postadolescent periods. DWI is sensitive to random microscopic motion of water molecules in the cerebral tissue. Restriction of the water molecular motion by microscopic biological barriers such as the cell membrane and myelin sheath can be evaluated by this method, providing quantitative metrics of the WM integrity. We focused on the subcortical WM for the following two reasons. First, it is widely believed that in the early periods of life, WM maturation (myelination) spreads from the central to the peripheral portions of the cerebrum. By observing the subcortical WM, we may be able to elucidate the later phase of the WM maturational process. Second, subcortical WM is closely related to the overlying cortex both anatomically and functionally. We therefore expected that we would be able to evaluate WM changes in individual cortical regions and could elucidate the regional difference in the WM maturational processes.

METHODS

Subjects

This study was approved by the Institutional Review Board of our university hospital. Written informed consent

was obtained from each subject or a person with parental authority when the subject was under 20 years of age. Healthy Japanese male subjects were prospectively recruited for this study. Only right-handed individuals were selected according to the 10-item version of Edinburgh Handedness Inventory [Oldfield, 1971]. Individuals whose laterality quotient lay 80 or higher were considered to be right-handed in this study. Individuals with any history of hypertension, diabetes mellitus, cardiovascular diseases, stroke, brain tumor, epilepsy, Parkinsonism, dementia, depression, drug abuse, and head trauma were specifically excluded. Each candidate received the Japanese version of the mini-mental state examination (MMSE) [Folstein et al., 1975] for surveillance of the general cognitive status, and individuals who achieved 27 points or less were excluded. Each candidate also received the Japanese version of the self-rating depression scale (SDS) [Zung, 1965] for screening for depression, and individuals who achieved 40 points or more were excluded. Individuals who exhibited organic lesions such as brain infarctions, hemorrhage or tumors on T2-weighted (T2W) images were excluded. The presence of non-specific hyperintensity in cerebral WM on T2W images was not used as an exclusion criterion since such findings are considered to be physiological unless they are extensive. Sixty healthy male subjects (age range: 12–67 years old, mean = 40.0 years) were finally involved in this study. The age distribution of the subjects was as follows: 10s, 8; 20s, 9; 30s, 12; 40s, 14; 50s, 9; 60s, 8.

MR Imaging

MR images were obtained using a 1.5 T clinical imager (Gyrosan Achieva Nova Dual, Philips Medical Systems, Best, Netherlands) and an 8-channel head array-coil for parallel imaging. DW images, high-resolution T1W images, and T2W images were obtained for each subject. For all types of images, a parallel acquisition technique (sensitivity-encoding or SENSE) was utilized in order to shorten the imaging time. The parallel imaging technique also contributed to a reduction of the echo-planar (EP) image distortion in the DW images [Alexander et al., 2006]. DW images were obtained using a DT pulse sequence based on single-shot spin-echo EP imaging technique. In order to reduce the signal from the cerebrospinal fluid (CSF) and thus minimize the partial volume effect of the CSF in the calculation of the apparent diffusion coefficient, a CSF-nulling inversion pulse was implemented in the DT pulse sequence [Kwong et al., 1991]. The following parameters were used: repetition time (TR)/echo-time (TE)/inversion-time = 5300 ms/68 ms/2100 ms, sense-factor = 2, number of averages = 2, field-of-view (FOV) = 230 mm, matrix size = 128 × 125. The DW images were obtained with a 15-directional diffusion-encoding scheme. The *b* value was set at 700 s/mm² for each direction, and images with no diffusion encoding (*b* value = 0 s/mm²) were obtained as a reference. Fifty contiguous slices (slice thickness/gap =

2.5 mm/0 mm) parallel to the line connecting the anterior and posterior commissures were scanned, covering the whole brain. The acquisition time for the DW images was 6 min. High-resolution T1W images were obtained using a three-dimensional (3D) fast gradient-echo pulse sequence: TR/TE = 25 ms/4.6 ms, flip angle = 30°, sense-factor = 4, FOV = 230 mm, matrix = 240 × 240, slice thickness = 1.0 mm, number of averages = 1, imaging time = 4 min 45 s. The T1W images were obtained in the sagittal planes and were then reconstructed at the same angle as the DW images, yielding 1 mm-thick contiguous transverse images. T2W images were obtained in a transverse plane using a turbo spin-echo pulse sequence (TR/TE = 4650 ms/100 ms, turbo-factor = 15, sense-factor = 1.5, FOV = 230 mm, matrix = 320 × 274, slice thickness/gap = 5 mm/1.5 mm, number of averages = 1, imaging time = 1 min 25 s).

Image Analysis

Diffusivity in the subcortical white matter was mapped onto the overlying cortex using a previously published method [Yoshiura et al., 2005]. Although we desired to evaluate the diffusivity in the white matter in indifferent cortical regions separately, it was difficult to anatomically label the white matter regions since there was no anatomical atlas available for white matter. Instead, we mapped the MD values of subcortical white matter onto the voxels in overlying cortex, for which established anatomical atlases were available. In order to correct image distortion due to the eddy current, DW images obtained at a b value of 700 s/mm² were first co-registered to the diffusion-unweighted image at $b = 0$ s/mm² using a manufacturer-provided software package (PRIDE, Philips Medical Systems, Best, Netherlands). Voxel-wise calculation of DT and subsequent mapping of diffusivity were performed using in-house software running on Matlab ver. 6.5 (The MathWorks Inc., Natick, MA, USA). Using 15 diffusion-weighted images ($b = 700$ s/mm²) and one diffusion-unweighted image ($b = 0$ s/mm²), a 3 × 3 DT was obtained for each voxel, from which three eigenvalues, λ_1 , λ_2 , and λ_3 , were calculated, where λ_1 , λ_2 , and λ_3 denote the largest, intermediate, and the smallest eigenvalues, respectively. The diffusivity of the water molecules in the local brain tissue was measured as mean diffusivity (MD), which is defined as an average of the three eigenvalues $((\lambda_1 + \lambda_2 + \lambda_3)/3)$. Isotropic diffusion-weighted images were also created from the 15 raw diffusion-weighted images obtained at a b value of 700 s/mm².

The high-resolution T1W images were segmented into GM and WM maps using SPM 99 software (The Wellcome Department of Cognitive Neurology, University College London, UK). Each voxel in the GM on the T1W image was assigned with the nearest subcortical WM voxel by searching within 21 × 21 voxels surrounding the GM voxel of interest. This step of the analysis was carried out using an in-house Matlab script.

The MD map was co-registered with the corresponding high-resolution T1W image employing SPM99 using a

method described in the previous report [Yoshiura et al., 2005]. Each voxel in the gray matter in the high-resolution T1W image was then given the MD value of the underlying subcortical WM voxel. Following the original method, a minimum MD value among the 5 × 5 voxels surrounding the nearest subcortical voxel was adopted, instead of adopting the MD value of the nearest subcortical WM voxel itself, in order to reduce the chance of sampling a CSF-contaminated voxel [Yoshiura et al., 2005].

In order to measure subcortical MD within the different cortical region, a free software package (Individual Brain Atlases using Statistical Parametric Mapping Software or IBASPM, Cuban Neuroscience Center) was used. This software divides the gray matter of individual subjects into 116 regions according to a standardized brain atlas. In IBASPM, the high-resolution T1W image of the individual subject is normalized to the Montreal Neurological Institute (MNI) space and the transformation matrix for the normalization is obtained. The T1W image in the native space is segmented into GM, WM, and CSF segments. Each individual GM voxel is anatomically labeled based on a labeled brain in the MNI space, which is called automated anatomical labeling, or AAL [Tzourio-Mazoyer et al., 2002] and the transformation matrix obtained in the previous step. MD values of subcortical voxels mapped onto the cortical voxels were averaged within each cortical region and were reported. In our analysis, 78 cortical regions were selected excluding the cerebellum and deep GMs nuclei (i.e., bilateral caudate nuclei, putamina, globus pallidi, and thalami), bilateral hippocampi, and amygdalae out of the predefined 116 GM regions. The cerebellum and hippocampi were excluded since the spatial resolution of the T1WI was not high enough for accurate gray/white segmentation within the respective structures. The deep GMs were excluded because they have no “cortical” structure. The amygdalae were not included for a similar reason, that it forms a mass of gray matter rather than a cortical shape.

In order to visually evaluate the age-related MD change in subcortical WM, the mean MD in each cortical region was averaged across subjects within each decade of life (from the second to seventh decade), resulting in 6 averaged maps.

In order to quantitatively evaluate the age-related MD change in subcortical WM, a regression analysis was performed for each cortical region. Based on the results of previous imaging reports [Bartzokis et al., 2001, 2003; Ge et al., 2002a,b], we expected an early decrease followed by a late increase in MD, which may correspond to progression in myelination and loss of WM integrity by aging, respectively. Therefore, we attempted fitting by quadratic functions. When the p value for the quadratic term of age (term of age²) in the quadratic regression did not reach <0.05, which means that the quadratic term did not contribute to the fitting, a linear regression was used. A significance level for the regression analysis was set at 0.01 after correction for multiple comparisons (Bonferroni correction for 78 comparisons).

Figure 1.

Maps of mean diffusivity (MD) in subcortical white matter. Each set of maps consists of top (top row), right side (second row), left side (third row), and bottom (bottom row) views, and represents mean MD values within each cortical region across the subjects in each decade of life.

RESULTS

Averaged subcortical MD maps for 6 decades are shown in Figure 1. There was a clear overall decline in subcortical WM MD during the first 3 decades (second, third, and fourth decades), followed by a relative plateau thereafter.

Table I summarizes the results of the regression analysis. Age-related MD change was modeled by either a linear or quadratic function in 27 cortical regions, among which 16 regions were fitted by a linear function with a negative slope while the other 11 were fitted by a quadratic function. A topographical representation of the regression results is shown in Figure 2. These areas spread primarily over the temporal and occipital lobes. In the left hemisphere, the sensorimotor cortex and pars opercularis of the inferior frontal lobe, and supramarginal and angular gyri in the parietal lobe were also involved. As for the right-to-left comparison, age-related MD changes were observed more extensively in the left cerebral hemisphere than in the right hemisphere (8 cortical regions in the right hemisphere versus 19 in the left hemisphere). Figure 3 shows examples of plots of subcortical WM MD against age with regression curves.

DISCUSSION

Interpretation of the Present Results

Age-related changes of WM have been intensely studied using DW and DT imaging methods. Maturation change

in early periods of life has been the primary focus. In the first year after birth, especially during the first few months, cerebral WM shows rapid maturational change, which has been revealed as an age-related decrease in local diffusivity and an increase in diffusion anisotropy [Mukherjee et al., 2002; Provenzale et al., 2007]. After the infantile period, changes in DW and DT images appear to slow down but have been reported to continue during the childhood [Mukherjee et al., 2002]. Moreover, more recent DTI studies have revealed that WM maturational changes continue into adolescence [Barnea-Goraly et al., 2005; Schmithorst et al., 2002]. Age-related WM changes after adulthood have been studied from the perspective of aging. Such studies have typically focused on subjects in the third decade and older, and almost invariably a monotonic increase in WM diffusivity and/or decrease in diffusion anisotropy has been reported with increasing age, thus reflecting degradation of WM microstructures [Abe et al., 2002, 2008; Pfefferbaum et al., 2000; Rovaris et al., 2003]. Until recently, possible WM maturational changes in postadolescent periods have not been specifically investigated using DW/DT imaging methods, and it has not been fully determined until what age the WM maturation continues.

Our results have revealed that MD decreases with increasing age in subcortical WM in many cerebral cortical regions in postadolescent periods. The MD decrease appears to be rapid during the second to fourth decades,

TABLE I. Cortical regions where age-related subcortical MD change was modeled by either a linear or a quadratic function

Region	LN/Q	R^2	Regression coefficients		
			Age ²	Age	Intercept
L Precentral	LN	0.324	–	–0.001	0.759
L Pars opercularis inferior frontal	Q	0.365	2.266E–5	–0.003	0.798
L Opercular Rolandic	LN	0.357	1.789E–5	–0.002	0.808
L Insula	LN	0.306	–	–0.001	0.751
L Parahippocampal	LN	0.432	–	–0.001	0.858
R Parahippocampal	Q	0.307	3.638E–5	–0.004	0.860
L Calcarine	Q	0.312	3.199E–5	–0.003	0.830
L Lingual	Q	0.274	3.127E–5	–0.003	0.826
R Lingual	Q	0.259	2.818E–5	–0.003	0.808
L Superior occipital	LN	0.234	–	–0.001	0.770
L Inferior occipital	Q	0.313	3.372E–5	–0.004	0.802
R Inferior occipital	LN	0.244	–	–0.001	0.748
L Fusiform	LN	0.394	–	–0.001	0.802
R Fusiform	Q	0.292	2.182E–5	–0.003	0.796
L Postcentral	LN	0.313	–	–0.001	0.768
R Postcentral	LN	0.220	–	–0.001	0.772
L Inferior parietal	Q	0.313	2.436E–5	–0.003	0.800
L Supramarginal	Q	0.321	3.031E–5	–0.003	0.814
L Angular	Q	0.319	4.220E–5	–0.004	0.818
L Heschl	LN	0.363	–	–0.001	0.795
L Superior temporal	LN	0.383	–	–0.001	0.777
R Superior temporal	LN	0.256	–	–0.001	0.751
L Superior temporal pole	LN	0.284	–	–0.001	0.808
L Middle temporal	Q	0.362	2.447E–5	–0.003	0.799
R Middle temporal	LN	0.349	–	–0.001	0.766
L Inferior temporal	LN	0.441	–	–0.001	0.777
R Inferior temporal	LN	0.339	–	–0.001	0.756

R, right; L, left; LN, regression by linear function; Q, regression by quadratic function.

and the change slows down thereafter (Figs. 1 and 3). This finding is considered to represent continuous progression of myelination in subcortical WM, which has been predicted by MR imaging studies based on volumetry [Ge et al., 2002a; Bartzokis et al., 2001], T2 relaxometry [Bartzokis et al., 2003] and MT measurements [Ge et al., 2002] as well as pathological studies [Benes et al., 1994; Yakovlev and Lecours, 1967]. Moreover, our study has provided regional information that has not been provided by previous imaging studies.

The cortical regions with significant age-related MD change shown in Table I and Figure 2 can be classified into several functional systems. First, many language-related cortical regions, which are in the left hemisphere, were involved. The pars opercularis of the left inferior frontal gyrus which is within Broca's area was included while their counterpart in the right hemisphere was not. The left superior temporal gyrus which includes Wernicke's area was involved and showed a higher correlation coefficient than the right superior temporal gyrus (Table I). These findings are consistent with a previous report of maturational change in the arcuate fasciculus from the

childhood to adolescence revealed by T1-based [Paus et al., 1999] and DT-based [Giedd et al., 1999] imaging methods. Our results suggest that the maturational process in the core language system including Broca's and Wernicke's areas may continue into adulthood. The left Heschl's gyrus, the left inferior parietal lobule, the left supramarginal gyrus and the left angular gyrus also showed significant age-related WM MD changes. These cortical regions are also known to be involved in language processing. The second system included widespread cortical regions in the bilateral occipital and temporal lobes, which engage in visual and perhaps multimodal information processing (Table I and Fig. 2). These cortical areas were distributed roughly symmetrically although there appears to be some left-sided asymmetry. Barnea-Goraly et al. [2005] have reported an increase in diffusion anisotropy with increasing age in the WM of the ventral visual stream during the childhood and adolescence. Our finding is consistent with theirs, and suggests that WM maturation along the ventral visual pathway may continue into adulthood. Neville and Bavelier [2002] have discussed that the ventral visual pathway undergoes experience-based plasticity that permits learning and adaptation throughout life. Continuous maturational change in the bilateral occipital and temporal lobes revealed in our study may be related to such plasticity. Third functional system consisted of parts of the limbic system including the bilateral parahippocampal gyri. Benes et al. [1994] have histologically investigated the age-dependence of myelination in the superior medullary lamina of the parahippocampal gyrus. They found that the myelinated area progressively increases until the fifth to sixth decade. Our results are in line with their pathological finding. We are aware of very few published imaging studies that have specifically interrogated the maturational change in the limbic brain [Schneider et al., 2007]. The last functional system was the sensorimotor system: age-related subcortical MD reduction was seen in the left precentral and the bilateral postcentral gyri (Table I and Fig. 2). Paus et al. [1999] have reported an age-related increase in WM density in the bilateral corticospinal tracts during childhood and adolescence, as measured by T1W imaging. They speculated that the increase in WM density reflects an increase in diameter or myelination of the axons forming the corticospinal tract.

To the best of our knowledge, there is only a limited amount of published behavioral evidence of functional improvements during adulthood. Schaie [1994] reported based on his longitudinal study that some of the intellectual abilities such as the verbal ability of adults peak at middle age and is well maintained beyond it. In this study, we did not attempt to correlate our imaging results with any behavioral performance. Whether the continuous myelination in subcortical WM within several brain regions suggested in our study is associated with improved performance of the relevant brain functions needs to be clarified in future studies.

Figure 2.

Mapping of cortical regions where age-related subcortical MD change was modeled by either a linear (green areas) or a quadratic function (orange areas).

Technical Considerations

We measured MD in subcortical WM using an automated method instead of manual ROI methods. This method was originally used to evaluate MD abnormalities in subcortical WM in patients with Alzheimer's disease [Yoshiura et al., 2005]. It is fully automated and requires no human intervention, and thus is free from operator bias which is inherent in manual ROI methods. Statistical parametric mapping (SPM) is another automated method available to evaluate age-related changes in WM MD. However, the spatial registration used in SPM does not match the anatomical details among different subjects to the level of individual gyral shape. This imperfection in spatial registration and subsequent smoothing by a Gaussian filter may introduce contamination of subcortical MD with high MD values from CSF. As a result, SPM analysis could reflect not only the MD within the local brain tissue but also relative volumes of the brain tissue and CSF within local voxels. This can result in a serious bias because the fraction of CSF volume linearly increases with age as a consequence of the linear decline of the GM volume fraction with age, which is usually revealed as a widening of cortical sulci in older subjects. In our method, MD values of the subcortical WM were sampled from voxels within the WM segment of each individual subject in native space, and no smoothing process was included. Thus we believe that the effects of CSF contamination are minimized and that our method provides more accurate esti-

mation of age-related MD changes in subcortical WM. On the other hand, a major drawback of our method is the lack of ability to perform a voxel-wise analysis. Instead, we measured mean MD values within each cortical region defined in individual brain according to standard brain atlas by using IBASPM.

We used MD rather than diffusion anisotropy indexes such as fractional anisotropy (FA) to evaluate microstructural changes in subcortical WM. FA has proven useful in evaluating WM integrity under healthy and diseased conditions. Its usefulness is maximized when interrogating high anisotropy regions such as corpus callosum and internal capsule. However, subcortical WM, which is the object of this study, has low diffusion anisotropy, not necessarily because of the low density of neuronal fibers or myelination but because of normal divergence of local fiber orientation due to the subcortical U-fibers that connect neighboring cortical regions [Pierpaoli et al., 1996]. In such regions, FA may not be representative of WM maturity. On the other hand, MD is insensitive to the local fiber orientation and is considered to more linearly correlate with the WM maturity.

Comparison With Previous Studies

Very recently, Schneiderman et al. [2007] compared diffusion anisotropy within several WM tracts between adolescents (14–21 years old) and adults (22–64 years old)

Figure 3.

Plots of MD values against age with regression curves in the left precentral gyrus (a), where the MD change is modeled by a linear function, and in the pars opercularis of the left inferior frontal lobe (b), where the MD change was modeled by a quadratic function.

using the ROI method. They found increased anisotropy in adults within the anterior limb of the internal capsule, superior levels of the frontal superior longitudinal fasciculus, and the inferior portion of the temporal WM, while several other tracts showed decreased diffusion anisotropy in adults. Our results seem to be consistent with their results in that there exists postadolescent maturation of WM, although their results may not be directly comparable with ours since we focused on subcortical WM rather than WM “tracts.” On the other hand, our results appear to contradict those of previously published studies that have repeatedly reported linear increases of WM MD with age during adulthood [Abe et al., 2002, 2008; Pfefferbaum et al., 2000; Rovaris et al., 2003]. We believe the reason for this discrepancy to be as follows. First, only a few studies have used CSF-nulled diffusion-weighted sequences. Use

of such a sequence strongly suppresses the CSF signal and thus minimize the overestimation of WM MD due to CSF contamination. CSF contamination could be a serious problem especially when peripheral WM is studied. Second, in most previous studies, MD has been measured in deep WM and major WM tracts, and only a few studies have focused on subcortical WM. Our results may reflect microstructural changes in subcortical U fibers rather than projection and the long association fibers that have often been investigated. Third, non-linear regression has rarely been used in previous studies. Finally, our criteria for subject inclusion were stricter than those in previous studies. Our subjects were prospectively recruited from healthy volunteers. Moreover, we carefully excluded individuals with any history of brain diseases (see Materials and Methods). We paid particular attention to hypertension, diabetes mellitus, cardiovascular diseases and stroke, since these conditions are relatively common among older individuals and can result in degradation of the WM microstructure [Huang et al., 2006; O’Sullivan et al., 2001]. In a few previous studies, some of these conditions were not included in the subject exclusion criteria. Inclusion of subjects with such conditions would have significantly distorted the results.

Limitations of the Present Study

This study has several limitations. Since it was a cross-sectional study, it is subject to potential subject selection biases. Because we included only Japanese right-handed males, neither race, handedness, or sex can be a confounding factor. In addition, secular changes in subjects’ brain structure might have affected the results, as the ages of our subjects ranged from second to seventh decades. Only male subjects were included in the study. Therefore, our results may not hold true for women.

There is increasing evidence for the experience-dependent plasticity of brain structure. For example, Bengtsson et al. [2005] found using DTI that long-term piano practicing induces structural changes in white matter tracts. Draganski et al. [2006] reported that extensive learning in school can invoke gray matter volume changes in the bilateral parietal lobes and hippocampi. Moreover, Boyke et al. [2008] demonstrated that such an experience-dependent plasticity can occur even in the elderly. In our study, structural changes in brain were analyzed solely according to age, and the possible effect of the experience-dependent plasticity was not carefully considered. We should have been more careful to control the level of intelligence or type of profession of the subjects.

We chose a relatively low b value (700 s/mm²) to maintain a fair signal-to-noise ratio at a thin slice thickness (2.5 mm). This choice might have resulted in a higher sensitivity of our MD measurement to blood perfusion in the local brain tissue. However, it has been reported that cerebral blood flow (CBF) does not decline with age in healthy adult individuals [Meltzer et al., 2000]. Therefore, age-

related change in subcortical WM MD observed in our study cannot be explained by the change in local CBF.

CONCLUSION

We measured MD in the subcortical WM of healthy male subjects, and found an MD decrease with increasing age in the postadolescent period within many cortical regions, including language-related areas in the left hemisphere, visual or multimodal areas in the bilateral occipital and temporal lobes, parts of the limbic system, and the bilateral sensorimotor system, which may reflect continuous myelination. These results suggest that the maturational process in subcortical WM continues in adulthood.

ACKNOWLEDGMENTS

The authors have no competing interests to disclose.

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