Changes of axial and radial diffusivities in cerebral white matter led by normal aging


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Abstract

Purpose. – Purpose of the study is to reveal the changes of directional diffusion in cerebral white matter (WM) by normal aging.

Materials and methods. – Thirty-nine volunteers were recruited to examine the changes in the directional diffusion of cerebral white matter (WM) due to normal aging.

Results. – No significant difference between the older and younger group (P > .05) was detected in the axial diffusivity (λa) of any of the regions of interest (ROI), while radial diffusivity (λr) was significantly higher in the older group (P < .05) except for occipital lobe WM.

Conclusion. – λa and λr may be used as in vivo markers that differentially and specifically reflect the WM changes of normal aging.

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As standards of living improve, life spans increase and societies face new challenges in dealing with aging [1]. Normal aging, that is, disease-free aging [2], causes morphologic and functional changes in all human organs. The brain is no exception. Previous studies [3] have demonstrated that the brain experiences enormous changes with aging, including the atrophy of gray matter and selective loss of white matter (WM). The advent of diffusion tensor imaging (DTI) has enabled in vivo noninvasive detection of the integrity and microstructural changes of cerebral WM caused by normal aging. DTI studies of these effects have shown increased mean diffusion and decreased anisotropy [4–7], with one report demonstrating the selectivity of the decreased anisotropy [8]. Most of these studies examined fractional anisotropy (FA) or the apparent diffusion coefficient (ADC), or both. These indicators

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reflect changes in WM integrity and microstructure only generally and appear incapable of differential sensitivity to specific aspects of those changes due to normal aging. Recent studies have examined whether axial diffusivity \( (\lambda_{||}) \) and radial diffusivity \( (\lambda_{\perp}) \) might serve as markers that are differentially sensitive to specific pathologies, such as dysmyelination, remyelination and axon damage [9—12]. These markers may thus provide further insight into specific mechanisms of normal aging. In this study, we aimed to identify the effects of normal aging on the in vivo directional diffusion of cerebral WM and to discuss its underlying mechanism.

Materials and methods

Subjects

The study took place from January through May 2008. The local institutional review board approved the study procedures, and all subjects provided informed consent. The study included 39 volunteers classified in two groups: younger (age range: 21—39 years; nine men and 11 women; mean age \( \pm \) standard deviation [SD]: 31.70 \( \pm \) 5.51 years) and older (age range: 61—80 years; 10 men and nine women; mean age \( \pm \) SD: 68.05 \( \pm \) 5.76 years). Participants were required to be healthy and feel well, with normal physical examination results and no history of any neurological or psychiatric conditions, head trauma, head operation, drug abuse, or other disorders that might affect central nervous system function. All subjects underwent conventional brain MRI, including axial fluid-attenuated inversion recovery (FLAIR) images, \( T_2 \)-weighted images \( (T_2WI) \) and axial and sagittal \( T_1 \)-weighted images \( (T_1WI) \), and two experienced neuroradiologists blinded to the purpose of this study found these images to be normal.

MRI technique

DTI and conventional brain axial \( T_1WI \), \( T_2WI \), FLAIR and sagittal \( T_1WI \) images were acquired with a Signa 1.5 Tesla scanner (GE Medical Systems, Milwaukee WI, USA) with an 8-channel neurovascular array coil. DTI images were

![Figure 1](image-url)  
Figure 1. Illustration of ROI positioned on b0 images \( (b = 0 \text{s/mm}^2) \) in the genu (a) and splenium (a) of the corpus callosum, white matter of the frontal (a), temporal (b), parietal (c) and occipital (d) lobes and the centrum semiovale (e).
acquired with a single-shot spin-echo echo-planar imaging protocol (TR = 7000 ms, TE = 93.6 ms, FOV = 240 × 240 mm, matrix = 128 × 128, slice thickness = 5 mm, slice gap = 0 mm). Diffusion sensitizing gradient was applied along 25 non-collinear directions with two b values (0 and 1000 s/mm²).

**DTI data processing**

Original DTI data were processed with Functool software in an AW4.1 workstation (GE Medical Systems, Milwaukee, WI, USA) to generate maximum (λ₁), middle (λ₂), and minimum (λ₃) eigenvector maps. Oval regions of interest (ROIs) of 12–30 pixels each (10.50–26.40 mm²) were placed on the b0 images (b = 0 s/mm²) (Fig. 1) and simultaneously on the identical structures on the maximum, middle and minimum eigenvector maps. We then got maximum, middle and minimum eigenvalues for the genu and splenium of the corpus callosum, bilateral centra semioval, and WM of the frontal, temporal, parietal, and occipital lobes. For each ROI the λ₁ and λ₃ were calculated based on the following equations:

\[ \lambda_{\perp} = \lambda_1, \quad \lambda_{\parallel} = (\lambda_2 + \lambda_3)/2. \]

**Statistical analysis**

Data were analyzed with the Statistical Package for Social Sciences (SPSS for Windows, Version 11.5, SPSS, Chicago, IL, USA). For symmetrical structures, the difference in λ₁ or \( \lambda_{\perp} \) on the left and right sides was examined with Student’s t-test. If there was no significant difference between these sides, we averaged \( \lambda_{\parallel} \) or \( \lambda_{\perp} \) of the same structure from both sides for further comparison between younger and older groups. Student’s t-test was also used to find the difference in the \( \lambda_{\parallel} \) and \( \lambda_{\perp} \) of the same ROIs between the young and older groups. Statistical significance was defined as \( P < .05 \).

**Results**

For the symmetric structures, including both centra semioval and the WM of both sides of the frontal, temporal, parietal, and occipital lobes in both the younger and older groups, neither \( \lambda_{\parallel} \) nor \( \lambda_{\perp} \) differed significantly on the right or left side (\( P > .05 \)) (Tables 1 and 2). The \( \lambda_{\parallel} \) of the older group did not differ significantly from that of the young group (\( P > .05 \)) for any ROI, although a decreasing trend appeared (Table 3). In contrast, the \( \lambda_{\perp} \) in the older group was significantly higher than in the younger group (\( P < .05 \)), except for the occipital lobe WM. We also observed an increasing trend in \( \lambda_{\perp} \) for occipital lobes in the older group (Table 3).

**Discussion**

Disorders of the central nervous system can lead to myelin and axon dysfunction. Specific and correct assessment of these conditions can improve patient treatment. The advent of DTI has led to the widespread use of indicators such as FA,
ADC, and relative anisotropy (RA) in neuroradiological studies. Derived from the diffusion tensor eigenvalues described above, these indicators have different meanings. ADC, which characterizes isotropic diffusion, is the average of the three eigenvalues [13]. FA represents the fraction of the magnitude of tensor that is due to anisotropic water diffusion [14]; as a measure of intravoxel coherence, it reflects the integrity of the microstructure, that is, the myelin sheath, microtubule, and microfiber [4,15]. Although these indicators generally reflect microstructural changes that occur during the normal aging process, such as axon demyelination or loss, myelin loss, and increased extracellular space [16], they cannot provide a specific assessment of WM changes [10]. More recently, however, it has been suggested that specific DTI measures may differentially reflect aspects of WM changes in both normal and abnormal processes [17]. One study [9] reported increased $\lambda_\perp$ due to dysmyelination in the shiver mouse model. Furthermore, $\lambda_\parallel$ was sensitive to axon degeneration and $\lambda_\perp$ to both demyelination and remyelination [10,11].

In normal aging, gliosis, decreased myelinated axons [18], more subtle disruptions of myelin sheaths and the cytoskeletal components of axons [19,20], age-related loss of cholinergic nerve fibers and decreased myelin fiber length were reported [19]. $\lambda_\parallel$ and $\lambda_\perp$ may differentially reflect axonal and myelin changes of cerebral WM in normal aging and provide further in vivo evidence of the specific underlying pathology. Our results from comparisons of $\lambda_\parallel$ and $\lambda_\perp$ in a younger and an older group support this hypothesis.

DTI measures the random Brownian motion of water molecules, including their directionality and magnitude. Without barriers, movement in all directions is uniform, that is isotropic. Barriers such as the myelin sheath and the cell membrane, on the other hand, make this movement non-uniform in different directions—is anisotropy. The DTI requires the application of a diffusion sensitizing gradient along at least six noncollinear directions. Increasing the number of applications of the gradient increases the accuracy of the measurement: we thus applied it in 25 noncollinear directions. A diffusion tensor matrix is constructed from the data collected, and the three eigenvectors are calculated with matrix diagonalization [21]. Eigenvalues ($\lambda_1$, $\lambda_2$, and $\lambda_3$) are the magnitude of eigenvectors. The maximum eigenvalue, $\lambda_1$, represents the water diffusivity parallel to the axonal fibers. The middle and minimum eigenvalues, $\lambda_2$ and $\lambda_3$, represent water diffusion in the planes orthogonal to the long axis of the axon and are typically averaged ($\lambda_2 + \lambda_3)/2$ to yield a measure of $\lambda_\perp$ [22]. These two indicators of DTI are reported to reflect axon and myelin changes differentially [10,11,23].

Our data showed no significant differences ($P > .05$) between the two groups for $\lambda_\parallel$ in any ROI, including the WM of the genu and splenium of the corpus callosum, the centrum semiovale and the frontal, temporal, parietal and occipital lobes. It thus appears to conflict with previous studies that suggested that a decreased $\lambda_\parallel$ value correlates closely with axon damage [10,23]. As we know, normal aging leads to axon degeneration [17] and should thus decrease $\lambda_\parallel$. But our study showed no significant difference in $\lambda_\parallel$ between the two groups. The promise that $\lambda_\parallel$ showed early as a specific marker of axonal impairment [10] thus does not appear to be confirmed here. Nonetheless, despite the absence of any significant difference between the two groups, we did observe that the older group showed a trend toward a lower $\lambda_\parallel$ in all ROIs. This might be a sign of axon degeneration in normal aging. If so, the degeneration was so minor that it could not result in a statistical significance between the two groups, but could be expressed only as a decreased trend. Another possible explanation might lie in the age composition of our older group. At least one study suggests that WM degeneration is greatest in very old age [24]. Most of our older volunteers were aged only 60–69 (11 subjects), and only one was as old as 80 years. The relatively small number of very old participants might mean that the age effect on axon was quite minor and thus that it resulted in no significant $\lambda_\parallel$ difference between two groups.

The pattern for $\lambda_\perp$ in our study was different. Except for the occipital lobe WM, $\lambda_\perp$ was significantly higher in the older than the younger group ($P < .05$). This pattern is consistent with earlier studies [10,11,25] supporting a close correlation between $\lambda_\perp$ and changes in myelin, including demyelination, remyelination, and myelin loss. In normal aging, WM undergoes myelin loss and demyelination [15,17]. Myelin degeneration leads to increased $\lambda_2$ and $\lambda_3$ and thus increases the $\lambda_\perp$ of cerebral WM in the older group. We also note that although there was no significant difference

<table>
<thead>
<tr>
<th>ROI</th>
<th>$\lambda_\parallel$ (mean ± sd) × 10$^{-3}$ mm$^2$/s</th>
<th>$\lambda_\perp$ (mean ± sd) × 10$^{-3}$ mm$^2$/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger group</td>
<td>Older group</td>
</tr>
<tr>
<td></td>
<td>1.05 ± 0.08</td>
<td>1.04 ± 0.12</td>
</tr>
<tr>
<td></td>
<td>0.52 ± 0.04</td>
<td>0.59 ± 0.06</td>
</tr>
<tr>
<td>CS</td>
<td>1.66 ± 0.21</td>
<td>1.64 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>0.38 ± 0.04</td>
<td>0.42 ± 0.05</td>
</tr>
<tr>
<td>CC genu</td>
<td>1.62 ± 0.18</td>
<td>1.61 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>0.31 ± 0.07</td>
<td>0.38 ± 0.11</td>
</tr>
<tr>
<td>CC splenium</td>
<td>1.16 ± 0.10</td>
<td>1.13 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>0.55 ± 0.05</td>
<td>0.59 ± 0.06</td>
</tr>
<tr>
<td>FL WM</td>
<td>1.19 ± 0.12</td>
<td>1.16 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>0.55 ± 0.04</td>
<td>0.62 ± 0.06</td>
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<tr>
<td>TL WM</td>
<td>1.10 ± 0.10</td>
<td>1.09 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>0.54 ± 0.04</td>
<td>0.58 ± 0.05</td>
</tr>
<tr>
<td>PL WML</td>
<td>0.56 ± 0.05</td>
<td>0.57 ± 0.05</td>
</tr>
</tbody>
</table>

$\lambda_\parallel$ did not differ significantly between the younger and older groups. $\lambda_\perp$ was significantly higher in the older group compared with the young group except for occipital lobe white matter. $\lambda_\parallel$: axial diffusivity; $\lambda_\perp$: radial diffusivity; sd: standard deviation; CS: centrum semiovale; FL WM: frontal lobe white matter; TL WM: temporal lobe white matter; PL WM: parietal lobe white matter; OL WM: occipital lobe white matter.
in \( \lambda_\perp \) between the two groups (\( P > .05 \)) for occipital WM, we did observe a trend towards increased \( \lambda_\perp \) in the older group. An explanation for this finding may lie in the selectivity and degree of age-related WM degeneration. Studies [15,26—29] have suggested that age-associated WM degeneration is subject to an anterior-posterior gradient. Aging affected posterior WM less than it did anterior structures. Thus occipital WM, being located in the posterior cranium, might well be less likely to be affected by aging or undergo much more minor degeneration. The difference in \( \lambda_\perp \) in occipital WM between two groups failed to reach statistical significance (\( P > .05 \)) but showed an increasing trend in older group that may nonetheless be an indicator of age-associated minor demyelination and myelin loss.

Conclusion

Our results indicate that in the older group of subjects, \( \lambda_\perp \) did not change significantly, although a decreasing trend was observed, and that \( \lambda_\perp \) did increase, except the occipital WM (for which an increasing trend was observed). \( \lambda_\perp \) may reflect axon degeneration and \( \lambda_\perp \) reveal the myelin degeneration, both due to normal aging. They may be used as in vivo markers for differential and specific detection of normal aging-related WM degeneration.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

[28] Head D, Buckner RL, Shimony JS, Williams LE, Akbudak E, Conturo TE, et al. Differential vulnerability of ante-
