Validation of the anisotropy index ellipsoidal area ratio in diffusion tensor imaging

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Abstract

A new diffusion anisotropy index, ellipsoidal area ratio (EAR), was described recently and proved to be less noise-sensitive than fractional anisotropy (FA) by theory and simulation. Here we show that EAR has higher signal-to-noise ratios than FA in average diffusion tensor imaging data from 40 normal subjects. EAR was also more sensitive than FA in detecting white matter abnormalities in a patient with widespread diffuse axonal injury. Monte Carlo simulation showed that EAR’s mean values are more biased by noise than FA when anisotropy is small, both for single fiber tracts and when fiber tracts cross. However, the improved signal-to-noise ratio of EAR relative to FA suggests that EAR may be a superior measure of anisotropy both in quantifying both deep white matter with relatively uniform fiber tracts and pericortical white matter structure with relatively low anisotropy and fiber crossings.

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1. Introduction

Diffusion anisotropy indices (DAIs) are the measurements used to describe the diffusion dimensionality in diffusion tensor imaging (DTI) data. Fractional anisotropy (FA)\cite{1} is the most commonly used DAI because of its robustness to noise\cite{2–4}. However, FA has been faulted because it does not adequately characterize the morphological curvature of a tensor’s ellipsoid. A new DAI, ellipsoidal area ratio (EAR)\cite{5}, was proposed recently to more adequately capture the morphology of the diffusion tensor. Because it is defined in terms of the surface area of the diffusion ellipsoid, EAR relates directly to the shape of the diffusion ellipsoid, which reflects the essential biological characteristics of diffusion. Monte Carlo simulations\cite{5} demonstrated that EAR provided similar contrast-to-noise ratio (CNR) as FA in white matter regions in the presence of low levels of noise and better SNR than FA at high levels of noise (5–10%). Comparison of data from a single subject showed that EAR maps appeared smoother than FA maps, and EAR typically provided superior CNRs (improved by 49%) compared to FA in white matter.

To further evaluate EAR and FA measures of diffusion anisotropy, we compared the statistical properties of EAR and FA measures using the averaged population DTI data from 40 normal human subjects. We investigated the empirical properties of the two DAIs in both deep white matter tracts and in pericortical areas. In addition, we compared EAR and FA using simulations under a complete range of diffusion tensor shapes while evaluating both noise sensitivity and noise bias. In addition, the sensitivity of FA and EAR were compared in a patient with white matter damage due to traumatic brain injury (TBI).

2. Methods

2.1. Definitions of FA and EAR

EAR is defined\cite{5} in terms of the ratio of the surface area of the 3D diffusion ellipsoid with axes of three eigenvalues...
\(\lambda_1, \lambda_2, \lambda_3\) and EAR have comparable formulas:

\[
FA = 1 - \left( \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \right)^{\frac{1}{3}}
\]

\[
EAR = 1 - \frac{S^e}{\pi \lambda_1^2} \approx 1 - \frac{\left( \lambda_1^2 + \lambda_2^2 + \lambda_3^2 \right)^{\frac{1}{2}}}{\lambda_1^2}
\]

where \(\lambda_1 \geq \lambda_2 \geq \lambda_3\) are the ordered eigenvalues of the diffusion tensor, \(S^e\) is the surface area of the diffusion ellipsoid and \(p\) is a constant used when \(S^e\) is calculated using the Knud Thomson approximation. This approximation has minimal relative error (±1.061% worst case) when \(p \approx 1.6075\). Being similar to the square of FA, EAR provides a normalized measure of diffusion anisotropy that ranges from 0.0 to 1.0. By comparing Eqs. (1) and (2), EAR is seen to place more emphasis than FA does on the difference between the two largest eigenvalues (\(\lambda_1\) and \(\lambda_2\)) relative to the least eigenvalue. To get a sense of this, note what happens to the EAR value as \(p \rightarrow \infty\): the effect of \(\lambda_3\) disappears. Thus, we expect EAR properties to lie between those of FA and the normalized linear DAI \(C_l\):

\[
C_l = \frac{\lambda_1 - \lambda_2}{\lambda_1 + \lambda_2 + \lambda_3}
\]

used primarily to identify homogeneous linear fibers. Furthermore, EAR is normalized using only the strongest eigenvalue (\(\lambda_1\)) so that some noise reduction would be expected relative to FA given that the FA uses all three eigenvalues for normalization.

### 2.2. Diffusion tensor image acquisition and fiber bundle processing

Forty normal subjects (13 females, age 18–48, right-handed by self-report) underwent two sessions of cardiac-gated diffusion tensor imaging (DTI) (\(b=1000\) s/mm\(^2\), six directions, FOV=24×24 cm, matrix size: 80×48×80, voxel size 3×3×3 mm\(^3\)) on a clinical 1.5-T Phillips Eclipse MRI scanner. A 33-year-old patient with TBI also underwent the same DTI scans [6] on two separate days in order to detect white matter abnormalities. The diffusion-weighted images of each direction were coregistered to the high-resolution anatomical image (1×1×1 mm\(^3\), described below) and motion effects and image distortion were corrected using SPM5 [7]. FA and EAR were calculated based on the average of coregistered diffusion-weighted images (DWI) from the two scan sessions for each subject.

DTI data from different subjects require either ROI delineation or normalization to a common template in order to compare deep white matter tracts across subjects. One commonly used method is to normalize all the brains into 3D template space [8,9]. We normalized the T1 anatomical images into MNI-152 space using the default algorithm in SPM5 [10], using affine transformations only to avoid problems previously encountered in using more SPM’s nonlinear normalization in TBI populations [11]. The coregistered DTI data were also transformed into MNI space.

In order to extract DAI’s from specific white matter tracts, we used probabilistic tract atlases from Johns Hopkins [12] and Jülich [13] that have proven useful for extracting fiber tract data when doing group comparisons [14]. However, because we compared a single TBI patient to a control group, we augmented the MNI-based atlases with two additional restrictions. First, we only selected voxels that were classified as white matter according to SPM5’s white matter segmentation of the T1 image for each subject. Second, the primary eigenvector (the eigenvector associated with \(\lambda_1\)) had to agree with the known direction of the fiber tract segment under investigation.

### 2.3. Anatomical image acquisition and cortical surface processing

Although they are easy to use and widely accepted, 3D volumetric normalization methods are limited by intersubject variability in gyral structure when analyzing the cortical surface [15–17]. Alignment based on cortical surface structure is more precise than volumetric coregistration when quantifying properties near the cortical surface [15,18–20]. Here we generated a unified hemispheric coordinate system (described below) based on the inflation and coregistration of the cortical surfaces of all the subjects. FA and EAR data were averaged and compared in this common coordinate system across subjects and hemispheres to quantify cortical and pericortical DAI values.

High-resolution T1 anatomical images (TR=15 ms, TE=4.47 ms, flip angle=35°, FOV=24×24 cm, matrix size 256×256×256, voxel size 0.94×1.30×0.94 mm\(^3\)) of the 40 normal subjects and the patient were also acquired. These anatomical images were resliced to 1×1×1 mm\(^3\) resolution and then inflated to the cortical surface using FreeSurfer [21]. The inflated cortical surfaces of left and right hemispheres were then coregistered to a spherical coordinate system [15] based on FreeSurfer’s reference template derived from the average convexity pattern of 40 individuals. The curvature maps of left (LH) and right (RH) hemispheres were averaged over all subjects for visualization.

Two surfaces were generated by the segmentation of FreeSurfer [21]: the cortical surface (\(S_0\)), the surface between white matter (WM) and gray matter (GM), and the pial surface (\(S_p\)), the surface between GM and cerebrospinal fluid (CSF). In order to study the diffusion properties near the cortical surface with nearly fixed partial voluming on each surface, three more surfaces were interpolated from the above two surfaces: \(S_m\), the middle surface between cortical and pial surfaces, \(S_{-1}\) and \(S_{-2}\), the surface 1 and 2 mm inside the white matter from the cortical surface \(S_0\). Fig. 1 shows the five surfaces plotted on the anatomical image of a single subject. FA and EAR values and their intersubject coefficient of variation (CV, standard
deviation divided by mean in percentage) were then calculated and compared on the five surfaces after they had been averaged across 40 subjects and two hemispheres. We chose to focus on surface $S_{-2}$ in the current analyses because this pericortical surface showed the greatest anisotropies and should be least affected by partial voluming with GM.

2.4. Comparison of FA and EAR on the surface $S_{-2}$

The mean projection maps of FA and EAR on the surface $S_{-2}$ were generated across 40 normal subjects and two hemispheres after the two quantities were projected onto the cortical surface for each subject. CVs of FA and EAR of all subjects were calculated and compared on the whole surface and in different anatomical lobes. In addition, FA and EAR metrics were calculated on the $S_{-2}$ surface of the cortex of a TBI patient with bilateral frontal lobe cortical thickness abnormalities [22] and compared with the averaged data from the 40 subjects. z-score patterns of the reduction of FA and EAR were also calculated and displayed on the mean projection maps of the cortical surface to compare the sensitivity of FA and EAR in detecting pericortical white matter abnormalities.

In order to evaluate the performance of the two DAIs on normal cortical tissue, we performed a leave-one-out analysis on both $S_{-2}$ and $S_m$ to see how each control’s DAI values statistically compared to mean values created from the remaining 39 control subjects. We compared DAI values on both surfaces to evaluate DAI specificity. We also calculated the proportion of extreme/outlier DAI values within each control subject’s cortical surfaces to evaluate the noisiness within each DAI’s distribution.

2.5. Comparison of FA and EAR in deep white matter tracts

Distributions of means for FA and EAR were extracted (see Supplementary Section for details) using the probabilistic fiber tract atlases [13] for the 40 normal subjects for the following anterior–posterior tracts in both hemispheres: forceps major, forceps minor, cingulum and the uncinate. CVs of FA, EAR and $C_l$ of all subjects were calculated in different anatomical locations and compared to those of the patient as estimated from two independent imaging sessions. We also extracted (not shown) FA and EAR for the corticospinal tract, inferior occipitofrontal fasciculus and superior occipitofrontal fasciculus and obtained a similar pattern of results.

For a final check on how the two DAIs performed in normal brain matter, we again perform a leave-one-out analysis on mean deep white matter to see how each control’s DAI values compares to the other 39 controls’ DAI values. We used the SPM generated WM partition to identify DAI values in a volume that included all white matter at least 4 mm from any non-WM voxel and then extracted the mean to see how well each DAI captures normal tissue WM variation. We also calculated the proportion of extreme DAI values within each control subject’s isolated deep WM to look at the noisiness within each DAI’s distribution.

Measures of EAR and FA were also compared on five pericortical surfaces and in selected white matter tract ROIs as described above instead of in the whole 3D brain space in order to minimize variance introduced by intersubject differences in cortical folding and in the relative sizes and locations of different fiber tracts.

2.6. Monte Carlo analysis of noise robustness and noise bias of DAIs

The robustness of EAR and FA with respect to noise was tested by Xu et al. [5] for the important case of cigar-shaped diffusion tensor surfaces. We performed similar calculations here using more realistic DTI noise and augmented these comparisons with calculations for noisy diffusion tensor surfaces of other shapes (disk-shaped and asymmetric-shaped). Finally, we also investigated how each DAI was biased away from its true value by noise, an important fact that has previously been noted [23] but that is often overlooked.

Simulations were performed on a digital phantom containing tensors of three types: first, there were cylindrically symmetric tensors (rice-shaped) such that $\lambda_1=\lambda_2=\lambda_3>0$ for each of 15 sizes between a tensor surface of a sphere...
noise-free phantom. Nine different levels of noise were added in quadrature (i.e., in $k$-space) to create noisy phantom diffusion-weighted images from which FA, EAR and $C_l$ were computed after using ordinary DTI log-linear linear least squares [25] to solve for the tensors.

We also performed a simulated group analysis using the digital phantom above for two groups of 20 subjects each under two conditions: one where there was no mean group difference within four different levels of noise and another where the groups had one of three different levels of constant mean anisotropy difference. The two simulation conditions — null hypothesis true or false — allowed us to compute receiver operator characteristic (ROC) curves [26] to determine which DAI has the most theoretical specificity/sensitivity under various thresholds for each of the three main tensor conditions (rice-shaped, disk-shaped, asymmetric).

3. Results

Fig. 2 shows 3D image slices of FA and EAR values for a single subject. EAR had higher mean values than
FA throughout the brain. Fig. 3 shows the mean FA and EAR averaged across 40 subjects and two hemispheres and their CVs on the five surfaces from 2 mm inside the white matter to pial surface. EAR had higher average values than FA and lower CVs on all the five surfaces. For example, on the surface, $S_{-2}$ EAR values were 40% higher than FA while its CV was 28% less than that of FA.

Fig. 4A shows the reduction in both EAR and FA of the TBI patient compared with the averaged data from the 40 control subjects (top two rows, z-score threshold $>1.5$, $P<.01$, cluster size $>1$ cm$^2$; bottom two rows, DAI difference threshold $>0.1$.)
A

Cingulum LH  

FA

SAR

CI

Forceps Minor LH  

FA

SAR

CI

Forceps Major LH  

FA

SAR

CI

Uncinate LH  

FA

SAR

CI

Uncinate RH  

FA

SAR

CI
found where the \( z \) scores of FA reduction exceeded those of EAR reduction on both hemispheres.

Fig. 4B shows the results for the leave-one-out analysis of controls on the pericortical surface. A linear regression performed using each subject’s two DAI \( z \) scores produces highly significant slopes: 0.87 (\( P < .001 \)) and 0.92 (\( P < .0001 \)) for surface \( S_{-2} \) and \( S_m \), respectively. Thus, the mean hemisphere \( z \) scores when treating each control as a patient are consistently \(~10\%\) greater for FA than with EAR. Although this could imply that that FA generates more type I errors if these interindividual differences in mean \( z \) score are not real, the amount of data being averaged together plus the graph’s high linearity likely imply that small variations in overall anisotropy (e.g., if the tensors are asymmetric or disk-shaped, where FA is superior) are detected better by FA.

However, the proportion of extreme DAI values on the cortical surfaces in each normal control shown in Fig. 4C suggests that EAR is less noisy than FA. The scatterplot shows the number of extreme DAI values for EAR and FA for each of the 40 subjects, with the cluster being strongly below the diagonal (more extreme FA values) on surface \( S_{-2} \).

Fig. 5A shows the results of extracting FA, EAR and \( C_l \) in several different white matter fiber bundles. Locations for fiber data extracted from the patient are contained in a Supplementary Section to verify the performance of fiber tract identification procedures. All three DAI values capture apparent white matter abnormalities in the patient in the left hemisphere forceps minor and the superior cingulum bilaterally. Table 1 shows that the mean kurtosis of FA, EAR and \( C_l \) have no significant differences (ANOVA: FA< EAR,

<table>
<thead>
<tr>
<th></th>
<th>LH FA</th>
<th>LH EAR</th>
<th>LH ( C_l )</th>
<th>RH FA</th>
<th>RH EAR</th>
<th>RH ( C_l )</th>
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</thead>
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<tr>
<td>Forceps minor</td>
<td>3.38</td>
<td>3.07</td>
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<td>4.15</td>
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<td>2.27</td>
<td>2.68</td>
<td>2.95</td>
<td>2.86</td>
<td>2.98</td>
<td>2.84</td>
</tr>
<tr>
<td>Cingulum</td>
<td>1.97</td>
<td>2.04</td>
<td>2.19</td>
<td>2.67</td>
<td>3.03</td>
<td>3.07</td>
</tr>
<tr>
<td>Uncinate</td>
<td>3.96</td>
<td>3.48</td>
<td>3.21</td>
<td>2.66</td>
<td>2.69</td>
<td>3.03</td>
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</tbody>
</table>

Normal distributions have kurtosis=3.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>LH FA</th>
<th>LH EAR</th>
<th>LH ( C_l )</th>
<th>RH FA</th>
<th>RH EAR</th>
<th>RH ( C_l )</th>
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<td>Forceps minor</td>
<td>2.66</td>
<td>2.74</td>
<td>2.11</td>
<td>1.80</td>
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<td>1.38</td>
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<tr>
<td>Forceps major</td>
<td>1.15</td>
<td>0.95</td>
<td>0.67</td>
<td>2.82</td>
<td>2.62</td>
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<tr>
<td>Cingulum</td>
<td>2.32</td>
<td>2.41</td>
<td>2.66</td>
<td>2.27</td>
<td>2.35</td>
<td>2.37</td>
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<tr>
<td>Uncinate</td>
<td>1.35</td>
<td>1.41</td>
<td>1.68</td>
<td>–0.11</td>
<td>–0.33</td>
<td>–0.09</td>
</tr>
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</table>

Day 2

<table>
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<tr>
<th></th>
<th>LH FA</th>
<th>LH EAR</th>
<th>LH ( C_l )</th>
<th>RH FA</th>
<th>RH EAR</th>
<th>RH ( C_l )</th>
</tr>
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<td>Forceps minor</td>
<td>2.58</td>
<td>2.70</td>
<td>2.09</td>
<td>1.90</td>
<td>2.21</td>
<td>1.69</td>
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<tr>
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<td>0.75</td>
<td>1.93</td>
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<tr>
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<tr>
<td>Uncinate</td>
<td>1.48</td>
<td>1.30</td>
<td>1.40</td>
<td>0.32</td>
<td>0.11</td>
<td>0.19</td>
</tr>
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which means there were no obvious difference between each DAI's distributional “tightness.” However, EAR kurtosis values may be more normally distributed than those of FA ($P=0.035$, post hoc sign test).

Table 2 shows that that EAR is better in detecting abnormalities in the two areas with greatest likely abnormality, bilateral forceps minor and bilateral superior cingulum, when compared to FA (ANOVA $P<.02$ for all).

However, EAR is not consistently larger than $C_1$ in those cases.

Fig. 5B shows that in normal controls there appears to be no real difference in sensitivity in deep WM overall between FA and EAR. However, Fig. 5C clearly shows once again that the proportion of extreme DAI values is much greater for FA than for EAR indicating that EAR is likely the less noisy DAI.

Fig. 6. DAI noise bias graphs for FA, EAR and $C_1$ computed on the digital phantom. Left subplot is for the rice-shaped tensor surfaces (“linear fibers”), the middle for disk-shaped tensor surfaces (“fiber crossings”) and the right subplots for asymmetric surfaces. $x$-axis is the level of noise (ratio of SD to $B_0$ mean), and $y$-axis are DAI mean values. Flat lines represent DTI parameter values not biased from true values (noise is 0) by changes in SNR.
Fig. 6 shows representative Monte Carlo results concerning the response characteristics and noise bias of each of the three DAIs. EAR has significantly greater values for a given level of anisotropy than does FA or $C_1$ in the linear fiber case. However, EAR is generally more biased by noise than FA as reflected by the greater reduction in total range as more noise is added. Moreover, EAR’s performance on fiber crossing (disk-shaped) tensor areas and asymmetric DTI tensor surfaces shows the expected reduced overall range in addition to being more biased upwards by increases by noise. Both FA and EAR are obviously more useful in the fiber crossing case than that of $C_1$ whose value is 0 by design.

Fig. 7 shows the noise sensitivity of each of the DAIs. EAR has uniformly lower CVs than does FA or $C_1$ in both the linear fiber cases, as previously shown by [5], and in the case where fibers crossed or where tensors were altogether asymmetric.

The simulated group study results are shown in Fig. 8. It depicts the level of true group differences that are identified when a threshold is selected to obtain a particular false-positive rate. A DAI is favored in the ROC graphs when it contains more area below the curve than do the others under the same effect size and noise conditions. In general, it can be seen that for strong differences in anisotropy relative to the noise or to obtain very low false-positive rates within linear fibers (rice-shaped, top row), the EAR measure should be slightly preferred over either FA or even $C_1$. However, as the level of Gaussian noise increases (where curves are more diagonal), or the true tensor is asymmetric or rice-shaped, FA is preferred. In particular, FA is considerably superior to EAR in the disk-shaped tensor case.

4. Discussion

Theoretical considerations and simulations such as those whose results are illustrated in Figs. 6, 7 and 8 and by Xu et al. [5] suggest that EAR is a more sensitive and reliable measure of anisotropy in the linear fiber (one dominant eigenvalue) case than either FA or $C_1$. However, EAR is potentially more susceptible to SNR bias in low anisotropy regions than FA and less sensitive than FA in the case of two nearly equally large eigenvalues (e.g., fiber crossings). On the other hand, because population-averaged EAR has higher signals than FA but similar absolute variance, as shown in Fig. 2, this implies that EAR should have a lower coefficient of variation in all cases, including cases of crossing fibers (e.g., disk-shaped case). This latter point was confirmed with real data as shown in Figs. 3, 4C and 5C and via simulations as shown in Fig. 7.

Surprisingly, the performance of EAR was not substantially hampered (as suggested by Fig. 8) in the pericortical white
matter case despite the possibly greater fraction of disk-shaped tensors there. When used to detect pericortical white matter abnormalities in a TBI patient or differences in normal controls, the major reduction patterns were quite similar for EAR and FA. Fig. 4A shows that in the area where \( z > 1.5 \), EAR reduction has higher \( z \) scores than FA at several spots, especially at the locations where reduction was seen with both metrics in the two imaging sessions. This suggests that EAR is about as sensitive as FA in detecting even pericortical white matter abnormalities. Perhaps EAR’s reduction in random noise relative to FA (Fig. 4C) compensates for its slight reduction in sensitivity (Fig. 4B). The mean DAI values on the cortical surface \( S < 0.2, 0.4 \) and 0.28 for EAR and FA, respectively (Fig. 3), appear to be large enough to produce similar noise biases (Fig. 6), and fiber crossings are apparently not an overwhelming issue affecting DAI in the majority of pericortical WM. However, in cortical gray matter, there appears to be no reason to switch from FA to using EAR (Fig. 4B and C).

As expected, EAR appeared to slightly outperform FA and \( C_l \) overall when applied to detecting deep white matter abnormalities: the control distributions were at least as normally distributed for EAR as for FA (Table 1) and the EAR values were less noisy (Fig. 5C), allowing a greater range and sensitivity in detecting potential DAI deficits in abnormal tissue.

There are two remaining disadvantages to discuss when thinking about using EAR in future studies: (1) there is a large existing base of published studies performed using FA as the DAI of choice, and (2) EAR shows a greater apparent bias due to differences in DTI SNR which complicates comparisons of values across studies and scanners. However, it should be noted that to address the first point, it will often be possible to compute EAR values retrospectively; for
example, if FA and both axial and radial diffusivity values are available, then all eigenvalues can be solved for (a quadratic equation) and therefore EAR can be computed. And the second point may not be of great concern given the other differences in DAI values due to specific scanner and DTI scan parameters used by various research groups.

5. Conclusion

The new anisotropy index EAR has higher signal values and lower relative population variance than FA. While minor differences are seen in the distribution of pericortical white matter abnormalities with FA and EAR analyses of TBI patient data, EAR appears to be more sensitive than FA to deep white matter abnormalities and is also acceptable to use in characterizing pericortical white matter structures.

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Appendix A. Supplementary data


References


