Imaging Reveals Optic Tract Degeneration in Hemianopia

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PURPOSE. To investigate whether there is transsynaptic degeneration in the human optic tract in hemianopia. To consider how the degeneration varies with duration of hemianopia and location of insult.

METHODS. Seven patients with damage to the primary visual cortex (V1), the lateral geniculate nucleus (LGN), or the optic tract were scanned with structural MRI. The volume and cross-sectional area of the left and right optic tracts were computed based on the intensity values of the T1-weighted image. High values correspond to voxels with high white matter content, and the values decrease as the white matter content drops (indicating degeneration). A laterality index to compare the tract size in the two hemispheres was calculated at different intensity values.

RESULTS. The three hemianopic patients with longstanding damage to either V1 or LGN showed laterality indices greater than 0.5 at the highest intensity values, indicating significant optic tract degeneration. Those with recent damage to the optic tract had even higher laterality indices due to direct degeneration. Even 18 months after V1 lesion, there was a significant correlation between the cross-section and volume indices at different intensity thresholds, whereas no control subject showed any correlation.

CONCLUSIONS. Transsynaptic degeneration had already begun 18 months after lesion. Although there was no visible decrease in volume at this stage, the white matter integrity was compromised. Significant decrease in volume could be visualized at longer durations of hemianopia. This method of objectively assessing structural images provides an effective, noninvasive approach to monitor the timescale of optic tract degeneration. (Invest Ophthalmol Vis Sci. 2011;52:382-388) DOI:10.1167/iovs.10-5708

Hemianopia occurs as a result of damage to the postchiasmal visual pathway in humans. The damage can be an ischemic event, trauma, surgical resection, or congenital lesion. Most commonly, hemianopia is due to damage to the optic radiations or the primary visual cortex, removing the principal visual input to the cortex. Damage to the optic tract or lateral geniculate nucleus can also occur, in which case the retinal ganglion cell axons are affected directly, leading to degeneration and loss of corresponding RGCs.

The presence of transsynaptic retrograde degeneration of the ganglion cells after damage to the occipital lobe remains controversial. There is evidence that damage sustained very early in life results in this type of degeneration,1,2 although not in all cases.3 In older children and adults, however, the reports are contradictory with the report of a patient with a longstanding lesion showing little postmortem degeneration.4 These data suggesting a lack of transsynaptic retrograde degeneration in humans are contrary to the published literature on nonhuman primates5 and have been attributed to species differences.3 In the absence of postmortem data, degeneration of the retina has been identified through optic pallor.1 One of the difficulties before high-resolution magnetic resonance imaging (MRI) was widely available is exclusion of direct trauma to the optic nerve, tract, or retina.1 Even when neuroimaging evidence is available, at least in the case of arteriovenous malformations, it is possible to have vascular damage remote to the cortical damage.6

It has been recently shown, however, using optical coherence tomography (OCT), that there is thinning of the retinal nerve fiber layer implying loss of retinal ganglion cells (RGCs) in both acquired and congenital human hemianopia,7 as previously shown in the macaque monkey.5,8,9 Indeed it had previously been observed in a single patient with congenital quadrantopia using standard ophthalmoscopic examination.10 The retinal thinning strongly suggests that damage to primary visual cortex can lead to retrograde transsynaptic degeneration. The study by Jindabran et al.7 did not consider the factors contributing to the variability in the amount of degeneration. The most likely possibilities include the time elapsed since the lesion, the extent of the damage, and even its location (e.g., optic radiation or visual cortex). The finding that cases of congenital hemianopia showed greater RGC loss suggests that the time elapsed since the damage could be correlated with the magnitude of the transsynaptic degeneration. In support of this hypothesis, Cowey et al.8 showed that though both geniculate and retinal degeneration correlate significantly with survival time in macaque monkeys, the best predictors of RGC degeneration after lesions of striate cortex were the size of the lesion, the overall number of surviving dLGN neurons, and the volume of the dorsal LGN. Even when the occipital lesions were limited to the gray matter of the striate cortex, significant loss of RGCs and dLGN cells was reported, suggesting degeneration is primarily a result of transsynaptic retrograde degeneration rather than direct degeneration caused by underlying white matter damage.9

RGC loss can be measured using OCT of the retinal nerve fiber layer but also potentially by measuring the volume of the optic tract. The aim of the present study was to measure the degeneration of the ipsilesional optic tract compared with the contralateral side in subjects with homonymous hemianopia using MRI. Subjects with postgeniculate lesions have been selected along with subjects in whom the LGN itself is damaged. In the latter,
some damage to the optic tract cannot be excluded. Two additional subjects with optic tract damage are also included for comparison. Measuring such small neural structures can be difficult using standard T1-weighted scans, but the optic tract is a straightforward tract to identify given its origin at the chiasm. One of the important considerations is whether to measure the total volume of the tract or its cross-sectional area. Once the tract becomes contiguous with the white matter of the brain, it becomes impossible to identify in the images, so it is only possible to measure the volume of the visible portion. On the other hand, the slicing of the brain in the image makes determination of the cross-sectional area problematic because tilting of the head can introduce areal variations in any given slice. Nonetheless, where there is a real difference in optic tract volume in the two hemispheres, the cross-sectional area and the volume ratios should be correlated.

Here we show that the volume and cross-sectional area of the optic tract on the ipsilesional side are significantly decreased in three subjects with longstanding hemianopia (greater than 10 years). At 18 months after damage to V1, changes in the white matter integrity of the tract are present, whereas a very recent lesion to the LGN does not show any tract degeneration. The two patients with optic tract trauma, of 11 months' and 4 years' duration, had the greatest degeneration of the tract.

SUBJECTS AND METHODS

Subjects

Six hemianopic subjects were recruited from the National Hospital, and data from a patient imaged for a previous study (here referred to as patient 1) were also included. Brief subject details are provided in Table 1. Data from five age-matched controls and an additional five young control subjects (mean age, 25.2 years) were also analyzed to ensure that any asymmetries were not present in the general population. The study, which adhered to the tenets of the Declaration of Helsinki, was conducted under ethical approval from the Oxfordshire National Health Service Research Ethics Committee (08/80605/156); all subjects gave written informed consent.

Visual Field Definitions

Visual field analysis was performed using the Humphrey visual field analyzer. Patients were included in the study if there was substantial loss in either the left or the right homonymous hemifield using the 24–2 protocol. In subject OT2 the damage is to the right optic tract, but in all other subjects the left hemisphere is the affected side, leading to right-sided hemianopia. The mean deviation loss, ranging from 20.8 dB to 31.7 dB in the visual field contralateral to the lesion, is shown in Table 1. The ipsilateral field is within normal limits. The full visual fields can be viewed in Supplementary Figure S1, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.10-5708/-/DCSupplemental.

Retinal Nerve Fiber Layer Thickness

The retinal nerve fiber layer thickness (RNFL) thickness was measured for all hemianopic patients, as described previously. Briefly, the mean thickness was calculated for each eye using optical coherence tomography (OCT). The specific paradigm measures the cross-sectional RNFL of a 3.4-mm-diameter circle centered on, but exceeding the size of, the optic disc. For comparison, the mean thickness for a group of 22 controls (age range, 23–74 years) was 101.1 ± 9.7 μm for the right eye and 101.3 ± 10.9 μm (mean ± SD) for the left eye.

Image Acquisition

Data were acquired with 3T MRI (TIM Trio; Siemens, Berlin, Germany) at the Oxford Centre for Clinical Magnetic Resonance Research. Whole head structural T1-weighted scans were acquired axially at a resolution of 1 mm³ (MP-RAGE; repetition time, 15 ms; echo time, 6.0 ms).

Definition of the Optic Tract

To ensure that the specific head orientation of the subject in the scanner did not bias results, the brain images were resliced using Osirix to visualize slices parallel with the optic tract path and perpendicular to this plane. Such an approach allowed the identification of the optic tract in a fairly liberal way while ensuring that these definitions were of equal volume in the two hemispheres. Two masks were drawn by hand using fsview (one of the tools from the FSL toolbox www.fmrib.ox.ac.uk/fsl) in the perpendicular plane: the cross-sectional area at the third slice posterior to the optic chiasm and the tract volume across all slices in which the tract was both visible and distinct from adjacent white matter. These masks were deliberately drawn to be equal in the two hemispheres for patients and controls to prevent any experimenter bias in determining the sizes of the tracts. The unthresholded masks were not used in any calculations of tract size.

To obtain objective boundaries of both the cross-sectional area and the volume of the optic tract, the intensity of the T1-weighted image was used. A threshold was applied to the images such that voxels not corresponding to white matter were excluded. The number of voxels in each mask was then measured as the threshold was increased. Such an increase meant that the tissue contributing to the mask would contain a higher proportion of white matter and that the size of the mask would be reduced.

A laterality index was computed to quantify the difference in both the cross-sectional area and the volume of the left and right optic tracts. This index was defined as \( L = ( \text{contralesional} - \text{ipsilesional} ) / ( \text{contralesional} + \text{ipsilesional} ) \) and was computed for all threshold values provided >3 mm³ was present in at least one tract mask. In control subjects, the index was calculated, but the order of the numerator was arranged such that the index was positive on average.

### Table 1. Characteristics of Hemianopic Patients

<table>
<thead>
<tr>
<th>Subject</th>
<th>Damage Location</th>
<th>Duration (y)</th>
<th>Insult Type</th>
<th>Age at Scan (y)</th>
<th>HVFA Mean Deviation (dB)</th>
<th>RNFL Thickness (μm)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>Left striate cortex</td>
<td>45</td>
<td>Traumatic</td>
<td>53</td>
<td>−31.5 [−5.1]</td>
<td>72.0</td>
</tr>
<tr>
<td>C2</td>
<td>Left striate cortex</td>
<td>18</td>
<td>Tumor resection</td>
<td>72</td>
<td>−25.2 [−2.3]</td>
<td>84.2</td>
</tr>
<tr>
<td>C3</td>
<td>Left striate cortex</td>
<td>1.5</td>
<td>Ischemic</td>
<td>65</td>
<td>−30.8 [−2.1]</td>
<td>92.0</td>
</tr>
<tr>
<td>L1</td>
<td>Left LGN</td>
<td>Up to 30 (possibly congenital)</td>
<td>Arteriovenous malformation</td>
<td>30</td>
<td>−20.8 [−0.5]</td>
<td>72.5</td>
</tr>
<tr>
<td>L2</td>
<td>Left LGN</td>
<td>0.25</td>
<td>Ischemic</td>
<td>40</td>
<td>−22.1 [−2.9]</td>
<td>83.6</td>
</tr>
<tr>
<td>OT1</td>
<td>Left optic tract</td>
<td>4</td>
<td>Traumatic</td>
<td>57</td>
<td>−30.8 [−2.8]</td>
<td>60.3</td>
</tr>
<tr>
<td>OT2</td>
<td>Right optic tract</td>
<td>0.9</td>
<td>Traumatic</td>
<td>37</td>
<td>−31.7 [−3.8]</td>
<td>66.4</td>
</tr>
</tbody>
</table>

C, lesion to the striate cortex; L, lesion to the lateral geniculate nucleus; OT, lesion to the optic tract.

* Computed for the affected hemifield, with the good hemifield in brackets.

† Mean of right and left eye measurements.
because there was no reason for predicting one side to be larger than the other.

The T1-weighted images used for this analysis were not quantitative and, therefore, depended on various factors such as the size of the subject’s head. The absolute intensity thresholds were not meaningful, though the relative measure between the two hemispheres was informative.

RESULTS

The anterior portion of the optic tract, from the optic chiasm to the base of the brain, is clearly visible on standard T1 whole brain structural images. Figure 1 shows examples of the optic tract in slices chosen to be parallel to the plane of the tract (upper panel) and perpendicular to this plane. The upper row shows images from three of the hemianopic patients, and the lower row shows images from three of the age-matched controls. The damaged hemisphere in each of these patients is the left, and the optic tract is indicated by the white arrow. Hemianopic patients C2 and OT1 appear to have visible degeneration of the left tract, whereas patient L2 is indistinguishable from the controls. None of the controls appear to show any asymmetry between the tracts on the two sides.

The volume and cross-sectional area were computed for both the left and the right optic tracts for all subjects using increasing intensity thresholds. Figure 2 shows examples of the mask size at two different intensity thresholds for a

Figure 1. Slices parallel and perpendicular to the optic chiasm in three hemianopic patients and controls. Orthogonal slices are located approximately 3 mm posterior to the chiasm, as shown in the sagittal slice.

Figure 2. Top: same data shown in Figure 1 for three of the hemianopic patients and one control subject. C1 has damage to the occipital cortex, L1 has damage to the LGN, and OT2 has damage to the optic tract. Bottom: masks for the left and right optic tract volume in the same slice. Blue masks indicate the optic tracts defined using voxels with a low white matter intensity threshold. Yellow masks indicate the effect on the mask size as this threshold is increased.
control subject, one patient with V1 damage, and one with LGN damage; patient OT2 has damage to the right optic tract. The blue regions are the optic tract masks when a low white matter threshold is used to determine the extent of the tract. As this threshold is raised (yellow masks) all the masks get smaller. However, the high threshold masks for the hemianopic subjects appear to become relatively smaller in the ipsilesional tract compared with the other tract. This indicates that the white matter content of the voxels is lower in these tracts compared with the control side (and control subjects).

Laterality Index of Optic Tract Volume

The volume of the optic tract was measured separately on each side at a range of increasing white matter intensity thresholds. The laterality index \((\text{contralesional} - \text{ipsilesional})/(\text{contralesional} + \text{ipsilesional})\) was calculated for the tract volume and is shown for hemianopic patients and controls in Figure 3. Figure 3A shows the data for patients with either LGN or occipital lobe damage, and Figure 3B shows data for the two patients with optic tract lesions. Figure 3C shows data for the age-matched controls, whereas the data from the young controls can be seen in Supplementary Figure S2, http://www.iovs.org/lookup/suppl/doi: 10.1167/iovs.10-5708/-/DCSupplemental. Age-matched controls are shown in the same color used for the patient with whom they are matched. If the volume in the left and right tracts were equal, the index would be 0, whereas if the tract were absent on one side, the value would be 1. The patients with optic tract damage have indices very close to 1 at the highest thresholds. The three patients with the longest standing damage beyond the optic tract (C1, C2, and L1) have relatively high laterality indices at all intensity thresholds, though the difference is greatest at the highest thresholds. For some of the control subjects, there is an increase in the index at the highest thresholds, presumably because these measurements involve fewer voxels and there is a corresponding increase in noise.

The mean laterality index across all thresholds (unthresholded values are excluded) was lower for the three hemianopic

![Figure 3.](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932967/)
patients with longstanding lesions than for controls and those with more recent lesions (Table 2). Not surprisingly, the patients with optic tract damage showed the greatest laterality, even when the damage occurred less than 12 months before imaging.

Laterality Index of Cross-Sectional Area

Although the absolute values of the laterality index for the cross-sectional tract area clearly differ from the volume measurements, the pattern for the three patients with longstanding LGN or occipital cortex lesions (patients C1, C2, and L1) was similar (Fig. 3A), as was the pattern for the patients with optic tract lesions (Fig. 3B). The change in index for the cross-sectional area in control subjects was sometimes in the opposite direction from the index change in volume (Fig. 3C). This was not true of the hemianopic patients (with the exception of L2, whose lesion was only 3 months old at the time of imaging).

Quantification of the mean index for both volume and cross-sectional area is shown in Table 2. On both measures, the two patients with recent LGN or V1 lesions of less than 2 years’ duration appeared indistinguishable from controls. Across the 10 control subjects (five age-matched and five young), there was little correlation between mean volume and cross-sectional indices ($r = 0.42$; not significant). In contrast, the hemianopic patients showed a high correlation ($r = 0.94$; $P < 0.005$).

Detection of Subtle Changes in Tract Size

Patients C1 and C2 clearly show an asymmetry in the size of the optic tract in the ipsilateral and contralesional sides, which was evident even when low-intensity thresholds were used. In contrast the laterality index in patient C3, whose damage occurred 18 months before imaging, did not differ from that of controls at low intensities but showed a gradual, and consistent, increase with threshold value. Although some controls showed an increase in the laterality for either cross-sectional area or volume, none showed a correlated increase in both. In patient C3, the indices for volume and cross-sectional area were significantly correlated ($r = 0.98$; $P = 0.0001$), suggesting that the laterality could have reflected a real decrease in the integrity of the white matter in the tract ipsilateral to the lesion.

Degeneration of the Lateral Geniculate Nucleus

The primary route from the optic tract to the striate cortex in primates is through the LGN, although there are additional routes, such as the superior colliculus and the pulvinar. Given the strength of the connection between V1 and the LGN, it is not surprising that degeneration of the optic tract is associated with, and preceded by, structural change in the LGN of the macaque. Therefore, we have examined the condition of this structure in all patients (Fig. 4). The LGN volume is difficult to quantify from a T1-weighted image, and only qualitative data are presented. In the control subject, the LGN can be seen as a dark blob superior to the hippocampus, indicated by the black arrows. In patients with longstanding lesions in the striate cortex appear to have reduced integrity of the LGN in the lesioned side, whereas this appears not to be true for C3. In patients with optic tract damage, the LGN is visible on both sides. However, patient OT1 appears to have a reduction in the size of the nucleus ipsilateral to the tract damage.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Cross-Section Ratio</th>
<th>Volume Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>0.29</td>
<td>0.44</td>
</tr>
<tr>
<td>C2</td>
<td>0.31</td>
<td>0.27</td>
</tr>
<tr>
<td>C3</td>
<td>0.09</td>
<td>0.10</td>
</tr>
<tr>
<td>L1</td>
<td>0.33</td>
<td>0.38</td>
</tr>
<tr>
<td>L2</td>
<td>0.09</td>
<td>−0.02</td>
</tr>
<tr>
<td>OT1</td>
<td>0.51</td>
<td>0.67</td>
</tr>
<tr>
<td>OT2</td>
<td>0.27</td>
<td>0.35</td>
</tr>
<tr>
<td>Control 1 (54)</td>
<td>0.03</td>
<td>−0.02</td>
</tr>
<tr>
<td>Control 2 (30)</td>
<td>0.05</td>
<td>0.10</td>
</tr>
<tr>
<td>Control 3 (73)</td>
<td>0.03</td>
<td>0.12</td>
</tr>
<tr>
<td>Control 4 (65)</td>
<td>0.10</td>
<td>0.09</td>
</tr>
<tr>
<td>Control 5 (35)</td>
<td>0.09</td>
<td>0.16</td>
</tr>
<tr>
<td>Young control 1</td>
<td>0.01</td>
<td>0.09</td>
</tr>
<tr>
<td>Young control 2</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>Young control 3</td>
<td>0.11</td>
<td>0.01</td>
</tr>
<tr>
<td>Young control 4</td>
<td>0.05</td>
<td>−0.03</td>
</tr>
<tr>
<td>Young control 5</td>
<td>0.00</td>
<td>0.05</td>
</tr>
</tbody>
</table>

For patients, the index was (ipsilesional − contralesional)/(ipsilesional + contralesional). For control subjects, the numerator is computed as tract with lower mean size - tract with greater mean size across all intensity values.
hemisphere can be clearly visualized. However, it does not appear to be visible in the left hemisphere. In patient C3, with less optic tract degeneration, the LGN is visible bilaterally. In both patients with damage to the optic tract, the LGN is visible bilaterally, though it appears more symmetric in OT2, who has more recent damage.

**DISCUSSION**

We have shown evidence from standard MRI structural images for transsynaptic retrograde degeneration of the ipsilesional optic tract in 3 of 5 patients with homonymous hemianopia caused by LGN or occipital damage. This result is consistent with findings of a recent study that showed degeneration of the RGCs in a population of similar subjects using OCT. The data are also consistent with the loss of ganglion cells evident in hemianopic macaque monkeys.9

**Use of MR Images**

To quantify the size of the optic tract, the image intensity of the white matter within the tract was used as an objective measurement. The intensity level of a voxel within the white matter was related to the density of white matter within the voxel. Therefore, if there is any degeneration of fibers within a given voxel, there will be a drop in signal intensity. Despite the use of intensity as an objective measurement, the position of the subject’s head in the scanner is particularly problematic for using MRI to measure the tract. First, head position in the scanner can affect the relative size of the left and right tract in any given slice. Second, though the anterior portion of the tract is distinct and external to the subcortical white matter, the posterior portion cannot be easily determined. Similarly, different head positions can differentially affect the extent of the visible tract. To limit the effect of head position, all images were resliced parallel to the path of the optic tract. Although not a perfect solution, major artifactual asymmetries could be significantly reduced.

**Measurement of Both Cross-Sectional Area and Tract Volume Is Important**

In this report, both the volume and the cross-sectional area of the optic tract were measured. These two approaches were used because, despite the best attempts to reslice the image, it is possible that small asymmetries remained, but area and volume were likely to be differentially affected. Furthermore, the increase in intensity threshold and the corresponding decrease in the number of voxels included in the tract definition led to an increase in the noise between the tracts. Again, there is no obvious reason why this noise should be correlated in the volume and area measurements. In support of these arguments, the data show that there is no correlation between the left/right ratio of the area and volume of the tract in the 10 control subjects.

In contrast to the control subjects, there is a very high correlation between the area and volume ratios in the hemianopic patients, reflecting a real difference in optic tract integrity and volume in five of the patients.

**Correlation between Regions of Retrograde Degeneration**

If damage occurs to the primary visual cortex, it may be predicted that any retrograde degeneration in the optic tract would be correlated to degeneration at the level of the LGN. Similarly, it would be difficult to envision ganglion cell loss as measured with OCT in the absence of optic tract degeneration. Indeed, in the four hemianopic subjects in whom the RGC layer was thin, there was considerable reduction in the optic tract volume. For C2, degeneration of the LGN and optic tract was considerable, but RGC loss was not very different from that of patients showing little evidence of tract degeneration. In a longitudinal study of hemianopic patients, it should be possible to measure degeneration throughout the retina-geniculo-striate pathway over time. The time scale over which such degeneration occurs remains to be determined.

LGN degeneration was more difficult to quantify using T1-weighted images, but it appeared that degeneration of the LGN was greater on the ipsiliteral side in the two patients with longstanding damage to V1. In C3, who experienced more recent damage to V1 along with optic tract damage, there was less effect on LGN integrity.

**Comparison of Techniques for Measuring Transsynaptic Retrograde Degeneration**

Using standard MR images and analysis, we have shown that transsynaptic retrograde degeneration caused by damage to the primary visual cortex can affect the optic tract ipsilaterally to the lesion. It is possible to detect such degeneration as early as 18 months after cortical insult. Previous studies in the macaque monkey have used RGC counts to measure degeneration from striate cortex lesions. Similarly, in humans, degeneration has been determined by measurement of the RGCs either with an ophthalmoscope or with OCT. In the patients presented here, there appeared to be reasonable correspondence between the measures of optic tract asymmetry and mean retinal nerve fiber layer. However, because the latter technique uses an absolute measure, the amount of degeneration was difficult to ascertain because it occurred in both eyes. Quantification of band atrophy, similar to that used in Jindahra et al., is more comparable to the relative measurement between the two optic tracts used here. Comparison using nerve fiber layer thickness depends on the preservation of the nasal and temporal sectors around the optic disc in the eye with the nasal hemianopia. This is a technically difficult task, but in the optic tract comparison the same axons are totally separate. To gain a complete understanding of the relationship between ganglion cell loss and optic tract degeneration, postmortem measurements in nonhuman primates would be useful.

**Consequences for Functional Performance**

Multiple laboratories are working to improve rehabilitation in homonymous hemianopia; methods include restitution therapy, in which visual performance in the damaged field is targeted (see Ref. 12 for review). The finding of transsynaptic degeneration from striate cortex lesions even 18 months after lesion suggests that any attempts to improve visual function in the blind field must begin as soon as possible after the insult. However, even when therapy is begun at the earliest possible time, it remains to be determined whether degeneration can be arrested.

A related issue is the correspondence between the amount of transsynaptic degeneration and blindsight function. Complete transsynaptic degeneration after postgeniculate lesions has never been reported because there are other pathways to which fibers in the optic tract project. Indeed, blindsight depends on such connections because some residual visual input is required to support this phenomenon. In conclusion, though longstanding damage to the postchiasmatic visual system can cause a loss in volume in the optic tract, both direct and transsynaptically, more subtle loss of
white matter integrity can also be detected using the white matter voxels from MR images in individual patients.

Acknowledgments
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References