Changes in fiber tract integrity and visual fields after anterior temporal lobectomy

C.R. McDonald, PhD
D.J. Hagler, Jr., PhD
H.M. Girard, BA
C. Pung, BS
M.E. Ahmadi, MD
D. Holland, PhD
R.H. Patel, MD
D. Barba, MD
E.S. Tecoma, MD, PhD
V.J. Iragui, MD, PhD
E. Halgren, PhD
A.M. Dale, PhD

Address correspondence and reprint requests to Dr. C.R. McDonald, Multimodal Imaging Laboratory, Suite C101, 8950 Villa La Jolla Drive, La Jolla, CA 92037
camcdonald@ucsd.edu

ABSTRACT

Objective: To investigate postoperative changes in fiber tract integrity in patients with temporal lobe epilepsy (TLE) following anterior temporal lobectomy (ATL) and to determine whether postoperative changes are 1) stable vs progressive and 2) related to visual field defects.

Methods: Diffusion tensor imaging (DTI) was obtained in 7 patients with TLE before, 2 months after, and 1 year after ATL. Changes in fractional anisotropy (FA) were evaluated in a whole-brain voxel-wise analysis, as well within specific fiber tracts. Repeated-measures analysis of variance was performed to examine the time course of FA changes within ipsilateral and contralateral fiber tracts. Quantitative visual field analysis was performed to determine whether decreases in regional FA were related to the extent or location of visual field defects.

Results: Patients showed decreased FA 2 months post-ATL in ipsilateral fiber tracts transected during surgery (parahippocampal cingulum, uncinate fasciculus, inferior longitudinal fasciculus, and fornix), as well as in fiber tracts not directly transected (inferior fronto-occipital fasciculus and corpus callosum). Additional decreases in FA were not observed from 2 months to 1 year post-ATL. Visual field defects in most patients were characterized by incomplete quadrantanopsias. However, FA reductions in one patient extended into temporo-occipital cortex and the splenium of the corpus callosum and were associated with a complete hemianopia.

Conclusions: Wallerian degeneration is apparent 2 months following unilateral ATLs in ipsilateral fibers directly and indirectly affected during surgery. These changes do not appear to progress over the course of a year, but may correlate with the nature and extent of postoperative visual field defects. *Neurology*® 2010;75:1631-1638

GLOSSARY

ATL = anterior temporal lobectomy; **CC** = corpus callosum; **CING** = cingulate bundle; **CST** = corticospinal tract; **DTI** = diffusion tensor imaging; **DW** = diffusion-weighted; **FA** = fractional anisotropy; **FORX** = fornix; **IFOF** = inferior fronto-occipital fasciculus; **ILF** = inferior longitudinal fasciculus; **MD** = mean deviation; **PDPP** = pattern deviation probability plot; **PHC** = parahippocampal cingulum; **SLF** = superior longitudinal fasciculus; **THAL** = thalamic radiation; **ROI** = region of interest; **TLE** = temporal lobe epilepsy; **UNC** = uncinate fasciculus.

Anterior temporal lobectomy (ATL) is a highly successful treatment for alleviating seizures in patients with refractory temporal lobe epilepsy (TLE).¹ However, the residual effects of surgery on surrounding brain tissue remain poorly understood. Because many fiber tracts are severed during surgery, understanding the effects of ATLs on remaining white matter networks could have important clinical implications for predicting postsurgical morbidity.^{2,3} In particular, Wallerian degeneration may occur when severed fiber tracts are disconnected from their afferent and efferent projections, and there is some evidence that degeneration along temporo-occipital fiber tracts correlates with postoperative visual field defects.^{2,4,5}

Diffusion tensor imaging (DTI) is a quantitative method that can be used to evaluate changes in white matter integrity by measuring the directionality of water along a fiber tract (fractional anisotropy [FA]).⁶ We investigate preoperative to postoperative changes in white

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From the Department of Psychiatry (C.R.M.), Multimodal Imaging Laboratory (C.R.M., D.J.H., H.M.G., C.P., D.H., R.H.P., E.H., A.M.D.), Department of Radiology (D.J.H., M.E.A., E.H., A.M.D.), Department of Neurosciences (D.H., E.S.T., V.J.I., A.M.D.), and Department of Surgery (D.B.), University of California, San Diego.

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Table	Characteristics of the TLE sample						
	TLE01	TLE02	TLE03	TLE04	TLE05	TLE06	TLE07
Gender	Female	Male	Male	Female	Male	Female	Male
Age, y	43	21	22	25	29	23	55
Handedness	Right	Right	Right	Right	Right	Right	Right
Education, y	12	14	12	14	14	14	16
Seizure focus	Left	Right	Right	Left	Right	Left	Right
IAP language laterality	Left	Left	Left	Left	Left	Left	Left
Age at seizure onset, y	39	16	19	18	16	4	30
Duration of seizures, y	4	5	3	7	8	19	25
Mean seizures, n/mo	8	8	1	7	6	20	12
Preoperative MRI/pathology report	L MTS	R MTS	R MTS	Normal	Normal	L MTS	R MTS
Distance from temporal tip, cm	4.5	3.0	4.0	4.0	4.0	4.5	3.0
MD, dB ^a							
Ipsilateral	−9.85	−1.48	−2.90	−3.74	−3.62	−4.13	—
Contralateral	−6.37	−1.90	−3.31	−3.07	−1.78	−4.65	—
PSD, dB ^b							
Ipsilateral	16.18	2.64	2.89	4.04	7.01	9.88	—
Contralateral	9.25	1.71	2.16	4.77	4.51	8.72	—

Abbreviations: IAP = intracarotid amobarbital procedure; MD = mean deviation; MTS = mesial temporal sclerosis; PSD = pattern standard deviation; TLE = temporal lobe epilepsy.

^a The overall extent of depression of the field measured in decibels. Zero is normal for age.

^b Quantified the standard deviation of the points in the pattern deviation probability plots relative to neighbor and indicates how much each point differs from its neighbor.

matter integrity in postoperative seizure-free patients before, 2 months after, and 1 year after unilateral ATLs. We use DTI with probabilistic atlas-based fiber tract segmentation to determine 1) which fiber tracts are affected by surgery, 2) whether FA changes progress over the course of a year, and 3) whether regional FA reductions are related to the extent of visual field defects. We hypothesized that ipsilateral temporal lobe fibers would undergo Wallerian degeneration that would continue from 2 months to 1 year after surgery, whereas contralateral white matter would not change. We also hypothesized that the extent of FA reductions in the ipsilateral temporo-occipital fiber tracts would correlate with the degree of visual field defects.

METHODS **Standard protocol approvals, registrations, and patient consents.** This study was approved by an ethical standards committee on human experimentation at University of California, San Diego. Written informed consent was obtained from all patients participating in the study.

Participants. We enrolled 9 patients with TLE who were part of a preoperative DTI study, had undergone a standard unilateral ATL, and were available for postoperative follow-up. Preoperatively, all patients with TLE were identified by unequivocal

left (n = 4) or right (n = 5) seizure onset by video-EEG recordings, seizure semiology, and neuroimaging. Diagnoses were supported in 7 patients by the presence of mesial temporal sclerosis. None of the patients showed dual pathology on conventional MRI and all were seizure-free at the time of the postoperative imaging. Two patients were removed from the analysis due to severe artifacts in the MRI data. Demographic and clinical information is presented in the table.

Procedure. Patients with TLE underwent volumetric MRI and DTI prior to surgery and 2 months after surgery. Two months postsurgery was selected because measurements taken at this time are unlikely to reflect the acute effects of surgery (i.e., tissue edema and inflammation), but rather a more chronic course of myelin degradation not often observed on conventional MRI.⁷ Four of the 7 patients also completed postoperative DTI 1 year following surgery.

Automated visual field analysis. Six of the 7 patients completed automated visual field analysis to evaluate for visual field defects 2 months post-ATL. Visual fields were tested using the 30-2 threshold test, Zeiss-Meditec Humphrey Field Analyzer HFA2.⁸ Pattern deviation probability plots (PDPP; showing areas of age-controlled visual field sensitivity) and mean deviation (MD) values (representing the overall extent of depression of the visual field measured in decibels) were obtained for each eye.

Image acquisition. MRIs were performed on a GE 1.5-T EXCITE HD scanner with an 8-channel phased-array head coil. Image acquisitions included a conventional 3-plane localizer, GE calibration scan, 2 T1-weighted 3-dimensional structural scans (echo time = 3.8 msec, repetition time = 10.7 msec, bandwidth = 31.25 Hz/pixel, field of view = 25.6 cm, matrix =

Figure 1 Diffusion tensor imaging atlas of white matter tracts

Automated probabilistic fiber atlas of white matter tracts for a healthy individual. CC = corpus callosum; CST = corticospinal tract; FORX = fornix; IFOF = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; PHC = parahippocampal cingulum; SLF = superior longitudinal fasciculus; THAL = anterior thalamic radiations; UNC = uncinate fasciculus.

256 × 256, slice thickness = 1.0 mm), and a diffusion-weighted (DW) sequence. Diffusion data were acquired using single-shot echoplanar imaging with isotropic 2.5-mm voxels (matrix size = 96 × 96, field of view = 24 cm, 47 axial slices, slice thickness = 2.5 mm, partial k-space acquisition, echo time = 75.6 msec, repetition time = 12.3 seconds, $b = 1,000$ s/mm², 51 diffusion gradient directions, 1 $b = 0$ volume), covering the entire cerebrum and brainstem without gaps. For use in B0 distortion correction, 2 additional volumes were acquired using opposite phase-encoding polarity. All patients were seizure-free for a minimum of 24 hours prior to the MRI scan to avoid the possible effects of acute postictal changes on diffusion parameters.⁹

Image processing. Image files in DICOM format were transferred to a Linux workstation for processing with a customized, automated, processing stream written in MATLAB and C++. The 2 T1-weighted images were rigid body registered to each other and reoriented into a common space, roughly similar to alignment based on the AC-PC line. Images were corrected for nonlinear warping caused by nonuniform fields created by the gradient coils.¹⁰ Image intensities were corrected for spatial sensitivity inhomogeneities in the 8-channel head coil by normalizing with the ratio of a body coil scan to a head coil scan. DW images were corrected for eddy current distortion, head motion, magnetic susceptibility B0 distortion,¹¹ gradient nonlinearity distortion,¹⁰ and then resampled to 1.875 mm³ isotropic voxels. Eddy current distortion and motion correction were performed separately, but both methods involved comparisons with synthesized volumes based on tensor fits and automated censoring of slices with low signal caused by abrupt head motion. Minimization of eddy current distortion was achieved by an iterative conjugate gradient method, minimizing the difference between each DW image and its corresponding tensor-synthesized volume. There were 3 parameters per DW image defining spatial scaling in the phase-encode direction as a function of the 3 cardinal axes. Within-scan motion correction was performed by rigid-body

registration between each DW image and its corresponding tensor-synthesized volume.

Fiber tract segmentation and region of interest calculations. Fiber tract regions of interest (ROIs) were obtained using a probabilistic atlas containing information about the expected locations and local orientations of major white matter fiber tracts as described elsewhere (figure 1).¹² The T1-weighted images were used to nonlinearly map the brain into a common space,¹³ and diffusion tensor orientation estimates were compared to the atlas to obtain the relative probability that a voxel belonged to a particular fiber given the location in atlas space and the similarity of diffusion orientations. Voxels containing primarily gray matter or CSF, as segmented using the FreeSurfer software package,¹⁴ were excluded from the fiber ROIs. FA was calculated for each voxel from the eigenvalues of a tensor fit^{15,16}; an average weighted by fiber probabilities was calculated for each fiber ROI. Results obtained from the atlas-generated fibers are highly correlated with those from manual tracings.¹² In this study, the 4 temporal lobe fiber tracts transected during surgery—inferior longitudinal fasciculus (ILF), uncinate fasciculus (UNC), fornix (FORX), and parahippocampal cingulum (PHC)—as well as fiber tracts not directly transected—superior longitudinal fasciculus (SLF), anterior thalamic radiations (THAL), corticospinal tracts (CST), cingulate bundle (CING), inferior fronto-occipital fasciculus (IFOF), and corpus callosum (CC)—were of interest.

Pre to post image analysis. Postoperative FA volumes were registered to the corresponding preoperative FA volume for each subject using a high degrees of freedom nonlinear morph.¹⁷ Smoothed brain masks were used to define the ROI for the nonlinear morph; these were derived from FreeSurfer's automatic segmentation, and excluded the majority of the postoperative lesion. For comparison of the 2 postoperative time points, the FA volumes for each visit were directly registered to each other, in addition to registration to the preoperative FA volume. After registration, the difference in FA was calculated for each voxel.

The trivial reduction in FA at the site of lesion was ignored by the use of a lesion mask that was expanded ~5 mm beyond the lesion border. This lesion mask was created by calculating the difference between affinely registered brain masks for the 2 visits, and it was expanded by 2 rounds of smoothing ($\sigma = 10$ mm) and thresholding (0.01). Average FA differences were extracted for each fiber tract ROI defined in the space of the earlier visit of the pair.

Statistical analysis of fiber tract ROIs. Repeated measures analyses of variance were performed for each fiber tract on the change in FA values with side (ipsilateral vs contralateral) and time (pre to 2 months postsurgery vs 2 months to 1 year postsurgery) as repeating factors. Post hoc paired t tests were conducted to further characterize significant main effects or interactions. Spearman correlations were used to examine the relationship between temporo-occipital fiber tract (ILF) FA change and visual field MD scores for the ipsilateral and contralateral eye.

RESULTS Voxel-wise analysis. Figure 2 displays the pre to 2-month and 2-month to 1-year postsurgical FA changes in individual patients. Visual field PDPPs obtained at 2 months post-ATL are shown at right. FA reductions are apparent in the ipsilateral ILF and PHC across subjects from pre to 2-months post ATL. In TLE01, FA reductions extend along the ipsilateral ILF from the resection zone into occipital regions and the splenium of the CC. In patients for whom the 1-year post-ATL scan was available, few additional changes in FA are apparent.

Fiber tract ROI analysis. Repeated measures analyses of variance revealed a side by time interaction for the ILF ($F_{1,3} = 9.6$; $p < 0.05$), PHC ($F_{1,3} = 15.1$; $p < 0.05$), UNC ($F_{1,3} = 20.2$; $p < 0.05$), and IFOF ($F_{1,3} = 19.2$; $p < 0.05$). For each fiber tract, the interaction was due to a decrease in FA in the ipsilateral, but not contralateral, fiber tract from pre to 2-months post-ATL only (figure 3). Paired t tests confirmed that the decrease in FA for each ipsilateral fiber tract was only significant for the pre to 2-month post-ATL time period. Main effects of time were observed for CC ($F_{1,3} = 11.0$; $p < 0.05$) and FORX ($F_{1,3} = 9.4$; $p < 0.05$). In both cases, FA reductions occurred from pre to 2 months post-ATL only. For the FORX, this effect was observed in the ipsilateral and contralateral tracts. There were no main effects or interactions in the CING, CST, THAL, or SLF.

Visual field analysis. Inspection of the PDPPs (figure 2, right panel) revealed a hemianopia in TLE01. In most patients, visual field defects involved the medial sector of the upper quadrant with some defects extending in the lateral sector. Spearman correlations revealed a relationship between ipsilateral change in ILF FA and ipsilateral MD score ($r = 0.83$, $p < 0.05$; figure 4). The correlation did not reach significance for the contralateral MD score ($r = 0.71$).

DISCUSSION In this study, we evaluated the nature and course of preoperative to postoperative white matter changes over the course of a year in seizure-free patients with TLE using probabilistic atlas-based fiber tract segmentation. In support of our first hypothesis, we observed significant 2-month post-ATL reductions in FA of the ipsilateral ILF, PHC, UNC, and FORX. All 4 of these fiber tracts innervate the temporal lobe and are directly transected during surgery. These reductions were consistent across patients, with greatest FA reductions in the ipsilateral ILF and PHC relative to the other fiber tracts. In addition, 2-month postoperative FA reductions were observed in the ipsilateral IFOF and contralateral FORX. Although these fiber tracts are presumably not directly affected by surgical resection, there is evidence to suggest that Wallerian degeneration can occur along fiber tracts indirectly connected to the resection zone.¹⁸ The temporal portion of the IFOF forms the posterior-medial boundary of surgical resection.¹⁹ Therefore, the proximity of the IFOF to the resection zone and overlap with neighboring fiber tracts directly transected during surgery (i.e., ILF) may make it vulnerable to postoperative degeneration. However, it is worth noting that the ILF and IFOF may share voxels. Therefore, we conducted our analyses both including and excluding voxels shared by the ILF and IFOF. Both analyses yielded similar results, demonstrating that the effects observed in the IFOF were not due to voxel-wise overlap with the ILF. It is of interest that the FORX alone showed a pattern of bilateral FA decrease. Unlike the other fibers that innervate the temporal lobe, the 2 halves of the FORX are joined by a commissural component. The significant, but milder, FA decrease in the contralateral FORX FA suggests downstream Wallerian degeneration via its interhemispheric component. One previous study has evaluated preoperative to postoperative changes in the FORX and surrounding white matter following ATLs.¹⁸ This study revealed FA reductions in the ipsilateral FORX and CING, as well as a failure of normalization in the contralateral tracts at 1 year post-ATL. We extend the literature by demonstrating ipsilateral reductions within numerous temporal and extratemporal fiber tracts, and by providing evidence of downstream, interhemispheric degeneration affecting contralateral white matter tracts (i.e., FORX).

Decreased FA was also observed in the CC following surgery. Fibers from the tapetum, which constitutes the middle portion of the CC, extend laterally and downward into the temporal lobe and are interposed between the optic radiations and the temporal horn of the lateral ventricle.²⁰ A portion of

Figure 2 Preoperative to postoperative fractional anisotropy (FA) change and visual field defects

Voxel-wise FA change maps for each patient superimposed on their postoperative T1-weighted MRI with fiber tract overlays. FA change values from pre to 2 months post anterior temporal lobectomy (ATL). FA change range from a decrease of 0.01 (pure red) to a decrease of 0.05 (pure yellow) for each individual (B). Pattern deviation probability plots (PDPPs) for each individual obtained at 2 months post-ATL (C). The measured visual field values are represented as the percentage of age-matched controls with lower sensitivity or no response to stimuli at each spatial location. The PDPPs also correct for typical vision changes in the height of the hill of vision. Shaded values range from areas of relatively normal vision (small white dots) to areas in which 99.5% of age-matched controls show greater sensitivity at that spatial location (percent <0.5%).

Figure 3 Fractional anisotropy (FA) change for ipsilateral and contralateral fiber tracts

Mean FA change values for each of the ipsilateral (A) and contralateral (B) fiber tracts. Negative values represent a decrease in FA and positive values represent an increase in FA. Fibers with a significant time $\times$ side interaction are denoted with *. Fibers with a significant main effect of time are denoted with +. CING = cingulum (superior part); CST = corticospinal tract; FORX = fornix; IFOF = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; PHC = parahippocampal cingulum; SLF = superior longitudinal fasciculus; THAL = anterior thalamic radiations; UNC = uncinate fasciculus.

these fibers is likely affected by unilateral ATLs. In addition, fibers from the splenium of the CC interconnect the temporal lobes. Wallerian degeneration may occur along the tapetum and through the splenium of the CC once the anterior temporal lobe has been removed.^{18,21,22}

Contrary to our second hypothesis, fiber tract integrity did not change from 2 months to 1 year post-surgery. These data support the presence of potentially irreversible, underlying structural changes in axonal/myelin integrity rather than temporary fluid shifts related to ongoing seizures.¹⁸ We extend the literature by demonstrating that fiber tract compromise apparent at 2 months post-ATL does not continue to progress within the first year. In fact, post hoc inspection of the data revealed a trend for

fiber FA to increase in the ipsilateral CST relative to the preoperative scan ($p = 0.079$). If present, post-operative increases in FA may be very subtle and protracted in seizure-free patients and would only be detected with a larger sample or longer time interval.

Finally, we examined whether reductions in FA along temporo-occipital fibers would be related to extent of visual field defects. In the temporal lobe, the optic radiations project from the lateral geniculate of the thalamus, anteriorly and laterally over the temporal horn of the lateral ventricles before coursing posteriorly toward the occipital pole.²³ In ATLs, the anterior portion of the ventral visual pathway (i.e., Meyer's loop) is removed, producing an incomplete (medial sector) quadrantanopia in a majority of patients.^{24,25} Concurrent damage to the pos-

Figure 4 Relationship between inferior longitudinal fasciculus (ILF) fractional anisotropy (FA) change and visual field mean deviation (MD) scores

Scatterplots of the relationship between pre to 2-month changes in FA of the ipsilateral ILF and the MD score for the ipsilateral (A) and contralateral (B) eyes.

terior portion of Meyer's loop can affect the lateral sector, resulting in a complete quadrantanopia, and damage to the superior portion of the optic radiations can cause a hemianopia.⁴ This would appear to be the case for TLE01, who sustained a hemianopia and widespread FA reductions along the ILF, splenium of the CC, and adjacent temporo-occipital white matter likely encompassing part of Meyer's loop and the superior optic tracts. Our other patients showed visual defects primarily to the medial sector of the upper quadrant, with more modest involvement of the lateral sector. The optic pathways are located just medially and superior to the ILF and generally represent the posterior-superior and deep limit of ATL.¹⁹ However, there is substantial overlap between the fibers of the ILF and optic pathways. Therefore, it is likely that FA reductions observed in the ipsilateral ILF ROI are due to degenerative changes in both tracts. Two previous tractography studies found the involvement of Meyer's loop to predict the extent of visual field defects.^{3,26} Our data extend this literature, revealing a relationship between temporo-occipital tract compromise and the extent of the visual field depression using a novel, automated probabilistic atlas of fiber locations and orientations that can be applied to individual patient data.

Several limitations of this study should be addressed. First, the time points selected for the postoperative DTI did not allow us to evaluate very early or late Wallerian degeneration. Previous research has shown decreased FA in the sagittal striata (which includes the ILF and optic radiations) a mean of 4 weeks postsurgery that correlated with the degree of visual field defect.² The decrease in FA tended to be greater in cases where the time after surgery was longer, suggesting that white matter compromise increases over time. Although we did not study patients until 2 months post-ATL, it is interesting to note that no significant changes occurred between the 2-month and 1-year period in any patient. Second, we only studied patients who were seizure-free. It is possible that additional decreases in FA would have been observed in patients who continued to have seizures postoperatively. Third, we did not measure changes in FA isolated to Meyer's loop. Like previous studies,^{2,4} we measured a broader area of white matter that likely included Meyer's loop to infer associations between optic tract damage and visual field defects. Meyer's loop is challenging to isolate due to its overlap with other fiber tracts and its sharp bend into the temporal pole. Future studies using techniques better suited to handle crossing fibers would be beneficial, as would the use of smaller voxel size, higher *b* values, and a larger number of gradient di-

rections. Finally, we provide data from a small group of patients. Our data highlight postsurgical changes in fiber tract integrity that are robust within and across patients, but may obscure more subtle changes in fiber tract degeneration or normalization that can be captured when data are averaged across a large number of subjects in group studies. Rather, our findings demonstrate an approach that may be most useful in a clinical setting for understanding relationships between fiber tract compromise and clinical morbidity in individual patients.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. C.R. McDonald.

DISCLOSURE

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