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The acute phase of Wallerian degeneration: Longitudinal diffusion tensor imaging of the fornix following temporal lobe surgery

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ABSTRACT

Numerous animal studies have shown the applicability of diffusion tensor imaging (DTI) to track Wallerian degeneration that occurs after injury to the neural fiber. Non-invasive biomarkers that may differentiate the early axonal breakdown and later myelin degradation have been attributed to either reduced parallel and elevated perpendicular diffusivity, respectively. While several human DTI studies have shown this potential at subacute and chronic time points, the diffusion changes that occur within the first week are unknown. Anterior temporal lobectomy (i.e. resection of hippocampus) is the standard surgical treatment of medically refractory temporal lobe epilepsy. The concomitant transection of the fimbria-fornix serves as a unique opportunity to examine the process of Wallerian degeneration since the timing is known. Six temporal lobe epilepsy patients underwent brain DTI before the surgery, three to four times within the first week post-operatively, and at one to four months following surgery. Both parallel and perpendicular diffusivities decreased markedly by a similar amount in the ipsilateral fornix within the first two days post-surgery. Approaching the end of the first week, perpendicular (but not parallel) diffusivity pseudo-recovered towards its pre-surgical value, but then increased dramatically months later. Fractional anisotropy, as a result of the combined action of the parallel and perpendicular diffusivities, stayed relatively stable within the first week and only reduced drastically at the chronic stage. DTI demonstrated acute water diffusion changes within days of transection that are not just limited to parallel diffusivity. While the chronic diffusion changes in the fornix are compatible with myelin degradation, the acute changes may reflect beading and swelling of axolemma, granular disintegration of the axonal neurofilaments, ischemia induced cytotoxic edema, and/or changes in the extra-axonal space including inflammatory changes and gliosis.

Introduction

Non-invasive measures of water diffusion and its anisotropy in neural fibers have long been shown to be a sensitive indicator of micro-structural changes associated with Wallerian degeneration (Beaulieu et al., 1996; Ford et al., 1994). These studies in both central and peripheral nervous systems demonstrated concurrent reductions of parallel diffusivity (axial, $\lambda_{||}$) and increases of perpendicular diffusivity (radial, λ) yielding reductions in anisotropy that were linked with histology to both axonal injury and demyelination. However, the diffusion measurements were performed late at 7 days after the spinal cord injury in rats (Ford et al., 1994) or after 1 month for the sciatic nerve injury in frogs (Beaulieu et al., 1996). This combined set of diffusion changes was also observed in ipsilateral internal capsule in chronic stroke patients (Pierpaoli et al., 2001).

Serial measurements including early time points in an optic nerve injury model led to the observation that the individual diffusivities may yield more specific tissue indicators as the reduction of $\lambda_{||}$ early post retinal ischemia, without a change in λ, correlated with axonal damage and the elevation of λ later was associated with myelin break down (Song et al., 2003). This diffusion eigenvalue hypothesis has been supported by similar observations in other experimental models including trauma, multiple scleroses and stroke (Budde et al., 2008; Kozlowski et al., 2008; Mac Donald et al., 2007a; Sun et al., 2008; Zhang et al., 2009).

Since a series of histological examinations are not generally applicable in humans in vivo, could diffusion tensor imaging (DTI) provide similar insights into the progression of Wallerian degeneration that is otherwise not evident with conventional MRI? In patients with atonic seizures, transection of the anterior 2/3 of the corpus callosum resulted in a markedly similar evolution of the diffusion eigenvalues as shown in the experimental models, namely reduction of $\lambda_{||}$ with

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little change of λ at 1 week and then major increases of λ at 2 months (Concha et al., 2006). However, the pattern and time course of water diffusion within the first week following white matter injury remain unknown in human brain. Surgical transection studies such as this have the advantage of being able to perform pre-operative DTI and have a definitive injury to the tract at a precise time.

Anterior temporal lobectomy (ATL) and selective amygdalohippocampectomy (SelAH) are surgical treatments for intractable temporal lobe epilepsy (TLE). In standard ATL, the anterior portion of the temporal lobe is completely removed while during SelAH, mesial temporal structures that are involved with seizures are selectively removed and much of the lateral temporal lobe is spared with the goal of reducing postoperative morbidity (Wheatley, 2008). During both procedures, the crus of the fornix is completely resected anterior to the surgical margin under direct visualization with hippocampal efferent fibers originating anterior to the resection margin expected to then undergo Wallerian degeneration. Other DTI studies have shown post-surgical reductions of anisotropy in the ipsilateral fornix of epilepsy patients; however, the diffusion parameters have been measured greater than 2 months post-surgery (Concha et al., 2007; McDonald et al., 2010; Nguyen et al., 2011; Yogarajah et al., 2010). While there are challenges in performing MRI on patients within the first week after brain surgery, this time frame is needed to understand what diffusion changes occur at the early phases of Wallerian degeneration. The objective of this study was to assess the acute changes of water diffusion in a white matter bundle, namely the ipsilateral crus of the fimbria-fornix, after a transection injury in temporal lobe epilepsy patients.

Material and methods

Approval of the research protocol was obtained from the University of Alberta Health Research Ethics Board, and informed consent was obtained from all participants.

Subjects

Six patients with medically intractable epilepsy as well as three healthy individuals were included in this study. Sutures were used instead of the conventional staples to enable the MRI scanning post-surgery. All patients were entirely seizure free after surgery throughout the imaging period. The postoperative T1 weighted MPRAGE scans clearly show the surgical cavities (Fig. 1). Surgical pathology was available in four of six subjects. For the remaining two subjects, hippocampal T2 relaxometry, which has been demonstrated to correlate strongly with hippocampal sclerosis, was used to define presumptive hippocampal sclerosis using a T2 value of >120 ms (Concha et al., 2005a, 2009).

Patient 1 (33 years, right-handed male) suffered medically refractory complex partial seizure originating from the left mesiotemporal lobe as revealed by EEG-video telemetry. Clinical MRI showed clear evidence of left mesiotemporal sclerosis. The patient demonstrated elevated T2 relaxometry value in the left hippocampus (left 128 ms, right 113 ms). He underwent left selective amygdalohippocampectomy and was scanned with our imaging protocol 6 months before surgery and 1, 2, 3, 6 days, 2 months, and 4 months after surgery. Post-operative histological examination of the resected hippocampus confirmed typical hippocampal sclerosis.

Patient 2 (55 years, right-handed female) suffered frequent generalized and complex partial seizures. Intracranial EEG-video telemetry demonstrated an epileptic generator in the left mesiotemporal region. Clinical MRI showed diffuse atrophy without obvious focal lateralized structural abnormality. The patient demonstrated elevated T2 relaxometry value in the left hippocampus (left 126 ms, right 110 ms). She underwent left anterior temporal lobectomy and was scanned 3 months before surgery and 2, 3, 6, 7 days, and 2 months after surgery. Post-operative histological examination of the resected left hippocampus confirmed typical hippocampal sclerosis.

Patient 3 (45 years, right-handed male) suffered typical complex partial seizures and was demonstrated to have a right temporal ictal generator on EEG-video telemetry. Clinical MRI showed clear evidence of right mesiotemporal sclerosis. The patient demonstrated elevated T2 relaxometry value in the right hippocampus (left 114 ms, right 139 ms). He underwent right selective amygdalohippocampectomy and was scanned 12 months before surgery and 1, 5, 6 days, and 2 months after surgery. Post-operative histological examination of the resected right hippocampus confirmed hippocampal sclerosis.

Patient 4 (39 years, right-handed female) suffered medically refractory complex partial seizures originating from the right temporal lobe detected with EEG-video telemetry. Clinical MRI showed increased signal in right hippocampus consistent with MTS, however the patient did not show elevated T2 relaxometry value in either side of the hippocampus (left 114 ms, right 113 ms). She underwent right anterior temporal lobectomy and was scanned 7 months before surgery and 1, 2, 3, 7 days, and 2 months after surgery. Post-operative histological examination of the resected right hippocampus showed no evidence of hippocampal sclerosis.

Patient 5 (29 years, left-handed male) suffered complex partial seizures with a focal ictal onset in the right temporal lobe demonstrated on EEG-video telemetry. Clinical MRI suggested right hippocampal sclerosis; however, the patient did not present elevated T2 relaxometry value in either side of the hippocampus (left 113 ms, right 103 ms). He underwent right anterior temporal lobectomy and was scanned twice (10 months and 4 days) before surgery and 1, 2, 3, 6 days, 1 month, and 4 months after surgery.

Patient 6 (26 years, left-handed male) suffered complex partial seizures with ictal and interictal epileptic discharges confined to the left temporal lobe as demonstrated with EEG-video telemetry. Clinical MRI suggested left hippocampal sclerosis. The patient demonstrated elevated T2 relaxometry value in the left hippocampus (left 148 ms, right 114 ms). He underwent left anterior temporal lobectomy and was scanned 1 month before surgery and 1, 2, 3, 6 days, and 2 months after surgery.

Three controls (age: 20, 22 and 33 years, all right-handed male) were scanned six times corresponding to the scan time points in patients: initial, and 1, 2, 3, 6 days and 2 months after to investigate the variability of the diffusion measurements in the absence of surgery. One scan acquired at 1 day after the initial time point from a control was excluded due to a MRI data acquisition problem. A total of 17 scans from controls were used in the variability analysis.

Image acquisition

Fluid-attenuated inversion recovery (FLAIR) DTI was performed on a 1.5T Siemens Sonata (Erlangen, Germany) using a dual spin-echo, single shot echo planar imaging sequence with the following parameters: 2 mm thick slices with no inter-slice gap, TR = 10 s, TE = 88 ms, TI = 2200 ms, acquisition matrix = 128 × 128 with 75% phase partial Fourier (interpolated to 256 × 256), FOV = 256 mm × 256 mm, voxel dimension 2 × 2 × 2 mm^3 (interpolated to 1 × 1 × 2 mm^3), 26 axial slices with coverage of fornices, 6 diffusion directions, b = 1000 s/mm^2, 8 averages, and scan time = 8:30 min (Concha et al., 2005b). The FLAIR DTI was adopted for its advantages of suppressing signal from cerebrospinal fluid and minimizing partial volume artifacts (Papadakis et al., 2002), which is very important for the fornix (Concha et al., 2005b). The SNR of the non-diffusion weighted images in this study was ~56.

Diffusion tensor tractography and measurements of diffusivity and T2-intensity ratio

Fractional anisotropy and diffusion maps were calculated with DTIstudio V2.4 (Johns Hopkins University, Baltimore, USA). For each

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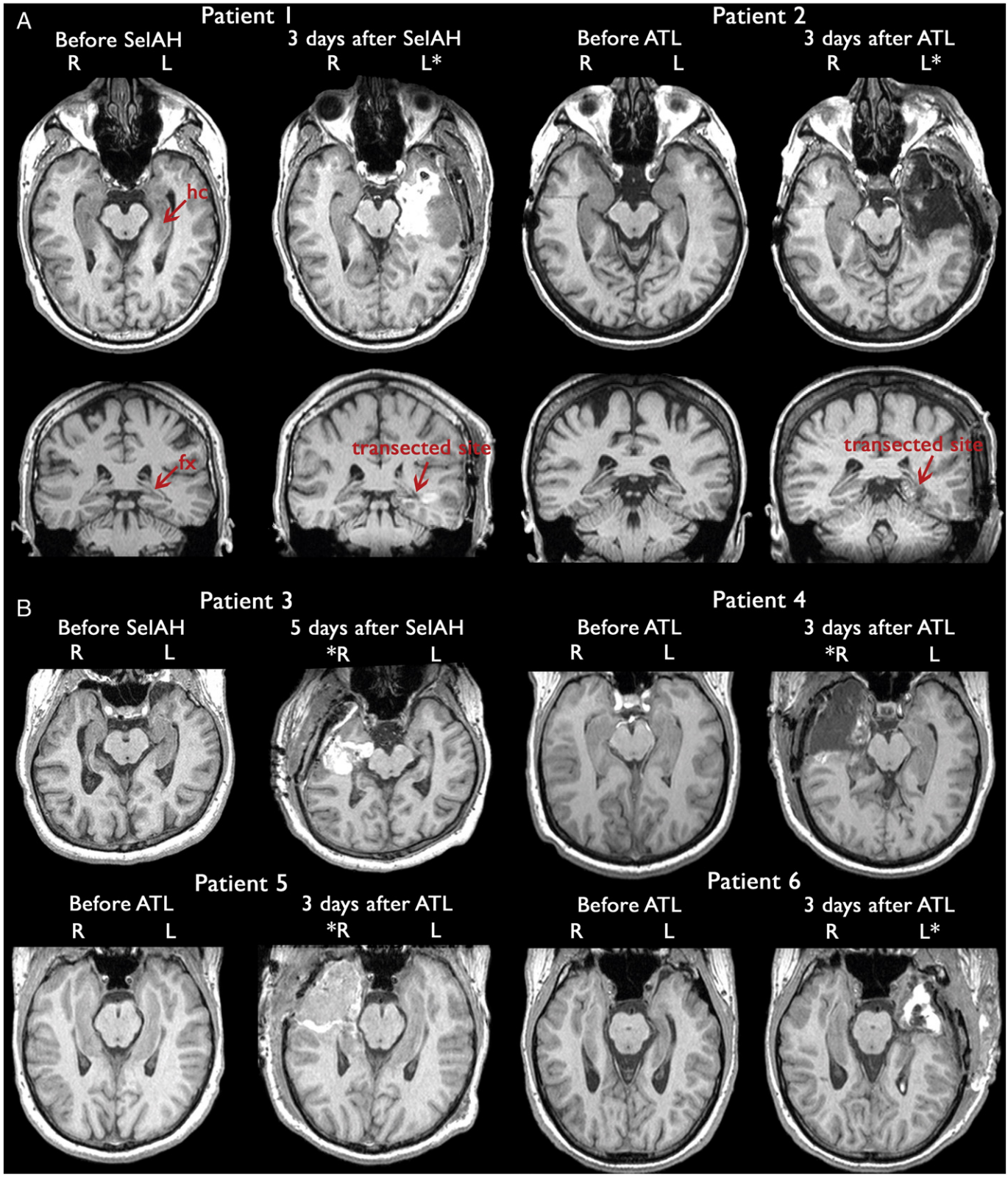

Fig. 1. Demonstration of resection site before and after surgery (side indicated by *) on T1-weighted MPRAGE scans. (A) Axial (top row) and coronal (bottom row) slices on Patient 1 who underwent a left selective amygdalohippocampectomy (SelAH) and Patient 2 who underwent a left anterior temporal lobectomy (ATL). Part of the head of the left hippocampus (hc) was removed and the left fimbria-fornix (fx) was transected in both surgery techniques. (B) Axial slices for the other four patients who underwent surgery.

time point before the surgery and within the first week after surgery, diffusion tensor tractography of fimbria-fornix crus (fornix for short) both ipsilateral and contralateral to the surgery side was performed manually and separately using the fiber assignment by continuous tracking (FACT) algorithm adopted by DTIstudio with FA threshold 0.25 and angular threshold 70° (Mori et al., 1999). The region-of-interests used to select the tracts were drawn on color maps based on the methods and anatomy described before (Concha et al.,

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2005b). Each fornix was defined as the portion posterior to the most anterior coronal slice where the two crura were separated and only contained fibers traveling from the corresponding hippocampus to the body of the fornix. The manual tracing has an inter-rater reliability of 0.80 and intra-rater reliability of 0.81 (Malykhin et al., 2008). For the chronic scans, because deterministic tractography was unable to trace the middle portion of the fornix which was severely degenerated, the pre-surgical non-diffusion-weighted images (i.e., b0 images) in patients or the initial scans in controls were nonlinearly registered to their corresponding chronic scans using diffeomorphic demons algorithm (Vercauteren et al., 2009) in MedINRIA (v1.6, INRIA-Asclepios Research Team, France). The same deformation was applied to the tract from the pre-surgical/initial time point to derive an approximate fornix for the chronic scans. An FA threshold of 0.25 was applied to the quantitative analysis of the approximate fornix in order to exclude a small number of voxels misregistered to the adjacent gray matter. This approach yielded consistent measurements for the chronic scans in controls (see section Quantitative analysis); however, given the FA threshold, it may lead to an underestimation of the change in fornix. Four diffusion parameters including fractional anisotropy (FA), mean diffusivity (MD), $\lambda_{||}$ and $\lambda_{\perp}$ were obtained by overlaying the tracts on the corresponding diffusion maps and averaging across all voxels occupied by the tracts in order to generate a single value for each fornix using an in-house program. The diffusion parameters of the left and right fornix were also queried in controls by the aforementioned method to define a normal variation range of the four diffusion parameters. The occipital callosal fibers that were not transected during surgery were analyzed as an internal reference in patients by the same method since the FLAIR DTI covers this structure completely. No apparent diffusion changes were expected since occipital callosal fibers are not injured during either anterior temporal lobectomy or selective amygdalohippocampectomy.

The longitudinal T2-weighted signal intensity of the fornix was measured in each tractography defined fornix on the non-diffusion-weighted FLAIR images ($b=0$ s/mm^2) that have a long echo time of 88 ms. To account for scanner variability in different imaging sessions, the fornix T2 signal intensity was normalized by the non-transected occipital callosal fibers T2 signal intensity, yielding a T2-intensity ratio of 1.01 ± 0.03 in the 3 healthy volunteers over all time points.

Quantitative analysis

The absolute difference of later scans relative to the first scan was calculated for each side of the fornix of each control. Left and right fornices showed similar longitudinal variability for all diffusion parameters in the healthy controls (Fig. 2). The normal variation range was defined as twice the average absolute deviation relative to zero for all three controls which was 0.031 for FA, 0.033×10^{-3} mm^2/s for MD, 0.063×10^{-3} mm^2/s for $\lambda_{||}$, 0.031×10^{-3} mm^2/s for $\lambda_{\perp}$, and 0.049 for T2-intensity ratio. For patients, the absolute difference of each post-surgery scan relative to the pre-surgical baseline was calculated to query the longitudinal alteration of the ipsilateral and

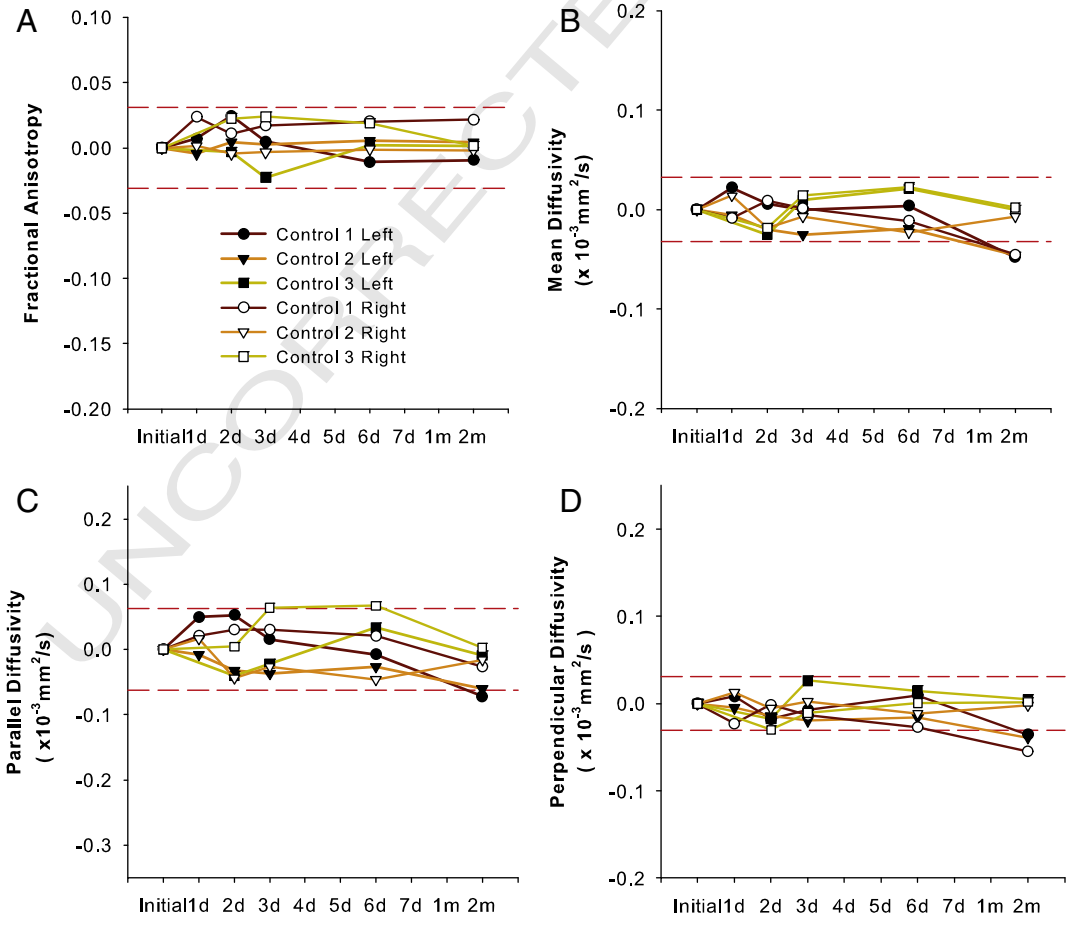

Fig. 2. Time course of normalized DTI parameters of crus of fimbria-fornices in each hemisphere from three controls repeatedly measured over a similar time span as patients. The four DTI parameters were normalized to the first scan. The normal variation range was defined as twice the average absolute deviation from the initial time point of the six fornices (shown by the two red dashed lines). Vertical scales are kept the same as subsequent patient plots.

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contralateral fornix separately as well as occipital callosal fibers. The change was considered significant if it surpassed the normal variation range.

Results

Qualitative visualization of diffusion changes on tractography

As expected, the non-transected callosal fibers of patients showed minimal changes of the four diffusion parameters by visual inspection of the color-coded tracts (Fig. 3). There was some small variation of the shape of the fornix at different time points in patients within the first week resulting from the displacement of brain after surgery (Fig. 4) yet the tract volume did not differ from each other by more than 10% (data not shown). It was not possible to measure the fornix volume at the chronic stage as the low FA values made the tractography algorithm ineffective. The four diffusion parameters of the ipsilateral fornix showed unique changes over time (details in section Quantitative assessment of fornix parameters post-surgery below). All parts of the ipsilateral crus of the fornix appeared to demonstrate simultaneous changes, rather than a graded change along the tract. These changes were similar for patients who underwent either anterior temporal lobectomy or selective amygdalohippocampectomy. The diffusion maps of the contralateral fornix (not shown) appeared quite consistent over time.

Quantitative assessment of fornix parameters post-surgery

All four diffusion parameters were within the normal variation range in the non-transected occipital callosal fibers over all time points (Fig. 5). The mean percentage of the absolute variation across all time points and patients was 2% for FA (range: 1–3%), 2% for MD (range: 1–2%), 2% for $\lambda_{||}$ (range: 0.1–2%) and 3% for $\lambda_{\perp}$ (range: 2–4%).

In contrast, the transected ipsilateral fornix crus had alterations in the four diffusion parameters post-surgery, although with different timing patterns (individual participant data normalized to their first scan in Fig. 6). The FA was relatively stable within the first week after surgery except Patient 1 that showed a decrease beyond normal variation range at 6 days. All six patients had major reductions of FA (19%, range 10–30%) at 1–4 months post-operative. In contrast, immediate reductions of MD, $\lambda_{||}$, and/or $\lambda_{\perp}$ were observed in all six patients as early as the first one or two days after surgery. Specifically, MD was reduced within the first two days (reduced by 8%, range: 4–13%) and rebounded back to some extent at 6–7 days post-operative yet still remained lower than the initial. At 1–4 months, five out of six patients showed an elevated MD (7%, range: 4–12%) with only Patient 3 presenting MD at pre-surgery levels. A reduction of $\lambda_{||}$ occurred in the first two days for five out of six patients (reduced by 10%, range: 5–15%) except Patient 5 that remained within the normal variation range. The $\lambda_{||}$ stayed low for the rest of the week. At the chronic stage, $\lambda_{||}$ remained low in four of six patients and did not reverse back to baseline, but Patients 2 and 5 rebounded back to the pre-surgical level. For $\lambda_{\perp}$, an acute reduction occurred at 1–2 days after surgery (8%; range: 6–11%) for five of six patients, which then showed a rebound pattern closer to baseline by the end of the first week whereas Patient 4 remained within the normal variation over the first week. At 6–7 days, $\lambda_{\perp}$ in four patients recovered to pre-surgical level while $\lambda_{\perp}$ in Patients 2 and 3 stayed unrecovered (reduced by 9% and 6%, respectively). At 2 months post-operation, $\lambda_{\perp}$ increased beyond pre-surgical levels in all patients (increased by 17%, range: 10–33%).

In contrast, the contralateral fornix showed very little change over time (Fig. 7) in five of six patients with the exception of Patient 1.

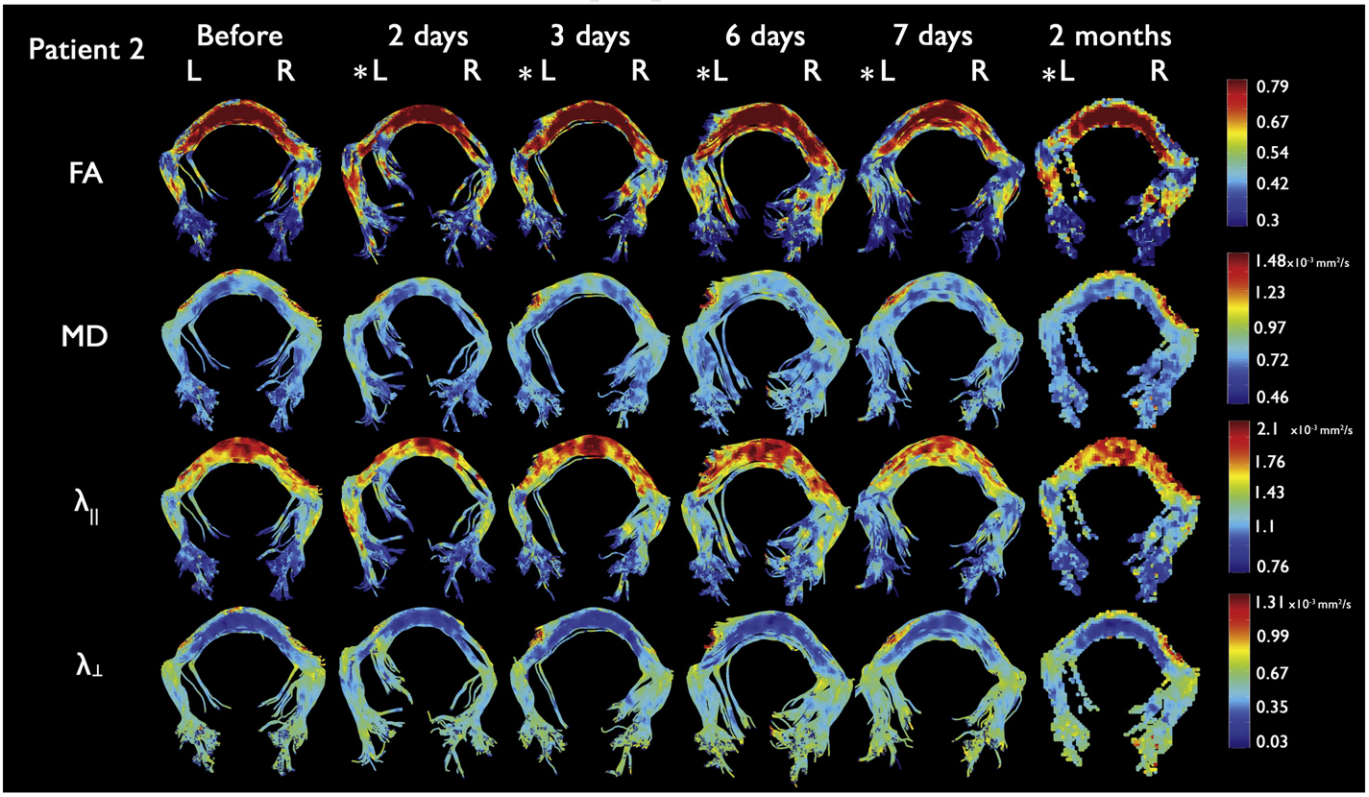

Fig. 3. Visualization of non-transected occipital callosal fibers (viewed from above) before and after left anterior temporal lobectomy surgery in Patient 2 where FA, MD, $\lambda_{||}$, and $\lambda_{\perp}$ values are color-coded for each voxel. The parameters showed minimal changes as expected. The occipital callosal fibers at 2 months were coregistered from the pre-surgical fibers and are displayed as voxels rather than streamlines at the earlier time points. L, left; R, right. The surgery side is marked by asterisks.

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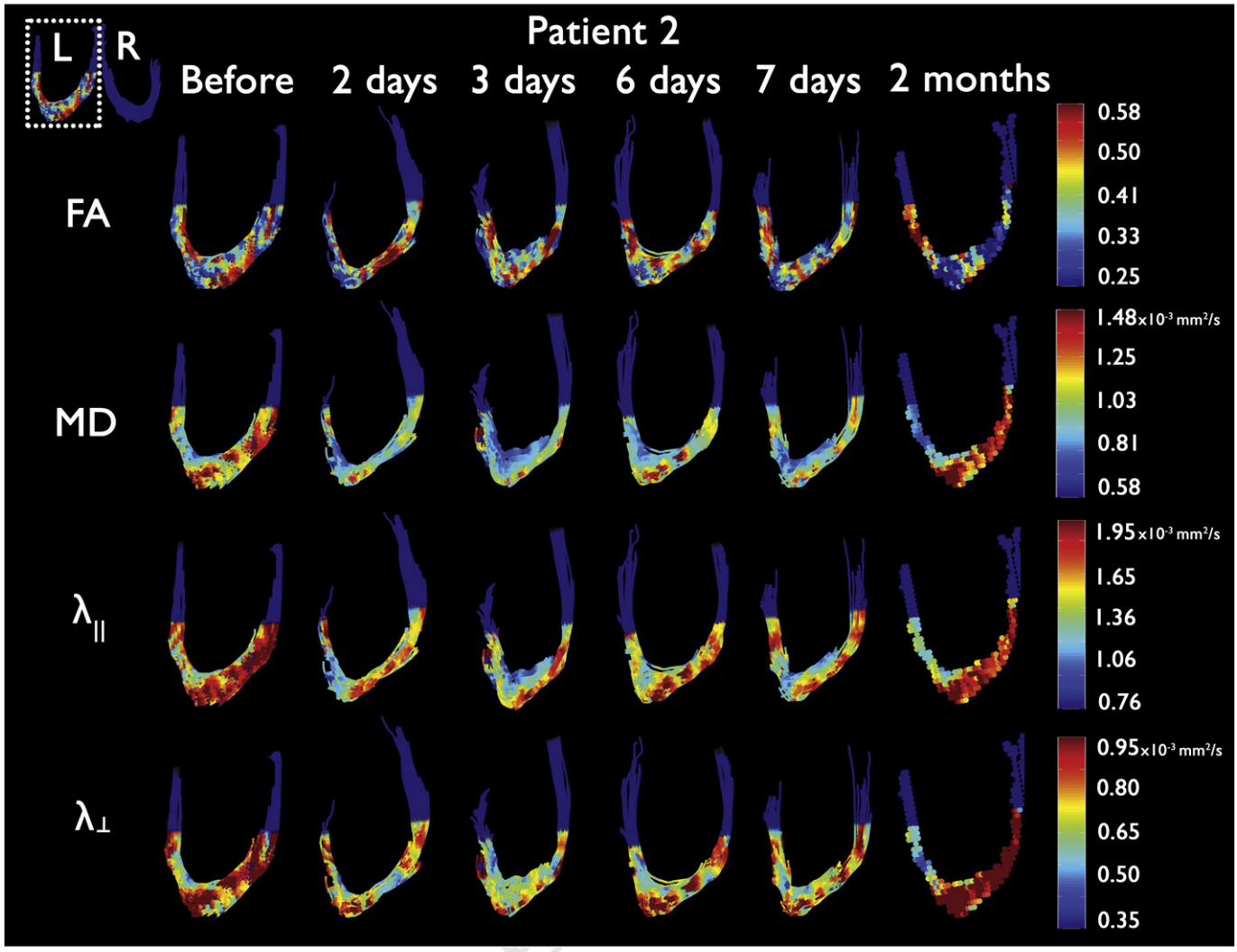

Fig. 4. Visualization of the ipsilateral/left crus of fimbria-fornices (viewed from above) before and after surgery in Patient 2 where FA, MD, $\lambda_{||}$, and λ values are color-coded for each voxel. The non-measured part (i.e. the body of fornix and the fimbria-fornix adjacent to hippocampi) is colored in uniform dark purple. The FA was relatively stable within the first week after surgery and decreased at 2 months. The $\lambda_{||}$, λ, and MD were reduced at 2 days, stayed low up to 7 days, and then increased at least to ($\lambda_{||}$) or beyond (λ, MD) the pre-surgical values at 2 months.

Patient 1, who had a left selective amygdalohippocampectomy, demonstrated FA reduction and MD and λ elevation beyond the normal variation range from 6 days to 4 months. Notably, Patient 1 also showed the greatest FA reductions in the ipsilateral fornix. Patient 2 and Patient 3 showed some changes slightly beyond the normal variation range at one or two time points but they were not consistent over time.

An increase of the normalized ipsilateral fornix T2-intensity (normalized to the non-transected occipital corpus callosum) was observed within the first two days after surgery (increased by 10%, range: 8–16%) except Patient 4 who showed a slight decrease of 5% (Fig. 8A). T2-intensity peaked at two days and gradually returned to its pre-surgical level in four out of six patients at the end of the first week except Patients 2 and 3. At 1–4 months, the ratio in four patients totally returned to its pre-surgical state while Patients 4 and 6 had a decrease of 11% and 7%, respectively. The contralateral fornix of five patients had relatively stable T2-intensity ratios except Patient 6 who showed a consistent ~6% decrease post-surgery (Fig. 8B).

Compared to Patients 1–3 and 6 who demonstrated T2 evidence of hippocampal sclerosis, Patients 4 and 5 who did not exhibit T2 evidence of hippocampal sclerosis showed an absolute reduction of mean, parallel and perpendicular diffusivities to a lesser extent within the first week after surgery (Fig. 9); in many cases the values were still within the normal variation range of controls.

Discussion

Wallerian degeneration can be caused by a variety of axonal injuries such as trauma, ischemia, metabolic abnormalities, toxins and inflammation (Coleman and Perry, 2002; Raff et al., 2002; Vargas and Barres, 2007). It is characterized by a series of chronological events, namely, axonal degeneration at both the proximal and distal ends as early as 30 min post injury (Kerschensteiner et al., 2005), axonal beading and swelling close to the injury site between 1 and 48 h (Beirowski et al., 2010; George et al., 1995; Sievers et al., 2003; Zhai et al., 2003), granular disintegration of axonal cytoskeleton resulting in axon fragmentation with the initiation of narrowing and dilating myelin sheath, myelin ovoid formation, and clearance of myelin debris in the long term (George and Griffin, 1994). In this study, distinct acute (1–7 days) and chronic (1–4 months) water diffusion changes were shown after transection of the ipsilateral fornix during temporal lobe epilepsy surgery. These diffusion changes reflect presumably the different stages of Wallerian degeneration. The reduced FA and

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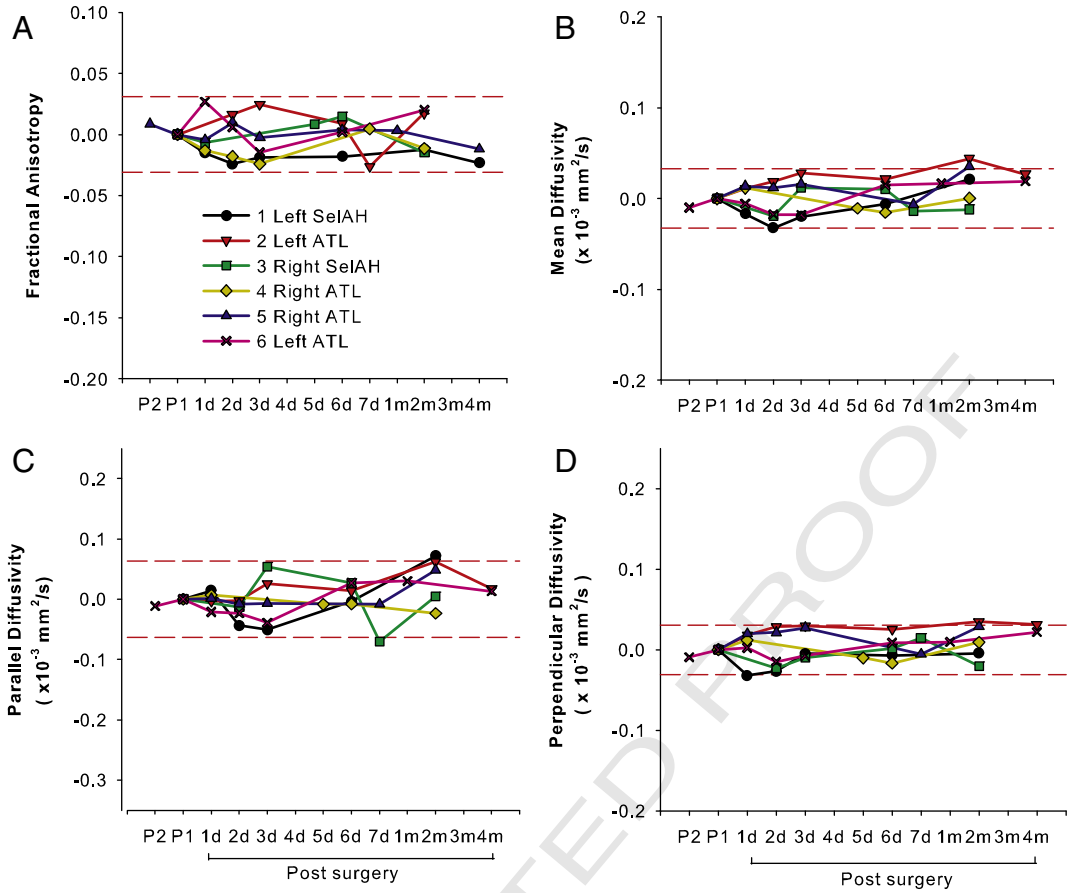

Fig. 5. Time course of normalized DTI parameters of the non-transected occipital callosal fibers from six patients with temporal lobe epilepsy prior to (P1, P2) and after (days, d and months, m) surgery. The time point prior to surgery serves as a baseline. DTI parameters were normalized by subtracting the baseline value from each time point. The red dashed lines showed the normal variation range defined from repeated measures of three controls spanning a similar period of time. The diffusion parameters showed minimal changes within the normal variation range over time. SelAH, selective amygdalohippocampectomy; ATL, anterior temporal lobectomy.

elevated perpendicular diffusivity ($\lambda_\perp$) were expected at chronic stages. The acute reduction of parallel diffusivity ($\lambda_{||}$) within the first week is also in line with previous literature, but the concomitant reduction of $\lambda_\perp$ yielding reduced mean diffusivity (MD) and preserved fractional anisotropy (FA) is a new observation.

Acute diffusion changes within the first week post-surgery

Temporal lobe surgery serves as a unique opportunity to examine the process of Wallerian degeneration since the timing of the transection of fimbria-fornix crus is known, requirements not usually met by naturally occurring neurological disease. To date, there is a lack of literature investigating acute diffusion changes within days of axonal transection in human brain; not surprising given the practical issues of performing an MRI on a patient so soon after brain surgery. Experimental models have been used to explore the acute DTI changes post injury. An early decrease of $\lambda_{||}$ and FA without significant increase of $\lambda_\perp$ until later time points has been reported in the white matter after neuronal injury from retinal ischemia (Song et al., 2003; Sun et al., 2008), trauma (Kim et al., 2007; Mac Donald et al., 2007a, 2007b; Zhang et al., 2009) and experimental autoimmune encephalomyelitis (EAE) (Budde et al., 2008). Immunohistochemistry and optical/electron microscopy examinations in these studies confirmed axonal injury without demyelination at an early post-injury stage, strongly suggesting $\lambda_{||}$ as an imaging marker for axonal degeneration.

In contrast, we observed concurrent reduction of both parallel and perpendicular diffusivities, which reduces mean diffusivity, with a relatively stable fractional anisotropy of the transected fornix within the first two days after surgery. This acute diffusion change may reflect the axonal swelling/spheroid formation immediately after axonal injury. Demonstrated recently, axonal swellings arise as soon as 1 h post injury starting from the surrounding of the injury to more distal sites after transection of the optic nerve in rats and mice (Beirowski et al., 2010). Swelling persists at least for 24 h post injury with clear continuity of the axons and no appearance of axonal fragmentation. Confocal imaging revealed that axonal swellings extended over the entire corpus callosum fiber of the mice by 24 h, marking its rapid progression in the central nervous system. A simulation biophysical model showed that the morphometric changes of axons such as neurite beading was sufficient enough to hinder water mobility and thereby decrease $\lambda_{||}$ in both the intra- and extracellular compartments and $\lambda_\perp$ mainly in the extracellular compartment (Budde and Frank, 2010). The simulations predicted that $\lambda_{||}$ would decrease to a greater extent than $\lambda_\perp$; this was confirmed in axons injured by stretching although FA was not significantly reduced. However, here the transected fornix showed similar percentage reductions of both $\lambda_{||}$ and $\lambda_\perp$ also leading to a lack of change of FA in the first week. These reduced diffusion coefficients, particularly parallel, are consistent with disintegration of the axonal cytoskeleton. It is unclear why earlier experimental studies performing DTI within days after injury do not observe a reduction of $\lambda_\perp$. This may be partly due to the fact that the magnitude of $\lambda_\perp$ in rodent white matter is only about one-fifth of $\lambda_{||}$ which increases the difficulty of detecting a change in $\lambda_\perp$ (Xu et al., 2008), while the magnitude of $\lambda_\perp$ in the fornix in human is only about half of the magnitude of $\lambda_{||}$ (Table 1).

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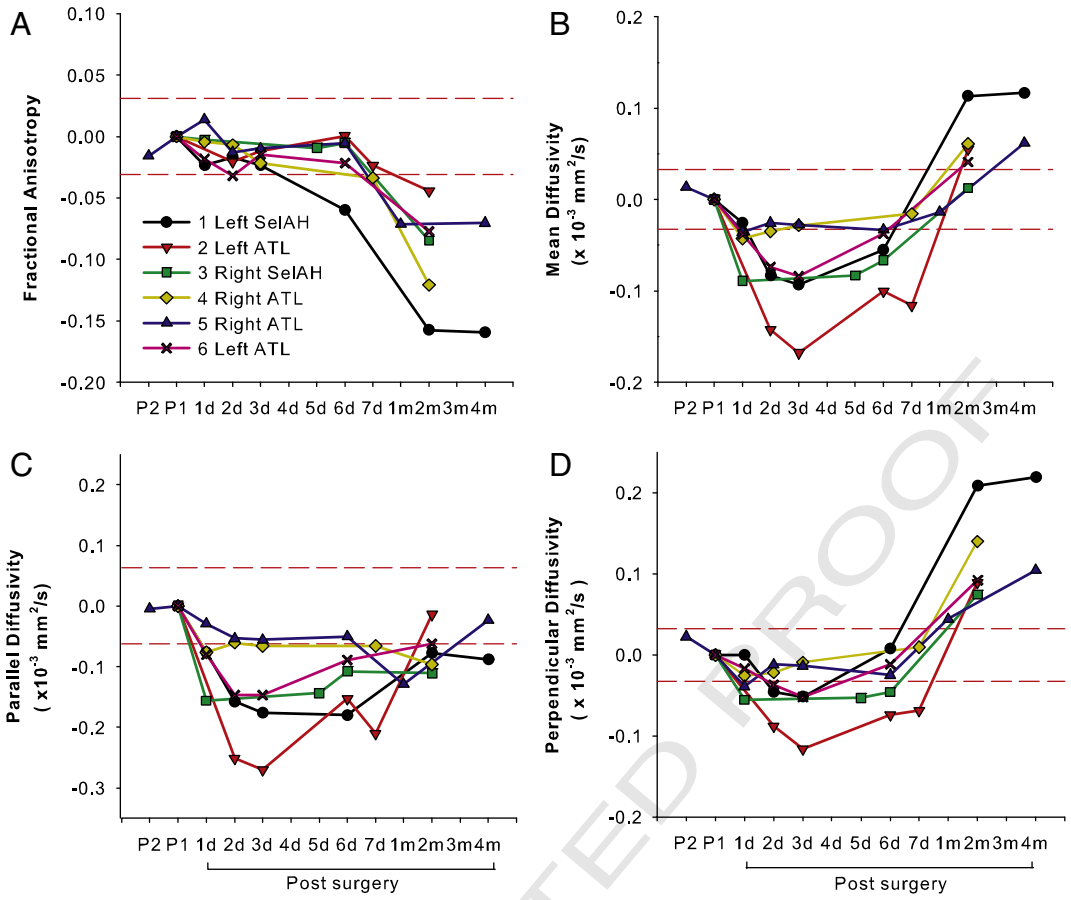

Fig. 6. Time course of normalized DTI parameters of the ipsilateral crus of fimbria-fornices from six patients with temporal lobe epilepsy prior to (P1, P2) and after (days, d and months, m) surgery. DTI parameters post-surgery were normalized by subtracting the baseline value prior to surgery. The red dashed lines show the normal variation range defined from repeated measures of three controls spanning a similar period of time. (A) The FA was relatively stable within the first week after surgery and dramatically decreased at 1–4 months. (B) The MD dropped markedly within the first two days, recovered slightly but still remained lower than the pre-surgical level at the end of the first week and increased at 1–4 months. (C) The $\lambda_{||}$ decreased within the first two days, stayed low at the end of the first week, and rebounded slightly but remained still lower than the pre-surgical level at 1–4 months. (D) The λ decreased within the first two days, recovered to its pre-surgical level in most cases at the end of the first week, and increased markedly at 1–4 months. SelAH, selective amygdalohippocampectomy; ATL, anterior temporal lobectomy.

Alternatively, the concomitant reduction of both parallel and perpendicular diffusivities in the transected fornix at 1–2 days post-surgery could also be a result of other factors such as inflammation and cytotoxic edema. Inflammation has been shown to occur rapidly at the nerve distal stump including microglia activation, macrophage infiltration and massive astrocytic reaction within hours after neural injury such as transection of the fornix in the rat (Stichel and Muller, 1994). The influx of a large population of "isotropic" glial cells in the injured tract could concurrently reduce both parallel and perpendicular diffusivities. Although the major blood supply to the fornix, i.e. medial central arteries, was not injured during surgery, the hippocampal transection might cause some vasospasm in the anterior choroidal artery that could lead to ischemia in the fornix. Our observation of a limited decrease of MD (~8%) within the first two days after surgery is not of sufficient magnitude to be attributed to cytotoxic edema alone. Vasogenic edema as a result of surgery may counteract reductions of diffusion due to the Wallerian degeneration mechanisms, cytotoxic edema, or inflammation. The elevated T2-weighted signal intensity of the ipsilateral fornix in the first few days after surgery (Fig. 8) and its resolution at a week is consistent with vasogenic edema. Overall, all the above mentioned physiological processes could happen with Wallerian degeneration simultaneously and play a part in the acute diffusion changes we observed in the study.

It is interesting to note that Patients 1, 2, 3 and 6, who presented with histologically confirmed hippocampal sclerosis or elevated T2 relaxometry value, showed a greater reduction of the diffusivities at 1–2 days after surgery than Patients 4 and 5 who did not present with evidence of hippocampal sclerosis (Fig. 9). Electron microscopy of the excised fimbria-fornix has shown that TLE patients with hippocampal sclerosis have increased extra-axonal space, less myelin fraction, and decreased number of axons in the fimbria-fornix compared to patients without hippocampal sclerosis (Concha et al., 2010). While a larger sample size is needed to confirm the apparent differences in the longitudinal diffusion parameters post-surgery in patients with and without hippocampal sclerosis, these findings suggest that the acute diffusion changes (less than a week after surgery) may be driven by extra-axonal processes (inflammation etc.).

At 6–7 days after transection, parallel diffusivity remains reduced in all six subjects. This is in contrast to perpendicular diffusivity where 4 of 6 subjects pseudo-normalize to within the normal range at this time point. This may be due to persistent discontinuities along the disrupted tracts whereas demyelination and reduced membrane integrity may be slowly causing perpendicular diffusion to increase towards its chronic elevated values. This result of reduced parallel diffusivity and relatively unchanged perpendicular diffusivity fits well with our earlier finding of the corpus callosum one week after its transection (Concha et al., 2006); although there the corpus callosum showed slightly elevated λ at 1 week. Note that no scans were performed within six days after corpus callosotomy and it is unknown whether similar reductions of λ would have been observed.

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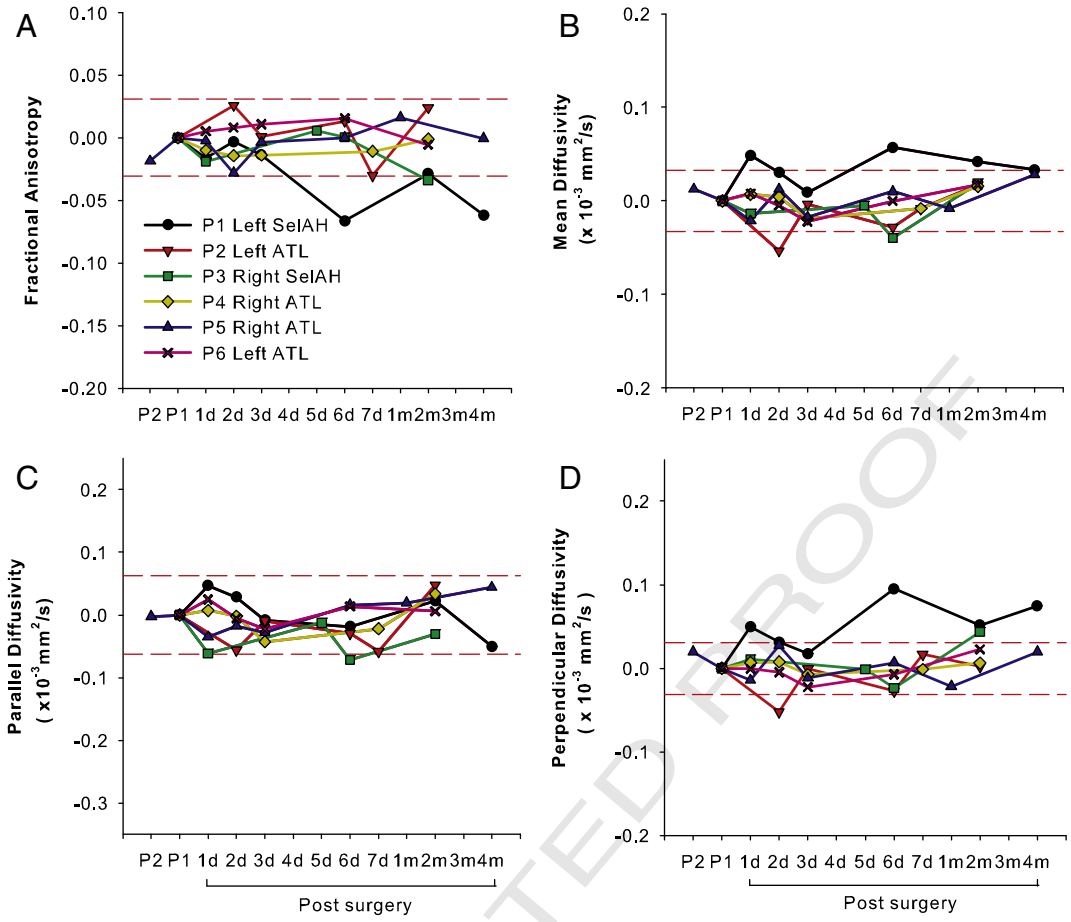

Fig. 7. Time course of normalized DTI parameters of the contralateral crus of fimbria-fornices from six patients with temporal lobe epilepsy before and after surgery. Although most measurements were within the normal variation, the main exception was Patient 1 with decreased FA and elevated MD and λ beyond the normal variation range at a number of time points after surgery. SelAH, selective amygdalohippocampectomy; ATL, anterior temporal lobectomy.

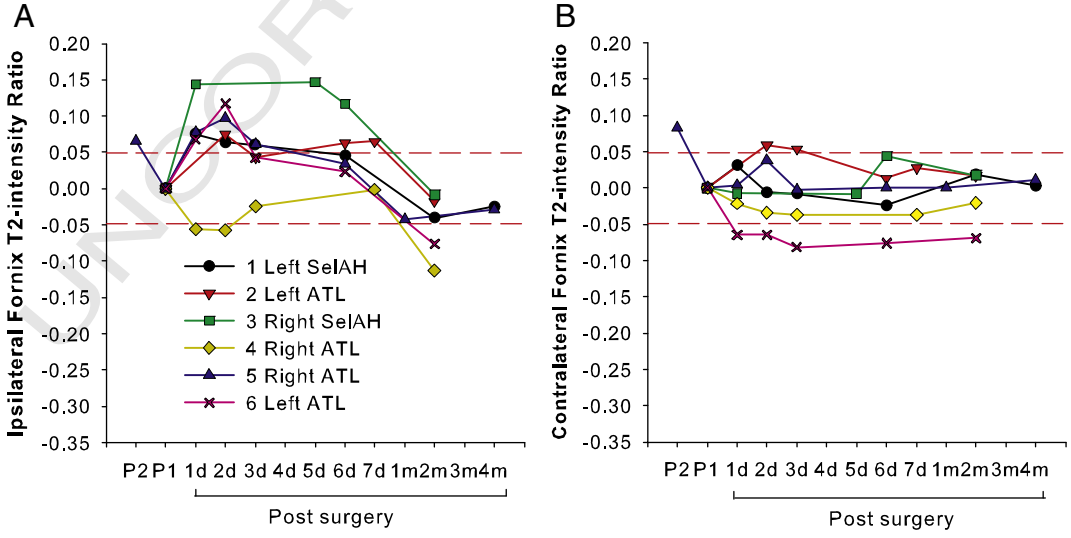

Fig. 8. Time course of normalized T2-weighted intensity from b0 images of the ipsilateral (A) and contralateral (B) crus of fimbria-fornices (normalized to occipital corpus callosum T2-weighted intensity per scan) from six patients with temporal lobe epilepsy before and after surgery. The time point prior to surgery serves as a baseline and was subtracted from each time point. The red dashed lines show the normal variation range defined from repeated measures of three controls spanning a similar period of time. (A) The ipsilateral fornix T2-intensity ratio immediately increased within the first two days after surgery and then returned to its pre-surgical level at 1–4 months in four out of six patients and below normal at 1–4 months in Patients 4 and 6. Notably, Patient 4 did not show increases of T2-intensity at any time point. (B) The contralateral fornix T2-intensity ratio was relatively stable over time in five out of six patients, but was actually reduced in Patient 6 consistently over time. SelAH, selective amygdalohippocampectomy; ATL, anterior temporal lobectomy.

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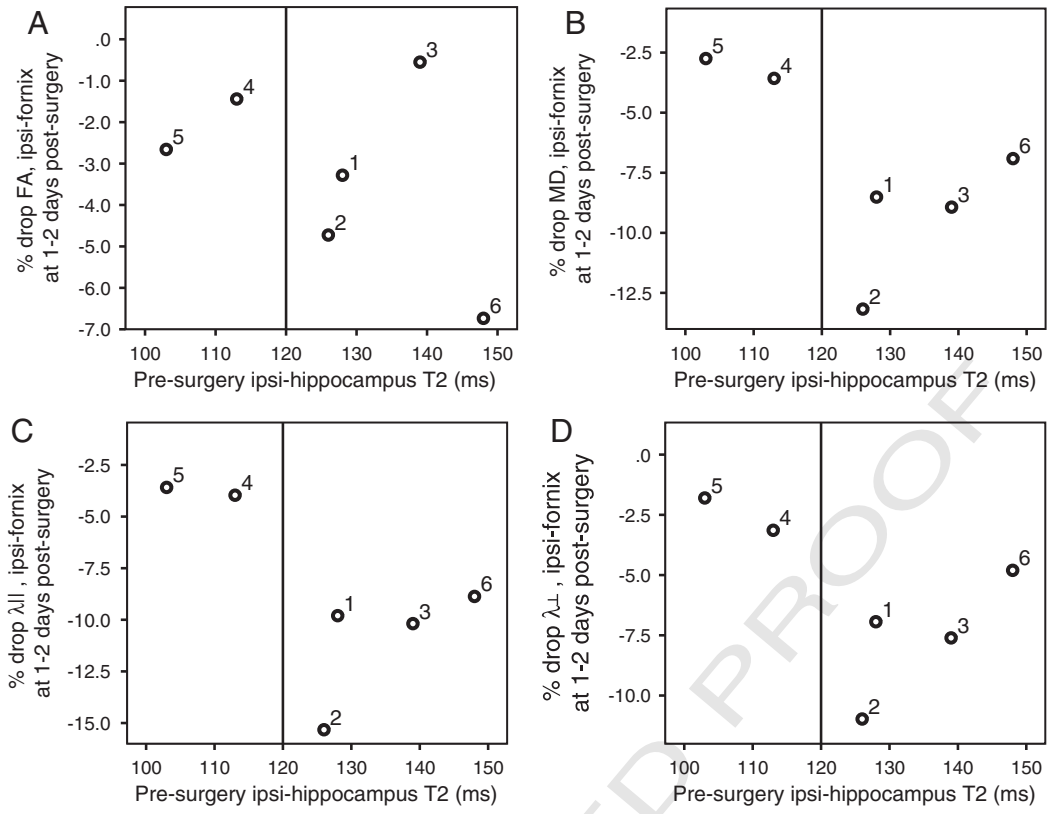

Fig. 9. Scatter plots of percentage reduction of ipsilateral diffusion parameters of fornix at 1–2 days after surgery (the data at 2 days was used if both data at 1 and 2 days were available) versus pre-surgical ipsilateral T2 of hippocampus. Patients 1–3 and 6 had elevated ipsilateral T2 above 120 ms, among whom Patients 1–3 had histologically confirmed hippocampal sclerosis. Notably, Patients 4 and 5 did not show elevated T2 (and patient 4 had no histological evidence of hippocampal sclerosis) but showed less reduction of mean, parallel and perpendicular diffusivities acutely.

Chronic diffusion changes post-surgery

Past efforts have focused mainly on chronic diffusion changes of white matter tracts several months or years after transection in epilepsy patients (Concha et al., 2007; McDonald et al., 2010; Nguyen et al., 2011; Schoene-Bake et al., 2009; Taoka et al., 2005; Wieshmann et al., 1999; Yogarajah et al., 2010). Our findings of reduced fractional anisotropy and elevated mean diffusivity in the ipsilateral fornix 1–4 months after surgery are in agreement with the previous studies that compared post- to pre-operative fornix as early as 2 months after anterior temporal lobectomy (Concha et al., 2007; McDonald et al., 2010; Nguyen et al., 2011; Yogarajah et al., 2010). Interestingly, one study acquired DTI at two time points, 2 months and 1 year, and the reduction of FA and elevation of MD did not progress further in the ipsilateral fornix at 1 year relative to at 2 months following transection (McDonald et al., 2010), which suggests a completion of Wallerian degeneration within 2 months post injury in human central nervous system. The same pattern of diffusion changes was also observed in other white matter tracts including both directly transected (parahippocampal cingulum, uncinate fasciculus, inferior

Table 1
Baseline diffusion measurements prior to surgery (time point P1) for six patients and three controls.

	FA	MD (10^{-3} mm^2/s)	$\lambda_{\|\|}$ (10^{-3} mm^2/s)	λ (10^{-3} mm^2/s)	FA	MD (10^{-3} mm^2/s)	$\lambda_{\|\|}$ (10^{-3} mm^2/s)	λ (10^{-3} mm^2/s)
	Ipsilateral fornix				*Contralateral fornix*			
Patient 1	0.52	0.98	1.61	0.66	0.54	0.93	1.57	0.61
Patient 2	0.43	1.08	1.64	0.80	0.42	1.08	1.62	0.80
Patient 3	0.45	1.00	1.53	0.73	0.46	0.97	1.51	0.70
Patient 4	0.48	0.97	1.53	0.69	0.47	0.99	1.54	0.71
Patient 5	0.49	0.93	1.49	0.66	0.50	0.92	1.48	0.64
Patient 6	0.47	1.07	1.66	0.77	0.46	1.04	1.61	0.75
Mean	0.47	1.01	1.58	0.72	0.48	0.99	1.56	0.70
Std	0.03	0.06	0.07	0.06	0.04	0.06	0.06	0.07
	Left fornix				*Right fornix*			
Control 1	0.46	0.97	1.51	0.71	0.44	1.00	1.52	0.74
Control 2	0.51	0.98	1.60	0.67	0.51	0.98	1.60	0.66
Control 3	0.50	0.99	1.61	0.69	0.47	1.00	1.58	0.71
Mean	0.49	0.98	1.57	0.69	0.47	0.99	1.57	0.70
Std	0.03	0.01	0.06	0.02	0.04	0.01	0.04	0.04

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longitudinal fasciculus, geniculo-calcarine tracts) and other non-transected tracts (inferior fronto-occipital fasciculus, corpus callosum, anterior commissure) more than 2 months after anterior temporal lobectomy (McDonald et al., 2010; Taoka et al., 2005; Yogarajah et al., 2010). The chronic FA reduction in this study was driven by both a decrease of $\lambda_{||}$ in 4 of 6 subjects (pseudo-normal in the other 2) and increase of $\lambda_{\perp}$ in all subjects, which is compatible with myelin degradation and slow clearance of axonal and myelin debris (George and Griffin, 1994; Vargas and Barres, 2007) and/or the persistence of isotropic cells associated with gliosis, as previously shown in a rat model of fornix transection (Stichel and Muller, 1994). A previous study on chronic stroke patients discussed that the diffusion "signature" of reduced $\lambda_{||}$, and elevated $\lambda_{\perp}$, and limited increase of MD were consistent with gliosis (Pierpaoli et al., 2001).

Minimal diffusion change in the contralateral fornix

The contralateral fornix, on the other hand, did not show much change in five out of six patients. Since fornices contain commissural fibers as well as bidirectional fibers linking hippocampus and septal regions in each hemisphere, it is unclear whether the contralateral fornix would be affected by Wallerian degeneration initiated from the cut lesion on the ipsilateral side. From six days to 4 months, Patient 1 showed elevated perpendicular (12%) and mean diffusivity (5%), normal parallel diffusivity, and reduced FA (10%) in the contralateral fornix. The lack of T2-intensity changes in this contralateral tract in Patient 1 (Fig. 8) would argue against possible edema. The remaining five patients did not have alterations of these diffusion parameters in the contralateral fornix over this period of time. Previous findings regarding the contralateral fornix at the chronic stage vary. In accordance with the current observation, our previous study did not observe significant diffusion changes of the contralateral side at 1 year post-surgery in comparison with its presurgical level (Concha et al., 2007). On the other hand, significant FA reduction in the contralateral fornix, was observed at 2 months post-surgery in temporal lobe epilepsy patients, and was sustained at 1 year (McDonald et al., 2010). Similarly, relative to pre-surgical measurements, reduced FA in the contralateral fornix was shown in both left and right temporal lobe epilepsy patients at 4.5 months post-surgery (Yogarajah et al., 2010). However, increased FA in the contralateral fornix was reported at 4 months after surgery, suggestive of a structural reorganization in response to epilepsy surgery (Nguyen et al., 2011). Further investigation is required to elucidate the diffusion changes of the contralateral fornix at both acute and chronic stages after temporal lobe surgery.

Limitations

Due to the extreme difficulties of scanning patients within days after brain surgery, the sample size of the current study is small. Therefore, little can be inferred on potential responses due to type of surgery since two had selective amygdalohippocampectomy and four had anterior temporal lobe resection. However, in the four patients with hippocampal sclerosis, the responses of the diffusion parameters of Patients 1 and 3 with selective amygdalohippocampectomy is similar to that of Patients 2 and 6 with anterior temporal lobe resection (Figs. 6 and 9). In addition, more frequent post-operative DTI acquisitions, e.g. between 7 and 30 days after surgery, might facilitate catching the transition of perpendicular diffusivity from reduction to elevation compared to the pre-surgical level, which could help in understanding the timing of Wallerian degeneration in the central nervous system. Because of severe Wallerian degeneration at 1–4 months following surgery and subsequent reduction in FA, a middle portion of the fornix was unable to be traced by tractography; instead the fornix measured for the chronic scans was nonlinearly deformed from the one tracked from the pre-surgical scan based on coregistration of the b0 images between the two time points. Such transformation might not be accurate due to the brain shift and incomplete resolution of subdural edema at the chronic scans. To help minimize quantitative errors, we attempted to eliminate voxels located outside of the fornix by excluding voxels with fractional anisotropy lower than 0.25; however, this approach may lead to an underestimation of the change in fornix fractional anisotropy (19% change in FA at the chronic time point) since those heavily degenerated tract voxels would be excluded from the overall tract mean. Without setting a fractional anisotropy threshold of 0.25, the fractional anisotropy would be reduced by 29% (range 23–42%); mean diffusivity would be elevated by 12% (range 7–17%) and perpendicular diffusivity would be elevated by 29% (range 20–46%) in all patients at the chronic time points. A further explanation for the observation that the changes in diffusion parameters are perhaps less than expected following transection of a fiber bundle is the fact that the portion of fimbria-fornix posterior to the surgical margin was preserved. While the efferent axons originating from the resected hippocampus anterior to the surgical margin were expected to undergo Wallerian degeneration, the remaining efferent axons originating from the unresected hippocampus posterior to the surgical margin as well as the afferent axons coming from the septal region were expected to remain intact. As the surgical transection would not disconnect these axons from their cell bodies, the axons would be expected to be preserved following surgery and not undergo Wallerian degeneration. The presurgical DTI scan of some patients was acquired months before surgery and then served as a baseline for all post-surgical analyses. The time gap in which epilepsy may still evolve and cause seizure related degenerative changes may contribute to the variation seen post-surgically. This concern is partly addressed by the demonstration of similar diffusion parameters derived from the two presurgical scans (at 10 months and 4 days prior to the surgery) for Patient 4.

Conclusions

In summary, Wallerian degeneration can be followed by diffusion tensor imaging. In this paper, we report novel diffusion changes of transected white matter in the challenging hyperacute (1–2 days), acute (3–7 days), and chronic (1–4 months) periods following temporal lobe epilepsy surgery in human brain. A unique pattern was observed in the ipsilateral fimbria-fornix crus featuring a notable decrease of both parallel and perpendicular diffusivities within the first two days, followed by a pseudo-recovery over the first week, and then highly elevated perpendicular diffusion at several months with a reduced or normal parallel diffusivity. While the reduced parallel diffusivity (sub)acutely and elevated perpendicular diffusivity chronically fit with the notion of using the diffusion eigenvalues as markers of axon and myelin health, respectively, the reduced perpendicular diffusivity in the acute phase is tougher to rationalize but may reflect a number of pathologies including axon swelling, increased axoplasmic viscosity, ischemia-induced cytotoxic edema, and/or infiltration of inflammatory cells. Fractional anisotropy did not change during the first week post-transection necessitating the use of other complementary diffusion metrics for monitoring the white matter degeneration process in vivo in human brain.

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