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Progressive white matter changes following anterior temporal lobe resection for epilepsy☆

Gavin P. Winston *, Jason Stretton, Meneka K. Sidhu, Mark R. Symms, John S. Duncan

Epilepsy Society MRI Unit, Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London WC1N 3BG, England, UK

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ABSTRACT

Anterior temporal lobe resection (ATLR) is an effective treatment for refractory temporal lobe epilepsy (TLE). Widespread abnormalities in diffusion parameters involving the ipsilateral temporal lobe white matter and extending into extratemporal white matter have been shown in cross-sectional studies in TLE. However longitudinal changes following surgery have been less well addressed. We systematically assess diffusion changes in white matter in patients with TLE in comparison to controls before surgery and look at the longitudinal changes following ATLR at two timepoints (3–4 months, 12 months) using a whole brain approach.

We find predominantly unilateral baseline changes in temporal and extratemporal structures compatible with altered myelination (reduced fractional anisotropy, increased mean and radial diffusivity). Following surgery, these changes progress in efferent tracts from the resected temporal lobe compatible with Wallerian degeneration. However more superiorly in the corona radiata, internal and external capsules and nearby tracts, changes compatible with plasticity are observed (increased fractional anisotropy and axial diffusivity, reduced radial diffusivity).

There is little progression between 3–4 months and 12 months following surgery in patients with left TLE, but the changes become more widespread in patients with right TLE suggesting that plasticity occurs more slowly in this population. The neuropsychological correlates of such plasticity should be explored further.

1. Introduction

Temporal lobe epilepsy (TLE)[1] is the most common cause of refractory focal epilepsy with up to 40% of patients refractory to medication (Semah and Ryvlin, 2005). Anterior temporal lobe resection (ATLR) is an established and effective treatment (Wiebe et al., 2001). Cross-sectional white matter changes in TLE have been extensively studied but longitudinal changes following surgery have been less well addressed.

Diffusion tensor imaging (DTI) enables the non-invasive assessment of white matter structure (Basser, 1995) and is ideally suited for both cross-sectional and longitudinal studies. Widespread abnormalities in diffusion parameters have been demonstrated in patients with TLE not only involving the ipsilateral temporal lobe white matter but also extending into structures such as the fornix, cingulum, external capsule and corpus callosum (reviewed in (Gross, 2011)).

Several indices of tissue microstructure can be derived from DTI (reviewed in (Winston, 2012)). Following surgical axonal transection, Wallerian degeneration of downstream white matter tracts leads to a reduction in fractional anisotropy (FA), a measure of the degree of directionality of water diffusion and by inference tissue integrity, and an increase in mean diffusivity (MD), a measure of the magnitude of diffusion (Werring et al., 2000; Wieshmann et al., 1999). Wallerian degeneration comprises two phases with an acute phase of fragmentation and dying-back of axons (lasting days to weeks) followed by a chronic phase of degradation and phagocytosis of myelin sheaths (lasting weeks to months). These can be distinguished by considering two components of mean diffusivity, axial diffusivity (AD) along the length of the axon and radial diffusivity (RD) perpendicular to this. An initial decrease in AD representing axonal degeneration is followed by a later increase in RD representing the myelin loss in both animal models (Song et al., 2003) and in patients with epilepsy undergoing corpus callosotomy (Concha et al., 2006).

Diffusion parameters may also be altered by seizures themselves and a localized reduction in MD without alteration in FA may be observed immediately after a seizure (Diehl et al., 2005). Baseline alterations in diffusion parameters could either represent acute functional changes through fluid shifts induced by seizures or chronic structural changes

* Corresponding author at: UCL Institute of Neurology (Box 29), Queen Square, London WC1N 3BG, UK. Tel.: +44 20 3448 8612; fax: +44 20 3448 8615.
E-mail address: g.winston@ucl.ac.uk (G.P. Winston).

[1] AD = axial diffusivity, ATLR = anterior temporal lobe resection, DTI = diffusion tensor imaging, EEG = electroencephalography, FA = fractional anisotropy, IFOF = inferior fronto-occipital fasciculus, ILF = inferior longitudinal fasciculus, MD = mean diffusivity, PHC = parahippocampal cingulum, PTR/OR = posterior thalamic radiation/optic radiation, RD = radial diffusivity, SLF = superior longitudinal fasciculus, TBSS = tract-based spatial statistics, TFCE = threshold-free cluster enhancement, TLE = temporal lobe epilepsy, UF = uncinate fasciculus.

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Table 1
Previous studies on longitudinal diffusion changes following temporal lobe surgery. ATLR = anterior temporal lobe resection, HS = hippocampal sclerosis, ROI = region-of-interest analysis, SAH = selective amygdalo-hippocampectomy. Abbreviations for tracts as per text.

Paper	Cohort (laterality)	Surgery (imaging timepoints)	Analysis	Findings
Concha et al. (2007)	8 HS (6L, 2R) 22 controls	ATLR/SAH (before, 1 year after)	Tractography of fornix, cingulum ROI of EC, CC	Baseline reduced FA, increased MD/RD in bilateral fornix, cingulum, EC Progressive ipsilateral changes but no contralateral normalization after surgery
Schoene-Bake et al. (2009)	40 HS (19L, 21R) 28 controls	ATLR/SAH (3–11 years after only)	Whole brain (TBSS)	Reduced FA in predominantly ipsilateral tracts including cingulum, SLF, ILF, IFOF, corpus callosum
McDonald et al. (2010)	7 HS (3L, 4R) No controls	ATLR (before, 2 months and 12 months after)	ROI of key tracts	Reduced FA in bilateral fornix, ipsilateral UF, PHC, ILF, IFOF, CC by 2 months, no further change at 12 months
Yogarajah et al. (2010)	46 TLE (26L, 20R) No controls	ATLR (before, 4 months after)	Whole brain (TBSS)	LHS: reduced FA ipsilateral UF, PHG, SLF, OR, bilateral fornix, ILF; increased FA IC, EC, corona radiata; increased MD ipsilateral UF, EC, ILF RHS: reduced FA ipsilateral UF, PHG, SLF, IFOF, OR, bilateral fornix, ILF; increased FA corona radiata; increased MD ipsilateral UF, EC, bilateral fornix
Nguyen et al. (2011)	22 HS (11L, 11R) Only 10 post-op No controls	ATLR (before, 2–7 months after)	Whole brain (TBSS) Images flipped to combine analysis	Baseline asymmetry in FA within hippocampus, fornix, UF, corpus callosum (no controls for comparison) Postoperative increased MD in ipsilateral anterior temporal region but no change in FA
Faber et al. (2013)	20 TLE (left) No controls	SAH (before, 3–6 months and 12 months after)	Whole brain (TBSS)	Reduced FA in left cingulum, fornix at early timepoint and subsequently reduced FA in left UF
Liu et al. (2013)	6 TLE (3L, 3R) 3 controls	ATLR/SAH (before, multiple early scans)	Tractography of fornix	Ipsilateral reduction in MD/AD/RD by 2 days, reduction in FA and rise in MD/RD by 1–4 months

(Concha et al., 2006). Following surgery, Wallerian degeneration would be expected to occur only in tracts transected during surgery. Therefore changes elsewhere, including contralateral cortex, could result from a reversal of the acute effects of seizures or structural plasticity, whereby chronic structural changes are reversed.

Although several studies have investigated changes in white matter structure following temporal lobe surgery (Concha et al., 2007; Faber et al., 2013; Liu et al., 2013; McDonald et al., 2010; Nguyen et al., 2011; Schoene-Bake et al., 2009; Yogarajah et al., 2010), key limitations include small group sizes, a lack of healthy controls or preoperative data for comparison, heterogeneity in the surgical approaches or the timing of the postoperative imaging and only studying a single postoperative timepoint, predefined regions of interest or a single diffusion parameter (Table 1).

The aim of the present study is to systematically assess the longitudinal changes in white matter following surgery avoiding these limitations. We investigate the baseline white matter changes in a large cohort of patients with TLE in comparison to healthy controls and then determine the longitudinal changes following a single surgical operation (ATLR) at two predefined postoperative timepoints using a whole brain approach. We employ tract-based spatial statistics (TBSS), a voxel-based technique optimized for diffusion data (Smith et al., 2006) that has high sensitivity to white matter changes in TLE (Focke et al., 2008) and avoids the problems of spatial smoothing (Jones et al., 2005) inherent in other techniques. This study design enables separation of the effects of the underlying disease from post-surgical changes, and a better understanding of the reversibility or otherwise of the baseline changes.

2. Methods

2.1. Subjects

We studied 20 patients with medically refractory left TLE (age range, 18–52 years; median, 35 years; 10 male) and 19 patients with right TLE (age range, 17–66 years; median, 41 years; 4 male) undergoing ATLR at the National Hospital for Neurology and Neurosurgery, London, United Kingdom. All patients had structural MRI scans performed at 3T, video electroencephalographic (EEG) telemetry, neuropsychology, neuropsychiatry, and if necessary intracranial EEG recordings prior to surgery (2 left, 1 right).

Diffusion tensor imaging (DTI) scans were acquired before surgery and at 3–4 months and 12 months following surgery. All patients underwent ATLR by a single surgeon who employed a modified Spencer approach. Access to the temporal horn of the lateral ventricle was from the floor of the middle cranial fossa via the collateral sulcus. An anterolateral resection was followed by en bloc resection of the mesial structures. In addition, 14 healthy age-matched controls without any history of neurological or psychiatric disease were studied with DTI scans at three similar timepoints. None of the subjects have been previously reported in longitudinal DTI studies.

The study was approved by the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee, and written informed consent was obtained from all subjects. Demographics and clinical data are listed in Table 2. There was no significant difference in the distribution of age, age of onset or duration of epilepsy between the groups (independent samples Kruskal–Wallis test). Postoperative seizure outcome was determined at 12 months using the ILAE classification (Wieser et al., 2001).

Table 2
Clinical and demographic characteristics of patients and healthy controls. Data are given as range (median). HS = hippocampal sclerosis, DNET = dysembryoplastic neuroepithelial tumor, EFS = end folium sclerosis, FCD = focal cortical dysplasia.

Group	Controls (n = 14)	LTLE (n = 20)	RTLE (n = 19)
Gender (M/F)	8/6	10/10	4/15
Handedness (R/L)	10/4	17/3	17/3
Age at scan	22–53 (39.5)	18–52 (35)	17–66 (41)
Age at onset	N/A	0.3–35 (12)	1–44 (11)
Duration of epilepsy	N/A	2–51 (16)	3–52 (22)
Days to first postoperative scan	75–361 (168)	81–183 (105.5)	75–243 (103)
Days to second postoperative scan	217–944 (456)	284–473 (377.5)	337–445 (384)
ILAE outcome at 12 months	N/A	Group 1: 15 Group 2: 3 Group 3: 1 Group 4: 1	Group 1: 14 Group 2: 1 Group 3: 2 Group 4: 1 Group 5: 1
Histological diagnosis	N/A	HS (n = 13) HS + DNET (n = 2) EFS (n = 1) Gliosis (n = 1) Cavernoma (n = 2) Ependymoma (n = 1)	HS (n = 11) HS + FCD (n = 1) EFS (n = 4) DNET (n = 3)