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COVERSHEET

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Tract-specific atrophy in focal epilepsy

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Tract-specific atrophy in focal epilepsy: disease, genetics or seizures?

ABSTRACT

Objective: To investigate whether genetics, underlying pathology or repeated seizures contribute to atrophy in specific white matter tracts.

Methods: Medically-refractory unilateral temporal lobe epilepsy with hippocampal sclerosis (HS-TLE, n=26) was studied as an archetype of focal epilepsy, using fixel-based analysis of diffusion-weighted imaging. A genetic effect was assessed in first-degree relatives of HS-TLE who did not have epilepsy themselves (HS-1°Rel; n=26). The role of disease process was uncovered by comparing HS-TLE to unilateral TLE with normal clinical MRI (MRI-neg TLE; n=26, matched for seizure severity). The effect of focal seizures was inferred from lateralized atrophy common to both HS-TLE and MRI-neg TLE, in comparison to healthy controls (n=76).

Results: HS-1°Rel had bilaterally small hippocampi, but no focal white matter atrophy was detected, indicating a limited effect of genetics. HS-TLE had lateralized atrophy of most temporal lobe tracts, and hippocampal volumes in HS-TLE correlated with parahippocampal cingulum and anterior commissure atrophy, indicating an effect of the underlying pathology. Ipsilateral atrophy of the tapetum, uncinate and inferior fronto-occipital fasciculus was found in both HS-TLE and MRI-neg TLE, suggesting a common lateralized effect of focal seizures. Both epilepsy groups had bilateral atrophy of the dorsal cingulum and corpus callosum fibers, which we interpret as a consequence of bilateral insults (potentially generalized seizures and/or medications).

Interpretation: Underlying pathology, repeated focal seizures and global insults each contribute to atrophy in specific tracts. Genetic factors make less of a contribution in this cohort. A multi-factorial model of white matter atrophy in focal epilepsy is proposed.

INTRODUCTION

Abnormal white matter structure is an important aspect of focal epilepsy, which relates to both the causes and the consequences of the disease. Such changes are often widespread, may occur with a seizure focus in different brain regions[1–3], and have been found in the presence of diverse pathologies including hippocampal sclerosis[4], focal dysplasia[5], malformations of cortical development[6] and even when no visible lesion is present[7–9].

Temporal lobe epilepsy with hippocampal sclerosis (HS-TLE) is often considered the archetype of focal epilepsy[10] as it has been extensively studied, and accounts for around one third of patients with chronic medically-refractory TLE[11]. The hippocampus is the focus for seizure onset[12], and has the diagnostic histopathology of pyramidal neuronal loss, granule cell dispersion and reactive gliosis[13]. Patients with TLE who have no evidence of hippocampal sclerosis on imaging (MRI-neg TLE) provide an informative comparison group. They have clinical seizures that are individually indistinguishable from HS-TLE, but several group-level differences indicate that there is different underlying pathological process. Seizures begin at a later age in MRI-neg TLE, there is a lower proportion of antecedent childhood febrile convulsions[14,15] and histological examination does not show the classical pattern of hippocampal neuronal loss[16,17]. Genetic factors may contribute to the structural brain abnormalities in HS-TLE, and this can be isolated by investigating first degree relatives of people of HS-TLE who do not have seizures themselves (HS-1°Rel)[18].

White matter abnormalities in TLE have previously been investigated with either volumetry of T1-weighted imaging, or microstructural analysis of diffusion weighted imaging. Voxel-based morphometry in HS-TLE has shown widespread atrophy affecting bilateral temporal and extratemporal regions[19–22] or a more restricted pattern involving the ipsilateral temporal lobe[1,4]. Relatives of HS-TLE show the genetic traits of bilaterally small hippocampi[18] and reduced total white matter volume[23]. In MRI-neg TLE no consistent alteration of white matter morphometry has been detected[24]. Previous diffusion weighted imaging studies of TLE have all employed the diffusion tensor model (DTI) within various analysis frameworks, although DTI examines only

microstructural changes in the white matter and does not deal well with the crossing fibre problem[25].

Therefore, to assess atrophy of specific white matter tracts in this study we use the recently developed metric of Fibre Density and Cross-section (FDC)[26]. This measure is calculated from diffusion-weighted MRI, for each *fi*bre population within a vo*xel* (a *fixel*)[27], and combines the morphometric information of Fibre Cross-section (FC) with the microstructural information of Fibre Density (FD)[28].

Thus we investigate three well-defined cohorts (HS-TLE, MRI-neg TLE and HS-1°Rel) asking the question of whether genetics, the underlying disease process and the effects of ongoing seizures produce injury to specific tracts.

METHODS

Participants

Patients with medically-refractory unilateral TLE, between the ages of 14 and 65 years, were studied prospectively during work-up for epilepsy surgery between 2007 and 2015, at the Austin Hospital, Melbourne, Australia. This included a subset of patients (17 HS-TLE and 16 MRI-neg TLE) for whom functional MRI data has already been reported[29]. The diagnosis of TLE was based on clinical history, video-EEG recording of typical seizures, and a congruent abnormality on nuclear medicine studies (temporal lobe hypometabolism on FDG-PET, or ictal hyperperfusion on ictal-interictal SPECT). Patients with independent seizures from both left and right temporal lobes were excluded.

Routine clinical MRIs acquired with our epilepsy protocol[30] were reviewed by both a Neuroradiologist and an Epileptologist. Patients were only included if there were characteristic features of unilateral hippocampal sclerosis (HS-TLE) or if the mesial temporal regions appeared normal and no other potentially epileptogenic abnormality was seen (MRI-neg TLE). Patients were excluded if there was previous neurosurgery or any other potentially epileptogenic intracranial abnormality.

Twenty-nine HS-TLE and 28 MRI-neg TLE patients met inclusion criteria and consented to participate. Two MRI-neg TLE participants were excluded; one had inadequate image acquisition, and the other had subtle but pathological enlargement

of the amygdala on subsequent imaging. To balance epilepsy groups for gender and epileptic side, three female patients with right HS-TLE were randomly selected and removed. The final analysis included 26 HS-TLE, and 26 MRI-neg TLE (Table 1).

First-degree relatives of HS-TLE, who had no personal history of seizures themselves, were drawn from our previous study[18]. Of 32 participants, 2 were excluded to meet age criteria, and a further 4 males were randomly selected and removed to balance the cohort for gender. The final analysis included 26 HS-1°Rel participants drawn from 15 families. In four of these families (27%) the proband had a known first-degree family history of seizures, compared to 8 families (31%) in the HS-TLE cohort.

Healthy adult volunteers were selected from historical controls that had diffusion weighted imaging performed at our institution. An equal number of males and females between ages 14 and 65 years of age were selected, resulting a group of 76 controls.

Consent was obtained from all participants, or their legal guardian in the case of minors. The study was approved by the Austin Health Human Research Ethics Committee.

MRI acquisition

Diffusion-weighted images were acquired on a 3T Siemens Tim Trio MRI scanner (60 directions, b-value 3000s/mm^2, 2.5mm isotropic voxels, echo time 110ms, repetition time 8300ms, parallel acceleration factor 2). An anatomical T1-weighted MPRAGE image was also acquired (voxel size 0.9mm isotropic, repetition time 1900ms, inversion time 900ms, echo time 2.6ms, flip angle 9°).

T1-weighted image processing

Hippocampal volumes were evaluated by manual tracing on the coronal T1-weighted image, using ImageJ software[18,31], with operators blinded to subject group and side of the brain. Estimated total intracranial volume was calculated using FreeSurfer 5.3[32] Volumes were compared between groups using a linear mixed model, with intracranial volume as a covariate and family membership as a random effect.

Diffusion image pre-processing

Diffusion images were analysed using MRtrix3[33] (www.mrtrix.org). Pre-processing included correction for head motion, bias fields, and spatial up-sampling by a factor of two[28]. Global intensity normalization was performed by scaling all volumes by the median intensity of white-matter voxels on b=0 s/mm^2 images. The fibre orientation distribution (FOD) was calculated at each voxel using robust constrained spherical deconvolution[34] with a group average response function[28].

Patients with right-sided TLE had their FOD images flipped right-to-left, with re-orientation of FOD lobes, so that the epileptic side was aligned across all patients. An equal proportion (50%) of participants within the Control and HS-1°Rel cohorts were randomly selected, stratified by gender and age-by-decade, and their FOD images flipped right-to-left also.

Study-specific FOD template and tractogram

A left-right symmetrical study-specific FOD template was created from a subset of participants (12 HS-TLE, 12 MRI-neg TLE, 12 controls), randomly selected with stratification for gender and epileptic side. FOD images (l_{max}=4) and their left-to-right flipped mirror counterparts, were repeatedly non-linearly registered to the previous group mean[35]. The registration step included reorientation of the FOD[36]. This process was iterated until sufficient convergence of the group mean FOD image, obtained after 10 iterations. FOD images for all participants were then registered to this unbiased symmetrical template.

Whole-volume probabilistic tractography was performed on the final group mean FOD image (at l_{max} = 8) to generate 20 million streamlines, and filtered to 2 million streamlines using the SIFT algorithm[37].

Fixel-based calculation of Fibre Density and Cross-section (FDC)

The amplitude of an FOD lobe, at the relatively high b-value used here, is proportional to the volume of restricted water within axons of the given orientation, and can be interpreted as the apparent Fibre Density (FD) in that direction[28]. The FD is calculated for each fixel by integrating over the respective FOD lobe[37].

Additional valuable information about tract morphology is available from the registration of each image to the template. By considering the local expansion or

contraction of the warp field perpendicular to the fixel orientation, a relative measure of the fibre cross-section (FC) is obtained[26].

Multiplying FD and FC at each fixel gives a combined measure of fibre density and cross-section (FDC)[26]. FDC is a more comprehensive measure of intra-axonal volume within a pathway, as it accounts for both microscopic axonal changes (detected as differences in diffusion signal), as well as macroscopic changes in a fibre-bundle (detected as relative differences in the registration warps).

Fixel-based statistical comparison between groups

Statistical comparisons of FDC between groups were performed at each fixel, by one-way ANCOVA with the contrasts of (i) HS-TLE versus controls, (ii) MRI-neg TLE versus controls, and (iii) 1st-Rel-TLE versus controls. Covariates of no interest were age, the estimated total intracranial volume and whether the image had been flipped right-to-left. Connectivity-based Fixel Enhancement (CFE) was used for statistical inference, using streamlines from the template tractogram and default parameters (smoothing=10mm FWHM, C=0.5, E=2, H=3)[27]. A corrected p-value was assigned to each fixel using permutation testing, with 5000 permutations and preserving family grouping within each permutation.

Definition of tracts-of-interest

Seventeen named white matter tracts were selected for further characterization: the fornix, dorsal cingulum, parahippocampal cingulum, uncinate, arcuate, inferior fronto-occipital and inferior longitudinal fasciculi on each side, and the anterior commissure, bi-temporal fibers of the tapetum (traversing the splenium of the corpus callosum), and bi-frontal fibers traversing the anterior corpus callosum. For each tract, appropriate streamlines were selected from the template tractogram using a semi-automated rule-based approach, and used to create a fixel-mask (see images in Fig. 4).

Comparison of mean FDC within tracts-of-interest

The weighted mean FDC was calculated for each tract-of-interest, by summing along each streamline, dividing by streamline length, and averaging over all streamlines. Each group was compared to controls using a linear mixed model (‘lme4’, ‘lsmeans’ and ‘pbrktest’ packages in R) with covariates for intracranial volume, age and

whether right-to-left flipped, and with family membership included as a random effect. Multiple comparisons were corrected using the Dunnett procedure between groups ('multcomp' package) then Bonferroni correction for 24 tracts. Results are displayed as the percentage difference in mean FDC from controls, with 95% confidence intervals.

An individual asymmetry index (AI) was calculated for each bilateral tract-of-interest, with results displayed as difference from controls $\left(\overline{AI_{\text{HS-TLE}}} - \overline{AI_{\text{Controls}}}\right)$.

$$AI = \frac{tractFDC_{Left} - tractFDC_{Right}}{tractFDC_{Left} + tractFDC_{Right}}$$

White matter atrophy versus hippocampal volumes, seizure frequency and epilepsy duration

An exploratory post-hoc analysis was performed to examine the relationship between hippocampal volumes and tract-specific white matter atrophy (in 'R' notation):

```
tractFDC ~ Group + RLFlip + Age + IntracranialVolume + HippVol:Group
```

Ipsilateral hippocampal volumes (`HippVol`) were mean centered within-group to remove collinearity. For each tract-of-interest, a partial F-test was first performed for any difference between groups, and significant tracts were further tested for pairwise differences in the `HippVol` coefficient (unpaired t-tests with Dunnett correction, uncorrected for the number of tracts examined).

A second post-hoc linear model was used to explore the relationship between FDC and patient-estimated seizure frequency and epilepsy duration, again with these predictors mean-centered within group:

```
tractFDC ~ Group + SeizureFrequency:Group + EpilepsyDuration:Group
                 + RLFlip + IntracranialVolume
```

RESULTS

TABLE 1 AROUND HERE

Clinical findings

Patients with HS-TLE had a longer duration of epilepsy than those with MRI-neg TLE (mean 22.2 years versus 14.0 years, 2-tailed t-test p=0.004, Table 1), reflecting

generally earlier onset of epilepsy in the HS-TLE group. Frequency of focal and generalized seizures was not significantly different between the TLE groups. Most patients were on 2 or 3 anti-epileptic medications. This was not significantly different between groups and included similar medications and dose ranges. Of the HS-TLE patients, 22 (12 right, 10 left) subsequently proceeded to anterior temporal lobe resection, with hippocampal sclerosis demonstrated in all, and a good outcome with respect to seizures in 86% (19 of 22). In MRI-neg TLE, 8 patients (6 right, 2 left) proceeded to surgery with 7 having anterior temporal lobectomy and one a focal posterior temporal resection. Seven had no evidence of hippocampal sclerosis or dysplasia, however in one patient neuronal loss consistent with mild hippocampal sclerosis was found. A good outcome with respect to seizures was achieved in 63% (5 of 8).

FIGURE 1 AROUND HERE

Hippocampal Volumetry

In HS-TLE, the volume of the affected hippocampus was significantly smaller than in controls (Fig. 1a; Left hippocampal volume [mean±sd] in Left HS-TLE 1981±273mm^3 versus Controls 3364±318mm^3 adjusted for intracranial volume, 95% CI on difference [-1102, -1667mm^3]; Right hippocampal volume in Right HS-TLE 2194±486mm^3 versus Controls 3450±345mm^3, 95% CI on difference [-956, -1557mm^3]). There was no significant difference between HS-TLE and controls at the contralateral hippocampus.

In MRI-neg TLE, hippocampal volumes were not different to controls (Fig. 1b; Left hippocampal volume in Left MRI-neg TLE 3312±434mm^3; Right hippocampal volume in Right MRI-neg TLE 3622±350mm^3).

In HS-1°Rel, left and right hippocampal volumes were both significantly smaller than controls (Fig. 1c; Left hippocampal volume in HS-1°Rel 2938±244mm^3, 95% CI on difference [-188, -710mm^3]; Right hippocampal volume in HS-1°Rel 2856±259mm^3, 95% CI on difference [-322, -853mm^3]). Volumes were also smaller than the contralateral hippocampus in HS-TLE (95% CI on difference [-155, -813mm^3]).

FIGURE 2 AROUND HERE

Fixel Based Analysis

Reduced white matter fiber density and cross-section (FDC) was seen in both HS-TLE and MRI-neg TLE compared to controls. In the HS-1°Rel group no fixels were identified as significantly different from controls.

Fixel based analysis: HS-TLE versus Controls

In HS-TLE, decreased FDC was seen ipsilateral to the epileptic focus in fixels of the fornix, uncinate fasciculus, ILF, IFOF, parahippocampal cingulum and arcuate fasciculus (Fig. 2a). Bilateral reduction was seen at fixels of the anterior commissure, tapetum, anterior corpus callosum and dorsal cingulum (more ipsilateral than contralateral). The fixels showing greatest magnitude in reduction of FDC, typically 30-40% smaller than controls, were at the temporal pole, inferior temporal white matter, and at the anterior commissure. The reduction in FDC in most tracts was produced by both reduced fiber density (FD) and reduced cross-sectional area (FC). Exceptions were the fornix and anterior commissure, which are thin tracts only a few voxels across and show reduction primarily in FD.

Fixel based analysis: MRI-neg TLE versus Controls

In MRI-neg TLE, lateralized reduction in FDC ipsilateral to the epileptic focus was seen in a small number of fixels, at the ILF and tapetum fibers of the affected temporal lobe. Bilateral reduction in FDC was more extensive, seen symmetrically in the tapetum, anterior corpus callosum, and in the dorsal cingulum bilaterally (Fig. 2). The greatest FDC reduction was at the ipsilateral tapetum and bilateral dorsal cingulum (~25% decrease). Reduced FDC in the corpus callosum and the tapetum was primarily a consequence of reduced fiber density (FD). Reduced FDC in the bilateral dorsal cingulum bilaterally had similar contributions from FD and FDC.

FIGURE 3 AROUND HERE

Tract-of-Interest Analysis

Within the tracts-of-interest, HS-TLE showed greatest atrophy at the ipsilateral uncinate, parahippocampal cingulum, fornix, arcuate and at the anterior commissure (Fig. 3a). The MRI-neg TLE group had mildly reduced FDC at the uncinate, but the remainder of these tracts were not significantly different from controls.

Both HS-TLE and MRI-neg TLE showed similar atrophy at the bilateral dorsal cingulum, frontal corpus callosum, tapetum and ipsilateral IFOF. The magnitude of FDC reduction here was similar in both forms of TLE (Fig. 3b).

FIGURE 4 AROUND HERE

Left-right asymmetry in tracts-of-interest showed that atrophy was strongly lateralized to the epileptic side in HS-TLE (Fig. 5). This effect was strongest in the uncinate fasciculus, parahippocampal cingulum and hippocampal fornix. No significant asymmetry was seen in MRI-neg TLE, although a non-significant trend toward ipsilateral atrophy may be present at the uncinate fasciculus and ILF.

White matter atrophy within tracts-of-interest in HS-1°Rel

The HS-1°Rel group did not show any significant tract-of-interest atrophy compared to controls (Fig. 3) nor any significant asymmetry (Fig. 4). However, in all tracts tested the group-mean FDC was around 4-8% smaller than in controls, suggesting a global trend in this direction.

Relationship between hippocampal volume and atrophy within tracts-of-interest

The post-hoc linear model relating ipsilateral hippocampal volume to white matter atrophy showed a difference between groups at the ipsilateral parahippocampal cingulum ($F_{139,3}$=2.93, p=0.036) and at the anterior commissure ($F_{139,3}$=2.82, p=0.041). This was driven by the HS-TLE group, where a smaller affected hippocampus corresponded to the extent of white matter atrophy, a relationship that was not seen in controls (Ipsilateral parahippocampal cingulum: -19.3% FDC per mL of hippocampal atrophy, -2.0% per mL in controls, p=0.028; Anterior commissure: -9.6% FDC per mL of hippocampal atrophy, +4.4% per mL in controls, p=0.049). Surprisingly there was no detected difference between the groups for this relationship at the hippocampal fornix ($F_{139,3}$=0.80, p=0.49).

Relationships between seizure frequency, epilepsy duration and white matter atrophy

The linear relationships between seizure frequency and FDC, and between epilepsy duration and FDC, did not reach statistical significance at any of the tracts-of-interest. However the estimated effect size for patient-reported seizure frequency was maximal at the bilateral dorsal cingulum in both epilepsy groups (around -1.4% per seizure/month in HS-TLE and -0.8% per seizure/month in MRI-neg TLE). Epilepsy

duration in HS-TLE had greatest effect size at the hippocampal fornix, ipsilateral parahippocampal cingulum and anterior commissure (range -2.0% to -2.5% per decade of epilepsy). In MRI-neg TLE the maximal effect of epilepsy duration was at the ipsilateral uncinate fasciculus, anterior commissure and tapetum fibers (range -2.7% to -4.6% per decade of epilepsy).

DISCUSSION

In this study we considered HS-TLE as an archetype of focal epilepsy. Atrophy of specific white matter tracts was identified using the metric of Fiber Density & Cross-section in temporal lobe tracts ipsilateral to the seizure focus (parahippocampal cingulum, uncinate, fornix, inferior longitudinal and inferior fronto-occipital fasciculi, tapetum and anterior commissure), as well as in bilateral tracts that are less directly associated with the seizure focus (bilateral dorsal cingulum, frontal and parieto-occipital fibers of the corpus callosum).

To interpret these findings we applied the following premises: (1) abnormalities that are common to HS-1°Rel and HS-TLE are likely to have a genetic basis and predate the onset of epilepsy; (2) abnormalities that are unique to HS-TLE compared to MRI-neg TLE are likely to be related to the underlying pathological process of HS; (3) correlation between severity of white matter abnormalities and amount of hippocampal atrophy is further evidence of a relationship to the underlying pathological process; (4) abnormalities that are common to both HS-TLE and MRI-neg TLE are likely to be the consequence of seizures and/or anti-epilepsy medications.

Common abnormalities in HS-1°Rel and HS-TLE: weak evidence for a trend toward diffuse mild white matter atrophy as a familial trait?

Bilaterally reduced hippocampal volumes in the relatives of people with HS-TLE (by ~15%) indicates a familial trait with a likely genetic basis[18]. In HS-TLE hippocampal atrophy was greatest at the affected hippocampus (by 38%), but no atrophy was found on the contralateral side. Although reduced contralateral volume might be expected in HS-TLE given our findings in the relatives, this was largely precluded by our recruitment criteria of strictly unilateral hippocampal atrophy in the HS-TLE group. An alternative speculative explanation may be that contralateral hippocampal volume increases in HS-TLE following the development of epilepsy.

No significant white-matter difference was found between HS-1°Rel and controls, either in the fixel-based or the tracts-of-interest analysis. However there is a trend toward reduced FDC in HS-1°Rel in all tracts studied (by ~4-8%), indicating that a mild but diffuse reduction in white matter as identified by Scanlon[23] could also be present in our cohort. Overall our interpretation is that the white matter atrophy found in HS-TLE is related to the disease and/or treatment, rather than primarily being a familial trait.

Unique abnormalities in HS-TLE: specific associations of the underlying disease

White matter atrophy in HS-TLE, but not in MRI-neg TLE, is found at the antero-mesial temporal lobe tracts on the epileptic side: the ipsilateral parahippocampal cingulum, fornix, uncinate, ILF, arcuate and the anterior commissure (Figs. 2a & 3a). Possible causative factors that are unique to HS-TLE include the occurrence of childhood febrile convulsions (more frequent in HS-TLE than MRI-neg TLE), the age of onset of epilepsy (earlier in HS-TLE), hippocampal pathology (neuronal loss and gliosis in HS, but minimal changes in MRI-neg TLE), and subtle differences in functional network abnormalities (with a mesial temporal rather than neocortical emphasis[29].

Correlated hippocampal atrophy and white matter atrophy in HS-TLE: an indicator of common causation in a subset of tracts?

In HS-TLE, the parahippocampal cingulum and the anterior commissure both show an association between the hippocampal volume and the extent of white matter atrophy. This proportional relationship between the extent of injury at these tracts and in the hippocampus suggests that a common cause is at work, with the underlying process driving hippocampal sclerosis also being a contributor to white matter atrophy in these tracts.

We did not find a correlation between hippocampal volume and the extent of atrophy at the corpus callosum or cingulum, unlike Scanlon et al.[8]. This may relate to our different statistical approach which employed a separate linear regression slope for each group. Otherwise our results are in agreement with previous studies that have not shown any association between hippocampal volume and the ILF, uncinate or arcuate fasciculus[38] or temporal lobe white matter[39]. It was surprising that we found no linear

relationship at the ipsilateral fornix given the well-established histological abnormalities of the fornix in HS-TLE[40]. This may represent a "floor" effect due to the severe epilepsy in our cohort and the extent of fornix atrophy.

Common bilateral abnormalities in HS-TLE and MRI-neg TLE: a non-specific effect of global insults

Regions of common white matter atrophy were found in both forms of TLE at the bilateral dorsal cingulum, and at the inter-hemispheric fibres of the anterior corpus callosum (projecting symmetrically toward bilateral dorsolateral frontal cortex) and posterior corpus callosum (projecting symmetrically toward bilateral parietal cortex). Similar diffusion changes affecting the cingulum and/or corpus callosum have also been detected in other forms of epilepsy, including frontal lobe epilepsy with cortical dysplasia[1,3], and in a mixed cohort of both focal and generalized epilepsy[41], suggesting that the causation is independent of both the underlying disease pathology and the location of the epileptic focus. The location and connections of these tracts makes it difficult to explain this atrophy as a direct consequence of unilateral focal seizures in TLE, particularly as the expected connecting pathway from the temporal lobe of the parahippocampal cingulum appears to be relatively spared in MRI-neg TLE. Neither patient-reported seizure frequency nor disease duration showed a significant correlation at these tracts in our analysis, although a correlation with epilepsy duration has been found at the corpus callosum by some diffusion studies[39,42]. Furthermore, greater change at the corpus callosum has been found with refractory versus benign epilepsy[43], in association with bilateral temporal interictal epileptiform discharges[44], as well as in an experimental rat model of focal epilepsy where no anti-epileptic medications were used[45]. Thus our interpretation is that atrophy in these tracts is likely to be a consequence of factors that have a bilateral and symmetrical impact, with generalized seizures, anti-epileptic medications, and other global factors such as psychological and socioeconomic status all being possible causes.

Common ipsilateral abnormalities in HS-TLE and MRI-neg TLE: focal seizures as a cause of lateralized white matter atrophy

A common unilateral finding in both TLE groups was reduced FDC of the ipsilateral tapetum, where this tract leaves the posterior temporal lobe (Fig. 2). The spatial

association of this tract with the expected seizure focus points to propagation of focal seizures as the possible cause. As the only finding that was clearly lateralized in MRI-neg TLE, targeted assessment of this region may be useful in future studies that aim to lateralize TLE on the basis of white matter atrophy. In the tract-of-interest analyses, the ipsilateral uncinate and IFOF were also abnormal in MRI-neg TLE, but as they did not show abnormal asymmetry are less likely to be useful markers for determining the epileptic side.

The idea that recurrent focal seizures can cause localized chronic white matter injury has been widely discussed but remains controversial, with some longitudinal studies detecting no change[46,47]. We did not find a significant association between FDC and the retrospective patient-report of seizure frequency, although this measure may not be an individually accurate estimate of the true number of events[48]. If seizures are assessed prospectively on EEG, white matter measurements at the ipsilateral uncinate, arcuate and ILF in HS-TLE can be associated with time since last seizure[38], indicating that seizure-related vasogenic oedema can occur in propagation tracts. Other studies have compared lateralized diffusion abnormalities with duration of epilepsy and found ipsilateral correlations at the temporal lobe, parahippocampal gyrus and internal capsule[39], the uncinate and arcuate in left TLE[49], or in the ipsilateral cingulum, fornix and external capsule in right TLE[50]. Taken together, these findings support recurrent focal seizures as a cause of progressive ipsilateral white atrophy, but that demonstrating this conclusively is susceptible to variability between cohorts and methodologies.

FIGURE 5 AROUND HERE

Factors contributing to white matter atrophy: a model for focal epilepsy

Our findings in HS-TLE suggest a multi-factorial model for the development of tract-specific white matter atrophy in focal epilepsy. Genetic factors predisposing to HS-TLE (Fig. 5A) are associated with bilaterally small hippocampi but produce minimal white matter change. An initial triggering insult (Fig. 5B), such as a febrile convulsion, may cause both grey and white matter injury at the hippocampus and closely related tracts (especially the parahippocampal cingulum and anterior commissure), with the development of epilepsy. Repeated focal seizures (Fig. 5C) may cause progressive white matter injury in tracts radiating away from the seizure

focus (eg. the tapetum, uncinate fasciculus and IFOF). Meanwhile, repeated global insults such as generalized seizures and/or the effects of medications (Fig. 5D) contribute to bilateral changes in tracts distant from the focus, particularly at the bilateral dorsal cingulum and the corpus callosum.

Several aspects of this model require further validation, as the main limitation of this study is its cross-sectional design. Longitudinal studies in both human focal epilepsy and in experimental animal models will be needed to further isolate and confirm the consequences of repeated focal seizures, generalized seizures and anti-epileptic medications in specific white-matter tracts.

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AUTHOR CONTRIBUTIONS

Concept and study design: D.N.V. and G.D.J. Data acquisition and analysis: D.N.V., D.R., E.C., M-H.T. and J-D.T. Drafting the manuscript and figures: D.N.V., D.R., J-D.T., A.C., G.D.J.

POTENTIAL CONFLICTS OF INTEREST

Nothing to report

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FIGURE LEGENDS

Figure 1 - Hippocampal volumes in Patients and Controls

Hippocampal volumes for each participant, measured by manual tracing on T1-weighted images, and corrected for intracranial volume by linear regression. (a-c) Crosshairs show the mean for each group, surrounded by the 95% confidence ellipse. Crosshairs that fall outside another ellipse indicate a significant difference in group means ($p<0.05$). (d) Boxplots show the median and interquartile range for each group, with whiskers to 1.5x interquartile range.

574 **Figure 2 - Fixels with significant white matter atrophy in TLE**

575 Fixels where Fiber Density & Cross-section (FDC) is less than in Controls ($p<0.05$
576 FWE corrected), after accounting for intracranial volume, age and brain side (right-to-
577 left flip). The background image is the symmetrical study template, showing the
578 scalar magnitude of the fiber orientation distribution at each voxel. Tracts affected in
579 both HS-TLE and MRI-neg TLE are labelled in bold.

Figure 3 - White matter atrophy in Tracts-of-interest

Fiber Density & Cross-section (FDC) averaged within tracts-of-interest, displayed as percentage difference from the Control mean, adjusted for age, intracranial volume and brain side. Horizontal bars show the 95% confidence interval. Non-significant results cross the control mean and are shown in lighter grey. (Left column) Tracts-of-interest with significant atrophy in HS-TLE compared to Controls. (Right column) Tracts-of-interest which show atrophy in both HS-TLE and MRI-neg TLE, of similar magnitude in both groups. Tracts-of-interest that did not reach statistical significance are omitted. 'HS'=TLE with Hippocampal Sclerosis. 'MRI-n'=MRI-negative TLE. '1°Rel': First degree relatives of people with HS-TLE. ILF: inferior longitudinal fasciculus. IFOF: inferior fronto-occipital fasciculus.

Figure 4 - Asymmetry of white matter atrophy in tracts-of-interest

Relative asymmetry index of Fiber Density & Cross section (FDC) for each tract-of-interest. Relative asymmetry index = $(FDC_{left}-FDC_{right})/(FDC_{left}+FDC_{right})$ - $mean(AI_{controls})$.

595 **Figure 5 - Factors contributing to white matter atrophy in Focal Epilepsy**

596

TABLES

Table 1: Study participants

	N (M:F)	Epilepsy Side L:R	Age mean (range)	Onset age mean (range)	Focal Sz per month med (range)	Gen Sz per year med (range)	# AEDs mean (range)
HS-TLE	26 (13:13)	13:13	39.2 (14-65)	14.0 (1-31)	7.6 (0.1-35)	0.3 (0-39)	2.5 (1-5)
HS-1°Rel	26 (13:13)	-	37.6 (14-65)	-	-	-	-
MRI-neg TLE	26 (12:14)	13:13	34.8 (16-52)	22.2 (4-52)	8.7 (0.3-46)	0.7 (0-12)	2.2 (1-4)
Controls	72 (36:36)	-	36.5 (17-65)	-	-	-	-
			NS*	p=0.004†	NS†	NS†	NS

*(*one-way ANOVA, †Mann-Whitney U test. Sz=seizures. Gen=Generalized)*

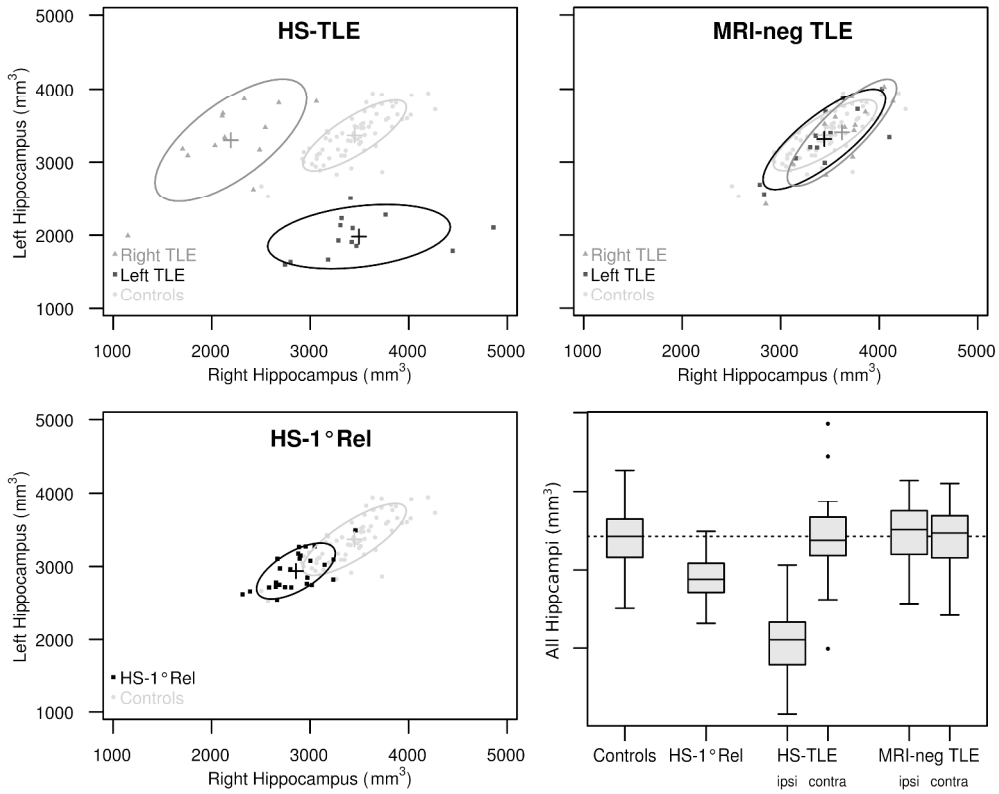
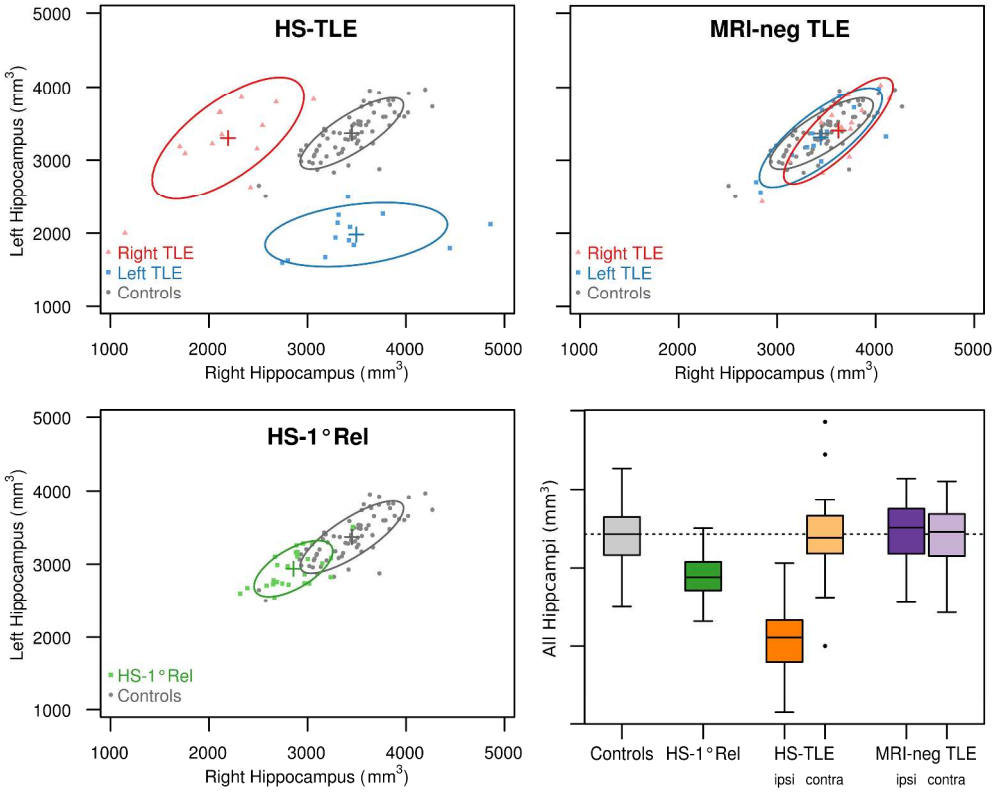


Figure 1 - Hippocampal volumes in Patients and Controls
Hippocampal volumes for each participant, measured by manual tracing on T1-weighted images, and corrected for intracranial volume by linear regression. (a-c) Crosshairs show the mean for each group, surrounded by the 95% confidence ellipse. Crosshairs that fall outside another ellipse indicate a significant difference in group means ($p<0.05$). (d) Boxplots show the median and interquartile range for each group, with whiskers to 1.5x interquartile range.
Fig. 1



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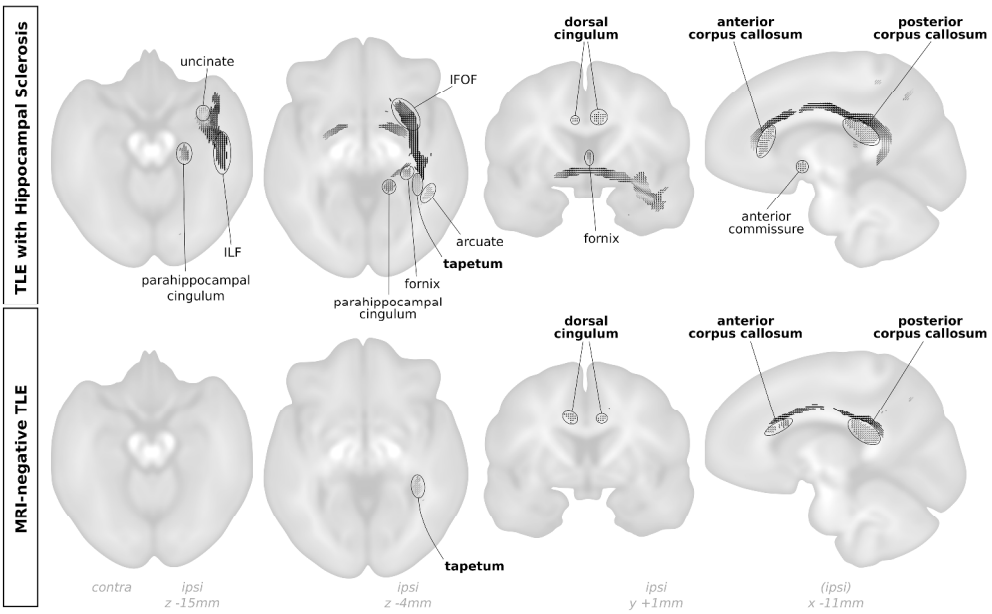
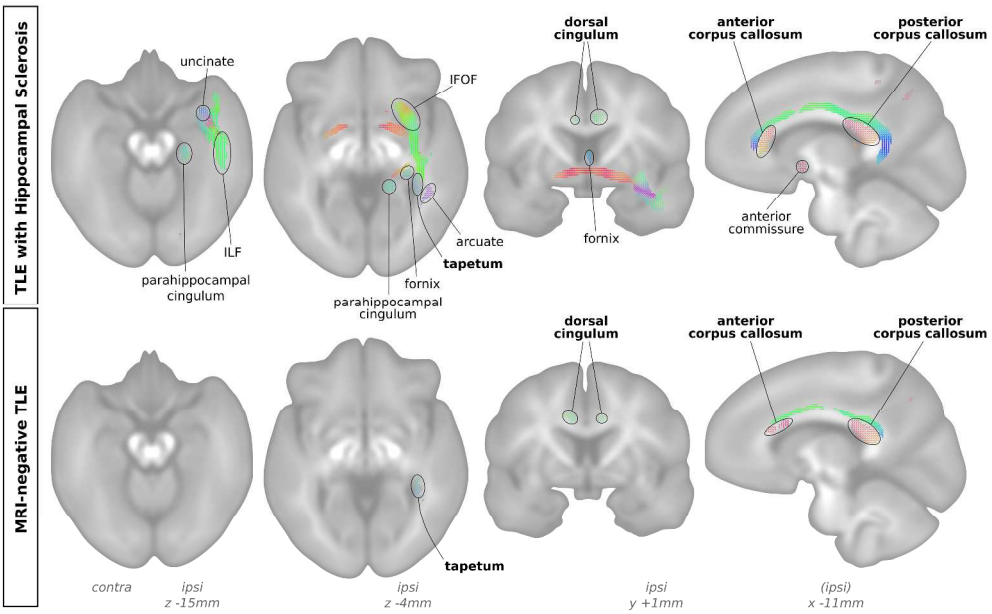


Figure 2 - Fixels with significant white matter atrophy in TLE
Fixels where Fiber Density & Cross-section (FDC) is less than in Controls ($p<0.05$ FWE corrected), after accounting for intracranial volume, age and brain side (right-to-left flip). The background image is the symmetrical study template, showing the scalar magnitude of the fiber orientation distribution at each voxel. Tracts affected in both HS-TLE and MRI-neg TLE are labelled in bold.
Fig. 2



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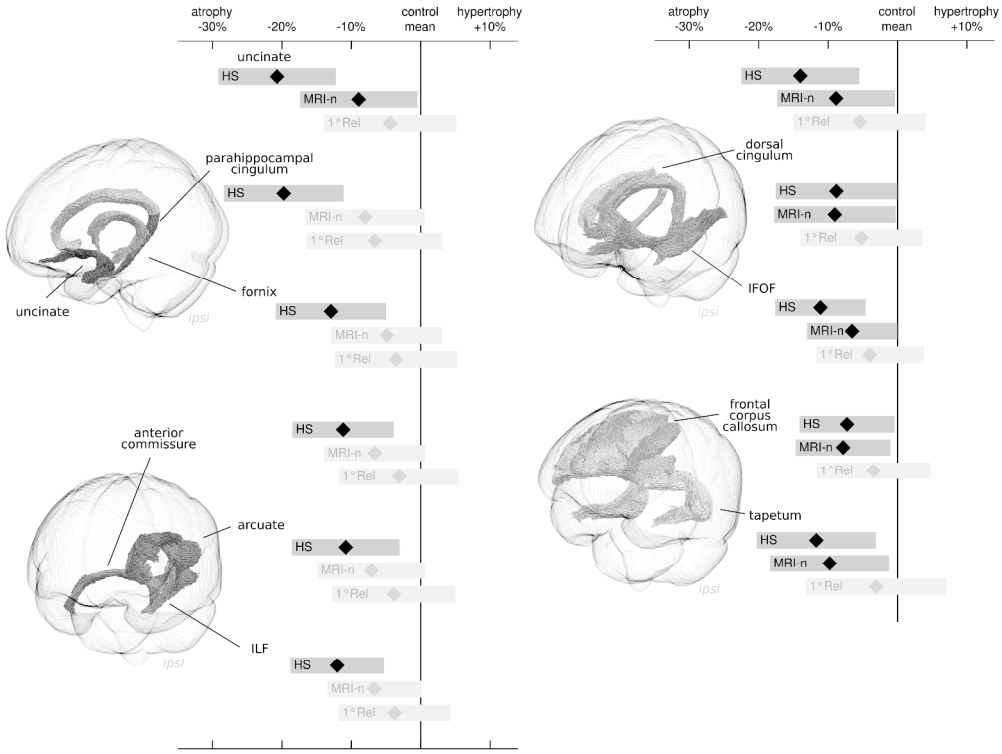

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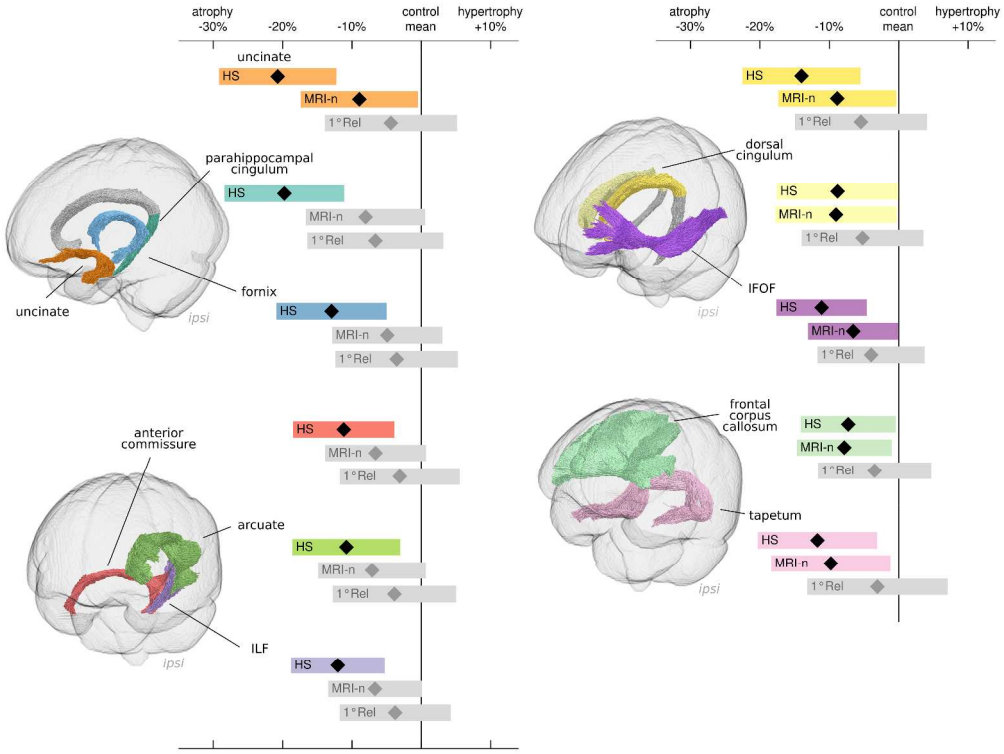
Fig. 3



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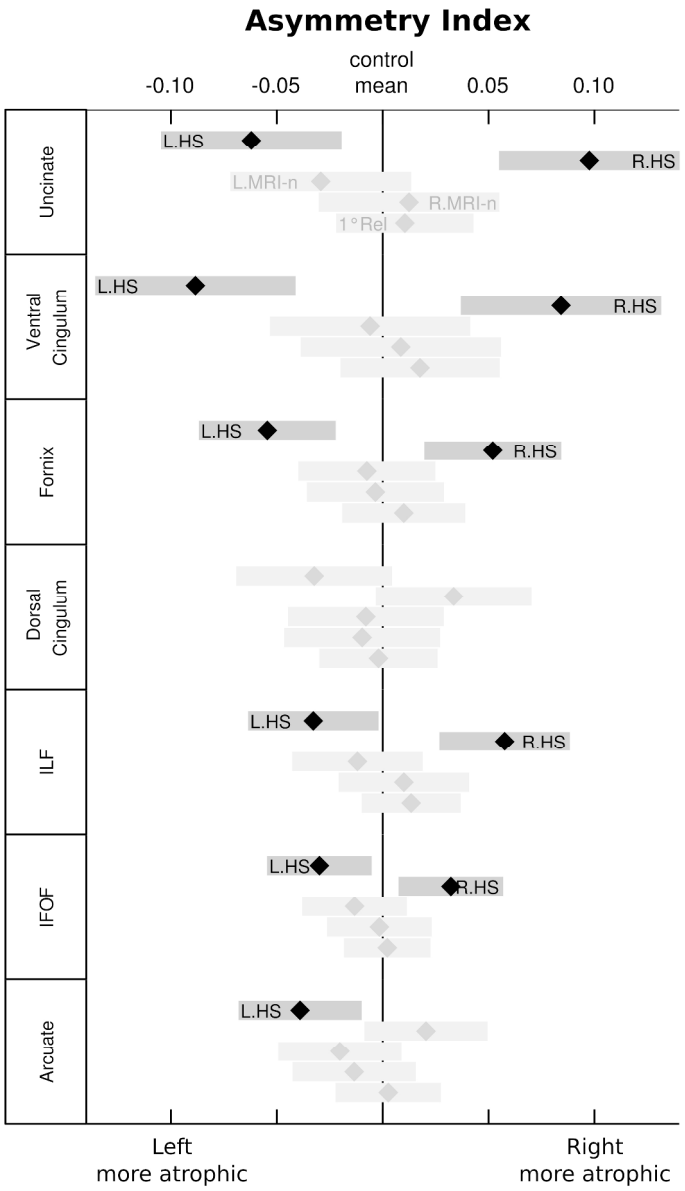

Figure 4 - Asymmetry of white matter atrophy in tracts-of-interest
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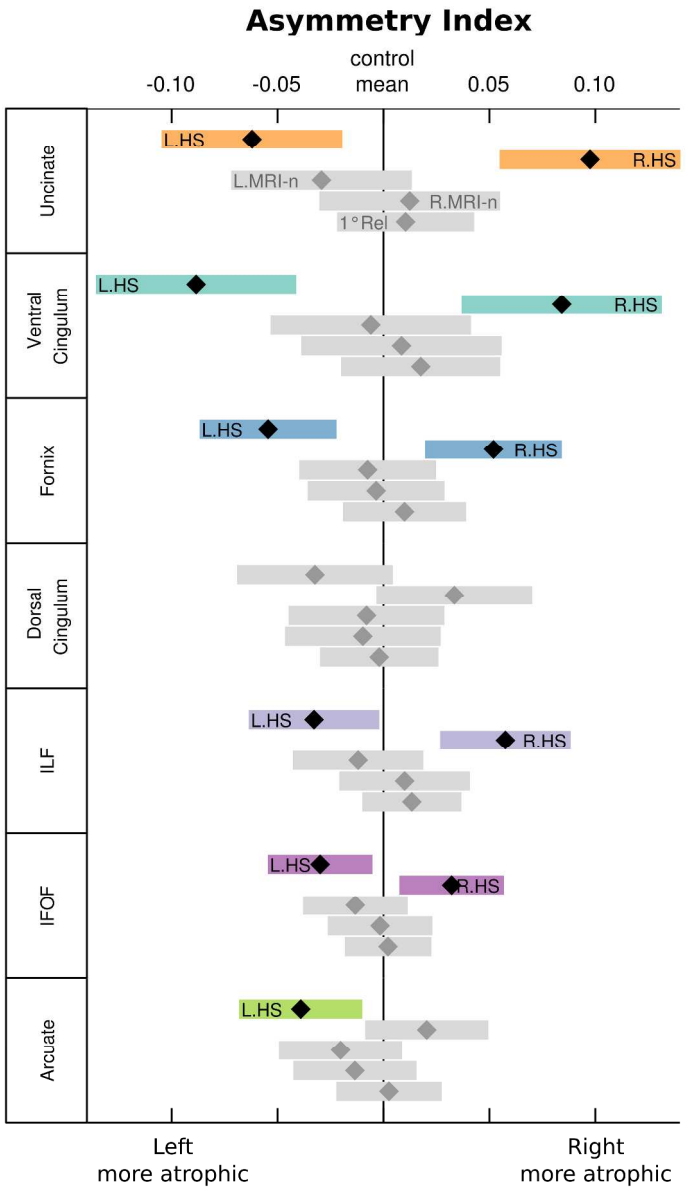
Fig. 4



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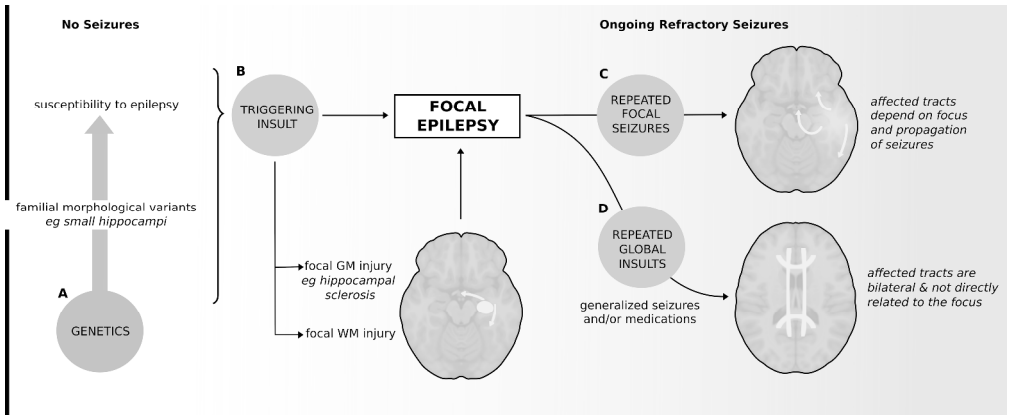
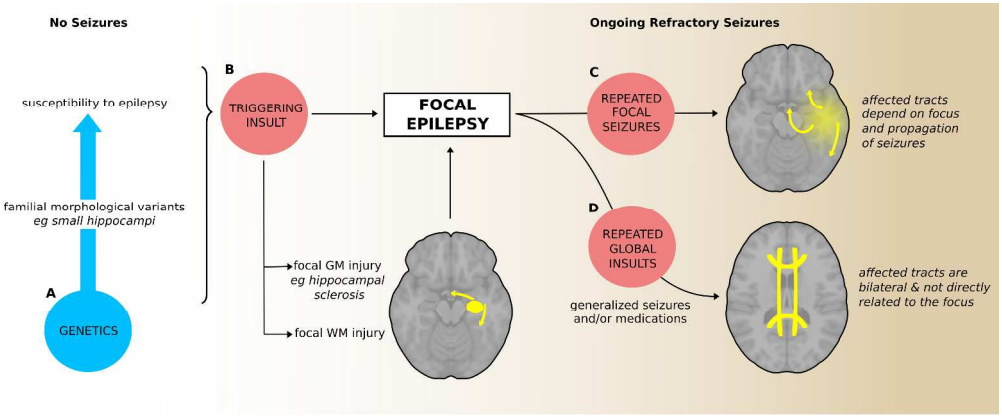


Figure 5 - Factors contributing to white matter atrophy in Focal Epilepsy
Fig. 5



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