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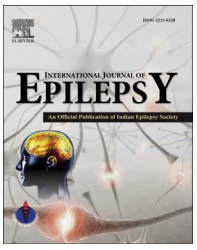

Original Article

Diffusion tensor imaging correlates of hippocampal sclerosis and anterior temporal lobe T2 signal changes in pharmacoresistant epilepsy

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ABSTRACT

Background and purpose: Our goal was to determine fiber tract integrity in hippocampal sclerosis (HS) using diffusion tensor imaging (DTI) and to correlate white matter damage with other pathology in this disease.

Methods: Twenty-six patients and eight controls were studied with DTI tractography for 8 pairs of white matter fiber tracts and 2 commissural tracts. Fractional anisotropy (FA) of the fiber tracts was compared with controls. The FA of select fiber tracts was also compared with change in T2 signal in the anterior temporal lobe (ATC), and the performance on neuropsychological tests.

Results: In comparison with controls, subjects with left sided hippocampal sclerosis (L-HS) had 3 ipsilateral fiber tracts with decreased FA. The FA of fiber tracts was similar in right sided HS (R-HS) to controls. The ipsilateral inferior longitudinal fasciculus had a decrease in FA that correlated with the ATC (T2 signal change). The right superior longitudinal fasciculus had a decrease in FA proportional to lower performance on tests of memory and language.

Conclusion: The subjects with L-HS had more extensive structural abnormalities involving white matter tracts, both ipsilateral and contralateral. In contrast, subjects with R-HS had limited changes in white matter integrity. Pathology of white matter appears to be involved in deficits associated with HS, including ATC and cognitive performance.

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Abbreviations: MTLE, mesial temporal lobe epilepsy; HS, hippocampal sclerosis; FA, fractional anisotropy; ATC, anterior temporal lobe change in T2 signal.

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1. Introduction

Mesial temporal lobe epilepsy (MTLE) is the most common form of epilepsy, and hippocampal sclerosis (HS) is the most frequently observed anatomic lesion found in MTLE.[1,29] Up to a third of patients with HS typically develop medically intractable epilepsy,[2] and the anatomical extent is currently being characterized.[3] Our study aims to (1) use a homogeneous patient sample to assess white matter fiber damage throughout the brain, (2) characterize differences between a right and left focus of hippocampal sclerosis, (3) assess associated MRI findings with DTI, and (4) correlate neurocognitive deficits associated with these tracts.

Hippocampal sclerosis (HS) is identified by increased T2 signal and atrophy within the hippocampus on conventional MR imaging, these imaging findings predict neuronal loss of CA1 and CA4 cells on subsequent pathological evaluation.[4,5,31] HS is associated with additional structural abnormalities of gray matter[6,7] and white matter, including temporal lobe sclerosis[8] and temporal lobe atrophy.[9]

Investigations of whole brain maps of fractional anisotropy (FA), a measure of the structural integrity of white matter,[10] have found reductions in the temporal, frontal and collosal fibers in patients with HS.[11] Follow-up studies have noted a unique pattern of structural deficits in patients with HS when compared to patients without HS.[12,13] Additionally, the change in white matter measured with DTI in R-HS patients was found to be less severe in comparison to L-HS patients.[12] These findings may be contained within specific white matter tracts, which can be investigated with DTI tractography in a well-selected patient sample with HS.

Patients with hippocampal sclerosis have an increased risk of concurrent abnormalities on neuroimaging or neuropathologic investigation, including anterior temporal lobe change in T2 signal (ATC), temporal lobe sclerosis, and temporal lobe atrophy.[14,5] The former includes several degrees of involvement, including the temporal pole alone (mild), to extension deeper into the temporal lobe (severe). The underlying histopathology of ATC is undetermined; however, it is unlikely due to changes in neuron density or distribution,[9,15,16] but more likely due to changes in myelin.[17] DTI may provide a method to examine microstructural pathological change in white matter tracts in HS associated pathology.

Adding to the burden of this disease, patients with medically intractable epilepsy have established neurocognitive deficits, and the neural substrate of these deficits lacks characterization. To date, mixed samples of subjects with TLE with HS and without HS have demonstrated deficits in memory and language proportional to white matter damage measured with DTI tractography.[18,19] These cognitive functions may have a unique correlation to the changes in white matter tracts in MTLE with HS due to the unique pattern of damage to white matter identified in other measures of in vivo pathology.

Our aim was to address these issues by investigating DTI tractography in patients with HS. Comparisons of white matter tract compromise with both ATC and neurocognitive deficits may provide a neuroanatomical pathway for these pathologies.

2. Materials and methods

2.1. Human subjects

The study received approval from the institutional review board of UCLA and study participants provided written consent before enrollment in the study. The study was performed in compliance with the Health Insurance Privacy and Portability Act. Twenty-six patients with hippocampal sclerosis (HS) and 8 healthy subjects were enrolled in the study (Table 1). Fourteen of the patients had HS on the left (L-HS) and 12 had HS on the right (R-HS). Patients were recruited during presurgical evaluation from the Epilepsy Center at UCLA, and patients were included in the study if all of the following criteria were met: (1) diagnosis of epilepsy by a board-certified neurologist with expertise in epilepsy, (2) unilateral ictal and interictal temporal lobe epileptiform activity as recorded by video-electroencephalogram, (3) unilateral hippocampal sclerosis read on magnetic resonance imaging by a board-certified neuroradiologist with expertise in epilepsy, (4) pathologically proven hippocampal sclerosis by a board-certified neuropathologist with expertise in epilepsy. Patients with bilateral seizure onset, bilateral pathology read on MR imaging, lack of hippocampal sclerosis either on MR imaging or pathology were excluded from the study. Control subjects did not have a history of neurological disease and had normal T1, T2 and FLAIR weighted imaging on conventional MRI.

2.2. Image acquisition and processing

The patients reported to have had no seizures for 24 h prior to MR imaging. Conventional and Diffusion weighted MR images were acquired using a 1.5 T Siemens ($n = 21$ patients, $n = 8$ control subjects) and a GE Signa ($n = 5$ patients), with similar acquisition parameters. The high-resolution MRI images were acquired on a GE Signa 1.5-T clinical scanner (Milwaukee, WI) at UCLA. Three-dimensional T1-weighted coronal images were acquired using spoiled gradient recalled acquisition in the steady state with the following acquisition parameters: acquisition matrix 256 × 256, TR/TE 40/9 ms, flip angle 35°, number of excitations 1, field of view 24 cm, and contiguous

Table 1 – Demographics and anterior temporal lobe T2 signal change (ATC) of the subjects.

	Right HS	Left HS	Controls
Number of subjects	12	14	8
Age (years)	31.1 ± 3.4	33.5 ± 3.5	38.8 ± 7.1
Gender (females:males)	(8:4)	(7:7)	(6:2)
Right-handed	12	11	8
Duration of illness (years)	23.7 ± 3.3	21.9 ± 3.7	-
ATC	6	13*	-
Severe ATC	4	9	-

Abbreviations: HS, hippocampal sclerosis; ATC anterior temporal change in T2 signal; - , Not applicable.
*$p < 0.05$.
All values are mean ± SD.

1.8-mm-thick slices covering the entire brain. The DTI acquisition included diffusion weighted sequence isotropic 2 mm voxels (matrix size 256 × 256), 5 mm contiguous slices without gap, 12 directions, 2 *b* values (0 and 1000 s/mm^2).

2.3. *Fiber tracking utilizing DTIStudio*

DICOM image files were moved to a PC workstation for reconstruction of fiber tracts. Fiber tractography was computed using the FACT algorithm in DTI Studio (Johns Hopkins University, Baltimore, MD).[20] Each fiber tract was constructed using the method described by Wakana and colleagues[21] while blinded to the conventional MRI and clinical data of the subject. This method was chosen for its demonstrated high inter-rater reliability and used to construct the corticospinal tract (CST), cingulum (CGC), cingulum hippocampal (CGH), anterior thalamic radiation (ATR), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFO), uncinate fasciculus (UF), forceps major, and forceps minor. Each fiber tract was reviewed on axial, coronal, and sagittal planes in conjunction with a white matter atlas to exclude fibers from neighboring tracts.[30]

2.4. *Statistical analysis*

Statistics were performed with SPSS version 19. Group characteristics, including age and epilepsy duration, were compared with independent *t*-tests. The right and left HS groups were combined for a characterization of the involvement of the temporal pole. The temporal lobe was characterized as either atrophic or normal volume with normal (0), mild (+1), or severe (+2) extent of T2 signal change. An analysis of variance (ANOVA) compared the age, the age of epilepsy at diagnosis, and the duration of epilepsy in subjects with varying degrees of anterior temporal lobe change in T2 signal (ATC).

An ANOVA compared the FA values of each fiber tract for the three groups (controls, R-HS and L-HS). Follow-up analyses were performed with detection of a significant omnibus ($p < 0.05$). Homogeneity of the variance was assessed with the Levene test, and post-hoc comparisons were corrected with the Tukey honestly significant difference tests with $p < 0.05$. For distributions that did meet the Levene criteria, comparisons were performed with Dunnett T3.

The FA values for temporal lobe fibers, ILF, IFO, and UF were correlated with the severity of the ATC using Spearman's rank correlation coefficient. The fiber tract asymmetry was calculated in the 7 tracts examined in past studies (CGC, CGH, ILF, IFO, ATR, UF, SLF).[22] The FA values for tracts demonstrated in literature[18,19] to be correlated with memory and language, including the SLF, UF, and IFO, were compared with the performance on the Boston Naming Test (BNT), the WMS-III Logical memory Recall test part 1 (LM I) and 2 (LM II). Additionally, the L-ILF was compared to the performance on these tests with Spearman's rank correlation coefficient.

Fiber tractography was repeated by the same rater (KS), 6 months apart, for assessment of reliability by Cronbach's alpha value.

3. Results

The age of the subjects in the L-HS, R-HS, and control groups were similar (ANOVA *F* 0.670, $p = 0.5$). The age, the age of onset, and the duration of epilepsy were similar in the 3 levels of severity of ATC (ANOVA *F* 1.1 $p = 0.3$; *F* 0.51, $p = 0.6$; *F* 0.94, $p = 0.5$). The R-HS and L-HS groups had similar number of subjects with temporal lobe atrophy and severe T2 signal change in the anterior temporal lobe. The L-HS group had a greater number of subjects overall with some amount of T2 signal change in the AT lobe (Fischer test, $p = 0.026$) (results summarized in Table 1).

3.1. *Group comparisons*

Comparison of FA for the three groups with ANOVA identified 4 fiber tracts with a decrease in the L-HS group: L-IFO ($p = 0.010$), ILF (F 11.244, $p = 0.02$), L-CST (F 4.23, $p = 0.02$), and R-CST (F 7.56, $p = 0.010$) (Fig. 1). No fiber tracts in the R-HS group demonstrated statistically significant difference in FA from the controls.

3.2. *Fiber tract hemispheric asymmetry*

Asymmetry of fiber tract integrity, calculated by subtracting the FA of the left from right hemispheric tract, is a second index of seizure lateralization compared with controls.[23] The R-HS group had fiber asymmetry of the UF ($p = 0.0002$) and a trend for the IFO ($p = 0.05$). The L-HS group had asymmetry of the IFO ($p = 0.003$) and UF ($p = 0.04$).

3.3. *ATC compared to individual fiber tracts*

For the L-HS group, the L-ILF was found to have a decrease in FA in proportion to the severity of ATC changes (Spearman's rho = −0.646, $p = 0.001$) (Fig. 2). The L-IFO had a decrease in proportion to the severity of ATC; however, this did not reach statistical significance (Spearman's rho = −0.294, $p = 0.07$).

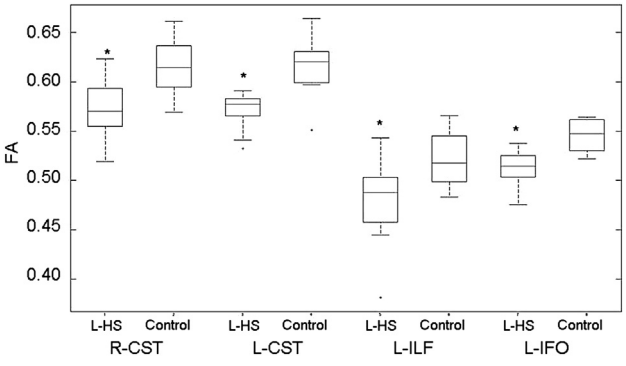

Fig. 1 – Subjects with Left sided Hippocampal Sclerosis (L-HS) have several fiber tracts with decreased fractional anisotropy (FA). Boxplot of fiber tracts with decreases in FA for fiber tracts in L-HS subjects as compared to controls. Asterisk ("*") indicates $p < 0.05$. CST corticospinal tract, ILF inferior longitudinal fasciculus, IFO inferior fronto-occipital fasciculus, R right, L left.

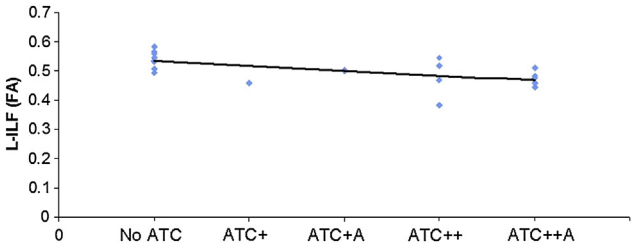

Fig. 2 – The severity of white matter compromise in the left inferior longitudinal fasciculus (L-ILF) in subjects with left hippocampal sclerosis (L-HS) is related to the severity of the change in anterior temporal lobe change T2 signal (ATC). Correlation of fractional anisotropy (FA) of the L-ILF with the severity of the change in anterior temporal lobe change T2 signal (ATC) (Spearman's rho = −0.646, $p = 0.001$). A decrease in FA of the L-ILF was noted for L-HS subjects with increased ATC of the temporal pole (ATC+). ATC of temporal pole was separated for subjects with atrophy (ATC+A) and without atrophy (ATC+) of the anterior temporal lobe. Further reduction of FA of the L-ILF was noted in subjects with ATC extending beyond the temporal pole (ATC++). The FA was plotted separately for subjects with atrophy (A) of the anterior temporal lobe (ATC+A and ATC++A). The FA for the L-ILF was grouped for subjects with R-HS or L-HS that did not have ATC (No ATC).

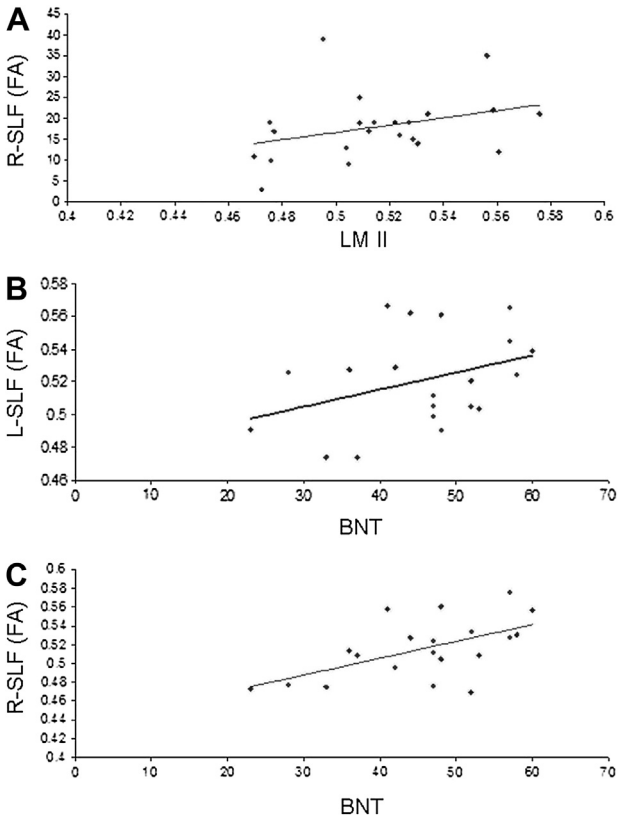

Fig. 3 – The fractional anisotropy (FA) of the right superior longitudinal fasciculus (R-SLF) is correlated performance on neurocognitive tests of language and memory. Scatterplots of the relationship between neurocognitive test score and FA of selected fiber tracts. (A) The R-SLF is correlated with performance on the WMS-II Logical Memory test II (LM II). The R-SLF (B) but not the L-SLF (C) is correlated with performance on the Boston naming test (BNT).

Similarly, the FA of the L-UF was not correlated with severity of ATC (Spearman's rho = −0.44, $p = 0.06$). These 3 fiber tracts in the right hemisphere did not correlate with ATC severity for the R-HS group.

3.4. *DTI tractography correlations with neuropsychological test performance*

The L-ILF did not correlate with performance on the BNT ($p = 0.4$), LM I ($p = 0.2$), or LM II ($p = 0.2$). The R-UF and L-UF were not correlated with BNT ($p = 0.45$ and $p = 0.32$, respectively). The L-IFO did not correlate with BNT ($p = 0.418$).

The L-SLF had a trend for correlation with BNT (rho = 0.281, $p = 0.11$). The R-SLF was correlated with the BNT (Spearman's rho = 0.568, $p = 0.004$) and LM II (Spearman's rho = 0.393, $p < 0.035$) (Fig. 3).

3.5. *Intrarater reliability on DTI tractography*

Intrarater reliability was assessed with Cronbach's alpha with value of 0.959. This value is comparable with values obtained in the literature.[18,22,21]

4. Discussion

The present study adds to the growing body of literature describing white matter deficits in HS. The pattern of fiber tract damage is unique in subjects with right versus left hippocampal sclerosis. The subjects with L-HS demonstrated decrease in FA in 4 tracts, whereas in R-HS the FA of fiber tracts was similar to controls. One commonality was that subjects with HS have decrease in FA of tracts ipsilateral to the hemisphere with HS, and this asymmetry was noted to exceed that of controls in the temporal lobe. We found that the decrease in integrity of a long white matter tract that spans the temporal lobe was associated with the severity of anterior temporal lobe T2 signal change. Finally, one white matter tract was associated with deficits in language and memory, suggesting its involvement in performing these neurocognitive tasks.

The present study contributes to the examination of HS populations with DTI tractography. The L-HS and R-HS had different patterns of white matter integrity as measured by FA. The L-HS had 4 tracts with decreased FA: L-ILF, L-IFO, L-CST, and R-CST. These tracts had not been investigated in this population previously. Two of the tracts were in the temporal lobe, ILF and IFO, and these expand on prior findings of whole brain investigations of FA in patients with HS; these studies found large areas of adjacent voxels in the white matter of the temporal lobe in the course of these 2 fiber tracts.[11,12] The

present study suggests that the contiguous voxels in the whole brain mapping studies represent portions of these 2 fibers. Additional decreases in FA were noted in the right and left CST in L-HS subjects. The involvement of these extra-temporal fibers suggests that wide ranging and diffuse white matter damage occur in L-HS. Overall, an ipsilateral pattern was appreciated in L-HS, in congruence with existing studies of whole brain mapping.[12,11] The CST has not been examined in HS in the past, but in L-TLE patients without HS, the L-CST was found to have decreased FA.[24] In prior studies, hippocampal pathways including the fornix and cingulum have been examined, with the combination of R-HS and L-HS patients into a single group.[25] In our sample, we found a decrease in FA trend in the dorsal portion of the ipsilateral cingulum in L-HS subject. It is possible that the acquisition of thin slice diffusion weighted imaging in the former study may reconstruct the cingulum with more accuracy[26]; however, our study suggest that L-HS subjects contribute more to this finding than R-HS subjects.

The present study examined the largest number of tracts with DTI tractography in subjects with HS, yet failed to identify a reduction in FA when R-HS subjects were compared to controls. In whole brain mapping of FA, the number of contiguous voxels in the white matter of R-HS subjects is few in comparison to the L-HS group[12]; nevertheless, clinically, HS on the right and left are comparable. These studies may suggest that extra-hippocampal damage in R-HS predominantly involves gray matter.[6] In the past, L-TLE has been noted to have more extensive white matter damage, which has been suggested to be due to the increased connectivity in the dominant hemisphere.[27] In mixed samples of TLE, some containing HS, the R-TLE patients have had fewer tracts with decreased FA in comparison to L-TLE patients,[22] and our sample expands this conceptual framework to patients with HS.

The pattern for within-subject-asymmetry in FA for fiber tracts is a measure used to describe a pattern of diffuse versus ipsilateral white matter damage. In studies of mixed populations of TLE with and without HS, the L-TLE had diffuse and R-TLE had ipsilateral white matter damage. In our study, the R-HS and L-HS groups were similar suggesting a diffuse pattern of WM damage, with focal asymmetry of temporal lobe fibers. The asymmetry was found in the UF in both L-HS and R-HS groups, as expected in consideration of this fiber tracts strong connectivity with the hippocampus. In a prior study of R-HS subjects,[18] the fiber asymmetry in the UF was not identified and further studies are needed to determine the role of this fiber tract in MTLE with HS. Overall, the diffuse symmetric pattern is similar to prior to studies of homogenous HS samples.[25]

The anterior temporal lobe change in T2 signal (ATC), also referred to as dual pathology or temporal pole change, has been found to be associated with HS in past studies.[5,9] The ILF is an ideal structure to compare with ATC, as the ILF extends and synapses throughout the rostro-caudal extend of the temporal lobe, including the temporal pole.[28] In contrast, DTI changes to fibers such as the UF may not be expected to correlate with ATC because the UF fibers are concentrated at the temporal pole, while as ATC severity increases, the change extends caudally. The reduction of FA in the ILF was in proportion to the severity of the ATC, suggesting that the ATC is due to white matter changes. This expands on earlier histopathological studies of ATC, which suggested myelin deficits, rather than dysplasia, may underlie ATC.[5,15,16] In R-HS subjects, this association could not be demonstrated; however, this may be due to the less frequent occurrence of ATC in our sample of subjects with R-HS.

To date, studies of mixed sample TLE subjects have found correlations between measure of diffusivity of individual fiber tracts with performance on neuropsychological tests[18,19] In Diehl and colleagues' study, apparent diffusion coefficients (ADC) but not FA of the UF was found to correlate with performance on memory tests.[18] Likewise, mean diffusivity (MD) of the UF was found to correlate with performance on these tests in general rather than FA in a subsequent study; however, the decrease in FA of SLF did have correlations with neurocognitive performance. Our study found that subjects with HS also have a correlation between the integrity of the R-SLF and performance on the LM II and BNT, tests of memory and language. The L-SLF also showed a trend that did not reach statistical significance for correlation with performance on the BNT. Since the R SLF was found to have this relationship to memory and language performance, confirming the literature, future studies may use this measurement, in conjunction with other features, to predict memory and language deficits. The increased contribution of the R-SLF and decreased contribution of the L-SLF to language performance in MTLE with L-HS has been demonstrated previously with correlation of fMRI and FA,[27] and may explain the difference in right and left SLF in the present study. In our DTI tractography study, as in prior studies,[19] the R-HS and L-HS groups were combined prior to comparison to performance on neurocognitive tests to improve power for statistical examination. Future studies with larger samples are needed to further investigate R-HS and L-HS for unique patterns of language re-organization.

Past studies have not included the ILF, and this is the first investigation of the ILF relation to standard memory and language tasks in subjects with epilepsy. We found no significant relationships between FA of ILF and the memory and language test scores. Our study may not be using the most precise test to select the function of the ILF, and from review of the literature, these tasks may not be represented in this fiber tract. The ILF is suspected to carry anterograde information from visual association cortex to the temporal lobe, as well as, retrograde information from the amygdala and temporal lobes to these same association-level visual cortices. From the anatomy, one may predict that a test for recognition of objects with emotional salience may be a superior test to investigate the role of the ILF in normal subjects as well as patients with HS.

The strengths of the study included the construction of a sample with a unifying pathology, HS, which is also the most frequent pathology in medically intractable epilepsy. This inclusion allowed for novel investigation of both temporal and extratemporal fibers in these patients. The subjects were analyzed for additional pathologies associated with HS, including ATC, and this allowed for the first advanced MR imaging investigation. Finally, neurocognitive correlation with DTI data was studied in this group, adding to the limited literature investigating the relationship of extra-hippocampal pathology and the deficits in memory and language in this disease. One limitation was the thick slices collected for DTI that limited construction of curved fibers; thus, the fornix was

not included in this study, although it is expected to have white matter damage in HS and perhaps different fiber integrity in right and left HS subjects. The cingulum was constructed in two separate parts, an established and reliable method[21,22]; however, construction of the cingulum as a single tract may more accurately represent white matter integrity. Another limitation was the small number of subjects. The results may be considered to be a conservative representation of white matter damage in HS. Including more subjects may have allowed detection of other fiber tracts, which were noted to have a trend for reductions in comparison to controls.

5. Conclusion

In conclusion, the data suggest that L-HS is associated with extra-hippocampal white matter damage, while R-HS may be a disease of predominantly gray matter changes. The severity of ATC, a HS associated pathology, is proportional to the integrity of the ILF, a white matter tract with connectivity throughout the temporal lobe, in subjects with L-HS. The white matter damage has functional implications, as performance on memory and language tests appear to be partially dependent on the integrity of the tracts investigated in this study.

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Conflicts of interest

All authors have none to declare.

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