Is manual drawing of region of interest to measure fractional anisotropy a reliable method of determining white matter integrity? Medial Temporal Lobe Epilepsy model

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In patients with Medial Temporal Lobe Epilepsy (MTLE), more severe impairment in the ipsilateral than the contralateral hemisphere white matter tracts, including Superior Longitudinal Fasciculus (SLF), are demonstrated on diffusion tensor imaging (DTI). Many clinicians and researchers conclude that drawing regions of interest (ROI) in the white matter can demonstrate these asymmetries. In this study we demonstrate that fractional anisotropy (FA) values derived from manually drawing ROI's on diffusion tensor imaging (DTI) of SLF differ between the side of seizure onset compared to the contralateral side in each individual patient with MTLE does not demonstrate these previous conclusions. We therefore believe that clinicians should recognize that this method of measurement can be inaccurate and should not be interpreted independently.

1. Introduction

Epilepsy has long been considered a gray-matter only disease. However, as the development of the gray and white matter is closely linked through neuronal migration processes, developmental malformations likely affect both the cortex and the underlying white matter. In addition, the hyperexcitability associated with seizure activity propagates through the functionally and structurally connected cerebral network potentially altering the white matter [1–5].

Diffusion-tensor imaging (DTI) can examine the microstructural integrity of white matter with quantitative measures of diffusivity and fractional anisotropy. For example, in a prior study, DTI measurements of pathological change in white matter tracts were discovered adjacent to focal cortical dysplasia (FCD). It's important to note that there are structural and functional asymmetries in the normal brain, which can be demonstrated on DTI, that can confound these conclusions [4].

Kim et al., demonstrated major white matter fibers including the Superior Longitudinal Fasciculus (SLF) ipsilateral to the side of "seizure onset zone" are affected more than the contralateral side, which may provide clinically useful information for epilepsy lateralization [1]. In patients with MTLE, more severe impairment in the ipsilateral than the contralateral hemisphere white matter tracts, including SLF [4], are demonstrated on diffusion tensor imaging (DTI) [6].

Many clinicians and researchers conclude that drawing regions of interest (ROI) in the white matter can demonstrate these asymmetries. In this study we aim to determine whether fractional anisotropy (FA) values derived from drawing ROI's on diffusion tensor imaging (DTI) of SLF differ between the side of seizure onset compared to the contralateral side in each individual patient with Medial Temporal Sclerosis (MTS) – Medial Temporal Lobe Epilepsy (MTLE).

2. Material and methods

Institutional Review Board approval was obtained for this retrospective study. The patient group consisted of 18 adult male and female epileptics with mesial temporal lobe epilepsy (MTLE) and imaging evidence of Medial Temporal Sclerosis (MTS) (age range: 20 – 68; median age: 44). The laterality of the seizure focus was confirmed by imaging (demonstration of hippocampal – medial temporal sclerosis), seizure semiology, and EEG findings in all cases. DTI images were obtained using an 8 Channel Head coil, on a 1.5 Tesla General Electric magnet (GE medical system, USA). The parameters for the DTI acquisition were as follows: axial 2D
single-shot-spin-echo echo-planar imaging (EPI) diffusion weighted sequence with TE/TR = 103.6/10,000 ms, two *b*-values of 0 and

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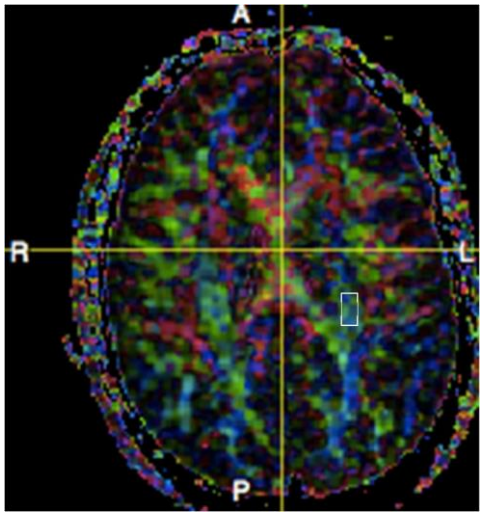

Fig. 1. Depiction of manually drawn region of interest in the region of Left Superior Longitudinal Fasiculus (SLF) on a 2-Dimentional DTI directional color map.

a. b.

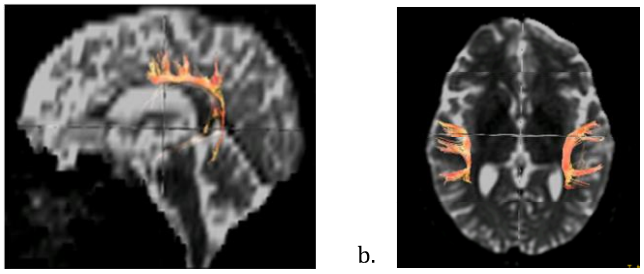

Fig. 2. 3-D depiction of the SLF tract on lateral (2a) and caraniocaudal (2b) orientations after drawing 2 ROI's in the expected anatomic location of SLF on 2-D DTI directional color maps (not shown).

1000 s/mm2, 25 directions. Field of view (FOV) = 28x 34 cm; Size of the acquisition matrix = 128 mm ×128 mm, and the slice thickness = 4 mm with 0.4 mm gap.

Data from the patients was transferred to a PC workstation and processed using TrackVis© (http://trackvis .org/). Maps for fractional anisotropy (FA) were then created. The investigators were blinded to the subjects' clinical data at the time of image processing. ROIs were delineated in the region of SLF and on the axial color-coded maps, using the color information and intensity to identify fiber bundles and avoid gray matter (Fig. 1). ROIs were drawn at the same size of voxels bilaterally. Measures of FA were determined at each ROI (mean ± SD) on TrackVis© software, where the regions of interest (ROIs) in the SLF were selected. (See Fig. 2.) Once FA values were calculated bilaterally, they were compared to those of the ipsilateral side in order to determine a correlation with the seizure focus.

3. Results

In the patient group as a whole, and in each individual patient, there were no significant differences in the FA values of the SLF in comparing the side of the epileptogenic zone to the contralateral brain region.

In the right MTLE-MTS group, the ipsilateral (R SLF) FA mean was 0.512 while the contralateral side had an average of 0.511. The left MTLE-MTS group also showed an insignificant difference with the L SLF FA mean of 0.554 and the R SLF mean of 0.539 (Table 1 and Figs. 3a and 3b).

Table 1

Numerical values of Fractional Anisotropy (FA) in SLF of patients with Medial Temporal Lobe Epilepsy (MTLE) and Medial Temporal Sclerosis (MTS), upon manually drawn ROI.

Seizure Focus	R SLF	L SLF
Right MTS	**0.533 ± 0.145**	0.531 ± 0.132
Right MTS	**0.459 ± 0.108**	0.461 ± 0.097
Right MTS	**0.467 ± 0.114**	0.546 ± 0.146
Right MTS	**0.554 ± 0.146**	0.562 ± 0.155
Right MTS	**0.501 ± 0.159**	0.447 ± 0.153
Right MTS	**0.568 ± 0.166**	0.537 ± 0.165
Right MTS	**0.502 ± 0.138**	0.493 ± 0.154
Left MTS	0.596 ± 0.156	**0.561 ± 0.154**
Left MTS	0.451 ± 0.142	**0.571 ± 0.169**
Left MTS	0.515 ± 0.167	**0.549 ± 0.168**
Left MTS	0.528 ± 0.14	**0.529 ± 0.15**
Left MTS	0.571 ± 0.149	**0.529 ± 0.146**
Left MTS	0.543 ± 0.145	**0.526 ± 0.138**
Left MTS	0.561 ± 0.18	**0.611 ± 0.185**
Left MTS	0.555 ± 0.152	**0.579 ± 0.139**
Left MTS	0.439 ± 0.129	**0.445 ± 0.112**
Left MTS	0.561 ± 0.15	**0.591 ± 0.156**
Left MTS	0.611 ± 0.155	**0.604 ± 0.143**

4. Discussion and conclusion

Our study has multiple limitations. Lack of significant differences between FA values on the side of MTS (confirmed by EEG abnormality) compared to the contralateral side could be due to lack of optimum spatial resolution and signal-to-noise ratio on images obtained on a 1.5 Tesla scanner. Furthermore, there was no cohort of control cases available for comparison to the patient group with the same scanner parameters. Most importantly, the ROIs are not always entirely within the SLF region and are "contaminated" by other white matter fiber tracts in the region due to the spatial resolution of our images and relatively small size of the tract. Similar difficulties are faced when there is a source of susceptibility artifact such as blood products in the region of white matter tracts of interest [7]. There are also inherent asymmetries in white matter tracts depending on hemispheric dominance [8] that need to be taken into consideration when comparing FA values of one side of the brain to the other.

The limitations of our technique, especially lack of accuracy in location of ROIs, is the case at most clinical institutions. Lack of significant differences in FA values of Superior Longitudinal Fasciculus (SLF) between the side of seizure onset compared to the contralateral side in our small group of patients, suggests that this method of measurement adds no clinically significant value to lateralization in cases of medial temporal lobe epilepsy in the current clinical practice.

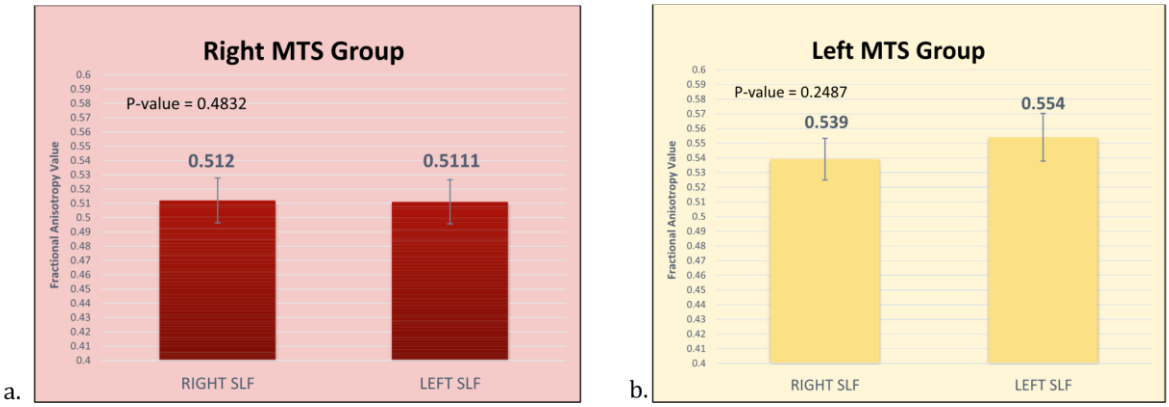

Fig. 3. Pictorial presentation of FA values of patients with Right (3a) and Left (3b) MTLE-MTS.

Development and improvement of more sophisticated and userfriendly imaging and image-processing methods and softwares such as Tract-Based Spatial Statistics (TBSS) of diffusion tensor imaging [9] in the future may help determine the side of the epileptogenic focus. In addition, more optimal spatial resolution and signal-to-noise ratio by using 3Tesla or & Tesla scanners will likely improve the accuracy of FA measurements.

Declaration of competing interest

The authors have no conflict of interest with the content of this paper to disclose.

References

[1] Z. Li, Q. Gao, K. Peng, et al., Quantitative evaluation of gray matter alterations in patients with mesial temporal lobe epilepsy (MTLE), Neuroscience Informatics 1 (4) (December 2021) 100018.
[2] H. Kim, A. Harrison, P. Kankirawatana, et al., Major white matter fiber changes in medically intractable neocortical epilepsy in children: a diffusion tensor imaging study, Epilepsy Res. 103 (2–3) (Feb 2013) 211–220, https://doi .org /10 .1016 / j .eplepsyres .2012 .07.017, Epub 2012 Aug 21.
[3] J.S. Duncan, Imaging in the surgical treatment of epilepsy, Nat. Rev. Neurol. 6 (2010) 537–550.
[4] X. Zhao, Z.Q. Zhou, Y. Xiong, et al., Reduced interhemispheric white matter asymmetries in medial temporal lobe epilepsy with hippocampal sclerosis, Front Neurol. 10 (Apr 2019) 394.
[5] S.S. Spencer, Neural networks in human epilepsy: evidence of and implications for treatment, Epilepsia 43 (2002) 219–227;
A. Bernasconi, N. Bernasconi, B.C. Bernhardt, D. Schrader, Advances in MRI for 'cryptogenic' epilepsies, Nat. Rev. Neurol. 7 (2011) 99–108.
[6] W.M. Otte, P. van Eijsden, J.W. Sander, et al., A meta-analysis of white matter changes in temporal lobe epilepsy as studied with diffusion tensor imaging, Epilepsia 53 (2012) 659–667.
[7] O.M. Topcuoglu, K. Yaltirik, Z. Firat, et al., Limited positive predictive value of diffusion tensor tractography in determining clinically relevant white matter damage in brain stem cavernous malformations: a retrospective study in a single center surgical cohort, J. Neuroradiol. 48 (6) (November 2021) 432–437.
[8] K. Egger, S. Yang, M. Reisert, et al., Tractography of association fibers associated with language processing, Clin Neuroradiol. 25 (Suppl 2) (Oct 2015) 231–236.
[9] S.M. Smith, M. Jenkinson, H. Johansen-Berg, et al., Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data, NeuroImage 31 (2006) 1487–1505.