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Abnormal neurite density and orientation dispersion in unilateral temporal lobe epilepsy detected by advanced diffusion imaging

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ABSTRACT

Background: Despite recent advances in diffusion MRI (dMRI), there is still limited information on neurite orientation dispersion and density imaging (NODDI) in temporal lobe epilepsy (TLE). This study aimed to demonstrate neurite density and dispersion in TLE with and without hippocampal sclerosis (HS) using whole-brain voxel-wise analyses.

Material and methods: We recruited 33 patients with unilateral TLE (16 left, 17 right), including 14 patients with HS (TLE-HS) and 19 MRI-negative ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)-positive patients (MRI-/PET+ TLE). The NODDI toolbox calculated the intracellular volume fraction (ICVF) and orientation dispersion index (ODI). Conventional dMRI metrics, that is, fractional anisotropy (FA) and mean diffusivity (MD), were also estimated. After spatial normalization, all dMRI parameters (ICVF, ODI, FA, and MD) of the patients were compared with those of age- and sex-matched healthy controls using Statistical Parametric Mapping 12 (SPM12). As a complementary analysis, we added an atlas-based region of interest (ROI) analysis of relevant white matter tracts using tract-based spatial statistics.

Results: We found decreased neurite density mainly in the ipsilateral temporal areas of both right and left TLE, with the right TLE showing more severe and widespread abnormalities. In addition, etiology-specific analyses revealed a localized reduction in ICVF (i.e., neurite density) in the ipsilateral temporal pole in MRI-/PET+ TLE, whereas TLE-HS presented greater abnormalities, including FA and MD, in addition to a localized hippocampal reduction in ODI. The results of the atlas-based ROI analysis were consistent with the results of the SPM12 analysis.

Conclusion: NODDI may provide clinically relevant information as well as novel insights into the field of TLE. Particularly, in MRI-/PET+ TLE, neurite density imaging may have higher sensitivity than other dMRI parameters. The results may also contribute to better understanding of the pathophysiology of TLE with HS.

1. Introduction

Epilepsy is a common neurological disease affecting approximately 50 million individuals worldwide (Leonardi and Ustun, 2002). Despite advances in antiepileptic drugs (AEDs) since the last century, over 30% of adult patients still have refractory seizures (Loscher and Schmidt, 2011). In current clinical practice, neurosurgical treatment is a widely performed option for such pharmacoresistant epilepsy (Rathore and Radhakrishnan, 2015).

Temporal lobe epilepsy (TLE) is the most common type of adult epilepsy (Engel Jr., 1996). It often shows pharmacoresistance but a relatively favorable response to surgical resection (Wiebe et al., 2001). Hippocampal sclerosis (HS), which is characterized by neuronal loss in the Ammon's horn, astrogliosis, or granule cell dispersion, is considered the most frequent pathology and etiology in TLE (Cendes et al., 2014). Whereas HS can often be detected visually on clinical MRI (Cendes

Abbreviations: AEDs, Anti-epileptic drugs; TLE, Temporal lobe epilepsy; HS, Hippocampal sclerosis; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; MRI-/PET+, MRI-negative/PET-positive; dMRI, Diffusion MRI; NODDI, Neurite orientation dispersion and density imaging; ICVF, Intracellular volume fraction; ODI, Orientation dispersion index; RSI, Restriction spectrum imaging; FA, Fractional anisotropy; MD, MEAN DIFFUSIVITY; EEG, Electroencephalogram; FSL, FMRIB Software Library; SPM, Statistical parametric mapping; DARTEL, Diffeomorphic anatomical registration using the exponentiated lie; TBSS, Tract-based spatial statistics; ROI, Region of interest; JHU, Johns Hopkins University

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Table 1
Clinical demographics of patients with TLE and healthy controls.

	Left vs right comparison				Etiology-specific comparison			
	L-TLE (n = 16)	R-TLE (n = 17)	Controls (n = 33)	p	TLE-HS (n = 14)	MRI-/PET+ TLE (n = 19)	Controls (n = 33)	p
Age at examination (years)								
Mean ± SD	40.5 ± 12.2	43.1 ± 11.5	42.1 ± 9.2	0.78[a]	45.6 ± 12.5	39.0 ± 10.5	42.1 ± 9.2	0.20 [a]
Sex (no.)								
Men:women	9:7	6:11	13:20	0.42[b]	6:8	9:10	13:20	0.85 [b]
Laterality (no.)								
Focus side (L:R)	N/A	N/A	N/A	N/A	5:9	11:8	N/A	0.36 [c]
Etiology (no.)								
HS:MRI-PET+	5:11	9:8	N/A	0.36 [c]	N/A	N/A	N/A	N/A
Disease duration (years)								
Mean onset age ± SD	20.3 ± 10.1	18.4 ± 14.2	N/A	0.66 [d]	15.5 ± 10.7	22.1 ± 12.8	N/A	0.13 [d]
Mean duration ± SD	20.3 ± 17.4	24.7 ± 11.4	N/A	0.39 [d]	30.1 ± 13.7	16.9 ± 12.8	N/A	< 0.05 [d]
Current treatment (no.)								
Mean no. of AEDs ± SD	2.38 ± 0.96	2.12 ± 0.93	N/A	0.44[d]	2.43 ± 0.94	2.11 ± 0.94	N/A	0.34 [d]
Seizure types (no.)								
Patients with aura	7	9	N/A	0.86[c]	9	7	N/A	0.23 [c]
Patients with sGTCs	3	4	N/A	0.93[c]	5	2	N/A	0.19 [c]

sGTCs, secondarily generalized tonic-clonic seizures.
[a] One-way ANOVA.
[b] Pearson's χ^2 test.
[c] Pearson's χ^2 test with Yates's correction
[d] Unpaired t-test.

et al., 2014), TLE may show no visual abnormality on MRI (i.e., MRI-negative TLE). However, even in MRI-negative TLE, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) can detect the focus lesion as a glucose hypometabolic area (Chassoux et al., 2010), and MRI-negative/PET-positive (MRI-/PET+) TLE is also regarded as an important group with favorable surgical outcomes (Kuba et al., 2011; Lopinto-Khoury et al., 2012). Although FDG-PET is a highly useful examination with a sensitivity of 85%–90% for TLE (Kumar and Chugani, 2013), there is still a need for a more advanced methodology for focus detection considering the limited availability and high cost of PET and the inherent radiation exposure.

Recent advances in diffusion MRI (dMRI) have allowed the visualization of more detailed brain microstructures such as neurites (Zhang et al., 2012) and myelin tissues (Fujiyoshi et al., 2016). In particular, neurite orientation dispersion and density imaging (NODDI), which can evaluate neurite density as the intracellular volume fraction (ICVF) and neurite dispersion as the orientation dispersion index (ODI) (Zhang et al., 2012), is expected to contribute to the understanding and localization of focal epilepsy (Winston, 2015) because decreased neurite density has been found in MRI-visible focal cortical dysplasia (Winston et al., 2014). The applications of NODDI to idiopathic epilepsy or neurodegenerative diseases are also reported (Kamagata et al., 2016; Sone et al., 2018). Additionally, Loi and colleagues (Loi et al., 2016) showed reduced neurite density in left and right TLE, mixing both TLE with HS and MRI-negative TLE, by using restriction spectrum imaging (RSI). Decreased neurite density was also suggested to correlate with executive dysfunction in TLE (Reyes et al., 2018). On the other hand, clinical NODDI studies in TLE are still limited, except for a more experimental application study (Lemkaddem et al., 2014). To detect possible abnormalities in neurite density and dispersion in TLE with HS and MRI-/PET+ TLE, we considered that an etiology-specific NODDI application in TLE would provide significant clinical and pathophysiological information to this field.

The aims of this whole-brain voxel-wise statistical neuroimaging study were the following: (1) to confirm and demonstrate neurite density and dispersion in left and right TLE using NODDI, (2) to investigate etiology-specific findings (i.e., TLE with HS and MRI-/PET+ TLE), (3) to compare these findings with conventional dMRI parameters [i.e., fractional anisotropy (FA) and mean diffusivity (MD)], and (4) to explore the correlations of these dMRI metrics with disease duration.

2. Material and methods

2.1. Participants

We recruited 33 patients with TLE (18 females, 15 males; mean ± SD age: 41.8 ± 11.7 years) at our institute between November 2016 and November 2017. TLE was diagnosed based on the presence of focal seizures consistent with TLE and focal epileptiform discharge predominantly in temporal areas on a conventional scalp electroencephalogram (EEG).

Of the 33 patients, unilateral HS was found on conventional MRI in 14 (the TLE-HS group), whereas the other 19 visually showed ipsilateral glucose hypometabolism in interictal FDG-PET and no abnormalities on conventional MRI (the MRI-/PET+ group). Visual assessment of the MRI was performed by experienced neuroradiologists, and the visual diagnostic criteria for HS were the following: ipsilateral reduced hippocampal volume, increased T2 signal in the hippocampus, and abnormal morphology (i.e., a loss of internal architecture of the stratum radiatum, the thin layer of white matter that separates the dentate nucleus and Ammon's horn). Hypometabolism of the ipsilateral temporal lobe was visually diagnosed by a nuclear medicine specialist based on left–right differences.

Clinical data were also reviewed and included seizure onset age, duration of disease, seizure semiology, AEDs, long-term video-EEG monitoring, surgical treatments, and histopathology. The detailed clinical demographics of the groups are shown in Table 1 and in the Results section.

Patients with the following criteria were excluded: a significant medical history of acute encephalitis, meningitis, severe head trauma, or ischemic encephalopathy; suspicious epileptogenic lesions (e.g., tumor, cortical dysplasia, or vascular malformation) on MRI other than ipsilateral HS; contradictory lateralization of focus among MRI, FDG-PET, and long-term video-EEG monitoring; or epileptic paroxysms in extratemporal regions on EEG.

As controls, we also recruited 33 healthy age-matched adults with