Association of white matter diffusion characteristics and cognitive deficits in temporal lobe epilepsy

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ABSTRACT

Objective: The purpose of this study was to evaluate the relation between cognitive performance and white matter (WM) integrity in patients with temporal lobe epilepsy (TLE) with mesial temporal sclerosis (MTS).
Methods: We included 26 patients with TLE (10 right, 16 left onset) as well as 24 healthy controls matched for age, gender, and years of education. In addition to quantitative hippocampal volume and transverse relaxation (T2) evaluation, whole-brain WM was analyzed using fractional anisotropy (FA) maps, derived from the diffusion tensor model. Average FA values were obtained from 38 regions of interest (ROI) of the main WM fascicles using an atlas-based approach. All subjects underwent extensive coFignitive assessments, Wechsler Adult Intelligence Scale (WAIS-IV) and Wechsler Memory Scale (WMS-IV). Fractional anisotropy was correlated with neuropsychological scores, and group effects were evaluated. Finally, patients were clustered based on their cognitive performance to evaluate if clinical and structural variables relate to specific cognitive profiles.
Results: Patients had differential alterations in the integrity of the WM dependent on seizure laterality and presence of hippocampal sclerosis. Patients with TLE showed, on average, lower scores in most of the cognitive assessments. Correlations between cognition and WM followed specific trajectories per group with TLE, particularly in Left-TLE, in which we found a marked association between cognitive abilities and WM abnormalities. Cluster analysis of cognitive performance revealed three cognitive profiles, which were associated with the degree and spread of WM abnormalities.
Significance: White matter diffusion characteristics differ between patients, particularly in relation to seizure laterality and hippocampal damage. Moreover, WM abnormalities are associated with cognitive performance. The extent of WM alterations leads to disrupted cerebral intercommunication and therefore negatively affects cognition.

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1. Introduction

Temporal lobe epilepsy (TLE) is the most common of all focal epilepsies [1]. Many patients show mesial temporal sclerosis (MTS), a specific set of tissue abnormalities related to neuronal death and gliosis in the affected hippocampus, amygdala, and entorhinal cortex [2]. This lesion is commonly observed on conventional magnetic resonance imaging (MRI) as decreased volume and T2 hyperintensity of the hippocampus and, when present unilaterally, is prognostic of good outcome following surgical treatment [3].

Seizures are generated in the epileptogenic temporal lobe, but brain abnormalities in patients with TLE are not restricted to this lobe. Diffusion MRI, particularly using diffusion tensor imaging (DTI) [4], has repeatedly shown white matter (WM) diffusion abnormalities within and beyond the affected temporal lobe [5] that are thought to reflect damage of the microstructural architecture of WM fascicles [6]. Moreover, these abnormalities are greater when MTS is present [7–9]. Although WM changes could be secondary to ongoing seizures, it is unknown if they antecede the diagnosis or could serve as a predisposing factor.

Cognitive impairment is common in patients with TLE [10]. Given the crucial role that hippocampus plays in memory consolidation, it is not surprising that patients with TLE often report memory problems, with verbal memory deficiencies commonly associated with left-hemisphere TLE (L-TLE) and nonverbal memory deficits occurring more often in right-hemisphere TLE (R-TLE) [11]. However, nearly a third of all patients with TLE exhibit cognitive deficits in domains not typically associated with the temporal lobe, such as executive function and processing speed [12].

Cognitive functions rely on the orchestrated activity of multiple cortical and subcortical regions interconnected by WM. Previous studies have demonstrated a relation between performance in specific cognitive tasks and WM diffusion metrics in several WM bundles [13–16]. However, most studies have either focused on memory and language functions or have not investigated whether TLE lateralization or the presence of MTS independently modulate cognitive performance and WM characteristics. To address these shortcomings, we performed full cognitive assessments and DTI evaluations of patients with TLE with and without MTS.

We hypothesized that if cognitive performance relies on the proper communication of different brain areas, then WM diffusion abnormalities should be related to cognitive deficits in patients with TLE. Furthermore, such correlations might be modulated by epileptic focus localization and the presence of MTS. We performed an automated analysis of WM diffusion characteristics and correlated these metrics with scores derived from extensive neuropsychological assessment, factoring for clinical characteristics. Finally, cognitive scores were used to subdivide patients to identify the structural and clinical characteristics that are particular to specific cognitive profiles.

2. Methods

2.1. Participants

The Ethics Committee of the Institute of Neurobiology approved the project, and all participants provided signed informed consent. We included 26 patients with medically refractory TLE and 24 healthy controls. All participants were adults, Spanish speakers, right-handed, and had an overall IQ greater than 69 points. They did not have any contraindications for the use of MRI.

Patients with TLE were recruited between 2012 and 2015 from outpatient clinics and were diagnosed by certified neurologists based on the criteria of the International League Against Epilepsy (ILAE). We excluded patients whose current drug therapy is associated with reversible cognitive deficits (i.e., barbiturates, benzodiazepines, or topiramate). We also excluded patients with psychiatric or neurological comorbidities or with MRI findings other than MTS. Patients with TLE were subclassified into two groups according to semiology, clinical features, interictal electroencephalography recordings, and neuroimaging findings, into R-TLE (n = 10) and L-TLE (n = 16; for MTS classification see Supplementary material).

2.2. Cognitive assessments

All participants completed the Wechsler Adult Intelligence Scale (WAIS-IV) and Wechsler Memory Scale (WMS-IV). These tests evaluate the cognitive domains recommended by the ILAE Neuropsychology Task Force. The WMS-IV consists of seven subtests and derives in five indices that evaluate memory performance: auditory memory index (AMI), visual memory index (VMI), visual working memory index (VWMI), immediate memory index (IMI), and delayed memory index (DMI). The WAIS-IV has fifteen tests and estimates four cognitive spheres whose average is the full scale IQ: verbal comprehension index (VCI), working memory index (WMI), processing speed index (PSI), and perceptual reasoning index (PRI). All reported indices are normalized based on a Mexican population and adjusted by age and education level.

2.3. MRI acquisition

All MRIs were obtained with a 3 T Philips Achieva TX scanner, using a 32-channel head coil. T1-weighted volumes (3D-SPGR (three-dimensional spoiled gradient echo); TR: Repetition time/TE: Echo time = 8.1/3.7 ms, flip angle = 8°) had a resolution of $1 \times 1 \times 1$ mm^3. Diffusion-weighted images (DWI) were obtained using echo-planar imaging (EPI) with resolution of $2 \times 2 \times 2$ mm^3 (TR/TE = 11.86/64.3 ms); these images were acquired sensitized to diffusion in 60 directions with b = 2000 s/mm^2, and one b = 0 s/mm^2 volume. To correct geometric distortions, an additional non-DWI volume was obtained with reversed phase encoding polarity with respect to the full DWI data set. A multiecho acquisition (TE$_1$/TE$_{spacing}$ = 15/15 ms; 8 spin-echoes, resolution = $0.5 \times 0.5 \times 2$ mm^3) was acquired with an oblique orientation perpendicular to the antero-posterior axis of the hippocampus. Additionally, we collected functional images that are not discussed here. Total scan time was approximately 1 h.

2.4. T1 processing

Hippocampal volumes were derived from segmentation of the T1 volumes using a patch-based method [17], as implemented in *volbrain* (http://volbrain.upv.es/). Anatomical T1-weighed volumes and associated labels were nonlinearly registered to the corresponding T2 and DWI. Hippocampal volume (Vol) was expressed as the percentage of total brain volume.

2.5. Diffusion imaging processing

The off-resonance field was estimated from a pair of volumes with reversed phase encoding, and used to correct geometric distortions in the full DWI data set using *fsl*'s tools (v.5.0.6, FMRIB, http://fsl.fmrib.ox.ac.uk). Diffusion gradient vectors were rotated accordingly. The tensor model was fitted to the corrected DWI data sets, and diagonalized to obtain fractional anisotropy (FA) and mean diffusivity (MD) maps.

2.5.1. Tract-Based Spatial Statistics (TBSS)

Each FA map was coregistered via nonlinear transformations to a custom unbiased FA template derived from all subjects. Registered FA maps were averaged to create a skeleton of the common WM structures. This WM skeleton was thresholded (FA > 0.2), and data at each voxel within it were populated from each subject's maximum FA value within a search region perpendicular to the direction of the skeleton [18]. The Johns Hopkins University White Matter (JHU-WM) template [19] was registered to our FA template and was used to obtain each subject's average FA values within 38 regions of interest (ROI).

2.6. T2 processing

A single exponential decay model was fitted to the multiecho images for each voxel to estimate T2. To minimize partial volume averaging of tissue and cerebrospinal fluid (CSF), individual T2 maps were thresholded using a value defined as the mean + 2 standard deviations of all voxels having a T2 < 2 s.

2.7. Statistical analysis

To test for differences between groups in clinical and neurophychometric variables, ANOVA tests were used followed by Tukey *post hoc* correction. The TBSS analyses were used to compare FA values of each group with TLE to healthy controls using Student's *t*-tests corrected for multiple comparisons by threshold-free cluster enhancement permutation analysis [20]. Pearson's correlation coefficient (r) was used to evaluate relations between cognitive test scores and FA derived from the 38 ROIs; correlations showing r between −0.5 and 0.5 were discarded. To test for interactions (i.e., whether the