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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.

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.

Abbreviations: TLE, Temporal lobe epilepsy; MTS, Mesial temporal sclerosis; MRI, Magnetic resonance imaging; DWI, diffusion weighted imaging; DTI, Diffusion tensor imaging; MD, Mean diffusivity; FA, fractional anisotropy; TBSS, Tract-Based Spatial Statistics; L-TLE, Left temporal lobe epilepsy; R-TLE, Right temporal lobe epilepsy; AMI, Auditory memory index; VMI, visual memory index; VWMI, visual working memory index; IMI, immediate memory index; DMI, delayed memory index; IQ, full scale intelligence quotient; VCI, verbal comprehension index; WMI, working memory index; PSI, processing speed index; PRI, perceptual reasoning index; ROI, region of interest; AED, antiepileptic drug.

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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

Group factor modulates correlations between cognitive performance and FA values), we used an analysis of covariance corrected for multiple tests (p_{corr} = p / (38 WM regions × 10 psychometric test)).

2.8. Cognitive profiling

We performed a cluster analysis using z-scores based on controls of all cognitive metrics. The classification was performed using Ward's hierarchical method with squared Euclidean distance dissimilarity between patients with TLE [12]. All statistical analyses were carried out using R (version 3.2.1).

3. Results

3.1. Clinical data

There were no statistically significant differences between groups in the distribution of age, gender, or years of studies. All subgroups with TLE had similar clinical characteristics (Table 1). Mesial temporal sclerosis was identified in 8/10 patients with R-TLE and in 7/16 patients with L-TLE. Patients with MTS showed reduced volume and increased T2 and MD of the ipsilateral hippocampus (Supplementary Table 1).

3.2. Cognitive evaluations

Control subjects performed adequately for their age and years of education. In contrast, patients with TLE had lower cognitive performance (Fig. 1). Patients with R-TLE had significantly decreased scores in all cognitive tests. Patients with L-TLE showed deficits in intelligence quotient, verbal comprehension, processing speed, and working, immediate and delayed memory. No differences were found between patients with TLE (see Supplementary Table 1 for cognitive scores for subgroups with TLE).

3.3. Clinical and psychometric interactions

We searched for linear relations between clinical variables and indices of cognitive performance, as well as their interactions with the Group factor. Years of education, in particular, showed a strong interaction with the Group factor (Supplementary Table 2). Although scores of the cognitive tests are corrected by educational level, we found relations between this variable and intelligent quotient, verbal comprehension, perceptual reasoning, processing speed, working memory, and visual memory in patients with L-TLE. In patients with R-TLE, years of education showed a positive slope with respect with processing speed (uncorrected-p = 0.01). Other linear regressions were not statistically significant in either group. Presence of MTS did not modulate these correlations.

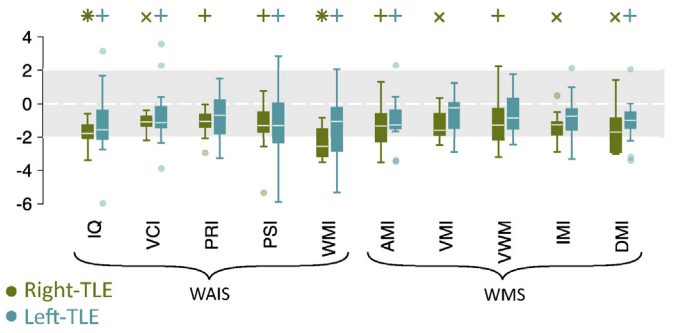

Fig. 1. Cognitive evaluations. Boxplot of the cognitive scores presented as z-scores based on the control group. TLE vs Control: $^{+}p < 0.05$, $^{\times}p < 0.005$, $^{*}p < 0.001$. No differences between groups with TLE were found. WAIS: IQ-intelligence quotient, VCI-verbal comprehension index, PRI-perceptual reasoning index, PSI-processing speed index, WMI-working memory index. WMS: AMI-auditory memory index, VMI-visual memory index, VWM-visual working memory index, IMI-immediate memory index, DMI-delayed memory index.

3.4. WM diffusion characteristics

While we found no difference in FA values between groups with TLE, comparisons with respect to controls revealed patterns specific to each group with TLE. Groups with Left- and Right-TLE have multilobar reductions of FA compared with controls (Fig. 2.a,b), but changes were more extensive in R-TLE, which had a higher prevalence of MTS (Table 1.b and Supplementary Table 1). In the subgroup analysis, R-TLE patients with MTS had the most extended reductions of diffusion anisotropy throughout the brain (Supplementary Fig. 1).

3.5. Correlations between cognitive evaluations and WM diffusion characteristics

Average FA values from within 38 anatomical ROI were correlated with cognitive evaluation scores (Fig. 3). Full-scale intelligence quotient, being a summary of other indices, was not analyzed.

Healthy volunteers have linear correlations ($r \approx 0.6$, uncorrected-$p < 0.05$) between verbal comprehension, processing speed, and working memory, with several left and right structures (Fig. 3.a). After correction for multiple comparisons, only the correlation between working memory and posterior thalamic radiation remains as significant.

Patients with L-TLE (n = 16; 7 with MTS) showed the largest number of correlations among all groups (Fig. 3.b), and patterns differed in relation to MTS (Supplementary Fig. 2). Most of these correlations were positive, except those seen in the left posterior thalamic radiation in both subgroups with L-TLE. In all patients with L-TLE, positive correlations between FA and most of the cognitive scores were seen in left and right anterior corona radiata, left internal capsule, left and right superior corona radiata, left and right external capsule, and inferior fronto-occipital fasciculus (Fig. 3.b). Voxel-wise analyses confirmed these correlations (Supplementary Figs. 3 and 4).

Patients with R-TLE (n = 10; 8 with MTS) showed positive correlations between diverse WM regions such as left superior and right posterior corona radiata, right posterior limb of internal capsule, and right

Table 1
Sample characteristics.

		Controls n = 24		R-TLE n = 10		L-TLE n = 16	
a) Clinical characteristics							
Age (years)		32.0	(12.5)	29.1	(15.1)	30.8	(9.8)
Gender		F17	M7	F6	M4	F10	M6
Years of education		13.3	(2.3)	11.9	(2.7)	13.1	(3.1)
Onset (years)				9.4	(6.1)	15.2	(11.2)
Duration (years)				20.5	(18.9)	15.6	(10.2)
Seizures per month				4.7	(9.6)	3	(3.3)
Number of AEDs				1.7	(1.0)	1.6	(0.6)
b) History							
Traumatic brain injury				50%		45%	
Family history of epilepsy				30%		56%	
Trigger identification				70%		69%	
c) Mesial temporal sclerosis							
				8 (80%)		7 (47%)	
d) Hippocampal evaluation							
Left hippocampus	Vol%	0.28	(0.02)	0.28	(0.03)	0.26	(0.05)
	T2	131.5	(4.2)	137.2	(6.6)*	139.3	(8.6)*
	MD	0.79	(0.03)	0.83	(0.02)**	0.84	(0.06)**
Right hippocampus	Vol%	0.29	(0.03)	0.24	(0.04)*,§	0.29	(0.03)
	T2	128.5	(5.1)	138.9	(10.5)**	133.8	(3.8)*
	MD	0.79	(0.02)	0.87	(0.07)***,§	0.82	(0.05)

Clinical features. Data are presented as mean (standard deviation). TLE: Temporal lobe epilepsy, F: female, M: male, AEDs: antiepileptic drugs. Volume is expressed as percentage of total brain volume. T2: Quantitative transverse relaxation (ms), MD: Mean diffusivity ($\times 10^{-3}$ mm^2/s). No significant differences were found between groups with R-TLE and L-TLE. $^{*}p < 0.05$, $^{**}p < 0.005$, $^{***}p < 0.001$; §TLE + MTS vs TLEnl, *TLE vs Control.

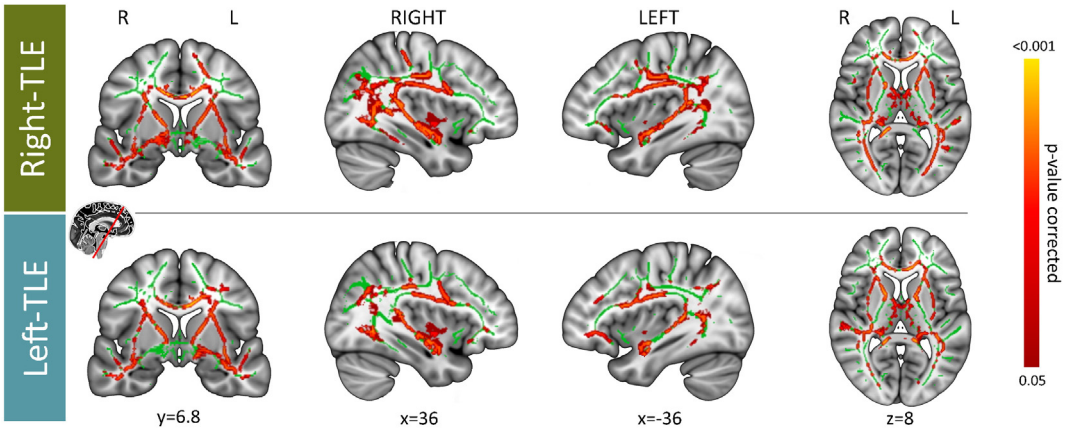

Fig. 2. White matter abnormalities. Tract-Based Spatial Statistics (TBSS) of the areas with significantly reduced FA compared with controls for the different groups with TLE. The green area shows the analyzed regions. Significant FA differences (corrected for multiple comparisons) are shown in warm colors. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

uncinate fasciculus, and different cognitive indices mainly related to memory (working, visual, and immediate).

3.6. Relation between FA and cognitive performance modulated by group

Interaction analyses (ANCOVA, corrected for multiple comparisons) showed that among R-TLE, L-TLE, and Controls, only the patients with L-TLE have significant regressions between neuropsychometric scores and diffusion characteristics of WM structures ($p_{corr} < 0.05$). In L-TLE, the change in FA of the left anterior corona radiata, right superior corona radiata, and left external capsule has a positive relation with the WMI score. A similar relation was seen in patients with L-TLE between FA of the left external capsule and processing speed (Fig. 4). These relations remained significant after regressing out years of education.

3.7. Cluster analysis of cognitive abilities

We found three clusters of patients derived from cognitive performance scores. Cluster 1 had all cognitive scores within 2 standard

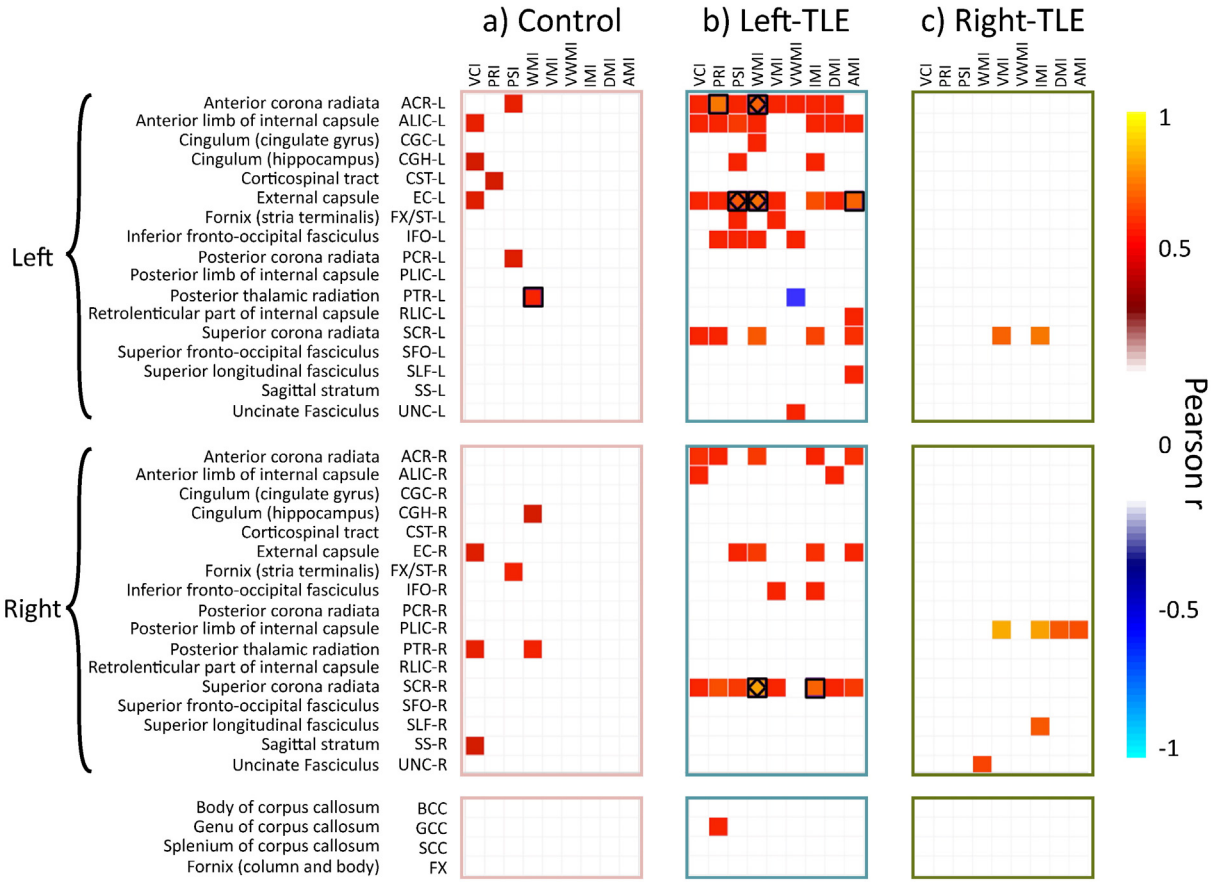

Fig. 3. Correlations between white matter and cognitive assessments. Pearson correlation coefficient was used to reveal relations between cognitive scores (columns) and FA of the white matter ROIs (rows). Only the correlations with an uncorrected $p < 0.05$ are shown. Correlations with a Bonferroni-corrected $p < 0.05$ are marked with a black square. Diamonds represent a significant group-effect interaction. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

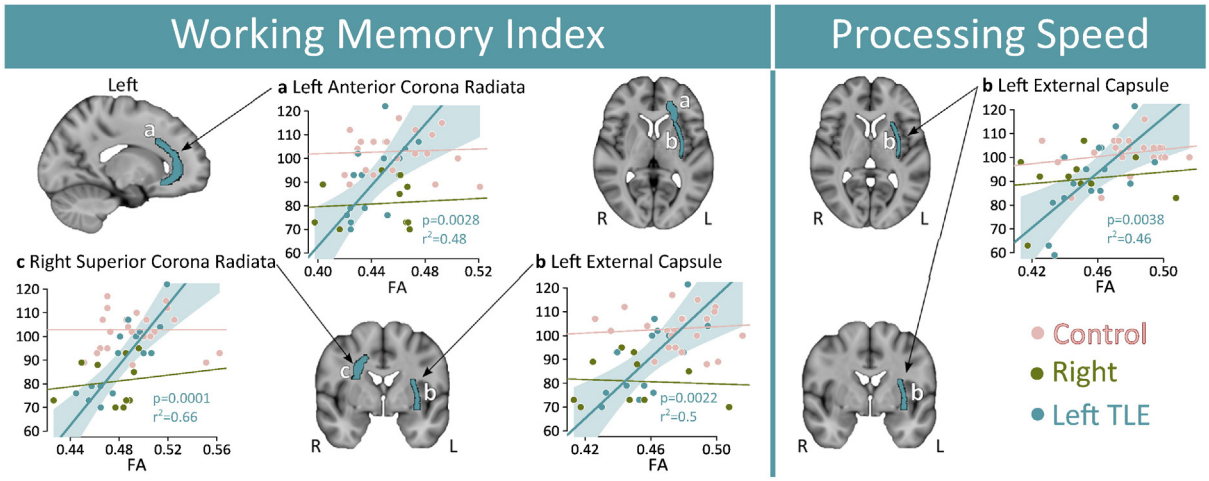

Fig. 4. Group dependent modulations. Only the group with L-TLE showed significant positive correlations between neuropsychometric assessment and white matter diffusion anisotropy in specific structures. White matter regions shown here are identified as diamonds in Fig. 3b, and represent a significant interaction effect with corrected $p < 0.01$.

deviations of the mean of controls ($n = 8$). Cluster 2 had decreased IQ and WMI ($n = 14$). Cluster 3 showed impairment across domains ($n = 4$; Fig. 5.a–b). Temporal lobe epilepsy lateralization was homogeneously distributed between clusters.

Cluster 3 was characterized by the lowest average of years of education, epilepsy onset at younger age, and hippocampal sclerosis in all patients. Patients in the least cognitively altered group (Cluster 1) have the most years of education, and oldest age at epilepsy onset. The laterality of TLE, seizures per month, number of AED, or other clinical features were not different between clusters (Supplementary Table 3).

Fractional anisotropy values from WM ROI were transformed to z-scores based on controls (Fig. 5.c-left). Cluster 3 had lower z-scores

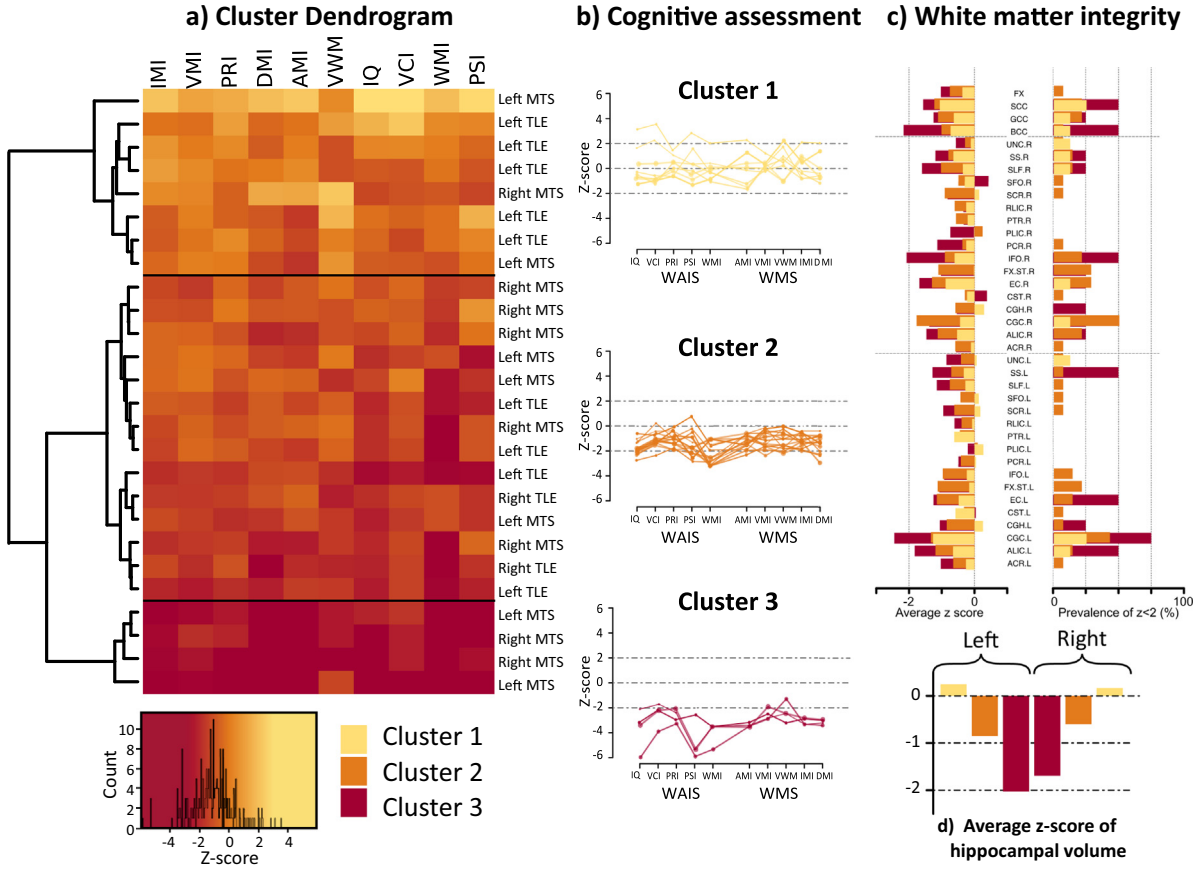

Fig. 5. Cluster analysis. Patients with TLE were grouped based on their psychometric assessment z-scores based on controls. a) Heatmap and dendrogram of the three groups classified across the neuropsychometric indices. b) Plots of the three clusters show each patient as a line. The different psychometric scores of the WAIS and WMS are shown on the x-axis and the corresponding z-score on the y-axis (horizontal black lines indicate the mean and ±2 standard deviations of the controls). c) Visualization of the FA as z-scores of 38 white matter ROIs. Left bars indicate the average score of each ROI per cognitive cluster coded by color. Right bars show the percentage of subjects per ROI with FA z-values lower than −2. Abbreviations of cognitive scores in panel a) are the same as in Fig. 1; abbreviations of white matter structures in panel c) are the same as in Fig. 4. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in regions related with associative and commissural fascicles and is the only cluster of patients having structures with FA z-values lower than −2 (Fig. 5.d). Cluster 2 had higher scores than Cluster 3 but a similar pattern. Cluster 1 was the most similar to controls in all ROIs. Bilateral hippocampal volume was lower in Cluster 3 than in the other groups (Fig. 5.d). The percentage of subjects per group with WM structures with FA values below two standard deviations from controls was highest in Cluster 3 (15.79%), followed by Cluster 2 (11.65%) and Cluster 1 (4.28%) (Fig. 5.c-right).

4. Discussion

We evaluated how cognitive performance is modulated by microstructural characteristics of WM in patients with TLE. Using an automated whole-brain approach to evaluate diffusion anisotropy as a proxy for WM micro-architecture, we found extensive abnormalities in patients with TLE that are related to cognitive performance. While patients with R-TLE had more severe diffusion abnormalities, only patients with L-TLE showed positive correlations between WM characteristics and cognitive performance. The presence of MTS was indicative of more profound diffusion abnormalities and cognitive deficits in patients with TLE. Moreover, clustering of patients based on their psychometric assessment showed that decreased cognitive performance is associated with an increased load of WM diffusion alterations.

Cognitive deficits have long been known to occur in patients with TLE [10,21]. Interestingly, not all patients with TLE exhibit the same kind of cognitive abnormalities. A previous study showed that nearly half of patients with TLE studied had normal cognitive performance, while 24% showed isolated memory impairment, and 29% presented deficits across cognitive domains [12]. The patients we studied were classified into the same three cognitive profiles as in said study, with memory-specific deficits being the most common profile seen in our cohort (Cluster 2, Fig. 5). Proportional gray matter atrophy has been associated with these cognitive profiles [22]. In line with these reports, we found a proportional relation between the severity of cognitive disabilities and WM abnormalities (Fig. 5). The degree of hippocampal atrophy (but not seizure laterality) markedly influenced the resulting cognitive profiles.

White matter is paramount for the integration of cortico-cortical networks that underlie cognitive functions [23]. Several fascicles throughout the brain have consistently shown diffusion abnormalities in patients with TLE [5,6]. Reductions of FA and increased MD are the most commonly found diffusion changes, and generally assumed to correspond to axonal loss and myelin abnormalities. White matter directly underneath the cortex has shown similar diffusion anomalies that are independent of cortical thinning, but mediated through hippocampal sclerosis [24]. Similar to other groups [8,9], we found FA reductions in the corpus callosum and bilaterally in the internal and external capsules, corona radiata, cingulum, and temporal WM. These abnormalities were not related to hemispheric lateralization of TLE. There have been conflicting reports on the effect of seizure laterality on diffusion metrics [25–27]. Although often bilateral, reductions of FA are more marked in the ipsilateral lobe, while increased MD appears to be bilateral, and abnormalities gradually diminish as tracts extend away from the epileptogenic temporal lobe [28]. Presence of MTS has been linked with more severe diffusion abnormalities, as compared with patients with TLE with normal imaging. In our sample of patients with L-TLE, those with associated MTS had more reductions of diffusion anisotropy in the frontal and temporal lobes, ipsilateral to seizure focus, than patients without MTS. Unfortunately, as we did not have a large enough group of patients with R-TLE without MTS, we could not ascertain whether this pattern is true regardless of seizure laterality, yet previous reports support this hypothesis [7–9].

Similar to controls, patients with R-TLE showed few correlations between WM characteristics and cognitive abilities, and none were significant after correction for multiple comparisons. Since patients with R-TLE showed more profound cognitive deficits, a “floor effect” might be responsible for the lack of correlations with diffusion metrics in this group. In contrast, correlations of this kind were plentiful in the group with L-TLE, and seven specific correlations were significant after strict correction for multiple comparisons. Interaction with group effect was significant, providing further evidence of the different trajectories of correlations in patients with L-TLE. These correlations did not occur randomly, but were seen in three specific WM structures: left anterior corona radiata, external capsule, and right superior corona radiata. Diffusion anisotropy of these structures correlated with nearly all cognitive performance scores, and consistently with WMI. It has been reported that patients with L-TLE have more working memory deficits [29], yet we found a larger variability of working memory performance in patients with L-TLE, while patients with R-TLE showed consistently lower scores (Fig. 4). This type of memory relies on a bilateral fronto-parietal cortical network that is supported mainly by the superior longitudinal fasciculus (SLF) and the cingulum [30]. While we found no correlations specifically between FA of the SLF and working memory, the anterior and superior portions of the corona radiata demonstrated clear correlations between these two metrics. The latter structure contains a large proportion of association fibers that are integral to the fronto-parietal network involved in working memory. The superior portion of the corona radiata is typically considered as consisting mainly of projection fibers; however, as evaluated through the tensor model, this structure may also contain other fiber systems [31]. We projected the WM skeleton voxels that intersect with the ROI for the superior corona radiata back to each patient with L-TLE's native space and found that roughly 10% of all voxels had directions of main diffusivity running anterior to posterior (i.e., compatible with the SLF), around a third had left–right main diffusivity (i.e., corpus callosum), and the rest were compatible with projection fibers. Despite the heterogeneity of this structure, diffusion metrics of both the anterior and superior portions of the corona radiata have been related to attentional abilities, which is tightly associated with working memory and other executive functions [32]. The diffusion abnormalities we demonstrate, in addition to previous reports of reduced FA of the SLF [33], likely disrupt the cortical network involved in working memory in TLE [30,33].

Reduced diffusion anisotropy of the uncinate fasciculus has been associated with deficits in immediate and delayed memory [14]. In our cohort, diffusion anisotropy of the left uncinate fasciculus did not show significant correlations after correction for multiple comparisons. At an uncorrected level, we found a correlation only for visual working memory in patients with L-TLE. Closer inspection showed that patients with L-TLE with hippocampal sclerosis were driving this correlation, with a similar significant correlation found for the contralateral structure. The left anterior corona radiata and external capsule, and the right superior corona radiata, were closely associated with working memory in our patients, with the last structure also being associated with immediate memory. Except for the right anterior limb of the external capsule, delayed memory was associated with diffusion anisotropy of the same structures related to working memory in patients with L-TLE. Finally, auditory memory was tightly associated with the left external capsule, and (at an uncorrected level) with structures similar to those described for working memory. Previous studies have reported similar associations between delayed memory and diffusion metrics of the uncinate, inferior fronto-occipital and arcuate fasciculi, and the temporal portion of the cingulum [13,34]. The fornix, being the WM structure most closely related to the hippocampus, is of particular interest but, unfortunately, difficult to evaluate with the methods used herein. Despite this limitation, the left hemisphere structure showed an association with processing speed and visual working memory in patients with L-TLE (uncorrected). Fractional anisotropy of this tract has been shown to correlate with memory [15]. Immediate verbal and nonverbal memory has been associated with diffusion properties of the parahippocampal cingulum in patients with TLE [35]. While the cingulum generally shows reduced FA in these patients [5], only patients

with L-TLE showed an (uncorrected) association between the ipsilateral cingulum and immediate memory and processing speed.

Processing speed was correlated with FA of the left external capsule only in patients with L-TLE. This cognitive score correlated with anisotropy of the majority of structures that also correlated with working memory, which included many association fascicles. The similarity of the patterns of correlations is likely due to the tight interdependence of many executive functions (and working memory) with processing speed. Executive functions are correlated with diffusion metrics of association tracts [36]. However, while said study found that these associations are present in control subjects and disrupted in patients with TLE, we found that the correlation between processing speed and FA of the external capsule was only significant for patients with L-TLE. Verbal abilities have been shown to correlate with diffusion anisotropy of the arcuate, uncinate, and inferior fronto-occipital fasciculi in patients with TLE, but not in controls [16,34]. We, however, did not find a pattern of left-hemispheric abnormalities being linked with verbal deficits.

Several factors can independently cause WM damage [37]. In the case of focal epilepsy, Vaughan et al. have proposed that a predisposing factor (in addition to a precipitating insult) may induce abnormalities of the WM associated with the epileptogenic structure, while ongoing seizures elicit further WM damage in a centrifugal fashion, and the negative effects of medication or repeated generalized seizures result in distributed WM abnormalities [38]. In our cohort of patients with TLE, those with most profound and distributed cognitive deficits and diffusion abnormalities (i.e., Cluster 3) all presented MTS, although their seizure frequency was not different, on average, to patients with minimal or selective cognitive deficits (Clusters 1 and 2). Disease duration was similar between patients classified as Clusters 2 and 3, yet the latter group (albeit small in size) was composed of patients with onset at an early age. The clinical and demographical characteristics of the patients included in our study, as well as their patterns of WM abnormalities, are supportive of the multifactorial WM damage hypothesis outlined above.

It is difficult to disentangle the many factors that influence cognitive abilities and, in the case of epilepsy, these are further compounded by neuro-psychiatric comorbidities and social and psychological considerations, as well as the effects of medication and ongoing seizures [38]. The causal direction of gray and white matter abnormalities and clinical characteristics of patients with TLE has also been difficult to identify, yet the progressive nature of brain changes in patients with ongoing seizures is suggestive of a progressive condition with consequences on cognitive performance [39]. Longitudinal cognitive evaluations have revealed that only a subset of patients with TLE (~20%) show progressive cognitive decline [40], and these patients also showed reduced cognitive abilities at baseline, and gray and white matter atrophy, as compared with patients who did not show progressive cognitive decline over a 4-year interval. Our data shows that different cognitive profiles are associated with varying degree of WM abnormalities and provides further avenues for prediction of cognitive decline.

Some factors potentially limit the generalizability of our findings. As compared with most studies of patients with TLE, which include patients referred for presurgical evaluation, our patients were largely recruited from ambulatory clinics. This is reflected in the relatively smaller proportion of patients with MTS (58%), as compared with the prevalence of MTS seen in tertiary care centers, which can exceed 75% [3]. In line with the characteristics of this population, and although great efforts were undertaken to identify TLE laterality and MTS, there is lack of nonequivocal evidence of seizure laterality and hippocampal pathology. While we excluded patients who were using antiepileptic drugs (AED) that are known to hamper cognitive performance, there was considerable heterogeneity in the type and number of AED that patients were taking, as well as in the degree of seizure control. Overall sample size is relatively small, particularly when considering subgroups of patients and, unfortunately, we could not recruit enough patients with R-TLE without MTS to do a full evaluation of the differential effect of the presence of hippocampal sclerosis. The tensor model is known to have important methodological limitations, particularly in regions of fiber crossings, and our analytical methods (TBSS and ROIs) limit the evaluations to small areas of the brain. This analytical method was chosen, however, as we expect better replicability of our findings by using a standardized analytical pipeline.

5. Conclusion

Our results are indicative that the often reported widespread WM diffusion abnormalities are associated with cognitive impairment and that the degree and extent of said abnormalities are related to performance in patients with TLE. Understanding the mechanisms that drive the different cognitive phenotypes seen in patients with TLE will lead to better prognosis of cognitive decline and prompt referral of patients at risk.

Disclosure

None of the authors has any conflicts of interest to disclose.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and we affirm that this report is consistent with those guidelines.

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Appendix A. Supplementary data

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