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Cortical disconnection in temporal lobe epilepsy

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Abstract:	A critical concept in neurology is cortical disconnection, in which seemingly normal gray matter can have reduced function due to loss of white matter (WM) connections. WM damage has been extensively described in temporal lobe epilepsy (TLE), but the anatomical distribution of cortical disconnection in TLE is not fully characterized. Here, we studied 221 participants (64 left-TLE, 55 right-TLE, 102 controls) from three different epilepsy treatment centers. We employed a group connectometry diffusion imaging tractography approach to identify WM fibers with reduced integrity in TLE. We then assessed the anatomical distribution of the gray matter endpoint projections of abnormal fibers to map the anatomical pattern of disconnections. As expected, left- and right-TLE were associated with multiple WM pathways with reduced integrity, which were associated with extensive cortical disconnection involving predominantly limbic structures. Controlling for medial temporal gray matter atrophy, cortical disconnection of the left cingulum and the thalamus as well as disconnection of the bilateral putamen and the amygdala was associated with lower verbal memory immediate recall.In conclusion, our results support that cortical disconnection is an underappreciated but pervasive phenomenon in TLE, and cortical disconnection of limbic structures beyond the medial temporal regions is related to verbal memory performance.
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Figure 1

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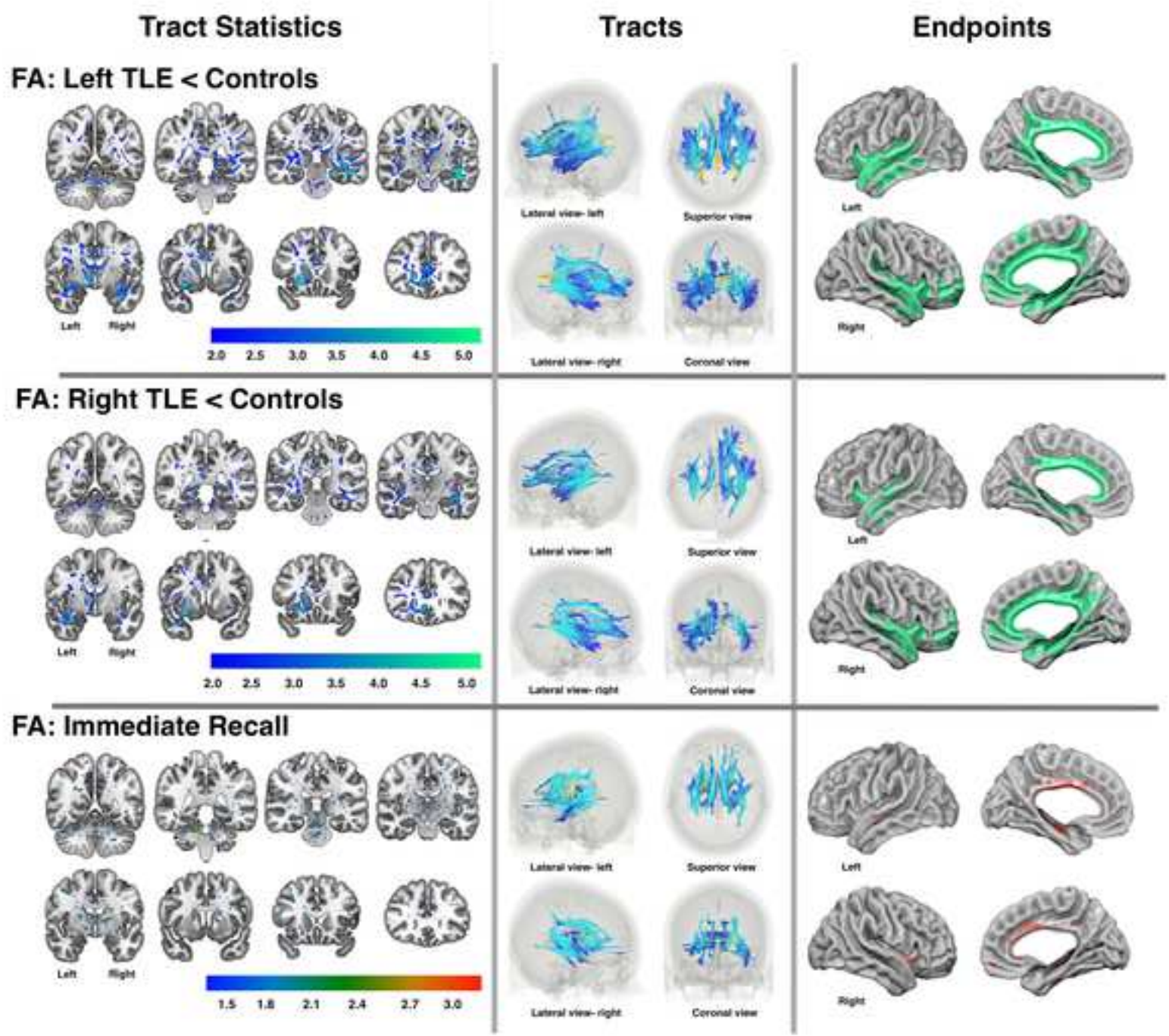

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Running title: Cortical disconnection in TLE

Abstract

A critical concept in neurology is cortical disconnection, in which seemingly normal gray matter can have reduced function due to loss of white matter (WM) connections. WM damage has been extensively described in temporal lobe epilepsy (TLE), but the anatomical distribution of cortical disconnection in TLE is not fully characterized. Here, we studied 221 participants (64 left-TLE, 55 right-TLE, 102 controls) from three different epilepsy treatment centers. We employed a group connectometry diffusion imaging tractography approach to identify WM fibers with reduced integrity in TLE. We then assessed the anatomical distribution of the gray matter endpoint projections of abnormal fibers to map the anatomical pattern of disconnections. As expected, left- and right-TLE were associated with multiple WM pathways with reduced integrity, which were associated with extensive cortical disconnection involving predominantly limbic structures. Controlling for medial temporal gray matter atrophy, cortical disconnection of the left cingulum and the thalamus as well as disconnection of the bilateral putamen and the amygdala was associated with lower verbal memory immediate recall.
In conclusion, our results support that cortical disconnection is an underappreciated but pervasive phenomenon in TLE, and cortical disconnection of limbic structures beyond the medial temporal regions is related to verbal memory performance.

1. Introduction

Cortical disconnection is a critical concept in neurology where gray matter has reduced function due to reduced white matter connections[1]. Disconnection plays an essential role in many neurological disorders such as stroke[2], dementia[3] and traumatic brain injury[4]. Nonetheless, even though many imaging studies have shown extensive white matter (WM) abnormalities in temporal lobe epilepsy (TLE)[5], the gray matter locations associated with reduced WM fibers in TLE remains poorly defined. A better understanding of the gray matter systems associated with reduced WM connections could inform on cognitive and other phenotypical aspects of epilepsy.

One approach to measure cortical disconnection involves using diffusion MRI tractography to identify WM fibers with reduced integrity and map the anatomical locations of their projections[6]. Conventional diffusion MRI and tractography studies in TLE have been often used to identify WM regions or fibers with abnormal integrity[5], but they have seldom explored the gray matter regions supported by suboptimal connections and thus at risk for reduced function. Certainly, WM loss and gray matter disconnections are not independent phenomenon since WM fibers originate from cell bodies in gray matter, and isolated WM focal lesions are rare in epilepsy. However, understanding structural brain damage from the perspective of gray matter supported by reduced connections can inform on the anatomical distribution of cortical regions with compromised integrity. Given the well-known magnitude of WM loss in epilepsy, particularly within the limbic system, and the strong association between cortical disconnection and neurological symptoms[2-4], it is likely that the impact of cortical disconnection in TLE remains underappreciated.

In this brief communication, we performed an introductory study of cortical disconnection in TLE by assessing the spatial distribution of termination sites (endpoints) of abnormal WM fibers in TLE across a large sample size of patients from TLE from multiple epilepsy centers. Our goal was to examine the regional anatomical prevalence of disconnection and to test the hypothesis that reduced WM connections are prevalent within the limbic system

in TLE. We also performed an initial exploration of whether WM disconnection was associated with verbal memory in TLE in a subset of patients.

2. Methods

2.1. Participants

This study included 119 patients with medication-refractory TLE according to criteria from International League Against Epilepsy[7] (64 left-TLE, 55 right-TLE) from three different epilepsy centers (Medical University of South Carolina - MUSC, Emory University, and the University of Bonn). 102 controls from MUSC, Emory University, and the University of Bonn were also included. The study was approved by the Institutional Review Board (IRB) at each site. Patient informed consent was obtained when the neuroimaging data were collected beyond the standard of care. Otherwise, a waiver of consent was approved by IRB. Patients with TLE and controls showed no significant differences in age (t = 1.635, p = 0.10) or biological sex (χ^2 = 1.12, p = 0.738). All patients included in this study were refractory to anti-seizure medications, and their data were collected during pre-surgical evaluation. Table 1 summarizes sociodemographic and clinical information for patients and controls.

Table 1 about here

Memory assessments were available for a subset of patients (n = 39). Immediate recall scores from a verbal list learning task were derived from the Rey Auditory Verbal Learning Test (RAVLT)[8], in which patients were asked to learn 15 unrelated words over a 5-trial presentation.

2.2. MRI Acquisition and Preprocessing

All DTI scans were acquired on a 3.0 Tesla MRI system (Table 1). Group connectometry analysis was performed using DSI-Studio http://dsi-studio.labsolver.org[9] to test which white matter fibers had different FA values in patients than controls (n = 221), or to determine changes in FA that were associated with the RAVLT (n=39). The gray matter endpoints of the

fibers whose FA values were statistically significant in each analysis were evaluated to determine the topology of their cortical projections. The methodological steps are further described in the Supplementary Materials. Hippocampal and parahippocampal volumes were used as covariates to control for the confounder effect of medial temporal atrophy on memory scores.

2.3. Data availability

The data that support the findings of this study are available upon request to the corresponding author.

3. Results

3.1. Left-TLE (*n* = 64) versus controls (*n* = 102)

Patients with left TLE had lower FA in comparison with controls across multiple fibers in left (L) and right (R) hemisphere pathways: inferior fronto-occipital fasciculus (R), corpus callosum, cingulum (R), uncinate fasciculus (R), fornix (L), inferior longitudinal fasciculus (L), cingulum (L), inferior fronto-occipital fasciculus (L), inferior longitudinal fasciculus (R), corticothalamic pathway (R), arcuate fasciculus (L), extreme capsule (L), corticothalamic pathway (L). Figure 1 (top row).

The location of the endpoints of tracts with reduced FA in left TLE (i.e., the location of gray matter disconnection) is shown in Figure 1 (first row, rightmost column) and described in Supplementary Table 1. Note the widespread distribution of gray matter endpoints across limbic structures and lateral temporal neocortices, although more prominent in the side ipsilateral to seizure onset.

3.2. Right-TLE (n=55) versus controls (n=102)

Patients with right TLE had fibers with lower FA in comparison with controls in the: inferior fronto-occipital fasciculus (R), uncinate fasciculus (R), cingulum (R), inferior longitudinal fasciculus (R), corpus callosum, corticothalamic pathway (R), cingulum (L), inferior fronto-occipital fasciculus (L), inferior longitudinal fasciculus (L). Figure 1 (middle row). Similar to left TLE, the endpoints of tracts with reduced FA in right TLE were located across limbic structures and lateral temporal neocortices, with a predominance in the ipsilateral hemisphere (Figure 1, Supplementary Table 1).

3.3. Immediate recall in TLE (n = 39)

Left and right TLE showed no significant differences in immediate recall (left TLE: mean score: -1.5314 ± 1.33441; right TLE: mean score: -1.5720 ± 1.43175; F=0.06, t=0.88; p=0.930). Individual data performance is summarized in Supplementary Table 2.

Controlling for hippocampal and parahippocampal volumes (L and R), lower immediate recall was associated with fibers with lower FA in the: cingulum (L), inferior fronto occipital fasciculus (R), fornix (R), inferior fronto occipital fasciculus (L), fornix (L), cingulum (R), dentatorubrothalamic tract (L), extreme capsule (R), corpus callosum, dentatorubrothalamic tract (R), corticothalamic pathway (R), inferior longitudinal fasciculus (L), corticostriatal pathway (L), inferior longitudinal fasciculus (R), corticopontine tract (L), corticospinal tract (L), uncinate fasciculus (L), corticothalamic pathway (L). The endpoints of the tracts whose reduced FA was associated with lower immediate recall were located in the cingulum (L), putamen (L and R), amygdala (L and R) and thalamus (L).

4. Discussion

The results from this study corroborate the hypothesis that TLE is associated with widespread cortical disconnection, particularly within the limbic system. They also demonstrate that damage to fibers with endpoints in the cingulum, putamen, amygdala, and thalamus is

associated with reduced verbal recall, suggesting a relationship between these anatomical regions and memory impairments in TLE.

4.1. The pervasiveness of cortical disconnection in TLE

White matter damage has been frequently observed in TLE[5]. Previous studies have demonstrated the association between white matter damage and memory impairments in this population[10, 11], highlighting the cognitive consequences of superficial white matter changes[12]. However, many studies have focused on voxel-wise microstructural white matter changes, which only provide indirect information about abnormal pathways. The present study expanded on the existing literature by demonstrating fiber-specific changes and the anatomical distribution of their projections, thus providing empirical evidence on the topology of cortical disconnection in TLE.

Disconnection in epilepsy likely remains an underappreciated phenomenon. Disconnection, i.e., gray matter regions supported by WM connections with reduced integrity, is not routinely measured during disease phenotyping or treatment planning. Considering the importance of cortical disconnection in the symptomatology of other neurological diseases[1-3], disconnection likely plays a similarly crucial role in TLE. The findings from this short communication provide evidence regarding the pervasiveness of gray matter disconnection in TLE.

4.2. The cognitive importance of cortical disconnection in TLE

Disconnections of the left cingulum, bilateral putamen, bilateral amygdala, and left thalamus were associated with lower immediate recall in TLE, controlling for hippocampal and parahippocampal damage, which are per se associated with worse verbal recall in TLE[12]. By controlling for medial temporal region atrophy, the results from this study suggest that regional extra-medial temporal cortical disconnection resulting from white matter damage may be an important part of the mechanism underlying network damage and memory impairment in TLE.

4.3. Limitations

This is an initial pilot study to investigate the anatomical distribution of cortical regions subserved by reduced WM connections. The findings from this study promote the need to further investigate the mechanism underlying the relationship between white matter changes and behavioral outcomes. Namely, it will be important to determine whether disconnection in epilepsy occurs as a primary process or whether it is merely the result of neuronal dysfunction. It will also be critical to explore how other confounders mediate the relationship between disconnection with clinical and behavioral phenotypes, particularly seizure dynamics and seizure spread patterns, effects of anti-seizure medications, and seizure burden, among others.

In this brief communication, we explored a single cognitive measure in a subsample (n = 39 TLE) from which cognitive data was available. Other cognitive functions and clinical phenotypes (e.g., the effect of seizure lateralization) may play an important role in the relationship between cortical disconnection and memory, and these questions could be targeted by future studies. In addition, immediate verbal recall is only one of many aspects of memory relevant to TLE. Future studies may examine how disconnection is related to different types and features of memory or other neuropsychological measures.

5. Conclusions

Structural network changes in TLE have been mostly characterized by voxel-based microstructural changes in white matter pathways. However, connectivity changes lead to gray matter regions with reduced WM connections, i.e., cortical disconnection, a phenomenon with well-recognized importance in neurology but still relatively underappreciated in TLE. The present study leveraged the analytical advantage of connectometry analysis to demonstrate that gray matter disconnection is present in patients with TLE and related to verbal memory performance.

Ethical Publication Statement

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

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Disclosures

The authors report no disclosures relevant to the manuscript.

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Figure legend

Figure 1 – The leftmost column demonstrates the directional voxel-based distribution of T-statistics related to reduced fractional anisotropy (FA) in patients with TLE relative to controls (top and middle rows) and the relationship between lower FA and worse immediate recall (bottom row). The corresponding significant white matter fibers are shown in the center column. The rightmost column demonstrates the gray matter locations of the projection endpoints for the significant fibers, i.e., cortical disconnection areas associated with each statistical analysis.

Table legend

Table 1. Demographic and clinical profile of healthy controls and patients with temporal lobe epilepsy (TLE), including a breakdown by the acquisition site. The table also shows the summary of the neuroimaging acquisition protocol for this study.

	Controls *n = 102*	**TLE** *n = 119*	**MUSC** *n = 35*	**Bonn** *n = 37*	**Emory** *n = 47*
Gender (% male)	43.2	37.0	31.4	43.2	36.2
Age at onset (years)	37.2 (12.4)	17.8 (12.7)	20.4 (15.6)	16.0 (11.3)	17.3 (11.3)
Laterality (% left)		52.9	42.9	59.5	44.7
Median seizure frequency /month		4	4	4	8
Radiographic signs of MTS (% present)		69.7	51.4	100	59.6
Age at surgery (years)		40.3 (12.5)	41.9 (10.9)	39.9 (13)	39.5 (13.4)
Surgery Type (% resection)		69.7	100	100	23.4
Seizure Outcome (% SF)		56.3	51.4	64.9	55.3

Scanner Type	Siemens Verio	Siemens Magnetom	Siemens Prisma
Head Coil	12-channel	8-channel	12-channel
T1-weighted	$1mm^3$ isotropic (TR = -2250 ms, TE = 41ms, FOV = 256mm, flip angle 10°)	$1mm^3$ isotropic (TR = 650ms, TE = 3.97ms, TI = 650ms, flip angle 10°)	$0.8mm^3$ isotropic (TR = 2300ms, TE = 2.75ms, TI = 1100ms, flip angle 8°)
Diffusion	30 runs; TR = 10,600ms, TE = 100 ms, FOV = 224, thickness = 2 mm, 60 axial slices, isotropic voxel size of 3 mm, GRAPPA	60 runs; TR = 1200ms, TE = 100 ms, 72 axial slices, voxel size 1.726 × 1.726 × 1.7 mm, no cardiac gating, GRAPPA	60 runs; TR = 3430ms, TE = 90ms, FOV = 224mm, 81 slices, isotropic voxel size of 1.75 mm GRAPPA

MTS = medial temporal sclerosis; SF = seizure-free

Cortical disconnection in temporal lobe epilepsy

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