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Article type : Critical Review – Invited Commentary

NEUROIMAGING AND CONNECTOMICS OF DRUG-RESISTANT EPILEPSY AT MULTIPLE SCALES: FROM FOCAL LESIONS TO MACROSCALE NETWORKS

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/EPI.14688](https://doi.org/10.1111/EPI.14688)

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KEY WORDS: Epilepsy, MRI, connectivity, biomarker, connectome

Number of words (summary): 155

Number of words (main text): 3614

Number of tables (main and supplementary): 0

Number of figures (main and supplementary): 5 color figures

** equal contribution*

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KEY BULLET POINTS

- Advances in multimodal neuroimaging provides increasing sensitivity to identify and profile localized anomalies in neocortical and hippocampal subregions
- Connectome analyses in drug-resistant syndromes consistently show large-scale network anomalies, suggesting that these are not purely focal disorders
- Integrating multimodal MRI with macroscale connectomics promises to better understand both the local and network-level substrates of drug-resistant epilepsies
- Integrated approaches that bridge lesional and connectome scales have a high potential to serve as clinically useful tools, including routines for the prediction of post-operative outcomes

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SUMMARY

Epilepsy is among the most common chronic neurological disorders with 30-40% of patients suffering from seizures despite antiepileptic drug treatment. The advent of brain imaging and network analyses has greatly improved the understanding of this condition. In particular, developments in magnetic resonance imaging (MRI) have provided measures for the non-invasive characterization and detection of lesions causing epilepsy. MRI techniques can probe structural and functional connectivity, and network analyses have shaped our understanding of whole-brain anomalies associated with focal epilepsies. This review considers progress made by neuroimaging and connectomics in the study of drug-resistant epilepsies due to focal substrates, particularly temporal lobe epilepsy related to mesiotemporal sclerosis and extratemporal lobe epilepsies associated with malformations of cortical development. In these disorders, there is evidence for widespread disturbances of structural and functional connectivity. Studying the interplay between macroscale network anomalies and lesional profiles is hoped to improve our understanding of focal epilepsies and assist treatment choices.

KEY WORDS: Epilepsy, MRI, connectivity, biomarker, connectome

INTRODUCTION

Epilepsy is a chronic neurological disorder affecting 0.5-1.5% of the world population and contributing an estimated 0.7% to the global disease burden ¹. More than a third of patients continue to experience seizures despite anti-epileptic drug therapy ². Individuals with drug-resistant seizures show markedly elevated risk of morbidity, functional impairment, and premature mortality compared to those with seizure control ³. Cross-sectional and longitudinal studies have emphasized that uncontrolled epilepsy may cause cognitive impairment and brain damage ⁴. There is a pressing need to improve our understanding of the epilepsies and to develop better diagnostic tools, improved stratification, and more effective therapies.

This review highlights the contributions and potential of neuroimaging and connectome analyses to understand the neurobiological substrate of drug-resistant epilepsy. MRI has improved our ability to detect lesions associated with the epileptogenic region, enabling surgery in patients previously considered ‘non-lesional’⁵. In parallel, there has been a rapid rise in techniques to estimate and quantify structural connectivity and functional interactions between distributed regions⁶. Applications of brain connectivity studies have collectively contributed to the evolving concept of focal epilepsy as a disorder of large-scale networks. Here, we try to bring both levels of disease description together and discuss how their integration refines our understanding of drug-resistant epilepsy and how this can aid prognostication and therapies.

IMAGING THE LESION SPECTRUM

The most common surgically-amenable syndromes are temporal lobe epilepsy (TLE) associated with mesiotemporal sclerosis (MTS) and extratemporal epilepsies (ETE) related to malformations of cortical development, particularly focal cortical dysplasia (FCD). Together, these account for 60-80% of presurgical patients in tertiary epilepsy centers.

In TLE, the epileptogenic circuitry generally encompasses mesial temporal structures, and these structures also show marked histopathological changes. Neuronal loss and gliosis is indeed seen across hippocampal subfields⁷, amygdala⁸, and parahippocampal subregions⁹. Classically, these changes were visualized using volumetric techniques, with atrophy predominantly localized ipsilateral to the focus^{10; 11}, involving predominantly the hippocampus and entorhinal cortex. Given its sensitivity to reactive astrogliosis, sometimes the only detectable pathology in patients with subtle neuronal loss¹², T2-weighted MRI and T2 relaxometry offer complementary information for MTS detection¹³. Furthermore, increased access to high-field scanners provides contrast-rich data with submillimetric resolution in feasible acquisition times, sufficient to resolve hippocampal subfields^{14; 15} and their internal structure¹⁶. In TLE, subfield assessments have shown improved detection of subtle MTS¹⁴ and combinations of subfield imaging and surface-shape modeling can increase analysis resolution^{17; 18}, allowing continuous parameter analyses along the long axis. Surface-based integration of different contrasts, such as local volume, T2 intensity, and diffusion parameters can assist in lateralization of the focus and predict MTS pathological grades *in vivo* [FIGURE 1, left¹⁹].

FCD Type-II is highly epileptogenic and histologically characterized by dyslamination and cytological anomalies, including dysmorphic neurons sometimes in conjunction with balloon cells²⁰. Ectopic neurons and hypertrophic astrocytes may also be present in the white matter immediately below the cortical boundary. On T1-weighted MRI or FLAIR, Type-II lesions often show increased cortical thickness and blurring, together with grey and white matter signal changes²¹. Lesions vary in size, ranging from filling a gyrus to a few voxels; small lesions seem to preferentially occur at the bottom of sulci²². There are several automated identification algorithms employing different imaging techniques⁵, including voxel based morphometry, intensity, and texture analyses^{23; 24} and analyses of surface features such as cortical thickness, blurring, and folding [FIGURE 1, right^{25; 26}]. Detection rates may reach 60-70% in cohorts with histologically-verified FCD-II²⁵. Selection bias is a major factor to be considered, as is the need to balance sensitivity and specificity when applying the method to individual subjects. In some series, relatively low false positive rates in healthy individuals make them clinically appealing, but there remains a need to evaluate algorithms across different imaging sites to determine how robust, generalizable, and accessible they are.

[FIGURE 1 HERE]

Up to 50% of individuals referred to tertiary centers are MRI-negative²⁷. These patients often undergo intracranial electrophysiological investigations and chances of seizure freedom are reduced compared to cases in whom a lesion was found on MRI²⁸. Retrospective histological series in patients with unremarkable MRI indicate high proportions of subtle FCD Type-II and Type-I²⁹, a malformation of cortical organization characterized only by laminar architectural disturbances²⁰, and re-inspection of the MRI often confirms subtle anomalies that were initially missed³⁰.

Ultra-high field MRI at 7T and beyond offers theoretical possibilities to increase spatial resolution to 350-500 μm , a scale at which cortical columns and layers may be visualized *in vivo*. Paralleling increases in resolution, the use of quantitative MR contrasts may better separate intracortical myelin from iron compared to “weighted” contrasts, and thus add specificity to identify typical and atypical cortical laminar architecture. Preliminary assessments suggest

benefits for localization ³¹. In TLE, a recent quantitative intracortical analysis – even at conventional 3T MRI - identified intracortical anomalies suggestive of myelin alterations in hippocampal allocortices and other temporo-limbic areas, suggesting coupled microstructural perturbations in mesiotemporal and adjacent paralimbic networks ³².

In sum, advances in MR acquisition and processing offer a window into tissue microstructure and morphology. These approaches increase sensitivity for the identification of lesions giving rise to epilepsy and lend *in vivo* signatures of specific pathological anomalies that may inform patient prognosis and therapy. Given the association between postoperative seizure freedom and identification of a lesion on MRI, there is a need to take advantage of best-practice, three dimensional, and whole-brain imaging techniques. Improvements in MRI can provide a wealth a new information. These new approaches need to be validated through large multi center studies regarding their diagnostic accuracy, sensitivity and specificity before they can be fully integrated into clinical practice. Nonetheless, they promise a quantifiable improvement to a diagnostic process that, for the most part, remains reliant on visual inspection. Explorations of network changes in epilepsy should be anchored on optimal structural imaging as a baseline for lesion detection, in order to understand the role of lesions in the pathological network and to derive networks from the most meaningful representations of participant anatomy.

TOWARDS A NETWORK LEVEL CONCEPTUALIZATION OF FOCAL EPILEPSY

In addition to increasingly detailed *in vivo* characterizations of epileptogenic lesions, neuroimaging has been instrumental in unveiling network pathology in focal epilepsies. In TLE, diffusion MRI analyses of white matter tracts have outlined widespread architectural alterations, generally characterized by reduced anisotropy and increased diffusivity of deep ^{33; 34} and superficial fibers ³⁵. Although findings are not limited to a specific lobe or circuit, they appear more marked in ipsilateral temporo-limbic tracts. Tract-based profiling of diffusion parameters reveals severe microstructural anomalies close to the temporal lobe ³⁶, while effects taper off towards other regions, suggesting most prominent anomalies in the vicinity of the mesiotemporal disease epicentre. Interestingly, the topography of whole-brain diffusion changes appears to be different from whole-brain grey matter morphometric findings in TLE. Indeed, in contrast to the pattern of diffusion MRI changes that may be widespread but generally most severe in ipsilateral temporo-limbic regions, MRI-based analyses of grey matter morphology and cortical thickness

have shown a rather consistent association between TLE and bilateral neocortical atrophy, which affects prefrontal, lateral temporal, frontocentral, and parietal regions [FIGURE 2, top left; ³⁷⁻³⁹] also involving subcortical structures such as the thalamus ⁴⁰. In a previous report, diffusion MRI anomalies of the superficial white matter regions were furthermore found to be rather stable even after local cortical thickness variations were statistically corrected for ³⁵. Collectively, these findings suggest that diffusion and morphological markers tap into different structural anomalies as well as also potentially different disease processes. In fact, diffusion MRI changes likely reflect downstream effects of hippocampal pathology on white matter connectivity, also supported by tractographic findings showing more marked white matter anomalies in cohorts with hippocampal anomalies compared to those without ⁴¹. On the other hand, cortical thickness changes seem to be somewhat independent from the overall degree of hippocampal anomalies, irrespective of the side of the seizure focus ³⁷.

In ETE related to FCD, morphometric analyses have found widespread structural anomalies, which differ across histological subtypes. Analyzing frontal lobe epilepsy patients with FCD I and II, widespread cortical thinning was shown in Type I while patients with Type II presented with scattered thickening [FIGURE 2, top right; ⁴²]. In light of findings showing aberrant synaptogenesis of dysmorphic neurons, failure of oligodendroglia differentiation, and perturbation of axonal processes in FCD II ⁴³, the primary lesion and mutually connected cortices may show delayed pruning, ultimately manifesting as gray matter excess in regions participating in the same maturational-trophic network as the lesion. Conversely, widespread cortical thinning in FCD Type I may reflect the post-migratory malformation ⁴⁴, and which may compromise the efficacy of focal resections. Although structural connectivity anomalies in dysplasia-related epilepsy has been less studied than cortical morphology, there are findings of alterations of intra-hemispheric fibers as well as the corpus callosum ⁴⁵. Recent data in ETE related to FCD found anomalies in thalamic tracts ⁴⁶, indicating subcortical network reconfigurations with these cortical lesions.

Alterations in morphology and structural wiring may perturb functional network organization, as probed using task-free (“resting-state”) functional MRI (rs-fMRI). rs-fMRI offers a window to resolve dynamic interactions between distributed regions. rs-fMRI network descriptors are consistent and replicable across subjects, suggesting that they may serve as patient specific biomarkers ⁴⁷. In TLE, rs-fMRI studies have shown mainly decreased functional

connectivity within ipsilateral mesiotemporal circuits ⁴⁸, between ipsilateral and contralateral mesiotemporal regions ⁴⁹, and between mesial and lateral temporal regions ⁵⁰. Connectivity reductions, sometimes together with scattered increases ⁵¹, have also been reported between mesiotemporal regions and nodes of the default mode network (DMN), notably prefrontal and midline parietal cortices ^{19; 52}. In healthy populations, hippocampal and parahippocampal cortices closely interact with the default network and form an important subcomponent that is relevant for memory ¹⁶. Interestingly, the severity of hippocampal structural pathology in TLE directly relates to reductions in its functional connectivity, with patients displaying marked sclerosis generally showing lower connectivity to DMN hubs than those with isolated gliosis [**FIGURE 2, bottom left**; ¹⁹]. Similar findings have also been shown for diffusion derived connectomes, with patients with MTS being more severely affected than those with only subtle cell loss ⁵³. Reduced connectivity between hippocampal and DMN hubs may contribute to more severe impairments in memory processes in those with marked hippocampal damage ⁵⁴.

In ETE, task-based ⁵⁵ and rs-fMRI studies ⁵⁶ have also suggested functional reorganization beyond the primary lesion. Studying an ETE patient, specific reductions in whole brain functional connectivity have been shown to closely overlap with the area that needed to be surgically removed, suggesting potential benefits of connectomics features for presurgical lesion localization [**Figure 2; bottom right**; ⁵⁷]. A recent study of FCD identified diverging patterns of hyper- as well as hypo-connectivity to different areas of cortex across the lesion spectrum, suggesting distributed alterations in functional connectivity profiles ⁵⁸. The analysis also highlighted differences in whole-brain functional anomalies based on the specific connectivity embedding of the lesion. In fact, patients that had overall hyper-connected lesions had more marked whole-brain network reorganization, while connectome signatures were modest in patients with generally disconnected lesions ⁵⁸.

[FIGURE 2 HERE]

In sum, a growing number of studies have shown alterations in large-scale morphology, structural connectivity, and functional connectivity in “focal” epilepsies. In TLE, diffusion MRI data suggest a more temporo-limbic distribution closely associated with hippocampal pathology,

while grey matter changes seem to affect widespread and bilateral networks, possibly also related to progressive effects³⁷. Functional anomalies in TLE are rather broad, although temporo-limbic and DMN reorganization is among the more consistent findings. Reorganization of functional networks appears closely related to the severity of hippocampal pathology¹⁹. In dysplasia-related ETE, distributed patterns of cortical morphological changes mirror the lesional substrate, with thinning in FCD-I and thickening in FCD-II, potentially suggesting a developmental pathology affecting the formation and maturation of a distributed and more extensive network. As in TLE, diffusion and functional findings in FCD-related ETE suggest more widespread anomalies.

It is important to consider that abnormal neuroplasticity may play a role in epilepsy. Over time, the recruitment of recurrent excitation pathways can lead to reinforcement of seizure generation and seizure propagation networks. Therefore, network abnormalities may not only provide important information about the location of seizure onset, but may also illuminate how the disease changes dynamically in relationship with epilepsy severity. Network analyses may provide important information about the pathophysiology of the disease, and help phenotype individuals with seemingly similar classification, for example, in distinguishing individuals with TLE regarding their epileptogenic potential and likelihood of success with medication or surgery.

EPILEPSY CONNECTOMICS

The increasing abilities to map large-scale networks with neuroimaging is paralleled by a rise in analytics capturing principles of system-level organization. One of the most widely used frameworks is graph-theory, the analysis of topological properties of networks made up of nodes (regions) and edges (connections). In TLE, structural MRI covariance^{59; 60}, diffusion MRI⁶¹, rs-fMRI connectivity⁶², and inter-ictal EEG coherence analyses⁶³ have employed graph theoretical analyses (**FIGURE 3**), and showed an association between TLE and increases in path length, sometimes together with increases in local clustering. Increases in clustering and path length reflect overall network regularization (*i.e.*, a more lattice-like configuration of the brain network, related to increased local but reduced global efficiency). A meta-analysis across twelve studies also confirmed increased clustering and path length⁶⁴, but noted methodological heterogeneity across studies and limitations in sample size. More regularized network topology has also been

reported at the time of seizure onset in intra-cerebral EEG analysis ⁶⁵, possibly representing a mechanism to contain seizure-related activity, or reflecting the process of seizure initiation ⁶⁶. Seizure termination, on the other hand, often relates to an increasing randomization of network configurations – *i.e.*, a shift towards a globally integrated communication ⁶⁶.

[FIGURE 3 HERE]

As in TLE, diffusion and rs-fMRI network analyses in ETE have suggested a more regularized network topology ⁶⁷. Analyzing task-free fMRI data in patients with polymicrogyria, a malformation of cortical development associated with atypical cortical folding, a recent study showed increased clustering and path length in the lesion compared to contralateral areas ⁶⁸, suggesting that lesional anomalies may disproportionally contribute to widespread changes. An association between lesional and network phenotypes was also demonstrated in ETE associated to several cortical malformations ⁶⁹. Although patients overall presented with more regular structural networks compared to controls, network rearrangement was more severe in late-stage malformations (FCD-I, polymicrogyria) while patients with FCD-II showed only modest disruptions, suggesting an interaction between the timing of the malformative process and network anomalies. Later gestational stages are characterized by extensive cortico-cortical network formation, and disruptions in these periods may result in a potentially more widespread cortico-cortical network perturbation than anomalies affecting early proliferative stages of development that are characterized by neuroglial proliferation and radial migration to a more confined cortical territory.

In sum, previous studies suggest increases in path length often (but not always) together with increases in network clustering in patients with drug-resistant epilepsy. As for localized network changes, whole brain network phenotypes seem to be additionally modulated by the specific lesional substrate and histopathological subtype, which may suggest common developmental and disease related processes affecting the lesion and macroscale network organization. A series of recent studies utilized network diffusion models, a formalism that simulates signal spread following a local perturbation ⁷⁰ to develop spatial predictors of structural alterations in TLE. Similarly, hippocampal covariance networks have been leveraged

as spatial predictors of changes in intracortical FLAIR intensity, potentially suggesting that network models can delineate pathways of preferential susceptibility to epilepsy related brain anomalies⁷¹.

CLINICAL CONNECTOMICS

In focal epilepsy, an increasing body of work has begun to examine the utility of network analytical measures as markers of clinical and cognitive state in patients.

Network features have been used to identify surgical targets, complementing state-of-the-art neuroimaging, particularly in cases where anomalies are subtle or ambiguous. Functional and structural network information have shown potential to be useful to lateralize the seizure focus in TLE⁷². In a previous rs-fMRI connectivity study of temporal and extratemporal epilepsy, seizure onset zone as defined by intracranial EEG also displayed intrinsic local connectivity anomalies⁷³, warranting further investigations on the specificity of these techniques. Co-registering intracranial EEG information with diffusion MRI derived structural connectome data across a cohort of patients with temporal and extra-temporal foci, a recent study suggested a divergence of connectivity patterns in epileptogenic compared to non-epileptogenic areas, with epileptogenic networks displaying more intact local connectivity while whole brain connectivity strength seemed to be reduced⁷⁴. The biological implications of these data are not yet clear.

While network markers may ultimately improve surgical target localization, or guide neuromodulatory treatments, they may also serve as predictors of post-surgical outcome (**FIGURE 4A**). Diffusion connectome features have been assessed most frequently, given their ability to probe networks in single patients, in TLE⁷⁵. A recent study combined structural connectome features with deep learning, providing high positive and negative predictive values for postoperative outcome prognosis⁷⁶. Data from rs-fMRI analysis has furthermore shown an association between increased thalamic hubness and seizure recurrence, and these features allowed for individualized prediction with moderate accuracy⁷⁷. Preselection of relevant features may improve accuracies, and a previous rs-fMRI study has achieved up to 100% accuracy in outcome prediction based on connectivity patterns in temporo-limbic and DMN areas⁷⁸. As for the lesion detection paradigms, however, surgical outcome prediction experiments have so far been generally based on small, single-site datasets, motivating additional

efforts to share and pool resources. Furthermore, benefits of network-based outcome predictors in TLE, when advanced MRI phenotyping is applied (which also yields >90% accuracy in selected series ¹⁷) still need to be established, especially given data suggesting marked interactions between hippocampal damage and structural and functional networks. In ETE related to FCD, network features may also be useful for outcome prediction (**FIGURE 4B**). Specifically, classifying lesions based on the degree of functional connectivity between lesional tissue and its overarching network community may improve prediction of outcome in single patients when using supervised learning algorithms ⁵⁸.

[FIGURE 4 HERE]

A third field of application of connectome tools has been the identification of structural and functional substrates of cognitive variables. In mixed epilepsy cohorts, network markers have been used to predict verbal competences ⁷⁹ and episodic memory ⁸⁰. Network features have furthermore been used to identify language network organization and efficiency [**FIGURE 5A**; ⁸¹]. As a surgically amenable disorder, the study of epilepsy offers additional opportunities to assess functional network reorganization post-op. Several studies combined pre- and postoperative imaging to track network rearrangement in surgical candidates with TLE [**FIGURE 5B**; ⁸²], improving understanding and the prediction of memory ⁸³ and language outcomes ⁸⁴. Based on diffusion MRI tractographic mapping, there has been work observing an association between fiber tract resection and functional deficits ⁸⁵

[FIGURE 5 HERE]

In short, connectomics is increasingly utilized in an attempt to better inform clinical care in drug-resistant epilepsy. This promising approach can lead to a more precise detection of the seizure onset zone, a key node in the epileptogenic network, and thus contribute to better post-surgical outcome and quality of life in patients. Combinations of connectomics with machine learning

have achieved encouraging results to predict seizure recurrence in TLE. Network markers have also been used to predict cognitive functioning in epilepsy, and longitudinal data in particular can be used to study how network reorganization relates to functional changes pre- and post-surgery. Thus, by tracking structural and functional substrates of important factors for better quality of life in patients, network-level phenotyping may ultimately improve diagnosis and clinical care in drug-resistant epilepsy. As with any new methodology, epilepsy connectomics requires careful validation to be systematically included in routine clinical practice. For a meaningful biomarker assessment, this requires a careful evaluation of validity, reliability, sensitivity, specificity, and applicability⁴⁷. Notably, the literature is so far largely devoid of studies that systematically compare the reliability and diagnostic utility of connectome-based measures against simpler imaging and connectivity metrics, including volumetric MRI techniques, tract-wise measures of diffusivity, or seed-based functional connectivity measures. Connectome-level analyses are also not ‘turnkey’ yet, and often rely on relatively complex imaging processing and multimodal integration pipelines. As for other imaging techniques, high-quality data is key to rule out confounds and inferential failures. Nonetheless, connectomic techniques have profound theoretical potential to improve the diagnosis and treatment of epilepsy, by moving from a visual lesion inspection paradigm to a system-level approach centered on the analysis of personalized maps of aberrant connectivity.

SUMMARY AND FUTURE AVENUES

Neuroimaging and network neuroscience have brought forward tools to profile local lesions, whole-brain anomalies, and large-scale networks. These can capture the impact of the disease on micro- and macroscale structural and functional organization. Drug-resistant focal epilepsies can be generally characterized by a continuum between a focal lesional condition and a network disorder. An understanding of network-level perturbations needs to consider the putative lesion as being a pivotal node in the patient-specific network. Conversely, even the most detailed lesion models may suffer from residual limitations in surgical target definition and the prediction of treatment outcomes, and will likely benefit from the incorporation of network data.

As it is a surgically-amenable disorder, the study of drug-resistant epilepsy offers important opportunities to validate non-invasive imaging and network models. Recently, MR

imaging was co-registered to quantitative histopathological specimens, allowing for regionally specific *in vivo/ex vivo* correlation analysis⁸⁶. Moreover, diffusion parameters have been related to microstructural measures of the fimbria-fornix pathway⁸⁷ suggesting a link between diffusion anisotropy and markers of membrane integrity, findings that are relevant and informative to the epilepsy and neuroimaging communities at large.

Connectome-informed computational models of both healthy and diseased brains⁸⁸ may lend features to enrich neuroimaging and network neuroscience markers and to make simulation-based predictions⁸⁹. In epilepsy, computational models have proven useful for target definition and post-surgical outcome prediction⁹⁰, and recent work used computational simulations operating on connectomes to delineate pathways of seizure propagation⁹¹.

The interplay between network and lesional phenotypes points to coupled pathological mechanisms affecting different elements in the brain simultaneously. Several epilepsy syndromes show a progressive course, characterized by cumulative brain changes in areas close to the primary lesion and in remote cortical targets⁴. Longitudinal studies will be of value as they can be used to assess causality between lesional and network level changes, and address clinical, psychosocial, and medication related factors. As the necessity for treatment in drug-resistant cohorts precludes the study of within-patient change over extended time frames, structured and accelerated designs that systematically enroll patients at different time points in their disease course, from new-onset to chronic long-standing, are recommended. Specifically, prospective analysis of new-onset patients may help to better disentangle medication related effects from those related to seizures. Additional inclusion of healthy individuals, scanned at comparable intervals, will help to differentiate epilepsy disease progression from structural and functional changes seen in healthy aging⁴.

Recent efforts have also begun to explore pre-existing genetic underpinnings of anomalies in brain structure, function, and connectivity across common epilepsy syndromes. These include patient-sibling studies in both generalized and focal syndromes (*e.g.*,⁹²), aiming at dissociating disease effects that are only observable in patients from endophenotypes that are shared by patients and their non-epileptic siblings.

International initiatives such as ENIGMA-epilepsy⁹³ have shown that it is possible to aggregate multimodal neuroimaging metrics and clinical information across different sites, and

to coordinate analytical strategies. Such large-scale, open, and concerted efforts will be instrumental for the robust validation of novel approaches and biomarkers.

ACKNOWLEDGEMENTS

Leonardo Bonilha receives research support from the National Institutes of Health / National Institute on Deafness and Other Communication Disorders (DC014021 and DC014664) and from the American Heart Association (SFDRN26030003). Neda Bernasconi was funded by CIHR and received salary support from FRQS. Andrea Bernasconi acknowledges funding from CIHR, National Science and Engineering Research Council of Canada (NSERC), and the Quebec BioImaging Network (QBIN). Boris Bernhardt acknowledges research support from NSERC (Discovery-1304413), CIHR (FDN-154298), Azrieli Center for Autism Research of the Montreal Neurological Institute (ACAR), SickKids Foundation (NI17-039), and salary support from FRQS (Chercheur Boursier Junior 1). We apologize to all the investigators whose research could not be appropriately cited owing to space limitations.

DISCLOSURE

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

ETHICAL PUBLICATION

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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FIGURE LEGENDS

FIGURE 1. Left: Neuroimaging of hippocampal sclerosis (HS, cell loss and gliosis in the hippocampal formation). Upper panels show histological specimens and corresponding high-resolution T1- and T2-weighted images in two TLE patients with variable degrees of HS. Lower panels illustrate preoperative imaging findings in two cohorts with TLE relative to controls, with the one on the *left* presenting with isolated gliosis but only little cell loss while patients on the right showed marked HS. For details, see ¹⁹. TLE-HS shows decreased volume together with T2-weighted intensity increases compared to controls. TLE-gliosis only showed focal increases in T2-weighted intensity but no reductions in columnar volumes. CA: *Cornu Ammonis Subfield*, DG – *Dentate Gyrus – Sub – Subiculum*. **Right:** Neuroimaging profiles of FCD subtypes (i.e., FCD Type-IIA, red, and IIB, black). Features include T1w- and FLAIR-intensity, vertical, and horizontal gradients. Features were analyzed at different intracortical depths (25-100%). Compared to controls, abnormalities in FCD Type IIB were seen across most intracortical layers, whereas alterations remained closer to the gray matter/white matter boundary in IIA. The innermost marker indicates significant differences between an FCD subtype and healthy controls, while the outermost marker indicates significant differences between both FCD subtypes i.e., IIA and IIB (* FDR < 0.05; • Uncorrected p < 0.05). For details, see ⁹⁴.

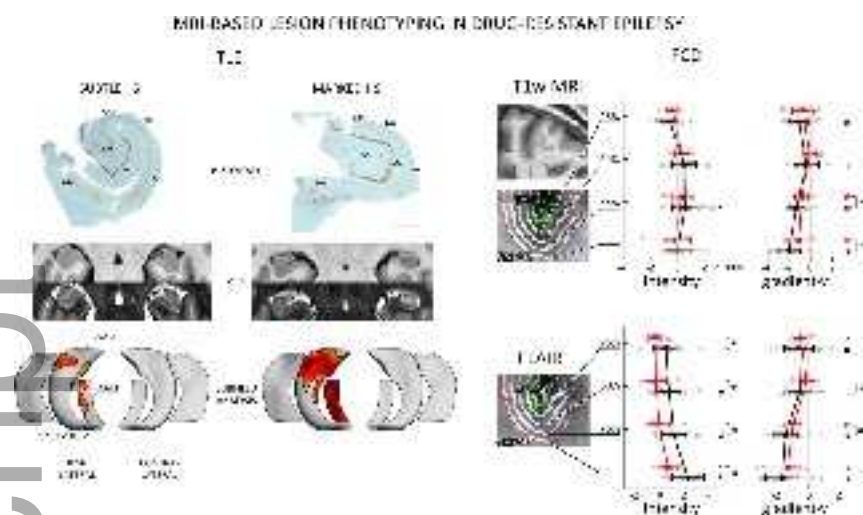
FIGURE 2. Structural and functional connectivity anomalies in TLE and ETE. Top left: Top left: Widespread cortical thinning in temporal and fronto-central neocortices in (MRI-defined) subgroups of patients with hippocampal atrophy (TLE-HA) and patients with normal hippocampal volume (TLE-NV) compared to controls, based on a sample of TLE patients and healthy individuals scanned at 1.5T ³⁷. **Top right:** In dysplasia-related ETE, a study has shown that the direction of overall morphometric anomalies may be different as a function of the

specific histological subtype of the primary lesion⁴². **Bottom left:** Disruptions in hippocampal functional connectivity are selectively seen in TLE subgroups, who had postoperative histological assessment of hippocampal pathology, compared to healthy controls. Functional connectivity anomalies were seen in patients with hippocampal sclerosis (TLE-HS) but not in the subgroup of TLE patients that showed isolated astrogliosis (TLE-G), suggesting an association between hippocampal structural integrity and its functional network embedding. For details, see¹⁹. Please note that results in the *Top Left* and *Bottom Left* were obtained from two independent TLE cohorts, scanned at different MRI platforms, with different procedures to assess the degree of hippocampal structural alterations. **Bottom right:** Functional connectivity anomalies in a patient with ETE co-localizing with the surgical target. The patient has been seizure-free post-op⁵⁷.

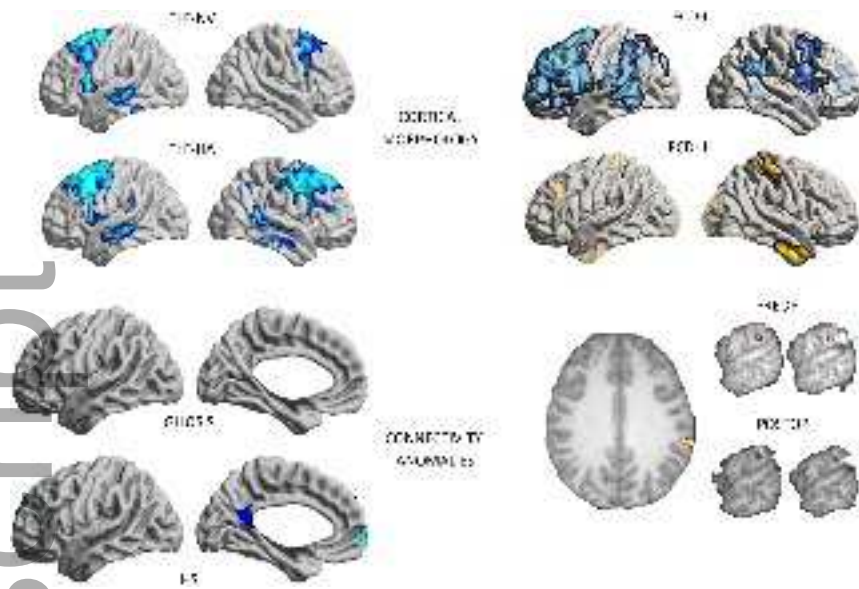
FIGURE 3. Connectome-level findings in focal epilepsy. **Top left:** Structural covariance anomalies in TLE, showing increased path length and clustering in left and right TLE (LTLE/RTLE) patients compared to controls, suggesting network-level regularization⁵⁹. **Top right:** Covariance network analyses in extra-temporal epilepsy also suggest an increased clustering and path length across all subtypes, with however more marked effects in late stage cortical malformations (PMG – polymicrogyrias) compared to those thought to occur mainly in early (FCD Type-II) and intermediary stages (HET – heterotopia) of corticogenesis. **Bottom left:** Functional connectivity anomalies in TLE relative to controls, also showing increased path length⁹⁵. **Bottom right:** Functional network anomalies in a cohort of ETE showing an increase in local efficiency and higher clustering coefficient compared to healthy controls, suggesting increased local network segregation⁹⁶.

FIGURE 4. Connectome models of postsurgical seizure outcome in TLE (*left*) and dysplasia-related ETE (*right*). For details, please see^{58; 76}.

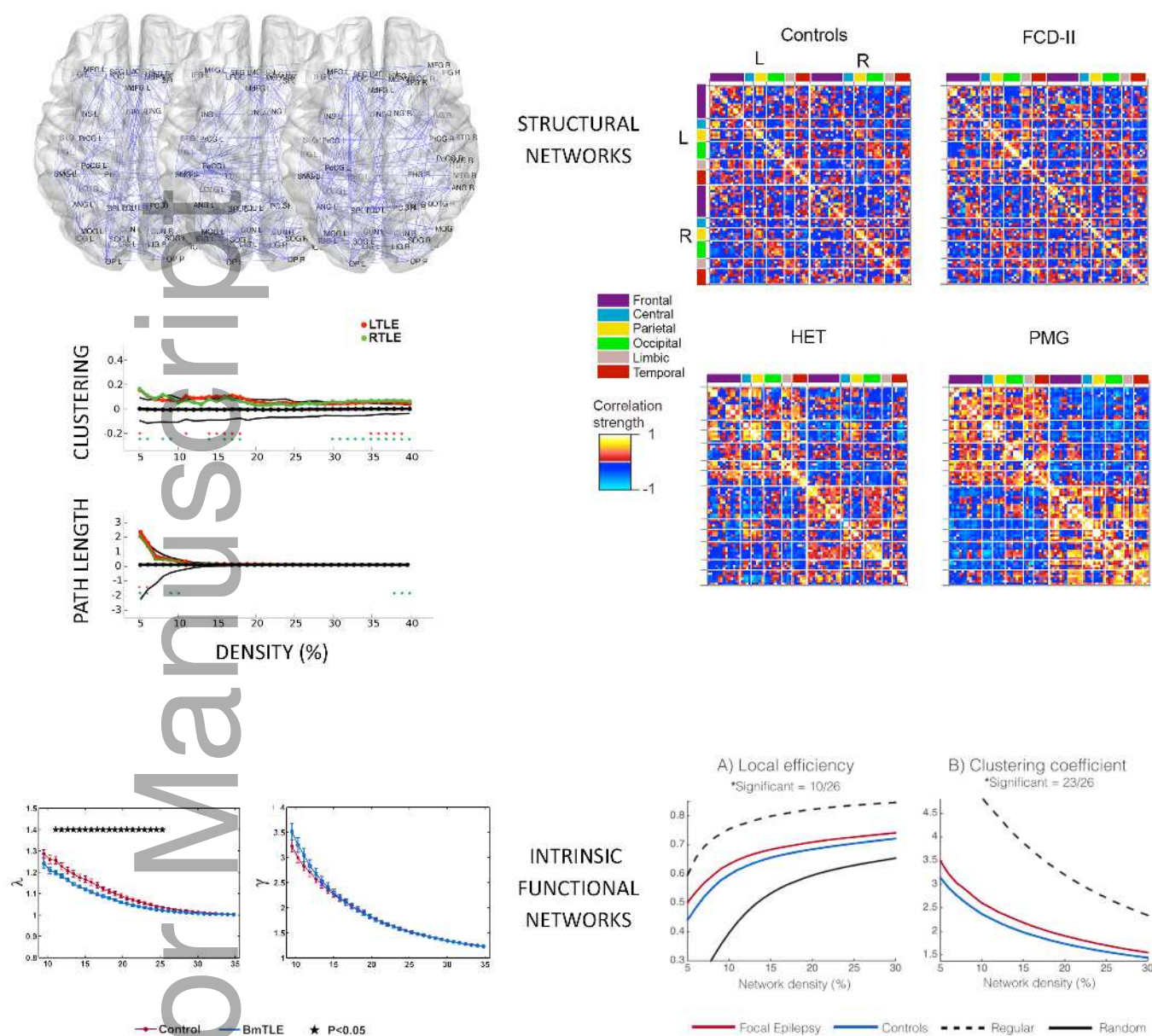
FIGURE 5. **Left:** Dynamic functional connectome markers of language networks in TLE, which can be used to predict impairments in verbal fluency⁸¹. **Right:** Pre- to postoperative changes in diffusion-derived macroscale connectivity, with differ between seizure free and non-seizure free patients⁸².



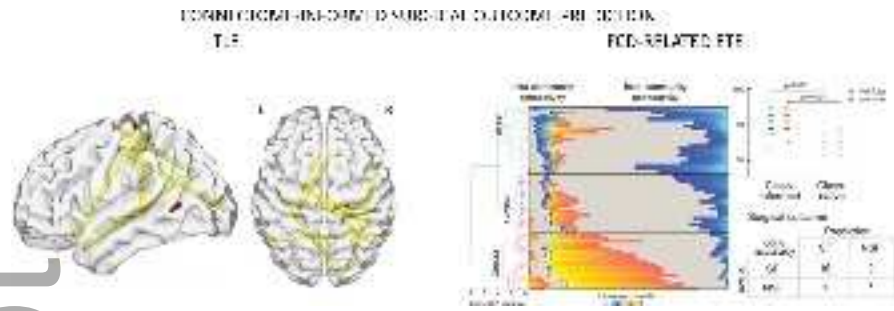
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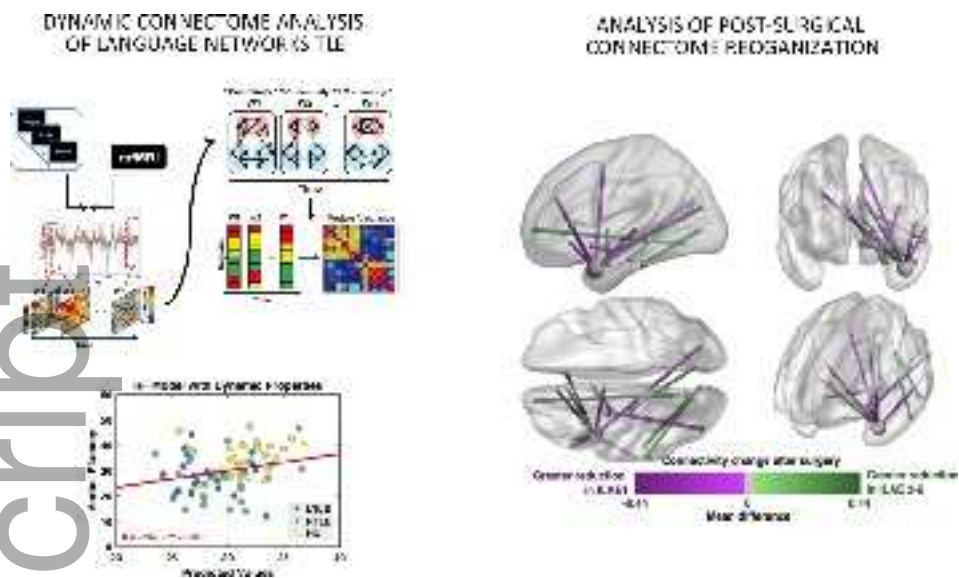
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