MULTIMODAL CONNECTOME BIOMARKERS OF COGNITIVE AND AFFECTIVE DYSFUNCTION IN THE COMMON EPILEPSIES

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ABSTRACT

Epilepsy is one of the most common chronic neurological conditions, traditionally defined as a disorder of recurrent seizures. Cognitive and affective dysfunctions are increasingly recognized as core disease dimensions and can affect patient wellbeing sometimes more than the seizures themselves. Connectome-based approaches hold immense promise for revealing mechanisms that contribute to dysfunction, and to identify biomarkers. Our review discusses emerging multimodal neuroimaging and connectomics studies that highlight network substrates of cognitive/affective dysfunction in the common epilepsies. We first overview work in drug-resistant epilepsy syndromes *i.e.*, temporal lobe epilepsy related to mesiotemporal sclerosis (TLE) and extratemporal epilepsy (ETE) related to malformations of cortical development. While these are traditionally conceptualized as ‘focal’ epilepsies, many patients present with broad structural and functional anomalies. Moreover, the extent of distributed changes contributes to difficulties in multiple cognitive domains as well as affective-behavioral challenges. We will also review work in idiopathic generalized epilepsy (IGE), a class of generalized epilepsy syndromes that involve subcortico-cortical circuits. Overall, neuroimaging and network neuroscience studies point to both shared and syndrome specific connectome signatures of dysfunction across TLE, ETE, and IGE. Lastly, we point to current gaps in the literature and formulate recommendations for future research.

KEY WORDS: Epilepsy, cognition, affect, dysfunction, connectomics, neuroimaging, network neuroscience

INTRODUCTION

Epilepsy is a neurological disorder characterized by recurrent seizures, affecting around 1% of the world population (approximately 50 million people)¹. While seizures can be controlled with anti-seizure medications in most patients, 30-40% of individuals are drug-resistant, and are at higher risk of widespread and cumulative brain damage²⁻⁷. Moreover, cognitive impairment has been reported to encompass multiple domains⁸, including memory, executive function, and language abilities. Difficulties in mood and emotion regulation are also increasingly recognized, challenging patient wellbeing and quality of life^{9; 10}. Collectively, these findings underscore the broad impact of epilepsy on brain health and function and emphasize the importance of shifting our understanding and clinical management of epilepsy as a disorder characterized by more than seizures¹¹.

Temporal lobe epilepsy related to mesiotemporal sclerosis (TLE) as well as extratemporal epilepsy related to malformations of cortical development (ETE) are among the most common drug-resistant epilepsy syndromes. While both TLE and ETE have been traditionally labelled as ‘focal’ epilepsies related to a confined brain region, they are increasingly understood as system-level disorders of interconnected networks¹²⁻¹⁴. A growing body of neuroimaging as well as histopathological findings demonstrates diffuse network anomalies in both syndromes, affecting regions beyond the area responsible for the onset of seizures¹⁵⁻¹⁷. Moreover, emerging work combining neuroimaging and cognitive testing suggests clear associations between atypical brain connectivity and measures of cognitive as well as affective function. Idiopathic generalized epilepsies (IGE), on the other hand, constitute approximately 20% of all patients with epilepsy, and include childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic-clonic seizures alone. Neuroimaging studies in IGE have detected widespread anomalies in brain structure, connectivity, and function—paralleling the mounting evidence in TLE and ETE on system-level dysfunction. Furthermore, multiple studies assessing cognitive abilities point to syndrome specific impairments, with for example measurable deficits in executive function as well as social and affective disturbances in patients with juvenile myoclonic epilepsy, and visuo-spatial and language deficits in absence epilepsies^{18 19}. Collectively, these studies suggest that widespread network anomalies contribute not only to the clinical manifestations of the disease, such as seizure burden and treatment response, but also to cognitive and affective difficulties affecting many patients’ lives.

Advances in multimodal neuroimaging and connectome analysis have contributed to our growing understanding of the structural and functional organization of brain networks²⁰, and promise to provide candidate metrics that could inform clinical care¹². In this targeted review, we will survey recent literature assessing connectome biomarkers of cognitive and affective dysfunction across common epilepsy syndromes, notably TLE, ETE, and IGE. Specifically, we will present the current literature on structural and functional network anomalies in each of these syndromes, outline the prevailing notions of syndrome related cognitive dysfunction, and summarize the emerging literature that relates network neuroscience findings to neuropsychological assessments. We will then highlight gaps in the literature and make recommendations for future research on brain and cognition in the common epilepsies.

TEMPORAL LOBE EPILEPSY (TLE)

The most common and widely studied drug-resistant epilepsy in adults is TLE. This syndrome is traditionally associated with variable degrees of histopathological alterations within mesial temporal lobe structures, such as the hippocampus, amygdala, and entorhinal cortex²¹⁻²³. Mounting histopathological and neuroimaging literature, however, challenges the notion that the condition can be reduced to localized pathology in the mesiotemporal lobes. Histological data suggests that mesiotemporal alterations often co-occur with broad rearrangements of cortical architecture, together with cell loss and gliosis in temporal and extratemporal cortices as well as subcortical structures, particularly the thalamus^{24; 25}. These findings have been confirmed *in vivo*, based on structural MRI assessments applying volumetric analysis, as well as with automated surface-based measures^{15; 26-30}. These studies have reported, in both single and multi-site

datasets, that TLE is often associated with diffuse cortical atrophy affecting mesiotemporal, lateral temporal, frontal, and centro-parietal cortices, as well as profound atrophy of several subcortical structures^{31; 32}. While the distribution of grey matter atrophy appears relatively widespread and bilateral, analysis of cortical asymmetries has pointed more directly to marked changes in ipsilateral structures, particularly in temporo-limbic regions. These findings have been complemented by quantitative analysis of other MRI contrasts, such as FLAIR/T2w imaging³³ as well as quantitative T1 relaxometry³⁴, suggesting that structural alterations are broad, yet nevertheless most concentrated in paralimbic areas ipsilateral to the seizure focus. Similarly, several diffusion MRI studies have described anomalies in structural connectivity and subcortical white matter microstructure, affecting strongly temporo-limbic pathways and with more moderate effect sizes in extralimbic collateral and commissural pathways³⁵⁻³⁹. Analysis of brain function and connectivity, as measured by task-based and resting-state fMRI, has shown atypical functional interactions between temporal and extratemporal areas in TLE patients relative to controls, with findings appearing most marked in temporo-limbic and default mode networks, systems known to be anatomically connected to the mesiotemporal lobe^{40; 41}. Overall, and despite sometimes diverging topographies of regional changes across different neuroimaging modalities, findings converge towards widespread network compromise in TLE, likely modulated by anatomical connections to a mesiotemporal/paralimbic disease epicenter.

Considering cognitive function, a majority of TLE patients has traditionally been reported to show memory impairment, while around 30-40% present with difficulties in language function⁴²⁻⁴⁵. Paralleling the widespread anomalies revealed by neuroimaging and histology, an increasing body of work suggests that impairments in executive⁴⁶, sensory, and motor functions are also prevalent in TLE^{10; 43-45}. As such, the landscape of cognitive difficulties in TLE emphasizes a broad profile of impairments across patients affecting multiple cognitive domains. Adding to the complexity of the cognitive dysfunction landscape in TLE, impairments are also quite variable across patients. Several groups have previously suggested the existence of graded abnormalities across TLE patient subgroups, with approximately a third of patients presenting with marked dysfunction while the remaining patients show mild or no measurable impairments compared to age-matched healthy individuals⁴⁷⁻⁴⁹. In TLE, the degree and laterality of structural pathology in the hippocampus have been associated with verbal memory and language impairments^{50; 51}. Further, functional connectivity measures of the hippocampus and cortical networks have been used to probe language lateralization⁵²⁻⁵⁴ and to predict deficits in episodic memory⁵⁵. In the latter study, the investigators reported an atypical organization of functional connections that link the hippocampus to wide areas of cortex; the data suggests that the structural reorganization of the hippocampus and its functional interactions with the rest of the brain underpins reorganization of memory networks towards a potentially less efficient functional architecture⁵⁵. Such findings are in line with earlier fMRI findings in TLE patients during memory tasks, showing a reorganization of both ipsilateral and contralateral hippocampal and extrahippocampal functional networks⁵⁶⁻⁵⁹. Other work studied intrinsic functional hubs in TLE and reported an association between functional network reorganization and both language and memory impairment in patients⁶⁰. Together, these studies emphasize the role of (i) hippocampal-neocortical subnetworks, and (ii) structural alterations in the mesiotemporal lobes, in determining cognitive deficits in TLE, particularly relating to memory and language function.

A separate and complementary series of studies identified associations between structural connectivity measures and cognitive phenotypes in TLE. There has been robust evidence for an association between diffusion abnormalities of deep white matter fiber tracts as well as the superficial white matter, and reduced language and memory performance in TLE patients⁶¹. In one study, the authors combined dimensional and categorical multivariate approaches to show that more marked degrees of impairment across several cognitive functions related to overall less efficient and less inter-connected white matter network organization⁶². Another study leveraged communication models, which simulate functional interactions from structural connectivity data, and reported that overall delays in regional interactions related to broad impairments in several cognitive domains⁶³. Moving towards a biomarker evaluation framework,

connectome-based machine learning—with cross-validation and the use of an independent hold-out dataset—has shown utility in predicting memory and language impairment, proving an optimistic outlook that brain network models can aid in indexing patient-specific functional impairments^{64, 65}. In one of these studies, structural connectivity features achieved improved performance when they were combined with hippocampal imaging features, pointing to benefits of combining targeted assessments of the mesiotemporal epicenter with large-scale network models⁶⁴. These studies, thus, emphasize the importance of efficient network communication in preserving cognition in TLE patients, and hold promise in serving as robust biomarkers of cognitive difficulties in this population.

Cognitive dysfunction may co-occur with socio-affective deficits. A substantial proportion of patients suffer from depressive symptoms, anxiety, and personality disorders^{66, 67}. As for cognitive dysfunction, affective difficulties may have a considerable impact on patient wellbeing and quality of life. In one previous study, the investigators related self-reports from the Beck Depression Inventory to structural and functional connectivity measures in both TLE patients and controls^{68, 69}. The authors could observe that structural and functional organization of fronto-limbic circuits—in particular connectivity between the hippocampus and anterior frontal regions—reflected depressive symptoms. Fronto-limbic involvement was also suggested by one study relating resting-state fMRI connectivity measures to measures of neuroticism, depression, and anxiety⁷⁰. The authors showed that neuroticism (a personality trait that is associated with depressive symptoms) relates to atypical functional connectivity between mesiotemporal and frontal lobe regions, with connectivity alterations that were partially overlapping to those related to depression and anxiety symptoms⁷¹. In an earlier study, the authors also reported associations between affective symptoms and reductions in grey matter volumes, again targeting both frontal and temporal neocortices, as well as mesiotemporal lobe structures such as the hippocampus and amygdala⁷². Collectively, previous efforts to study socio-affective functioning in TLE highlight the role of fronto-limbic circuits, as well as the structural integrity of these regions, in mood-related symptoms.

EXTRATEMPORAL LOBE EPILEPSY (ETE)

Extratemporal lobe epilepsy refers to a broad class of location-related syndromes in which the seizures originate from regions outside of the temporal lobe. The most common ETE subsyndrome is frontal lobe epilepsy, which accounts for approximately 50% of ETE patients^{73, 74}. Although lesional etiologies are quite variable in ETE, several patients present with a suspected or histologically confirmed malformation of cortical development, such as focal cortical dysplasia (type-1 or type-2), heterotopia (subcortical nodular, band), or polymicrogyria. Some of these lesions may be subtle and overlooked upon conventional radiological examination, contributing to diagnostic uncertainty and difficulties in offering targeted surgical therapy^{75, 76}. While significant effort has been invested in characterizing malformations in single patients using structural MRI and, increasingly, connectomics techniques⁷⁷⁻⁸¹, a few recent studies have also characterized the whole-brain substrates of ETE cohorts at a group level. These studies have shown that structural and functional network substrates across different ETE subsyndromes likely vary with respect to the primary lesional etiology. Patients with type-1 focal cortical dysplasia (a late-stage malformation associated with subtle alterations in cortical architecture and intensity) present with widespread cortical thinning relative to controls. In contrast, patients with type-2 dysplasia (early stage cortical malformations that manifest on MRI as cortical thickening and interface blurring, together with FLAIR/T2w intensity changes^{82, 83}) present with patches of increased cortical thickness beyond the primary lesional perimeter⁸⁴. A previous network analysis of frontal lobe epilepsy patients with different cortical malformations revealed a gradient of functional and structural network anomalies, showing only subtle structural network reorganization in type-2 dysplasia, moderate effects in heterotopias, and maximal changes in late-stage malformations such as type-1 dysplasia and polymicrogyria⁷⁸. Findings were paralleled by a gradient of functional network anomalies, pointing to reductions in functional network efficiency across the malformation spectrum, again being more pronounced in late-stage cortical malformations such as polymicrogyria compared to early-stage proliferative etiologies⁸⁵. Previous work on ETE thus emphasizes

the importance of considering the developmental etiology of lesional subtypes to understand structural and functional network anomalies in specific patient subgroups.

In ETE, the landscape of cognitive impairment is less well characterized than in TLE, owing to heterogeneity of the patients' primary etiology, and variable extent of the epileptogenic network. Findings nevertheless suggest an important modulation of impairments with respect to the location of the disease epicenter. For instance, ETE patients with a suspected or confirmed anomaly in the frontal lobes will often present with executive dysfunction⁸⁶⁻⁹⁰, ranging from impaired attention to difficulties in goal-oriented behaviors. Verbal competencies also appear impaired^{91; 92}, and reports have also pointed to poorer motor coordination and reduced psychomotor speed^{87; 93}. Patients with primary lesions in central and posterior regions may show deficits in visuo-spatial functions, often together with attentional and motor dysfunction. Similar heterogeneity exists even within subgroups of patients with the same lesional subtype, where deficits can range from no apparent cognitive impairment to marked disability.

Studies assessing brain substrates of cognitive deficits in patients with ETE are less frequent than in TLE, and are also more difficult to aggregate due to the above-mentioned heterogeneity across the patient spectrum. However, prior work in ETE cohorts (sometimes mixed with TLE) reported structural and functional connectivity alterations that relate to overall reductions in cognitive function^{94; 95}. In mixed focal epilepsy cohorts including patients with ETE, prior work highlighted fronto-temporal connectivity abnormalities and global alterations of functional network architecture during language tasks^{96; 97}, and prefrontal connectional rearrangements during verbal working memory⁹⁸. In children with frontal lobe epilepsy, recent studies showed altered functional connectivity among fronto-temporo-parietal cortices during a working memory task compared to controls⁹⁹, and also reported an association between atypical functional network modularity, consisting of reduced long-range connectivity and increased short-range connections, and reductions in cognitive performance⁹⁴. Notably, associations between cognitive impairment and network topology have been reported in structure as well as function. For example, structural networks estimated from diffusion MRI tractography evince marked alterations in segregation and integration in patients with more severe cognitive impairment⁹⁵; similarly, increased clustering in structural covariance networks derived from T1-weighted data was not only associated with markers of disease severity, but also with lower general intelligence¹⁰⁰. In a recent study, we combined a comprehensive cognitive profiling of language and working memory abilities with task-based fMRI analysis and connectome-level contextualization in a cohort with frontal lobe epilepsy, and compared findings to both patients with TLE and healthy controls¹⁰¹. Our study showed that working memory and language impairment in frontal lobe epilepsy was associated with reduced activation across attentional and executive systems, together with an attenuated deactivation of default mode regions, suggesting a reorganization of functional recruitment at the systems level. While atypical activation patterns were similar to those in TLE patients, reductions in default mode network deactivations appeared more marked in frontal lobe epilepsy patients, whereas those with TLE presented with less activations in posterior language areas during semantic tasks¹⁰¹. Collectively, these findings provide emerging evidence of both shared and syndrome specific impacts of different location-related epilepsies on brain functional networks. Moreover, this work broadly illustrates the utility of network neuroscience approaches in capturing important substrates that contribute to inter-patient variability in cognitive dysfunction.

Studies of socio-affective functioning are less common than studies of cognitive function in ETE, but represent an important and growing area of research. One previous study in a cohort of 40 frontal lobe epilepsy cases reported that 25% have elevated anxiety scores, 40% have either elevated depression or elevated anxiety scores, and 25% have depression scores above the clinical cut-off¹⁰². These values appear higher than in patients with generalized epilepsies¹⁰², but are not as high as those observed in TLE¹⁰³. Further, prior work highlights that executive dysfunction in frontal lobe epilepsy can co-occur with reduced response inhibition, hyperactivity, obsession, and addictive behaviors that may interfere with overall adaptation to everyday life¹⁰³. While there is abundant literature on behavioral and emotional difficulties

in patients with specific lesions, including foundational case studies in patients with frontal lobe lesions, there are, to our knowledge, no systematic assessments of the relationship between whole-brain connectome architecture and affective difficulties in ETE patients.

IDIOPATHIC/GENETIC GENERALIZED EPILEPSY (IGE)

Idiopathic generalized epilepsy refers to a group of epilepsy syndromes with likely polygenetic inheritance, and characterized by generalized spike and slow-wave discharges on EEG. While multiple syndromes are subsumed under the umbrella term of IGE¹⁰⁴⁻¹⁰⁶, converging evidence supports a key role of thalamo-cortical networks¹⁰⁷. Fronto-thalamo-cortical involvement during generation and propagation of generalized seizures has been solidified by electrophysiological work^{108; 109}. Structural MRI studies complemented these findings, by indicating grey matter volume reductions in both the thalamus and neocortex¹¹⁰, albeit to a lesser extent than in syndromes such as TLE^{31; 111}. In addition to atrophy, recent work also pointed to atypical cortical folding and cortex-cortical distance relationships in juvenile myoclonic epilepsy, with the latter also being present in non-affected siblings¹¹². Atypical cortical folding may signify perturbations in underlying brain connections; resting-state fMRI approaches have indeed supported atypical organization of cortico-thalamic networks in different IGE syndromes, showing aberrant connectivity when seeding from either cortical or thalamic regions¹¹³⁻¹¹⁵. Similar reports have appeared in diffusion MRI studies, which showed atypical structural connectivity between thalamic and medial frontal regions in IGE subgroups with juvenile myoclonic epilepsy¹¹⁶.

The cognitive landscape of IGE is also characterized by atypical function across several domains. A systematic review and meta-analysis conducted across 26 studies revealed broad reductions in cognitive function across multiple domains in IGE patients, involving generalized cognitive ability, fluid/crystallized intelligence, processing speed, and memory abilities¹¹⁷. Impairments were observed in studies assessing mixed IGE cohorts, but also when considering specific IGE subsyndromes such as juvenile myoclonic, childhood absence epilepsies, as well as epilepsy with generalized tonic-clonic seizures alone. Executive dysfunction represent a common trait across IGE subsyndromes¹⁸, pointing to frontal lobe involvement, while impairment of visuospatial abilities may generally be subtle¹¹⁷. Another review focusing on childhood absence epilepsy also showed reductions in verbal skills across language and learning tasks, as well as mild impairments in executive functions¹¹⁸. In juvenile myoclonic epilepsy, several studies also point to impaired social cognition^{18; 19}, which may possibly relate to the consistent frontal lobe dysfunction seen in the disorder. Profiles of cognitive difficulties in IGE are thus seemingly broad, with specific subsyndromes possibly showing more circumscribed patterns of impairment.

Taken together, studies using cognitive and neuroimaging measures have supported an overall perturbation in the organization of prefronto-central-thalamic connections. A positron emission tomography study reported prefrontal and subcortical glucose hypometabolism in patients with juvenile myoclonic epilepsy, and associations with reduced working memory and mental flexibility¹¹⁹. These findings are complemented by task fMRI studies in the same IGE subsyndrome, which report altered motor activation across a battery of cognitive tasks^{120; 121}, and atypical connectivity between prefrontal and motor networks during a working memory paradigm,¹²¹ which may constitute heritable traits^{120; 122}. Atypical functional connectivity between prefrontal and thalamic regions was also observed during a verbal fluency task¹¹⁶, and was shown to relate to both reduced verbal fluency and decremented structural connectivity between these regions. Other structural and diffusion MRI studies also support a network basis for impairment, by underscoring associations between grey and white matter alterations in both cortical and thalamic regions and cognitive impairments in mental flexibility, language, and memory function¹²³⁻¹²⁵. Compared to the broad literature on network correlates of dysfunction in juvenile myoclonic epilepsy, association studies between imaging measures and cognitive variables are less frequent in absence epilepsy¹⁸. One study reported atypical cortical morphology and folding in frontal and temporal cortices, and indirectly supported a potential contribution to reductions in verbal and performance IQ measures¹²⁶. During a sustained attention paradigm, a functional imaging study revealed an association between lower activation of the medial frontal

cortex and impaired performance, which co-existed with reduction of fronto-insular resting-state connectivity¹²⁷. Collectively, although the amount of work associating cognitive phenotypes with brain network information is at times more limited for certain IGE subsyndromes, the literature overall suggests that atypical wiring and cross-talk of thalamic and cortical regions may contribute to the sometimes rather broad impairments seen in IGE patients.

CONCLUSIONS AND CURRENT GAPS

Neuroimaging and connectomics approaches are beginning to reveal structural, functional, and network level substrates in TLE, ETE, and IGE. These studies support both shared and syndrome specific patterns of cortico-subcortical reorganization across different epilepsy syndromes, with TLE being associated with marked and widespread network reorganization that is particularly extensive in the proximity of the mesiotemporal epicenter. While memory and language deficits are most commonly reported cognitive difficulties, mounting evidence suggests that white matter microstructure and functional alterations also contribute to dysfunction in other cognitive domains, such as executive function. Fronto-limbic alterations in brain structure and function also contribute to commonly observed affective comorbidities, including depression and anxiety, and may potentially underpin other traits associated with TLE, such as neuroticism. In ETE, neuroimaging and connectomics studies suggest widespread impairments in structural and functional brain network organization, which seems to be modulated by both location and etiology of the primary lesion. For example, ETE patients with a suspected or confirmed anomaly in frontal circuits will often present with executive dysfunction as well as reduced verbal competence, sometimes together with poorer motor coordination and reduced psychomotor speed. Emerging literature has furthermore begun to reveal structural and functional substrates of cognitive impairments in ETE, suggesting reorganization in multiple brain subnetworks, often characterized by atypical activation/deactivation patterns of large-scale functional systems. Finally, although the different syndromes subsumed under the IGE umbrella term are relatively heterogenous, consistent structural and functional imaging findings point to thalamo-cortical structural and functional dysfunction. Across different IGE subsyndromes, most work has been performed in juvenile myoclonic epilepsy, pointing to similar, albeit somewhat more subtle cognitive impairment than in ETE patients with a frontal lobe seizure focus.

Epilepsy is truly more than a seizure condition, and it is thus important to continue to identify underlying mechanisms of cognitive function across the spectrum of common epilepsies. This expansion will involve increasing research efforts into less prevalent syndromes and further studying sources of inter-patient variability. For these studies, we emphasize the need to combine multidimensional cognitive phenotyping approaches with multimodal neuroimaging, given the likely complementary power of structural and functional imaging techniques. In TLE, prior clustering and multivariate associative studies are already beginning to shed light on covariations in atypical connectome organization and cognition, and further help to clarify sources of inter-individual variations across the patient spectrum. Paralleling current trends in the study of the brain and mental health, we recommend cross-syndrome investigations that can identify shared and syndrome specific effects on brain network organization and cognition. Such approaches will provide higher granularity in studying the panorama of cognitive and affective impairments and associated connectome anomalies in TLE, ETE, and IGE. Finally, to generalize from potential idiosyncrasies of specific epilepsy centres and to allow for an unbiased evaluation of network biomarkers in the prediction of dysfunction at the single-patient level, we recommend multi-site data aggregation and analysis efforts such as ENIGMA-Epilepsy,¹²⁸ along with strategies for prospective as well as retrospective data harmonization at the level of brain and cognition alike.

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FIGURES

Figure 1. Studying cognitive and affective dysfunction across the common epilepsies requires an integrative approach, combining multidimensional behavioral phenotyping, multimodal neuroimaging, and ideally the incorporation of several common epileptic syndromes. In the current review, we will cover the literature that has so far populated this space.

Figure 2. Prior multimodal imaging studies on connectome markers of dysfunction in the common epilepsies.

In TLE (*top row*), structural network measures were associated to cognitive dysfunction across multiple domains (*top left*)⁶². Using stepwise functional connectivity analysis, alterations in hierarchical functional network organization were shown to reflect multi-domain cognitive impairment (*top right*)¹²⁹. In ETE (*middle row*), a study focusing on children with frontal lobe lesions demonstrated that despite the absence of significant differences in structural network parameters in patients, structural modularity increased with stronger cognitive impairment (*middle left*)¹³⁰. Additionally, when comparing fMRI activation patterns in a verbal working memory task, frontal lobe epilepsy patients showed targeted reductions in the recruitment of specific networks, notably fronto-parietal and dorsal attention systems, while effects in TLE patients were more widespread (*middle right*)¹⁰¹. As for IGE (*bottom row*), a study in patients with juvenile myoclonic epilepsy and their unaffected siblings studied left hippocampal shape/positional anomalies, and found associations to atypical activation during a verbal memory task (*bottom left*)

¹²⁵. An endophenotype of atypical activation in patients and their siblings could also be seen when assessing both memory and language tasks combined (*bottom right*) ¹²⁰.