Current Literature
In Clinical Science

It’s All About Who You Know: The Importance of Connections in Understanding Epilepsy and Associated Cognitive Dysfunction

Frontal Lobe Connectivity and Cognitive Impairment in Pediatric Frontal Lobe Epilepsy.

PURPOSE: Cognitive impairment is frequent in children with frontal lobe epilepsy (FLE), but its etiology is unknown. With functional magnetic resonance imaging (fMRI), we have explored the relationship between brain activation, functional connectivity, and cognitive functioning in a cohort of pediatric patients with FLE and healthy controls. METHODS: Thirty-two children aged 8–13 years with FLE of unknown cause and 41 healthy age-matched controls underwent neuropsychological assessment and structural and functional brain MRI. We investigated to which extent brain regions activated in response to a working memory task and assessed functional connectivity between distant brain regions. Data of patients were compared to controls, and patients were grouped as cognitively impaired or unimpaired. KEY FINDINGS: Children with FLE showed a global decrease in functional brain connectivity compared to healthy controls, whereas brain activation patterns in children with FLE remained relatively intact. Children with FLE complicated by cognitive impairment typically showed a decrease in frontal lobe connectivity. This decreased frontal lobe connectivity comprised both connections within the frontal lobe as well as connections from the frontal lobe to the parietal lobe, temporal lobe, cerebellum, and basal ganglia. SIGNIFICANCE: Decreased functional frontal lobe connectivity is associated with cognitive impairment in pediatric FLE. The importance of impairment of functional integrity within the frontal lobe network, as well as its connections to distant areas, provides new insights in the etiology of the broad-range cognitive impairments in children with FLE.

Default Mode Network Connectivity Indicates Episodic Memory Capacity in Mesial Temporal Lobe Epilepsy.

PURPOSE: The clinical relevance of resting state functional connectivity in neurologic disorders, including mesial temporal lobe epilepsy (mTLE), remains unclear. This study investigated how connectivity in the default mode network changes with unilateral damage to one of its nodes, the hippocampus (HC), and how such connectivity can be exploited clinically to characterize memory deficits and indicate postsurgical memory change. METHODS: Functional magnetic resonance imaging (fMRI) resting state scans and neuropsychological memory assessments (Warrington Recognition Tests for Words and Faces) were performed on 19 healthy controls, 20 patients with right mTLE, and 18 patients with left mTLE. In addition, postsurgical fMRI resting state and memory change (postsurgical memory performance–presurgical memory performance) data were available for half of these patients. KEY FINDINGS: Patients with mTLE showed reduced connectivity from the posterior cingulate cortex (PCC) to the epileptogenic HC and increased PCC connectivity to the contralateral HC. Stronger PCC connectivity to the epileptogenic HC was associated with better presurgical memory and with greater postsurgical memory decline. Stronger PCC connectivity to the contralateral HC was associated with less postsurgical memory decline. Following surgery, PCC connectivity to the remaining HC increased from presurgical values and showed enhanced correlation with postsurgical memory function. It is notable that this index was superior to others (hippocampal volume, preoperative memory scores) in explaining variance in memory change following surgery. SIGNIFICANCE: Our results demonstrate the striking clinical significance of the brain’s intrinsic connectivity in evaluating cognitive capacity and indicating the potential of postsurgical cognitive morbidity in patients with mTLE.
Commentary

While it is not novel to state that epilepsy and many of its associated cognitive comorbidities are disorders of brain connections, until recently, our ability to image such connections has been very limited. While the anatomy of gray matter could be clearly outlined by high-resolution MRI, and individual gyri and deep nuclei labeled and classified, white matter has always been a more amorphous and elusive entity. Individual tracts and fiber bundles cannot be visualized by conventional imaging, and our standard way of characterizing lesions in cerebral white matter has generally been limited to describing an area of signal intensity abnormality without very much anatomical precision.

The advent of diffusion tensor tractography has allowed for a 3D visualization of the estimated locations and trajectories of large white matter tracts based on the anisotropic diffusion of water molecules, but this technique still does not image actual axonal fiber bundles (1). Furthermore, the information that tractography does provide is merely structural—suggesting which regions of gray matter “wire together”—without the ability to determine what the functional significance of any of the projected connections might be (2).

The use of fMRI for connectivity imaging, however, attempts to determine just that. The concept of functional connectivity is based on the fundamental principle that areas of gray matter that show high degrees of correlation in their BOLD signal over time (either in association with the performance of a particular task or in the so-called resting state) are presumed to be functionally connected to each other—that is, they “fire together.” While there is perhaps some imprecision to the use of the term “connectivity” in this context, it is clear that there could be great biological and clinical significance in understanding why certain spatially distinct regions of brain—particularly those with pathology—co-activate with other regions in a temporally correlated fashion (3).

The two papers discussed here illustrate different approaches to functional connectivity, both showing that this imaging method can be used to expand our understanding of epilepsy and its cognitive comorbidities and even potentially improve our management of patients with medically uncontrolled seizures.

The article by Braakman et al. from the Netherlands takes a task-based approach to functional connectivity. Children with frontal lobe epilepsy were scanned during the performance of a working memory task to determine whether they differed from matched healthy controls in their brain activation or task-related functional connectivity, and to examine whether any differences were related to cognitive impairment or clinical epilepsy characteristics. The investigators found that while children with frontal lobe epilepsy appeared to have intact working memory-associated fMRI activation patterns, they exhibited a global decrease in functional brain connectivity compared to healthy controls. Children with epilepsy and cognitive impairment had less frontal lobe functional connectivity when compared to those with epilepsy but without cognitive impairment; this difference comprised both connections within the frontal lobe as well as connections between the frontal lobe and other brain areas. These frontal connectivity measures were not significantly associated with recorded clinical epilepsy characteristics.

The article by McCormick et al. from Toronto, by contrast, examines BOLD signal imaging acquired during the resting state, using a related but distinct approach to determining functional connectivity. In resting-state research, functional data are acquired for several minutes while patients are asked to relax and not focus on any particular task. Different regions of interest are then studied for correlation to see which areas of brain tend to show temporal correlation in their spontaneous BOLD signal fluctuations during the task-free resting state (4). Much of resting-state research has focused on the default mode network, a collection of brain regions that are active together during fMRI experiments when no specific cognitive task is being performed (5). Activation of the default mode network may represent autobiographical memory, social processing, and other stimulus-independent cognitive activities, and indeed the hippocampus is a node within this network.

The Toronto investigators studied patients with mesial temporal lobe epilepsy (MTLE), both pre- and postoperatively, using resting-state functional imaging and neuropsychological memory assessments. They found that patients with MTLE showed reduced connectivity from the posterior cingulate cortex (a node within the default mode network) to the epileptogenic hippocampus and increased connectivity from the posterior cingulate to the contralateral hippocampus. Importantly, stronger connectivity to the epileptogenic hippocampus was associated with better presurgical memory function but with worse memory loss following resective surgery, while stronger connectivity to the contralateral hippocampus was associated with less severe postsurgical memory loss. Postoperatively, connectivity between the posterior cingulate and the remaining hippocampus increased and was correlated with postoperative memory function; indeed, posterior cingulate–hippocampal connectivity was a better predictor of postsurgical memory change than preoperative memory function or hippocampal volume.

Both these studies highlight the utility of connectivity imaging in understanding and managing epilepsy. With the results from Braakman et al., we can better appreciate the possible mechanisms through which patients with frontal lobe epilepsy may be susceptible to dysfunction in working memory and other frontal network-based cognitive skills. In fact, in the future, quantifiable connectivity metrics might serve as an additional marker for epilepsy-associated comorbid cognitive issues; identifying the responsible networks is the first step in being able to address these deficits. The default mode network findings in MTLE are even more exciting since they not only confirm an important hypothesis regarding the functional role of epileptogenic and nonepileptogenic hippocampi in supporting material-specific memory functions but also show that connectivity metrics might serve as useful prognostic measures of postoperative memory decline, which would be a valuable addition to the current preoperative counseling of MTLE patients considering temporal lobectomy.

There are important limitations to functional connectivity research. First, as with all functional imaging, it is critical that there be clear hypotheses driving the work—as there were in these two papers—since it is all too easy to obtain large

Connectivity Imaging in Epilepsy
volumes of functional data and find activation or connectivity results that may withstand tests of statistical significance but not answer clinically relevant questions or have biological meaning. Unfortunately, functional connectivity results cannot speak to the causality or directional influence of any relationship between two regions, and they change dynamically depending on task and circumstance, unlike structural imaging. For resting-state research, certainty regarding subject compliance and our understanding of what cognitive functions are actually happening during “rest” are still quite nebulous.

Despite these drawbacks, functional connectivity research is emerging as a major advance in the study of epilepsy and associated cognitive dysfunction. Indeed, it may be that the ability to image functional networks becomes clinically useful in specific circumstances sooner than we might think.

References

by Bernard S. Chang, MD
American Epilepsy Society
Epilepsy Currents Journal
Disclosure of Potential Conflicts of Interest

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

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   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
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4. **Manuscript/Article Title:** It's All About Who You Know

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