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Metrics of brain network architecture capture the impact of disease in children with epilepsy

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ABSTRACT

Background and objective: Epilepsy is associated with alterations in the structural framework of the cerebral network. The aim of this study was to measure the potential of global metrics of network architecture derived from resting state functional MRI to capture the impact of epilepsy on the developing brain.
Methods: Pediatric patients were retrospectively identified with: 1. Focal epilepsy; 2. Brain MRI at 3 Tesla, including resting state functional MRI; 3. Full scale IQ measured by a pediatric neuropsychologist. The cerebral cortex was parcellated into approximately 700 gray matter network nodes. The strength of a connection between two nodes was defined as the correlation between their resting BOLD signal time series. The following global network metrics were then calculated: clustering coefficient, transitivity, modularity, path length, and global efficiency. Epilepsy duration was used as an index for the cumulative impact of epilepsy on the brain.
Results: 45 patients met criteria (age: 4–19 years). After accounting for age of epilepsy onset, epilepsy duration was inversely related to IQ (p: 0.01). Epilepsy duration predicted by a machine learning algorithm on the basis of the five global network metrics was highly correlated with actual epilepsy duration (r: 0.95; p: 0.0001). Specifically, modularity and to a lesser extent path length and global efficiency were independently associated with epilepsy duration.
Conclusions: We observed that a machine learning algorithm accurately predicted epilepsy duration based on global metrics of network architecture derived from resting state fMRI. These findings suggest that network metrics have the potential to form the basis for statistical models that translate quantitative imaging data into patient-level markers of cognitive deterioration.

1. Introduction

Epilepsy has a substantial influence on the development and maintenance of cognitive functions. Although it is not clear whether such effects are mediated by ongoing seizure activity, anti-seizure medication or both, long-term epilepsy and poor seizure control have been consistently associated with poor cognitive outcomes (Elger et al., 2004; Hermann et al., 2002; Czochanska et al., 1994). These effects on intellectual function are exaggerated in children, which may reflect the fact that developmental physiology is primed to prioritize cerebral growth and reorganization (Bjornaes et al., 2001). While together these observations suggest that neural plasticity acts as a negative prognostic factor in children with epilepsy, these same characteristics likely contribute to their capacity for cognitive and neurologic recovery after successful epilepsy surgery (Spencer and Huh, 2008; Freitag and Tuxhorn, 2005). Despite the benefits of early intervention, however, surgery is frequently deferred, especially in imperfect candidates or in patients whose seizures have yet to meet the standard for intractability. Early markers of cognitive deterioration in these children would be of great value toward defining the optimal timing of surgical intervention.

As a result of advances in computational neuroscience, network organization of the brain is now accessible to systematic study. Although the field capitalizes on diverse techniques, one prominent approach leverages graph theory to characterize global topological features of the cerebral network (Hagmann et al., 2008). In this context, the brain is represented as a collection of nodes, or anatomical elements in the network, and their mutual connections as edges (Bullmore and Sporns, 2009; Guye et al., 2010; Xia and He, 2011). Graph theory-based analyses of networks constructed from functional imaging data have demonstrated that focal epilepsies are associated with global alterations in the cerebral network (Liao et al., 2010; Bernhardt et al., 2011; Vlooswijk et al., 2011; DeSalvo et al., 2014; Vaessen et al., 2013). More recently, it was observed that inter-individual differences in network efficiency, as quantified by graph theory, correlate with cognitive function

Abbreviations: FSL, FMRIB Software Library; ICA, independent components analysis; IQ, intelligence quotient.

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in healthy populations of adults and children (Kim et al., 2016; Li et al., 2009; van den Heuvel et al., 2009). Together, these findings support the potential for topological features of the brain to provide markers of cognitive function in children. However, at any given time, the cognitive abilities of a child with epilepsy will reflect the intersection of his/her individual trajectory of brain development with maladaptive changes related to the cumulative impact of his/her disease. As yet, no data exist regarding the potential for network analyses to dissociate these processes to specifically capture those alterations that relate to epilepsy and its treatment.

The aim of this study was to measure the potential of global network metrics derived from resting state functional brain networks to capture the impact of epilepsy on the developing brain. Although there is no gold standard to measure these effects, the duration of a patient's disease has been shown to be a meaningful marker of the cumulative burden of epilepsy, particularly with regard to cognitive function (van Iterson et al., 2014). We therefore used the duration of each patient's epilepsy as an index for the overall impact of their disease on the brain.

2. Material and methods

2.1. Study population

This HIPAA-compliant, retrospective study was approved by the local institutional review board. Written informed consent was waived. Consecutive patients were identified from the medical record with the following inclusion criteria: 1. Pediatric age (less-than-or-equal-to 21 years), 2. a clinical diagnosis of focal epilepsy (Berg et al., 2010) by a pediatric epileptologist based on clinical history and seizure semiology, 3. available 3 Tesla MRI of the brain, including a resting state fMRI sequence, 4. Full scale intelligence quotient (IQ) according to an age-appropriate version of the Wechsler Intelligence Test administered by a pediatric neuropsychologist within 3 months of the MRI. Refinements to the above-defined population were planned based on the following exclusions: 1. prior brain surgery.

2.2. Neuropsychological assessment

Intelligence tests were performed by a single pediatric neuropsychologist (MC) with more than 25 year experience using an age-appropriate Wechsler Intelligence Scale test. In each patient, full scale IQ was determined by evaluation of 4 cognitive domains including verbal comprehension, perceptual/fluid reasoning, working memory, and processing speed.

2.3. MR imaging

All imaging was performed on a 3 Tesla magnet (Philips, Achieva Platform, Andover, Massachusetts) equipped with a 32-channel phased array head coil. For structural imaging, a T1-weighted, axial three-dimensional volume acquisition fast field echo was obtained with TR/TE: 7.2/2.9 ms, flip angle: 7°, inversion time: 1100 ms, voxel size: $0.9 \times 0.9 \times 0.9$ mm^3. Functional MRI data were acquired in the resting state using a single-shot echo planar acquisition depicting blood oxygenation level dependent contrast with TR/TE: 2000/30 ms, flip angle: 80°, voxel size: $3 \times 3 \times 3.75$ mm^3. Functional imaging was performed for 10 min, resulting in 300 volumes for each patient. Patients were instructed to lie quietly in the scanner with their eyes closed. All images were visually inspected for artifacts, including susceptibility and subject motion.

2.4. Image processing and analysis

2.4.1. Network node definition

Nodes in the network were defined for each patient according to parcellation of whole-brain gray matter on the structural images. The processing pipeline was implemented using MATLAB scripts (version 7.13, MathWorks, Inc.) in which adapter functions were embedded to execute FreeSurfer reconstruction (version 5.3.0; http://surfer.nmr.mgh.harvard.edu) and several FMRIB Software Library (FSL) suite tools (Smith et al., 2004). First, FreeSurfer reconstruction of cerebral cortical surfaces was performed on the T1 structural image. This processing stream includes motion correction, skull stripping, intensity normalization, segmentation of white matter and gray matter structures, parcellation of the gray matter and white matter boundary, and surface deformation following intensity gradients which optimally place the gray matter/white matter and gray matter/cerebrospinal fluid borders (Fischl et al., 2001; Fischl et al., 2004). The pial and gray white surfaces were visually inspected using the Freeview software for accurate placement.

Next, a self-developed MATLAB program was applied to the FreeSurfer output to further subdivide the 75 standard gray matter parcels according to their surface area. During this process, each parcel was iteratively divided into two new parcels of equal size until the surface area of each parcel (as defined on the FreeSurfer gray-white surface mesh) was less than a 350-mm^2-threshold value. Each surface parcel was then converted into a volume mask of gray matter at that region to form a node on the network. The number of nodes in each patient's network ranged from 511 to 841 (mean: 684; standard deviation: 68).

2.4.2. Network edge definition

The first 5 volumes in each resting state functional data were removed to allow magnetization to reach equilibrium. Preprocessing and independent component analysis (ICA) of the functional data sets was performed using FSL MELODIC (Smith et al., 2004), consisting of motion correction, interleaved slice timing correction, brain extraction, spatial smoothing with a Gaussian kernel full width at half maximum of 5 mm, and high pass temporal filtering equivalent to 100 s (0.01 Hz). Noise related to motion and other physiologic nuisance was addressed according to an ICA technique (Thomas et al., 2002). All non-signal components were removed manually by an expert operator. Motion parameters measured during preprocessing were summarized for each patient as “translation” (the root mean square of the three translational parameters) and “rotation” (root mean square of three rotational parameters). FSL's FLIRT was then used to align the functional image volumes for each patient to that individual's structural T1 dataset using linear registration. Mean BOLD-signal time series were computed for each node. The strength of an edge between two nodes was defined as the absolute value of the Pearson correlation coefficient between their time series.

2.4.3. Construction of the brain functional network

Weighted, undirected graphs were constructed for each patient consisting of the pair-wise correlation between BOLD signal time series over all network nodes. Non-significant correlations were excluded

Table 1
Characteristics of the patient cohort.

Patient characteristics		
Sample size	45 patients	
Gender	26 males; 19 females	
Age	Mean (SD): 12.1 (4.7) years	
Age at epilepsy onset	Mean (SD): 5.1 (4.1) years	
Duration of epilepsy	Mean (SD): 7.1 (5.3) years	
Findings at MRI	Focal cortical dysplasia	14
	Mesial temporal sclerosis	7
	Low-grade tumor	5
	Hypothalamic hamartoma	4
	Tuberous sclerosis complex	3
	Sturge-Weber syndrome	2
	Subependymal gray matter heterotopia	1
	Cavernous malformation	1
	Hypoxic ischemic injury	1
	Rasmussen's encephalitis	1