Research report

Mapping the landscape of cognitive development in children with epilepsy

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ABSTRACT

Objective: Normal childhood development is defined by age-dependent improvement across cognitive abilities, including language, memory, psychomotor speed and executive function. Epilepsy is often associated with a global disruption in cognitive development, however, it is still largely unknown how epilepsy affects the overall organization of overlapping cognitive domains. The aim of the study was to evaluate how childhood epilepsy affects the developmental interrelationships between cognitive domains.

Methods: We performed a comprehensive assessment of neuropsychological function in 127 children with new onset epilepsy and 80 typically developing children matched for age, gender, and socio-demographic status. A cross-correlation matrix between the performances across multiple cognitive tests was used to assess the interrelationship between cognitive modalities for each group (patients and controls). A weighted network composed by the cognitive domains as nodes, and pair-wise domain correlation as links, was assessed using graph theory analyses, with focus on global network structure, network hubs and community structure.

Results: Normally developing children exhibited a cognitive network with well-defined modules, with verbal intelligence, reading and spelling skills occupying a central position in the developing network. Conversely, children with epilepsy demonstrated a less well-organized network with less clear separation between modules, and relative isolation of measures of attention and executive function.

Conclusion: Our findings demonstrate that childhood-onset epilepsy, even within its early course, is associated with an extensive disruption of cognitive neurodevelopmental organization. The approach used in this study may be useful to assess the effectiveness of future interventions aimed at mitigating the cognitive consequences of epilepsy.

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1. Introduction

Normal cognitive development is characterized by the age dependent harmonious improvement across multiple cognitive abilities. There is now considerable agreement that childhood onset epilepsy disrupts this systematic developmental process with adverse impact on executive function (Bell, Lin, Seidenberg, & Hermann, 2011; D'Agati, Cerminara, Casarelli, Pitzianti, & Curatolo, 2012; Seidenberg et al., 1986), academic skills (Berg et al., 2005; Seidenberg et al., 1986), linguistic abilities (Caplan et al., 2008, 2009) and emotional/behavioral status and quality of life (Berg et al., 2008; C. Camfield, Breau, & Camfield, 2003; P. Camfield & Camfield, 2003). However, cognitive domains do not operate in isolation and it remains undefined how epilepsy influences the interactions among different neuropsychological domains.

Recent cognitive training studies support the notion that the interrelationship among domains is crucial for academic success in school-aged children. First, fluid intelligence and problem solving skills can be improved when children engage in working memory exercises (Jaeggi, Buschkuehl, Jonides, & Shah, 2011). Second, training in executive function enhances other domains including language and mathematical skills (Goldin et al., 2014). Therefore, the understanding of the interrelationship among cognitive domains can provide crucial insight on how childhood-onset epilepsy interferes with the global structure of cognitive development. It may also aid in the identification of strategies for future targeted intervention.

In this study, we employed graph theory to investigate the impact of epilepsy on the global cognitive landscape. Graph theory is a mathematical method that has recently been applied to examine brain network structure in epilepsy, revealing global disruption in brain architecture (Bonilha et al., 2013, 2012; Vaessen et al., 2014, 2012). Large-scale structural morphometrical brain changes have been correlated with specific cognitive deficits in epilepsy (Alexander, Concha, Snyder, Beaulieu, & Gross, 2014; Bonilha, Tabesh, et al., 2014). However, to date, there has not been a comprehensive examination of neuropsychological measures, as a cognitive network per se, using graph theory. To our knowledge, this study is the first to use graph theory measures to investigate the cognitive network in children with epilepsy.

We investigated the global cognitive network in a large cohort of children with new-onset epilepsy and healthy controls by examining the inter-correlations of 23 neuropsychological measures. The neuropsychological tests were selected to provide a broad profile of cognitive function, indexing abilities in six discrete cognitive domains: intelligence, academic performance, language, memory, executive function, and psychomotor speed.

We hypothesized that epilepsy may disrupt age-related cognitive development, which is manifested in altered interactions among different cognitive domains. We therefore expected to find a different arrangement of the cognitive network in children with epilepsy compared with healthy controls.

2. Methods

2.1. Subjects

We assessed data from 127 children with epilepsy (mean age: 12.31 years; s.d. = 3.17; girls = 67, boys = 60) and 80 healthy controls (mean age: 12.69 years; s.d. = 3.17; girls = 39, boys = 41) (Table 1). There were no significant differences between the epilepsy and control families in terms of parent intelligence quotient (IQ; Wechsler Abbreviated Scale of Intelligence (WASI), controls: 109.7 ± 12.22, patients: 110.82 ± 15.41, $p = .80$), or parental employment status (full-time, part-time, unemployed; mother's, chi-square = 4.72, $p = .19$; father's, chi-square = 2.68, $p = .44$), indicating similar socioeconomic status between the groups. The educational background was also similar between patients and controls (patient mean grade = 6.2, control mean grade = 6.4, $p = .69$). About 53% of patients with epilepsy and 20% of controls received educational services in the past. All subjects included in this study were enrolled in regular schools.

Inclusion criteria for the patient group were: 1) diagnosis of epilepsy within the past 12 months, 2) no other neurological disorders, 3) normal neurological examinations, and 4) normal clinical imaging results. A board-certified pediatric neurologist (blinded to neuropsychological and interview data) confirmed that all patients had idiopathic epilepsies and provided independent confirmation of syndrome diagnosis. All patients were diagnosed according to the criteria defined by the International League Against Epilepsy (ILAE) (Blume et al., 2001; Engel, 2006). We excluded children with intellectual disability (IQ < 70), autism, and/or other neurological disorders. Specifics regarding the participant selection process have been described in detail in a previous publication (Hermann et al., 2006). In general, we tried to stay true to the concept of "epilepsy only" as defined broadly in the literature: normal neurological exams, average intelligence, and attendance at regular schools.

Healthy controls were age- and gender-comparable first-degree cousins of the epilepsy participants. All controls had no history of seizures, early initial precipitating injuries (e.g., febrile convulsions), other developmental or neurologic disease, or episodes of loss of consciousness. Research approval was obtained from the Institutional Review Board at the University of Wisconsin Medical School. Written informed consent was obtained for all subjects from legal guardians. Parents underwent a clinical interview and completed questionnaires to characterize gestation, delivery, neurodevelopment, and seizure history. All pertinent medical records were obtained after signed release of information was obtained from the parent. Parents were also interviewed through a structured questionnaire about their child's school progress and any specific educational services provided to address academic problems (AP). These services included the traditional individualized educational plan (IEP) as well as early childhood interventions (e.g., speech, physical or occupational therapy), mandatory summer school, grade retention, special tutoring services, and other related services. This interview was conducted blinded to cognitive and behavioral results.

Table 1 – Characteristics of controls and epilepsy participants by subsyndrome (mean and s.d.)[a]

Variable	Healthy controls (n = 80)	Patients (n = 127)
Age (y, s.d.)	12.69 (3.17)	12.31 (3.17)
Sex (number female)	39	67
FSIQ (total, s.d.)	107.65 (12.01)	101.29 (13.61)
Age of seizure onset (y, s.d.)		11.44 (3.25)
Duration (months, s.d.)		8.65 (3.53)
Specific Syndrome		BECT = 31
		BOE = 2
		TLE = 12
		Frontal = 9
		CAE = 10
		JAE = 6
		JME = 32
		IGE NOS = 12
		Focal NOS = 11
		Epilepsy NOS = 2

[a] FSIQ = full-scale intelligence quotient; BECT = benign epilepsy of childhood with centrotemporal spikes; BOE = benign occipital epilepsy; TLE = temporal lobe epilepsy; CAE = childhood absence epilepsy; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy; PGE = primary generalized epilepsy.

2.2. Neuropsychological assessment

A neuropsychological test battery involving 23 different cognitive tests was administered to all subjects, all of which are listed in Table 2. This battery assessed multiple domains including intelligence, academic skills, language, memory, executive function and cognitive/psychomotor speed. The measures listed in Table 2 came from the following tests: WASI (Wechsler, 2003), Peabody Picture Vocabulary Test (PPVT) (Dunn & Hottel, 1961), Expressive Vocabulary Test (EVT) (Williams, 1997), Wide Range Achievement Test-IV (WRAT-IV, 2006), Wechsler Intelligence Scale for Children (WISC-IV) (Wechsler, 2003), Continuous Performance Task (CPT), (Conners, 1992), Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001), and Boston Naming Test (BNT) (Kaplan, Godglass, & Weintraub, 1983).

2.3. Network analysis

In order to define the inter-relationship between cognitive domains, we assessed a network of cognitive functions defined as the correlation matrix between performances on the neuropsychological tests (separately for each group, i.e., patients and controls). Specifically, a correlation coefficient was calculated between each possible pair of tests, resulting in 253 possible test combinations. A correlation table was constructed based on these associations, representing an undirected (i.e., symmetrical along the diagonal) weighted adjacency matrix for each group (patients and controls).

Prior to being submitted to the correlations, all tests were adjusted to reflect a higher score for better performance. After the adjacency matrices were constructed, only positive correlation coefficients were maintained to enable the visual representation of networks and graph theory metric calculations. Thus, the cognitive network was comprised of 23 nodes, each one representing each cognitive test, and weighted links between nodes representing the strength of positive correlation between each pair of nodes.

2.3.1. Visual representation of network structure

In order to appreciate the overall structure of cognitive development in each group, we reconstructed two-dimensional graphs based on the correlation adjacency matrices. The data were exported to the software Gephi (http://gephi.github.io/),

Table 2 – Neuropsychological test battery.

	Abbreviation	Test name	Cognitive ability
1	IQVOCS	WASI Vocabulary	Verbal intelligence
2	IQBDS	WASI Block Design	Nonverbal Intelligence
3	IQSIMS	WASI Similarities	Verbal intelligence
4	IQMRS	WASI Matrix Reasoning	Nonverbal intelligence
5	PPVTSTN	Peabody Picture Vocabulary Test	Language (word recognition)
6	EVTSTN	Expressive Vocabulary Test	Language (word naming)
7	READSTN	WRAT-IV Reading	Word recognition
8	SPELSTN	WRAT-IV Spelling	Spelling
9	ARITSTN	WRAT-IV Arithmetic	Arithmetic calculation
10	IQDSYMS	WISC-IV Digit symbol	Speed
11	WLLSS	Children's Memory Scale-III	Verbal memory
12	WLDSS	Children's Memory Scale-III	Verbal memory
13	CPOMT	Continuous Performance Test-II	Executive function (attention)
14	CPCOMMT	Continuous Performance Test-II	Executive function (attention)
15	CPRTBLKT	Continuous Performance Test-II	Executive function (attention)
16	LETFLUS	D-KEFS Letter Fluency	Language (lexical fluency)
17	CATFLUS	D-KEFS Category Fluency	Language (semantic fluency)
18	CATSWS	D-KEFS	Executive function (category switching)
19	COLSS	D-KEFS Color-Word	Speed
20	WORDSS	D-KEFS Color-Word	Speed
21	INHSS	D-KEFS Inhibition	Executive function (response inhibition)
22	CORSORS	D-KEFS Card Sorting Test	Executive function (problem solving)
23	BNTTOT	Boston Naming Test	Language (naming)

where they were displayed using a Force Atlas algorithm (Jacomy, Venturini, Heymann, & Bastian, 2014) (attraction strength = 10, repulsion strength = 100, gravity = 30). To improve visualization of the network structure, we reconstructed the graphs based on networks containing only the links above the 70% percentile of weight in each group, i.e., links below the 70% percentile were given weight = 0, while the remaining links maintained their original weights. The use of a fixed density threshold based on link weight was chosen in order to preserve the overall network architecture, while preserving only the strongest and more meaningful links (Bonilha, Nesland, Rorden, & Fridriksson, 2014; van Wijk, Stam, & Daffertshofer, 2010; Zalesky et al., 2011).

The community structure of each network was calculated using the software Gephi and each node was coded in accordance with module participation. Nodes within a module are those with a higher strength of inter-relationship, with relative lower relationship with nodes outside the modules.

2.3.2. Global network parameters

Graph theory metrics were employed to evaluate global network properties. These calculations were performed using the Brain Connectivity Toolbox within the software MATLAB (Rubinov & Sporns, 2010). For each group, we assessed network small worldness by evaluating the relation between the normalized whole-network clustering coefficient and the normalized whole-network characteristic path length, as described by Brown et al., (2011). The normalized whole-network clustering coefficient was defined as the ratio between the clustering coefficient of the observed network and the average clustering coefficient from 100 random networks; similarly, the normalized whole-network characteristic path length was defined as the ratio between the path-length of the observed network and the average path-length from 100 random networks.

Other global network measures such as mean network clustering coefficient, mean betweenness centrality, mean degree and mean network efficiency were calculated. In order to enable a quantitative assessment of each metric per group, we assessed the distribution of node-wise correlation by calculating an adjacency matrix from cognitive data where the values were resampled with replacement (i.e., bootstrapped). This was repeated 1000 times, yielding 1000 adjacency matrices per group. For consistency, only positive entries were maintained.

Global network metrics were assessed for each bootstrapped matrix in each group, and differences in dispersion across groups were calculated employing t-tests.

2.3.3. Local network parameters

To investigate the participation of nodes within the same community structure, we calculated the network modularity using a well-defined stochastic test of modularity (Rubinov & Sporns, 2010). With this approach, module classification may vary slightly between calculations due to the variations in the probability distributions of local and global minima. This approach confers the advantage of enabling the frequency with which nodes are classified as belonging to the same module. Thus, after repeating the calculation of modularity 1000 times for each group, we calculated the frequency of co-association of nodes within a module (irrespective of the module label). For example, 2 nodes could have been placed in the same module 90% of the times in patients, but only 20% in controls. These frequencies were compared using a series of Chi-squared tests to evaluate differences in link-wise associations in patients versus controls.

For all quantitative analyses, the level of statistical significant was set of $p < .05$ adjusted for multiple comparisons utilizing Bonferroni correction.

3. Results

3.1. Visual representation of network structure

The adjacency matrices representing the cross-correlations between tests are demonstrated in Fig. 1.

The two-dimensional graphs illustrating the structure of the cognitive network for each group is demonstrated in Fig. 2.

From a qualitative perspective, there were remarkable differences in network arrangement between groups. While controls demonstrated an organized separation between functional modules, patients exhibited a poorly organized pattern, with significant overlap between multiple modalities.

In controls, there was a clear separation between modules composed mostly of executive function tests, verbal and arithmetic performance, memory and attention. Non-verbal intelligence served as the interface between verbal performance and executive function modules, while speed and response inhibition represented the interface between executive function and verbal skills. Interesting, reading and writing abilities were central in the cognitive structure of normally developing children.

Among children with epilepsy, a poor separation between modules was observed, with multiple domains being represented in the same module, indicating a higher degree of co-dependence between variable functions. Measures of attention and executive function were relatively peripheral to the network, possibly suggesting an immature pattern of development.

Children with new onset epilepsy exhibited a significantly higher rate of academic problems (AP) compared to healthy controls. AP was defined in the broad sense of requiring ancillary educational services to address school based struggles (e.g., IEP, school based tutoring, summer school). 53% of children with epilepsy exhibited AP, while 20% of controls exhibited AP. We did not observe a significant qualitative interaction between AP and epilepsy on the conformation of the cognitive networks, indicating that the diagnosis of epilepsy, whether concurrent or not with AP, was the most important determinant of the arrangement of the cognitive network conformation.

3.2. Global network metrics

We observed a mildly reduced normalized measure of small-worldness in the cognitive network of patients, compared with controls (1.003 vs 1.004).

Overall, global network metrics were different in patients compared with controls. These are demonstrated in Fig. 3. Children with epilepsy demonstrated an increase in average
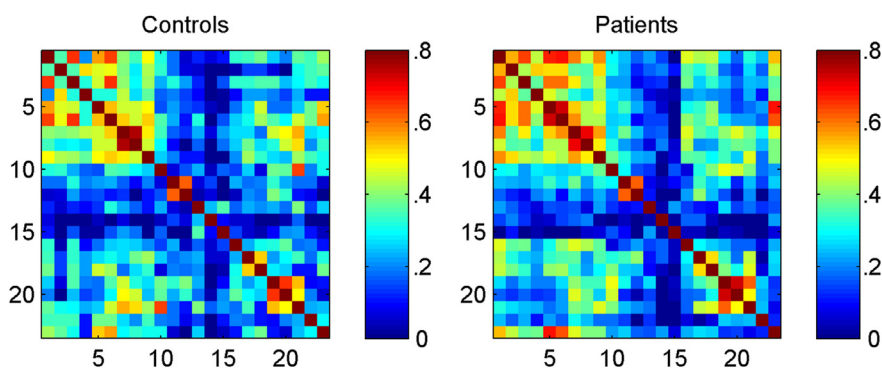
Fig. 1 – Adjacency matrices demonstrating the cross-correlations between scores in neuropsychological tests for controls and patients. Neuropsychological tests are numbered in accordance with Table 2.

clustering coefficient (controls = .28 ± .04, patients = .29 ± .03), degree (controls = 20.6 ± 1.0, patients = 21.4 ± .6) and efficiency (controls = .30 ± .03, patients = .31 ± .02), while average betweenness centrality was reduced in patients (controls = 32.6 ± 5.9, patients = 31.2 ± 5.6). These results indicate that children with epilepsy exhibited a network less organized into a well-segregated structure.

3.3. Local network metrics

We observed a significant rearrangement of nodal participation in community structure across groups. Statistical results comparing nodal modularity co-occurrence matrices are demonstrated in Supplementary Fig. 1. As expected from the visual demonstration of network structures shown in Fig. 1,
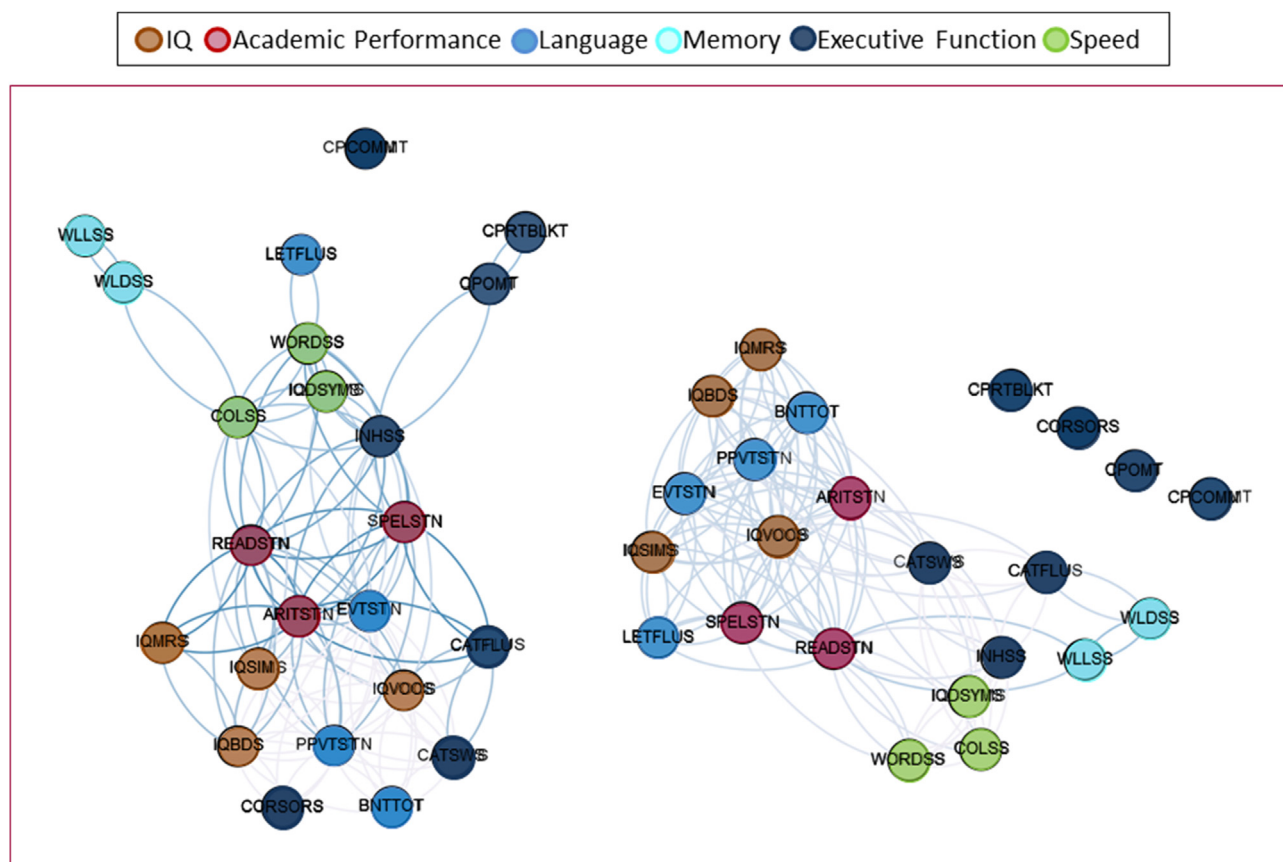

Fig. 2 – This two-dimensional graph representation illustrates the cognitive networks representing the spatial relationship between cognitive tests. The spatial distribution of nodes was calculated using a force–atlas graph algorithm, where nodes that demonstrated stronger connections are located closer in space, whilst nodes with fewer connections tend to drift away. Nodes with a similar color belong to the same module, whereas each module is composed of nodes with the highest association (i.e., connectivity strength) between in-module nodes, and the lowest association with nodes outside the module.
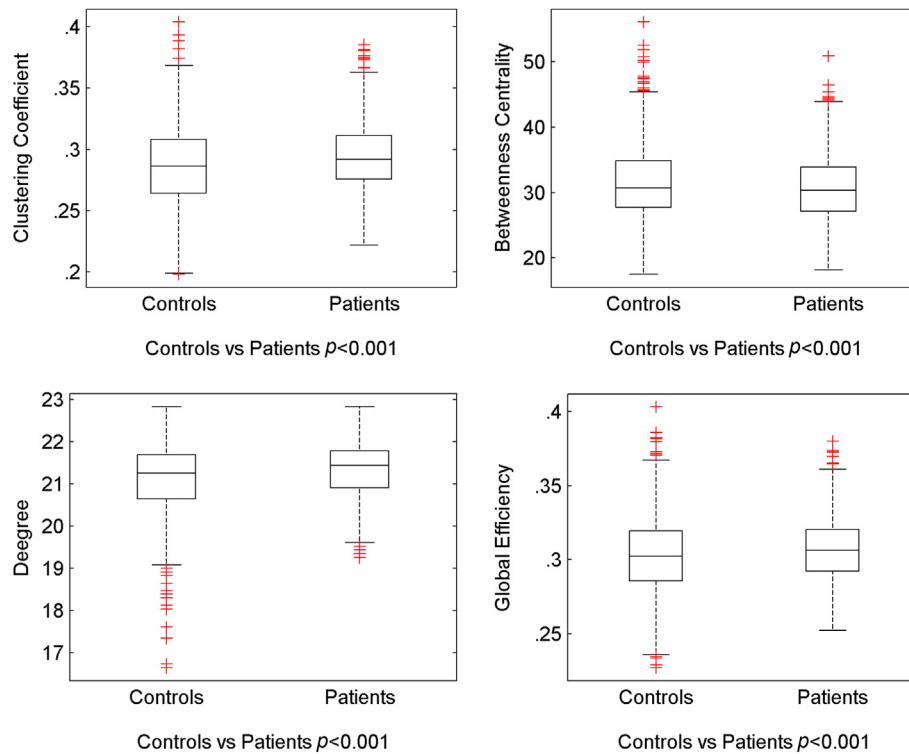
Fig. 3 − **Box-whisker plots demonstrating global network measures. Average clustering coefficient, degree and efficiency were increased in patients, while average betweenness centrality was reduced in patients.**

several tests associations were different in patients compared with controls. A comprehensive list of significant changes in associations is presented in Supplementary Table 1. Overall, it is possible to note a pattern of changes indicating that patients exhibited a higher association between non-verbal intelligence with other tests, while a relative decrement of associations between verbal skills and other modalities.

4.   Discussion

In this study, we employed graph theory to chart the structure of the cognitive network across multiple neuropsychological domains in children with new-onset epilepsy compared to normally developing children. To our knowledge, this study is the first to use graph theory measures to investigate the cognitive network in children with epilepsy.

There were two main findings. First, children with epilepsy, compared to healthy controls, demonstrated a less well-organized network with poorly separated modules. Moreover, measures of attention and executive function were isolated from other modules. Second, the less demarcated modularity arrangement was also reflected by global network measures. Specifically, the cognitive networks of children with epilepsy were organized into a less well-segregated architecture with higher cluster coefficient, greater degree connectivity, and shorter path length.

Whereas numerous studies have documented the impact of epilepsy on cognition, our study stands out from the traditional pediatric cognitive literature. Instead of focusing

on general intelligence or multiple domain specific deficits, which, when simultaneously examined, can be confounded by multiple comparisons (i.e., type 1) errors [for a review see (Lin, Mula, & Hermann, 2012)], we characterized the cognitive network organization in its entirety using graph theory (Fair, Bathula, Nikolas, & Nigg, 2012). Using community detection methods, we demarcated the internal network organization and found important distinctions between children with epilepsy and healthy controls. Compared to controls, children with epilepsy demonstrated less distinct separation among the modules and greater dependency among cognitive domains. Whereas higher-level skills such as reading, arithmetic, and spelling were central to the modular organization of healthy controls, these academic skills were intermixed among other cognitive abilities in children with epilepsy. Importantly, speed and executive function were not well integrated and placed conspicuously peripheral in the network of children with epilepsy. The lack of interaction of processing speed and attention into the other cognitive domains in the epilepsy group might support the consistent findings in the literature of impaired attention and processing speed in these children (Austin et al., 2001, 2010; Helmstaedter & Witt, 2012; Semrud-Clikeman & Wical, 1999).

Academic skills are uniquely complex and require integration of other cognitive abilities including general intelligence, speed, and executive function (Rohde, 2007). Specific learning disorders, such as those affecting reading, writing or mathematical skills, are more frequently impaired in people with epilepsy than in the general population, even in children with normal intelligence (Sillanpaa, 1992). This poor relationship

between executive function and academic skills exhibited in children with epilepsy provides potentially important insights into the underlying mechanism of poor academic performance. Indeed, attention deficit hyperactive disorder (ADHD) is significantly overrepresented in children at the time of diagnosis of epilepsy compared to controls (Hermann et al., 2007).

Further, patients compared to controls exhibited a higher association between non-verbal intelligence with other tests, while a relative decrement of associations between verbal skills and other modalities. The association with nonverbal tests, albeit only few of these were included in the study, might suggest a compensatory mechanism for the poor verbal related functioning.

In summary, children with epilepsy exhibited a pattern of suboptimal network arrangement with greater inter-relationship among most of the cognitive domains but fragmented from executive function.

Global network measures also highlighted the greater inter-reliance among cognitive domains in children with epilepsy. Overall, the network architecture in epilepsy exhibited reduced small-worldness, suggesting less optimal balance between local connectivity and global integration. Further, it showed greater average degree of connectivity among the cognitive domains and increased network segregation as indicated by augmented cluster coefficient.

The altered cognitive landscape in epilepsy may represent a compensatory process, the underlying abnormality, or a combination of the two effects.

5. Limitations and considerations

In spite of its success, a few conceptual limitations of this study should be considered. Although our sample was not balanced between children with epilepsy and controls, our sample size in general was quite high. We also want to note that our sample did not differ significantly in age, education or parental education and employment status. We did not present specific information about those subjects experiencing AP as defined in this investigation, a factor that one might suspect to drive findings in the epilepsy group, being more common in the epilepsy than control group (53% *vs* 20%). We did inquire into the impact of this concept on the obtained findings and there was not a significant qualitative interaction between AP and epilepsy on the conformation of the cognitive networks, indicating that the diagnosis of epilepsy, whether concurrent or not with AP, was the most important determinant of the arrangement of the cognitive network.

Finally, most existing neuropsychological tests require verbal and language skills, even if the test does target these domains. Our findings were predominantly related to the differential influence of language domains between groups. Therefore, they should be interpreted in the context of the neuropsychological tests that were utilized.

6. Conclusion

The current approach provides new insights regarding the impact of epilepsy on cognition and the response of the cognitive systems to epilepsy. Characterization of network perturbations might serve as the basis for the assessment of specific effects associated with epilepsy phenotypes, or to evaluate future therapies designed to mitigate the neuropsychological effects of epilepsy. Whereas childhood onset epilepsy influences diverse cognitive abilities, current therapy has focused on domain specific cognitive rehabilitation such as memory and attention. Overall, these treatment approaches have produced mixed results and why only some children improve is unclear. Understanding the inter-relationship between cognitive domains will improving our understanding of how performances in one domain may influence abilities in other domains. Such insights derived from this study will allow the development of rationale cognitive rehabilitation in individuals with epilepsy and hopefully intervene at early in the course of epilepsy.

Disclosure

Acknowledgments

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cortex.2015.02.001.

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