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Review

Rethinking cognition and behavior in the new classification for childhood epilepsy: Examples from frontal lobe and temporal lobe epilepsies

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ABSTRACT

The new approach to classification of the epilepsies emphasizes the role of dysfunction in networks in defining types of epilepsies. This paper reviews the structural and neuropsychological deficits in two types of childhood epilepsy: frontal lobe and temporal lobe epilepsy. The evidence for and against a pattern of specificity of deficits in executive function and memory associated with these two types of epilepsies is presented. The evidence varies with the methodologies used in the studies, but direct comparison of the two types of epilepsies does not suggest a clear-cut mapping of function onto structure. These findings are discussed in light of the concept of network dysfunction. The evidence supports the conceptualization of epilepsy as a network disease. Implications for future work in the neuropsychology of pediatric epilepsy are suggested.

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1. Introduction

Wilson and Baxendale [1] have elegantly laid out the implications for the field of neuropsychology of the impact of the recent ILAE report on the new way of classifying the epilepsies [2]. The new classification system reconceptualizes seizures as arising from dysfunction in cortical and/or subcortical networks; the dysfunction may be focal (arising from a network in one hemisphere) or generalized (arising from or rapidly involving networks that are bilateral). The present paper provides a selective review of the literature on two types of epilepsy in children that fell within the former classification system as localization-related, partial epilepsies: frontal lobe epilepsy (FLE) and temporal lobe epilepsy (TLE). This review examines whether the neuropsychological profiles of these two subtypes are consistent with the previous strictly localization model or whether such profiles are better accounted for under the network approach. It concludes with some speculations on future directions for understanding the neuropsychology of pediatric epilepsy.

One way to examine the construct of childhood epilepsy as a network disease is to identify whether the abnormalities are specific to an anatomic region associated with site of seizure onset. If such abnormalities are specific to what would be expected with dysfunction confined to that site, then a localized classification may seem appropriate. If the underlying abnormalities extend beyond what is conceptualized to be associated with that site, then it is clear that the localization approach is limited, and the concept of networks may be applicable. This analysis can be taken at a structural and at a neuropsychological level.

2. Evidence from structural and functional neuroimaging

2.1. Frontal lobe epilepsy

FLE can be characterized by a rapid spread of seizure activity as a result of the extensive network of connections between the frontal lobe and other cortical and subcortical areas [3]. The impact of this dense connectivity has been demonstrated in studies on brain structure. Measures of cortical thickness have yielded a picture of widespread effects extending beyond the frontal lobe, affecting not only the hemisphere ipsilateral to the seizure focus but also the contralateral hemisphere. For example, Widjaja et al. [4] found that children with left FLE had cortical thinning in the left superior frontal, paracentral, precuneus, cingulate, inferior parietal, supramarginal, postcentral, and superior temporal gyri and in the right superior and middle frontal, medial orbitofrontal, supramarginal, postcentral, banks of superior temporal sulcus, and parahippocampal gyri. Children with right FLE had similarly widespread thinning affecting both hemispheres; in the right hemisphere, the precentral and postcentral, transverse temporal, parahippocampal,

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lingual, and lateral occipital gyri were affected, and in the left hemisphere, significant thinning was present in the superior frontal, inferior parietal, postcentral, superior temporal, posterior cingulate, and lingual gyri. Thus, irrespective of the laterality of seizure onset, widespread thinning was evident in both hemispheres and throughout wide areas of the cortex.

The findings on cortical thinning in FLE, suggesting widespread abnormalities beyond the frontal lobe, have been extended to measures of white matter integrity, using diffusion tensor imaging. As indicated earlier [3], FLE in children can affect pathways beyond the frontal lobes. Interictal discharges may be present bilaterally, and children with FLE are more likely to have secondarily generalized seizures than are children with TLE [5,6]. Children with FLE have been found to have reductions in fractional anisotropy, representing a disruption of axonal or myelin integrity, in the superior longitudinal fasciculi, in the right forceps minor, and in the corpus callosum; there were no differences between left and right onset FLE or between white matter tracts ipsilateral and contralateral to the seizure focus [7]. The authors speculated that the white matter abnormalities could have been due either to seizure activity or to potential abnormalities in the development of gray and white matter predating the onset of epilepsy.

Studies such as those reviewed above have established the presence of abnormalities in the structure of gray and white matter extending beyond the frontal lobe identified as the epileptogenic focus even in children in whom there is no identifiable structural lesion on MRI. As well, neuroimaging studies have examined brain connectivity at a functional level, with some research examining resting state networks and others examining the functional activation patterns elicited by performance on specific cognitive tasks.

Resting state networks are thought to represent intrinsic functional connections in discrete neuroanatomical systems [8]. In a study of resting state networks in children with FLE, six such networks could be identified: default mode, frontal, attention, sensorimotor, auditory, and visual [9]. Of these, reduced connectivity relative to healthy controls was observed in the frontal network, and in the other five networks, both reduced connectivity and increased functional connectivity were observed. The participants were administered a battery of neuropsychological tests, and the children with FLE were impaired on executive function, fine motor skills, and attention. Reduced connectivity in the right superior frontal gyrus of the frontal network was related to executive function, and fine motor performance was associated with reduced connectivity in the right paracentral lobule of the sensorimotor network. However, attention scores were not related to regions of abnormal connectivity in either the default mode network or the attention network. Atypical functional connectivity between networks was also demonstrated. Relative to controls, the patients showed not only reduced functional network connectivity between default mode network–attention, frontal–sensorimotor, and frontal–visual but also increased functional connectivity between frontal–attention, default mode network–sensorimotor, and frontal–visual. The reduction in functional connectivity was thought to represent network dysfunction, whereas increased connectivity presumably represents a mechanism of compensatory reorganization.

A different approach to understanding the functional properties of the brain in children with FLE was undertaken through brain connectivity analysis of the functional activation patterns derived from fMRI during performance of a verbal working memory task [10]. Relative to healthy controls, the group with FLE had reduced functional connectivity throughout the brain, with differences being most marked in the right superior parietal lobe, the thalami, the anterior cingulate cortex, and the right hippocampus. The decrease in functional connectivity was apparently not secondary to general cognitive impairment per se, as it was present in children with and without evidence for cognitive deficits. The authors suggested that the widespread set of connections marked by decreased functional connectivity could explain the large number of cognitive and behavioral deficits that have been described in children with FLE.

2.2. Temporal lobe epilepsy

In TLE, gray and white matter abnormities have also been detected, even in children with MRI-negative scans. Analyses using DTI and diffusion kurtosis imaging of gray and white matter in children with TLE and normal MRI scans found evidence of abnormalities in both the ipsilateral and contralateral temporal lobes [11,12]. A study using voxel-based morphometry [13] demonstrated a reduction of gray matter in the ipsilateral hippocampus and the parahippocampal gyrus in children with TLE. In the subset with mesial TLE, there was significant atrophy not only in the ipsilateral hippocampus but also in the ipsilateral cingulate gyrus and in the contralateral middle frontal lobe. Together, the results from these studies suggest that the pathogenesis of TLE involves a network of structures extending beyond the area of the lobe of seizure onset.

3. Evidence from neuropsychological studies

Are the neuropsychological features of FLE and TLE specific to the localization of the site of seizure onset? This question is addressed by a review of studies on the neuropsychological features of these two types of epilepsy, with particular attention paid to studies that have included both types. Most of the research has investigated executive function skills, thought to be subserved by the frontal lobes, and memory, thought to be a function of the temporal lobe. Table 1 shows the sample sizes and ages of children included in the studies reviewed in the following sections.

3.1. Executive function in children with FLE

Some of the early publications on the neuropsychology of pediatric FLE were case studies. One described a teenager with bilateral frontal foci who experienced a transitory “frontal lobe syndrome” during the

Table 1
Sample sizes and ages of children included in the studies reviewed in Section 3.

	Frontal lobe epilepsy			Temporal lobe epilepsy		
Reference	N	Mean age (years)	Range	N	Mean age (years)	Range
Boone et al. [14]	1	13		n/a[a]		
Roulet-Perez et al. [15]	4	6.13	3–8	n/a		
Jambaque et al. [16]	1	8		n/a		
Luton et al. [17]	20	12.4	8–18	n/a		
Riva et al. [18]	17	10.27	6.25–13.92	n/a		
Sinclair et al. [19]	15	11.3	6–16	n/a		
Longo et al. [20]	19	11.63	8–17	47	13.91	8–18
Prevost et al. [21]	21	n/r[b]		n/a		
Cohen [23]	n/a			24	11.21	6–16.3
Jambaque et al. [24]	n/a			28	n/r	7–14
Gonzalez et al. [25]	n/a			43	12.06	5–16
Nolan et al. [26]	25	12.8	n/r	32	12.5	n/r
Smith & Lah [27]	n/a			66	13.55	5.17–18.17
Rzezak et al. [28]	n/a			19	14.46	8–16
Hershey et al. [29]	n/a			28	11.20	7–16
Gascoigne et al. [30]	n/a			23	12.5	n/r
Oitment et al. [31]	n/a			41	n/r	6–18
Gonzalez et al. [32]	n/a			44	12.23	6–16
Gascoigne et al. [33]	n/a			21	12.16	6–16
Lendt et al. [34]	12	11.3	7–15	12	11.8	8–15
Hernandez et al. [35]	16	11.34	7.11–15.11	8	12.44	8.5–16.1
Hernandez et al. [36]	16	11.34	7.11–15.11	8	12.44	8.5–16.1
Culhane-Shelburne et al. [37]	12	13.0	8–12	15	11.7	9–17
Auclair et al. [38]	8	11.8	8.3–15.5	10	13.3	11.0–15.9
Fuentes & Smith [39]	27	12.41	8–17	100	13.25	5–18
Jocic-Jakubi & Jovic [40]	n/a			36	n/r	7–16

[a] n/a: no patients within this group included in study.
[b] n/r: data not reported in paper.