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Review

Imaging and genetics of language and cognition in pediatric epilepsy

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ABSTRACT

This paper presents translational aspects of imaging and genetic studies of language and cognition in children with epilepsy of average intelligence. It also discusses current unanswered translational questions in each of these research areas. A brief review of multimodal imaging and language study findings shows that abnormal structure and function, as well as plasticity and reorganization in language-related cortical regions, are found both in children with epilepsy with normal language skills and in those with linguistic deficits. The review on cognition highlights that multiple domains of impaired cognition and abnormalities in brain structure and/or connectivity are evident early on in childhood epilepsy and might be specific for epilepsy syndrome. The description of state-of-the-art genetic analyses that can be used to explain the convergence of language impairment and Rolandic epilepsy includes a discussion of the methodological difficulties involved in these analyses. Two junior researchers describe how their current and planned studies address some of the unanswered translational questions regarding cognition and imaging and the genetic analysis of speech sound disorder, reading, and centrotemporal spikes in Rolandic epilepsy.

This article is part of a Special Issue entitled "The Future of Translational Epilepsy Research".

1. Introduction

The integration of language and cognition matures by the end of adolescence and reflects age-related changes in cortical association areas and language-related brain regions and pathways [1]. The wide range of linguistic [2], cognitive/academic [3], and related social and psychiatric comorbidities (See review in [4]) in children with epilepsy with average intelligence implies impairment in these higher-level linguistic/cognitive skills and their associated brain regions and neural pathways. Therefore, biomarkers of these deficits could promote early identification and treatment of children with epilepsy at risk for language impairment.

From a translational perspective, there currently are no animal models of language and its impairments and no biological tests for risk of language impairment or other epilepsy comorbidities. In addition, models of cognitive abnormalities in animals with seizures cannot tap into the higher-level integration of language and cognition that enable children to function adequately across multiple domains. However, studies using multimodal imaging of the brain and genetics provide a window into the brain–behavior relationships involving language and cognition.

This paper briefly reviews current trends in the translational research of language, cognition, and the genetics of speech and language in pediatric epilepsy and identifies unanswered translational questions. Two junior researchers describe how their current and planned studies address some of the unanswered translational questions regarding cognition and imaging (Dr. Lin) and genetic analysis of speech sound disorder, reading, and centrotemporal spikes in Rolandic epilepsy (Dr. Addis).

2. Language and imaging in pediatric epilepsy

2.1. Rochelle Caplan, M.D.

2.1.1. State of the art

2.1.1.1. Language, development, and pediatric epilepsy. During the complex growth in thought, cognitive flexibility, and integration of knowledge with language in childhood and adolescence, there is an increase in syntactic complexity [5], advanced use of grammar and vocabulary, as well as abstraction [6–8]. The parallel ongoing and protracted development of fronto-temporal language-related regions (e.g., superior temporal gyrus, Heschl's gyrus, and inferior frontal gyrus) and pathways [9] (Fig. 1) increases their vulnerability to the effects of ongoing seizures [10].

Thus, particularly in older children with epilepsy, seizure variables are associated with impaired basic linguistic skills (e.g., syntax, semantics,

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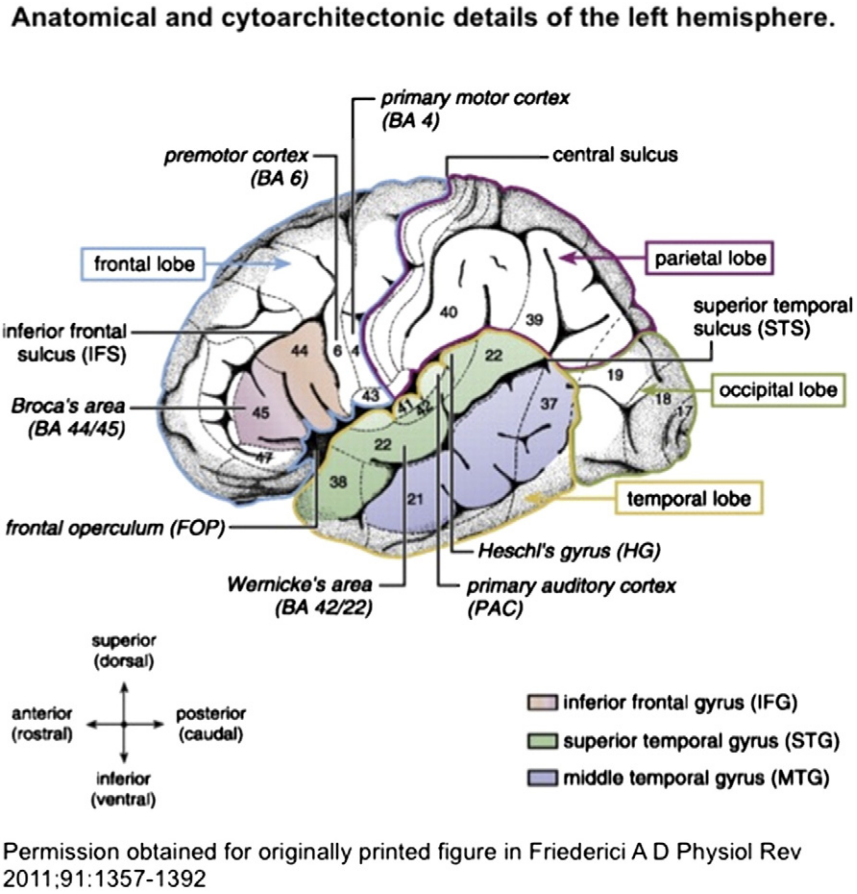

Fig. 1. Anatomical and cytoarchitectonic details of the left hemisphere. The different lobes (frontal, temporal, parietal, and occipital) are marked by colored borders. Major language relevant gyri (IFG, STG, MTG) are color coded. Numbers indicate language-relevant Brodmann Areas (BA) which Brodmann (1909) defined on the basis of cytoarchitectonic characteristics. The coordinate labels superior/inferior indicate the position of the gyrus within a lobe (e.g., superior temporal gyrus) or within a BA (e.g., superior BA 44; the superior/inferior dimension is also labeled dorsal/ventral). The coordinate labels anterior/posterior indicate the position within a gyrus (e.g., anterior superior temporal gyrus; the anterior/posterior dimension is also labeled rostral/caudal). Broca's area consists of the pars opercularis (BA 44) and the pars triangularis (BA 45). Located anterior to Broca's area is the pars orbitalis (BA 47). The frontal operculum (FOP) is located ventrally and more medially to BA 44 and BA 45. The premotor cortex is located in BA 6. Wernicke's area is defined as BA 42 and BA 22. The primary auditory cortex (PAC) and Heschl's gyrus (HG) are located in a lateral to medial orientation.

and phonetics) [2,11–15] and higher-level discourse skills (i.e., use of language to formulate and organize thoughts into coherent speech) [16]. However, evidence for linguistic deficits in children with new-onset seizures [13,17] and their continuation over time irrespective of seizure control in children with chronic epilepsy [18], together with impaired phonological awareness in benign Rolandic epilepsy (RE) (a disorder associated with few lifetime seizures) [14], also imply a role for the neuropathology underlying epilepsy. The findings of the few imaging studies conducted to date on language in children with epilepsy with average intelligence might reflect combined effects of the underlying neuropathology, ongoing seizures, or both factors on plasticity in these brain regions.

2.1.1.2. Structural imaging studies

2.1.1.2.1. Normal brain development. Gray matter volume and cortical thickness increase during childhood, peak at about puberty, and gradually decrease during adolescence (See reviews in [19] and [20]). These morphometric changes progress in an antero-posterior direction first involving the sensory-motor cortex and then secondary and multimodal cortical brain regions (See review in [20]). The frontal and temporal lobes, particularly the language-related superior temporal gyrus, are the last brain regions to undergo these maturational changes. Synaptic remodeling (pruning) with reduction in the number of synapses, neuropil, and number of glial cells and experience-dependent molding of the architecture of cortical columns along with dendritic spine and axonal remodeling underlie these developmental changes in gray matter volume and thickness [20–23]. G proteins, such as the G protein-coupled receptor, the super conserved receptor expressed in the brain (SREB2), play a prominent role in plasticity, neural integrity, and cortical thickness [24,25].

Although white matter volume also increases markedly in the first few years of life, in contrast to gray matter, it expands linearly and simultaneously in the parietal, frontal, and temporal lobes from the onset of puberty and continues into adulthood (See review in [26]). Myelination brings about the increase in white matter and the relative decrease in gray matter [23,27].

In addition to age, twin studies have identified the role of heritability in the gray matter density of the (pre-) frontal and temporal areas [28] and in the cortical thickness of the left middle and inferior frontal gyri, lateral fronto-orbital and occipitotemporal gyri, pars opercularis, planum temporale, precentral, and parahippocampal gyri as well as the medial region of the primary somatosensory cortex [29]. In 9- and 12-year-old twins, cortical thinning is also highly heritable in both Broca's and Wernicke's areas [30]. However, heritability for later developing brain structures involved in language and executive function is higher in adolescence than in childhood [31]. Although white matter density is highly heritable in fronto-occipital and superior longitudinal fascicles [28], this is not the case for the age-related growth in white matter [26].