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Note

Atypical language laterality is associated with large-scale disruption of network integration in children with intractable focal epilepsy

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ABSTRACT

Epilepsy is associated with disruption of integration in distributed networks, together with altered localization for functions such as expressive language. The relation between atypical network connectivity and altered localization is unknown. In the current study we tested whether atypical expressive language laterality was associated with the alteration of large-scale network integration in children with medically-intractable localization-related epilepsy (LRE). Twenty-three right-handed children (age range 8–17) with medically-intractable LRE performed a verb generation task in fMRI. Language network activation was identified and the Laterality index (LI) was calculated within the pars triangularis and pars opercularis. Resting-state data from the same cohort were subjected to independent component analysis. Dual regression was used to identify associations between resting-state integration and LI values. Higher positive values of the LI, indicating typical language localization were associated with stronger functional integration of various networks including the default mode network (DMN). The normally symmetric resting-state networks showed a pattern of lateralized connectivity mirroring that of language function. The association between atypical language localization and network integration implies a widespread disruption of neural network development. These findings may inform the interpretation of localization studies by providing novel insights into reorganization of neural networks in epilepsy.

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1. Introduction

A unifying framework in the understanding of functional brain networks is the notion of simultaneous segregation and integration (Sporns, Tononi, & Edelman, 2000; Tononi, Sporns, & Edelman, 1994). Segregation in brain networks allows for the localization of function, the tendency of neurons to be organized into populations representing common responses. This is evident from findings where lesions in particular cortical areas result in specific deficits. A classic example of this is that lesions of the left inferior frontal gyrus are known to produce expressive aphasia, as this region is strongly specialized for expressive language function. Conversely, integration relates to communication among specialized neural elements, which permits complex cognitive and behavioral experiences. Segregation is often tested in neuroimaging studies by measuring activation in focal responses to a specific task or stimulus, whereas integration may be interrogated through functional connectivity analyses.

Epilepsy is a network disorder associated with deficits in both neural segregation and integration. Language localization in epilepsy is a classic example of dysfunctional network segregation. Approximately 20–30% of children with epilepsy demonstrate atypical (bilateral- or right-lateralized) language representation, compared with only 5% of strongly right-handed healthy volunteers (Berl et al., 2014; Knecht et al., 2000; Springer et al., 1999). Similarly, an increasing number of functional connectivity studies have identified deficits in the integration of spontaneous oscillatory networks (known as intrinsic connectivity networks, or resting-state networks) in children with epilepsy (Ibrahim et al., 2014).

Intrinsic connectivity networks reflect hierarchically organized brain processes at rest and include primary input–output networks, such as the visual, sensorimotor and auditory networks, as well as higher integrative networks, including language, attention and salience networks, as well as the default mode network [DMN; see Zhang and Raichle for review (Zhang & Raichle, 2010)]. The cognitive functions served by these networks is reflected by the nodes or brain regions that demonstrate connectivity at rest. The DMN for instance is composed of the posterior cingulate, a highly anatomically connected hub region that forms a structural core within large-scale brain networks (Hagmann et al., 2008), as well as the ventromedial prefrontal cortex (vmPFC), which overlaps with brain regions that are activated during self-reflective thoughts and judgments that depend on inferred social and emotional context (Gusnard, Akbudak, Shulman, & Raichle, 2001). The salience network, which is preferentially activated by behaviorally-salient stimuli, consists of the dorsal anterior cingulate cortex (ACC) and bilateral insulae (Seeley et al., 2007). This network, which is important for the initiation of cognitive control, is thought to be driven the right insula (a "cortical outflow hub"), which provides an early cognitive control signal (Ham, Leff, de Boissezon, Joffe, & Sharp, 2013). The salience network is activated by conditions, which require a change in behavior, particularly errors and signals the need for behavior adaptation (Carter et al., 1998).

An understanding of the network correlates of atypical language localization would also greatly enhance clinical interpretation of language fMRI and the long-term follow-up of patients with atypical language patterns. At present, it is unclear why atypical functional localization occurs in children with epilepsy. Previous studies have reported that early seizure onset and brain injury are associated with atypical language representation (Rasmussen & Milner, 1977; Springer et al., 1999). Given that a shift towards more specific localization of function in circumscribed cortical regions occurs with development, these data support the notion that atypical language segregation represents a disruption in normative network development (Kadis et al., 2011). Contrary to this assertion, however, children with atypical language segregation do not uniformly demonstrate measurable difficulties with language processing or more global cognitive outcomes, although differences of up to 37 Intelligence Quotient points have been reported between different language activation patterns (Berl et al., 2014). Impairments in intrinsic connectivity networks, associated with atypical language laterality may explain reports of abnormal cognitive function in children with atypical language patterns. To better characterize the neural mechanisms of atypical language localization in children with epilepsy, we tested the hypothesis that atypical functional segregation is associated with disruption of oscillatory integration in distributed networks.

2. Methods

2.1. Study population and data acquisition

Twenty-three right-handed, English-speaking children aged 7–17 years with localization related-epilepsy were recruited into the study at the Hospital for Children, Toronto, Canada (see Table 1 for complete demographics). Structural T1 and fMRI data were obtained (3T Phillips Achieva scanner with 8 channel coil, resolution: 80 × 80, voxel size: 2.875 mm × 2.875 mm × 4 mm, 32 slices, TR/TE: 2000/30 msec, flip angle: 90°, number of TRs: 180). Both task- and resting-state fMRI were acquired. The task-based fMRI was a 6-min verb generation block-design experiment, with alternating 30 sec blocks of language and motor tasks presented via MRI-compatible goggles (Benson et al., 1999). The verb generation task involves the presentation of nouns and subjects are asked to generate a semantically-appropriate associated verb (e.g., ball/"kick"). This paradigm is widely used in neuroimaging studies to explore the retrieval of semantic information. Six minutes of continuous resting-state fMRI data were also collected, during which subjects were fixating on a gray cross inside a gray circle.

Functional data were preprocessed using standard AFNI and FMRIB Software Library (FSL) tools. Slice-timing and motion correction were performed before aligning the data to the MNI152 2 mm atlas via the subject's high-resolution anatomical T1-weighted images. All subjects had maximum head displacement from median head position of less than 2 mm on both scans. Data were smoothed using a 6.6 mm FWHM Gaussian kernel and were bandpass filtered at .01 Hz–.2 Hz for the resting-state scan. Mean signals from white matter and cerebrospinal fluid, in addition to a motion signal generated from maximum displacement motion estimates and the