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Regional brain volumes and cognition in childhood epilepsy: Does size really matter?

Frank A. Zelko[a,b,*], Heath R. Pardoe[c,d], Sarah R. Blackstone[e], Graeme D. Jackson[c,f], Anne T. Berg[g,h]

[a] *Department of Child and Adolescent Psychiatry, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, United States*
[b] *Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, United States*
[c] *Florey Institute of Neuroscience and Mental Health, Melbourne, Australia*
[d] *New York University School of Medicine, New York, NY, United States*
[e] *Department of Public Health, Northern Illinois University, DeKalb, IL, United States*
[f] *Department of Medicine, University of Melbourne, Parkville, Victoria, Australia*
[g] *Epilepsy Center, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, United States*
[h] *Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, United States*

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Summary
Purpose: Recent studies have correlated neurocognitive function and regional brain volumes in children with epilepsy. We tested whether brain volume differences between children with and without epilepsy explained differences in neurocognitive function.
Methods: The study sample included 108 individuals with uncomplicated non-syndromic epilepsy (NSE) and 36 healthy age- and gender-matched controls. Participants received a standardized cognitive battery. Whole brain T1-weighted MRI was obtained and volumes analyzed with FreeSurfer (TM).
Key findings: Total brain volume (TBV) was significantly smaller in cases. After adjustment for TBV, cases had significantly larger regional grey matter volumes for total, frontal, parietal, and precentral cortex. Cases had poorer performance on neurocognitive indices of intelligence and variability of sustained attention. In cases, TBV showed small associations with intellectual indices of verbal and perceptual ability, working memory, and overall IQ. In controls, TBV

* Corresponding author at: Department of Child and Adolescent Psychiatry, Ann and Robert H. Lurie Children's Hospital of Chicago, 225 East Chicago Ave. Box 10, Chicago, IL 60611-2605, United States. Tel.: +1 312 227 8343; fax: +1 312 227 9460.
E-mail address: fzelko@luriechildrens.org (F.A. Zelko).

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showed medium associations with working memory and variability of sustained attention. In both groups, small associations were seen between some TBV-adjusted regional brain volumes and neurocognitive indices, but not in a consistent pattern. Brain volume differences did not account for cognitive differences between the groups.
Significance: Patients with uncomplicated NSE have smaller brains than controls but areas of relative grey matter enlargement. That this relative regional enlargement occurs in the context of poorer overall neurocognitive functioning suggests that it is not adaptive. However, the lack of consistent associations between case—control differences in brain volumes and cognitive functioning suggests that brain volumes have limited explanatory value for cognitive functioning in childhood epilepsy.

Introduction

Though most childhood-onset epilepsies have no obvious structural lesion and occur in children who are otherwise neurotypical (normal exam and intelligence) (Arts et al., 1999; Berg et al., 1999; Camfield et al., 1996), they exhibit deficits of cognitive function relative to neurotypical children without epilepsy (Fastenau et al., 2009; Hermann et al., 2006; Oostrom et al., 2003; Taylor et al., 2010). Variations of brain structure have been studied using volumetric techniques to quantify differences that are not appreciable with visual interpretation of clinical imaging. Recent studies of normal brain development are providing a context within which to consider volumetric findings (Giedd et al., 1999; Shaw, 2007).

Volumetric variations of brain structure can be seen in children and adults with chronic epilepsy which may be attributable to seizures, underlying pathology, or medication effects (Bernhardt et al., 2009; Betting et al., 2006; Chan et al., 2006; Lawson et al., 2000; Pardoe et al., 2013). Given that neurocognitive differences are present at the onset of childhood epilepsy, some investigators have considered whether subtle structural variations are also present at or near epilepsy onset and whether they explain variations in cognitive function. Most evidence has come from analyses in two cohorts. Studies in one cohort provide limited evidence of grey matter cortical volumetric differences between children with idiopathic epilepsy and healthy controls (Hermann et al., 2010, 2006; Hutchinson et al., 2010; Pulsipher et al., 2011; Tosun et al., 2011b). At the same time, academic difficulties and ADHD were found to be associated with grey matter differences (Hermann et al., 2007a, 2006), and anomalies of white matter and subcortical structures were identified (Hermann et al., 2010; Lin et al., 2012; Pulsipher et al., 2011; Pulsipher et al., 2009). In a subsample of the same cohort, microstructural white matter differences were indicated by diffusion tensor imaging in the absence of white matter volume anomalies (Hutchinson et al., 2010). In a second cohort, cortical grey matter anomalies were reported in subsamples with childhood onset absence epilepsy (Caplan et al., 2009; Tosun et al., 2011c) and cryptogenic epilepsy characterized by complex partial events (Caplan et al., 2010; Tosun et al., 2011a).

Volumetric measurements have been examined in relation to cognitive functioning in the same cohorts (Caplan et al., 2009; Hermann et al., 2006; Pulsipher et al., 2009; Tosun et al., 2011b,c). The results of those analyses suggest that associations between cognitive variables and brain volumes in childhood epilepsy differ from those in controls, though only one study directly tested interaction effects (Tosun et al., 2011c). A common limitation of prior studies has been heterogeneity of clinical samples combining epilepsy syndromes having specific neurocognitive signatures such as childhood absence epilepsy (CAE), benign epilepsy with central temporal spikes (BECTS), and juvenile myoclonic epilepsy (JME), and samples including both generalized and focal epilepsies.

We studied total and regional brain volumes and neurocognitive functioning in a prospective community-based sample with well-controlled or remitted childhood-onset non-syndromic epilepsy with focal features, with or without generalization (NSE), approximately nine years after initial diagnosis, and compared them to healthy controls. Our goals were (1) to determine whether case—control brain volume differences were present, (2) to examine case—control differences in neurocognitive functioning, and (3) to see whether case—control differences in regional brain volumes account for differences in cognitive functioning.

Methods

Participants

Participants were recruited when first diagnosed with epilepsy (onset 0—15 years) in the state of Connecticut between 1993 and 1997 (Berg et al., 1999). Approximately 8—9 years following their initial diagnosis, 298 members of the original cohort participated in a follow-up research protocol which included an MRI brain scan conducted on a 1.5 T research scanner under a uniform protocol and a standardized neurocognitive test battery (Berg et al., 2008b). Of these, 108 cases having uncomplicated non-syndromic epilepsy with focal features, with or without generalization, (NSE) were identified. Participating cases had no indications of a brain lesion and their research MRI scans were normal to clinical interpretation. They also had a normal neurologic exam, IQ $\geq$ 70, and were seizure free at the time of participation. Thirty-six healthy siblings of participants, recruited as matched controls, completed the same imaging and neurocognitive test protocol, with the goal of collecting identical data from a sibling as close as possible to the case's age. All controls were