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Intelligence and cortical thickness in children with complex partial seizures

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ABSTRACT

Prior studies on healthy children have demonstrated regional variations and a complex and dynamic relationship between intelligence and cerebral tissue. Yet, there is little information regarding the neuroanatomical correlates of general intelligence in children with epilepsy compared to healthy controls. In vivo imaging techniques, combined with methods for advanced image processing and analysis, offer the potential to examine quantitative mapping of brain development and its abnormalities in childhood epilepsy. A surface-based, computational high resolution 3-D magnetic resonance image analytic technique was used to compare the relationship of cortical thickness with age and intelligence quotient (IQ) in 65 children and adolescents with complex partial seizures (CPS) and 58 healthy controls, aged 6–18 years. Children were grouped according to health status (epilepsy; controls) and IQ level (average and above; below average) and compared on age-related patterns of cortical thickness. Our cross-sectional findings suggest that disruption in normal age-related cortical thickness expression is associated with intelligence in pediatric CPS patients both with average and below average IQ scores.

Introduction

Several structural neuroimaging studies have demonstrated significant associations between measures of intelligence and structural variation in specific brain regions (Frangou et al., 2004; Reiss et al., 1996; Shaw et al., 2006; Wilke et al., 2003). Cross-sectional region of interest volume analysis has localized the association between intelligence and neuroanatomy to the prefrontal regions (Reiss et al., 1996) and a voxel-based morphometry (VBM) investigation to the anterior cingulate cortices (Brodmann's area 32) in healthy children, aged 5–19 years (Wilke et al., 2003). A cross-sectional VBM study of adolescents and young adults, aged 12–21 years, identified significant positive associations between intelligence and gray matter density in the orbitofrontal (Brodmann's areas 10, 11, and 47) and middle frontal cortical regions in addition to the cingulate cortices (Frangou et al., 2004).

A longitudinal study using surface-based morphometry methods (Shaw et al., 2006) on a large sample of 307 typically developing subjects described a developmental shift from a predominantly negative correlation between intelligence and cortical gray matter thickness in early childhood (age range 3.8–8.4 years) to a pronounced positive correlation in late childhood (age range 8.6–11.7 years), followed in adolescence (age range 11.8–16.9 years) by a positive correlation, albeit with relatively smaller r values. The cortical regions associated with IQ in these developmental shifts included the frontal cortex, supramarginal and angular gyri in the parietal cortex, fusiform gyrus in the temporal cortex, and extrastriate cortex in the occipital cortex. These specific brain regions play a role in auditory and visual processing, attention, working memory, and response selection (Cabeza and Nyberg, 2000). Shaw et al.'s findings, therefore, suggest involvement of an extensive neural network in the development of general intellectual ability of healthy youth.

Epilepsy is a frequent disorder of a wide range of behavioral and emotional problems, as well as cognitive and linguistic difficulties (Austin and Caplan, 2007; Caplan et al., 1997, Caplan et al., 2006, Caplan et al., 2004, Caplan et al., 2008; Datta et al., 2005; Hermann et al., 2008; Ott et al., 2003). Surprisingly, little is known about the association between age and cortical morphometry, and how this is related to intelligence which is adversely affected in some children with epilepsy (see review in (Nolan et al., 2003)). Neuropsychological studies have demonstrated that an earlier age at onset of recurrent seizures is associated with poorer cognitive functioning. This relationship, first reported early in the last century (Fox, 1924), has been noted in studies of adult patients with diverse seizure types and observed in neuropsychological studies of

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younger patients with complex partial and other types of seizures (Desai, 2008; Dodrill and Matthews, 1992; Hermann et al., 2000; Nelson and Fischer, 2007).

While the mean intelligence level may be significantly lower compared to healthy controls in some children with epilepsy, most children with epilepsy have a wide intellectual range with average and above average IQ levels. However, it has proven somewhat difficult to understand this intellectual variability in the context of clearly defined syndromes of epilepsy based on studies conducted to date (Nolan et al., 2003; Strauss et al., 1995). Therefore, the degree to which these variations in intelligence may be associated with deviations from normal patterns of brain development remains an open question.

To address these unstudied issues, we examined the relationship between age and cortical morphometry in children and adolescents with cryptogenic complex partial seizures (CPS) compared to healthy controls, focusing on the relationship of these associations to intelligence using the described analysis of whole-brain gray matter geometry (Tosun et al., 2006; Tosun and Prince, 2008). We predicted that the children with epilepsy would exhibit different relationships between age and cortical thickness measures compared to the control group after adjusting for gender differences (Dammann, 2007; Klein et al., 2000; Nolan et al., 2003; Suchy and Chelune, 2001; van Mil et al., 2008). Furthermore, we hypothesized that the predicted differences in the association between age and cortical morphometry would be related to the level of intellectual ability among the children with epilepsy. Therefore, we posited that the CPS children with below average IQ scores would differ in their relationship between age and cortical thickness measure compared to both the control group and the CPS children with average IQ scores. However, we anticipated no significant differences in these relationships between the CPS children with average IQ and the control groups. Given the relationship between earlier age of onset of epilepsy and lower IQ, we examined whether the predicted difference in the relationship between age and cortical thickness in the children with lower IQ scores reflected earlier age of onset of epilepsy.

Methods

Subjects

Study subjects were recruited from two epilepsy research centers, the University of Wisconsin-Madison (UW-Madison) and the University of California Los Angeles (UCLA). Subject groups included children with CPS (n = 65), aged 7–18 years, and healthy controls (n = 58), aged 6–18 years. To be included in the study, the patients had to have a diagnosis of cryptogenic epilepsy with CPS as defined by the International Classification of Epilepsy (Commission, 1989) and at least one seizure during the year prior to the child's participation in the study. According to the recent revised ILAE classification (Berg et al., 2010) these subjects had to present with focal seizures of unknown cause characterized by altered consciousness and normal MRI. As described in this classification, children with a clinical history of CPS with or without EEG evidence for focal epileptic activity were included in the study sample. We excluded patients with a mixed seizure disorder (i.e., generalized tonic clonic convulsions and minor motor seizures), an underlying neurological disorder, a metabolic disorder, chronic medical illness, a hearing disorder, and past epilepsy surgery.

One pediatric neurology investigator reviewed the history, EEG records performed at about the time of the child's diagnosis, and diagnosis of each child with epilepsy from the different recruitment sites. If he did not concur with the diagnosis or EEG findings, the child was not included in the study. Clinical MRIs were interpreted as normal in all cases by a clinical pediatric neuroradiologist, none of the children in the study had an underlying lesion, and cases varied from recent onset to established/chronic epilepsy. Patients underwent MR imaging as part of their routine clinical evaluation and no patient was included who presented with structural or space occupying lesions.

The pediatric neuroradiology reports indicated no evidence for mesial temporal sclerosis (MTS) and focal cortical dysplasia (FCD). None of the children were called back for repeat MRI nor were children sedated for their scans.

Children with epilepsy were recruited from tertiary centers (e.g., UCLA Pediatric Neurology services, Children's Hospital of Los Angeles), from the community (e.g., Kaiser Sunset, Kaiser-Orange County, private pediatric neurologists, Los Angeles and San Diego branches of the Epilepsy Foundation of America), and from pediatric neurology clinics at two Midwestern medical centers (University of Wisconsin-Madison, Marshfield Clinic). The primary pediatric neurologist at each recruitment site reviewed the clinical history, EEG records, and diagnosis of potential CPS subjects and referred them for the study.

Of the 65 children with CPS, EEG reports available for 44 indicated that 8 children had non-lateralized EEG findings, 15 had a left focus, 5 a right focus, and 16 bilateral foci. Regarding focal EEG findings, six children had no focal finding, four children had interictal spikes in the frontal lobe, 18 in the temporal lobe, six in the frontal and temporal lobes, and ten in other areas including parietal or occipital regions.

All control subjects presented without a history of prior afebrile or febrile seizures, neurological or chronic medical disease, loss of consciousness longer than 5 min, or a psychiatric disorder. All children, both epilepsy and controls, were attending regular schools.

The projects were approved by the IRB at each institution and IRB approvals were also obtained for transferring MR data to the Image Data Archive (IDA) system in the Laboratory of Neuro Imaging (LONI) at UCLA, where image processing and statistical analysis were carried out. Image processing was performed on each subject blind to both diagnosis and IQ scores. Table 1 describes the demographic and cognitive features of the study subjects.

Table 1
Demographic features of study groups.

	CPS		Controls	p-values[a]		
	Average+ IQ	Below average IQ	Average+ IQ	Average+ IQ versus Controls	Below average IQ versus controls	Average+ IQ versus Below average IQ
N	41	24	58	–	–	–
N at UCLA/N at UW-Madison	20/21	21/3	27/31	0.841	0.001	0.003
Age (mean ± std years)	10.6 ± 2.3	10.9 ± 2.4	11.5 ± 2.9	0.096	0.373	0.606
Gender (M/F)	17/24	14/10	29/29	0.230	0.306	0.175
Age of onset (mean ± std years)	8.2 ± 3.1	8.7 ± 2.4	–	–	–	0.764
Duration (mean ± std months)	29.2 ± 33.1	26.9 ± 21.0	–	–	–	0.500
Full Scale IQ (mean ± std)	101.8 ± 8.2	78.5 ± 7.9	106.4 ± 6.9	0.03	$<10^{-25}$	$<10^{-15}$

[a] Categorical data were compared with *Fisher's exact* test and continuous data were compared with student's *t*-test.