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Cognitive and MR Volumetric Abnormalities in New Onset Pediatric Epilepsy

Bruce P. Hermann, PhD¹, Jana Jones, PhD¹, Raj Sheth, MD¹, and Michael Seidenberg, PhD²

¹ Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison, WI

² Department of Psychology, Rosalind Franklin University of Medicine and Science, North Chicago, ILL

Neuropsychological impairment is an important co-morbidity of chronic epilepsy¹. A rich literature has characterized relationships between adequacy of mental status and a variety of clinical epilepsy factors including etiology, age of onset, seizure type and severity, duration, antiepilepsy medications, and other factors^{2–9}. In addition, modal cognitive profiles have been derived for several syndromes of epilepsy and efforts have been undertaken to identify the shared versus unique cognitive abnormalities evident across these syndromes^{1, 10–16}.

The nature, timing and course of cognitive impairments in epilepsy remains an issue of substantial interest and concern, particularly the degree to which chronic medication-resistant epilepsy may lead to progressive cognitive impairment¹⁷. While evidence to this effect has been reviewed⁴, the early cognitive substrate upon which subsequent chronic epilepsy may exert its effects is an important consideration. The possibility that early onset or childhood epilepsy may adversely alter a child's cognitive substrate in a greater than expected fashion despite their increased plasticity is an issue of clinical interest.

Indirect evidence implicating an adverse neurodevelopmental effect of childhood onset epilepsy has come from studies of adults with chronic epilepsy grouped by age of onset categories where fairly robust relationships have been reported between earlier age of onset of recurrent seizures and cognitive abnormality. This relationship, reported early in the last century¹⁸, confirmed in studies of adult patients with diverse seizure types^{19–23} and observed in neuropsychological studies of younger patients with complex partial and other types of seizures^{24–27}. In addition, greater than expected neuropsychological abnormalities have been reported in adults with the syndrome of mesial temporal lobe epilepsy²⁸, a syndrome defined by a focal neuropathological substrate and early onset of recurrent seizures or initial precipitating injury²⁹. These findings suggest that early onset epilepsy, including localization-related syndromes of epilepsy such as mesial temporal lobe epilepsy, may be associated with widespread influence on brain development and structure.

In the case of mesial temporal lobe epilepsy, quantitative volumetric magnetic resonance (MR) imaging studies have reported abnormalities in neural regions involved in the genesis and propagation of seizures, including the hippocampus^{30–33}, amygdala³⁴, entorhinal cortex³⁵, fornix³⁶, thalamus and basal ganglia³⁷, and temporal lobe^{38–41}. Additional

Address for correspondence: Bruce Hermann, Department of Neurology, University of Wisconsin, 600 N. Highland Ave, Madison WI 53792, Phone: 608-263-5430, Fax: 608-265-0172, E-mail: hermann@neurology.wisc.edu.

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investigations have reported abnormalities in more wide ranging volumes of gray and white matter in extratemporal lobar³⁹, regional⁴² or total brain morphometrics^{40, 43}. These distributed volumetric abnormalities, interesting in their own right, are also consistent with the widespread cognitive abnormalities that can be observed in chronic temporal lobe epilepsy. The potential impact of early versus late age of seizure onset on quantitative MRI volumetrics in temporal lobe epilepsy has however rarely been systematically investigated, surprising given the neuropsychological literature reviewed above as well as animal studies demonstrating that seizures in the immature brain may adversely affect brain growth and development^{44–46}.

However, more direct evidence of the neurodevelopmental impact of recurrent seizures on cognition has been provided by controlled studies of children and adolescents with chronic but substantially shorter duration epilepsy. Studies such as these have also reported considerable neuropsychological impairment^{16, 26, 47–50} consistent with an early adverse neurodevelopmental impact on cognition. However, even these effects could be a combination of pre-epilepsy onset (etiological) insults, factors which may have contributed to the development of epilepsy and simultaneously contributed to abnormal mental status. In order to derive perhaps the clearest perspective of the natural course of cognitive status in epilepsy, it is important to characterize the earliest status of the cognitive substrate and to that end, investigation of children with new onset epilepsy may contribute to this literature. To date, a modest number of studies have examined cognition in children with new onset epilepsy^{51–55}. Three of the five studies identified cognitive impairments at epilepsy onset and these mixed results may be attributable, at least in part, to the variable age ranges, test batteries, and epilepsy characteristics across studies. Also interesting and very pertinent to this topic are reports of academic underachievement prior to and/or at the onset of idiopathic/cryptogenic epilepsy^{52, 56, 57}, suggestive of an antecedent neurobiological insult of uncertain etiology.

One factor that may underlie cognitive pathology in children with epilepsy is structural brain abnormality. As noted previously, quantitative MR volumetrics have been used to characterize the nature and pattern of brain abnormality in adults with epilepsy, especially temporal lobe epilepsy^{58–61}. Volumetric anomalies are of clinical consequence as demonstrated by their relationship with impaired cognition^{62–69}. In contrast, there are very few volumetric studies of children with epilepsy. Most studies to date have involved children with *chronic* epilepsy and the findings reveal abnormalities in cerebrum, cerebellum and hippocampus^{70–73, 74}. A recent voxel based morphometric investigation of children with chronic temporal lobe epilepsy reported a distributed pattern of abnormality in temporal and extratemporal lobe gray matter⁷⁵, similar to that reported in the adults with temporal lobe epilepsy^{76–81}. Examination of the relationship between volumetric abnormalities and cognition are rare in the pediatric epilepsy literature. Byars et al.⁸² recently investigated 249 children within 3 months of the first recognized seizure and reported a relationship between cognition and clinically significant MR abnormalities (i.e., deemed related to the epilepsy).⁷⁴ examined the relationship of volumetric abnormalities to IQ. To date, there has been no investigation of the morphometric status of children with new onset epilepsy, the relationship between cognitive and academic achievement and volumetric abnormalities, or examination of patterns of brain development in children with epilepsy versus controls.

Our group recently examined neuropsychological status and MR volumetrics in a sample of children with recent onset idiopathic/cryptogenic epilepsy (n =53) and healthy first-degree cousin controls (n =50), aged 8–18 years. The children with epilepsy were diagnosed within the past 12 months, had no other developmental or neurological disorders, and normal clinical MRI. Control participants were healthy age and gender-matched first-degree cousins and all children with epilepsy and controls were attending regular schools. All children were administered a comprehensive test battery that included standard clinical measures of intelligence, language, immediate and delayed verbal and visual memory, executive functions,

speeded fine motor dexterity, and academic achievement (Table 1). Also obtained were high resolution MRIs that were processed using a semi-automated volumetric software package, i.e., Brain Research: Analysis of Images, Networks, and Systems (BRAINS-2)^{83–86}, the details of which have been described previously⁸⁷. The volumetric variables of interest were age and ICV adjusted total and segmented total cerebral tissue volumes as well as total lobar tissue volumes (frontal, temporal, parietal and occipital). Mothers were questioned about their children's academic history and need for educational services and the timing of delivery of those services. Table 2 provides information regarding the sociodemographic characteristics of the epilepsy and control groups and there were no significant group differences in overall age, gender, or years of education, but significantly more left-handed children in the epilepsy group ($p=.013$).

The participants with epilepsy had an average age of onset of 11.5 years and an average duration of epilepsy of 10.0 mos.

Figure 1 provides mean adjusted (age, gender, education) cognitive domain z-scores. Data were analyzed using ANOVA and univariate effects were significant for intelligence ($p = .003$), language ($p=.033$), executive function ($p<.001$) and speeded psychomotor abilities ($p<.001$). In all cases, the epilepsy patients performed significantly worse than the controls. Memory performance showed a trend toward poorer performance in the epilepsy group ($p=.086$).

To determine whether these general trends were present in both epilepsy syndrome groups, subjects with idiopathic generalized epilepsies (IGE) and localization related epilepsy (LRE) were compared to controls using one-way ANOVA. There was a significant group effect across all cognitive domains including intelligence ($p=.001$), language ($p=.043$), memory ($p=.021$), executive function ($p=.001$) and psychomotor speed ($p<.001$). Figure 2 shows mean adjusted z-scores for the groups across the cognitive domains. Post-hoc pairwise comparisons revealed that both the LRE and IGE groups performed significantly worse than controls across the domains of intelligence ($p's<.006$), executive function ($p<.005$), and psychomotor speed ($p's<.001$). The LRE but not IGE group differed from controls on the language and memory domains. There were no significant differences between the two epilepsy syndrome groups in any cognitive domain. Thus, close to the time of the onset of epilepsy there appears to be a mild but statistically significant cognitive effect that are relatively generalized in nature, and characteristic of children with both LRE and IGE.

These findings are consistent with and replicate prior reports including Oostrom et al.⁵² who assessed newly diagnosed children with epilepsy prior to administration of antiseizure medications. The cognitive results for their children are presented in a similar format in Figure 3. Again, there is a relatively widespread impact on cognition including attention, reaction time, and learning, with a trend for academic skills.

In our sample of recent onset cases, quantitative volumetrics were completed for a consecutive sample of 31 controls and 43 children with epilepsy. The groups were compared in regard to total cerebral gray and white matter as well as total tissue volumes for frontal, temporal, parietal and occipital lobes via MANCOVA with age and ICV as covariates. Figure 4 depict the mean volumetric measurements for the LRE, IGE and control groups. There was no significant difference across groups.

Thus, the aforementioned cognitive effects were obtained in the absence of gross structural abnormalities in brain structure.

Some indication of the possibility of an antecedent neurobiological insult of clinical significance would be provided by data pertaining to the presence of educational difficulties experienced by children with epilepsy prior to their first recognized seizure compared to

controls. In our epilepsy group we found 26% to present with a history of pre-epilepsy academic problems (AP+) versus 4% of controls ($p < .001$). Similar findings have been reported by others. In the new onset sample of Ostrom et al.⁵² 51% of their epilepsy sample presented with a history of special education assistance compared to 27% of the controls—a significant difference. Similarly, Berg et al. 2005⁵⁶ reported 203 of 415 children with epilepsy or 48.9% had received services at some point in time. Educational services started before epilepsy onset in 66 or 15.9% of the children with epilepsy. Thus, a history of significant academic difficulties was present and antedate epilepsy onset in a significant proportion of children.

What are the cognitive correlates of this group? Again the results appear to be consistent across studies. In our sample, children with academic problems (AP+) were not different from the epilepsy group without academic problems (AP-) in epilepsy syndrome ($p=.63$), age ($p=.38$), gender ($p=.45$), handedness ($p=.07$), grade ($p=.25$), age of onset of epilepsy ($p=.24$), duration ($p=.12$) or number of medications ($p=.19$). As might be predicted, the AP+ epilepsy group performed significantly worse than healthy controls and AP- epilepsy children on measures of reading ($p's < .001$), spelling ($p's < .002$) and arithmetic ($p's < .001$). When compared across the cognitive domains (Figure 5), the epilepsy AP+ group performed significantly worse than controls across all cognitive domains (all $p's < .02$) and significantly worse than epilepsy AP- children in the intelligence, language, executive function and psychomotor speed domains (all $p's < .004$) with a trend for memory ($p=.052$). The epilepsy AP- children continue to score significantly below controls in executive function ($p=.032$) and psychomotor speed ($p < .001$). Similar trends were evident in academic achievement scores with the AP+ group performing significantly worse than both the controls and AP- group in word reading, spelling and calculation (all $p's < .003$), with the AP- and controls only differing in computation ($p < .05$) but not reading or spelling. Similar findings were reported by Ostrom et al.⁵² in that clinical seizure features did not discriminate the children with epilepsy who did versus did not present with prior history of special education needs and the children positive for such needs scored significantly worse across their test battery.

A problematic early academic history in conjunction with discrepant test scores might suggest that subtle anomalies in brain structure may underlie these difficulties. Examination of lobar gray and white matter volumes using MANCOVA with age and ICV as covariates revealed significant univariate effects for left parietal gray ($p=.018$) and left occipital gray ($p=.047$) matter. Post-hoc pairwise comparisons revealed that the epilepsy AP+ group had significantly lower gray matter volumes compared to controls in parietal ($p=.027$) and occipital regions ($p=.033$) as well as significantly lower volumes compared to the epilepsy AP- group in parietal ($p=.005$) and occipital ($p=.016$) regions, with no differences between the controls and epilepsy AP- group ($p's > .39$). (Figure 6).

In summary, there appears to be evidence in the literature that: 1) mild diffuse neuropsychological problems may be evident in children with new onset idiopathic/cryptogenic epilepsy, regardless of epilepsy syndrome, 2) academic difficulties may be evident at the time of diagnosis and may have existed prior to the first recognized seizure in a subset of children suggesting an antecedent neurobiological abnormality, 3) children presenting with such a history have an abnormal cognitive profile despite the fact that they are attending regular schools and have normal intelligence, and 4) while quantitative MR volumetrics do not differ between children with new onset epilepsy, regardless of epilepsy syndrome, those with a history of prior academic problems at the onset of epilepsy demonstrate the most impaired cognition as well as volumetric reductions in left occipital and parietal gray matter compared to controls and children with epilepsy without academic problems.

The findings presented here indicate that the neuropsychological substrate and academic status of children with *new or recent onset* epilepsy is adversely affected early in the course of the

disorder, regardless of syndrome type. Children with new onset epilepsy as a group exhibit a pattern of mild but diffuse cognitive impairment. Significantly poorer neuropsychological status can be observed across a variety of cognitive abilities, an effect that can be quite comparable across LRE and IGE. While the underlying neurobiology of these findings are of interest, Fastenau et al.⁸⁸ have demonstrated that family factors may play a significant moderating role and may be a target for intervention.

Why cognitive and other associated comorbidities may appear prior to the onset of recurrent unprovoked seizures in children with idiopathic epilepsies is a critical issue. Cortez et al.⁸⁹ reviewed evidence reaffirming that the onset of recurrent spontaneous seizures represents the end result of the complex process of epileptogenesis, a process involving a cascade of transcriptional changes in brain triggered by genetic and environmental factors. As Cortez et al. point out, the neurobiological results of these transcriptional changes include plasticity, apoptosis and further neurogenesis, all of which could conceivably affect behavior or cognition prior to the appearance of overt seizures. While there are a diversity of animal models of epilepsy including seizure prone strains^{90, 91}, and preferred models for testing cognition and behavior in animals with recurrent seizures^{92, 93}, it is uncommon for behavioral or cognitive testing to be conducted prior to seizure onset which would address the question of whether neurobehavioral abnormalities may be associated with underlying epileptogenesis. Available results, however, support the position of Cortez et al.⁸⁹ including findings of learning and behavioral abnormalities in the seizure prone baboon prior to onset of spontaneous unprovoked seizures⁹⁴, learning impairments in young genetically seizure susceptible rats (F substrain Ihara) prior to onset of spontaneous seizures⁹⁵; developmental delays, increased exploratory behavior and altered habituation in EL/Suz mice two months prior to onset of seizure susceptibility⁹⁶, decreased social investigation in seizure susceptible EI mice⁹⁷, and abnormalities in behavior and cognition consistent with attentional disturbance in rat lines selectively bred for differences in amygdala excitability indexed by fast or slow kindling epileptogenesis⁹⁸. Thus, neurobehavioral impairments can be identified in seizure prone strains of animals prior to seizure onset, presumably related to processes underlying epileptogenesis, which might prove pertinent to the disorders evident antecedent to epilepsy onset in children with epilepsy.

A critical concern is subsequent cognitive and brain development in children with epilepsy compared to controls, an issue for which little empirical attention has been devoted. Neurodevelopmental processes of cortical pruning and increasing myelination with concomitant declines in cerebral gray and increasing cerebral white matter volumes in normally developing children have been elegantly demonstrated^{99–105}, with a preponderance of change occurring in the frontal and parietal regions in late childhood/early adolescence, the mean age range of the children studied here. How these processes develop in children with epilepsy and how it relates to any identified differences in cognitive development remains to be determined.

Clinical and theoretical implications

Concern has focused on the cumulative neurobiological burden associated with chronic epilepsy and the risk of progressive cognitive impairment¹⁷. In addition, interest is growing in lifespan models of the neuropsychology of epilepsy^{106, 107}. Characterization of neuropsychological status at or near the onset of epilepsy provides insight into the cognitive substrate upon which the effects of medically intractable seizure, medications, and other potentially adverse seizure-related factors may accumulate. It is becoming increasingly clear that this early substrate is not unaffected, the abnormalities more diffuse than one might initially anticipate, with comparable effects across broad syndromes of epilepsy. An important clinical implication of these findings is that efforts are needed to identify and remediate these early

neurobehavioral problems, especially in light of the known poor long-term psychosocial prognosis of persons with even remitted childhood epilepsy¹⁰⁸. It would seem that the children with academic problems at epilepsy onset would be an especially important group to target in that prospective research¹⁰⁹ has demonstrated that a history of learning problems is a major marker for poor long-term psychosocial outcome.

In addition to the neuropsychological findings at epilepsy onset, reports have appeared indicating that psychiatric/behavioral and academic problems may antedate the diagnosis of epilepsy in both children^{52, 56, 110–113} and adults^{114, 115} with epilepsy. The mechanisms underlying these effects remain to be determined and remain an important issue for future research. In that these antecedent insults can be observed even in children with idiopathic-cryptogenic epilepsy, without abnormalities in overall brain volumetrics, raises the possibility that factors associated with underlying epileptogenesis leading to the onset of seizures may play a role⁸⁹.

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Figure 1.

Performance of epilepsy and control groups across cognitive domains. The epilepsy group performs significantly worse than controls in intelligence, language, executive function and psychomotor speed, with a trend for memory.

Figure 2.

Both the LRE and PGE groups perform significantly worse than controls in intelligence, executive function and psychomotor speed. LRE but not PGE differ from controls in language and memory. There no significant differences between LRE and PGE groups in any cognitive area.

Figure 3.

Test performance of new onset epilepsy group compared to controls across cognitive domains (Oostrom et al, 2003). Epilepsy group significantly different from controls in attention ($p=.01$), reaction times ($p=.02$), learning ($p=.05$) with a trend for academic skills ($p=.07$).

Figure 4. Age and ICV adjusted total cerebral volumes and total lobar tissue volumes for controls and epilepsy syndrome groups.

Figure 5.

Children with epilepsy with (AP+) and without (AP-) history of academic achievement problems. AP+ group performs significantly worse across all domains compared controls and AP- group with exception of memory. AP- group differs from controls in executive and speed domains.

Figure 6.

Children with epilepsy with (AP+) and without (AP-) a history of academic achievement problems. AP+ group exhibits significant reduction in ICV and age corrected volumes of left parietal and left occipital lobe gray matter compared to controls and AP- epilepsy group. AP- epilepsy group does not differ from controls.

Table 1

Neuropsychological Test Battery

Domain	Ability	Tests
Intelligence	Verbal	WASI Verbal IQ ²
	Nonverbal	WASI Performance IQ ²
Language	Confrontation naming	Boston Naming Test ¹
	Expressive naming	EVT ²
	Receptive language	PPVT ²
	Generative naming	D-KEFS Verbal Fluency ²
Memory	Verbal memory	CMS Word List-immediate ²
		CMS Word List-delayed ²
	Nonverbal memory	CMS Dot Location-immediate ²
		CMS Dot Location-delayed ²
Executive function	Problem Solving	D-KEFS Card Sort ²
	Response inhibition	D-KEFS Color-Word Interference Test ²
	Divided attention	D-KEFS Switching Fluency ²
	Inattentiveness	CPT Omission errors ²
Motor function	Speeded fine motor dexterity	Grooved Pegboard ³
	Psychomotor speed	WISC-III Digit Symbol Test ²

¹ raw scores,

² scaled scores,

³ seconds

Table 2

Demographic and Clinical Characteristics

	Epilepsy (N=53) Mean (SD)	Controls (N=50) Mean (SD)
Age (yrs)	12.7 (3.3)	12.7 (3.2)
Gender (M/F)	31/22	23/27
Handedness (R/L)	46/7	50/0
Years of education	6.5 (3.3)	6.4 (2.9)
Age of onset (yrs)	11.5 (3.5)	----
Duration of epilepsy (mos)	10.0 (4.1)	----
Localization-related ¹	30 (57%)	
Generalized ²	23 (43%)	

¹ Including localization-related epilepsies such as temporal, frontal, occipital, centrottemporal, and NOS.

² Including primary generalized epilepsies such as childhood absence, juvenile absence, and juvenile myoclonic epilepsy.