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The frequency, complications and aetiology of ADHD in new onset paediatric epilepsy

Bruce Hermann,[1] Jana Jones,[1] Kevin Dabbs,[1] Chase A. Allen,[1] Raj Sheth,[1] Jason Fine,[3] Alan McMillan[2] and Michael Seidenberg[4]

[1]Department of Neurology, [2]Department of Medical Physics, [3]Department of Biostatistics, University of Wisconsin School of Medicine and Public Health, Madison, WI 53792 and [4]Department of Psychology, Rosalind Franklin University of Medicine and Science, North Chicago IL, USA

Correspondence to: Dr Bruce Hermann, Matthews Neuropsychology Lab, Department of Neurology, University of Wisconsin, Madison, WI 53792, USA
E-mail: hermann@neurology.wisc.edu

Recent studies suggest that Attention Deficit Hyperactivity Disorder (ADHD) is a common comorbid condition in childhood epilepsy, but little is known regarding the nature, frequency and timing of associated neurobehavioural/cognitive complications or the underlying aetiology of ADHD in epilepsy. This investigation examined: (i) the prevalence of ADHD and its subtypes; (ii) the association of ADHD with abnormalities in academic, neuropsychological, behavioural and psychiatric status and (iii) the aetiology of ADHD in paediatric epilepsy. Seventy-five children (age 8–18) with new/recent onset idiopathic epilepsy and 62 healthy controls underwent structured interview (K-SADS) to identify the presence and type of DSM-IV defined ADHD, neuropsychological assessment, quantitative MR volumetrics, characterization of parent observed executive function, review of academic/educational progress and assessment of risk factors during gestation and delivery. The results indicate that ADHD is significantly more prevalent in new onset epilepsy than healthy controls (31% versus 6%), characterized predominantly by the inattentive variant, with onset antedating the diagnosis of epilepsy in the majority of children. ADHD in childhood epilepsy is associated with significantly increased rates of school based remedial services for academic underachievement, neuropsychological consequences with prominent differences in executive function, and parent-reported dysexecutive behaviours. ADHD in paediatric epilepsy is neither associated with demographic or clinical epilepsy characteristics nor potential risk factors during gestation and birth. Quantitative MRI demonstrates that ADHD in epilepsy is associated with significantly increased gray matter in distributed regions of the frontal lobe and significantly smaller brainstem volume. Overall, ADHD is a prevalent comorbidity of new onset idiopathic epilepsy associated with a diversity of salient educational, cognitive, behavioural and social complications that antedate epilepsy onset in a significant proportion of cases, and appear related to neurodevelopmental abnormalities in brain structure.

Keywords: epilepsy; ADHD

Abbreviations: ADHD = attention deficit hyperactivity disorder; ANOVA = analysis of variance; BRI = behavioural regulation; BRIEF = behaviour rating inventory of executive function; GEC = global executive composite; IEP = individual education plan; MCI = metacognition; PD = proton density; VBM = voxel-based morphometry

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Introduction

Youth with chronic epilepsy, especially complicated epilepsy, are at increased risk of mental health problems compared to both the general population and children with other chronic non-neurological conditions. The Isle of Wight study (Rutter *et al.*, 1970) documented mental health problems in 7% of children in the general population, 12% of children with non-neurological physical disorders, and significantly higher rates in paediatric epilepsy including 29% in children with uncomplicated and 58% in complicated epilepsy (i.e. structural brain abnormalities and seizures). Remarkably similar results were obtained approximately 30 years later in an independent population-based UK epidemiological investigation (Davies *et al.*, 2003), with further replication and refinement in a large number of clinical investigations using self-report and

proxy-based measures of emotional-behavioural status (Noeker *et al.*, 2005).

While the adult epilepsy literature has characterized the full spectrum of DSM and ICD defined psychiatric disorders (Swinkels *et al.*, 2005), similar efforts in the paediatric epilepsy literature have essentially just begun (Ott *et al.*, 2001; Caplan *et al.*, 2005; McLellan *et al.*, 2005; Jones *et al.*, 2007), again with a focus on children with chronic epilepsy. Of the potential psychiatric comorbidities of childhood epilepsy, attention deficit hyperactivity disorder (ADHD) has been of longstanding interest. Ounsted (1955) was among the first to call attention to the syndrome of hyperkinetic disorder and its complications in children with epilepsy. A growing literature has characterized disorders of attention in youth with epilepsy using a diversity of methods including proxy (parent, teacher) rating scales, behavioural checklists, or formal cognitive tests (Dunn and Kronenberger, 2005). However, only three investigations determined the rate of ADHD and its subtypes in paediatric epilepsy using contemporary diagnostic criteria that now recognize specific subtypes of the disorder (DSM-IV). One of these studies was population based (Hesdorffer *et al.*, 2004) while the others were derived from tertiary care clinical settings (Dunn *et al.*, 2003; Sherman *et al.*, 2007). All studies reported a significantly elevated rate of ADHD in childhood epilepsy with an overrepresentation of the inattentive subtype; a distribution that appears different compared to clinically derived samples of ADHD children seen in tertiary care centres where the combined subtype predominates (Barkley, 2006). None of the studies of ADHD in epilepsy examined the neurobehavioural or neuroradiological complications compared to children with epilepsy without ADHD or healthy controls.

ADHD affects ~3–7% of all children in the general population (Rappley, 2005; Polanczyk *et al.*, 2007) and in clinical populations the majority (80%) are diagnosed with the combined inattentive, hyperactive and impulsive type; and a substantially smaller proportion of children are diagnosed with the predominantly inattentive (10–15%) or hyperactive and impulsive types (5%) (Rappley, 2005), although recent *population based* investigations of DSM-IV subtypes note that the inattentive type may be at least as common as the combined type (Graetz *et al.*, 2001; Barkley, 2006). ADHD is a costly disorder in terms of direct medical expenditures as well as associated personal and social consequences (Pelham *et al.*, 2007) given the relationship of ADHD with learning/education problems and school failure, poor peer relationships, additional psychiatric comorbidities (mood, anxiety, conduct disorder) and potential to adversely affect life course including occupational and economic attainment (Wilens *et al.*, 2002; Barkley, 2006; Spencer *et al.*, 2007). A diversity of abnormalities in brain structure in ADHD have been reported including decreased overall cerebral tissue volume with preferential involvement of the prefrontal region or its asymmetry, cerebellum and/or posterior–inferior cerebellar vermis, with more variable reports of atrophy in the corpus callosum or caudate (Giedd *et al.*, 2001; Castellanos *et al.*, 2002; Sowell *et al.*, 2003b; Mackie *et al.*, 2007), abnormalities that appear to be static and non-progressive (Castellanos *et al.*, 2002; Shaw *et al.*, 2006). Functional imaging studies (fMRI, FDG-PET) have suggested particular disruption of frontal-striatal and frontal-parietal circuitry (Dickstein *et al.*, 2006), which are consistent with the prominence of impaired executive functioning in neuropsychological investigations of ADHD (Roth and Saykin, 2004).

Importantly, the presence and nature of associated comorbidities as well as the underlying aetiology and neurobiology of ADHD in children with epilepsy are issues that remain to be clarified. Academic, cognitive and behavioural complications in paediatric epilepsy are often assumed to be due to the consequences of recurrent seizures, medical treatment, or fundamental characteristics of the disorder. The possibility that diverse neurobehavioural problems might bear a close relationship to an underlying co-occurring disorder such as ADHD has not been considered. In addition, accumulating evidence suggests that some comorbid disorders, including ADHD (Hesdorffer *et al.*, 2004; Jones *et al.*, 2007), academic problems (Oostrom *et al.*, 2003; Berg *et al.*, 2005; Hermann *et al.*, 2006), depression and suicidal ideation (Hesdorffer *et al.*, 2006) and behavioural maladjustment (Austin *et al.*, 2001) may antedate the onset of epilepsy, suggesting that both epilepsy and several associated comorbidities may represent epiphenomena of underlying neurobiological abnormalities that remain to be identified. This would not be surprising in children with symptomatic or so called complicated epilepsies where early central nervous system lesions would reasonably result in comorbid behavioural and cognitive disorders. However, it would be less expected in idiopathic or uncomplicated epilepsies where identifiable aetiological insults and neurological and neuroimaging abnormalities are typically absent.

The purpose of this investigation is to characterize the rate, type, correlates and aetiology of ADHD in children with new/recent onset idiopathic epilepsy. Comprehensively examined are domain-specific neuropsychological status; the presence, nature and timing of early childhood and school-based services provided for academic underachievement; the adequacy of self-directed social, cognitive and behavioural repertoires dependent on executive function; and patterns of psychiatric comorbidity. Also critically examined are issues pertinent to the aetiology of ADHD in paediatric epilepsy including the timing of onset of ADHD and its complications in relation to the onset of epilepsy and the role of an array of potential risk factors for neurodevelopmental anomalies during gestation and delivery. Finally, quantitative MRI morphometrics address the potential underlying structural brain

abnormalities that may be associated with ADHD in paediatric epilepsy.

Methods

Participants

Research participants included children with new/recent onset epilepsy ($n = 75$) and healthy first-degree cousin controls ($n = 62$), aged 8–18 years, all attending regular schools. Children with epilepsy were recruited from paediatric neurology clinics at two Midwestern medical centres (University of Wisconsin-Madison, Marshfield Clinic) and initial selection criteria included: (i) diagnosis of epilepsy within the past 12 months; (ii) chronological age between 8–18 years; (iii) no other developmental disabilities (e.g. autism); (iv) no other neurological disorder and (v) normal clinical MRI. Epilepsy participants met criteria for classification of idiopathic epilepsy in that they had normal neurological examinations, no identifiable lesions on MR imaging and no other signs or symptoms indicative of neurological abnormality (Engel, 2001). Control participants were age and gender-matched first-degree cousins. Criteria for controls included no histories of: (i) any initial precipitating event (e.g. simple or complex febrile seizures); (ii) any seizure or seizure-like episode; (iii) diagnosed neurological disease; (iv) loss of consciousness greater than 5 min; or (v) other family history of a first-degree related with epilepsy or febrile convulsions.

First-degree cousins were used as controls rather than siblings or other potential controls groups for the following reasons: (i) first-degree cousins are more genetically distant from the participants with epilepsy and thus less pre-disposed than siblings to shared genetic factors that may contribute to anomalies in brain structure and cognition; (ii) a greater number of first-degree cousins are available than siblings in the target age range and (iii) the family link was anticipated to facilitate participant recruitment and especially retention over time (which is our intent) compared to more general control populations (e.g. unrelated school mates). The IRB approved recruitment strategy for controls was to ask study participants and/or parents to identify potential first-degree cousin controls of the children with epilepsy and initially inquire into the family's interest in study participation. The parents of the participants with epilepsy provided the research coordinator with contact information for interested control families and a similar recruitment process to that described above ensued.

This study was reviewed and approved by the Institutional Review Boards of both institutions and on the day of study participation families and children gave informed consent and assent and all procedures were consistent with the Declaration of Helsinki (1991).

Procedures

Assessment of DSM-IV ADHD

Lifetime-to-date psychiatric status was assessed using the Kiddie-SADS-PL (K-SADS), the semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-IV criteria (Ambrosini, 2000). The K-SADS was completed separately with the child and parent(s) and summary ratings included all sources of information in arriving at a diagnosis. Children and adolescents were interviewed first followed by interview with parents. Administration of the K-SADS included completion of the Diagnostic Screening Interview and the appropriate Diagnostic Supplements. Interviews were videotaped with patient/family consent and IRB approval. Fifteen percent of subjects were randomly selected for independent review with an outside consultant to insure reliability of diagnoses and prevent rater drift. The interviewer was not blinded to seizure history as this often arose spontaneously during the interview. Impairment and/or distress criteria were evaluated in order to accurately reflect the diagnostic criteria of the DSM-IV. The primary dependent measures were the rate of lifetime-to-date ADHD and the specific ADHD subtypes (predominantly inattentive, hyperactive, combined, or NOS). Secondary K-SADS outcome measures included the rate of other specific Axis I disorders (depressive, anxiety, psychotic, oppositional defiant/conduct and tic disorders) in order to characterize any additional psychiatric comorbidity in children with epilepsy with (ADHD+) or without (ADHD−) ADHD. An important concern in assessing symptoms of inattention, and ADHD in particular, is the possible confounding effect of periictal, postictal or frank ictal activity. Parents were specifically instructed not to consider symptomatic anything that could be construed as seizure related phenomena and this was reconfirmed during the interviews. In addition, one purpose of the independent review of 15% of the interviews was to guard such potential errors and no diagnostic changes were made through this process.

Finally, medical record review and structured interview by an independent investigator, blinded to the psychiatric information, identified the age of diagnosis of epilepsy as well as the date/timing of the first-recognized seizure as reported either by parent, observed by proxy (e.g. school nurse), or reported in medical records and confirmed by parent. The onset of ADHD and special educational services to be described below were examined in relation to the first-recognized seizure and formal diagnosis of epilepsy. Retrospectively dating the actual onset of ADHD can be a challenge as parental report is not always accurate (Angold *et al.*, 1996; Barkley, 2006). However, the DSM-IV criteria require that several symptoms be present prior to age 7 and as the children in our study were age 8–18, all parental reports involved retrospective recall. In that this was a study of new onset epilepsy, it was not difficult for the parents to consider symptoms as beginning before versus after the onset of epilepsy.

Neuropsychological assessment

Children with epilepsy and controls were administered a comprehensive test battery that included standard clinical measures of intelligence, language, immediate and delayed verbal memory, executive functions and speeded motor/psychomotor processing. Table 1 overviews the target cognitive domains, the specific abilities assessed within each domain, the administered test measures and the nature of the dependent measure (i.e. number correct, errors, or time). The raw cognitive test scores were adjusted for the influence of age (especially important given the wide age range) and gender. The relationships of age and gender to test performance were determined in the controls after excluding a small number of outliers (exceeding ± 3 SD, involving 9 of 1116 cells or 0.8%) and similar corrections were then applied to the epilepsy patients. These age and gender adjusted z-scores for the individual cognitive tests were then converted to mean cognitive domain scores as defined in Table 1

Table 1 Neuropsychological test battery

Domain	Ability	Tests
Intelligence	Verbal	Wechsler Abbreviated Scale of Intelligence (verbal IQ)
	Non-verbal	Wechsler Abbreviated Scale of Intelligence (performance IQ)[a]
Language	Confrontation naming	Boston Naming Test[d]
	Expressive naming	Expressive Vocabulary Test[a]
	Receptive language	Peabody Picture Vocabulary Test-III[a]
	Generative naming	Delis–Kaplan Executive Function System (letter fluency)[b]
Memory	Verbal learning	Children's Memory Scale (word list–immediate)[b]
	Verbal memory	Children's Memory Scale (word list–delayed)[b]
Executive function	Problem solving	Delis–Kaplan Executive Function System (card sort–confirmed)[b]
	Response inhibition	Delis–Kaplan Executive Function System (color-word interference test)[b]
	Divided attention	Delis–Kaplan Executive Function System (switching fluency–accuracy)[b]
	Inattentiveness	Connors' Continuous Performance Test-II (omission errors)[c]
	Impulsiveness	Connors' Continuous Performance Test-II (commission errors)[c]
Motor function	Speeded fine motor dexterity	Grooved Pegboard[d]
	Psychomotor speed	Wechsler Intelligence Scale for Children-III (Digit Symbol Test)[b]

[a]Sandard scores. [b]Scaled scores. [c]*T*-scores. [d]Raw scores.

(intelligence, language, memory/learning, executive function, psychomotor speed). These procedures serve to reduce the number of comparisons and experiment-wise Type I error and also place all cognitive test scores on a common metric so that relative performance differences across diverse cognitive abilities can be readily appreciated. All resulting domain scores were normally distributed (Kolmogorov–Smirnov Test) and examined for heterogeneity of variance using Levine's Test prior to group comparison.

Most neuropsychological measures are known to be multi-factorial and assignment to *a priori* cognitive domains should be viewed with caution. Our sample size precludes the likelihood that a stable factor structure for the administered cognitive tests would be derived. However, most of the measures have been validated to assess the cognitive constructs we have used. For interested readers, supplementary files are included that provide the mean scaled/standard scores for the individual test measures (supplemental file 1) as well as a table containing adjusted *z*-scores and SD for each measure (supplemental file 2) so that alternative groupings of tests can be considered.

Parent interview

Parents participated in independent clinical interview and completed questionnaires to characterize the neurodevelopmental, health, seizure history and behavioural status of their child; and the mother or other primary caretaker of each child was administered a brief test of intelligence (WASI 2-subtest). The IQ of the biological mother was assessed to rule out the possibility that group differences in the children's scores might be referable to systematic variation in maternal intelligence (which was not the case). Non-biological caretakers (e.g. foster parents) were not included in this analysis. All medical records pertinent to the child's epilepsy and treatment were reviewed after obtaining appropriate signed consents.

Parents underwent structured interview to characterize the presence (yes/no) and type of special educational services provided to children with epilepsy including participation in pre-school programs (e.g. birth to age 3 or other early childhood programs), completion of an official individual education plan (IEP), or provision of other supportive educational services (e.g. tutoring, summer school). Finally, it was determined whether these services were provided prior to the diagnosis of epilepsy/first-recognized seizure (yes/no).

Behaviour rating inventory of executive function (BRIEF)

To characterize day-to-day executive function, parents completed the BRIEF (Gioia, 2000), an 86-item parent-report rating scale with eight theoretically and empirically derived clinical scales that measure behavioural aspects of executive function. The BRIEF can be reduced to three overall summary scores which represent the dependent variables of interest including: (i) behavioural regulation (BRI) which subsumes specific scales assessing the ability to control impulses (inhibit); solve problems flexibly and move from one situation/activity to another as the situation demands (shift); modulate emotional reactions (emotional control); (ii) metacognition (MCI) which subsumes specific scales assessing the ability to begin or activate a task and independently generate ideas (initiate); hold information in mind/stay with and stick to an activity (working memory); anticipate future events, set goals and develop appropriate steps ahead of time to carry out a task in a systematic manner (plan/organize); keep workspace and materials in an orderly fashion (organization of materials); and check work and assess performance to ensure attainment of a goal (monitor) and (iii) global executive composite (GEC) which provides a total summary of parent reported executive function. BRIEF scores are age and gender standardized with a mean of 50 and SD of 10, with higher scores reflecting greater executive dysfunction. Internal consistency reliability (Chronbach's alpha) of the BRIEF is high and ranges from 0.80 (initiate) to 0.98 (GEC) and evidence for the convergent and divergent validity of the BRIEF is strong (Gioia, 2000).

Yale neuropsychoeducational assessment scale (YNPEAS)

The 60-item subsection of the YNPEAS (Shaywitz, 1982) was completed by each child's mother in order to review their health history during gestation and delivery. This questionnaire provides

information regarding four major dimensions of potential complications and composite measures were derived reflecting medical complications during pregnancy (e.g. hypertension, rubella, diabetes, toxemia) (12 items), use of prescribed medications (12 items), adverse health habits (e.g. cigarettes, alcohol) (3 items), and complications during labour and delivery (e.g. nuchal birth, transfusion) (24 items). Items pertaining to use of illegal substances were not endorsed and were not further considered nor were three additional disparate items.

MRI procedures

Images were obtained on a 1.5 Tesla GE Signa MR scanner. Sequences acquired for each participant included: (i) T_1-weighted, three-dimensional SPGR acquired with the following parameters: TE = 5, TR = 24, flip angle = 40°, NEX = 1, slice thickness = 1.5 mm, slices = 124, plane = coronal, FOV = 200, matrix = 256 × 256, (ii) proton density (PD) and (iii) T_2-weighted images acquired with the following parameters: TE = 36 ms (for PD) or 96 ms (for T_2), TR = 3000 ms, NEX = 1, slice thickness = 3.0 mm, slices = 64, slice plane = coronal, FOV = 200, matrix = 256 × 256. MRIs were processed using the Brains2 software package (Andreasen *et al.*, 1996; Harris *et al.*, 1999; Magnotta *et al.*, 1999; Magnotta *et al.*, 2002). MR processing staff was blinded to the clinical, sociodemographic and neuropsychological characteristics of the participants.

The T_1-weighted images were resampled to 1.0 mm cubic voxels, then spatially normalized so that the anterior–posterior axis of the brain was realigned to the ACPC line, and the interhemispheric fissure was aligned on the other two axes. A piece-wise linear transformation was defined providing the ability to warp the standard Talairach atlas space (Talairach, 1988) onto the resampled image. Images from the three-pulse sequences were then coregistered using a local adaptation of automated image registration software. Following alignment of the image sets, the PD and T_2 images were resampled into 1mm cubic voxels following which an automated algorithm classified each voxel into gray matter, white matter, CSF, blood, or unclassified (Harris *et al.*, 1999).

The brains were then 'removed' from the skull using a neural network application that had been trained on a set of manual traces (Magnotta *et al.*, 2002). Manual inspection and correction of the output of the neural network tracing was conducted. The brain images were then volume rendered using local utilities, producing tissue volumes for regions of interest within the brain. Because all measurements were obtained in the image space of the subject and not normalized, ICV was used as a covariate in the analysis. The dependent variables included total and segmented tissue volumes for the frontal, temporal, parietal and occipital lobes; and total tissue volumes for the cerebellum and brainstem.

Volumetric data could not be obtained for a subset of children for the following reasons: artefacts due to braces ($n = 7$), excessive movement ($n = 8$), anxiety which prevented scan completion ($n = 5$), acquisition errors/technical problems not attributable to the children ($n = 4$), or processing not completed ($n = 5$). There was no difference in the rate of unusable scans for children with epilepsy versus controls ($X^2 = 0.79$, df = 1, $P = 0.41$) or controls and epilepsy ADHD groups ($X^2 = 0.57$, df = 2, $P = 0.75$). Scans were available for 46 control, 40 epilepsy ADHD− and 18 epilepsy ADHD+ children.

Voxel-based morphometry (VBM) (Ashburner and Friston, 2000) was subsequently used to provide greater specificity regarding the anatomic localization of abnormalities in lobar tissue volume detected by the above analyses. The VBM procedure was modified such that the same input data used in the total brain gray matter analysis could be used. Images were segmented into a gray matter image using masks defined from the BRAINS2 segmentation procedure which includes a manual cleanup of the gray matter partition These images were then spatially normalized to the template space of the SPM2 software (Wellcome Department of Imaging Neuroscience, University College, London UK) and voxel intensities were adjusted to preserve gray matter volume (modulated). The spatially normalized gray matter images were smoothed with a 14-mm FWHM Gaussian kernel. Analysis of covariance was used to assess differences between control subjects and the epilepsy subjects with and without ADHD, using age and total gray matter volume as covariates, the latter to sensitize the analysis to regional changes beyond global gray matter differences. To restrict the statistical analysis to the same regions described in the aforementioned global gray matter analysis, input data was masked to include only those voxels used in that analysis, and additionally masked to restrict the analysis to gray matter regions as defined from the SPM2 *a priori* gray matter template.

Statistical analysis plan

The first set of analyses are primarily descriptive in nature and involve characterizing the sample, the rate of ADHD in children with epilepsy versus controls and potential confounding differences in outcomes for children treated versus untreated (for ADHD) using two sample *t*-test for continuous outcomes or tests for categorical outcomes.The primary analyses focus on assessing differences among controls and epilepsy ADHD+/− groups on the core set of variables including cognition ($n = 5$), education history ($n = 4$), psychiatric status ($n = 5$), BRIEF ($n = 3$), aetiology ($n = 5$) and MR volumes ($n = 8$). For each endpoint, we first tested whether there was any difference between the three groups using *F*-test from one way analysis of variance (ANOVA) for continuous outcomes, or tests for differences between two proportions for binary outcomes in epilepsy ADHD+ versus ADHD− groups (where control data was not included). Because there are 30 primary endpoints, the determination of statistical significance was conservatively based on the Bonferroni correction, where significance occurs only if *P*-value is less than 0.05/30 = 0.002. In the case of ANOVA, this overall test was followed by exploratory two sample *t*-tests comparing all pairs of groups (three possible pairs) using two sample *t*-test. The resulting *P*-values should not be interpreted rigorously in terms of statistical significance but rather in the context of the exploratory analysis, which is meant to suggest where differences may be occurring following a significant *F*-test. MR analyses were supplemented by region of interest driven VBM, which was itself corrected for multiple comparisons as is the convention.

Results

Characterization of ADHD rate and type in children with epilepsy

Figure 1 provides summary information regarding the rate and types of DSM-IV defined ADHD in the sample.

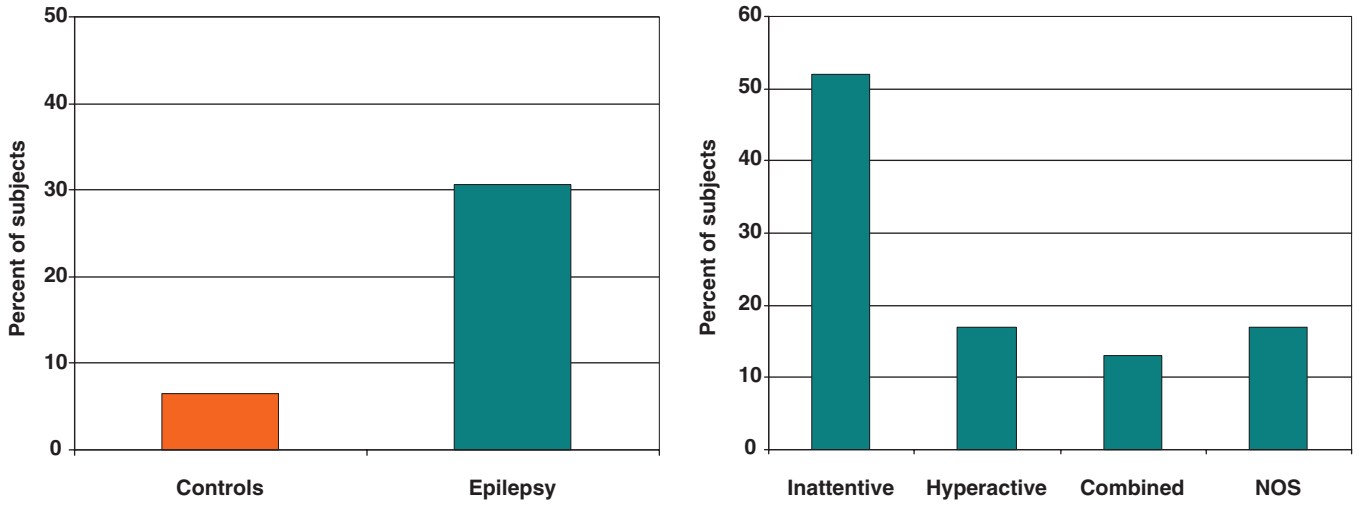

Fig. 1 ADHD is significantly elevated in youth with epilepsy (left panel) and predominantly characterized by the inattentive subtype (right panel).

Children with epilepsy exhibited a significantly higher rate of ADHD (31.5%) compared to controls (6.4%), $X^2 = 12.26$, df = 1, $P < 0.001$. Among epilepsy ADHD+ children, 52.1% (12/23) were inattentive subtype, 17.4% (4/23) were hyperactive subtype, 13.1% (3/23) were combined subtype and 17.4% (4/23) were NOS subtype. The four children in the NOS subtype had been diagnosed with ADHD prior to their participation in the study and development of epilepsy and three of the four were treated for their ADHD (Concerta, Ritalin, Strattera). They did not meet the full criteria for Combined type ADHD (i.e. 10 of 12 required symptoms were endorsed). Due to the fact that they had a prior diagnosis of ADHD and continued to exhibit a number of symptoms of ADHD, we felt that they should be identified as such but classified separately. A lifetime to date diagnosis of ADHD could be made prior to seizure onset in 19/23 children (82%). Ten of the twenty-three epilepsy ADHD+ children presented with prescribed treatments for their attention disorder (e.g. Strattera, Adderall, Ritalin, Concerta) compared to 0% of the epilepsy ADHD− group. Among the epilepsy ADHD+ children there were no significant differences between those who were treated versus not treated for their ADHD across the cognitive domain scores (all $P > 0.29$), BRIEF summary scales (all $P > 0.61$) and all quantitative volumetric measures (all $P > 0.13$). The four controls with ADHD were excluded from subsequent analyses. The epilepsy ADHD cases were first analysed as a group followed by a very limited number of exploratory analyses comparing inattentive versus non-inattentive types combined.

Table 2 characterizes the clinical and demographic features of the control and epilepsy ADHD− and ADHD+ groups. There were no differences between the groups (tested by ANOVA) in terms of the following variables: chronological age ($F = 1.63$, df = 2, 130, $P = 0.19$), grade ($F = 2.18$, df = 2, 130, $P = 0.12$), head circumference ($F = 1.95$, df = 2, 130, $P = 0.15$), or full scale IQ of the mother ($F = 1.6$, df = 2, 124, $P = 0.21$); but full scale IQ of the children differed ($F = 12.3$, df = 2, 130, $P < 0.001$) with lower IQ in epilepsy ADHD+ compared to controls and epilepsy ADHD− groups (all $P < 0.001$), but no ADHD− versus control difference ($P = 0.26$). There was no association between epilepsy ADHD+/− and gender ($X^2 = 2.9$, df = 2, $P = 0.23$), localization related versus idiopathic generalized epilepsy ($X^2 = 0.62$, df = 1, $P = 0.43$), number of AED medications ($X^2 = 2.96$, df = 2, $P = 0.23$) or the duration ($P = 0.30$) or age of onset ($P = 0.07$) of epilepsy. In summary, a wide range of clinical epilepsy and demographic characteristics were not associated with ADHD in childhood epilepsy.

Correlates and consequences of ADHD in children with epilepsy

Educational history

Fig. 2 depicts the lifetime-to-date educational histories of epilepsy ADHD−/+ groups. Regarding the specifics of this history, there were no differences between epilepsy ADHD− and ADHD+ groups in the proportion of children who participated in early childhood programs (e.g. birth to three) (17.3% versus 17.4%, $z = -0.012$, ns). When reaching school, however, there were differences between epilepsy ADHD− and ADHD+ groups in the proportion who completed a formal IEP (15.4% versus 52.2%, $z = -5.17$, $P < 0.001$) or were provided with other supportive academic services (38.5% versus 69.6%, $z = -4.02$, $P < 0.001$). Compared to epilepsy ADHD− children, these educational services were more likely to be provided to the epilepsy ADHD+ group before the formal diagnosis of

Table 2 Demographic and clinical characteristics

	Controls ($n = 58$) mean (SD)	Epilepsy ADHD− ($n = 52$) mean (SD)	Epilepsy ADHD+ ($n = 23$) mean (SD)
Age (years)	13.0 (3.1)	12.9 (3.2)	11.6 (3.2)
Gender (M/F)	25/33	28/24	14/9
Grade	6.9 (3.1)	6.9 (3.3)	5.4 (3.2)
Head circumference (cm)	54.7 (5.1)	55.4 (2.8)	52.9 (7.7)
Full scale IQ	106.5 (17.5)[a]	105.7 (11.7)[b]	93.9 (10.7)[a, b]
Parental full scale IQ	109.3 (14.3)	110.98 (14.97)	104.2 (12.4)
Age at diagnosis (years)	–	12.2 (3.3)	10.98 (3.1)
Duration of epilepsy (months)	–	8.2 (4.3)	9.4 (3.2)
Idiopathic generalized epilepsies	–	26	9
Localization-related epilepsies	–	26	14
Number of AEDs			
0	–	10	2
1	–	41	19
2	–	1	2

Groups with identical superscripts are significantly different (see the text for specific values). Parental full scale IQ controls ($n = 57$); Parental full scale IQ epilepsy ADHD− ($n = 51$).

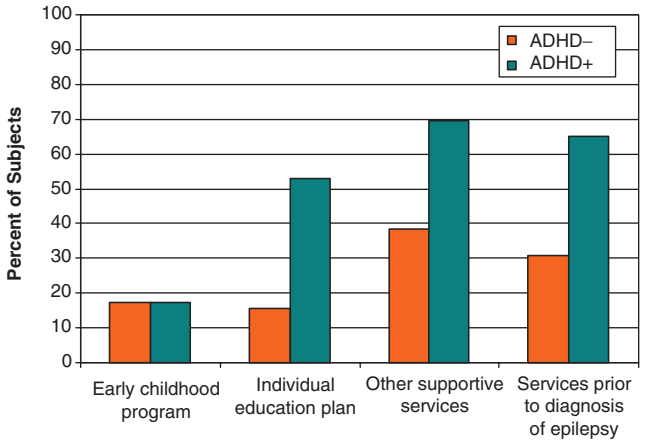

Fig. 2 Special educational services provided to children with epilepsy.

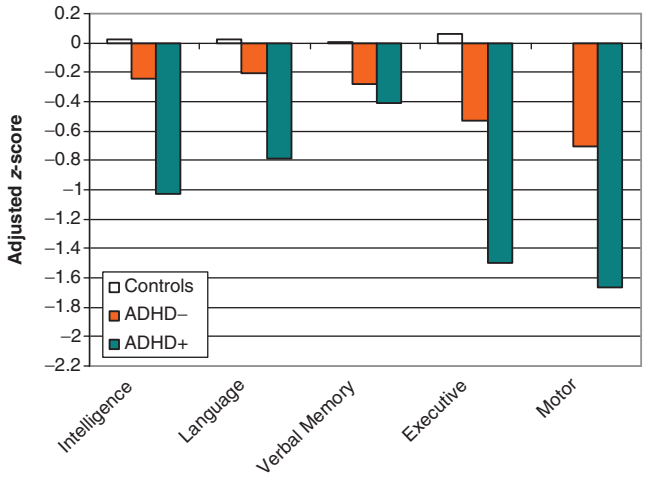

Fig. 3 Mean adjusted (age, gender) cognitive domain scores in controls and epilepsy ADHD+/− groups. Lower scores represent poorer performance.

epilepsy (30.8% versus 65.2%, $z = -4.4$, $P < 0.001$). In summary, epilepsy ADHD+ is associated with the provision of educational services to address academic underperformance, frequently provided before the onset of epilepsy.

Neuropsychological performance

Figure 3 provide a summary of the adjusted (age, gender) cognitive domain scores (supplemental file 1 provides group means for the individual cognitive tests). As can be seen, the epilepsy ADHD+ group performed in a poorer fashion across all cognitive domains. Because the epilepsy ADHD+ group had a significantly lower full scale IQ, the cognitive domain scores were assessed by ANCOVA with full scale IQ as the covariate, which revealed no significant group differences in language ($F = 0.75$, df = 2, 125, $P = 0.47$) or verbal memory ($F = 0.88$, df = 2, 127, $P = 0.42$). Significant group differences were observed in executive function ($F = 9.6$, df = 2, 122, $P < 0.001$) where the epilepsy ADHD+ group scored significantly lower than controls ($P < 0.001$) and epilepsy ADHD− ($P = 0.025$) groups and the epilepsy ADHD− group also scoring lower than controls ($P = 0.007$). Significant group differences were also evident in motor function ($F = 12.2$, df = 2, 126, $P < 0.001$) with the epilepsy ADHD+ group scoring significantly lower than controls ($P < 0.001$) and epilepsy ADHD− ($P = 0.021$) groups, with the epilepsy ADHD− group also significantly worse than controls ($P = 0.001$).

In summary, epilepsy ADHD+ children exhibit distinct patterns of cognitive morbidity characterized

predominantly by robust impairments in motor/psychomotor speed and executive function.

Parent reported executive function

BRIEF index scores were analysed by ANOVA and all comparisons were significant including BRI ($F = 20.1$, df = 2, 130, $P \leq 0.001$), GEC ($F = 33.6$, df = 2, 130, $P < 0.001$) and MCI ($F = 30.8$, df = 2, 30, $P < 0.001$). Group differences were stepwise in nature as shown in Fig. 4 with the epilepsy ADHD+ group scoring significantly higher (worse) across all scales compared to the controls (all $P < 0.001$) and epilepsy ADHD− groups (all $P < 0.001$) while the ADHD− group, with scores falling in the grossly average range, differed from controls on the GEC ($P = 0.003$), BRI ($P = 0.003$) and MCI ($P = 0.04$) indices. The proportion of children exceeding the recommended clinical cut-off point ($T = 65$) for the three BRIEF summary scores ranged between 1.7% to 3.5% for controls, 9.6% to 17.3% for epilepsy ADHD− and 47.8% to 52.2% for epilepsy ADHD+.

Psychiatric comorbidity

Patterns of K-SADS psychiatric comorbidity in the epilepsy ADHD− versus ADHD+ groups are shown in Fig. 5 where there were no differences in the proportion of cases with lifetime-to-date depressive disorders (17% versus 26%, $z = -1.31$, ns), anxiety disorders (36% versus 34%, $z = 0.22$, ns), tic disorders (7.7% versus 4.3%, $z = 0.85$, ns) or psychotic disorders (1.9% versus 0.4%, $z = -0.86$, ns). There was a significantly lower proportion of oppositional disorder in the ADHD− compared to ADHD+ group (2% versus 30.4%, $z = -5.1$, $P < 0.001$).

Etiological factors

There were no significant differences between groups in the proportion of epilepsy ADHD− versus ADHD+ groups endorsing at least one of the medical complications items during pregnancy (75% versus 71%, $z = 0.15$, ns), use of prescribed medications (21.1% versus 30.4%, $z = -1.31$, ns), use of habit substances (17% versus 9%, $z = 1.5$, ns), or complications during labour and delivery (23% versus 21%, $z = -0.79$, ns).

MR volumetrics

Fig. 6 depicts the adjusted (ICV, age) *z*-scores for total lobar and cerebellar and brainstem tissue volumes. Adjusted *z*-scores were analysed by ANOVA and there were no significant effects for total temporal lobe ($F = 1.4$, df = 2, 100, $P = 0.25$), parietal lobe ($F = 0.48$, df = 2, 101, $P = 0.62$), occipital lobe ($F = 1.35$, df = 2, 101, $P = 0.26$) or cerebellum ($F = 0.48$, df = 2, 101, $P = 0.62$), while significant group effects were evident for total frontal lobe ($F = 6.99$, df = 2, 101, $P = 0.001$) and with a (Bonferroni corrected) trend for brainstem ($F = 4.68$, df = 2, 101, $P = 0.01$) tissue volumes. *Post hoc* pair-wise comparisons revealed greater frontal lobe tissue volume in epilepsy ADHD+ compared to controls ($P = 0.013$) and epilepsy ADHD− groups ($P < 0.001$) with no difference between ADHD− and control groups ($P = 0.10$). Fig. 7 shows the examination of segmented frontal lobe measurements. Total tissue volume difference was due to increased gray but not white matter with the ADHD+ group exhibiting more frontal lobe gray matter then both controls ($P \leq 0.001$) and ADHD− children ($P = 0.03$), with no difference between ADHD− and control groups ($P = 0.11$). Exploration of total brainstem volume revealed smaller volume in ADHD+ compared to controls ($P = 0.003$) and ADHD− groups ($P = 0.03$), again with no difference between ADHD− and control groups ($P = 0.29$). Subsequent VBM analysis revealed increased gray matter in sensorimotor, supplementary motor and prefrontal regions (Fig. 8).

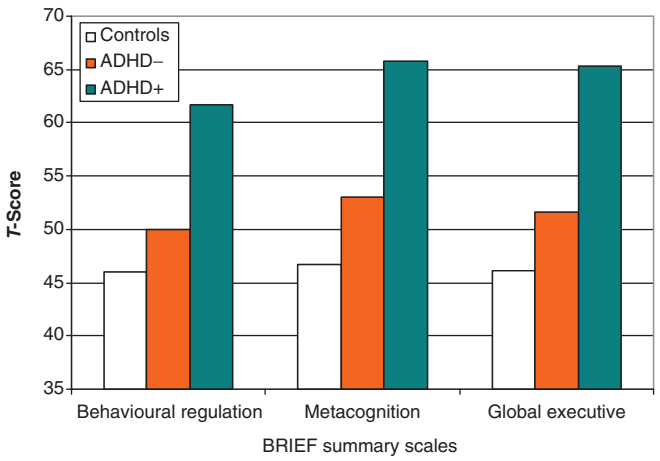

Fig. 4 Mean BRIEF scores in controls and epilepsy ADHD+/− groups. Higher scores represent greater abnormality.

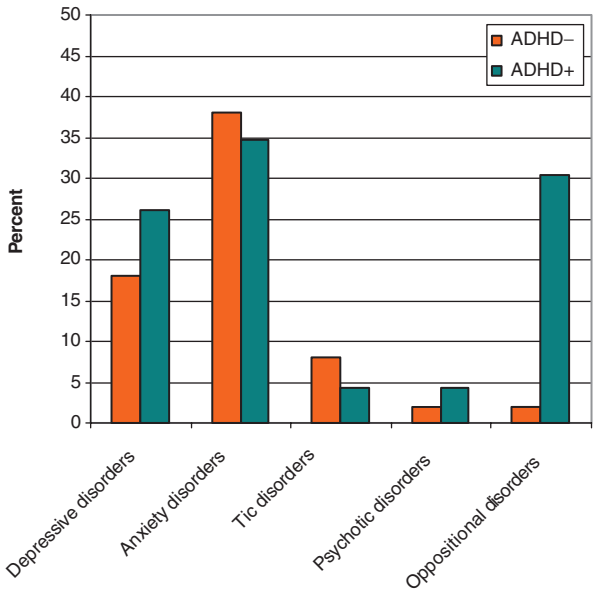

Fig. 5 Rates of K-SADS defined psychiatric comorbidities in epilepsy ADHD+/− groups.

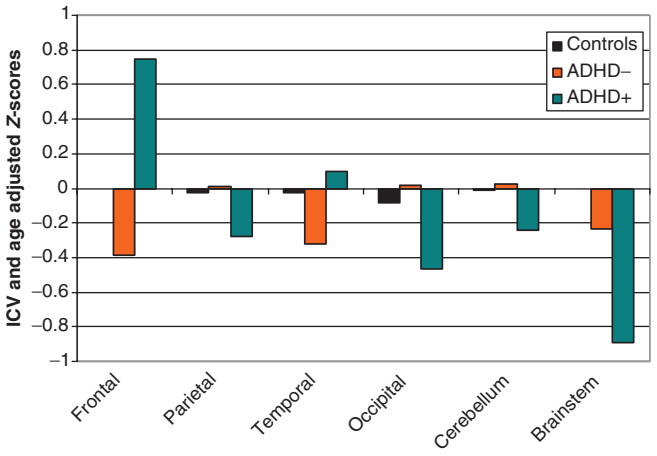

Fig. 6 Adjusted (age, ICV) *z*-scores for total lobar, cerebellum and brainstem volumes.

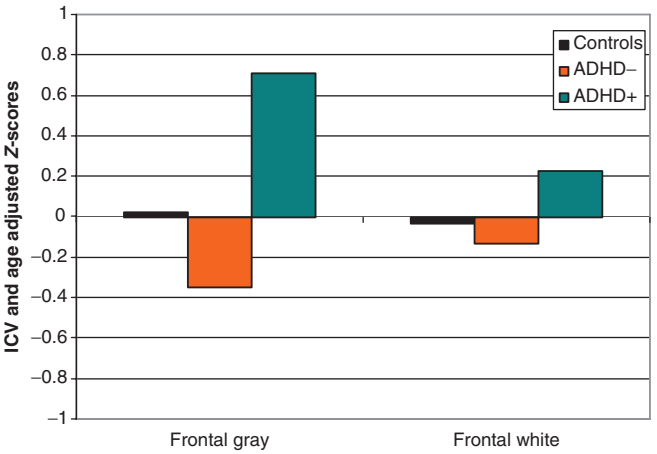

Fig. 7 Adjusted (age, ICV) *z*-scores for segmented frontal lobe volumes.

Discussion

Four key sets of findings speak to the rate, complications and aetiology of ADHD in children with epilepsy: (i) ADHD is a prevalent disorder in children with recent onset epilepsy characterized predominantly by the inattentive variant; (ii) ADHD in children with epilepsy is closely associated with several critical co-occurring problems including academic underachievement requiring provision of school-based educational services, neuropsychological complications and wide ranging problems in day-to-day behaviours dependent upon executive function; (iii) The aetiology of ADHD and its complications in epilepsy appear to have origin prior to the diagnosis of epilepsy and even the first-recognized seizure in a substantial proportion of children, but without significant associations with traditional clinical epilepsy or demographic characteristics, psychiatric comorbidities (depression/anxiety), or anomalies during pregnancy and delivery; and (iv) ADHD in paediatric epilepsy is associated with a distributed pattern of neurodevelopmental anomalies in brain structure. These points are discussed below.

Characterization of ADHD rate and type in children with epilepsy

There is growing interest in the clinical diagnosis of ADHD and related disorders among children with epilepsy (Ott *et al.*, 2001; Dunn *et al.*, 2003; Hesdorffer *et al.*, 2004; Thome-Souza *et al.*, 2004; Dunn and Kronenberger, 2005; Schubert, 2005; Sherman *et al.*, 2007), due in part to a longstanding neuropsychological literature that has documented both static and phasic abnormalities in attention (Sanchez-Carpintero and Neville, 2003) as well as concern regarding clinical disorders of attention (Ounsted, 1955). We confirmed that ADHD is significantly more prevalent

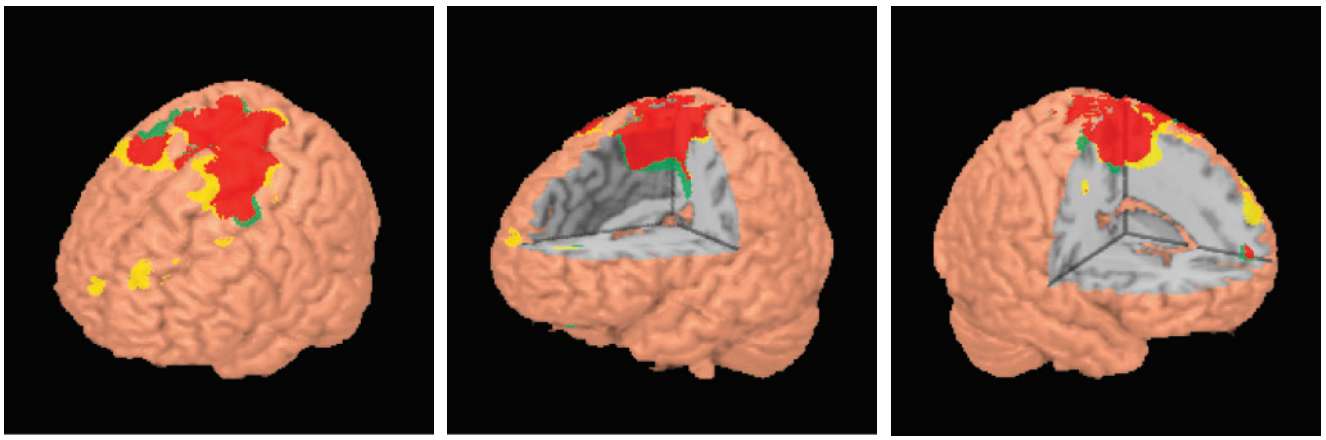

Fig. 8 VBM results showing regions of frontal lobe volume increase in epilepsy ADHD+ relative to controls (yellow), increases relative to epilepsy ADHD− (green), and increases relative to both groups (red). $P < .05$, corrected for multiple comparisons.

(31%) among children with recent onset epilepsy compared to controls (6.4%), with the inattentive subtype the most common form of the disorder in children with epilepsy (Fig. 1) as has been reported in previous studies (Dunn *et al.*, 2003; Hesdorffer *et al.*, 2004; Sherman *et al.*, 2007).

Consequences/correlates of ADHD in children with epilepsy

Investigations of ADHD in children with epilepsy have focused largely on the rate and type of ADHD and associated demographic and clinical epilepsy features. But here we also undertook a thorough assessment of potential associated neurobehavioural complications of ADHD (Wilens *et al.*, 2002; Spencer, 2006; Pelham *et al.*, 2007; Spencer *et al.*, 2007).

Academic/educational

Review of history of the supportive academic services and parental report of academic progress indicate significant academic/educational complications in new onset epilepsy ADHD+ children. Compared to epilepsy ADHD− children, epilepsy ADHD+ children present at the onset of epilepsy with higher rates of formal individual education plans (15.4% versus 52.2%) and provision of a diversity of other in- and out-of-school supportive services (tutors, summer school, reading programs) (38.5% versus 69.6%) suggesting a complicated early educational history in these children when presenting with new/recent onset epilepsy (Fig. 2).

Neuropsychological

Academic problems could be due to a variety of factors including but not limited to behavioural complications of ADHD or underlying cognitive abnormalities. Comprehensive neuropsychological assessment revealed considerable cognitive disruption in epilepsy ADHD+ children (Fig. 3 and supplementary file 1) with less adequate performance across all domains of cognitive function (intelligence, language, executive function, motor/psychomotor speed) except memory. When controlled for IQ, motor/psychomotor speed and executive functions appeared to represent especially salient neuropsychological complications in epilepsy ADHD+ children, characterized by impaired response inhibition, mental flexibility/working memory, concept formation and passive inattention. Overall, these results are consistent with meta-analyses of cognitive deficits in non-epilepsy ADHD children indicating prominence of impairments in executive function and other abilities mediated by frontal-striatal systems (Barkley *et al.*, 1992; Doyle, 2006; Seidman, 2006).

Behaviour

Consistent with the neuropsychological findings, we found that a diversity of day-to-day behaviours dependent upon and mediated by higher-level executive functions were significantly compromised in epilepsy ADHD+ children. Parents of epilepsy ADHD+ children reported a broad range of dysexecutive behaviours characterized by decreased ability to shift cognitive set, modulate emotions and behaviour through appropriate inhibitory control; and initiate, plan, organize and sustain problem solving behaviours compared to epilepsy ADHD− and control groups (Fig. 4). We previously demonstrated that the inventory used to assess these behaviours, BRIEF, is significantly related to objective measures of executive function and thus valid in children with epilepsy (Parrish *et al.*, 2007). Overall, the degree of executive dysfunction in epilepsy ADHD+ children is substantial and evident in both neuropsychological assessment and parent observation. To underscore the importance of executive dysfunction, it has been found to be significantly associated with poorer quality of life in paediatric epilepsy (Sherman *et al.*, 2006).

Aetiology of ADHD in epilepsy

Especially interesting are findings that address the aetiology of ADHD in epilepsy. To begin, initial characterization of the demographic or clinical epilepsy features of the groups (Table 2) revealed no differences between the epilepsy ADHD+/− groups in terms of seizure syndrome, treatment/non-treatment with AEDs, or age of onset or duration of epilepsy; nor were there differences in regard to demographic characteristics including age, gender, or parental IQ. Subsequent analyses of core outcome measures revealed no association between the presence/absence of ADHD in children with epilepsy and lifetime-to-date rates of DSM-IV mood or anxiety disorders, an important finding given the potential confounding role these disorders may have in the diagnosis of ADHD (Barkley, 2006) (Fig. 5).

Timing of ADHD and its comorbidities

These findings suggest that recurrent seizures and their treatment may not represent the core aetiological factor underlying ADHD in children with epilepsy. Care was taken to date the onset of ADHD in relation to the first-recognized seizure and the diagnosis of epilepsy. Both ADHD and its complications (e.g. provision of educational support services at school) antedated the diagnosis of epilepsy in the majority (82% for ADHD, 65% for academics) of cases. These results support the hypothesis that yet to be identified neurodevelopmental abnormalities antedate the onset of seizures and contribute to the development of ADHD and associated comorbidities. That said, review of educational and developmental history did not reveal higher rates of participation in 0–3 or other early childhood programs in epilepsy ADHD+ children suggesting absence of gross neurodevelopmental delays. Further, systematic review of risk factors during pregnancy

and birth failed to identify any factors that were uniquely associated with ADHD in epilepsy.

Neurobehavioural disorders prior to seizure onset in animal models

Why ADHD and associated comorbidities appear prior to the onset of recurrent unprovoked seizures in children with idiopathic epilepsies is a critical issue. Cortez *et al.* (2006) reviewed evidence reaffirming that the onset of recurrent spontaneous seizures is the end result of the complex process of epileptogenesis which involves a cascade of transcriptional changes in brain triggered by an interaction of genetic and environmental factors. The neurobiological results of these transcriptional changes include plasticity, apoptosis and further neurogenesis, all of which could conceivable affect behaviour or cognition prior to the appearance of overt seizures. While there are a diversity of animal models of epilepsy including seizure prone strains (Sarkisian, 2001; Stafstrom *et al.*, 2006), and preferred models for testing cognition and behaviour in animals with recurrent seizures (Stafstrom, 2002; Heinrichs and Seyfried, 2006), it is uncommon for behavioural or cognitive testing to be conducted prior to seizure onset which would address the question of whether neurobehavioural abnormalities may be associated with underlying epileptogenesis. Available results, however, support the position of Cortez *et al.* (2006) including findings of learning and behavioural abnormalities in the seizure prone baboon prior to onset of spontaneous unprovoked seizures (Weinberger and Killam, 1979), learning impairments in young genetically seizure susceptible rats (F substrain Ihara) prior to onset of spontaneous seizures (Okaichi *et al.*, 2006); developmental delays, increased exploratory behaviour and altered habituation in EL/Suz mice 2 months prior to onset of seizure susceptibility (McFadyen-Leussis and Heinrichs, 2005), decreased social investigation in seizure susceptible EL mice (Turner *et al.*, 2007), and abnormalities in behaviour and cognition consistent with attentional disturbance in rat lines selectively bred for differences in amygdala excitability indexed by fast or slow kindling epileptogenesis (Anisman and McIntyre, 2002). Thus, neurobehavioural 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.

Structural brain abnormalities in epilepsy with ADHD

For the first time in the epilepsy literature, structural brain correlates of ADHD are identified. ADHD+ children exhibit an abnormally increased volume of frontal lobe gray matter and Bonferroni corrected trend of reduced total brainstem volumes compared to epilepsy ADHD− and control children, the latter groups not different from one another (Figs 6 and 7). Region of interest driven VBM was then used to search for specific areas of increased gray matter volume in the frontal lobe of epilepsy ADHD+ children. Regions of increased gray matter volume were located in sensorimotor, supplementary motor and prefrontal regions (Fig. 8), areas congruent with the core neuropsychological abnormalities in motor/psychomotor processing, attention/execution function and parent reported dysexecutive behaviours (Anderson, 2002; Stuss and Levine, 2002; Miller and Cummings, 2007).

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 (Giedd *et al.*, 1999; Paus *et al.*, 1999; Sowell *et al.*, 2003*a*; Gogtay *et al.*, 2004; Sowell *et al.*, 2004; Lenroot and Giedd, 2006; Wilke *et al.*, 2006), 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. The increased frontal lobe gray matter volumes could be due to an attenuated rate of frontal lobe cortical pruning or a static frontal lobe mophometric abnormality. The current data cannot discriminate between these or other possibilities, but the history of ADHD and educational/cognitive problems antedating epilepsy onset might suggest a static abnormality. We will be following these children prospectively and should be able to address the stability of these morphometric findings.

Brainstem volume has been infrequently investigated in the general ADHD literature but the trend of abnormality is this region is provocative, given the role of the reticular activating system and the origin of several neurotransmitters in and around the brainstem that have been linked to ADHD, and the suggested role of brainstem pathology and related attentional effects in a diversity of neuropsychiatric disorders (Mirsky and Duncan, 2001).

The morphometric abnormalities identified here clearly differ from those reported in the general population of children with ADHD including abnormalities in overall cerebral tissue volume, prefrontal region, cerebellum/posterior–inferior cerebellar vermis, corpus callosum, and caudate (Eliez and Reiss, 2000; Hendren *et al.*, 2000; Giedd, 2004; Krain and Castellanos, 2006). The preponderance of inattentive ADHD in children with epilepsy as well as the fact that ADHD was comorbid to a primary neurological disorder are among the factors that could help account for these differences. Areas of increased gray matter concentration detected by VBM have been reported in childhood epilepsies including idiopathic generalized epilepsies (Woermann *et al.*, 1999; Betting *et al.*, 2006), but their association with neurobehavioural abnormalities has not been examined. While ADHD+ was not associated with

specific epilepsy syndromes in this investigation, the link between increased gray matter and a clinical syndrome (ADHD), cognitive and behavioural abnormalities are especially interesting.

Limitations

The limitations of this study require comment. First, we specifically strove for a comprehensive presentation of the consequences of ADHD in new onset pediatric epilepsy, and as a result, a large number of comparisons were made. The resultant breath of findings conveys a clearer sense of the impact of ADHD in paediatric epilepsy than would result from a number of smaller reports presenting components of the data where issues of multiple comparisons would not arise. That said, several steps were taken to reduce the probability of Type I error by Bonferroni correction. While this approach is conservative, it rigorously controls for the multiple ($n = 30$) primary outcomes. Importantly, the conclusions do not change qualitatively when employing this stringent criterion. Of course, there are cases where the loss in power did lead to lack of significance. An example is brainstem volume, where the *P*-value from ANOVA was 0.011. Here, the means were −0.00, −0.24 and −0.89, with SD roughly 1, giving an effect size of 0.89 for the resulting *F*-test. Using the standard cut-off of 0.05, power to detect this effect size is 0.69 with 20 per group, 0.87 with 30 per group and 0.95 with 40 per group, which are comparable to sample size in our study that is imbalanced. Using the 0.002 cut-off, the powers are 0.24, 0.48 and 0.69 for 20, 30 and 40 per group, respectively, representing substantial decreases. Larger sample sizes are needed to have adequate power to detect such effect sizes with this many outcomes. Second, the sample size was modest, given the number of outcomes, especially for epilepsy ADHD+ ($n = 23$). While the findings seem compelling, particularly given the stringent criterion used to define statistical significance, they should be interpreted cautiously. There is a clear need for replication in larger studies. Third, this study was not powered to detect differences across ADHD subtypes (Milich *et al.*, 2001; Barkley, 2006). However, preliminary comparison of the predominantly inattentive subtype versus other ADHD subtypes combined on a subset of the significant findings from each major outcome area (e.g. executive and motor function for cognition, completion of individualized education plan for educational history, BRIEF global executive composite, frontal lobe volume for MRI) failed to identify any statistically significant differences. We clearly recognize the limitations of these subtype analyses, but the overall impact of ADHD on diverse neurobehavioural outcomes suggests that this is a very significant comorbidity of pediatric epilepsy deserving further study. Fourth, it is important note that our case ascertainment method focused on children and adolescents with new onset epilepsy; not chronic and intractable epilepsy or epilepsy complicated by cognitive, educational, psychiatric, or other comorbidities, a critical difference. Many of these children were referred back to their primary care providers for ongoing treatment. Such unique samples (new onset idiopathic epilepsy with normal intelligence and normal clinical MRI) appear to provide a unique window with which to understand the neurobehavioural complications of pediatric epilepsy.

Finally, from a clinical perspective, Ott *et al.* (2003) have called attention to the unmet need for psychiatric treatment in pediatric epilepsy. Identification of ADHD is clearly important and the opportunity exists to intervene very early in the course of epilepsy. The long-term social prognosis of these children appears to be of considerable importance and warrants investigation.

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