Epileptic Disord 2012; 14 (1): 12-21

Starting at the beginning: the neuropsychological status of children with new-onset epilepsies*

Bruce P Hermann [1], Jana E Jones [1], Daren C Jackson [1], Michael Seidenberg [2]

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

Received January 23, 2012; Accepted February 16, 2012

ABSTRACT – This review examines the neurodevelopmental contribution to the cognitive and behavioural complications of epilepsy. Following a brief review of the lifespan complications of childhood epilepsies, attention turns to cognitive, psychiatric and social correlates of childhood epilepsies reported in population-based and tertiary care studies. The focus then becomes the neurobehavioural status of children with new-onset epilepsy; a point in time not confounded by the effects of years of recurrent seizures, medications, and social reactions to epilepsy. Recent research shows that abnormalities in cognition, brain structure and behaviour are present at or near the time of diagnosis. Further, careful history taking indicates that neurobehavioural problems may be present in advance of the first seizure suggesting the potential influence of epileptogenesis, antecedent neurodevelopmental abnormalities, genetic and environmental susceptibilities, and other risk factors. This becomes the substrate upon which to characterise the effects of epilepsy and its treatment on subsequent neurodevelopment. The review concludes with suggestions for future clinical care and research.

Key words: epilepsy, cognitive, psychiatric, social, neurobehavior, neurodevelopment

Correspondence:
Bruce P Hermann
Matthews Neuropsychology Lab,
Department of Neurology,
University of Wisconsin School of Medicine and Public Health,
1685 Highland Ave,
Madison, WI 537056, USA
<hermann@neurology.wisc.edu>

While defined by the presence of recurrent seizures, epilepsy can be associated with abnormalities in cognition, psychiatric status, and social-adaptive behaviours that are now referred to as *neurobehavioural comorbidities*. These complications of epilepsy have a long history.

* Updated following presentation and discussion at the *Progress in Epileptic Disorders Workshop* on "Neuropsychology in the Care of People with Epilepsy" held in Toronto, Canada. The workshop was partly supported by an educational grant from UCB. Full proceedings in: Helmstaedter C, Hermann B, Lassonde M, Kahane P, Arzimanoglou A, eds. John Libbey Eurotext editions, 2011, Montrouge (France).

doi:10.1684/epd.2012.0483

Variously referred to as the *psychosocial complications* or *burden of epilepsy*, problems in cognition, emotional-behavioural status and social function were investigated empirically, beginning early in the past century when people with epilepsy were often segregated in colonies or other specialised treatment facilities (Fox, 1924; Wallin, 1912), and subsequently examined by epileptologists seeking to provide a more representative picture of the consequences of epilepsy in community-dwelling patients (Lennox, 1960). These have been a focus and an ongoing concern of national commissions (DHEW, 1978), public health agencies including the Centers for Disease Control (Austin *et al*., 2006), and national and international health organisations including the International League Against Epilepsy, World Health Organization (2001), Institute of Medicine of the National Academies (2011), and others (White House, 2000). At the NIH/NINDS Curing Epilepsy Conference (2007), preventing or reversing the comorbidities of epilepsy was identified as a new major research benchmark area, joining established research benchmarks to cure existing epilepsy and prevent epilepsy and its progression. While undeniably a critical complication of the epilepsies, the aetiology and course of the neurobehavioural comorbidities remain to be fully characterised.

The focus of this paper is on children with epilepsy; what we have learned about the origin and development of neurobehavioural comorbidities and where we need to go in order to better understand, treat, and prevent these problems. We will first briefly review several trends that have been identified regarding cognitive and other neurobehavioural comorbidities of epilepsy and their potential neurodevelopmental roots, and then move to what has been learned through studying children with epilepsy at or near the time of the onset of their epilepsy.

Childhood epilepsy matters

Given the diverse medical, social, psychiatric, cognitive, and quality of life complications of the adult epilepsies (Téllez-Zenteno *et al*., 2005, 2007; Kobau *et al*., 2008; Hinnell *et al*., 2010; Ottman *et al*., 2011; Jalava and Sillanpää, 1996) and their associated direct and indirect costs (Begley *et al*., 2000; Jennum *et al*., 2011), interest has accelerated in understanding the origin, development and trajectory of these complications. At least three sets of evidence suggest a significant neurodevelopmental contribution.

First there is the *indirect* evidence linking the risk of comorbidities to the age at onset of recurrent seizures. For example, by studying *adults* with chronic epilepsy, many neuropsychological reports have shown that an earlier age at onset of recurrent seizures is associated with poorer cognitive function, compared to later onset (Dikmen *et al*., 1975, 1977; Dodrill and Matthews, 1992; Lennox, 1960; Hermann *et al*., 2002; Kaaden and Helmstaedter, 2009). This same relationship has been reported in some but not all neuropsychological studies of younger patients with complex partial and other types of seizures (O'Leary *et al*., 1981; Schoenfeld *et al*., 1999; Cormack *et al*., 2007). Complimenting these cognitive studies are neuroimaging investigations of brain structure. This is a much more limited source of literature, however, an adverse impact of childhood, compared to adulthood, onset of epilepsy has been shown in reductions in whole brain volume among patients with a history of complicated febrile convulsions (Theodore *et al*., 2003), altered volumes of the corpus callosum, whole brain white and/or grey matter tissue, and specific disrupted patterns of white matter connectivity in individuals with childhood, compared to adult-onset, chronic partial epilepsy (*e.g*. Hermann *et al*., 2002, 2003; Kaaden *et al*., 2011; Riley *et al*., 2010; Weber *et al*., 2007).

Second is the compelling evidence that childhood-onset epilepsy impacts the course of life. An important indication of the public health significance of childhood epilepsy is its association with adverse outcomes in later youth and adulthood. This impact is reflected in the international literature published during the past 30 years with studies emanating from the UK, Canada, Finland, Japan, Australia and the Netherlands. Collectively, these reports include both uncontrolled (Lindsay *et al*., 1979a, 1979b, 1979c; Wakamoto *et al*., 2000; Camfield *et al*., 1993; Harrison and Taylor, 1976; Micallef *et al*., 2010) and controlled community and population-based investigations (Jalava *et al*., 1997, Jalava and Sillanpää, 1997; Kokkonen *et al*., 1997; Wirrell *et al*., 1997; Sillanpää *et al*., 1998; Shackleton *et al*., 2003; Koponen *et al*., 2007; Geerts *et al*., 2011), as well as long-term (adult) follow-up of national birth cohorts (Cooper, 1965; Ross *et al*., 1980; Britten *et al*., 1986; Ross and Peckham, 1983; Chin *et al*., 2011).

Several aspects of this literature are important:

1) Groups of children with epilepsy have been followed prospectively for up to 30 or more years in controlled investigations (*e.g*. Sillanpää *et al*., 1998; Shackleton *et al*., 2003);

2) Problems in a diversity of major life outcomes have been reported including rates of marriage, employment, income, psychiatric status, independent living status, and other critical aspects of quality of life;

3) While it would not be surprising that children with severe and complicated epilepsies exhibit poor lifespan psychosocial outcomes (Lindsay *et al*., 1979a, 1979b, 1979c), most, but not all (*e.g*. Wakamoto *et al*., 2000) investigations report adverse lifespan outcomes in persons with intact intelligence, so-called "benign

epilepsies", and even persons with remitted childhood epilepsy who are no longer treated with antiepileptic medications (Camfield *et al*., 1993; Wirrell *et al*., 1997; Sillanpää *et al*., 1998; Jalava *et al*., 1997, Jalava and Sillanpää, 1997);
4) The causes underlying these adult outcomes and the factors associated with favourable *versus* unfavourable outcomes remain to be fully clarified. These poor lifespan outcomes are variably associated with clinical epilepsy features (*e.g*. seizure control);
5) While rarely considered as predictor variables, adverse lifespan outcomes have been found to be associated with histories of neurobehavioural comorbidities such as early learning/cognitive and psychiatric problems (Lindsay *et al*., 1979c; Camfield *et al*., 1993; Kokkonen *et al*., 1997; Koponen *et al*., 2007) including what is now called attention-deficit/hyperactivity disorder (ADHD) (Lindsay *et al*., 1979c).
Finally, an important set of background data involves the direct examination of comorbidities among children with established epilepsy (Lassonde *et al*., 2000; Gleissner *et al*., 2002; MacAllister and Schaffer, 2007). This literature benefits from both population-based and careful tertiary care investigations.

Population-based investigations

In regard to psychiatric status, the paediatric, psychiatric, epidemiological Isle of Wight study (Rutter *et al*., 1970) reported that 7% of children in the general population exhibited mental health issues compared to 12% of children with non-neurological physical disorders, 29% of children with uncomplicated epilepsy, and 58% of children with complicated epilepsy *(i.e*. structural brain abnormalities and seizures). Almost 30 years later, as part of the British Child and Adolescent Mental Health Survey, Davies *et al*. (2003) reported strikingly similar results and other controlled population-based investigations have been supportive of these findings (Alfstad *et al*., 2011a, 2011b).
In regard to cognition, population-based data have addressed the status of global intelligence (Berg *et al*., 2008) and specific cognitive abilities including nonverbal reasoning (Høie *et al*., 2005), executive function (Høie *et al*., 2006a), psychosocial problems (Høie *et al*., 2006b), and the combined burden of cognitive, executive and psychosocial problems (Høie *et al*., 2008). Defining subnormal cognitive function as consistent with a full scale IQ <80, Berg *et al*. (2008) reported that in the Connecticut Study of Epilepsy (*n*=613), cognition assessed a median of 10.5 years after epilepsy onset was considered largely normal in 73.6% of children, with mild mental retardation or worse in the remaining sample (26.4%). Independently predictive of level of function, was age at onset <5 years of age, symptomatic aetiology, epileptic encephalopathy, remission status, and current antiepileptic drug (AED) status (Berg *et al*., 2008). In their series of papers examining a population-based cohort of children (aged 6-12) with prevalent epilepsy (*n*=198) and controls (*n*=126), severe non-verbal learning problems (<10th percentile), as assessed by the Raven Matrices, were found in 43% of children with epilepsy, compared to 3% of controls. These problems were especially common in children with epilepsy characterised by remote symptomatic aetiology, undetermined epilepsy syndromes, myoclonic seizures, early seizure onset, high seizure frequency and polytherapy (Høie *et al*., 2005). Comparable investigations of executive function, school achievement, depression and other comorbidities documented the neurobehavioural burden carried by children with epilepsy (*e.g*., Høie *et al*., 2006a, 2006b, 2008) as well as preschool children with epilepsy including those with uncomplicated epilepsies (Rantanen *et al*., 2010, 2011).

Investigations from specialised centres

Investigations from clinical centres examining children with established epilepsy provide complimentary information and just a few examples from this extensive literature follow below. Farwell *et al*. (1985) examined 118 children with epilepsy (aged 6-15) and 100 controls using the Wechsler Intelligence Scale for Children-Revised and the age-appropriate Halstead-Reitan battery. Various epilepsy syndromes were represented (eight with absence seizures only, eight with absence seizures and generalised tonic-clonic seizures, 30 with generalised tonic-clonic seizures only, 31 with partial seizures only, 20 with partial seizures and generalised seizures, 15 with atypical absence seizures, and six with minor motor seizures). They reported that Full Scale IQ was significantly lower in the children with epilepsy and was related to seizure type. All seizure types were associated with lower intelligence compared to the healthy controls except classic absence only. Children with minor motor or atypical absence seizures had the lowest average FSIQ (70 and 74, respectively). They found a significant inverse correlation between years with seizures and intelligence. A rating of neuropsychological impairment was compiled for all children and the youths with epilepsy exhibited significantly more impairment than controls. Children with epilepsy had been placed in special education or repeated a grade in school almost twice as frequently as controls.
Nolan *et al*. (2004) examined intelligence in 169 children with a spectrum of epilepsy syndromes including generalised idiopathic epilepsy (*n*=22), generalised symptomatic epilepsy (*n*=25), frontal lobe epilepsy (*n*=34), temporal lobe epilepsy (*n*=40), central

epilepsy (*n*=16), and focal epilepsy NOS (*n*=32). They demonstrated a pattern of mildly-to-moderately depressed intellectual ability after accounting for covariates (age at onset, seizure frequency, and number of medications). They concluded that, regardless of epilepsy syndrome, children with epilepsy suffered from reduced intellectual efficiency as measured by IQ, particularly those children with remote symptomatic generalised epilepsy.

Cormack *et al*. (2007) characterised a downward shift in the distribution of intelligence in a sample of 79 children with temporal lobe epilepsy compared to the normal (expected) distribution. These children were surgical candidates who underwent assessment as part of the preoperative workup. Age at onset (earlier) was the best predictor of intellectual impairment (IQ<79) which was present in 57% of the cohort. Children with epilepsy onset in the first year of life had an especially high rate of intellectual impairment (84%). In regard to specific cognitive domains, Schoenfeld *et al*. (1999) demonstrated that among 57 children aged 7-16 years with complex partial seizures with a mean duration of five years, mild generalised cognitive impairment was evident across language abilities, verbal memory and motor functioning, compared to 27 sibling controls.

Review of studies of cognition in children with established chronic epilepsy have shown that a number of epilepsy-related factors appear to contribute to these problems, including seizure frequency, recurrent seizures, age at seizure onset, duration of illness, AEDs, type of epilepsy, and EEG findings (*cf*. Jones *et al*., 2010). However, across studies, the effects of epilepsy-related variables are not inconsistently replicated and often variables such as family factors, pre-existing learning problems, psychopathology, and neuropsychological impairments are found to be significant factors influencing academic underachievement, cognitive and linguistic deficits, as well as behaviour problems in children with epilepsy (Jones *et al*., 2010).

The questions that arise are when and why these abnormalities exist and how they develop over time. If cognitive abnormalities are present among children with short duration of epilepsy, an important question is whether they are apparent at epilepsy onset or develop following the onset and treatment of recurrent seizures. Further identification of neurobehavioural abnormalities at the onset of epilepsy would infer the presence of antecedent neurodevelopmental abnormalities or the effect of other factors. Examination of children at or near the onset of their epilepsy and following them over time would prove especially informative and it is to these issues that we turn for discussion.

Youth with new-onset epilepsy

Early investigations

Prior to approximately 2000, a small number of studies examined cognition in children with new-onset epilepsy (Bourgeois *et al*., 1983; Stores *et al*., 1992; Williams *et al*., 1998; Kolk *et al*., 2001). Several of these early papers tested children at onset to serve as a drug naïve baseline with which to assess subsequent treatment or comparative drug effects (Stores *et al*., 1992; Williams *et al*., 1998). Others focused solely on intelligence and were primarily interested in characterising clinical seizure factors associated with prospective IQ changes, especially declines (*e.g*. Bourgeouis *et al*., 1983). These studies examined children with epilepsy of various types, age ranges, test batteries, and clinical seizure characteristics. Comments that follow focus only on the baseline findings.

Bourgeois *et al*. (1983) examined intelligence in 72 children with mixed epilepsies within two weeks of diagnosis, aged 18 months to 16 years (with IQ 40+), compared to 45 siblings. The mean IQ of the children with epilepsy and matched siblings was 98 and 104.4, respectively; lower in those with epilepsies, but not significantly so. Children with idiopathic epilepsy had a higher IQ than symptomatic (102.5 *vs*. 89.1) at baseline.

Stores *et al*. (1992) examined 63 children (aged 7-12) with new-onset epilepsy both before and after initiation of AED treatment, as well as 47 similarly aged-healthy controls. Administered were measures of specific cognitive abilities (attention, memory, motor and psychomotor speed), general intelligence, and reading and arithmetic performance. At baseline, prior to AED initiation, the partial epilepsy group exhibited significantly poorer attention (establish and focus) and motor and psychomotor ability. Children with absence and other idiopathic generalised epilepsies exhibited fewer significant baseline cognitive abnormalities and differences limited to motor/psychomotor speed. A variety of behavioural abnormalities were also detected in the partial and generalised epilepsy groups at baseline.

Williams *et al*. (1998) compared 37 children with new-onset epilepsy (22 partial epilepsy and 15 primary generalised; aged 6-17) prior to initiation of AEDs and a control group of 26 children with new-onset diabetes using measures of attention and concentration, memory, complex motor processing speed, and behaviour. The children with epilepsy performed more poorly than the diabetic children across 9 of 11 measures, but none of the group differences were statistically significant.

Kolk *et al*. (2001) compared 14 healthy controls, 12 children with partial seizures, and 18 with

congenital hemiparesis and seizures (mean age of six years), the children with epilepsy were said to be of normal psychometric intelligence. The NEPSY was used for cognitive assessment which consisted of 37 tests falling into five cognitive domains (attention and executive function, language, sensorimotor, visuospatial, learning and memory). The children with new-onset partial epilepsy showed significantly poorer performance across four of the five composite cognitive domain scores.

Later investigations

This is an area of increased interest and several recent investigations have appeared. Oostrom *et al*. (2003) examined children (aged 5-16) with newly diagnosed epilepsy (n=51) prior to the administration of antiseizure medications (tested within 48 hours of diagnosis). The children with epilepsy had at least two unprovoked non-febrile seizures of idiopathic or cryptogenic cause, attended mainstream schools, and had no identified neurological disease, a diagnosis of another chronic illness, or previous use of AEDs. Controls were healthy classmates invited by the child with epilepsy and/or their family (n=48). A comprehensive test battery was administered which was reduced through factor analysis to measures of attention, reaction time, intelligence, academic skills, location learning and behaviour. Significantly poorer performance on the part of the children with new-onset epilepsy was observed in the areas of attention, reaction time, visual memory and behaviour, with a trend (p=0.07) of poorer academic achievement (Oostrom *et al*., 2003).

Very comparable results were subsequently reported by Hermann *et al*. (2006) who examined 75 children with new-onset localisation-related and idiopathic generalised epilepsy and 63 healthy controls, aged 8-18. Research participants underwent a comprehensive neuropsychological test battery, neuroimaging, and structured psychiatric interview. Similar to Oostrom *et al*. (2003), they found a pattern of mild generalised cognitive impairment evident across measures of intelligence, language, attention, executive function, and psychomotor speed. Also examined through a structured interview with the parents of the children with epilepsy and controls was the history of any educational services provided to the children for academic difficulties. Supportive educational services of interest included traditional individualised education programs, but also summer school, grade retention, directed homework clubs, tutoring, and other services. History of academic problems was significantly more frequent in children with epilepsy *versus* controls (53% *vs*. 18%; $p<0.001$), with no difference between children with localisation-related epilepsy (LRE) *versus* idiopathic generalised epilepsy (IGE) (44% *vs*. 58%; p=0.16). Moreover, rates of requirement for educational services were comparably elevated in specific syndromes of LRE (benign childhood epilepsy with centrotemporal spikes=65%, other focal=52%) and IGE (absence=45%, juvenile myoclonic epilepsy=46%). Lastly, children with recent-onset epilepsy exhibited an elevated rate of lifetime-to-date Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I disorders, compared to the healthy controls with significantly higher rates of depressive disorders (22.6 *vs*. 4%; p=0.01), anxiety disorders (35.8 *vs* 22%; $p<0.05$), and ADHD (26.4 *vs* 10%; p=0.01) with elevated but less prevalent rates of oppositional defiant and tic disorders (Jones *et al*., 2007).

Fastenau *et al*. (2009) examined a large community-based sample of children with first recognised seizures (n=282, aged 6-14 years, IQ$\geq$70) and 147 sibling controls, characterising their neuropsychological and academic status. They found that 27% of children with a single seizure and up to 40% of those with risk factors exhibited neuropsychological deficits at or near onset. Risk factors for neuropsychological deficit included multiple seizures (OR=1.96), use of AEDs (OR=2.27), symptomatic/cryptogenic aetiology (OR=2.15), and epileptiform activity on the initial EEG (OR=1.9). Absence epilepsy also carried increased odds for neuropsychological impairment (OR=2.0). Academic achievement appeared unaffected, suggesting an opportunity for early intervention (*see* Dunn *et al*. [2002] and McNelis *et al*. [2007] for additional information regarding academic achievement in both new-onset and chronic cases from the Indianapolis series).

Bhise *et al*. (2010) examined 57 children (aged 6-17) with new-onset idiopathic epilepsies using measures of new learning, memory, and attention. Seizures were classified as generalised convulsive (n=5), generalised non-convulsive (n=18), or focal (n=34). They found attention to be a particular area of weakness. Children with generalised, non-convulsive seizures performed worse than children with focal epilepsies on a measure of short-term auditory memory. All groups performed poorly on a test of visual-motor speed. The findings were viewed as suggesting intrinsic abnormalities in children with new-onset, idiopathic epilepsy at baseline.

In summary, cognitive, behavioural and academic abnormality can be identified at or shortly after the onset of childhood epilepsy, even among children with uncomplicated idiopathic epilepsies; children with "epilepsy-only" per Oostrom *et al*. (2003). Clinically, this would imply that careful attention to neurobehavioural status would be very appropriate in children with new-onset epilepsies.

"Comorbidities" before epilepsy appears: neurobehavioural status antecedent to epilepsy onset

Several interesting findings suggest that cognitive, psychiatric, and academic problems may antedate the diagnosis of epilepsy and recognition of the first seizure.

Austin and collaborators (Austin *et al*., 2001) examined behavioural problems in children aged 4-14 with new-onset epilepsy (*n*=224) compared to 135 sibling controls. Higher than expected rates of behaviour problems in the six months before the first recognised seizure were found in the total seizure sample, with 32.1% being in the clinical or at-risk range. Rates were highest in children who had previous events that were probably seizures, with 39.5% in the clinical or at-risk range. In a population-based investigation, Hesdorffer *et al*. (2004) found children with a spontaneous unprovoked seizure to be 2.5 times more likely to meet DSM-IV criteria for ADHD before the first seizure. Similar findings were subsequently reported by Jones *et al*. (2007) who indicated that a subset (45%) of children with epilepsy (45%) exhibited DSM-IV Axis I disorders before the first recognised seizure, including rates of ADHD, depression and anxiety antecedent to epilepsy onset.

Academic problems antedating epilepsy onset have also been reported by several groups. Examining the rate of provision of special school services of diverse types for academic difficulties, approximately 25% of children with epilepsy received these services even prior to their first recognised seizure (Berg *et al*., 2005, 2011; Oostrom *et al*., 2003; Hermann *et al*., 2006; McNelis *et al*., 2005). These psychiatric and cognitive/academic problems imply the presence of adverse antecedent effects that as of yet remain to be identified.

Family aggregation/clustering of cognitive and behavioural complications appears to be a promising path to pursue in order to account for some of this variance (Levav *et al*., 2002; Clarke *et al*., 2007; Iqbal *et al*., 2009; Wandschneider *et al*., 2010; Hesdorffer *et al*., 2012; Smith *et al*., 2012). In addition, neuroimaging investigations have demonstrated abnormalities in cortical and subcortical anatomy, white matter integrity, and ventricular volumes in children with new-onset localisation-related and idiopathic generalised epilepsies (Hutchinson *et al*., 2010; Jackson *et al*., 2011; Pulsipher *et al*., 2009; Tosun *et al*., 2011). These baseline anatomical abnormalities, certainly taking place prior to the onset of epilepsy, have been shown to be related to the integrity of cognition and behaviour (*e.g*. Pulsipher *et al*., 2009, 2011). In addition, ongoing abnormal neurodevelopmental changes in brain structure and connectivity in the context of active epilepsy and treatment (Hermann *et al*., 2010; Tosun *et al*., 2011; Pulsipher *et al*., 2011), as well as syndrome-specific anatomical abnormalities, are reported (Lin *et al*., 2012; Pulsipher *et al*., 2009). How these effects influence cognitive and behavioural development remains to be fully characterised.

Recommendations for advancing clinical care and research

Based on the findings reviewed, several suggestions for advancing clinical care and research were provided by the participants at the Toronto Conference (Helmstaedter *et al*., 2011). The suggestions for childhood cognition were as follows.

Clinical needs and directions

1. It is clear that children with new-onset epilepsies, including those with idiopathic syndromes, exhibit cognitive and behaviour problems at the time of diagnosis. While there is an understandable focus on the seizures themselves and the need for treatment, there is also a need for timely, efficient, cost-effective, and clinic-friendly screening of cognitive, behavioural, and academic problems at the time of diagnosis, preferably before the initiation of medication treatment. It would be helpful if there were a core uniform battery used across epilepsy centres so that collaborative clinical and research issues could be facilitated (*e.g*. EpiTrack Junior [Helmstaedter *et al*., 2010]). In addition, a core set of clinical information should also be collected across centres. The NIH CDE approach to developing these standard measures might prove helpful.

2. The literature pertaining to the neurobehavioural comorbidities of new-onset epilepsy is largely descriptive. A large number of problems have been identified, but there are no standard interventions to treat and prevent these complications. Such approaches could benefit from standard techniques (such as Cognitive Behavioral Therapy [CBT]) or take advantage of Internet technology to provide access to treatment (*e.g*. CDC depression treatment) and standard sets of information.

3. A finer characterisation of the developmental course of children with epilepsy is needed. The core test battery could be re-administered at standard (to be determined) intervals in order to monitor development of new neurobehavioural comorbidities and their relation to seizure variables (*e.g*. seizure frequency) and medications, as well as to track the development of abnormal trajectories.

Research needs and directions

1. There is agreement across centres that neurobehavioural comorbidities may antedate the first recognised seizure and formal diagnosis of epilepsy. This is observed in regard to academic/educational, social, and psychiatric comorbidities. Why is this the case and what are the responsible factors and causes? Identification of biomarkers would only serve to facilitate early identification and treatment.
2. Familial aggregation of comorbidities. There is emerging evidence of aggregation of cognitive and behavioural problems in families with a child with epilepsy. Greater clarification of this aggregation with examination of potential genetic and environmental contributions would be an important path to pursue.
3. Greater examination of the correlates of specific cognitive deficits and their structural, functional and connectivity-related patterns of underlying neurobiological abnormality, as well as development over time, would help us understand the mechanisms of these cognitive disorders. □

Disclosures.
This work was supported by NINDS RO1-44351. The authors have no financial conflicts of interest to report.

References

Alfstad KA, Clench-Aas J, Van Roy B, Mowinckel P, Gjerstad L, Lossius MI. Gender differences in risk-taking behaviour in youth with epilepsy: a Norwegian population-based study. *Acta Neurol Scand Suppl* 2011a; 191: 12-7.

Alfstad KA, Clench-Aas J, Van Roy B, Mowinckel P, Gjerstad L, Lossius MI. Psychiatric symptoms in Norwegian children with epilepsy aged 8-13 years: effects of age and gender? *Epilepsia* 2011b; 52: 1231-8.

Austin JK, Harezlak J, Dunn DW, Huster GA, Rose DF, Ambrosius WT. Behavior problems in children before first recognized seizures. *Pediatrics* 2001; 107: 115-22.

Austin DA, Carr D, Hermann BP. Living Well II: a review of progress since 2003. *Epilepsy Behav* 2006; 9: 386-93.

Begley CE, Famulari M, Annegers JF, *et al*. The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. *Epilepsia* 2000; 41: 342-51.

Berg AT, Smith SN, Frobish D, *et al*. Special education needs of children with newly diagnosed epilepsy. *Dev Med Child Neurol* 2005; 47: 749-53.

Berg AT, Langfitt JT, Testa FM, *et al*. Global cognitive function in children with epilepsy: a community-based study. *Epilepsia* 2008; 49: 608-14.

Berg AT, Hesdorffer DC, Zelko FA. Special education participation in children with epilepsy: what does it reflect? *Epilepsy Behav* 2011; 22: 336-41.

Bhise VV, Burack GD, Mandelbaum DE. Baseline cognition, behavior, and motor skills in children with new-onset, idiopathic epilepsy. *Dev Med Child Neurol* 2010; 52: 22-6.

Bourgeois BF, Prensky AL, Palkes HS, Talent BK, Busch SG. Intelligence in epilepsy: a prospective study in children. *Ann Neurol* 1983; 14: 438-44.

Britten N, Morgan N, Fenwick PB, Britten H. Epilepsy and handicap from birth to age 36. *Dev Med Child Neurol* 1986; 28: 719-28.

Camfield C, Camfield P, Smith B, Gordon K, Dooley J. Biologic factors as predictors of social outcome of epilepsy in intellectually normal children: a population-based study. *J Pediatr* 1993; 122: 869-73.

Chin RF, Cumberland PM, Pujar SS, Peckham C, Ross EM, Scott RC. Outcomes of childhood epilepsy at age 33 years: a population-based birth-cohort study. *Epilepsia* 2011; 52: 1513-21.

Clarke T, Strug LJ, Murphy PL, *et al*. High risk of reading disability and speech sound disorder in rolandic epilepsy families: case-control study. *Epilepsia* 2007; 48: 2258-65.

Cooper JE. Epilepsy in a longitudinal survey of 5,000 children. *Br Med J* 1965; 1: 1020-2.

Cormack F, Cross JH, Isaacs E, *et al*. The development of intellectual abilities in pediatric temporal lobe epilepsy. *Epilepsia* 2007; 48: 201-4.

Davies S, Heyman I, Goodman R. A population survey of mental health problems in children with epilepsy. *Dev Med Child Neurol* 2003; 45: 292-5.

DHEW (Department of Health, Education, and Welfare). *Plan for nationwide action on epilepsy*. Washington (DC): Public Health Service, NIH, 1978.

Dikmen S, Matthews CG, Harley JP. The effect of early *versus* late onset of major motor epilepsy upon cognitive-intellectual performance. *Epilepsia* 1975; 16: 73-81.

Dikmen S, Matthews CG, Harley JP. Effect of early *versus* late onset of major motor epilepsy on cognitive-intellectual performance: further considerations. *Epilepsia* 1977; 18: 31-6.

Dodrill CB, Matthews CG. The role of neuropsychology in the assessment and treatment of persons with epilepsy. *Am Psychol* 1992; 47: 1139-42.

Dunn DW, Harezlak J, Ambrosius WT, Austin JK, Hale B. Teacher assessment of behaviour in children with new-onset seizures. *Seizure* 2002; 11: 169-75.

Farwell JR, Dodrill CB, Batzel LW. Neuropsychological abilities of children with epilepsy. *Epilepsia* 1985; 26: 395-400.

Fastenau PS, Johnson CS, Perkins SM, *et al*. Neuropsychological status at seizure onset in children: risk factors for early cognitive deficits. *Neurology* 2009; 73: 526-34.

Fox J. The response of epileptic children to mental and educational tests. *Br J Med Psychol* 1924; 4: 235-48.

Geerts A, Brouwer O, van Donselaar C, *et al*. Health perception and socioeconomic status following childhood-onset epilepsy: the Dutch study of epilepsy in childhood. *Epilepsia* 2011; 52: 2192-202.

Gleissner U, Sassen R, Lendt M, Clusmann H, Elger CE, Helmstaedter C. Pre- and postoperative verbal memory in pediatric patients with temporal lobe epilepsy. *Epilepsy Res* 2002; 51: 287-96.

Harrison RM, Taylor DC. Childhood seizures: a 25-year follow up. Social and medical prognosis. *Lancet* 1976; 1: 948-51.

Helmstaedter C, Schoof K, Rossmann T, Reuner G, Karlmeier A, Kurlemann G. Introduction and first validation of EpiTrack Junior, a screening tool for the assessment of cognitive side effects of antiepileptic medication on attention and executive functions in children and adolescents with epilepsy. *Epilepsy Behav* 2010; 19: 55-64.

Helmstaedter C, Hermann B, Lassonde M, Kahane P, Arzimanoglou A. *Neuropsychology in the care of people with epilepsy*. Montrouge (France): John Libbey Eurotext, 2011.

Hermann B, Seidenberg M, Bell B, *et al*. The neurodevelopmental impact of childhood-onset temporal lobe epilepsy on brain structure and function. *Epilepsia* 2002; 43: 1062-71.

Hermann B, Hansen R, Seidenberg M, Magnotta V, O'Leary D. Neurodevelopmental vulnerability of the corpus callosum to childhood onset localization-related epilepsy. *Neuroimage* 2003; 18: 284-92.

Hermann B, Jones J, Sheth R, Dow C, Koehn M, Seidenberg M. Children with new-onset epilepsy: neuropsychological status and brain structure. *Brain* 2006; 129: 2609-19.

Hermann BP, Dabbs K, Becker T, *et al*. Brain development in children with new onset epilepsy: a prospective controlled cohort investigation. *Epilepsia* 2010; 51: 2038-46.

Hesdorffer DC, Ludvigsson P, Olafsson E, Gudmundsson G, Kjartansson O, Hauser WA. ADHD as a risk factor for incident unprovoked seizures and epilepsy in children. *Arch Gen Psychiatry* 2004; 61: 731-6.

Hesdorffer DC, Caplan R, Berg AT. Familial clustering of epilepsy and behavioral disorders: evidence for a shared genetic basis. *Epilepsia* 2012; 53: 301-7. doi: 10.1111/j.1528-1167.2011.03351.x

Hinnell C, Williams J, Metcalfe A, *et al*. Health status and health-related behaviors in epilepsy compared to other chronic conditions: a national population-based study. *Epilepsia* 2010; 51: 853-61.

Høie B, Mykletun A, Sommerfelt K, Bjørnaes H, Skeidsvoll H, Waaler PE. Seizure-related factors and non-verbal intelligence in children with epilepsy. A population-based study from Western Norway. *Seizure* 2005; 14: 223-31.

Høie B, Mykletun A, Waaler PE, Skeidsvoll H, Sommerfelt K. Executive functions and seizure-related factors in children with epilepsy in Western Norway. *Dev Med Child Neurol* 2006a; 48: 519-25.

Høie B, Sommerfelt K, Waaler PE, Alsaker FD, Skeidsvoll H, Mykletun A. Psychosocial problems and seizure-related factors in children with epilepsy. *Dev Med Child Neurol* 2006b; 48: 213-9.

Høie B, Sommerfelt K, Waaler PE, Alsaker FD, Skeidsvoll H, Mykletun A. The combined burden of cognitive, executive function, and psychosocial problems in children with epilepsy: a population-based study. *Dev Med Child Neurol* 2008; 50: 530-6.

Hutchinson E, Pulsipher D, Dabbs K, *et al*. Children with new-onset epilepsy exhibit diffusion abnormalities in cerebral white matter in the absence of volumetric differences. *Epilepsy Res* 2010; 88: 208-14.

Institute of Medicine of the National Academies. *The Public Health Dimensions of the Epilepsies*. 2011. http://www.iom.edu/Activities/Disease/Epilepsy.aspx.

Iqbal N, Caswell HL, Hare DJ, Pilkington O, Mercer S, Duncan S. Neuropsychological profiles of patients with juvenile myoclonic epilepsy and their siblings: a preliminary controlled experimental video-EEG case series. *Epilepsy Behav* 2009; 14: 516-21.

Jackson DC, Irwin W, Dabbs K, *et al*. Ventricular enlargement in new-onset pediatric epilepsies. *Epilepsia* 2011; 52: 2225-32.

Jalava M, Sillanpää M. Concurrent illnesses in adults with childhood-onset epilepsy: a population-based 35-year follow-up study. *Epilepsia* 1996; 37: 1155-63.

Jalava M, Sillanpää M. Physical activity, health-related fitness, and health experience in adults with childhood-onset epilepsy: a controlled study. *Epilepsia* 1997; 38: 424-9.

Jalava M, Sillanpää M, Camfield C, Camfield P. Social adjustment and competence 35 years after onset of childhood epilepsy: a prospective controlled study. *Epilepsia* 1997; 38: 708-15.

Jennum P, Gyllenborg J, Kjellberg J. The social and economic consequences of epilepsy: a controlled national study. *Epilepsia* 2011; 52: 949-56.

Jones JE, Watson R, Sheth R, *et al*. Psychiatric comorbidity in children with new-onset epilepsy. *Dev Med Child Neurol* 2007; 49: 493-7.

Jones JE, Siddarth P, Gurbani S, Shields WD, Caplan R. Cognition, academic achievement, language, and psychopathology in pediatric chronic epilepsy: short-term outcomes. *Epilepsy Behav* 2010; 18: 211-7.

Kaaden S, Helmstaedter C. Age at onset of epilepsy as a determinant of intellectual impairment in temporal lobe epilepsy. *Epilepsy Behav* 2009; 15: 213-7.

Kaaden S, Quesada CM, Urbach H, *et al*. Neurodevelopmental disruption in early-onset temporal lobe epilepsy: evidence from a voxel-based morphometry study. *Epilepsy Behav* 2011; 20: 694-9.

Kobau R, Zahran H, Thurman DJ, *et al*. Epilepsy surveillance among adults-19 States, Behavioral Risk Factor Surveillance System, 2005. *MMWR Surveill Summ* 2008; 57: 1-20.

Kokkonen J, Kokkonen ER, Saukkonen AL, Pennanen P. Psychosocial outcome of young adults with epilepsy in childhood. *J Neurol Neurosurg Psychiatry* 1997; 62: 265-8.

Kolk A, Beilmann A, Tomberg T, Napa A, Talvik T. Neurocognitive development of children with congenital unilateral brain lesion and epilepsy. *Brain Dev* 2001; 23: 88-96.

Koponen A, Seppala U, Eriksson K, *et al*. Social functioning and psychological well-being of 347 young adults with epilepsy only-population-based, controlled study from Finland. *Epilepsia* 2007; 48: 907-12.

Lassonde M, Sauerwein HC, Jambaqué I, Smith ML, Helmstaedter C. Neuropsychology of childhood epilepsy: pre- and postsurgical assessment. *Epileptic Disord* 2000; 2: 3-13.

Lennox WG. *Epilepsy and related disorders*. Boston: Little, Brown, 1960.

Levav M, Mirsky AF, Herault J, Xiong L, Amir N, Andermann E. Familial association of neuropsychological traits in patients with generalized and partial seizure disorders. *J Clin Exp Neuropsychol* 2002; 24: 311-26.

Lin JJ, Riley JD, Hsu DA, *et al*. Striatal hypertrophy and its cognitive effects in new-onset benign epilepsy with centrotemporal spikes. *Epilepsia* 2012. doi: 10.1111/j.1528-1167.2012.03422.x [Epub ahead of print]

Lindsay J, Ounsted C, Richards P. Long-term outcome in children with temporal lobe seizures. I: Social outcome and childhood factors. *Dev Med Child Neurol* 1979a; 21: 285-98.

Lindsay J, Ounsted C, Richards P. Long-term outcome in children with temporal lobe seizures. II: Marriage, parenthood and sexual indifference. *Dev Med Child Neurol* 1979b; 21: 433-40.

Lindsay J, Ounsted C, Richards P. Long-term outcome in children with temporal lobe seizures. III: Psychiatric aspects in childhood and adult life. *Dev Med Child Neurol* 1979c; 21: 630-6.

MacAllister WS, Schaffer SG. Neuropsychological deficits in childhood epilepsy syndromes. *Neuropsychol Rev* 2007; 17: 427-44.

McNelis AM, Johnson CS, Huberty TJ, Austin JK. Factors associated with academic achievement in children with recent-onset seizures. *Seizure* 2005; 14: 331-9.

McNelis AM, Dunn DW, Johnson CS, Austin JK, Perkins SM. Academic performance in children with new-onset seizures and asthma: a prospective study. *Epilepsy Behav* 2007; 10: 311-8.

Micallef S, Spooner CG, Harvey AS, Wrennall JA, Wilson SJ. Psychological outcome profiles in childhood-onset temporal lobe epilepsy. *Epilepsia* 2010; 51: 2066-73.

NIH/NINDS Curing Epilepsy Conference 2007. http://www.ninds.nih.gov/funding/research/epilepsyweb/curingepilepsy/index.htm, 2007.

Nolan MA, Redoblado M, Lah S, *et al*. Memory function in childhood epilepsy syndromes. *J Paediatr Child Health* 2004; 40: 20-7.

O'Leary DS, Seidenberg M, Berent S, Boll TJ. Effects of age of onset of tonic-clonic seizures on neuropsychological performance in children. *Epilepsia* 1981; 22: 197-204.

Oostrom KJ, Smeets-Schouten A, Kruitwagen CL, Peters AC, Jennekens-Schinkel A. Not only a matter of epilepsy: early problems of cognition and behavior in children with "epilepsy only"-a prospective, longitudinal, controlled study starting at diagnosis. *Pediatrics* 2003; 112: 1338-44.

Ottman R, Lipton RB, Ettinger AB, *et al*. Comorbidities of epilepsy: results from the Epilepsy Comorbidities and Health (EPIC) survey. *Epilepsia* 2011; 52: 308-15.

Pulsipher DT, Seidenberg M, Guidotti L, *et al*. Thalamofrontal circuitry and executive dysfunction in recent-onset juvenile myoclonic epilepsy. *Epilepsia* 2009; 50: 1210-9.

Pulsipher DT, Dabbs K, Tuchsherer V, *et al*. Thalamofrontal neurodevelopment in new-onset pediatric idiopathic generalized epilepsy. *Neurology* 2011; 76: 28-33.

Rantanen K, Nieminen P, Eriksson K. Neurocognitive functioning of preschool children with uncomplicated epilepsy. *J Neuropsychol* 2010; 4: 71-87.

Rantanen K, Eriksson K, Nieminen P. Cognitive impairment in preschool children with epilepsy. *Epilepsia* 2011; 52: 1499-505.

Riley JD, Franklin DL, Choi V, *et al*. Altered white matter integrity in temporal lobe epilepsy: association with cognitive and clinical profiles. *Epilepsia* 2010; 51: 536-45.

Ross EM, Peckham CS. School children with epilepsy. In: *Advances in epileptology*. Parsonage M, Grant RHE, Craig AG, Ward AA Jr. New York: Raven Press, 1983: 215-20.

Ross EM, Peckham CS, West PB, Butler NR. Epilepsy in childhood: findings from the National Child Development Study. *Br Med J* 1980; 280: 207-10.

Rutter M, Graham P, Yule W. *A neuropsychiatric study in childhood*. London: SIMP/William Heineman Medical Books, 1970.

Schoenfeld J, Seidenberg M, Woodard A, Hermann BP. Neuropsychological and behavioral status of children with complex partial seizures. *Dev Med Child Neurol* 1999; 41: 724-31.

Shackleton DP, Kasteleijn-Nolst Trenite DG, de Craen AJ, Vandenbroucke JP, Westendorp RG. Living with epilepsy: long-term prognosis and psychosocial outcomes. *Neurology* 2003; 61: 64-70.

Sillanpää M, Jalava M, Kaleva O, Shinnar S. Long-term prognosis of seizures with onset in childhood. *N Engl J Med* 1998; 338: 1715-22.

Smith AB, Kavros PM, Clarke T, Dorta NJ, Tremont G, Pal DK. A neurocognitive endophenotype associated with rolandic epilepsy. *Epilepsia* 2012. doi: 10.1111/j.1528-1167.2011.03371.x [Epub ahead of print].

Stores G, Williams PL, Styles E, Zaiwalla Z. Psychological effects of sodium valproate and carbamazepine in epilepsy. *Arch Dis Child* 1992; 67: 1330-7.

Téllez-Zenteno JF, Matijevic S, Wiebe S. Somatic comorbidity of epilepsy in the general population in Canada. *Epilepsia* 2005; 46: 1955-62.

Téllez-Zenteno JF, Patten SB, Jetté N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. *Epilepsia* 2007; 48: 2336-44.

Theodore WH, DeCarli C, Gaillard WD. Total cerebral volume is reduced in patients with localization-related epilepsy and a history of complex febrile seizures. *Arch Neurol* 2003; 60: 250-2.

Tosun D, Dabbs K, Caplan R, *et al*. Deformation-based morphometry of prospective neurodevelopmental changes in new onset paediatric epilepsy. *Brain* 2011; 134: 1003-14.

Wakamoto H, Nagao H, Hayashi M, Morimoto T. Long-term medical, educational, and social prognoses of childhood-onset epilepsy: a population-based study in a rural district of Japan. *Brain Dev* 2000; 22: 246-55.

Wallin JEW. Eight months of psycho-clinical research at the New Jersey State Village for Epileptics, with some results from the Binet-Simon testing. *Epilepsia* 1912; A3: 366-80.

Wandschneider B, Kopp UA, Kliegel M, *et al*. Prospective memory in patients with juvenile myoclonic epilepsy and their healthy siblings. *Neurology* 2010; 75: 2161-7.

Weber B, Luders E, Faber J, *et al*, Distinct regional atrophy in the corpus callosum of patients with temporal lobe epilepsy. *Brain* 2007; 130: 3149-54.

White House. Curing epilepsy: focus on the future. Washington (DC) : The White House, 2000 http://www.ninds.nih.gov/news_and_events/proceedings/conference_curing_epilepsy_summary.htm.

Williams J, Bates S, Griebel ML, *et al*., Does short-term antiepileptic drug treatment in children result in cognitive or behavioral changes? *Epilepsia* 1998; 39: 1064-9.

Wirrell EC, Camfield CS, Camfield PR, Dooley JM, Gordon KE, Smith B. Long-term psychosocial outcome in typical absence epilepsy. Sometimes a wolf in sheeps' clothing. *Arch Pediatr Adolesc Med* 1997; 151: 152-8.

World Health Organization. *Epilepsy: etiology, epidemiology and prognosis*. Fact sheet 165. Geneva: WHO, 2001 (see also: http://www.who.int/mental_health/management/globalepilepsycampaign/en/index.html).