The general population of all children with epilepsy, between a fifth and a quarter, have
developmental or intellectual impairment severe enough to qualify as intellectual disability
(formerly mental retardation) (Ellenberg et al. 1984; Camfield and Camfield 2007; Berg
et al. 2008; Geerts et al. 2011). Even in children whose overall cognitive function falls
within the “normal” range, there is overwhelming evidence of subtle or selective deficits in
various cognitive behavioral domains that may impact school performance. Understanding
the reasons for these findings has implications for prevention, treatment, management, and
anticipatory guidance.

The sources of cognitive comorbidity associated with epilepsy can be broken down into
at least the following categories: (1) shared underlying causes for epilepsy and cognitive
or behavior disorders; (2) the impact of seizures and of abnormal electrographic activity
on cognitive function and on brain development; (3) effects of drugs used to treat seizures;
(4) misdiagnosis; and (5) parental influences on proxy reports. There is good evidence that
each of these plays a role. Understanding these roles can implicitly pave the way for specific
preventive and interventional strategies.

Shared underlying causes
The most common, known causes of epilepsy in children are malformations of brain develop-
ment, intraventricular hemorrhage and other complications of preterm birth, central
nervous system infections, and neurocutaneous disorders (Berg et al. 2009; Wirrell et al.
2011). Cognition and behavior are brain functions, so it is no surprise that insults to or
disorders of the brain of the kind that can cause epilepsy are frequently accompanied by
alterations or impairments in cognition and behavior (Washburn et al. 2007; Lucas et al.
2011; Kihara et al. 2012; Als et al. 2013). In children with epilepsy who have an identified
congenital or acquired lesion, only about 35% fall in the overall “normal” range for cogni-
tive function, and almost 45% have moderate to severe intellectual disability (Berg et al.
2008). This contrasts with 85% of children with no recognized cause for their epilepsy
being in the normal range and only 2.5% being moderately to severely impaired (Berg et al.
2008). Of course, among those with no identified cause when these studies were carried
out, there are likely to be many who, with advances made in genetic testing, would now be considered to have a specific genetic disorder.

With the recent advances in genetic testing and the knowledge afforded by molecular genetics, many forms of epilepsy, especially those beginning in early life and associated with the worst outcomes, are now being linked to a host of genetic errors in genes and systems involved in brain development (Paciorkowski et al. 2011; Mastrangelo and Leuzzi 2012). In fact, most malformations of cortical development are genetic (Barkovich et al. 2012). Somatic mutations in many of these same genes, however, can still be associated with epilepsy and intellectual disability and autism even in the absence of obvious malformations (Gleeson et al. 2000; Matsumoto et al. 2001; Guerrini et al. 2004; Qin et al. 2010; Riviere et al. 2012; Mirzaa et al. 2013). Any single genetic disorder is likely to be rare and accounts for only a tiny fraction of all epilepsy. For example, one recent study estimated GLUT-1 deficiency syndrome to be present in 2.6/1 000 000 population (Ramm-Pettersen et al. 2013). The number of genes involved in epilepsy associated with intellectual disability is rapidly expanding, and the proportion of epilepsies, especially those occurring in young children, that are now associated with specific genetic factors is increasing as testing is more available and acceptable (Paciorkowski et al. 2011; Lemke et al. 2012; Mastrangelo and Leuzzi 2012). In addition to point mutations, larger deletions and duplications of a wide variety of genes are commonly associated with intellectual disability syndromes (Mefford et al. 2012). Currently in the United States, the American Academy of Neurology and Child Neurology Society recommend that a chromosome array be performed in children presenting with moderate to severe developmental delay or intellectual disability (Michelson et al. 2011). It is perhaps not surprising that many of the genes associated with intellectual disability and epilepsy are also associated with autism as well as early life epilepsy (Mefford et al. 2012).

Although a substantial proportion of children have frank intellectual disability, the vast majority do not. In fact, most children are in the normal intellectual range, have normal brain imaging, normal neurological examinations, and no obvious past insult that might explain their epilepsy. Of children with initial onset under the age of 15 or 16, roughly 20–25% have forms of epilepsy that, in the past, were presumed to be “genetic” (Callenbach et al. 1998; Berg et al. 1999), the so-called “idiopathic” epilepsies. These epilepsies occur in otherwise “normal” children (Berg et al. 2010). For the generalized genetic epilepsies (GGEs), long before genetic testing was available, strong family histories provided the evidence for a genetic-familial basis for these disorders (Marini et al. 2004; Vadlamudi et al. 2004a). For benign epilepsy with central-temporal spikes (BECTS), the evidence has been more elusive (Vadlamudi et al. 2004b). Our understanding of the genetic basis of these epilepsies is rapidly changing. For the moment, however, it is important to realize that these epilepsies were often considered “benign” because they responded well to medication and, in many instances, resolved after a few years, approximately 100% for BECTS and up to 70% for childhood absence epilepsy (CAE), the most common of the GGEs.

These epilepsies are associated with subtle but potentially important decrements in specific cognitive functions. BECTS and CAE are two of the best studied of these epilepsies. Specific language impairment has been found in children with BECTS (Lundberg et al. 2005;
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Northcott et al. 2005; Danielsson and Petermann 2009; Lillywhite et al. 2009). Not surprisingly, with advances in neuroimaging, both the structural (Pardoe et al. 2013) and functional (Lillywhite et al. 2009; Oser et al. 2014) correlates of this disruption are increasingly being revealed. Further, genetic studies are making inroads into identifying genetic bases for BECTS. Also not surprising are the findings that, even when the epilepsy itself is not found in other family members, the language disruption can be demonstrated in siblings (Smith et al. 2012; Verrotti et al. 2013), suggesting that this serves as an endophenotype for BECTS.

A similar sequence of findings is reported in children with CAE. Genetic associations are being established, specific cognitive disturbances are documented, particularly in attention (D’Agati et al. 2012; Masur et al. 2013), and the structural (Chan et al. 2006; Pardoe et al. 2008) as well as functional (Bai et al. 2011; Carney et al. 2012; Carney and Jackson 2014) correlates of these disturbances are increasingly being uncovered. As with BECTS, there is evidence for cognitive endophenotypes that may be found in relatives who do not have epilepsy (Chowdhury et al. 2014). Such findings in unaffected family members suggest that the complex underlying genetic predisposition involves more than seizures and that the cognitive elements may be a partial expression of the disorder.

Many epilepsies in “neurotypical” or “typically developing” children do not fit neatly into any of the well-defined syndromic categories. Yet all, to some degree, seem to be associated with an increased level of more subtle impairments in broad ranges of cognitive function with the greatest difference found for processing speed, a nonspecific marker of many disorders of the brain (Hermann et al. 2006; Zelko et al. 2014).

The onset of these relative cognitive impairments is key to understanding their nature. Good evidence suggests that they are present prior to or by the time epilepsy is diagnosed and before medications are initiated. Therefore, they do not appear to be a consequence of either uncontrolled seizures or medications used to suppress seizures. Three studies independently found that, compared to same-aged controls, neurotypical cases were more likely already to be receiving special education services before ever being diagnosed with epilepsy (Oostrom et al. 2003; Hermann et al. 2006; Berg et al. 2011). A few studies have also been able to perform detailed neurocognitive testing immediately following diagnosis and before the initiation of medications. In a large randomized trial of children with newly diagnosed CAE, evidence of attentional deficits was already present in a third of the children prior to initiation of medication (Masur et al. 2013). These deficits persisted despite treatment and despite seizure freedom. In another randomized trial, albeit of adults, a detailed analysis of new-onset patients with epilepsy compared cognitive test performance with healthy controls without epilepsy (Taylor et al. 2010). The affected adults scored lower (worse) on 11 of 14 measures, most particularly those related to memory and processing speed. Two pediatric studies documented similar patterns of results in children with newly or recently diagnosed epilepsy, although many of the children had already initiated medications to control seizures (Hermann et al. 2006; Fastenau et al. 2009). On the whole, these data suggest that subtle cognitive impairments may be part of the expression of the underlying disorder, that is, they may share the same underpinnings or be somehow related to the same factors that cause the brain to produce seizures.
Whether the cognitive variants normalize in time if and when the epilepsy resolves is not fully clear (Northcott et al. 2006).

**The impact of seizures and electrical brain storms**

The notion of epileptic encephalopathy has been around for many years. It was formally defined by DuLac in reference to a group of epilepsy syndromes in which cognitive declines seem to occur in association with and perhaps secondary to uncontrolled seizures and prolonged abnormal electrographic brain activity (Dulac 2001). These epilepsies, as a group, begin in infancy or very early childhood and most are highly drug resistant and include diagnoses such as West, Dravet, and Lennox-Gastaut syndromes. In 2010, the concept was redefined as a process and not a group of diagnostic entities: “the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g. cortical malformation), and that these can worsen over time” (Berg et al. 2010). This shift reflected the developing understanding of the cellular basis of learning, long-term potentiation (Lamprecht and LeDoux 2004). In essence, learning occurs when cells fire. Seizures and other abnormal activities in the brain occur as a result of the same firing of cells. In the developing brain, cells are rapidly growing processes, creating synapses, and organizing into networks. Some cells, processes, and synapses are pruned; in fact, programmed cell death is a normal part of development. The process follows a pattern set up by a predetermined program interacting with environmental factors (experiential and others) and unfolds over many years, arguably throughout the lifespan. It is most active, however, and sensitive to disruption early in life during the critical period or periods of development.

The role of development and critical periods in brain development comes with several predictions concerning cognition. First, cognition should be more severely and globally affected the earlier in life seizures begin. In addition, more severe presentations (more seizures, worse EEG) should be associated with poorer cognitive outcomes. The longer seizures and severe electrographic abnormalities persist, the greater the impact should be on development. Finally, because seizures can, in theory, interfere with normal developmental processes during critical periods in development, there is also the concern that their impacts on cognition will be to some degree irreversible.

The data supporting each of these predictions are substantial. In children with refractory epilepsy, those with the youngest age at onset tend to have worse cognitive performance than those at older onset (Vasconcellos et al. 2001; Freitag and Tuxhorn 2005; Cormack et al. 2007; Vendrame et al. 2009; Berg et al. 2012). Importantly, in children with well-controlled epilepsy, there does not seem to be any association between age at onset and cognitive function (Berg et al. 2012). Children with more frequent seizures may experience greater cognitive impairment relative to those with less frequent, and this is independent of age (Vasconcellos et al. 2001).

The conceptualization of epileptic encephalopathy as a process also comes with important implications, chiefly that early diagnosis and effective intervention can bend the encephalopathy curve and lead to better, if not entirely normal, cognitive outcomes. Evidence from a few sources now links the delay to diagnosis and initiation of treatment with
a decline in development (O’Callaghan et al. 2011; Auvin et al. 2012; Berg et al. 2014). The implications for ameliorating this source of negative impact on development are to identify and correct those reasons for delayed diagnosis and treatment (Auvin et al. 2012; Berg et al. 2014). Once a child is diagnosed, the decline in development continues in those whose seizures are treatment resistant (Berg et al. 2004; Humphrey et al. 2014). Following effective intervention for seizures, numerous studies demonstrate substantial cognitive improvement. Most of these studies are based upon surgical therapy (Jonas et al. 2004; Lee et al. 2010; Skirrow et al. 2011; Lee et al. 2014); however, survey data of parents and physicians suggest that this is also the case with nonsurgical interventions (Brunklaus et al. 2013).

While seizures are the obvious culprit in the concept of “epileptic encephalopathy,” they are likely to be only part of the problem. The syndromes of continuous spike wave in sleep and Landau-Kleffner syndrome (LKS), which are addressed in Chapter 13, are a prime example of “epileptic encephalopathy.” Few if any clinical seizures occur in these overlapping disorders, but the sleep EEG is dominated by a continuous spike wave pattern and is thought to be the source of the cognitive deficits that occur (Tassinari et al. 2009; Raha et al. 2012). By the same token, treatment goals for West syndrome include not only suppression of spasms but resolution of hypsarrhythmia, the chaotic EEG pattern that is practically pathognomonic for this form of epilepsy (Pellock et al. 2010).

The natural response to seizures is to treat them and suppress them
The first-line approach is generally with pharmacologic agents that alter neuronal function and in doing so suppress seizures. Many antiseizure medications (ASMs) are excellent at doing this; however, the seizure suppression often comes at a cost: cognitive, and behavioral side effects. In healthy volunteer adults, these have been beautifully demonstrated in an elegant series of randomized experimental studies (Meador et al. 2001; 2003; 2005). Drugs such as phenytoin, phenobarbital, and sodium valproate are particularly associated with cognitive impacts. Levetiracetam and lamotrigine are much less likely to produce cognitive side effect; however, levetiracetam does have negative behavioral impacts in some individuals (Halma et al. 2014). In children with childhood absence epilepsy, a group already predisposed to attentional difficulties, valproate was found to be inferior to both lamotrigine and ethosuximide in terms of cognitive impact despite good efficacy for seizure control (Glauser et al. 2010).

Prenatal exposure to common ASMs has also been examined in two studies from the United States and the United Kingdom (Meador et al. 2013; Shallcross et al. 2014). These studies found that, in children exposed prenatally to sodium valproate, IQ was on average several points lower at age 6 than expected based upon maternal IQ (one of the strongest predictors of a child’s IQ). Prenatal exposure to other ASMs was not found to be as strongly, if at all, associated with drops in IQ later in childhood. One study from Denmark did, however, report evidence of decreased IQ in young men prenatally exposed to phenobarbital compared to unexposed men (Reinisch et al. 1995).

Finally, a randomized trial of phenobarbital in young children with febrile seizures also demonstrated a several-point decline in developmental scores a few years after the medications
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had been stopped (Farwell et al. 1990; Sulzbacher et al. 1999). The evidence in humans thus supports reasons to be concerned about some of these medications.

In animal models, there is growing evidence that, at the right stage in development, exposure to many common ASMs can inappropriately increase programmed cell death (apoptosis) and that, in adulthood, exposed animals display selective cognitive and behavioral deficits (Bittigau et al. 2002; Bittigau et al. 2003; Forcelli et al. 2010). This finding was especially pronounced for phenobarbital. Lamotrigine by itself and levetiracetam appeared relatively safe with respect to apoptosis and later cognitive effects.

In all, when these drugs are effective in controlling seizures, there may be a price to pay in terms of some impacts on development. This means that, in the very young and rapidly developing brain, there is a balancing act between suppressing seizures and normalizing chaotic EEG activity to prevent interference with neurodevelopment versus potentially impairing those same neurodevelopmental processes with medications. There is currently no evidence to guide practice in this regard. It is likely, although again, there is no evidence, that most clinicians would emphasize seizure control initially.

Misdiagnosis
While there is undoubtedly an increased prevalence of intellectual disability among children with epilepsy and vice versa, not all diagnoses are equal. Several studies have examined the frequency of the misdiagnosis of epilepsy in children and young adults with intellectual disability and with autism, and the results are sobering. Children with intellectual disability or autism (and the two often co-occur together) have as part of their presentation a range of odd behaviors that can be interpreted as seizure-like (stereotypies, nonresponsiveness, motor tics, and other behavioral events). The standard EEG is often abnormal and results in an assumption that the behaviors must therefore be seizures. The criterion standard for diagnosis of epilepsy, however, is the recording of the “event” with simultaneous EEG and video. When this is done, a large proportion of children are found not to have epilepsy. This has been demonstrated from the perspective of a patient with intellectual disability (Chapman et al. 2011) as well as autism (Chez et al. 2006; Yasuhara 2010; Berg and Plioplys 2012).

Such an error can be serious and result in a child who is already intellectually and behaviorally challenged receiving treatments that pose their own array of cognitive and behavioral risks. Potentially, these may exacerbate cognitive and behavioral problems, and result in needless testing and use of multiple ASMs in an effort to control events that are not epileptic seizures.

The parents’ role
A large literature on cognitive and behavioral problems in children with epilepsy is available. An important segment of this literature is based on parent-reported outcomes. The parent of a child with epilepsy, however, is often under considerable stress him or herself. Recent studies have highlighted the role that parents’ stress and perceptions play in reporting children’s outcomes (Ronen Gabriel et al. 2003; Verhey et al. 2009; Baca et al. 2010; Wu et al. 2014; Eom et al. 2016). While much of this may be avoided by direct testing of
the children, this is not always possible in a research or even in a clinic setting. Consequently, parent reports must be taken for exactly that, parents’ report. Even if some children do not themselves actually have the cognitive or behavioral problems reported by the parents, they are still living with the parent’s perception that there is a problem. Thus, for the medical provider, just taking care of the child may not be enough. The parent is always part of the equation. The role of services directed to the parent may, in some cases, be extremely important and enable the parent to be a more effective member of the care team.

Conclusion
Cognitive disorders, whether they be frank and global intellectual disability, or more subtle disorders in otherwise normally developing children, are very common in children with epilepsy. The main types of reasons, reviewed above, have different implications for prevention, evaluation, and intervention. Perhaps most importantly is the need for developmental or cognitive screening to be a routine part of the initial evaluation of a child with epilepsy as well as part of routine follow-up care. The physician providing neurological care (a neurologist in the United States but typically a pediatrician in other settings) may assume that the primary care provider (the pediatrician in the United States but often the general practitioner elsewhere) has already performed recommended screening. A recent audit of a comorbidity screening program at a US tertiary epilepsy center found that one of five children with epilepsy (both new-onset and established patients) had developmental concerns that had not been previously recognized or addressed. This resulted in referrals for further evaluation for these children (Eom et al. 2014). Clearly early control of seizures is a goal of epilepsy care and may ameliorate some, although not necessarily all, of the cognitive impacts of the disorder. The implications that follow from this include the need for rapid and accurate diagnosis, and optimal treatment. Barriers obviously exist at each of these steps and need to be overcome. For children who might be surgical candidates, there is no reason to delay consideration of surgery, or at least a comprehensive evaluation, if there is any difficulty bringing seizure under complete control. Again, barriers exist in the form of physician and parent knowledge, availability of comprehensive epilepsy programs, and other parental concerns (Berg et al. 2013). While some drugs may induce a degree of cognitive dysfunction, few clinicians would use this as a reason to withhold therapy.

Involvement of parents as members of the care team and addressing their needs may help clarify the nature of some problems reportedly occurring in the child (Berg et al. 2013). Progress in this area hinges on filling in the evidence gaps that lead to uncertainty and training health care providers in the urgency to address cognitive concerns.

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