Uncovering the Lifespan Neurobehavioral Comorbidities of Epilepsy

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INTRODUCTION

Epilepsy is without question a costly and complicated major public health problem[1]. Also unquestioned is the fact that in addition to recurrent seizures, abnormalities in psychiatric status, cognition, and social-adaptive behaviors represent major sources of disability in children and adults with epilepsy–complications referred to collectively as the *neurobehavioral comorbidities* of the epilepsies. These comorbidities are not only problems in their own right, but also contribute to well-characterized difficulties in life performance (e.g., education, work, income)[2]. What has been controversial through the decades is the etiology of and best treatments for these comorbidities.

The goal here is to examine the neurobehavioral comorbidities and their potential mediators. Given that the incidence of epilepsy peaks in childhood and older adult years and the epilepsy is often chronic, coordinating care between pediatric and adult specialists is critical[3]. Therefore, we address the comorbidities in a lifespan perspective that is clinically useful and scientifically sound, identifying both strengths and limitations of the literature, and pointing to opportunities for intervention to improve the quality of life for both children and adults with epilepsy.

This review will proceed as follows (see Figure 1). First, we define the specific psychiatric, cognitive, and social comorbidities of pediatric and adult epilepsy, their epidemiology, and real life impact (*Neurobehavioral Comorbidities*). Second, we examine the relationship between epilepsy syndromes and the risk of neurobehavioral comorbidities (*Epilepsy Syndromes*). Third, we address the lifespan impact of epilepsy on brain neurodevelopment and brain aging and the risk of neurobehavioral comorbidities (*Brain Development and Aging)*, followed by discussion of the overarching impact of broader brain disorders on both epilepsy and neurobehavioral comorbidities (*Brain Disorders*). Directions of causality are considered, as are the contribution of selected epilepsy-related characteristics (e.g., epileptiform discharges, age of onset, years of epilepsy chronicity, seizure medications). In the final section of the review, we outline clinic-friendly screening approaches for these problems and recommended pharmacological, behavioral, and educational interventions.

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Increased risk of neurobehavioral comorbidities in epilepsy

The term comorbidity refers to a greater than coincidental presence of two conditions in the same person. Comorbidity does not infer a causal relationship, as co-occurrence of two disorders may arise by chance or share a common underlying mechanism. We focus here on population-and community-based studies, as these findings more representatively document the prevalence of psychiatric, cognitive, and social comorbidities of the epilepsies. This information is then supplemented with findings from specialized epilepsy centers, where typically more details can be provided regarding the nature, range, and correlates of these comorbidities.

Psychiatric comorbidities: Mood and anxiety disorders, psychotic disorder and attention deficit hyperactivity disorder—The burden of co-morbid psychiatric disorders is clear for both children and adults with epilepsy. Community- and population-based investigations uniformly report an increased prevalence of mood, anxiety, and other psychiatric disorders in epilepsy (Table 1).

In pediatrics, a unique set of unequivocal findings document the fact that psychiatric comorbidity is elevated in children with epilepsy compared to both the general population as well as children with other medical disorders. This elevated comorbidity is evident both in children with so-called uncomplicated epilepsies (normal neurological exam and intelligence, attending mainstream schools), but especially marked in those with complicated epilepsies (epilepsy plus brain lesion)—a set of findings reported in two independent epidemiological studies separated by 30-years.[4,5]

In adults, a recent United Kingdom population-based investigation involving 7,403 participants characterized the psychiatric burden associated with epilepsy[6]. After adjusting for confounders, people with epilepsy exhibited significantly elevated odds ratios for social phobia, agoraphobia, generalized anxiety disorder, and depression, as well as all measures of suicidality—these associations were significantly stronger than similar relationships in people with asthma or diabetes and comparable to chronic headache/migraine patients (Supplemental Figure 1).

As might be expected, psychiatric comorbidities in epilepsy are associated with more days of limitation and disability beyond that attributable to the epilepsy itself, and greater health care utilization and cost[7]. Given this psychiatric burden, it is unfortunate that routine screening is not a standard component of pediatric and adult care, especially in light of the potential lethality associated with depression and the widely documented increased risk of suicidal ideation, attempt, and completion[6].

Cognitive comorbidities: Intelligence, academic achievement, and specific cognitive domains (e.g., executive function)—A significant potential complication of any human brain disorder, including epilepsy, is impairment in some aspect of objectively assessed cognition including intelligence, language, visuoperception, learning and memory, executive function, and/or processing speed.

Pediatric epilepsy benefits from several population and community-based investigations (Table 2). These studies indicate an increased prevalence of cognitive abnormalities in children with epilepsy, even those with uncomplicated epilepsies, compared to community- or population-based controls. This literature has also characterized prevalent academic achievement problems with significantly higher rates of school-based interventions (e.g., grade retention, summer school, tutors) and parent characterizations of the struggles of their children at school. We are not aware of a community- or population-based investigation of

neuropsychological status in adults with epilepsy, clearly a major omission in this literature, but numerous clinical studies document this point[8].

The burden of cognitive abnormality in the epilepsies is obviously significant. Investigations from clinical centers have addressed the details of the presenting cognitive profiles associated with specific epilepsy syndromes-a point to be reviewed later. Given this cognitive burden, cognitive screening should be a routine component of clinical care, a point advocated recently by an international review group[9].

Social comorbidities: Adverse life performance outcomes—In addition to psychiatric and cognitive comorbidities, a germane issue is the negative impact of the epilepsies on real life performance, such as peer-to-peer interactions, marriage, independent living, employment and other facets of a productive life. The prevalence of social comorbidities in childhood onset epilepsies are reported in a nationally representative sample of 91,605 children in the United States (birth to 17 years) from the National Survey of Children's Health, including 977 children reported by their parents to have been diagnosed with epilepsy. The children with epilepsy exhibited lower social competence (the ability to have productive and mutually satisfying relationships with others), more physical and functional disabilities, and more unmet medical and mental health needs[10].

Similarly, real life burdens in adults with epilepsies are reported in community- and population-based studies. Especially important are findings from the 2005 Centers for Disease Control Behavioral Risk Factor Surveillance System[11]. Among 120,845 persons 18 years of age and older, there were 2,207 with a reported history of epilepsy (active in 919). Persons with epilepsy (and especially active epilepsy) exhibited significantly higher rates of unemployment, lower income (<$25K), less educational achievement, being single, and higher rates of problematic health conditions and lifestyle practices (e.g., obesity, inactivity, smoking). Persons with the most active epilepsy (i.e., seizures within the past 3 months) were most likely to report more mentally and physically unhealthy days and more activity limitations.

Multiple mediators of comorbidities

The prevalence of neurobehavioral comorbidities in epilepsy across the lifespan have triggered a concerted effort to uncover the potential mediators of these complications, which will inform treatment and prevention. Returning to Figure 1, we now examine the contribution of the type of epilepsy (Epilepsy Syndrome) on the risk of neurobehavioral comorbidities, a longstanding relationship of interest in the comorbidity literature. These studies highlight psychiatric, cognitive, and social impairments that are specific to the type of epilepsy, but also demonstrate some limitations of the syndrome classification approach. Next, we will delineate the impact of disrupted brain development, and accelerated brain aging, as well as broader considerations of intrinsic brain abnormalities on neurobehavioral comorbidities (Brain Development and Aging/Brain Disorder). Finally we will discuss psychosocial mediators of comorbidities.

The association between epilepsy syndromes and comorbidities—Therapeutic decisions and the prognosis of epilepsy rely on the accurate identification of specific epilepsy syndromes. Each syndrome consists of a constellation of clinical and laboratory variables (e.g. seizure semiology, age of onset, MRI, signature EEG findings, mode of inheritance) that set it apart from other disorders. Inherent in this assumption is that the core pathophysiology of each epilepsy syndrome governs both the type of manifested seizures and its associated neurobehavioral comorbidities. For decades, the syndromic model has

served as the basis to investigate the cognitive and psychiatric domain(s) most at risk (Table 3).

While it is logical to categorize comorbidities based on epilepsy syndromes, much remains to be learned about the distribution of shared versus syndrome-specific cognitive and psychiatric abnormalities given the lack of population-based investigations incorporating standardized, contemporary and comprehensive assessments. In point of fact, clinical evidence suggests that comorbidities do not necessarily respect pathophysiological boundaries. To exemplify this point, we first describe the spectrum of cognitive comorbidities that are unique to and common across selected epilepsy syndromes, followed by a discussion of associated psychiatric comorbidities. Then, we focus on temporal lobe epilepsy (TLE), the most frequent form of focal epilepsy, outlining a broad neuroanatomical basis for observed neurobehavioral comorbidities.

There has been a longstanding interest in the association between epilepsy syndromes and cognitive comorbidities. In Benign Epilepsy with Centrotemporal Spikes (BECTS), a syndrome with disturbances in the Sylvian and Rolandic regions, language problems are anticipated[12], but a mild degree of deficit in attention and executive function are also noted[13]. In juvenile myoclonic epilepsy (JME), a disorder of frontothalamic hyperexcitability, impairments extend beyond attention and executive function to include verbal and visual memory, processing speed, naming and language function[14]. While the cognitive complications of childhood absence epilepsy (CAE) would be expected to predominantly involve attention given the underlying thalamocortical network derangement[15], findings also demonstrate affected linguistic ability, broader executive function, and social competence[16]. While the cognitive complications of temporal lobe epilepsy (TLE) would be expected to center on memory disturbance given the underlying mesial temporal/hippocampal pathology, more widespread cognitive disorders have been reported including abnormal executive functions, processing speed, language, and other abilities[17].

Similarly, the association between epilepsy syndromes and the risk of psychiatric comorbidities has been intensely studied, the best example being a proposed link between TLE and an increased risk for depression and psychosis. While depression and psychosis are known complications of TLE, these psychiatric comorbidities have been documented across a wide range of epilepsy syndromes, including BECTS[18], JME[19], and CAE[20]. Further, many of the epilepsy syndromes share broader psychiatric, behavioral, and social problems including Attention Deficit Hyperactive Disorder (ADHD), aggression, conduct problems, unemployment, and social isolation[20, 21]. This controversy regarding the unique psychiatric vulnerability of TLE, decades long, has been replaced by the view that psychiatric disorders are represented across diverse epilepsy syndromes.

These distributed psychiatric and cognitive abnormalities have been linked to surprisingly widespread neuroanatomical derangements. Such functional-structural relationships are again best characterized in people with TLE. While the link between the degree of hippocampal atrophy and memory deficits are well documented, considerable structural abnormality exists outside of this region, including extratemporal lobes (i.e. frontal, parietal and occipital lobes) as well as subcortical and cerebellar regions and their direct and indirect connections[17]. Importantly, these anatomical abnormalities are correlated with specific cognitive deficits, both within and beyond the memory domain. For example, decreased integrity of the uncinate fasciculus (a white matter tract between the mesial temporal lobe and the frontal lobe) is related to poorer memory performances[22]. Likewise, the volume of the corpus callosum and the integrity of the frontostriatal connections are correlated with executive function[23, 24]. Temporal lobe abnormalities have also been implicated in the

neurocircuitry of depression and TLE. For example, the degree of hippocampal atrophy is inversely correlated with the severity and/or duration of depression in TLE with depression [25]. Patients with TLE and psychosis had 16–18% larger amygdala volumes, when compared to TLE patients without psychosis[26]. In parallel with the cognitive literature, widespread functional and anatomical abnormalities are associated with mood disorders in TLE, including orbital frontal cortex[27], cingulate gyrus[28, 29], subcortical regions[28], and brainstem[29].

In summary, epilepsy syndromes provide a useful framework for considering the risk and type of comorbidities, but there is variability in comorbidity presentation within and across syndromes suggesting that variable phenotypic presentations are driven by other factors. At present, treating clinicians must be aware that pediatric and adult epilepsy syndromes may be associated with classically unanticipated cognitive, psychiatric, and social complications —this very true even for what have been viewed as uncomplicated epilepsies. A broad assessment of potential cognitive, psychiatric, and social complications is indicated to fully characterize associated comorbidities. It is certainly possible that as more clearly defined phenotypes are identified, more characteristic neurobehavioral profiles and targeted treatment strategies will result.

The impact of altered brain development and accelerated brain aging on comorbidities—That children with established and chronic epilepsies exhibit subtle anomalies in brain structure and connectivity has been shown. How these anomalies develop is an important question. In healthy maturing children, gray matter volumes decline with concomitant white matter volume expansion[30] (Figure 2A). Against this dynamic backdrop, children with epilepsy exhibit abnormalities in brain structure at or near the time of seizure onset and an altered development trajectory early in the course of epilepsy. At baseline, quantitative MRI studies have revealed enlarged ventricular[31] and reduced thalamic volumes[32] in new-onset idiopathic generalized epilepsy. Over the prospective two years, children with epilepsy displayed a slowed white matter expansion and altered region-specific patterns of gray matter thinning, compared to age-matched controls[33] (Figure 2B). Cross-sectional studies supplement this literature, demonstrating the adverse impact of early-onset epilepsy on brain structure. The posterior corpus callosum appears to be particularly vulnerable, with earlier age of seizure onset consistently linked to reduced white matter volume or microstructural integrity[22, 23]. Clearly, developmental trajectories in children are divergent from their healthy peers and evident near the time of epilepsy onset, but the link between aberrant brain development and variable cognitive, psychiatrc, and social progress in children with epilepsy is uncertain. Preliminary findings suggest that such a relationship exists. In children with new-onset JME, baseline frontothalamic volume is correlated with deficits in executive function[34] and in children with new-onset BECTS, striatal enlargement predicted better executive function performances[35]. It remains uncertain to what degree an altered course of brain development is linked to reliable deviations in cognitive development, and whether these changes are permanent upon remission of seizures and cessation of treatment.

On the other end of the lifespan, the aging brain faces a different set of challenges with epilepsy[36]. Aging-related brain atrophy reflects a myriad of cellular changes including a loss of dendritic spine, as well as accumulation of inflammatory damage[37], and beta amyloid and tau protein[38] (Figure 2C). These changes likely lead to increased vulnerability to seizure-induced cognitive deficits. Although potential cognitive decline in aging patients with epilepsy is likely very slow, these patients start at a lower baseline cognitive level than healthy subjects and may reach a clinically significant threshold of impairment earlier in life[39] (Figure 2D). A particularly relevant question is whether cognitive reserve is associated with differential risks for cognitive impairment in elderly people. Greater cognitive reserve,

as measured by factors such as higher intelligence, education attainment or greater occupational complexity, appears to improve or protect cognitive outcome in cross-sectional[40] and 4-year prospective controlled studies[41] (Figure 2 arrow). In summary, the accumulative effects of normal and pathological aging on brain health may influence the later cognitive outcome of aging persons with chronic epilepsy, but direct examination of these relationships are lacking.

The impact of underlying brain disorder on comorbidities—One of the fundamental assumptions in the field is that epilepsy does not occur in a normal brain. Indeed, factors relating to the underlying brain structural abnormalities not only increase the risk for epilepsy, but also for cognitive, psychiatric, and social impairments. Although the associated neurobehavioral comorbidities can be variable, the structural-functional relationships appears to be stronger in lesional epilepsy such as malformation of cortical development (MCD)[42] and traumatic brain injury (TBI)[43], as compared to epilepsy patients without structural abnormalities. For example, periventricular nodular heterotopia is an MCD associated with both epilepsy and dyslexia. Aberrant cortical to cortical white matter integrity has been found to be correlated with poor reading fluency[42], while abnormal connections between the heterotopia and overlying cortex was related to longer seizures duration[44]. In TBI, the location and extent of injury are often closely related to the risk of developing epilepsy and cognitive complications. The presence of parietal lobe lesions and left insular involvement has been found to be associated with an increased risked of post-traumatic epilepsy and longer epilepsy duration was associated with a decline in full scale IQ[43]. In summary, the cause of epilepsy and the associated neuropathology often dictate the expression of cognitive comorbidities.

The link between an underlying brain disorder and psychiatric comorbidities has also emerged with evidence (Table 4) suggesting bidirectional relationships between epilepsy and a variety of cognitive, psychiatric, and social comorbidities in both pediatric and adult individuals. That is, psychiatric disorder may follow the onset of epilepsy, but, importantly, may also antedate incident epilepsy and serve as a "risk factor" for epilepsy- this is the case for depression, suicidality, ADHD, psychosis, and schizophrenia. Not only is there clear population-based evidence of shared susceptibilities between epilepsy and specific comorbidities, but family have revealed co-aggregation of cognitive[45] and behavioral abnormalities[46] in the siblings and/or parents of persons with epilepsy. Whereas these recent observations suggest that an intrinsic brain disorder, including a possible common genetic predisposition, may underlie both psychiatric comorbidities and epilepsy, the influence of environmental factors remains to be clarified. Furthermore it is unknown whether the co-aggregation of comorbidities is associated with similar structural or functional brain derangements, findings that have been demonstrated in other disorders such as siblings of patients with childhood onset schizophrenia[47].

One unstated but very clinically relevant implication of the bidirectional view is that neurobehavioral comorbidities may be present at diagnosis, early in the course of the disorder, and even occur prior to epilepsy onset. These effects have indeed been reported, especially in children, where multiple investigations of participants with epilepsy without clinical evidence of brain structural abnormalities have demonstrated a pattern of mild diffuse impairment across multiple cognitive domains, as well as elevated rates of behavioral problems including ADHD, with the suggestion that these problems antedated the first recognized seizure[48, 49]. Indeed, approximately 25% of children with new onset idiopathic epilepsies required special education services prior to clinical seizure onset[50]. In adults with new onset epilepsies, cognitive and behavioral disorders have also been reported[51]. From the clinical standpoint, the imperative would be to screen new onset cases for these issues in order to facilitate early intervention. That said, caveats regarding

bidirectional hypotheses include the following: 1) similar bidirectional relationships have been reported for several chronic conditions including stroke, diabetes and cardiovascular disease, inferring a broad and not epilepsy-specific phenomenon[52], 2) only a subset of persons with antecedent psychiatric disorders develop epilepsy and similarly a subset of those with new onset epilepsy present with or develop a psychiatric or cognitive comorbiditiy early on, so this relationship may apply to a unique phenotype.

The psychosocial impact of epilepsy—To this point we have focused largely on neurobiological biological mediators. However, the social and psychological impact of epilepsy can be profound. Narratives from people with epilepsy underscore the significant personal impact of exposure to essentially warningless events on the perception of personal control, the potential effect of epilepsy on many critical aspects of life (e.g., work and income, transportation, interpersonal relationships), exposure to real and perceived stigma, and the general fear of seizures[53]. These and other psychological, social and environmental factors influence the risk of psychiatric commorbities[54] and need to be integrated into comprehensive predictive models.

Relationships between core epilepsy characteristics and comorbidities

Thus far, we have provided a brief account of the evidence that neurobehavioral comorbidities are influenced by several important factors including the epilepsy syndrome, the divergent effects of epilepsy on neurodevelopmental and aging trajectories, as well as the underlying brain disorder. Questions remain as to the directionality of these relationships. While the number of possible permutations are large, we will focus on selected links that are particularly relevant to clinical practice (Figure 1) – the contribution of core epilepsy characteristics, including epileptiform discharges[55], the age of epilepsy onset[56] and years of epilepsy chronicity[57–59], and the prescribed medications, to neurobehavioral comorbidities.

Comorbidities are temporally influenced by epileptiform discharges and seizures—Interictal epileptiform discharges (IEDs) are abnormal neuronal discharges seen on the electroencephalogram (EEG) as a result of transient synchronous depolarization of neurons, producing trains of action potentials[60]. Whereas IEDs by definition occur when a patient is not having a seizure, they usually occur close to the seizure focus and are specific indicators of higher seizure risks[61]. The accumulative literature suggests that these discharges are not merely "harmless" biomarkers of epilepsy but have important behavioral and cognitive consequences. Cognitive deficits are related to the timing, duration, and spatial distribution of IEDs, with more pronounced impairment immediately before and after a prolonged (>3 seconds), generalized IED[55]. Although the most prominent effects of IEDs are attention and motor speed, transient cognitive impairment is not simply inattention[55]. Focal discharges have been temporally linked to material specific deficits, depending on the hemisphere (i.e. right-sided discharge associated with spatial memory deficits and left-side discharges related to verbal memory impairment[55]) and the particular brain region (occipital lobe discharges associated with decreased reaction time when material are presented in the visual field contralateral to the discharges[62]). However, applying these findings in the clinical setting is not straightforward. First, these cognitive deficits are ephemeral and long-term accumulative effects of IEDs are difficult to establish[55]. Second, pharmacological treatments to suppress IEDs, in addition to suppress seizures, have their own cognitive side effects (Table 5) and not all seizure medications can suppress IEDs. Finally, even when seizure medications suppress IEDs, corresponding cognitive improvements are not readily detected[55], suggesting an effect of the underlying pathological substrate. Whereas the views differ regarding the targeted treatment of IEDs, all views agree that rendering individuals

seizure free should be the primary objective, as seizure freedom is associated with reduced IEDs and improved cognition.

In the case of psychoses, the temporal relationship with seizures is particularly relevant (Supplemental Figure 2). Peri-ictal psychoses are more frequently reported than inter-ictal psychoses. In particular, post-ictal psychoses account for approximately 25% of all psychoses of epilepsy. They usually occur after a cluster of secondary generalized tonic-clonic seizures in patients with TLE[63]. These psychotic episodes are usually brief, last from 1 to 6 days[63], and often remit spontaneously within days or weeks. However, they are characterized by mixed mood and paranoid delusions with religious content, with an increased risk of self-harm[64]. Interictal psychoses are unrelated to seizures and typically develop after several years of active mesial TLE[65]. Despite their chronic course, differences with schizophrenia are quite striking with low rates of long-term institutionalization, a tendency of psychotic symptoms to attenuate over time, and the paucity of personality and cognitive deterioration[66]. Understanding these temporal relationships between seizures and psychosis are paramount, as specific types of epilepsy-related psychosis respond to different therapeutic strategies, a point we will elaborate in the treatment section. Finally, it is appreciated that there is an elevated time-limited risk of other psychiatric (e.g., depression) and cognitive (e.g., memory) complications in the post-ictal state that slowly resolve over time. The essential point is that the risk of neurobehavioral comorbidities may be transiently affected by intrinsic features of the disorder, a frequently overlooked consideration.

Early onset epilepsy is an important contributor of comorbidities—Although animal models suggest that seizures in the immature brain cause altered brain networks and poor cognition[67], direct evidence of such an effect in humans has been elusive. When examining children with established epilepsy, many studies show earlier age of seizure onset to be correlated with poorer cognitive function. Specifically, early-life seizures are related to lower IQ[68–70], poor academic performances[71] and developmental delay[72]. However, firm conclusions regarding the impact of early-life seizures on cognition can be confounded by several factors: 1) Many studies are retrospective and cross-sectional in design, 2) Most studies included children with a wide spectrum of epilepsy syndromes including idiopathic and symptomatic as well as focal and generalized epilepsies[68, 70], 3) Several investigations drew patients from specialized (e.g. surgical) populations with refractory epilepsy, which is difficult to apply to the general population of persons with epilepsy and uncomplicated epilepsy[69, 73], 4) Earlier seizure onset can be highly correlated with longer seizure duration and many studies fail to disambiguate this co-linearity, 5) IQ is the only measure of cognitive outcome in many studies and the degree to which other cognitive domains are at risk remains to be determined.

In prospective studies tracking children from the onset of their epilepsy, some groups report subsets of children to be at risk of cognitive decline, but factors in addition to earlier age of seizure onset also appear to contribute to adverse cognitive outcomes[74, 75] and there are mixed findings. Bourgeois and colleagues found that children with a decrement in IQ not only had earlier seizure onset but also had higher baseline IQ, higher incidence of seizure medication toxicity, and more refractory epilepsy[74]. In contrast, Oostrom and coworkers noted that persistent cognitive deficits were not associated with epilepsy-related factors but rather behavior problems prior to the diagnosis of epilepsy and a maladaptive family environment[75]. In summary, notwithstanding the small number of prospective investigations and their limitations, early-onset epilepsy appears to impart a greater risk for cognitive impairment than later-onset epilepsy, especially in children who have complicated epilepsy, behavior problems or difficult family environment.

Clinically, it is important to recognize that earlier seizure onset is an important but not sole contributor of neurobehavioral comobridities in children. Apparent from these studies is the need for a multidisciplinary team approach to aggressively control seizures, manage seizure medication toxicity, treat behavioral problems and mediate family environments.

Longer epilepsy chronicity is associated with lack of learning related improvements and development of psychiatric disorders—An important controversy is whether patients' psychiatric status and cognitive abilities decline with increasing duration of epilepsy, a controversial literature that began in 1924 with mixed results[59]. The disparate findings have been influenced by small sample sizes, heterogeneous epilepsy syndromes, restricted and variable neuropsychological batteries (e.g., IQ and memory), and lack of control groups in many studies. Recent studies have aimed to address some of these shortcomings. One investigation highlighted the differential cognitive trajectories between TLE patients and healthy controls over a prospective 4-year interval[41]. Whereas control subjects showed broad test-retest improvements over time (practice effects), TLE patients on average exhibited minimal practice effects, suggesting a reduced capacity to learn from prior experience. Note too that within the TLE group, variability in cognitive outcomes existed with abnormal cognitive trajectories in a subset of patients (20–25%), with their abnormal prospective cognitive trajectories predicted by smaller baseline brain volumes, lower IQ, older chronological age, and longer epilepsy duration[41].

Although the prospective controlled design is the optimal method to evaluate whether cognitive impairment is progressive, the study's follow up time is short and the cognitive course over a life span is uncertain. Helmstaedter and Elger used a cross-sectional design to indirectly address this challenge, comparing the age-related regression of memory in 1156 TLE patients and 1000 healthy controls over a wide age span (6–80 years)[39]. The epilepsy group showed an earlier learning peak (defined as highest performance prior to decline) than the control group, but subsequent age-related declines ran parallel between the groups, with the epilepsy group always performing worse.

Progression is often couched in terms of cognitive decline. Less examined are the progressive psychiatric complications that may occur in the face of chronic epilepsy. Jones et al.[76] examined temporal lobe epilepsy patients (n = 48) and healthy controls (n = 69) with structured psychiatric interview at baseline and 4 years later to characterize the course of DSM-IV Axis I disorders. Adjusting for the influence of prior psychiatric history, epilepsy subjects exhibited significantly greater risk of interval episodes of Total Axis I Disorders and Mood Disorders, indicating a poorer prognosis for these comorbidities in the context of chronic epilepsy.

While there may be divergent views regarding the long term psychiatric and cognitive course in chronic epilepsy, all views appear to agree on one important fact, which is that persons with chronic epilepsy appear to enter their elder years at a distinct cognitive disadvantage with what is best characterized as age-accelerated cognitive pathology, a point that was emphasized in the section regarding the impact of epilepsy on the aging brain.

Seizure medications have cognitive and psychotrophic effects—Given the large number of available seizure medications, selecting the appropriate medication becomes a daunting task for clinicians. Although there are clear guidelines as to which medication is efficacious for focal versus generalized epilepsy[77], head to head comparisons within this broad classification of epilepsy are rare. In practice, selecting seizure medications depends as much on efficacy as on side effect profile. We, thus, summarized a general consensus on the cognitive and psychiatric side effects of seizure medications (Table 5)[78]. A few broad trends are noted. Cognitively, drug-induced impairments have been associated with

barbiturates, phenytoin, and topiramate while milder cognitive effects are found for lamotrigine and oxcarbazepine. The link between depression and barbiturates, vigabatrin, and topiramate seems to be firmly established, as well as the mood stabilizing properties of carbamazepine, oxcarbazepine, lamotrigine, and valproate. In the majority of cases, a rapid titration of the drug, polypharmacy, a past history of a psychiatric disorder, and limbic system functional or structural abnormalities represent an increased risk for developing drug-induced cognitive and psychiatric complications.

Included in the psychiatric complications is the possible increased suicide risk associated with seizure medications, prompting the United States Food and Drug Administration to issue a warning[79]. Although this remains a controversial issue as studies on the topic have many confounders including a lack of consideration for past suicide attempts, what is clear is that a subgroup of people with epilepsy are more prone to develop psychiatric adverse event whenever a new seizure medication is introduced. Further, patients with a known history of depression and anxiety disorder experience more seizure medication related side effects than individuals without psychiatric diagnoses[80]. Therefore, screening for psychiatric comorbidities including suicidal thoughts and ideation with questionnaires such as the adverse event profile (AEP) should commence at the time of epilepsy diagnosis and prior to beginning treatment with seizure medications, with continual surveillance in company with medication titration and change.

CLINICAL AND TREATMENT CONSIDERATIONS

Typical and atypical features of mood, anxiety disorders, and psychosis

The phenomenology of psychiatric disorders associated with epilepsy has been a matter of debate with several implications for diagnosis, treatment and prognosis. Some authors contend that clinical syndromes comorbid to epilepsy are more often than not characterized by atypical features that are poorly reflected by conventional classificatory systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the International Classification of Disease (ICD-10)[81]. However, other studies demonstrate that it is possible to apply standardized criteria in a not negligible proportion of patients[76, 82]. In general terms, the psychopathological spectrum is likely to be large. On one hand, it is reasonable to hypothesize that patients with epilepsy can experience psychiatric disorders identical to those of patients without epilepsy. However, it is equally reasonable to assume that the underlying brain disorder might influence the expression of mood disorder symptoms, masking some features or emphasizing others. Concerning mood and anxiety disorders, we have reviewed in preceding sections a number of factors that may account for atypical features including: 1) the behavioral changes that may precede or follow seizures; 2) peculiar psychiatric syndromes such as the interictal dysphoric disorder; and 3) the psychotropic effect of seizure medications.

Screening and diagnosis of neurobehavioral comorbidities

To arrive at a definite diagnosis of a psychiatric syndrome in patients with epilepsy can be difficult. In fact, a number of symptoms, which are recognized as diagnostic criteria, may occur in epilepsy secondary to seizure activity or medication treatment. Moreover, one of the most frequent methodological errors in research studies on the subject is the sole reliance on clinical instruments that use measures or cut off scores that may not be valid in the epilepsy population. At present, very few measures exist that have been developed de novo for the assessment of comorbid psychopathology in epilepsy, using modern techniques of questionnaire development.

Among structured or semi-structured clinical interviews for diagnosis of psychiatric disorders following DSM criteria, Mintzer and Lopez [83] proposed the Epilepsy Addendum

for Psychiatric Assessment (EAPA) to be used with the Mini International Neuropsychiatric Interview (MINI); a specific version of the Structured Clinical Interview for Axis I disorders (SCID-I) adapted for patients with epilepsy, named SCID-E, has been developed [84]. Other clinical instruments have been developed specifically for patients with epilepsy in order to identify atypical manifestations of mood disorders not usually captured by DSM-based interviews such as the Seizure Questionnaire [85] and the Interictal Dysphoric Disorder Inventory [86]. Among self-rating screening instruments for depressive symptoms, the well-known Beck Depression Inventory (BDI) has been validated in patients with epilepsy [87]. A six-item, self-report questionnaire, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), was developed for the rapid and objective detection of major depressive episodes in patients with epilepsy. It has been found to be a very practical and user-friendly screening instrument in outpatient epilepsy clinics [88].

Treatment of Psychiatric Disorders

Systematic data on treatment strategies for psychiatric disorders in epilepsy remain limited, with clinical practice relying heavily on individual experience. Experts from U.S. [89] and international[90] panels advocate that treatment of primary psychiatric disorders outside epilepsy is valuable, if the underlying neurological condition is taken into consideration. In this regard, it is important to point out that it is still unclear whether patients with epilepsy respond equally to psychotropic medications or if they have different remission rates, compared to individuals without epilepsy.

Regarding mood disorders, the general impression is that depression in epilepsy is usually mild to moderate in severity with excellent response rates to adequate treatments. Selective serotonin reuptake inhibitors (SSRIs) (e.g. sertraline 50 mg or citalopram 20 mg) can be reasonably considered first choice, bearing in mind that drug doses need to be adjusted according to clinical response, especially if seizure medications with enzyme inducing properties are co-prescribed[91]. Fluvoxamine and nefazodone are the only difficult to use compounds because they are inhibitors of metabolic pathways of a number of seizure medications (especially carbamazepine, phenytoin)[91].

Regarding psychoses, the treatment of peri-ictal psychoses is related to the treatment of the epilepsy (Figure 3). Neuroleptics can be used for a short period of time in order to reduce morbidity and mortality. Interictal psychoses may require long-lasting antipsychotic drug treatment. In such cases, patients need to be followed up in a psychiatric setting. Dosages should be always tailored to patient's response because in almost all cases, enzyme inducers reduce the plasma levels of these drugs. In particular, the use of clozapine has to be carefully monitored because its metabolism has a high inter-individual and intra-individual variability and, especially in combination with valporate, interactions are difficult to predict[92].

The issue of worsening a patient's seizures with initiation of psychotropic medications is a special concern for clinicians[92]. However, for the majority of compounds prescribed at dosages within the therapeutic range, the incidence of seizures is less than 0.5% when other risk factors are excluded. In fact, the "proconvulsive" effect is likely to be dose-dependent, becoming significant for very high dosages. Among antidepressants, SSRIs can be considered reasonably safe while clomipramine and maprotiline are the only drugs that may represent a concern. Among antipsychotics, chlorpromazine and clozapine are considered "proconvulsant" in epilepsy patients. The former may be a concern only at high doses (1000 mg/daily) and the latter at medium and high doses (>600 mg/daily). New compounds are usually well tolerated and can be considered reasonably safe. In particular, olanzapine and quetiapine showed a seizure rate of 0.9% and risperidone an even lower risk of seizures (about 0.3%). Finally, it should be acknowledged that the electroconvulsive therapy is not

contraindicated in patients with epilepsy, it is well tolerated and worth considering in patients with very severe and treatment-resistant mood episodes.

Data on psychological therapies for mood and disorders in epilepsy appear promising. In general terms, cognitive behavioral therapy has showed utility in the management of depression in both adults[93] and children[94].

Treatment of Cognitive Disorders

In addition to psychiatric disorders, cognitive impairment also represents a major source of disability in people with epilepsy, but treatment options are more limited. One of the most practical approaches has been to minimize seizure medication side effects by utilizing a screening questionnaire such as the AEP. Rendering patients seizure free with a single agent at low dose would be the best strategy, as a recent study showed that their AEP was similar to controls[95]. In patients with refractory epilepsy, a tailored approach to select and adjust medications according to the patient's individual AEP can reduce cognitive impairment and improve quality of life[96].

Although medication adjustments can reduce cognitive deficits, they do not mitigate the underlying pathophysiology. Clearly, cognitive impairment in epilepsy has a distinctive mechanism from neurodengenerative diseases, as treatment with anticholinesterase inhibitor does not improve memory in people with epilepsy[97]. Recently, memory and cognitive training techniques have been applied to epilepsy and other neurological disorders, encompassing a wide range of strategies, including computer-assisted working memory programs, external aids (i.e. diaries, calendars), and exercises on self-regulation and problem solving activities. Helmstaedter and colleagues examined the impact of cognitive rehabilitation on 55 TLE patients after temporal lobe resection[98]. Positive effects of training were most evident in verbal learning, with little gain in long-term consolidation. Notably, performance improvements were only found in right TLE patients. These training improvements appears to be nonspecific as Koorenhof and coworkers found that 36% of TLE and 50% of control subjects had gains in memory test performances that were greater than expected from re-test or practice effect[99]. In summary, applying nonspecific strategies such as memory and attention trainings have produced mixed results and it is unclear why some people improve while others do not. Finally, it is also unclear if memory improvements has long-term benefits and would generalize to other cognitive domains.

Conclusions and future directions—Major advances have uncovered potential mediators of psychiatric, cognitive, and social comorbidities, but gaps remain in the early detection and treatment of these disorders. Whereas neurobehavioral comorbidities are present early in the course of epilepsy, standardized diagnostic and therapeutic modules are lacking to provide intervention. Brief, uniform, and clinic-friendly screening tools are needed to identify individuals at risk for neurobehavioral complications and homogenize their access to care. In this regard, the National Institute of Neurological Disorders and Stroke has provided leadership with funding of Neuro-QOL, a project aimed to develop psychometrically sound and clinical relevant quality of life measures in children and adult with neurological disorders[100]. Some of the instruments such questionnaires on executive function, depression and anxiety could be used to screen for comorbidities. However, the primary goal of these instruments is to facilitate longitudinal studies and large-scale clinical trials and thus the use in the clinical arena will require further validation.

Treatment options for neurobehavioral comorbidities remain to be developed. Aside from seizure medication management, strategies are largely adopted from the psychiatric literature and professional experiences. While similarities exit, distinctions are also present between psychiatric disorders and epilepsy-associated comorbidities. Further complicating

the issue is that epilepsy is not a single disorder but encompasses a wide spectrum of complex conditions with shared and unique features. Thus, research is needed to clearly identify biomarkers for specific clinical phenotypes. Once the biological basis of different epilepsies is better understood, large-scale randomized trials are needed to develop epilepsy specific and individualized treatment options.

It is important to understand that epilepsy is a dynamic process in which damage likely invokes compensatory mechanisms. Whether we can harvest these altered neurocircuits to enhance cognitive and psychiatry rehabilitation is unknown, but animal models of TLE have provided considerable insight – early life seizures may lead to functional reorganization of the memory network in which successful performance of memory tasks requires increasing reliance on the frontal lobe, indicating a possible compensation for the dysfunctional medial temporal lobe[101]. Human imaging studies have revealed similar adaptive changes, demonstrating reduced functional connections within the temporal lobe and enhanced functional connections between the temporal and frontal lobes during working memory tasks in TLE[102]. Collectively, these studies hold the promise of a targeted intervention, leveraging epilepsy-specific compensatory mechanisms to enhance and accelerate psychiatric and cognitive recovery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Search Strategy

- PubMed was searched for English-language papers reporting cognitive, psychiatric or social complications of adult and child epilepsies.

- Prior review papers of epilepsy and the cognitive, psychiatric and social comorbidities were examined.

- Papers known by the authors to be pertinent to the topics at hand were reviewed.

Key Message Panel

- Cognitive, psychiatric and social problems are common comorbidities of childhood and adult epilepsies.

- Epilepsy syndromes are relatively weak predictors of the cognitive, psychiatric and social complications of the epilepsies.

- Seizure-related factors (e.g., EEG, age of seizure onset, epilepsy duration) provide additional prognostic value, but the underlying mediating mechanisms remain unclear,

- Neurobehavioral comorbidities are evident at or prior to the onset of epilepsy in some patients, indicating the presence of antecedent factors that may include an abnormal neurological substrate.

- Brain development and brain aging may be influenced by epilepsy, secondarily affecting the rate and type of associated neurobehavioral comorbidities.

- Screening for cognitive, psychiatric and social comorbidities is critical in order to identify and facilitate treatment and improve quality of life.
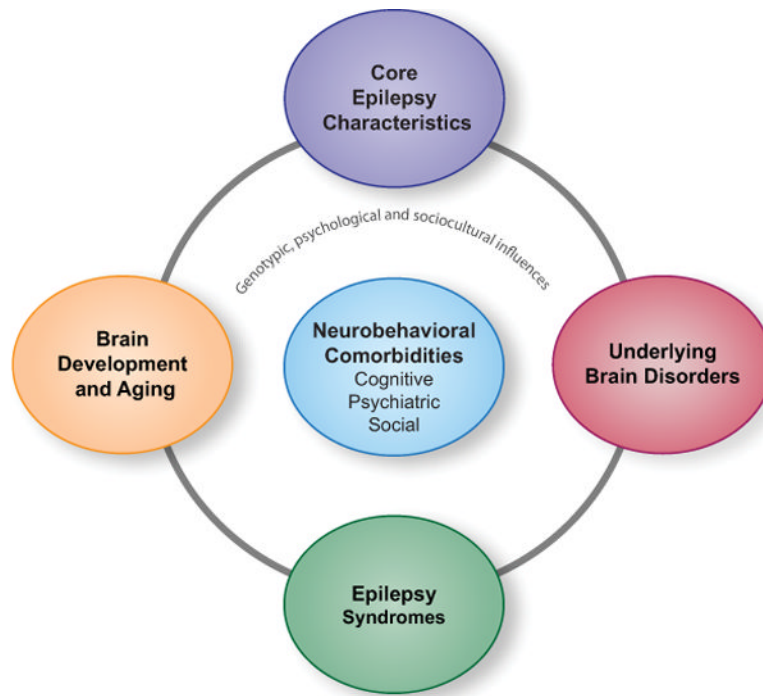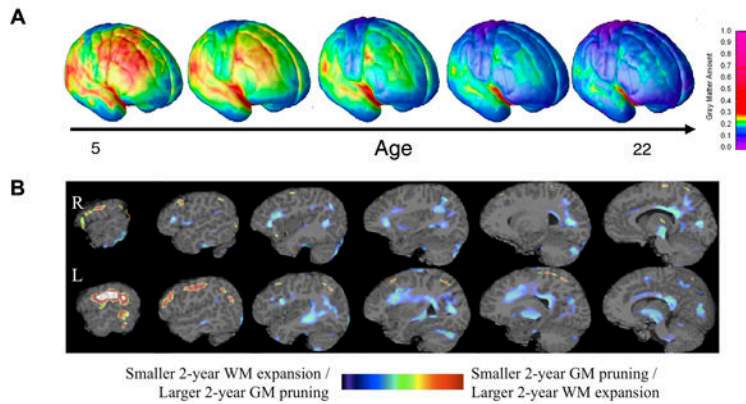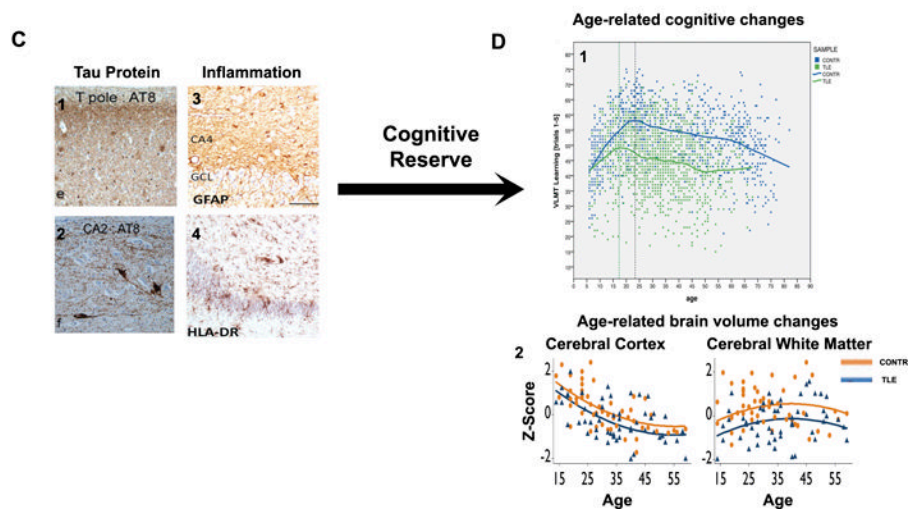
Figure 1.
Theoretical framework for understanding the major mediators of the neurobehavioral comorbities of epilepsy (psychiatric, cognitive and social). The potential mediators include epilepsy syndrome, brain development and brain aging, underlying brain disorders and core epilepsy characteristics (e.g., early age of seizure onset, longer epilepsy duration, epileptiform discharges and seizure medication).
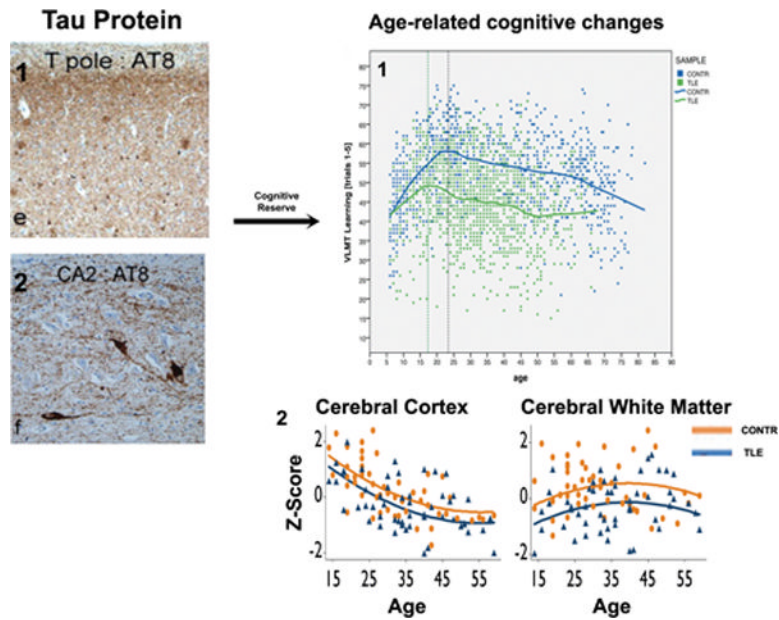
Figure 2.
Altered neurodevelopmental trajectory in pediatric epilepsy. A) Gray matter pruning during normal brain development, with red areas denoting thicker and blue areas denoting thinner cortical regions[30]. B) Children with new-onset idiopathic generalized epilepsy over prospective 2 years exhibited reduced gray matter pruning (red regions) and white matter expansion (blue regions), when compared to their healthy peers[33].

Figure 3.
The impact of aging on brain structure and cognition. C) Accumulation of tau protein[38] (stained with AT8) in the temporal pole (C1) hippocampus (C2) as well as inflammatory changes[37] (stained with GFAP, C3 and HLA-DR, C4) in the hippocampus of patients with TLE. D) These age-related changes might increase epilepsy induced cognitive changes[39] and brain atrophy[130], in which patients start and persist at a lower cognitive level and brain volume than healthy controls. Cognitive reserve is a potential mediator of these age-related changes. Abbreviations: TLE, temporal lobe epilepsy; CONTR, controls; AT8, anti-phosphorylated tau antibody; GFAP, glial fibrillary acidic protein; HLA, antihuman leucocyte antigen. Part A modified with permission from National Academy of Science, USA; Parts B, C, D1 modified with permission from Oxford University Press; Part D2 modified with permission from Wiley-Blackwell.

TABLE 1

Pediatric and Adult Psychiatric Epidemiological Studies

Authors – Pediatrics	Primary Findings
Rutter et al. (1970)[4]	CWE have higher rates of psychiatric disorder (55% complicated, 29% uncomplicated) vs. physical illnesses (12%) vs. HC (7%)
McDermott et al (1995)[103]	CWE with elevated problems (31.4%) vs. cardiac problems (21.1%) and HC (8.5%)
Davies et al. (2003)[5]	CWE with higher rates of psychiatric disorders (56% complicated epilepsy, 26.2% uncomplicated epilepsy) vs. diabetes (10.6%) and HC (9.3%)
Hoie et al. (2006)[104]	CWE have 5–9 times more behavioral problems vs. HC
Lossius et al. (2006)[105]	CWE more behavior problems vs. HC (OR = 1.82)
Berg et al. (2007)[106]	CWE worse behavioral and competency scores vs. sibling controls
Alfstad et al. (2011)[8]	CWE more likely to exhibit behavioral problems vs. HC (37.8% vs. 17%)
Russ et al. (2012)[10]	Increased depression, anxiety, ADHD, conduct, developmental delay, autistic spectrum disorder, social problems, parent aggravation
Cohen et al. (2012)[107]	CWE have elevated rates of ADHD (27.2%)
Authors – Adults	
Ettinger (2004)[108]	Depression more common in PWE (36.5%) compared to asthma (27.8%) and HC (11.8%). PWE had the most prior consultations and treatments for depression.
Ettinger (2005)[109]	48% of PWE screened positive for bipolar symptoms which was associated with significantly (p <.0001) more difficulties with work-related performance, social/leisure activities, and social/family interactions.
Tellez-Zentano et al. (2007)[110]	PWE more likely than individuals without epilepsy to report lifetime anxiety disorders or suicidal thoughts with odds ratio of 2.4 (95% CI = 1.5–3.8) and 2.2 (1.4–3.3), respectively.
Ottman et al. (2011)[111]	PWE more likely (p < 0.001) to report elevated anxiety, depression, bipolar disorder, attention-deficit/hyperactivity disorder, sleep disorder/apnea, and movement disorder/tremor (PR from 1.27–2.39); migraine headache, chronic pain, fibromyalgia, neuropathic pain (PR 1.36–1.96); and asthma (PR 1.25).
Kessler et al. (2011)[7]	PWE exhibit comorbid panic, PTSD, conduct disorder and substance use disorders. Comorbid disorders explain part of the association of epilepsy with impairment, but epilepsy remains associated with work disability, cognitive impairment and days of role impairment after controlling for comorbidities.
Rai et al (2012)[6]	PWE exhibit elevated social phobia and agoraphobia, generalized anxiety disorder, depression, and measures of suicidality, these associations stronger than in asthma or diabetes, and similar to those in people with migraine or chronic headaches.

Abbreviations: CWE, children with epilepsy; PWE, people with epilepsy; HC, healthy controls; CI, confidence interval; PR, prevalence ratio; ADHD, Attention Deficit Hyperactive Disorder; PTSD, Post-Traumatic Stress Disorder

TABLE 2

Pediatric Cognitive Epidemiological and Community Studies

Authors	Primary Findings
Ellenberg et al. (1986)[112]	IQ < 70 in 27% CWE
Hoie et al. (2005) [113]	Impaired nonverbal intelligence in 47% CWE vs. 3% HC
Hoie et al. (2006) [114]	Impaired executive function on 7 of 8 tests in CWE vs. HC
Berg et al. (2008) [115]	IQ < 80 in 25% of CWE
Fastenau et al. (2009) [116]	CWE worse on 4 of 4 cognitive domains vs. HC
Rantanen et al. (2010) [117]	Lower VIQ, FSIQ and learning in CWE (*uncomplicated*) vs. HC

TABLE 3

Epilepsy Syndromes and Anticipated Cognitive and Psychiatric Complications

Epilepsy Syndrome	Core Pathophysiology	Core Cognitive Deficit	Core Psychiatric Deficit
Temporal lobe epilepsy	Hippocampus and mesial temporal lobe	Anterograde memory	Depression and Anxiety
Frontal lobe epilepsy	Frontal lobe	Executive functions	Personality Disorders
Benign epilepsy with centrotemporal lobe	Sylvian and rolandic regions	Language abilities	Unknown
Absence epilepsy	Thalamocortical network	Attention	Unknown
Juvenile myoclonic epilepsy	Frontothalamic network	Executive function	Personality Disorders

TABLE 4

Bidirectional Psychiatric Disorder-Epilepsy Relationships

Authors	
Fosgren (1990)[118]	Depression a risk factor for epilepsy.
Hesdorffer et al. (2000)[119]	Depression a risk factor for epilepsy.
Hesdorffer et al. (2004)[120]	ADHD a risk factor for epilepsy in children.
Qin et al. (2005)[121]	Association between epilepsy and schizophrenia.
Hesdorffer et al. (2006)[122]	Depression and suicide attempt are risk factors for epilepsy.
McAfee et al. (2007)[123]	Psychiatric disorders are risk factors for epilepsy in pediatrics.
Chang et al. (2011)[124]	Bidirectional relationship between epilepsy and schizophrenia.
Adachi et al. (2011)[125]	Bidirectional relationship between epilepsy and psychosis.
Jennum et al. (2011)[126]	Higher health contacts, medical health care costs, lower work and antedate epilepsy onset.
Wotton & Goldacre (2012)[127]	Bidirectional relationship between epilepsy and schizophrenia.
Adelow et al. (2012)[128]	Bidirectional relationship of psychiatric hospitalization and epilepsy.
Hesdorffer et al. (In press)[129]	Bidirectional relationship of psychosis, suicidality and epilepsy.

Table 5

Cognitive and psychotrophic effects of seizure medications

Medication	Motor/cognitive speed	Memory	Mood	Psychosis
Phenobarbital	–	–	–	
Carbamazepine	–	–	+*/	
Phenytoin	–	–	–/	– (Related to toxicity)
Valporate	–	–	+*/	
Vigabatrin			–	–
Oxcarbazepine			+*/	
Gabapentin				
Lamotrigine			+*/	
Levetriacetam			–	–
Pregabalin	–/		+*/	
Topiramate	–/	–	–	–
Tiagabine	–	–	–	–
Zonisamide	–/	–	–	–

–: negative effect; +: positive effect;   : no effect; 0: no evidence *data from psychiatry literature