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Review

Social cognition and psychopathology in childhood and adolescence

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ABSTRACT

There is a substantial body of research on social cognition in adults with epilepsy, and in broad categories such as focal and generalized epilepsies, but much less has been written about social cognition in children with epilepsy (CWE), and in childhood-onset epilepsy syndromes specifically. In several of these syndromes, autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD), two disorders with social cognitive impairments, are reported. There is strong evidence for social cognitive deficits in juvenile myoclonic epilepsy (JME). There is also a considerable amount of evidence for such deficits in a number of syndromes that may be associated with ASD or ADHD, including West syndrome (WS), Dravet syndrome (DS), and the Landau–Kleffner syndrome (LKS). However, the evidence is of variable quality and incomplete across the range of childhood epilepsy syndromes. In some syndromes, childhood epilepsy substantially increases the risk of severe social cognitive impairment, which may persist after the seizures remit. This paper presents an overview of current research on social cognition in childhood epilepsy, with a particular focus on syndromes with a high prevalence of autistic and behavioral comorbidities. Social cognitive impairments represent a considerable additional challenge for patients and caregivers. Early diagnosis and intervention might significantly improve long-term social cognitive outcomes, highlighting the need for greater awareness among clinicians of this important topic.
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1. Introduction

There is considerable evidence that epilepsy can be associated with impairment in social cognitive functioning, irrespective of specific etiology or epileptic focus [1,2], although temporal lobe dysfunction may be particularly implicated [3,4]. Risk may be related to epilepsy syndrome [5], age at onset [1,6], duration of epilepsy [7], frequency of seizures [8,9], intelligence quotient (IQ) [10], and behavioral and psychological comorbidities [11]. However, the absolute and relative impact of many of these factors remains uncertain. Perhaps the most consistently reported predictor of social cognitive deficits is age at seizure onset, earlier onset correlating with more severe impairments [1,6,12–14]. Childhood is a critical phase in the development of basic social cognitive and linguistic abilities; these abilities underpin the advanced communicative competencies that are intrinsic to long-term social, academic, and behavioral outcomes [15,16]. The plasticity of the neuronal circuits that facilitate this development may be especially vulnerable to disruption caused by epileptiform activity in the brain [6,17]. Epilepsy onset in infancy, early childhood, or adolescence may consequently have particularly severe and long-lasting cognitive and social repercussions [1]. Both the underlying pathophysiology responsible for the seizure disorder, and the seizures themselves [8,9,18], may be implicated in lasting developmental impairments or in transitory cognitive disruption, but the picture is often complicated by the presence of one or more additional neuropsychological or developmental disorders [19,20]. The neurobehavioral comorbidities may be associated with functional network abnormalities, as well as genetic factors [6,11,21–26]. Autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) frequently occur in childhood epilepsy and are partly defined by specific deficits in social cognitive functioning.

While clinical factors correlated with deficits in social cognitive ability may be applicable throughout the lifespan [2,3,15,27–29], children may also be especially susceptible to the stigma associated with their condition and may be further restricted by parental protectiveness and fear of seizures or their consequences [30–32]. Limited social contact may represent an additional impediment to social development by depriving children of the basic opportunities to learn and rehearse fundamental communication skills [1,33–35]. School absenteeism is high in children with epilepsy (CWE) [36], and school attendance may correlate with social cognitive ability in children with uncomplicated epilepsy [37]. Children and adolescents may accordingly face a disproportionate burden of social impairment, often with life-long effects. Social cognitive deficits in epilepsy are therefore multifactorial and not

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adequately explained either by psychosocial factors (stigma, isolation, limited social contacts), psychiatric comorbidities, or pathophysiology alone [37–39]. Accordingly, impairments are often found to be independent of IQ and the presence or absence of behavioral problems [2,4].

Interest in social cognition in epilepsy has increased greatly over recent years. However, there are relatively few papers exploring social cognition in childhood epilepsy, despite a recognition several decades ago by Hermann and others of social competence deficits in CWE [11, 40]. The majority of studies have examined social cognitive impairment in either focal, particularly temporal, epilepsies or generalized epilepsies. Lunn et al. [27] published a study of theory of mind (ToM) abilities in children with idiopathic or cryptogenic epilepsy in mainstream education, which reported significant deficits in emotional perception and reasoning. Impaired reasoning in ToM tasks was correlated with communication and attention problems, irrespective of general cognitive function. Lew et al. [2] conducted a similar study of social understanding in children with generalized or focal epilepsy and found deficits in some ToM abilities in both groups; these findings were discussed further by Caplan [41]. More recently, Stewart et al. [42] studied children with generalized genetic epilepsy and reported an association between greater epilepsy severity and lower social competence. An association between higher doses of antiepileptic drugs, namely valproate, ethosuximide, and lamotrigine, and impairments in some aspects of social cognition was also apparent, although this might not be a direct effect of antiepileptic medication but rather, a reflection of the severity of the underlying condition. Raud et al. found multiple social cognitive deficits in children with both focal and generalized epilepsies [28]. Specific impairments in attention, executive, verbal, and fine motor skills, as well as on measures of more complex social cognitive reasoning and ToM tasks were found relative to normative controls. Zhang et al. [43] reported ToM impairments in children and adolescents with idiopathic generalized epilepsy, which, in some cases, were correlated with deficits in subcomponents of executive function, including inhibition, emotional control, initiation, working memory, and monitoring. Social responsivity in CWE in the context of common neurodevelopmental comorbidities such as ASD and ADHD, disorders in which impairments of social cognition play a major role, has received somewhat more attention. Childhood epilepsies encompass a broad range of syndromes, with very different implications in terms not only of seizure control but also of behavioral and social outcome; our aim was to review evidence for impairments of social cognition in a range of individual childhood epilepsy syndromes. Adopting an approach that is focused on the individual syndrome might provide clearer guidance on management than using much broader groupings such as focal epilepsy and generalized epilepsy. Early recognition of social cognitive impairments affords the clearest opportunity to mitigate or redress long-term social deficits through appropriate educational and/or behavioral interventions alongside therapies targeting seizures.

2. Background and definitions

2.1. Childhood epilepsy syndromes

Epilepsy syndromes are defined by the specific set of clinical and laboratory variables that are distinct to each syndrome, including seizure etiology and semiology, age at onset, magnetic resonance imaging (MRI), and electroencephalogram (EEG). Importantly, these definitions also include neurobehavioral comorbidities and an inference that the pathophysiological features responsible for the epilepsy are also implicated in these comorbidities [44]. Deficits in attention, executive function, verbal and visual memory, and linguistic ability, which might compromise complex social cognitive abilities, are characteristics of some epilepsy syndromes emerging in childhood, including the so-called benign epilepsy with centrotemporal spikes (BECTS), juvenile myoclonic epilepsy (JME), and childhood absence epilepsy [45]. More severe impairments are seen in the 'catastrophic' epilepsy syndromes including West syndrome (WS), Lennox–Gastaut syndrome (LGS), and Landau–Kleffner syndrome (LKS). Consideration of the social cognitive deficits found in ASD and ADHD is especially apposite for the present discussion, since these disorders are frequently comorbid in childhood epilepsy and often provide a context for the investigation of social cognitive deficits in pediatric epilepsy samples.

2.2. Autism spectrum disorder (ASD)

Autism spectrum disorder encompasses a heterogeneous group of neurodevelopmental disorders with common clinical characteristics. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnostic criteria specify persistent deficits in social communication and social interaction that must include deficits in social–emotional reciprocity, nonverbal communicative behaviors, and developing, maintaining, and understanding relationships, and restricted, repetitive patterns of behavior, interests, or activities. These characteristics must be present in the early developmental period [46]. Irrespective of epileptic syndrome, there is a recognized association between ASD and epilepsy [47], although the nature of the relationship remains to be fully elucidated. Within the large number of publications on this association, the contributions by Tuchman and colleagues are particularly notable [48–51]. There is some evidence that epileptiform abnormalities might play a role in the development of autistic features, and autistic regression is more prevalent in CWE with autism than those without [52,53]. Alternatively, the cooccurrence of ASD and epilepsy may reflect a common underlying pathophysiology [48] or a shared genetic susceptibility [21,23,25]. A meta-analysis of 31 studies found social cognitive traits characteristic of ASD, namely impaired facial emotion recognition and ToM, were significantly more common in people with epilepsy (PWE) than controls. However, only weak associations between epilepsy-related factors (age at onset, duration, laterality, and origin) were found [54]. As with social behavioral impairments in patients with temporal lobe epilepsy (TLE), amygdala damage may contribute to the deficits in perception of social stimuli seen in primary autistic disorders [55]. Other pathophysiological parallels have been found between the disorders. Functional magnetic resonance imaging (fMRI) studies in autism have revealed reduced white matter connectivity in functional networks supporting ToM reasoning, involving interconnections between the medial prefrontal cortex, temporal lobe, amygdala, and fusiform gyrus among others [56–59]. Similar findings have been reported in idiopathic generalized epilepsy [60] and TLE [61,62]. Autism spectrum disorder is more frequent in CWE with intellectual disability (ID). Seizures in the first year of life represent an additional predisposing risk for subsequent development of ASD. Childhood epileptic encephalopathies are strongly associated with autism. Among these, WS, as discussed later, incurs a particular risk with prevalence as high as 35% [63].

2.3. Attention-deficit hyperactivity disorder (ADHD)

Attention-deficit hyperactivity disorder is a neurodevelopmental disorder characterized by inattention, impulsivity, and hyperactivity. The DSM-5 criteria indicate a persistent pattern of inattention and/or hyperactivity–impulsivity that interferes with functioning or development. Symptoms should be present prior to the age of 12 years [46]. Children with ADHD have a reduced ability to process information from social cues [64], along with deficiencies in more abstract social cognitive reasoning [65]. Furthermore, many of the social cognitive deficits associated with autism and epilepsy have been noted in ADHD, including facial emotion recognition, prosody perception, ToM impairments, and reduced empathy [64]. A recent meta-analysis of studies not including patients with epilepsy compared social cognitive impairments in subjects with ADHD with similar deficits in individuals with ASD and healthy controls [66]. The study found that facial and

vocal emotion recognition and ToM abilities were significantly impaired in ADHD compared with controls, with more severe deficits found in pediatric samples. There is every reason to suppose that children with both epilepsy and ADHD also have such deficits, although there is a lack of research in this area. It is interesting to note that DSM-IV discouraged the diagnosis of ADHD in children with ASD whereas DSM-5 allows both diagnoses in the same child, perhaps indicating an increasing recognition of an overlap between the two conditions.

3. Specific epilepsy syndromes

3.1. West syndrome (WS)

West syndrome is an epileptic syndrome characterized by infantile spasms (IS) emerging within the first year of life, ID that can be profound, and hypsarrhythmia on the EEG. Subsequent autism and ADHD are common. In many cases, WS is symptomatic. West syndrome has been reported as being cryptogenic in around 28% of cases and idiopathic in a further 8% [67]. Among the symptomatic variants, tuberous sclerosis is predominant [68]. West syndrome is one of the epileptic encephalopathies particularly associated with developmental regression [69] with evidence that epileptic activity interferes with normal brain development during a critical phase [6], not least for social cognitive function, although few studies have expressly commented on this subdomain. The resulting disruption may compromise the establishment of functional connections, including those underpinning basic social responsivity, with the potential for long-term impairment. A study of EEG abnormalities in subjects with WS with and without autism found that frontal lobe abnormalities and persistent hypsarrhythmia were significantly related to later emergence of autistic behavior [70]. Symptomatic WS is often characterized by abnormalities in the temporal lobe, and children with WS and autistic or hyperkinetic behavior are significantly more likely to show temporal lobe dysfunction [71]. Temporal lobe lesions are further associated with poorer long-term neurodevelopmental outcomes and ASD [72–75]. Infantile spasms in the context of tuberous sclerosis present a particular risk of comorbid autism, with prevalence as high as 70% [76]. The correlation between IS and autism in these cases may indicate that the tubers, particularly in the temporal lobe, are a common underlying neurobiological mechanism, responsible for both the spasms and neurodevelopmental deficits [17]. Infantile spasms are independently correlated with autism, however, regardless of the presence of tubers. The success of treatment is largely dependent on etiology [77], with cryptogenic cases significantly more likely to achieve symptomatic control of both spasms and behavioral and cognitive dysfunction. Conversely, symptomatic variants are often resistant to treatment, however, significant improvements in both spasms and autistic behavior have been observed with vigabatrin [78]. Early diagnosis and intervention markedly increase the chances of a favorable long-term prognosis [79]. Control of spasms should be prioritized, especially in light of the likely deleterious effects on cognitive outcomes [68]. Recent work has indicated that combined treatment of IS with both vigabatrin and hormonal therapy (steroids or adrenocorticotropic hormone (ACTH) resulted in earlier cessation of spasms, but whether there will be any improvement in social cognitive outcome with combined therapy is still to be determined [80].

3.2. Dravet syndrome (DS) or severe myoclonic epilepsy in infancy

Dravet syndrome is associated with progressive cognitive decline, although early development before onset of epilepsy is often normal [81]. The majority of cases (70–80%) have been shown to be the result of a mutation in the sodium channel, neuronal type I, alpha subunit (SCN1A) gene [82,83]. Dravet syndrome is characterized by febrile or afebrile, generalized or unilateral, clonic or tonic–clonic seizures that appear within the first 1–4 years of life. Intellectual disability is prevalent [84] and correlated with the presence of comorbid ASD. Cognitive development commonly slows after the second year, with specific impairments in psychomotor development accompanied by behavioral disturbance, hyperactivity, autistic features or clinical autism, and ID. The frequency of ASD and attention-deficit disorder (ADD) or ADHD is relatively high. In recent studies, the prevalence of ASD has been reported as 33.6% [85], 24.3% [86], and 22.2% [87], and ADD/ADHD as between 20 and 40% [85,88] depending on age group. The number of patients with DS with inattentive/hyperactive symptoms and/or autistic features may be as high as 67% [89]. The risk of ASD may be especially pronounced with seizure onset before the age of one year [90]. Higher seizure frequency is associated with greater cognitive impairment and developmental regression [91]. Autistic regression is common and may be a direct result of epileptiform activity [92]. Successful treatment of seizures may ameliorate behavioral and autistic features. Chepure et al. [93] described three patients with DS and comorbid ASD. Reduction in seizure frequency with combinations of antiepileptic drugs, including valproate, clobazam, oxcarbazepine, and levetiracetam, was accompanied by improvement in behavioral problems, hyperactivity, and autistic features in all three cases. Cognitive and behavioral outcomes in cases with a failure to control seizures are, however, often profoundly negative, with regression in central nervous system function accompanied by ASD symptoms, including deficits in social interaction and language ability [93]. Dravet syndrome is one of several epileptic syndromes that exhibit genetic mutations commonly associated with autistic traits or autism [94].

3.3. Absence epilepsy

In contrast to the severe epilepsy syndromes just discussed, childhood absence epilepsy and juvenile absence epilepsy have previously been considered as having a good behavioral and cognitive outcome. However, there is an increasing body of evidence that indicates that there is a high rate of behavioral/psychiatric disorders associated with absence epilepsy, particularly ADHD which, as already discussed, is likely to be associated with social cognitive deficits [45]. Although social cognitive deficits might consequently be expected, there is a lack of published information specifically investigating such an association. There is a clear need for such studies.

3.4. Lennox–Gastaut syndrome (LGS)

Lennox–Gastaut syndrome is clinically defined by multiple seizure types (characteristically tonic seizures, although atonic, myoclonic, and atypical absence seizures also occur), abnormalities in the EEG in the form of diffuse slow spike–wave discharges while awake and fast rhythm patterns (≥10 Hz) during slow sleep [95], and a high degree of cognitive impairment. Many cases are symptomatic, and as high as 40% may follow an earlier diagnosis of WS [96]. The majority of patients with LGS have cognitive regression at the time of seizure onset, with a pattern of continued intellectual decline subsequently, even if seizures and EEG abnormalities abate [95]. All aspects of cognitive and social development are affected [5], and the majority of patients exhibit behavioral or psychiatric disorders [97], including autistic features, hyperactivity, impulsivity, anxiety, aggression, and depression [95, 98–100]. Cognitive skills may fluctuate according to seizure frequency [101], suggesting that the epileptic activity itself affects intellectual performance. Autism is not consistently identified in patients with LGS, although Camfield [98] suggested a high prevalence of autistic features, which may contribute significantly to the burden of the condition both for patients and their families. In contrast, He et al. [87] noted that only a few studies had previously reported autistic behavior in LGS [102,103]. In their own study, no patients among the 50 with LGS met the criteria for ASD (specified as deficits in social communication and social interaction, and restricted or repetitive patterns of behavior, interests, and activities). Three patients with LGS did exhibit autistic traits, although in two, only repetitive or restricted behaviors were

evident. The third showed some reduction in social interaction. Notably, all three had an earlier than average age at seizure onset (between 2 and 6 months) compared with the group as a whole. A common feature associated with risk of ASD in epilepsy, regardless of specific syndrome, is onset before 2 years of age, with earlier onset associated with greater risk [104]. This raises the question of how many of these subjects had IS preceding the LGS.

3.5. Atypical benign partial epilepsy (ABPE) or pseudo-Lennox syndrome

Atypical benign partial epilepsy is an idiopathic focal epilepsy that forms part of the 'epilepsy aphasia spectrum' along with the more benign Rolandic epilepsy and the more impairing LKS discussed in the following sections. The clinical features of ABPE include multiple seizure types, including focal, generalized (atonic, absence, or myoclonic), and occasional febrile seizures or status epilepticus; pronounced EEG abnormalities during sleep, often progressing to continuous spike–wave during sleep (CSWS); and sometimes reversible neurocognitive deficits, including deficits in language, motor function, and cognition. There is little specific mention of social cognitive impairments in ABPE, although Allen et al. [105] discussed the case of a male patient who was followed up between the ages of five and 13 years; during the most active periods of epilepsy, deterioration in language, oromotor, cognitive, and social communicative skills were observed, together with the development of ASD. Epileptic discharges appeared to contribute substantially to the observed neurodevelopmental deficits, suggesting that this might be an example of 'state-dependent cognitive impairment', previously described by the current author, rather than a permanent change [106].

3.6. Benign childhood epilepsy with centrotemporal spikes benign epilepsy with centrotemporal spikes or Rolandic epilepsy

Benign childhood epilepsy with centrotemporal spikes is associated with a notably more positive prognosis than the majority of childhood-onset epilepsies, in terms of both seizure resolution and cognitive outcome. Age at seizure onset is typically between four and 10 years, and the epilepsy resolves, with or without treatment, by the mid-teenage years. Camfield and Camfield reported that all 79 patients in a population-based study remitted within five years of diagnosis, with no residual psychosocial deficits. In a review of their clinical experience with patients with BECTS, they concluded that the disorder only threatens normal developmental outcomes if it impedes the formation of social relationships [5]. More recently, however, evidence has been presented that epileptiform activity in BECTS may have an effect on cognitive function and behavior, including the domains relevant to social competence, such as verbal learning and linguistic ability. Intelligence quotient may also be significantly impaired [107], showing a correlation with the frequency of EEG spikes. Attention-deficit hyperactivity disorder [108] and ADHD-like symptoms of impulsivity [109] and attentional impairments [110] have also been noted, with the prevalence of ADHD reported as 30–70% [111–114]. Attention-deficit hyperactivity disorder has variously shown correlations with younger age at onset, nocturnal epileptiform activity [111], and a history of febrile seizures [112]. Again, it is important to distinguish between 'state-dependent' impairments and those that are likely to be permanent.

Social cognitive impairments in BECTS were investigated by Genizi et al. [115]. Fifteen children aged between seven and 13 years were assessed on emotional and cognitive aspects of social cognition using tests of 'affective' (understanding a person's emotional states) and 'cognitive' (understanding a person's intentions) ToM. While subjects showed significant impairments in affective ToM compared with age-matched and education-matched controls, cognitive ToM appeared to be unaffected. The tasks also revealed lower scores on verbal and visual learning rate parameters and verbal processing. The authors concluded that BECTS may affect the neural networks underpinning social cognitive processes that are essential for appropriate social behaviors. No patient follow-up was reported. There was consequently no indication whether these deficits would resolve along with the seizures and EEG abnormalities in later years, in common with the pattern for other cognitive and behavioral impairments in BECTS. In a separate study, patients with BECTS were found to have specific deficits in facial fear recognition and reduced activation of functional networks underpinning social cognition, which were negatively correlated with age, suggesting that a delayed maturation process may be responsible [116].

3.7. Landau–Kleffner syndrome (LKS) or acquired epileptic aphasia

Landau–Kleffner syndrome is a severe encephalopathy designated as an epilepsy syndrome, although clinical seizures may only be present in around 70% of cases. The disorder is characterized by electrical status epilepticus of slow-wave sleep (ESES), verbal auditory agnosia, language impairment, and regression of language and social skills with many autistic features [117]. Hyperactivity, aggression, impulsivity, and attention-deficit are also common [118–123]. Attention-deficit hyperactivity disorder has been reported in around 50% of patients [124] and behavioral disturbances in between 50 and 70% [125]. The presentation may resemble that of primary autistic regression, but while there is a degree of overlap in semiology between LKS and ASD, there are distinguishing characteristics. For example, while language regression occurs before the age of 3 years in ASD, regression in LKS typically occurs later, between 5 and 7 years, with severe loss of acquired vocabulary and language [126]. It is not surprising that this can often be associated with behavioral problems in children who previously had normal language development. Long-term severity of language impairment in LKS is negatively correlated with age at onset [127]. Autism spectrum disorder has been diagnosed in patients with LKS, although autistic traits tend to be expressed as a predominant language deficit [128], with less clear deficits in social reciprocity [129]. It has been suggested that patients with LKS do not appear to exhibit the same abnormalities in reciprocal social relatedness and restricted patterns of interests and behaviors that are characteristic of ASD [126]. However, Lesca et al. [130] did report clinical characteristics of ASD, including inadequate social behavior, in 21% of patients, and evidence of autistic regression has also been found [118,131–133]. Overall, the relationship between LKS and ASD is complex with a potential for misdiagnosis: autistic features are often reported in LKS while EEG abnormalities are common in autism, and seizures occur in a relatively high proportion of patients [126,134]. It has been suggested that some cases presenting as autism might represent a variant of LKS [135,136]. Antiepileptic medication has resulted in improving language and social behaviors in some cases [92,137]. The prognosis for LKS itself is mixed. Seizures tend to resolve by mid-teenage years. However, language deficits may persist, and some patients are left with permanent impairments [126]. The original study by Morrell et al. [138] suggested that early surgical intervention with multiple subpial transection could result in a good language and cognitive outcome, but subsequent reports were less favorable [139].

3.8. Janz syndrome or juvenile myoclonic epilepsy (JME)

Juvenile myoclonic epilepsy is a genetic generalized epilepsy syndrome characterized by myoclonic, absence, and generalized tonic–clonic seizures. The typical age at onset is between 12 and 18 years. While the response of the seizures to antiepileptic drugs is often good, studies have indicated the presence of cognitive and imaging abnormalities consistent with frontal lobe dysfunction, with accompanying challenging behavioral traits, and often poor social outcomes. The dependence of ToM abilities on complex frontotemporal interactions has been reported in several studies, and patients with JME may exhibit functional impairments in ToM tasks. Giorgi et al. [140] assessed 20 children with JME on measures of social cognition and ToM, as well as measures of general cognitive ability. Compared with neurotypical controls, subjects scored lower on both social cognitive measures and general

cognitive ability, with deficits in executive function, psychomotor speed, and verbal and visual–spatial memory. In their original 1957 paper describing the syndrome, Janz and Christian identified particular characteristic personality traits in their patients [141]. Many patients were considered to have suggestible, unreliable, and immature personalities, which contributed to an inadequate level of social adjustment. A trend towards social maladjustment was also noted by Lund et al. [142] in a later study. While the terminology used by Janz and Christian might not explicitly indicate social cognitive deficits, the characteristics they describe may have much in common with the ToM impairments found by Giorgi et al.

4. Other childhood epilepsies

There are several other epilepsy syndromes with onset in infancy and childhood, but little, if any, information is available on the social cognitive aspects of these disorders. Past work and adult studies have reported on social cognition in TLE and frontal lobe epilepsy (FLE) with substantial evidence of marked deficits in both basic and complex social cognitive functioning [1,2,27,61,143,144]. Deficits in certain other differentiated cognitive functions, including verbal learning and memory, attention, language, and executive function, as well as generalized cognitive impairments, have been found to correlate with compromised social cognitive abilities in individuals with both focal and primary generalized epilepsies (PGEs) [1,145] and are more frequently the subject of investigation in pediatric samples. Findings from research into social cognition in these broader categories will be discussed briefly in the following sections.

4.1. Temporal lobe epilepsy

Temporal lobe epilepsy, in particular mesial-TLE, is characterized by more severe deficits in complex aspects of social cognition [146]. Most of the studies have been in adults. Theory of mind competency appears especially impaired [147] and is closely associated with compromised executive function [37]. Facial emotion recognition and mind-reading tasks in adult patients with TLE have been the subject of numerous studies with consistent deficits reported [148]. Studies in children are few. However, earlier age at epilepsy onset is consistently correlated with greater deficits [12,149], in particular, in the presence of damage to the amygdala, temporoparietal junction, or superior temporal sulcus and ventromedial prefrontal cortices, or to the integrity of the functional networks underpinned by these nodes [37,146]. Emotional recognition depends critically on mesial temporal structures with influences from the somatosensory, orbitofrontal, and cingulate cortices. The amygdala is particularly concerned with facial emotion recognition and mediating social behavioral responses [26,150]. Damage to the amygdala is implicated in compromised social abilities in specific areas [7,151], in particular, in negative emotion recognition, with disruption during childhood and adolescence contributing to immediate and long-lasting impairments [37]. Epileptic discharges originating in the mesial temporal lobe may also interfere with online ToM abilities [15,152].

Studies of social cognition in children with TLE remain remarkably lacking, despite the recognition of the importance of early development in establishing both basic and complex social competencies and the negative and lasting implications of disruption to critical networks at seminal developmental epochs for later social cognitive functioning [153]. Pediatric studies have found impairments in facets of basic social perception and socially directed memory function in the context of localizable temporal lobe lesions [15] and temporal network dysfunction [154]. Impairments in facial identity recognition, direction of gaze, facial emotion perception [15,155,156], and emotional prosody recognition [157] have been investigated, with children with TLE consistently performing below the level of age-matched healthy controls. Impairments are further associated with earlier age at onset and the presence of broader comorbid behavioral problems [156]. In some cases, impairments may be evident before the onset of overt seizures [154]. Deficits in basic social cognitive function persist in postsurgical patients and may show a decline in the immediate postsurgical period in younger patients [158].

4.2. Frontal lobe epilepsy

Functional magnetic resonance imaging studies indicate that the medial prefrontal cortex and bilateral posterior temporoparietal junction are central to processing social stimuli [148,159,160], in addition to mediating executive function and attention control [161]. Pathophysiologically, TLE and frontal lobe epilepsy (FLE) are similarly associated with lesions and impaired functioning of the temporolimbic and frontal networks, brain regions that are critical to the development and maintenance of ToM capabilities [162–167]. Indeed, studies in adults have found greater impairment in ToM tasks such as the faux-pas test in patients with FLE than those with TLE or healthy controls [37].

Frontal lobe epilepsy has a frequent association with neurobehavioral comorbidities, and attention deficits and impaired executive function are characteristic behavioral traits in pediatric patients with FLE [168]. As mentioned previously, studies in PWE have found deficits in executive function to be correlated with social cognitive impairments, and furthermore, primary attention-deficit disorders share many of the social impairments present in autism. A small number of pediatric studies in patients with FLE or children with epilepsy-related frontal lobe dysfunction have reported behavior characterized by inattention, hyperactivity, and impulsivity [169,170], or behavioral traits similar to those seen in autistic disorders [171]. Studies have also found impairments in visual–spatial reasoning, memory, psychomotor speed, and alertness, in addition to attentional shortfalls [172,173], cognitive deficits that may impede the ability of an individual to participate in social interactions. Impairments in these cognitive abilities, along with behavioral disorders, have also been found in children with cryptogenic FLE however [172], indicative of alternative mechanisms beyond frontal lesions influencing basic cognition in some individuals.

4.3. Generalized epilepsy

Patients with PGE may be equally susceptible to disrupted cognitive development and impaired social functioning as individuals with focal epilepsies [1,2], however, the specific impairments in social cognition may differ from those seen in focal epilepsy. Deficits in negative emotion perception may be especially pronounced [153], and broader cognitive and behavioral comorbidities are analogous to those seen in frontal lobe dysfunction. In pediatric samples, these may have a correspondingly severe impact on long-term psychosocial outcomes [174].

In common with the other epileptic disorders, research on the social cognitive aspects of idiopathic generalized epilepsy (IGE) in children is relatively sparse. The available studies in pediatric generalized epilepsy have found deficits in both basic cognitive substrates such as memory, attention, executive function, and basic verbal and fine motor skills [28], as well as more complex linguistic function and social cognitive processing, including pragmatic language ability, social communication [175], cognitive empathy [176], and ToM [43]. The effect of ToM impairments in children and adolescents with genetic generalized epilepsy on general social competence was assessed in a recent study by Stewart and colleagues [42]. Subjects were impaired in both cognitive and affective ToM compared with healthy controls, with performance in ToM tasks and severity of epilepsy found to correlate with deficits in everyday social functioning, independent of general IQ or impaired executive skills. The effect of antiseizure drugs and social functioning was also evaluated: higher doses of valproate were associated with poorer affective ToM and higher doses of ethosuximide and lamotrigine correlated with lower social competence. However, as stated previously, higher

doses of antiseizure drugs may be an indication of more severe epilepsy, which could be the underlying reason for poorer performance.

Deficits in cognition in PGE have been attributed to frontal lobe dysfunction [176] or to disruption by seizures of the functional integrity of wider neural networks underpinning complex social cognitive processes [153,177]. In addition, patients with PGE share the same greater apparent susceptibility to neurodevelopmental disorders, such as ASD, as patients with temporal or frontal focal epilepsies, as well as exposure to the same challenges living with a stigmatized condition may present to social interaction [153].

5. Conclusion

Social cognitive deficits are present in a number of epileptic syndromes across the lifespan but may be especially prevalent and debilitating in childhood-onset epilepsies. The particular impairments associated with childhood epilepsy syndromes have not been extensively investigated. The social cognitive impairments almost certainly result from several different causes, including underlying pathology, epileptiform discharges, especially ESES, and the seizures themselves. It is noteworthy that Janz and Christian described impairments in social adjustment in patients with JME as early as 1957, indicating that social deficits in CWE have long been recognized. There is growing evidence that, in at least some childhood epilepsy syndromes, early intervention to treat the seizures and EEG abnormalities may result in markedly improved social and cognitive outcome. The possibility that early psychological interventions might also improve outcome in CWE who have social cognitive deficits requires further research. Although the body of literature on the social cognitive abilities of children with specific early-onset epilepsy syndromes remains small, there is increasing research interest in this area. The hope is that this will lead to early recognition and intervention with better outcomes in terms of social cognitive abilities.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Bujarski KA, Flashman L, Li Z, Tosteson TD, Jobst BC, Thadani VM, et al. Investigating social cognition in epilepsy using a naturalistic task. Epilepsia 2016;57:1515–20.
[2] Lew AR, Lewis C, Lunn J, Tomlin P, Basu H, Roach J, et al. Social cognition in children with epilepsy in mainstream education. Dev Med Child Neurol 2015;57:53–9.
[3] Broicher SD, Kuchukhidze G, Grunwald T, Kramer G, Kurthen M, Jokeit H. "Tell me how do I feel"—emotion recognition and theory of mind in symptomatic mesial temporal lobe epilepsy. Neuropsychologia 2012;50:118–28.
[4] Schacher M, Winkler R, Grunwald T, Kraemer G, Kurthen M, Reed V, et al. Mesial temporal lobe epilepsy impairs advanced social cognition. Epilepsia 2006;47:2141–6.
[5] Camfield P, Camfield C. Epileptic syndromes in childhood: clinical features, outcomes, and treatment. Epilepsia 2002;43(Suppl. 3):27–32.
[6] Berg AT. Epilepsy, cognition, and behavior: the clinical picture. Epilepsia 2011;52:7–12.
[7] Amlerova J, Cavanna AE, Bradac O, Javurkova A, Raudenska J, Marusic P. Emotion recognition and social cognition in temporal lobe epilepsy and the effect of epilepsy surgery. Epilepsy Behav 2014;36:86–9.
[8] Holmes GL, Schachter SC, DGK-N Trenite. Behavioral aspects of epilepsy: principles and practice. Demos Medical Publishing; 2008.
[9] Austin JK, Risinger MW, Beckett LA. Correlates of behavior problems in children with epilepsy. Epilepsia 1992;33:1115–22.
[10] Caplan R, Sagun J, Siddarth P, Gurbani S, Koh S, Gowrinathan R, et al. Social competence in pediatric epilepsy: insights into underlying mechanisms. Epilepsy Behav 2005;6:218–28.
[11] Hermann BP, Whitman S, Hughes JR, Melyn MM, Dell J. Multietiological determinants of psychopathology and social competence in children with epilepsy. Epilepsy Res 1988;2:51–60.
[12] Monti G, Meletti S. Emotion recognition in temporal lobe epilepsy: a systematic review. Neurosci Biobehav Rev 2015;55:280–93.
[13] Hlobil U, Rathore C, Alexander A, Sarma S, Radhakrishnan K. Impaired facial emotion recognition in patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS): side and age at onset matters. Epilepsy Res 2008;80:150–7.
[14] Meletti S, Benuzzi F, Rubboli G, Cantalupo G, Stanzani Maserati M, Nichelli P, et al. Impaired facial emotion recognition in early-onset right mesial temporal lobe epilepsy. Neurol 2003;60:426–31.
[15] Laurent A, Arzimanoglou A, Panagiotakaki E, Sfaello I, Kahane P, Ryvlin P, et al. Visual and auditory socio-cognitive perception in unilateral temporal lobe epilepsy in children and adolescents: a prospective controlled study. Epileptic Disord 2014;16:456–70.
[16] Austin JK, Smith MS, Risinger MW, McNelis AM. Childhood epilepsy and asthma: comparison of quality of life. Epilepsia 1994;35:608–15.
[17] Bolton PF, Park RJ, Higgins JN, Griffiths PD, Pickles A. Neuro-epileptic determinants of autism spectrum disorders in tuberous sclerosis complex. Brain 2002;125:1247–55.
[18] Holmes GL. What is more harmful, seizures or epileptic EEG abnormalities: is there any clinical data? Epileptic Disord 2014;16:S12–22.
[19] Steiger BK, Jokeit H. Why epilepsy challenges social life. Seizure 2017;44:194–8.
[20] Berg AT, Caplan R, Hesdorffer DC. Psychiatric and neurodevelopmental disorders in childhood-onset epilepsy. Epilepsy Behav 2011;20:550–5.
[21] Srivastava S, Sahin M. Autism spectrum disorder and epileptic encephalopathy: common causes, many questions. J Neurodev Disord 2017;9:23.
[22] Frye RE, Casanova MF, Fatemi SH, Folsom TD, Reutiman TJ, Brown GL, et al. Neuropathological mechanisms of seizures in autism spectrum disorder. Front Neurosci 2016;10:192.
[23] Lee BH, Smith T, Paciorkowski AR. Autism spectrum disorder and epilepsy: disorders with a shared biology. Epilepsy Behav 2015;47:191–201.
[24] Nelson Sacha B, Valakh V. Excitatory/inhibitory balance and circuit homeostasis in autism spectrum disorders. Neuron 2015;87:684–98.
[25] Kang JQ, Barnes G. A common susceptibility factor of both autism and epilepsy: functional deficiency of GABA A receptors. J Autism Dev Disord 2013;43:68–79.
[26] Cristinzio Perrin C, Vuilleumier P. The role of amygdala in emotional and social functions: implications for temporal lobe epilepsy. Epileptologie 2007;24:78–89.
[27] Lunn J, Lewis C, Sherlock C. Impaired performance on advanced theory of mind tasks in children with epilepsy is related to poor communication and increased attention problems. Epilepsy Behav 2015;43:109–16.
[28] Raud T, Kaldoja M-L, Kolk A. Relationship between social competence and neurocognitive performance in children with epilepsy. Epilepsy Behav 2015;52:93–101.
[29] Li YH, Chiu MJ, Yeh ZT, Liou HH, Cheng TW, Hua MS. Theory of mind in patients with temporal lobe epilepsy. J Int Neuropsychol Soc 2013;19:594–600.
[30] Quintas R, Raggi A, Giovannetti AM, Pagani M, Sabariego C, Cieza A, et al. Psychosocial difficulties in people with epilepsy: a systematic review of literature from 2005 until 2010. Epilepsy Behav 2012;25:60–7.
[31] McCagh J, Fisk JE, Baker GA. Epilepsy, psychosocial and cognitive functioning. Epilepsy Res 2009;86:1–14.
[32] Jacoby A, Snape D, Baker GA. Epilepsy and social identity: the stigma of a chronic neurological disorder. Lancet Neurol 2005;4:171–8.
[33] Szemere E, Jokeit H. Quality of life is social—towards an improvement of social abilities in patients with epilepsy. Seizure 2015;26:12–21.
[34] Jacoby A, Austin JK. Social stigma for adults and children with epilepsy. Epilepsia 2007;48(Suppl. 9):6–9.
[35] 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.
[36] Aguiar BVK, Guerreiro MM, McBrian D, Montenegro MA. Seizure impact on the school attendance in children with epilepsy. Seizure 2007;16:698–702.
[37] Giovagnoli AR, Franceschetti S, Reati F, Parente A, Maccagnano C, Villani F, et al. Theory of mind in frontal and temporal lobe epilepsy: cognitive and neural aspects. Epilepsia 2011;52:1995–2002.
[38] Giovagnoli AR, Meneses RF, da Silva AM. The contribution of spirituality to quality of life in focal epilepsy. Epilepsy Behav 2006;9:133–9.
[39] Hermann BP, Seidenberg M, Bell B, Woodard A, Rutecki P, Sheth R. Comorbid psychiatric symptoms in temporal lobe epilepsy: association with chronicity of epilepsy and impact on quality of life. Epilepsy Behav 2000;1:184–90.
[40] Hermann BP, Black RB, Chhabria S. Behavioral problems and social competence in children with epilepsy. Epilepsia 1981;22:703–10.
[41] Caplan R. Social skills in pediatric epilepsy: important but understudied. Dev Med Child Neurol 2015;57:8–9.
[42] Stewart E, Catroppa C, Gill D, Webster R, Lawson J, Mandalis A, et al. Theory of mind and social competence in children and adolescents with genetic generalised epilepsy (GGE): relationships to epilepsy severity and anti-epileptic drugs. Seizure 2018;60:96–104.
[43] Zhang T, Chen L, Wang Y, Zhang M, Wang L, Xu X, et al. Impaired theory of mind in Chinese children and adolescents with idiopathic generalized epilepsy: association with behavioral manifestations of executive dysfunction. Epilepsy Behav 2018;79:205–12.
[44] Lin JJ, Mula M, Hermann BP. Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. Lancet 2012;380:1180–92.
[45] Caplan R, Siddarth P, Stahl L, Lanphier E, Vona P, Gurbani S, et al. Childhood absence epilepsy: behavioral, cognitive, and linguistic comorbidities. Epilepsia 2008;49:1838–46.
[46] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.
[47] Tuchman RF, Rapin I, Shinnar S. Autistic and dysphasic children. Epilepsy Pediatr 1991;88:1219–25.
[48] Tuchman R. What is the relationship between autism spectrum disorders and epilepsy? Semin Pediatr Neurol 2017;24:292–300.

[49] Tuchman R. Autism and social cognition in epilepsy: implications for comprehensive epilepsy care. Curr Opin Neurol 2013;26:214–8.
[50] Tuchman R, Moshé SL, Rapin I. Convulsing toward the pathophysiology of autism. Brain Dev 2009;31:95–103.
[51] Tuchman R. Autism and epilepsy: what has regression got to do with it? Epilepsy Curr 2006;6:107–11.
[52] Hrdlicka M. EEG abnormalities, epilepsy and regression in autism: a review. Neuro Endocrinol Lett 2008;29:405–9.
[53] Oslejsková H, Dusek L, Makovská Z, Pejcochová J, Autrata R, Slapák I. Complicated relationship between autism with regression and epilepsy. Neuro Endocrinol Lett 2008;29:558–70.
[54] Richard AE, Scheffer IE, Wilson SJ. Features of the broader autism phenotype in people with epilepsy support shared mechanisms between epilepsy and autism spectrum disorder. Neurosci Biobehav Rev 2017;75:203–33.
[55] Adolphs R, Sears L, Piven J. Abnormal processing of social information from faces in autism. J Cogn Neurosci 2001;13:232–40.
[56] Ameis SH, Catani M. Altered white matter connectivity as a neural substrate for social impairment in autism spectrum disorder. Cortex 2015;62:158–81.
[57] Kana RK, Maximo JO, Williams DL, Keller TA, Schipul SE, Cherkassky VL, et al. Aberrant functioning of the theory-of-mind network in children and adolescents with autism. Mol Autism 2015;6:59.
[58] Kana RK, Libero LE, Hu CP, Deshpande HD, Colburn JS. Functional brain networks and white matter underlying theory-of-mind in autism. Soc Cogn Affect Neurosci 2014;9:98–105.
[59] Maximo JO, Cadena EJ, Kana RK. The implications of brain connectivity in the neuropsychology of autism. Neuropsychol Rev 2014;24:16–31.
[60] McGill ML, Devinsky O, Kelly C, Milham M, Castellanos FX, Quinn BT, et al. Default mode network abnormalities in idiopathic generalized epilepsy. Epilepsy Behav 2012;23:353–9.
[61] Steiger BK, Muller AM, Spirig E, Toller G, Jokeit H. Mesial temporal lobe epilepsy diminishes functional connectivity during emotion perception. Epilepsy Res 2017;134:33–40.
[62] Riley JD, Fling BW, Cramer SC, Lin JJ. Altered organization of face processing networks in temporal lobe epilepsy. Epilepsia 2015;56:762–71.
[63] Saemundsen E, Ludvigsson P, Rafnsson V. Autism spectrum disorders in children with a history of infantile spasms: a population-based study. J Child Neurol 2007; 22:1102–7.
[64] Uekermann J, Kraemer M, Abdel-Hamid M, Schimmelmann BG, Hebebrand J, Daum I, et al. Social cognition in attention-deficit hyperactivity disorder (ADHD). Neurosci Biobehav Rev 2010;34:734–43.
[65] Demopoulos C, Hopkins J, Davis A. A comparison of social cognitive profiles in children with autism spectrum disorders and attention-deficit/hyperactivity disorder: a matter of quantitative but not qualitative difference? J Autism Dev Disord 2013;43:1157–70.
[66] Bora E, Pantelis C. Meta-analysis of social cognition in attention-deficit/hyperactivity disorder (ADHD): comparison with healthy controls and autistic spectrum disorder. Psychol Med 2016;46:699–716.
[67] Fois A. Infantile spasms: review of the literature and personal experience. Ital J Pediatr 2010;36:15.
[68] Shields WD. Infantile spasms: little seizures, BIG consequences. Epilepsy Curr 2006; 6:63–9.
[69] Khan S, Al Baradie R. Epileptic encephalopathies: an overview. Epilepsy Res Treat 2012;2012:403592.
[70] Kayaalp L, Dervent A, Saltik S, Uluduz D, Kayaalp IV, Demirbilek V, et al. EEG abnormalities in West syndrome: correlation with the emergence of autistic features. Brain Dev 2007;29:336–45.
[71] Riikonen R. A long-term follow-up study of 214 children with the syndrome of infantile spasms. Neuropediatrics 1982;13:14–23.
[72] Gomez MR, Sampson JR, Whittemore VH. Tuberous sclerosis complex. Oxford University Press; 1999.
[73] Taylor DC, Neville BGR, Cross JH. Autistic spectrum disorders in childhood epilepsy surgery candidates. Eur Child Adolesc Psychiatry 1999;8:189–92.
[74] Neville BGR, Harkness WFJ, Cross JH, Cass HC, Burch VC, Lees JA, et al. Surgical treatment of severe autistic regression in childhood epilepsy. Pediatr Neurol 1997;16:137–40.
[75] Raymond AA, Halpin SFS, Alsanjari N, Cook MJ, Kitchen ND, Fish DR, et al. Dysembryoplastic neuroepithelial tumour features in 16 patients. Brain 1994; 117:461–75.
[76] Askalan R, Mackay M, Brian J, Otsubo H, McDermott C, Bryson S, et al. Prospective preliminary analysis of the development of autism and epilepsy in children with infantile spasms. J Child Neurol 2003;18:165–70.
[77] Hamano S, Tanaka M, Mochizuki M, Sugiyama N, Eto Y. Long-term follow-up study of West syndrome: differences of outcome among symptomatic etiologies. J Pediatr 2003;143:231–5.
[78] Jambaqué I, Chiron C, Dumas C, Mumford J, Dulac O. Mental and behavioural outcome of infantile epilepsy treated by vigabatrin in tuberous sclerosis patients. Epilepsy Res 2000;38:151–60.
[79] Primec ZR, Stare J, Neubauer D. The risk of lower mental outcome in infantile spasms increases after three weeks of hypsarrhythmia duration. Epilepsia 2006; 47:2202–5.
[80] O'Callaghan FJK, Edwards SW, Alber FD, Cortina Borja M, Hancock E, Johnson AL, et al. Vigabatrin with hormonal treatment versus hormonal treatment alone (ICISS) for infantile spasms: 18-month outcomes of an open-label, randomised controlled trial. Lancet Child Adolesc Health 2018;2:715–25.
[81] Scheffer IE, Zhang Y-H, Jansen FE, Dibbens L. Dravet syndrome or genetic (generalized) epilepsy with febrile seizures plus? Brain Dev 2009;31:394–400.
[82] Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain 2012; 135:2329–36.
[83] Marini C, Scheffer IE, Nabbout R, Suls A, De Jonghe P, Zara F, et al. The genetics of Dravet syndrome. Epilepsia 2011;52:24–9.
[84] Berg AT, Plioplys S. Epilepsy and autism: is there a special relationship? Epilepsy Behav 2012;23:193–8.
[85] Lagae L, Brambilla I, Mingorance A, Gibson E, Battersby A. Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. Dev Med Child Neurol 2018;60:63–72.
[86] Li B-M, Liu X-R, Yi Y-H, Deng Y-H, Su T, Zou X, et al. Autism in Dravet syndrome: prevalence, features, and relationship to the clinical characteristics of epilepsy and mental retardation. Epilepsy Behav 2011;21:291–5.
[87] He N, Li B-M, Li Z-X, Wang J, Liu X-R, Meng H, et al. Few individuals with Lennox–Gastaut syndrome have autism spectrum disorder: a comparison with Dravet syndrome. J Neurodev Disord 2018;10:10.
[88] Villas N, Meskis MA, Goodliffe S. Dravet syndrome: characteristics, comorbidities, and caregiver concerns. Epilepsy Behav 2017;74:81–6.
[89] Brunklaus A, Dorris L, Zuberi SM. Comorbidities and predictors of health-related quality of life in Dravet syndrome. Epilepsia 2011;52:1476–82.
[90] Saemundsen E, Ludvigsson P, Rafnsson V. Risk of autism spectrum disorders after infantile spasms: a population-based study nested in a cohort with seizures in the first year of life. Epilepsia 2008;49:1865–70.
[91] Wolff M, Cassé-Perrot C, Dravet C. Severe myoclonic epilepsy of infants (Dravet syndrome): natural history and neuropsychological findings. Epilepsia 2006;47:45–8.
[92] Nass R, Gross A, Devinsky O. Autism and autistic epileptiform regression with occipital spikes. Dev Med Child Neurol 1998;40:453–8.
[93] Chepure AH, Somaiya MP, Subramanyam AA, Kamath RK. Epileptic encephalopathy and autism: a complex interplay. J Pediatri Neurosci 2018;13:273–5.
[94] Catarino CB, Liu JYW, Liagkouras I, Gibbons VS, Labrum RW, Ellis R, et al. Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology. Brain 2011;134:2982–3010.
[95] Arzimanoglou A, French J, Blume WT, Cross JH, Ernst J-P, Feucht M, et al. Lennox–Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol 2009;8:82–93.
[96] Jambaqué I, Lassonde M, Dulac O. Neuropsychology of childhood epilepsy. Springer Sci Bus Media; 2006.
[97] Glauser TA. Following catastrophic epilepsy patients from childhood to adulthood. Epilepsia 2004;45:23–6.
[98] Camfield PR. Definition and natural history of Lennox–Gastaut syndrome. Epilepsia 2011;52:3–9.
[99] van Rijckevorsel K. Treatment of Lennox–Gastaut syndrome: overview and recent findings. Neuropsychiatr Dis Treat 2008;4:1001–19.
[100] Markand ON. Slow spike-wave activity in EEG and associated clinical features: often called 'Lennox' or 'Lennox–Gastaut' syndrome. Neurology 1977;27:746–57.
[101] Dulac O, N'Guyen T. The Lennox–Gastaut syndrome. Epilepsia 1993;34:S7–S17.
[102] Ferlazzo E, Nikaronova M, Italiano D, Bureau M, Dravet C, Calarese T, et al. Lennox–Gastaut syndrome in adulthood: clinical and EEG features. Epilepsy Res 2010;89: 271–7.
[103] Orrico A, Zollino M, Galli L, Buoni S, Marangi G, Sorrentino V. Late-onset Lennox–Gastaut syndrome in a patient with 15q11.2–q13.1 duplication. Am J Med Genet Part A 2009;149A:1033–5.
[104] Tuchman R, Cuccaro M, Alessandri M. Autism and epilepsy: historical perspective. Brain Dev 2010;32:709–18.
[105] Allen NM, Conroy J, Deonna T, McCreary D, McGettigan P, Madigan C, et al. Atypical benign partial epilepsy of childhood with acquired neurocognitive, lexical semantic, and autistic spectrum disorder. Epilepsy Behav Case Rep 2016;6:42–8.
[106] Besag FMC. Treatment of state-dependent learning disability. Epilepsia 2001; 42:52–4.
[107] Weglage J, Demsky A, Pietsch M, Kurlemann G. Neuropsychological, intellectual, and behavioral findings in patients with centrotemporal spikes with and without seizures. Dev Med Child Neurol 1997;39:646–51.
[108] Al-Twaijri WA, Shevell MI. Atypical benign epilepsy of childhood with Rolandic spikes: features of a subset requiring more than one medication for seizure control. J Child Neurol 2002;17:900–3.
[109] Croona C, Kihlgren M, Lundberg S, Eeg-Olofsson O, Edebol Eeg-Olofsson K. Neuropsychological findings in children with benign childhood epilepsy with centrotemporal spikes. Dev Med Child Neurol 1999;41:813–8.
[110] Giordani B, Caveney AF, Laughrin D, Huffman JL, Berent S, Sharma U, et al. Cognition and behavior in children with benign epilepsy with centrotemporal spikes (BECTS). Epilepsy Res 2006;70:89–94.
[111] Danhofer P, Pejčochová J, Dušek L, Rektor I, Ošlejšková H. The influence of EEG-detected nocturnal centrotemporal discharges on the expression of core symptoms of ADHD in children with benign childhood epilepsy with centrotemporal spikes (BCECTS): a prospective study in a tertiary referral center. Epilepsy Behav 2018; 79:75–81.
[112] Kim EH, Yum MS, Kim HW, Ko TS. Attention-deficit/hyperactivity disorder and attention impairment in children with benign childhood epilepsy with centrotemporal spikes. Epilepsy Behav 2014;37:54–8.
[113] Bennett-Back O, Keren A, Zelnik N. Attention-deficit hyperactivity disorder in children with benign epilepsy and their siblings. Pediatr Neurol 2011;44: 187–92.
[114] Tovia E, Goldberg-Stern H, Ben Zeev B, Heyman E, Watemberg N, Fattal-Valevski A, et al. The prevalence of atypical presentations and comorbidities of benign childhood epilepsy with centrotemporal spikes. Epilepsia 2011;52:1483–8.

[115] Genizi J, Shamay-Tsoory SG, Shahar E, Yaniv S, Aharon-Perez J. Impaired social behavior in children with benign childhood epilepsy with centrotemporal spikes. J Child Neurol 2012;27:156–61.
[116] Ciumas C, Laurent A, Saignavongs M, Ilski F, de Bellescize J, Panagiotakaki E, et al. Behavioral and fMRI responses to fearful faces are altered in benign childhood epilepsy with centrotemporal spikes (BCECTS). Epilepsia 2017;58:1716–27.
[117] Neville BG. Epilepsy in childhood. BMJ 1997;315:924–30.
[118] Stefanatos G. Changing perspectives on Landau–Kleffner syndrome. Clin Neuropsychol 2011;25:963–88.
[119] Neville BG, Burch VM, Cass H. Behavioural aspects of Landau–Kleffner syndrome. In: Gillberg C, O"Brien G, editors. Developmental disability and behaviour. London, UK: Cambridge University Press; 2000. p. 55–63.
[120] Neville BG, Burch V, Cass H, Lees J. Motor disorders in Landau–Kleffner syndrome (LKS). Epilepsia 1998;39:123.
[121] Neville BG, Boyd SG. Selective epileptic gait disorder. Journal of Neurology Neurosurg Psychiatry 1995;58:371–3.
[122] Nass R, Heier L, Walker R. Landau–Kleffner syndrome: temporal lobe tumor resection results in good outcome. Pediatr Neurol 1993;9:303–5.
[123] Beaumanoir A. The Landau–Kleffner syndrome. In: Beaumanoir A, Bureau M, Deonna T, editors. Epileptic syndromes of infancy, childhood and adolescence. London, UK: John Libbey; 1991. p. 231–44.
[124] Caraballo RH, Cejas N, Chamorro N, Kaltenmeier MC, Fortini S, Soprano AM. Landau–Kleffner syndrome: a study of 29 patients. Seizure 2014;23:98–104.
[125] Nieuwenhuis L, Nicolai J. The pathophysiological mechanisms of cognitive and behavioral disturbances in children with Landau–Kleffner syndrome or epilepsy with continuous spike-and-waves during slow-wave sleep. Seizure 2006;15:249–58.
[126] Pearl PL, Carrazana EJ, Holmes GL. The Landau–Kleffner syndrome. Epilepsy Curr 2001;1:39–45.
[127] Bishop DVM. Age of onset and outcome in 'acquired aphasia with convulsive disorder' (Landau–Kleffner syndrome). Dev Med Child Neurol 1985;27:705–12.
[128] Billard C, Fluss J, Pinton F. Specific language impairment versus Landau–Kleffner syndrome. Epilepsia 2009;50(Suppl. 7):21–4.
[129] Deonna T, Roulet-Perez E. Early-onset acquired epileptic aphasia (Landau–Kleffner syndrome, LKS) and regressive autistic disorders with epileptic EEG abnormalities: the continuing debate. Brain Dev 2010;32:746–52.
[130] Lesca G, Rudolf G, Labalme A, Hirsch E, Arzimanoglou A, Genton P, et al. Epileptic encephalopathies of the Landau–Kleffner and continuous spike and waves during slow-wave sleep types: genomic dissection makes the link with autism. Epilepsia 2012;53:1526–38.
[131] Tassinari CA, Cantalupo G, Dalla Bernardina B, Darra F, Bureau M, Cirelli C, et al. Encephalopathy related to status epilepticus during slow sleep (ESES) including Landau–Kleffner syndrome. Epileptic Syndr Infancy Child Adolesc 2012:255–75.
[132] Mantovani JF. Autistic regression and Landau–Kleffner syndrome: progress or confusion? Dev Med Child Neurol 2000;42:349–53.
[133] Soprano A, Garcia E, Caraballo R, Fejerman N. Neuropsychologic and neurolinguistic aspects in acquired epileptic aphasia (AEA) or Landau–Kleffner syndrome. Pediatr Neurol 1992;8:398–9.
[134] Bolton PF, Carcani-Rathwell I, Hutton J, Goode S, Howlin P, Rutter M. Epilepsy in autism: features and correlates. Br J Psychiatry 2011;198:289–94.
[135] Landau WM. Landau–Kleffner syndrome: an eponymic badge of ignorance. Arch Neurol 1992;49:353.
[136] Nass R, Petrucha D. Acquired aphasia with convulsive disorder: a pervasive developmental disorder variant. J Child Neurol 1990;5:327–8.
[137] Tuchman R. Treatment of seizure disorders and EEG abnormalities in children with autism spectrum disorders. J Autism Dev Disord 2000;30:485–9.
[138] Morrell F, Whisler WW, Smith MC, Hoeppner TJ, Toledo-Morrell Ld, Pierre-Louis SJC, et al. Landau–Kleffner syndrome: treatment with subpial intracortical transection. Brain 1995;118:1529–46.
[139] Downes M, Greenaway R, Clark M, Helen Cross J, Jolleff N, Harkness W, et al. Outcome following multiple subpial transection in Landau–Kleffner syndrome and related regression. Epilepsia 2015;56:1760–6.
[140] Giorgi FS, Guida M, Caciagli L, Pagni C, Pizzanelli C, Bonanni E, et al. Social cognition in juvenile myoclonic epilepsy. Epilepsy Res 2016;128:61–7.
[141] Janz D, Christian W. Impulsiv-Petit mal. Dtsch Z Nervenheilkd 1957;176:346–86.
[142] Lund M, Reintoft H, Simonsen N. A controlled sociological and psychological study on patients with juvenile myoclonus epilepsy. Nervenarzt 1976;47:708–12.
[143] Meletti S, Benuzzi F, Cantalupo G, Rubboli G, Tassinari CA, Nichelli P. Facial emotion recognition impairment in chronic temporal lobe epilepsy. Epilepsia 2009;50:1547–59.
[144] Farrant A, Morris RG, Russell T, Elwes R, Akanuma N, Alarcon G, et al. Social cognition in frontal lobe epilepsy. Epilepsy Behav 2005;7:506–16.
[145] Byars AW, deGrauw TJ, Johnson CS, Perkins SM, Fastenau PS, Dunn DW, et al. Language and social functioning in children and adolescents with epilepsy. Epilepsy Behav 2014;31:167–71.
[146] Bora E, Meletti S. Social cognition in temporal lobe epilepsy: a systematic review and meta-analysis. Epilepsy Behav 2016;60:50–7.
[147] Thomas LA, De Bellis MD, Graham R, LaBar KS. Development of emotional facial recognition in late childhood and adolescence. Dev Sci 2007;10:547–58.
[148] Okruszek Ł, Bala A, Wordecha M, Jarkiewicz M, Wysokiński A, Szczepocka E, et al. Social cognition in neuropsychiatric populations: a comparison of theory of mind in schizophrenia and mesial temporal lobe epilepsy. Sci Rep 2017;7:484.
[149] Hermann B, Seidenberg M, Bell B, Rutecki P, Sheth R, Ruggles K, et al. The neurodevelopmental impact of childhood-onset temporal lobe epilepsy on brain structure and function. Epilepsia 2002;43:1062–71.
[150] Adolphs R. What does the amygdala contribute to social cognition? Ann N Y Acad Sci 2010;1191:42–61.
[151] Adolphs R, Baron-Cohen S, Tranel D. Impaired recognition of social emotions following amygdala damage. J Cogn Neurosci 2002;14:1264–74.
[152] Giovagnoli AR. Relation of sorting impairment to hippocampal damage in temporal lobe epilepsy. Neuropsychologia 2001;39:140–50.
[153] Edwards M, Stewart E, Palermo R, Lah S. Facial emotion perception in patients with epilepsy: a systematic review with meta-analysis. Neurosci Biobehav Rev 2017;83:212–25.
[154] Cantalupo G, Meletti S, Miduri A, Mazzotta S, Rios-Pohl L, Benuzzi F, et al. Facial emotion recognition in childhood: the effects of febrile seizures in the developing brain. Epilepsy Behav 2013;29:211–6.
[155] Pinabiaux C, Bulteau C, Fohlen M, Dorfmüller G, Chiron C, Hertz-Pannier L, et al. Impaired emotional memory recognition after early temporal lobe epilepsy surgery: the fearful face exception? Cortex 2013;49:1386–93.
[156] Golouboff N, Fiori N, Delalande O, Fohlen M, Dellatolas G, Jambaqué I. Impaired facial expression recognition in children with temporal lobe epilepsy: impact of early seizure onset on fear recognition. Neuropsychologia 2008;46:1415–28.
[157] Cohen M, Prather A, Town P, Hynd G. Neurodevelopmental differences in emotional prosody in normal children and children with left and right temporal lobe epilepsy. Brain Lang 1990;38:122–34.
[158] Braams O, Meekes J, van Nieuwenhuizen O, Schappin R, van Rijen PC, Veenstra W, et al. Two years after epilepsy surgery in children: recognition of emotions expressed by faces. Epilepsy Behav 2015;51:140–5.
[159] Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci 2006;7:268.
[160] Stuss DT, Alexander MP. Executive functions and the frontal lobes: a conceptual view. Psychol Res 2000;63:289–98.
[161] Chayer C, Freedman M. Frontal lobe functions. Curr Neurol Neurosci Rep 2001;1:547–52.
[162] Stone VE, Baron-Cohen S, Calder A, Keane J, Young A. Acquired theory of mind impairments in individuals with bilateral amygdala lesions. Neuropsychologia 2003;41:209–20.
[163] Rowe AD, Bullock PR, Polkey CE, Morris RG. 'Theory of mind' impairments and their relationship to executive functioning following frontal lobe excisions. Brain 2001;124:600–16.
[164] Gallagher HL, Happé F, Brunswick N, Fletcher PC, Frith U, Frith CD. Reading the mind in cartoons and stories: an fMRI study of 'theory of mind' in verbal and nonverbal tasks. Neuropsychologia 2000;38:11–21.
[165] Frith CD, Frith U. Interacting minds—a biological basis. Science 1999;286:1692–5.
[166] Stone VE, Baron-Cohen S, Knight RT. Frontal lobe contributions to theory of mind. J Cogn Neurosci 1998;10:640–56.
[167] Baron-Cohen S. Mindblindness: an essay on autism and theory of mind. Cambridge, MA, US: The MIT press; 1995.
[168] Kim E-H, Ko T-S. Cognitive impairment in childhood onset epilepsy: up-to-date information about its causes. Korean J Pediatr 2016;59:155–64.
[169] Sinclair DB, Wheatley M, Snyder T. Frontal lobe epilepsy in childhood. Pediatr Neurol 2004;30:169–76.
[170] Roulet Perez E, Davidoff V, Despland PA, Deonna T. Mental and behavioural deterioration of children with epilepsy and CSWS: acquired epileptic frontal syndrome. Dev Med Child Neurol 1993;35:661–74.
[171] Perez ER, Davidoff V, Desplartd P-A, Deonna T. Mental and behavioural deterioration of children with epilepsy and CSWS: acquired epileptic frontal syndrome. Dev Med Child Neurol 1993;35:661–74.
[172] Braakman HMH, Ijff DM, Vaessen MJ, Debeij-van Hall MHJA, Hofman PAM, Backes WH, et al. Cognitive and behavioural findings in children with frontal lobe epilepsy. Eur J Paediatr Neurol 2012;16:707–15.
[173] Hernandez M-T, Sauerwein HC, Jambaqué I, de Guise E, Lussier F, Lortie A, et al. Attention, memory, and behavioral adjustment in children with frontal lobe epilepsy. Epilepsy Behav 2003;4:522–36.
[174] Nickels KC, Zaccariello MJ, Hamiwka LD, Wirrell EC. Cognitive and neurodevelopmental comorbidities in paediatric epilepsy. Nat Rev Neurol 2016;12:465.
[175] Caplan R, Guthrie D, Komo S, Siddarth P, Chayasirisobhon S, Kornblum H, et al. Social communication in children with epilepsy. J Child Psychol Psychiatry 2002;43:245–53.
[176] Jiang Y, Hu Y, Wang Y, Zhou N, Zhu L, Wang K. Empathy and emotion recognition in patients with idiopathic generalized epilepsy. Epilepsy Behav 2014;37:139–44.
[177] Realmuto S, Zummo L, Cerami C, Agro L, Dodich A, Canessa N, et al. Social cognition dysfunctions in patients with epilepsy: evidence from patients with temporal lobe and idiopathic generalized epilepsies. Epilepsy Behav 2015;47:98–103.