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Review article

Autism and epilepsy: Historical perspective

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Abstract

Autism spectrum disorders (ASD) and epilepsy co-occur in approximately 30% of individuals with either ASD or epilepsy. While there is no single unifying ASD–epilepsy phenotype, understanding potential commonalities in subgroups of children with an ASD–epilepsy phenotype will help us disentangle the pathophysiology of both ASD and epilepsy. Throughout this brief historical perspective we selectively review critical trends in ASD–epilepsy research and highlight challenges to clinical and research efforts including terminology, heterogeneity of both ASD and epilepsy, and lack of careful characterization of children affected with both ASD and epilepsy. These complex issues continue to burden research on the diagnosis, neurobiology and management of children with ASD and epilepsy. A key concept that has emerged during the past 40 years is the strong association between intellectual disability and a higher prevalence of epilepsy in individuals with ASD. In addition, the two peaks of seizure onset, one in early childhood and one in adolescence and continuing through adulthood may be unique to individuals with ASD. The overlap of language and autistic regression to epilepsy, EEG epileptiform activity, sleep, and to epileptic encephalopathies such as Landau–Kleffner syndrome continue to be controversial areas of research and of clinical interest. An emerging consensus is that shared developmental genetic, molecular and pathophysiological mechanisms exist and account for the common co-occurrence of ASD and epilepsy.

Keywords: Epilepsy; Autism; EEG phenotype; Genetics

1. Introduction

The relationship of autism to epilepsy has been an area of scientific interest for decades. Autism was tied to epilepsy in Kanner's initial description of autism over 60 years ago [1,2] and further highlighted in his follow-up discussions in 1971 [3]. The initial studies on the relationship of autism to epilepsy and to electroencephalogram (EEG) abnormalities in the 1960s [4–7] were among the first to suggest that autism was a disorder of brain function. It was also during the 1960s that epilepsy was classified as a neurological versus mental disorder in the WHO classification system for epilepsy [8]. These seminal events mark critical periods for clinical and scientific investigation of autism and epilepsy as both separate and overlapping disorders.

Despite the early recognition of both autism and epilepsy as neurobiologic disorders, studies of their co-occurrence were hampered through the 1980s due in large part to the lack of adequate diagnostic criteria, particularly for autism. Early efforts to classify autism were led by Lorna Wing who introduced the concept of the "autism triad" and highlighted common impairments in social, language and repetitive behaviors among children with cognitive deficits [9]. Concurrent developments in classification systems for seizures and epilepsy [10,11] and standardized criteria for autism dur-

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ing this period [12,13] were critical for studies of the overlap in autism and epilepsy. Since that time, clinical conceptualizations of epilepsy [14] and autism spectrum disorders [15] have continued to evolve with persistent debate as to how best to classify children with autism or epilepsy as well as with both autism and epilepsy.

2. Definitions and terminology

Epilepsy is characterized by recurrent seizures. The diagnostic category of epilepsy includes multiple disorders with varying etiologies, pathophysiology and outcome [16]. Autism is a diagnostic category that includes a spectrum of disorders with fundamental impairments in social communication with no single cause or unifying explanation [17]. It is now well accepted and understood that the diagnostic constructs of autism and epilepsy represent complex disorders with tremendous clinical heterogeneity. Definitional issues have been addressed over the years and have greatly enhanced efforts to understand the intricate relationship between these two disorders. However, from a historical perspective the changing and evolving criteria for epilepsy and autism in particular, make it difficult to compare studies done during different time periods.

3. Autism definition

The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision (DSM IV-TR) [18] and the 10th Edition of the International Classification of Diseases (ICD 10) of the World Health Organization [19] use the terminology of Pervasive Developmental Disorder (PDD) to categorize children with qualitative impairments in three behaviorally defined domains; reciprocal social interaction, verbal and nonverbal communication, and restricted and repetitive interests. The five subtypes under the present DSM/ICD diagnostic schema are: (1) autistic disorder or childhood autism, which is the classic group of children described by Kanner in 1943 [3], (2) Asperger syndrome [20] in which IQ is greater than 70, language development is not delayed, and social impairments are less severe [21–23], (3) pervasive developmental disorder not otherwise specified or atypical autism [24], a disorder in which the lack of an operational definition makes it problematic to classify and study [25–27], (4) childhood disintegrative disorder [28–32] in which children have a late-onset autistic and cognitive regression that can include language regression, motor regression, and loss of bowel and bladder use, all usually occurring after age three, and (5) Rett disorder, a neurodevelopmental disorder in which mutations in MECP2 accounts for the distinct clinical phenotype seen in this group of girls [33].

The term autism spectrum disorders (ASD) is now commonly used to include children with autistic disorder, pervasive developmental disorders not otherwise specified (PDD-NOS) and those with Asperger syndrome (AS). The two other subtypes under PDD, childhood disintegrative disorder and Rett syndrome are typically not included under the ASD umbrella. Rett and childhood disintegrative disorder are rare disorders that account for a small proportion of children with PDDs [34]. Of interest to this discussion, rates of seizures are significantly higher in childhood disintegrative disorder and in Rett syndrome than in ASD and both clinical syndromes are always associated with regression of skills [35]. We use the term ASD throughout this discussion to include children with autistic disorder, PDD-NOS, and AS, understanding that some studies included only children with autistic disorder.

4. Seizure, epilepsy and EEG definitions

The term seizure is used to describe clinical events characterized by paroxysmal, stereotyped, relatively brief interruptions of ongoing behavior, associated with electrographic seizure patterns [36]. Seizures are differentiated into those that are provoked secondary to an acute event such as fever, infection, trauma, or metabolic illness and those that are unprovoked (i.e., seizures that are likely to be genetic). Although epilepsy is defined as two unprovoked seizures of any type, studies on autism–epilepsy have not always adhered to these definitions and have included children with provoked seizures as well as those with only one seizure [37]. The term sub-clinical or non-convulsive seizure is used to refer to electrographic patterns, without clinically recognizable cognitive, behavioral, or motor functions or any apparent impairment of consciousness [36]. The term "epileptiform abnormalities" is used to describe spikes and spike and wave discharges on an EEG. Complicating interpretations of findings relating to the co-occurrence of autism and epilepsy is that the standards used to determine epileptiform abnormalities in children with autism have varied among studies looking at children with autism and epilepsy, as has the type of EEG performed.

5. Historical timeline

Throughout this brief historical perspective we will identify what we consider to be key concepts that have emerged during the past 40 years and that continue to be important areas of research and of clinical interest. We will highlight challenges that have hampered research on the diagnosis, neurobiology and management of children with autism and epilepsy. Our goal is to describe important scientific observations and relevant research questions within the framework of a historical timeline.

6. 1970s and 1980s

Early work on children with ASD and epilepsy emphasized the overlap between the two disorders in time of onset (infantile or early onset versus pubertal onset), in different syndromes (e.g., tuberous sclerosis), and in the context of different states or conditions (epileptiform versus non-epileptiform EEG). In addition, the role of developmental regression as an indicator of epilepsy in autism was also investigated during these two decades. Mainly descriptive, many of the observations derived from these studies of children with ASD and epilepsy raised important questions that continue to have research and clinical relevance.

One of the earliest key observations was the relationship between infantile spasms, hypsarrhythmia, and ASD [38]. A finnish study in 1981 [39] expanded on the relationship between infantile spasms and ASD and found that 12.5% of 192 children with infantile spasms developed ASD. While this percentage was noteworthy, the investigators remarked that this was most likely an underestimate as many records lacked sufficient data to assign a diagnosis of infantile autism. In addition, this study noted that among the 24 children with ASD 19 had muscular hypotonia and all but one had intellectual disability (IQ < 70).

In contrast to the increased risk for development of ASD in early onset epilepsy, several studies reported the existence of a secondary peak of seizure onset in children with ASD during puberty. Deykin and MacMahon [40] studied 183 children with ASD and while they found an early peak of seizures, the highest prevalence of seizures was in children between the ages of 11 and 14 years. This study confirmed the results of a previous study that reported a higher prevalence of seizures in ASD during adolescence [41]. In their report, Deykin and McMahon suggested that the occurrence of seizures during adolescence is secondary to an ongoing pathological process in children with ASD.

A second body of research that developed during this period focused on the overlap of ASD and epilepsy in the context of different disorders or behavioral features. Early studies of tuberous sclerosis described a common set of clinical features including intellectual disability, seizures and specifically infantile spasms [42]. In the 1980s Hunt and Dennis studied 89 children with tuberous sclerosis and found that 57% of children with tuberous sclerosis and infantile spasms had ASD [43]. The relationship of tuberous sclerosis, infantile spasms and ASD was supported by Curatolo and his group who also suggested that the combination of EEG discharges and tuber location is crucial to the development of ASD in children with tuberous sclerosis [44]. This work highlighted a potential model for the co-occurrence of autism and epilepsy.

A third important observation that originated in studies of ASD and epilepsy conducted in the early 1970s described the relationship of intellectual impairments and impairments in language with "sub-clinical status epilepticus" induced by sleep [45]. This line of study was especially important in light of early studies that tied language regression to a specific EEG pattern and seizures as first described by Landau and Kleffner in 1957 [46]. The overlap with ASD was described in a number of subsequent studies [47–50]. In addition, during the late 1980s a number of studies pointed to the role of EEG abnormalities in language and cognitive processes suggesting that interictal epileptiform activity could impair brain function [51–53]. The role of epileptiform activity in children with language disorders [54–56] and the association of ASD to epileptic encephalopathies such as Lennox–Gastaut syndrome [57] raised the possibility that epilepsy or epileptiform activity could lead to ASD.

Whether epileptiform activity in language regression was causal or an epiphenomena was hotly debated [58] and continues to be a controversial subject—especially as to the role of developmental regression in autism and epilepsy. The association of developmental regression to ASD became a topic of increased research interest after Hagberg and colleagues [59] published a report of 35 girls with regression in higher brain functions, stereotypical hand movements and ASD with a significant proportion of the girls having epilepsy. This observation triggered a series of papers that clearly demonstrated behavioral overlaps of ASD to Rett disorder [60–62]. The relationship of Rett to epilepsy, EEG and polysomnographical abnormalities alerted neurologists to other disorders of autistic regression [63,64]. There was increased interest in "Heller's dementia" or childhood disintegrative disorder characterized by cognitive and language regression, motor regression, and loss of bowel and bladder use, all usually occurring after age 3 years [32,65–67]. The association of regression to ASD garnered further interest after Kurita [68] published a study in which 97 (37%) of 261 children with ASD had a total loss of either meaningful words or communicative gestures. The median age of communicative loss was 18 months; girls were more likely than boys to have speech loss and the children with speech loss were more likely to have or develop intellectual disability. In the group with speech loss 27% had what was described as paroxysmal EEG abnormalities as compared to 28.4% in those without speech loss, a difference which was non-significant. A subsequent study in children with speech loss suggested that there was a higher risk of developing seizures in those with regression in verbal and nonverbal communication [69].

Finally, attention turned to examining the relationship between ASD and epilepsy from an epidemiologic perspective. In the late 1980s the first population-based

study on children with ASD found that epilepsy, particularly partial complex seizures, occurred in 27% of children with infantile autism and with autistic-like condition and they found that epilepsy occurred even among children without severe mental retardation and ASD [70]. They found that infantile spasms accounted for 3% of those diagnosed with narrowly defined autism. In children with "autistic-like conditions" and significant cognitive handicap, the rate of epilepsy was 41%. They also described all seizure types among the ASD sample and reported that many children had more than one seizure type. Gillberg, Olsson, and Steffenburg had previously raised the question of whether epilepsy leads to ASD or whether the epilepsy and the ASD are secondary to common underlying brain dysfunction [71]. Their own series of studies on ASD and epilepsy during the 1980s provided evidence for a strong relationship between ASD, epilepsy, and cognitive impairments or degree of intellectual disability.

The early work on autism and epilepsy provided a wealth of information. This early work addressed age of onset of epilepsy in ASD as well as associated disorders and the role of epilepsy and an epileptiform EEG on developmental regression in children with language disorders or ASD. Studies on ASD and epilepsy during the 1970s and 1980s provided a foundation for future studies that emphasized defining core features associated with the co-occurrence of ASD and epilepsy.

7. 1990s

Building on the descriptive work of the previous two decades, the investigation of ASD and epilepsy during the1990s revolved around studies of associated symptoms and efforts to further describe the features common to individuals with ASD and epilepsy. For instance, Volkmar and colleagues [72] in a study on 192 individuals with ASD, ranging in age from 2 to 33 years, found that 21% developed epilepsy with two distinct peaks one before age 6 years and one in adolescence between 11 and 18 years of age. In addition these investigators found that seizures were more common in those with lower intellectual ability. Specific risk factors for the development of epilepsy in children with ASD were identified in a well-described cohort of 314 children with ASD and 237 children with language disorder without ASD, evaluated over a 30-year period [73]. The major risk factor for epilepsy was severe intellectual disability; this risk was heightened in the presence of severe intellectual disability with a motor deficit. In contrast, epilepsy occurred in 6% (10 of 160) of children in the ASD group that was negative for severe intellectual disability, motor deficit, associated perinatal or medical disorder, or a positive family history of epilepsy. The prevalence of epilepsy in this group was similar to the 8% (14 of 168) of language impaired non-ASD children. In addition, when the children were subtyped on the basis of language, the highest risk of epilepsy regardless of whether they had ASD or language impairment without ASD was seen in those with the most severe receptive language disorder [73]. Tuchman and colleagues also found a statistically significant higher percentage of epilepsy in girls with ASD (24%) compared to boys with ASD (11%), which was attributed to the increased prevalence of cognitive and motor deficit in girls. In addition this study found a high risk for developing seizures in the first 5 years of life and that infantile spasms were overrepresented in ASD. Finally, a follow up of this cohort of children into adulthood confirmed previous finding of a secondary peak of seizure onset during adolescence [74].

Subsequent studies corroborated previous findings that the subgroups of individuals with ASD with the highest prevalence of epilepsy are those with moderate to severe cognitive impairments (i.e., intellectual disability), as well as the two-peak distribution of seizure onset in the ASD population [75–77]. The emerging consensus during this decade was that epilepsy in ASD was secondary to a common underlying brain dysfunction [76]. Efforts to account for this association of autism and epilepsy remained at the descriptive level. This impasse was most likely the result of continuing problems with definition and grouping of very disparate conditions. However, Rossi and colleagues were among the first to speculate that genetic factors, common to both disorders, likely accounted for the common co-occurrence of autism and epilepsy [77].

This decade saw increasing evidence for the role of early age on onset as well as more refined studies of developmental regression. For instance, Wong and colleagues prospectively studied 246 children with ASD and found an increased prevalence of early onset seizures in individuals with ASD with the majority of seizures occurring during the first year of life [78]. Similarly, studies during the 1990s showed that all seizure types occur in children with ASD and epilepsy with partial complex seizures being the most common [73,77,79]. Furthermore the role of regression in ASD was re-examined and studies suggested that EEG abnormalities were more common in the histories of those with childhood disintegrative disorder than those with infantile autism [80] and that epilepsy was more common in children with ASD and regression [81]. However, Tuchman and Rapin [82] in a study of language regression in 585 children with ASD found no difference in the proportion of children with epilepsy or epileptiform EEGs who had regressed before or after 2 years of age. This study did find that children with lower cognitive function were more likely to have undergone regression than those with better cognitive skills. This comprehensive study of regression and epilepsy in a clinically ascertained ASD sample, strongly suggested that

language regression in ASD did not increase the risk for developing epilepsy.

Finally, during this decade there was an increased interest in examining treatment options for children with autism and epilepsy. In a study of 66 children with ASD and epilepsy Gillberg and colleagues suggested that the type of underlying disorders accounting for the epilepsy and the type of seizure were important variables in choosing an antiepileptic medication [83]. In addition, this decade saw an increased number of published case reports describing children with autism and epilepsy treated with antiepileptic medication (AEDs) [84–87] or epilepsy surgery in children with autism and regression [88–91]. All of these reports were controversial as some demonstrated improvement in language and social skills that was transient and not well documented. In those with autism and regression undergoing epilepsy surgery most did not show any consistent improvement in the core features of ASD. How to interpret the results of these case reports was difficult secondary to the small number of children included in the studies, the short period of observation between treatment and response, and the lack of adequate objective assessment and documentation of improvement in language and social skills.

Research on ASD and epilepsy during this decade strongly suggested that ASD and epilepsy were most likely to co-occur in children with intellectual disability and motor impairments. In addition, there were mixed results around regression in ASD as a predictor of increased risk for epilepsy, with the largest study done to date on this issue finding no association. Finally, studies suggested that treating seizures in children with ASD and epilepsy was not different than in children with epilepsy alone, while the usefulness of AEDs and epilepsy surgery for remediation of language and social skills in children with ASD, epilepsy and regression remained unproven and controversial.

8. The 21st century

A review of the present literature by Spence and Schneider [92] on the role of epilepsy and epileptiform activity on ASD found prevalence estimates of epilepsy in ASD of 5–46%, with epileptiform abnormalities in as many as 60% of children with ASD, dependent on the type of EEG study done and whether patients with and without epilepsy are included. Variables such as sample ascertainment, degree of intellectual disability (IQ), idiopathic versus non-idiopathic, age and gender all contribute to the variation in prevalence estimates of epilepsy and EEG findings in ASD. Efforts to further define the relationship between autism and epilepsy have continued over the past several years. In part, much of the work around the co-occurrence of autism and epilepsy has assumed greater importance in light of a shift toward closer examination of underlying biologic mechanisms.

Additional studies of prevalence and onset have also added to our knowledge base regarding ASD and epilepsy. This decade saw the first effort to examine the prevalence of ASD in an epilepsy cohort. Relative to the study of epilepsy in ASD, the study of ASD prevalence in individuals with epilepsy has not been investigated with the same intensity. Clarke and colleagues, in a study of children with epilepsy followed in a tertiary epilepsy clinic, found that approximately 30% of children with epilepsy screened positive for ASD on the Social Communication Questionnaire; the prevalence of autism was highest among children whose seizures started around age 2 years or earlier and those with low cognitive level [93]. Another study, also from an epilepsy perspective, estimated that approximately 6–7% of children with epilepsy whose seizure onset is in the first year of life go onto develop ASD with intellectual disability [94]. There is an increased interest in how the clinical features of co-occurring autism and epilepsy can be used to disentangle the biologic complexities of these disorders.

Determining the differences between children with ASD and epilepsy and those with ASD without epilepsy continues to be a work in progress. In a retrospective study of 130 individuals with "idiopathic" ASD followed over a 10 year period with routine EEG studies Hara [95] found poorer cognitive (lower IQ), adaptive, behavioral, and social outcomes in the ASD–epilepsy group versus the ASD only group. Turk [96] recently reported that children with ASD and epilepsy had increased motor problems, delayed daily living skills and increased behavioral challenges. While this study did not match the groups on verbal IQ it lends support to the presence of poorer outcomes in the ASD–epilepsy group. One of the most consistent findings over the past four decades is that severity of intellectual disability is a significant risk factor for the development of epilepsy in children with ASD [97] and that the highest rates of seizures are observed in those with the most severe intellectual disability [98]. Furthermore seizure frequency has a significant impact on individuals with ASD and individuals with ASD and epilepsy are as a group significantly impaired as young adults [99].

The secondary peak in adolescence remains an interesting finding that may reflect underlying etiology of ASD and epilepsy [95]. The suggestion is that the adolescence peak in epilepsy onset is more likely in idiopathic ASD and that symptomatic ASD is more likely to account for the epilepsy onset in the early years. This latter point is consistent with recent work, which found that children with ASD with early onset seizures probably represent a distinct subgroup with significant insults to the developing brain manifesting as epileptic encephalopathies such as infantile spasms [100,101]. The onset of seizures in adolescence in ASD remains poorly understood. A study by McDermott [102]

demonstrated that the prevalence of epilepsy in cerebral palsy and in adults with intellectual disability declines with advancing age, whereas it increases in individuals with ASD and in those with Down syndrome. These findings suggest that the observed second peak of seizure onset in adolescence and increasing prevalence of epilepsy into adulthood is secondary to an ongoing pathological process in individuals with ASD [40,95].

The phenomena of autistic regression in which the developmental trajectory of approximately 30% of children with ASD is characterized by a regression of verbal and nonverbal communication skills usually occurring prior to 24 months of age, is currently well accepted, but poorly understood at a biologic level [103–109]. The association of autistic regression in children with ASD and epilepsy continues to be an area of active research interest and controversy with studies showing mixed results. Some studies during this decade have found no differences in history of autistic regression in ASD children with epileptiform EEGs and epilepsy versus ASD children with a normal EEG and no epilepsy [95,110]. Contrary to results showing no relationship of regression to epilepsy in autism one study found that autistic regression was more frequent in children with ASD and epilepsy versus those with ASD and no epilepsy [111]. Giannotti et al. [112] also found that epilepsy was more likely to occur in children with autistic regression. This latter study also found that children with autistic regression had more disrupted sleep than those with ASD without regression.

The association of autistic regression to epilepsy remains unclear, differences in the cohorts studied, as well as other confounding variables may account for these mixed results [92]. One aspect of this association, specifically whether there are differences between children with language regression as occurs in LKS to those with autistic regression was specifically investigated during this decade. For example, a multicenter study showing that seizures are more common in children who regressed after the age of 3 years, suggesting that age is an important variable differentiating subgroups of children with regression [113]. In addition, a comparison of overnight EEG results of children with isolated language regression versus those of children with language and autistic regression found that children with isolated language regression were more likely to have epileptiform discharges and particularly focal spikes, than those with both language regression and a more global autistic regression [114]. Furthermore this study showed that Electrical Status Epilepticus during Slow Wave Sleep (ESES), which is the EEG pattern associated with LKS and other epileptic encephalopathies of sleep, is almost exclusively found in those with isolated language regression [114]. These studies suggest that children with autistic regression can be differentiated from those with LKS based on variables such as age of onset of regression (age less than 3 years versus greater that 3 years of age), type of regression (primarily language versus autistic), and sleep related EEG findings (frequency of epileptiform activity) [35].

Despite the differences in LKS and ASD overlaps between the two disorders do exist. For example, a common language subtype in children with LKS is a severe receptive language disorder or verbal auditory agnosia and the suggestion has been made that receptive language disorders, may be a risk factor in the development of epilepsy in children with ASD [37,115]. In addition high rates of interictal EEG epileptiform abnormalities are reported in children with ASD without epilepsy using magnetoencephalography (MEG) or 24-h ambulatory EEG studies [116,117]. However, there are clear differences between LKS and autistic regression and there are only rare case reports linking epilepsy or an epileptiform EEG to autistic regression [118,119]. The significance, if any, of interictal spikes in children with ASD is unclear. For example, one study using prolonged (>23 h) video-EEG in children with ASD detected interictal epileptiform abnormalities in 59% of children with ASD and approximately half of these children had recorded clinical events suspicious of epilepsy that on analysis of the video-EEG were not epileptic seizures [120]. Furthermore, despite the high prevalence of interictal EEG epileptiform activity in children with ASD and the overlap of LKS and ASD, no study to date has shown that spikes contribute to the pathogenesis or to the worsening of language, social or behavioral dysfunction of children with ASD [121].

The consensus emerging from studies on ASD and epilepsy is that the same brain pathology accounts for the majority of children with co-occurring ASD and epilepsy or with an epileptiform EEG. This brain pathology may represent a set of uniform underlying genetics as well. The complexity of the relationship of ASD, epilepsy and epileptiform EEG activity is highlighted in tuberous sclerosis complex (TSC) which has emerged as a unique clinical model to study the complex interplay between genetics, onset of seizures, and location of epileptiform activity to the development of ASD. TSC is an important clinical model for several reasons. First, 1–5% of children with autism have TSC [122]. Second, a more careful analysis reveals that TSC is present in 8–14% of those with the autism–epilepsy phenotype [123]. Third, autism or autism spectrum conditions have been reported in up to 50% of persons with TSC [122]. Fourth, approximately 60% of children with TSC have epilepsy and 50% have infantile spasms [124]. Finally, TSC is an important treatment model with implications for both epilepsy and ASD [125–128]. Two genes, TSC1 and TSC2, are responsible for the TSC phenotype and can offer important clues as to the relationship of epilepsy to cognition and to the development of ASD [129]. In TSC several risk factors for the development

of ASD have been identified and include tubers in the temporal lobes, temporal lobe epileptiform discharges, a history of infantile spasms, and onset of seizures in the first 3 years of life [130,131].

Deonna and Roulet [132] have proposed that other than assuming that ASD and epilepsy are totally independent conditions, several other overlapping scenarios could account for the common co-occurrence of ASD and epilepsy. These investigators suggest that the most common reason for the co-occurrence of ASD and epilepsy is that the same brain pathology causes both disorders. They also proposed that the co-occurrence of ASD and epilepsy could be secondary to an epileptic process occurring in early development interfering with the developing function of specific brain networks leading to the ASD phenotype. A third scenario accounting for the co-existence of both ASD and epilepsy is a focal or multifocal process affecting structures common to both ASD and epilepsy such as the limbic system as occurs in the TSC model. Finally, Deonna and Roulet [132] also suggest that an epileptic process could be a rare cause of specific sensory, language, or cognitive dysfunction with behaviors that overlap with the ASD phenotype. As we enter the end of this decade our current understanding is that ASD and epilepsy represent a combination of complex disorders that challenge our ability to identify causal mechanisms.

9. Future directions: the next decade

This brief overview of research developments in autism and epilepsy spanning the past 40 years offers a cross section of the critical issues that have been addressed and continue to be refined. The intersection of ASD and epilepsy has challenged clinicians and researchers. Clinically and at the descriptive level, it is not a significant challenge to identify ASD and epilepsy as co-occurring disorders. The challenge arises in identifying causal mechanisms, especially given that the high clinical or phenotypic variability in each of the disorders separately [133,134]. Interestingly, while this variability is seen in all features, it is in the associated features for both ASD and epilepsy that we see the greatest convergence of ASD and epilepsy. In part, this convergence may stem from autism and epilepsy both being disorders of large-scale neural networks with alterations in cortical–subcortical systems connectivity [135,136].

Etiology aside, both ASD and epilepsy show phenotypic convergence in several areas including lowered cognitive profiles or intellectual disability, motor delays or impairments, and neurobehavioral problems such as attention difficulties, hyperactivity, and mood problems. Thus, there are subgroups within each disorder that share these problems. There is no single unifying ASD–epilepsy phenotype but understanding potential commonalities in subgroups of children with an ASD–epilepsy phenotype should help us in understanding the pathophysiology of both ASD and epilepsy. The ASD–epilepsy phenotype remains descriptive. It is very likely that there are multiple biologic and genetic substrates that give rise to ASD–epilepsy phenotypes. For instance, the co-occurrence of ASD and epilepsy in individuals with early onset epilepsy is most likely a different phenotype than the co-occurrence of ASD and epilepsy with an adolescent onset. Nonetheless, a starting point is to examine ASD and epilepsy as a joint phenotype and then identify accompanying or associated features that distinguish the groups. This will assist in the search for underlying etiologies.

The co-occurrence of ASD and epilepsy is unlikely to have a single explanation. It is likely that genes common to both, particularly those involved in synaptic function, account for a significant, although unknown percentage, of children in whom ASD and epilepsy co-exist [137]. The debate on whether the co-occurrence of ASD and epilepsy is an epiphenomenon or if there are causal relationships needs to be framed within the molecular and genetic commonality of both disorders. The research question that needs to be addressed is whether there are specific causes or genes that differ in individuals with both ASD and epilepsy versus those with either disorder alone. The challenge is to identify these genes and the specific roles they play in the overlap and co-occurrence of both ASD and epilepsy. The genotypic and phenotypic heterogeneity of both ASD and epilepsy is daunting. Nevertheless both ASD and epilepsy are developmental disorders that can be identified early at a time of greatest plasticity of the brain and when interventions can have a maximum positive effect at changing abnormal developmental trajectory. Identification of the early processes that lead to ASD, to epileptogenesis, or both and identifying the genes involved in these processes and the pathways these genes regulate are a challenge worth pursuing.

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