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Autism Spectrum Disorder and Epilepsy: Two Sides of the Same Coin?

Shafali Spurling Jeste, MD¹ and Roberto Tuchman, MD²

Abstract

Autism spectrum disorders and epilepsy commonly co-occur. In this review, we consider some unresolved questions regarding the temporal relationship, causal mechanisms, and clinical stratification of this comorbidity, highlighting throughout the interplay between autism spectrum disorder, epilepsy, and intellectual disability. We present data on the clinical characterization of children with autism spectrum disorder and epilepsy, discussing distinctive phenotypes in children with this comorbidity. Although some distinctive clinical features emerge, this comorbidity also informs convergent pathways in genetic variants that cause synaptic dysfunction. We then move beyond diagnostic categorization and consider the extent to which electrophysiology as a quantitative biomarker may help guide efforts in clinical stratification and outcome prediction. Epilepsy, and atypical electrophysiological patterns, in autism spectrum disorder may inform the definition of biologically meaningful subgroups within the spectrum that, in turn, can shed light on potential targets for intervention.

Keywords

autism spectrum disorder, electroencephalography, epilepsy, intellectual disability, biomarkers

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The co-occurrence of epilepsy and autism spectrum disorder has been well established through large-scale prevalence studies. As the field of autism spectrum disorder research moves toward the elucidation of mechanism-based clinical stratification and targeted treatments, studies have begun to focus more deeply on understanding the clinical and biological basis of this comorbidity. In this review, we first present the most recent literature on the prevalence of epilepsy in autism spectrum disorder and of autism spectrum disorder in epilepsy. Throughout the discussion, we consider the additional role of global developmental delay/intellectual disability, both the temporal relationship between these comorbidities and whether there are defined clinical phenotypes that define individuals with this triad. We then move beyond diagnostic stratification and discuss the relationship between autism spectrum disorder and epileptiform discharges, and we introduce the emerging concept of electrophysiological biomarkers to help guide intervention and predict outcome in autism spectrum disorder. Lastly, we discuss the controversy surrounding the possibility of electrophysiological abnormalities serving as a treatment target in autism spectrum disorder. Throughout the review, we consider the following question: Can the presence of epilepsy or atypical electrophysiological patterns in autism spectrum disorder inform the definition of biologically meaningful subgroups within the spectrum and, in turn, shed light on potential targets for intervention?

What Is the Risk of Developing Epilepsy in Autism Spectrum Disorder?

The rate of epilepsy in individuals with an autism spectrum disorder diagnosis ranges from 6% to 27%,¹-⁷ with no single type of epilepsy more consistently reported. The range in rates is due, in large part, to the heterogeneity of the groups being studied, particularly with regard to cognitive function and age. Additionally, methodological differences in the measures used to diagnose autism spectrum disorder, from retrospective chart reviews to prospective parent questionnaires and clinician-performed diagnostic assessments, lead to differences in prevalence rates. Several factors have been associated with a greater risk of developing epilepsy, including regression of skills (language and social function) and female sex; however, the most robust data indicate that the single most important risk factor is

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overall cognitive function. Of note, although efforts have been made to characterize the autism spectrum disorder phenotype in these studies, few have taken similar efforts to define the epilepsy phenotype, with regard to patterns in the electroencephalogram (EEG) or seizure semiology.

A meta-analysis by Amiet and colleagues attempted to disentangle the relationship between intellectual disability, autism spectrum disorder, and epilepsy. They compared rates of epilepsy between subgroups of subjects based on IQ (<40, 40-50, 50-70, >70) and found that epilepsy rates increased as IQ decreased. The highest rate of epilepsy (46%) occurred in the group with an IQ <40. Furthermore, they found that the male-to-female ratio in autism spectrum disorder with epilepsy was 2:1, compared with the 3.5:1 ratio in non-epilepsy autism spectrum disorder. The authors were unable to determine whether sex, IQ, or the interaction between IQ and sex mediated the autism spectrum disorder–epilepsy relationship. In a subsequent study in a sample of 2644 children with simplex autism spectrum disorder, these same investigators found no significant increase of epilepsy associated with sex, but did confirm the association between epilepsy severity and cognitive impairment. This strong relationship between epilepsy and cognitive impairment was replicated by Viscidi and colleagues in a sample of 5185 children of autism spectrum disorder, where they demonstrated that in children over age 10, for every 1 standard deviation increase in IQ, the odds of having epilepsy decreased by 47%.

Age is the only other risk factor strongly associated with the development of seizures in individuals with autism spectrum disorder. Several studies have suggested there are 2 peaks of epilepsy, one in early childhood and a second in adolescence. Other large cross-sectional studies have found that the risk of epilepsy increases with age, with peak in early adolescence. In a population of children diagnosed as having autism spectrum disorder in the first decade, most seizures developed after age 10, and the risk of developing epilepsy continued to increase into the third decade of life. In the cross-sectional study by Viscidi and colleagues, the average prevalence of epilepsy was 12% in children with autism spectrum disorder, with the rate reaching 26% by adolescence. Furthermore, in a meta-analysis by Woolfenden, the pooled estimate of developing epilepsy was highest, 23.7%, in those with intellectual disability and age >12 years. To summarize the findings from these large recent studies, the prevalence of epilepsy in autism spectrum disorder is greatest among those with intellectual disability and in children in the second decade of life, and the risk of developing epilepsy continues into adulthood.

What Is the Risk of Developing Autism Spectrum Disorder in Epilepsy?

In studies of children with an epilepsy diagnosis, rates of autism spectrum disorder or positive screens for autism spectrum disorder symptoms have ranged from 5% to 37%. The strong association with intellectual disability is supported in these studies as well, with autism spectrum disorder rates higher in children with both epilepsy and intellectual disability. Data from several studies support the utility of developmental screening in children with epilepsy, as it is likely that neurodevelopmental disorders may already be present at the onset of the epilepsy. Fisher and colleagues conducted a widespread developmental screening program of patients with epilepsy in a tertiary medical center, with focus on symptoms of social communication impairment (autism spectrum disorder-related symptoms). Of 66 children under age 5 years screened (mean age, 2.5 years), 72% screened positive on a global developmental survey, the Ages and Stages Questionnaire, and 65% of those with an abnormal developmental screen also scored positive for autism spectrum disorder. The severity of developmental delay was highly related to autism risk. The authors then sought to disentangle the developmental delay from autism spectrum disorder through formal clinical evaluations, and they concluded, quite notably, that in 20 of 24 children, the positive autism spectrum disorder screening results could be explained by underlying developmental delays. In an extension of their previous work, this same group found that in 236 children with epilepsy screened with multiple instruments for autism spectrum disorder, approximately 7% had a clinical diagnosis of autism spectrum disorder, and 12 of these 15 children had other developmental delays or intellectual disability. Moreover, 20% of these children showed red flags that required further evaluation and potential intervention.

There exists no ambiguity in the fact that autism spectrum disorder, intellectual disability, and epilepsy co-occur. However, 2 critical questions require further investigation, the first regarding timing and the second regarding phenotype. First, in children with epilepsy, does atypical development precede or follow the onset of epilepsy and, to unpack the question further, does intellectual disability precede autism spectrum disorder, does autism spectrum disorder contribute to intellectual disability, or do the 2 develop synergistically? Second, can we identify specific behavioral, cognitive, and developmental characteristics in children with autism spectrum disorder and epilepsy, particularly in the setting of comorbid intellectual disability, that inform specific treatment targets? In other words, is there a distinctive autism spectrum disorder/epilepsy phenotype?

What Is the Temporal Relationship of Autism Spectrum Disorder, Epilepsy, and Intellectual Disability?

With regard to the first question, several studies have documented that epilepsy can both precede and follow a diagnosis of a neurodevelopmental disorder such as global developmental delay/intellectual disability or autism spectrum disorder. Matsumo and colleagues described a cohort of 79 patients with autism spectrum disorder and epilepsy and found that in 46.8% of cases, epilepsy was diagnosed prior to autism spectrum disorder. Similarly, in the Finnish cohort, more than half of the cohort was diagnosed with epilepsy prior to autism spectrum disorder or intellectual disability. It is possible that formal
diagnoses of neurodevelopmental disorders are deferred because of the initial focus on epilepsy management. However, it is also possible that subtle or subclinical signs of atypical development do occur early in infancy, but they are not identified until a formal clinical evaluation is performed. The second question regarding the temporal relationship between intellectual disability and autism spectrum disorder becomes much more complicated to understand, as the diagnosis of one can easily confound the other. Prospective studies of infants at risk for autism spectrum disorder and epilepsy are required to tease apart this phenomenon.

A recent longitudinal study of infants with tuberous sclerosis complex was designed to characterize early developmental trajectories and predictors of autism spectrum disorder. Children with tuberous sclerosis complex are at high risk for autism spectrum disorder (up to 50%21 and epilepsy (up to 80%)22,23 and can be studied from early infancy because of prenatal diagnosis of tuberous sclerosis complex.24 In this multisite study, the investigators followed infants with tuberous sclerosis complex from ages 3 to 36 months, performing comprehensive behavioral assessments (focused on cognition and social communication skills), clinical history, and resting state and event-related EEG.25,26 Ninety-five percent of infants had a diagnosis of epilepsy by age 24 months, and 55% met criteria for autism spectrum disorder based on standardized testing and clinical confirmation. By 12 months of age, infants who developed autism spectrum disorder had a significantly lower verbal and nonverbal IQ. Controlling for seizure severity, as defined by proportion of life with active epilepsy, infants diagnosed as having autism spectrum disorder demonstrated a significant decline in nonverbal IQ between ages 12 and 36 months. Moreover, only in infants later diagnosed with autism spectrum disorder was there a significant interaction between seizure severity and decline in nonverbal IQ.

These findings suggest that in infants at high risk for both autism spectrum disorder and epilepsy, delays can be quantified in the first year of life, and these delays are highly associated with the diagnosis of autism spectrum disorder. However, there is a dynamic interaction between cognition, autism spectrum disorder, and epilepsy in this population, as infants later diagnosed with autism spectrum disorder may be more vulnerable to the effects of epilepsy on cognitive and social development. It is also possible, consistent with the findings from the study by Fisher and colleagues, that the diagnostic process and standardized testing for autism spectrum disorder become confounded by global developmental delay. To address these concerns, this group has begun to focus on the characterization of discrete behaviors (joint attention) and event-related EEG domains (face processing) that may be more sensitive and specific to the social cognitive impairments that define autism spectrum disorder, especially in high-risk groups such as infants with epilepsy. These discrete measures, along with continued investigation of infants in the first year of life, will help us to understand both the timing and specific deficits in social cognition and communication skills in these high-risk infants which, in turn, will facilitate implementation of early interventions for children who are at highest risk for autism spectrum disorder.

Is There a Distinctive Autism Spectrum Disorder/Epilepsy Phenotype?

The clinical heterogeneity in autism spectrum disorder presents the greatest barrier to the establishment of reliable prognostic indicators and targeted treatment strategies. Efforts have been made to identify symptom clusters within the autism spectrum, in order to define clinically meaningful subgroups that may share a common mechanism of disease and therefore could benefit from a common treatment. The presence of epilepsy could serve as an entry point to the identification of a subgroup within the spectrum. In a recent study, Cuccaro and colleagues performed a latent class cluster analysis on a cohort of children with autism spectrum disorder to identify biologically and clinically meaningful subgroups. They identified 5 clusters based on IQ, autism severity, and autism symptoms. The cluster with the highest rate of epilepsy was characterized by early onset of autism spectrum disorder, greatest repetitive object use and unusual sensory interests, and highest frequency of gross motor coordination problems. Although these characteristics could actually relate to comorbid intellectual disability and perhaps reflect a global developmental delay, the prominent impairments in the repetitive behaviors/restricted interests domain, and in motor function, could serve as a quantifiable target for intervention. The results from this cluster analysis should spark future efforts in the characterization of social communication impairments in children with autism spectrum disorder and epilepsy, with focus on core deficits and features that not only would inform treatment targets but also could be measured longitudinally for treatment monitoring and for evaluation of outcomes with intervention.

The focus of research must move beyond diagnostic categories and toward the discrimination of behaviors and developmental features that can be improved or at least ameliorated by specific intervention strategies. In future analyses, addition of genetics data and, particularly, any known genetic variations in the patients, would enhance our understanding of the common mechanisms underlying these clusters.

Are There Convergent Pathways to Epilepsy, Intellectual Disability, and Autism Spectrum Disorder?

With regard to pathophysiological mechanisms of autism spectrum disorder and epilepsy, 2 primary hypotheses exist in the literature that, in fact, may not be mutually exclusive. First, both may reflect outcomes from common processes, such as dysregulation of excitation/inhibition imbalance, either due to defects in GABAergic fibers or in γ-amino butyric acid (GABA) receptor function. Several genetic syndromes and variants that cause such dysregulation lead to epilepsy and to autism spectrum disorder.25 Second, primary epilepsy may impact synaptic plasticity and corticai connectivity, which, in turn,
may predispose a developing brain to cognitive delays and behavioral impairments.\textsuperscript{27,28} Advances in our understanding of genetic causes of autism spectrum disorder have facilitated the investigation of these 2 hypotheses and, in fact, it is likely both mechanisms are at play.

Autism spectrum disorder is a heritable disorder, as has been identified convincingly in twin and sibling studies.\textsuperscript{29} With advances in genetic testing methods over the past decade, and routine use of chromosomal microarray analysis and, now, whole-exome and genome sequencing, more than 30\% of individuals with autism spectrum disorder have identifiable genetic correlates.\textsuperscript{30-33} Genetic causes of autism spectrum disorder include well-recognized single gene disorders, such as Fragile X and tuberous sclerosis complex, as well as de novo copy number variations and single gene mutations (see Table 1). Many of these single gene disorders and de novo variations are highly penetrant for comorbid epilepsy and intellectual disability, leading to the coining of the term “syndromic autism.”\textsuperscript{34}

Not surprisingly, the genes implicated in many of these syndromes and variants cause impairments at the level of the synapse, both structural and functional, thereby likely serving as a causative mechanism for epilepsy and for atypical development.\textsuperscript{35} For instance, copy-number variation alterations in genomic regions or associated genes were recently reported in children with continuous spike and waves during slow-wave sleep syndrome and Landau-Kleffner syndrome, suggesting genetic pathway overlaps may exist between autism spectrum disorder and this group of epilepsies.\textsuperscript{36} Specific mutations in the GRIN2A gene have been associated with Landau-Kleffner syndrome\textsuperscript{37} and are also associated with neurodevelopmental disorders, such as autism spectrum disorder.\textsuperscript{38}

From a clinical standpoint, these genetic variants and syndromes can be studied as a biologically based subgroup, with the goal of identifying clinical patterns that can help clinicians provide concrete information about prognosis and treatment (see Table 1). A timely example of this opportunity arises from maternal duplications on chromosome 15q11.2-q13.1 (Dup15q syndrome), as this syndrome confers a high risk for early-onset epilepsy, autism spectrum disorder, hypotonia, and intellectual disability.\textsuperscript{39-41}

### Table 1. Genetic variants and syndromes associated with ASD and epilepsy.

<table>
<thead>
<tr>
<th>Genetic variant or syndrome</th>
<th>Relevant genes</th>
<th>Epilepsy features</th>
<th>Developmental features</th>
<th>Potential treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2p16.3 deletion</td>
<td>NRXN1</td>
<td>Early onset, generalized, severe</td>
<td>Profound ID, ADHD</td>
<td></td>
</tr>
<tr>
<td>7q35 deletion</td>
<td>CNTNAP2</td>
<td>Both focal and generalized epilepsy</td>
<td>Profound ID</td>
<td>Profound language impairment Oxytocin</td>
</tr>
<tr>
<td>15q11.2-13.1 duplication</td>
<td>UBE3A, GABA&lt;sub&gt;A&lt;/sub&gt; receptors</td>
<td>Varied: Generalized and partial, multifocal, infantile spasms, possibly resistant to typical benzodiazepenes</td>
<td>Hypotonia Comorbid ID and ASD</td>
<td>Profound language impairment Excessive beta band activity Benzodiazepenes may be less effective</td>
</tr>
<tr>
<td>18q12.1 duplication or deletion</td>
<td>DTNA Cadherin superfamily genes</td>
<td>Focal and generalized</td>
<td>ID, language delay, deletions associated with motor delay</td>
<td></td>
</tr>
<tr>
<td>22q13.3 deletion</td>
<td>SHANK3</td>
<td>Varied: generalized, focal, absence</td>
<td>Hypotonia Comorbid ID and ASD</td>
<td>Profound language impairment</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>FMR1</td>
<td>Focal epilepsy, often with centrotemporal spikes</td>
<td>Comorbid ID, with ASD severity related to IQ, anxiety, sleep impairment</td>
<td>MGluR5 antagonists, NMDA antagonists (Memantine), GABA modulators (riluzole, acamprosate)</td>
</tr>
<tr>
<td>MECP2-related disorders (Rett syndrome)</td>
<td>MECP2</td>
<td>Generalized and multifocal, EEG shows background slowing (delta power), loss of normal sleep architecture</td>
<td>Microcephaly, regression, Profound ID, stereotypic hand movements, gait dyspraxia, hypotonia</td>
<td>IGF-1, Valproate</td>
</tr>
<tr>
<td>PTEN related disorders</td>
<td>PTEN</td>
<td>Both focal and generalized</td>
<td>Macrophagia, comorbid ID</td>
<td>IGF-1, mTORc inhibitors</td>
</tr>
<tr>
<td>Tuberous Sclerosis Complex</td>
<td>TSC 1/2</td>
<td>Infantile Spasms, Generalized and multifocal epilepsy</td>
<td>Comorbid ID, non-verbal IQ decline in early infancy, anxiety and ADHD</td>
<td>mTORc inhibitors, Vigabatrin</td>
</tr>
</tbody>
</table>
the most highly penetrant variants for intellectual disability and autism spectrum disorder. Duplication of this region leads to the overexpression of several genes, most notably UBE3A (E3 ubiquitin ligase gene) and a cluster of alpha-receptor subunits for the neurotransmitter GABA.

A recent large cohort study of 95 children with Dup15q syndrome sought to identify common characteristics and potential treatments for epilepsy in this population. 42 Investigators identified multiple seizure types, both generalized and focal, with infantile spasms present in 42% of cases. Both broad spectrum and focal antiepileptic medications (such as carbamazepine) demonstrated efficacy for seizure reduction, suggesting a multifocal etiology to the epilepsy. However, GABAergic medications, such as benzodiazepines, were relatively ineffective, possibly due to abnormalities in GABA transmission in the setting of duplications in GABA_A receptor genes in the duplicated 15q region. This trend has led to the recommendation that traditional benzodiazepines should not be considered as a first-line agent for these patients.

In parallel to the efforts in epilepsy, investigators have begun to better characterize the social communication abilities and impairments in children with Dup15q syndrome. In particular, given the ubiquitous finding of hypotonia in these children, investigators are studying the link between motor impairment and both language and social development. Elucidation of the nature of the core deficits of intellectual disability and autism spectrum disorder in Dup15q syndrome will facilitate the design and implementation of targeted behavioral interventions, such as those that focus on motor development, that will specifically benefit this subgroup within the spectrum of neurodevelopmental disorders.

### What Is the Relationship of Autism Spectrum Disorder to Epileptic Encephalopathy?

Epileptic encephalopathy is a conceptual term suggesting that epileptic activity, seizures, or interictal epileptiform discharges can lead to cognitive and behavioral impairment above and beyond what might be expected from the underlying pathology. 43 Because of case reports of children with early-onset seizures and autistic regression, 44-47 parallels have been drawn between children with “autistic regression” and Landau-Kleffner syndrome, an epileptic encephalopathy in which children (usually after age 3) lose language skills in association with an epileptiform EEG showing continuous spike-and-wave pattern in sleep. 48 In clinical disorders where regression, epilepsy, and autism spectrum disorder overlap, multiple variables need to be considered, such as type of regression (language vs autistic); age of onset of seizures or epileptiform activity; and the location, orientation, and quantity of the epileptiform activity, which can guide clinical management.

There is no quantifiable definition of autistic regression, and there continues to be debate in the field regarding its true prevalence, as it is a rather descriptive term that refers to children who seem to lose skills in language and social communication and who develop a restricted and repetitive pattern of behaviors and interests consistent with a diagnosis of autism spectrum disorder. There are 3 major differences between children with autistic regression and those with an epileptic encephalopathy such as Landau-Kleffner syndrome. The first is age of onset. The mean age of language or social communication regression in autism spectrum disorder is 18 to 24 months, and more than 90% of children with autism spectrum disorder who undergo a regression do so before age 3 years. 49 In Landau-Kleffner syndrome, only 12% to 14% of children regress before age 3 years. 50 Age at regression may explain the second difference, which lies in the features of language loss. Because autistic regression occurs in a stage of development that precedes the emergence of full language, the regression can be clinically subtle (eg, loss of single words, decreased gesturing), whereas in Landau-Kleffner syndrome the loss is dramatic, with loss of fully developed language.

The second difference lies in the behavioral profiles. In autism spectrum disorder, regression affects social communication skills, repetitive behaviors, and language, and it results in the behavioral profile that typifies autism spectrum disorder. In Landau-Kleffner syndrome, regression primarily affects language, whereas behavioral abnormalities are much less pervasive and may be attributable to the inability to communicate or cognitive regression. 51 Lastly, there are differences in the EEG findings. In autism spectrum disorder, the epileptiform activity associated with regression is characterized by centrotemporal spikes that can be infrequent and intermittent. 52 In Landau-Kleffner syndrome, the EEG is characterized by frequent temporoparietal spikes, strikingly activated by slow wave sleep and with the EEG pattern of electrical status epilepticus of sleep. 53 Furthermore, it has been shown that children with isolated language regression, as would be seen in Landau-Kleffner syndrome, have a significantly higher frequency of epileptic disorders (60%) versus those with language regression in the context of autistic regression (31%). 54

Despite studies showing that the prevalence of epileptic disorders in individuals with autism spectrum disorder and no clinical history of seizures range from 6% to 60%, 55,56 there is significant controversy regarding the specificity of these findings to the autism spectrum disorder phenotype, with or without regression. 57-59 On the basis of the current literature, the prognostic implications of epileptic disorders in individuals with autism spectrum disorder and the utility of a baseline EEG in individuals with autism spectrum disorder without epilepsy, with or without regression, is dubious. There have not been prospective studies of infants prior to onset of autism spectrum disorder that can definitively demonstrate that epileptic disorders are causative of autism spectrum disorder or autistic regression. Despite studies showing that antiepileptic medications can have a positive impact on behavior, 57,60 no studies have yet demonstrated that treatment of epileptic disorders positively impact social, language, cognitive, or behavioral outcomes. 55,61-66 The comprehensive treatment of autism spectrum disorder and epilepsy has recently been reviewed. 59,67
Despite the fact that children with an epileptic encephalopathy are more likely to develop autism spectrum disorder, it is important to point out that autism spectrum disorder is not an epileptic encephalopathy and, therefore, routine EEG is not warranted for an autism spectrum disorder diagnosis. An overnight EEG is clinically appropriate if there is a suspicion of seizures or a clear regression. Treatment with AEDs is warranted if seizures are diagnosed. If electrical status epilepticus of sleep is diagnosed based on overnight EEG, then treatment with protocols for epileptic encephalopathy would be indicated. However, there exists no evidence that supports the treatment of a child with autism spectrum disorder or with regression if the EEG is normal or only demonstrates infrequent spikes. However, as discussed earlier, children with an epileptic encephalopathy are at increased risk for developing autism spectrum disorder and, therefore, early implementation of behavioral, communication, and educational interventions should be considered a part of their comprehensive management.

**Independent of Epileptiform Activity, Is There an EEG Biomarker in Autism Spectrum Disorder?**

Recently there has been tremendous research interest in the identification of EEG biomarkers of autism spectrum disorder. The hope is that these biological correlates in autism spectrum disorder inform clinical stratification, predict outcomes and inform treatment monitoring. EEG is not only a more feasible, motion-tolerant imaging tool, but it also provides a temporally sensitive measure of cortical connectivity, likely to be aberrant in autism spectrum disorder. Perhaps not surprisingly, because of the wide range in ages and phenotype of the autism spectrum disorder group being studied, no single EEG biomarker has been identified that consistently distinguishes individuals with autism spectrum disorder from those without autism spectrum disorder. In the most comprehensive review of resting-state EEG studies in autism spectrum disorder, Wang and colleagues identified a possible "U-shaped" profile of EEG power alterations, with excess power displayed in theta frequency and gamma frequency bands and reduced power in mid-frequency bands compared with typically developing individuals.68 The authors speculated that, in part, this profile results from abnormal GABAergic tone in inhibitory circuits.

EEG can also inform neurophysiological mechanisms of disease in high-risk genetic variants, therefore bridging the gap from genes to behavior. For instance, in duplications on chromosome 15q11.2-q13.1, a subgroup of children exhibit a classic EEG pattern of excessive beta frequency activity, a feature often found in patients treated with GABAergic medications such as benzodiazepines.41 This signature in Dup15q syndrome likely reflects the upregulation of several GABA receptor genes located in the duplicated region. Studies are currently underway to better characterize this excessive beta activity, both in mouse models and in patients, in order to understand the mechanism underlying this EEG pattern and to investigate whether this EEG signature relates to or predicts clinical outcomes, particularly the development of epilepsy or autism spectrum disorder. Furthermore, recent efforts have been focused on relating specific EEG patterns to core deficits or individual behaviors within autism spectrum disorder, in order to facilitate clinical stratification. In fact, EEG patterns could be extremely informative in the separation of intellectual disability from autism spectrum disorder in genetic syndromes where the 2 are highly related.

There has been more success recently in the identification of EEG patterns that distinguish infants at high and low risk for autism spectrum disorder, with risk conferred by having an older sibling with autism spectrum disorder. Studies have quantified differences in the developmental trajectories of EEG power, particularly in the gamma band, which reflect the binding of neural information from different networks.69,70 Other studies have identified atypical pattern of hemispheric organization, based on alpha band asymmetry,71 as well as lower functional connectivity between frontal and parietal regions,72 in high-risk infants compared with low-risk infants, independent of autism spectrum disorder diagnosis.

Failure to identify consistently predictive patterns of autism spectrum disorder diagnosis stems from the fact that a variety of genetic variants contribute to the development of autism spectrum disorder in infant siblings, each of which may result in a unique electrophysiological signature that represents distinctive neural mechanisms of disease. Nevertheless, if electrophysiological patterns can reliably place infants into risk categories, such categorization could facilitate the initiation of early interventions, prior to the onset of symptoms, which could enhance cognitive and behavioral outcomes. The potential relationship, if any, between these electrophysiological patterns and the development of epilepsy has not yet been investigated.

If EEG patterns can detect risk for developing autism spectrum disorder and can be tracked reliably across development, it seems feasible that quantitative EEG could be used to inform treatment outcomes, especially when standardized clinical measures are less sensitive to change over short intervals. Only 1 study has attempted to integrate EEG measures with behavioral outcomes after intervention. Dawson and colleagues studied a standardized intervention called the Early Start Denver Model in toddlers with autism spectrum disorder. They found that after 2 years of treatment, toddlers receiving the treatment demonstrated an EEG pattern (based on an alpha: theta ratio) similar to that of typically developing children. Moreover, this EEG pattern related to gains in social behavior.73 The study did not include an EEG measure prior to intervention, which would have been informative in the characterization of changes with treatment, but the study was the first to demonstrate the potential for an EEG biomarker to refine the definition of outcome measures, especially in very young or impaired children.
More controversial in this area of treatment is the potential utility for treatments to target EEG patterns in an effort to improve behavior or cognition. In other words, can spike suppression or modulation of oscillatory patterns change a child’s functioning? The answer to this question leads us back to the original questions regarding mechanism of EEG abnormalities, and epilepsy, in autism spectrum disorder. If EEG patterns reflect the same underlying pathophysiological process causing the atypical development, then spike suppression or modification of the EEG pattern should not improve behavior. However, if these atypical patterns do truly precede and, in turn, cause atypical development, then an EEG modifier could, in fact, be effective. Carefully designed, hypothesis-driven studies in homogeneous subgroups of infants and young children must be performed to truly disentangle this issue.

**Future Directions**

In this review, we have examined the relationship between epilepsy and autism spectrum disorder, raising several themes that require further investigation, with the potential for insights that could elucidate mechanisms of disease, early detection, and, ultimately, treatment of these comorbidities. How do we disentangle intellectual disability from autism spectrum disorder in children with epilepsy? Is there an autism spectrum disorder phenotype that is specific to children with epilepsy? Are there characteristic phenotypes within genetic variant syndromes, both from the standpoint of epilepsy and behavior, that can give clues to earlier diagnoses and treatment? Are there electrophysiological precursors to epilepsy and autism spectrum disorder that can be quantified and provide accurate risk markers of disease? When and how should we treat atypical electrophysiological patterns in children with autism spectrum disorder?

The goal of precision medicine in neurodevelopmental disorders will be realized when we define mechanisms of disease that inform specific treatment targets. The comorbidity of epilepsy and autism spectrum disorder is a clue into such neural mechanisms, and through more rigorous methodology that moves beyond cross-sectional descriptions toward a quantification of the timing of onset, electrophysiological and behavioral characteristics, and underlying genetic etiologies, we will move one step closer toward identifying treatment targets for individuals within the heterogeneous autism spectrum.

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**Author Contributions**

SSJ and RT contributed equally to literature review and manuscript preparation.

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