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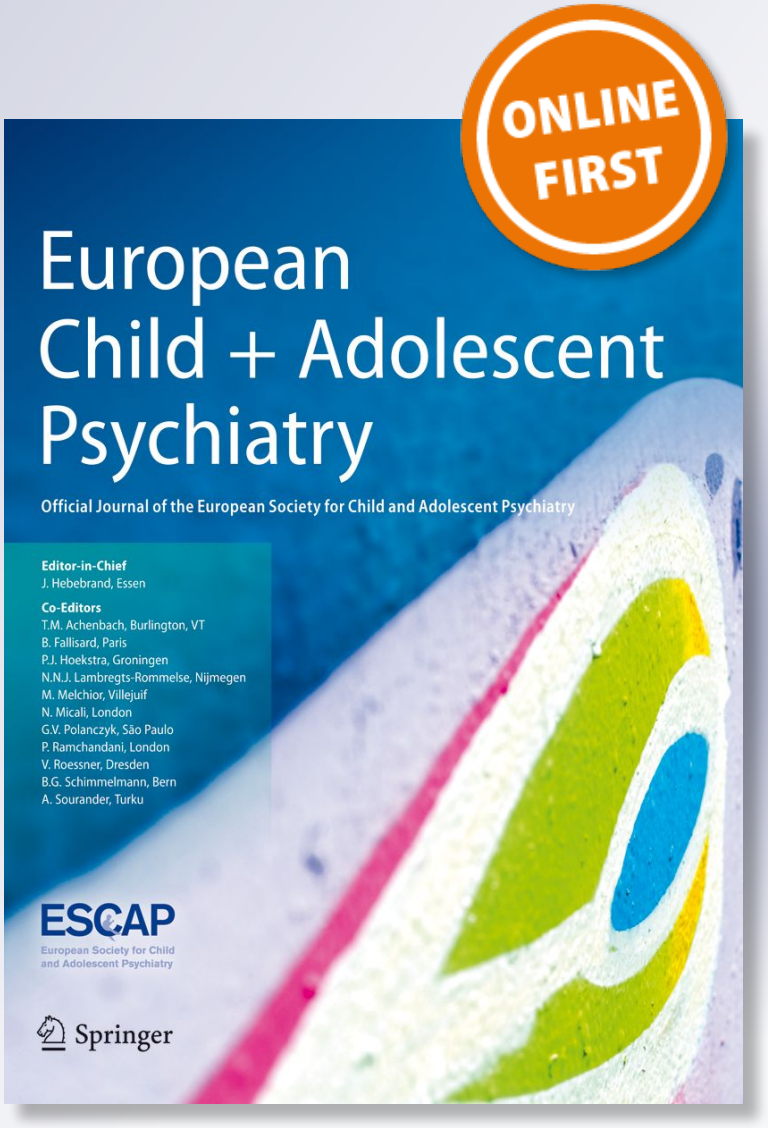

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ORIGINAL CONTRIBUTION

Electroencephalogram (EEG) for children with autism spectrum disorder: evidential considerations for routine screening

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Abstract

Routine electroencephalograms (EEG) are not recommended as a screen for epileptic discharges (EDs) in current practice guidelines for children with autism spectrum disorder (ASD). However, a review of the research from the last three decades suggests that this practice should be reevaluated. The significant comorbidity between epilepsy and ASD, its shared biological pathways, risk for developmental regression, and cognitive challenges demand increased clinical investigation requiring a proactive approach. This review highlights and explains the need for screening EEGs for children with ASD. EEG would assist in differentiating EDs from core features of ASD and could be included in a comprehensive assessment. EEG also meets the demand for evidence-based precision medicine and focused care for the individual, especially when overlapping processes of development are present.

Keywords Autism spectrum disorder (ASD) · Electroencephalography (EEG) · Epilepsy · Epileptic discharges · Screening · Evidence-based medicine

Introduction

Autism Spectrum Disorder (ASD) is a persistent and often severely impairing lifelong neurodevelopmental disorder as first described by Leo Kanner [1]. The prevalence of Autism Spectrum Disorder (ASD) 1 in 45 [2], is sufficient to prompt the American Academy of Pediatrics (AAP) to recommend standardized screening of all children at 18 and 24 months [3], particularly given the evidence that early intervention in ASD improves the child's long-term developmental outcome. An increased incidence of seizures in individuals with ASD has been recognized, beginning with Kanner's publication of his original case series [1]. The discovery of frequent EEG abnormalities in ASD was first reported in 1970 by Gubbay et al. [4].

Estimates for the risk of epilepsy in children with ASD range from approximately 1 in ten [5] to 1 in three [6, 7], yet there are no formal recommendations or clinical practice guidelines that recommend EEG as a routine screening tool in this high-risk group. Given the prevalence and significance of this comorbidity, it is likely that children with ASD may benefit from EEG screening and its incorporation into clinical practice guidelines. In the general population, the prevalence of epilepsy is less than 1% in

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adults 18 years and older [8] and less than 0.6% in children ages 0–17 [9]. When comparing those with ASD to other psychiatric disorders, epilepsy occurs at a significantly elevated rate [10, 11]. Furthermore, cognitive and behavioral impairments related to epilepsy, occurring in the context of ASD, are greater than with either condition alone [12].

Investigators have suspected that paroxysmal epileptiform discharges (EDs) without overt conventionally defined seizures may have neuropsychiatric and neurobehavioral consequences [13, 14] which can manifest as cognitive, language, or behavioral changes [15–17], including elevated levels of irritability and aggression in autistic youth with persistent epileptiform activity on EEG [18, 19].

Electroencephalogram records electrical activity from the underlying cortical surface [20]. The visual inspection of the EEG recording performed by an EEG expert (which we refer to as standard EEG) remains the *only* reliable method capable of detecting paroxysmal or epileptiform activity, particularly when the epileptic discharges are either infrequent or low in amplitude.

More than a decade ago, Kagan-Kushnir et al. [21] proposed that EEG should be used as a screening procedure in ASD, but concluded that there was insufficient evidence to recommend either for or against a clinical guideline. The current review intends to revisit the evidence for this conclusion. With the well-documented risk of seizures in this population, the authors examined currently available evidence for screening EEGs as a standard of care approach in children with ASD.

Methods

Articles addressing estimated rates of EDs in patients with ASD without a history of seizure were found using various search terms in PubMed including: Autism, epileptiform, non-epileptic, MEG, EEG and screening. Additional articles were found from references within the key articles. Other databases including Psych Info and Google Scholars were also probed but yielded no further relevant reports. Each study using EEG and MEG recordings was analyzed to identify the prevalence of EDs in the group of participants. After applying all exclusion and inclusion criteria, only 25 papers met all criteria and were included in the analysis. Healthy or neuro-typical control groups were only included in three of the analyzed studies, therefore not allowing statistical or meta-analysis calculations. All papers not utilizing the standard visually inspected EEG methodology to detect EDs were excluded.

EEG can be used to examine brain activity during rest or during evoked brain responses, using specific tasks known to elicit evoked responses, as well as by examining the effects of specific task paradigms (e.g., face recognition) on the EEG signal. In the current review, we focus on the resting or inactivated state, as it is essential to identify abnormalities that exist at baseline [22]. As the major emphasis of this review is on screening EEGs, all papers with specific clinical situations suggestive that an EEG may be abnormal were excluded under the category of "not focus" (see Fig. 1). Papers examining epilepsy (clinically diagnosed) in ASD were also excluded (under the comorbid category in the PRISMA chart). Other major exclusions included

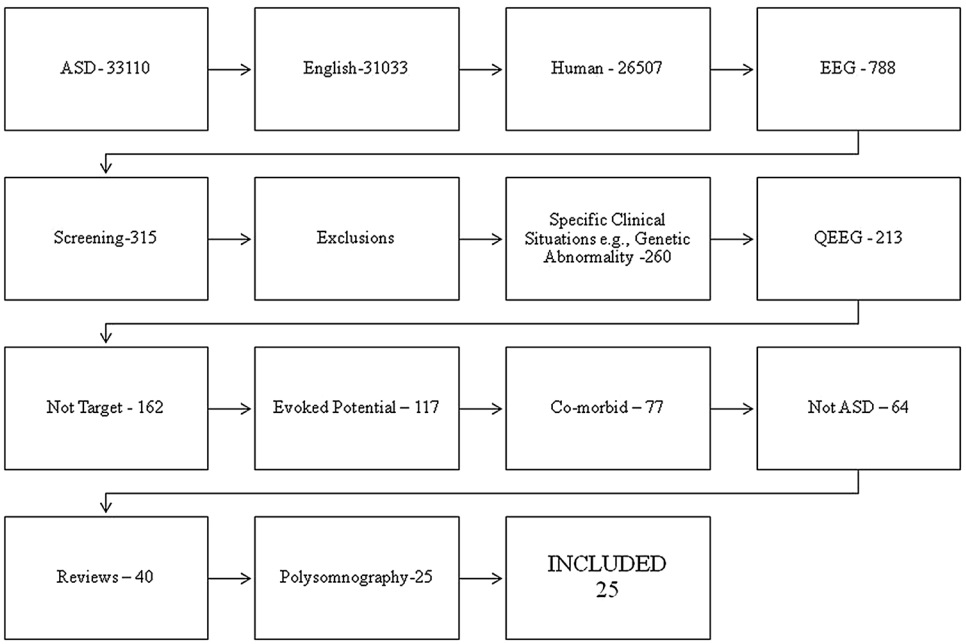

Fig. 1 PRISMA diagram flow of information through the different phases of the systematic review

evoked potentials, quantitative EEG, and polysomnography papers. Papers were also excluded if they only addressed ASD patients with epilepsy and had no ASD group without a history of seizure. The PRISMA diagram below illustrates the search strategy and resultant captured relevant literature.

Results

The summary in Table 1 illustrates available estimated rates of EDs in children with ASD without a diagnosis of epilepsy. The table indicates each study with the type of recording administered and the prevalence of each abnormality, in numerical quantity and percentage. The overall literature mean of the prevalence of EDs was 40% while the average prevalence of epileptiform abnormalities was 45% (range of 3–83%) with the majority above 20%.

Hara [26] concluded in a 10-year retrospective follow-up study ($n = 130$) of children with ASD without a history of seizures that childhood EDs predicted subsequent onset of epileptic seizures during adolescence. Twenty-five percent developed either partial seizures with secondary generalized seizures or generalized seizures, with onset of epilepsy distributed from 8 to 26 years of age. These data suggest

Table 1 Summary of electroencephalographic studies demonstrating subclinical and/or epileptiform abnormalities in autism spectrum disorder

Study	Type of recording	Subclinical abnormalities (*n*)	Prevalence (%)	Epileptiform abnormalities (*n*)	Prevalence (%)
Volkmar and Nelson [72]	EEG Awake and sleep	24/135	17.8	54/135	40.0
Tuchman et al. [75]	EEG Variable	11/181	6.1	41/181	22.7
Rossi et al. [74]	EEG Awake and sleep	20/106	18.9	45/106	42.5
Kawasaki et al. [78]	EEG Sleep	45/158	28.5	96/158	60.8
Tuchman and Rapin [57]	EEG, variable, Min. 1 h. sleep	43/392	11.0	82/392	20.9
Lewine et al. [42]	1 h EEG	4/33	12.1	13/33	39.3
Lewine et al. [42]	24 h EEG	9/29	31.0	21/29	72.4
Lewine et al. [42]	MEG	27/50	54.0	41/50	82.0
Rossi et al. [10]	EEG Awake and sleep	4/60	6.7	23/60	38.3
Hashimoto et al. [46]	EEG Sleep	24/86	27.9	37/86	43.0
Hrdlicka et al. [33]	EEG Awake and sleep	11/77	14.0	24/77	31.0
Canitano et al. [77]	EEG Awake and sleep	10/46	22.0	6/46	13.0
Gabis et al. [31]	EEG Awake and sleep	17/56	30.3	16/56	28.6
Hughes and Melyn [33]	EEG Awake and sleep	44/59	75.0	27/59	46.0
Reinhold et al. [24]	EEG Overnight	85/316	27.0	55/85	65.0
Chez et al. [27]	EEG, overnight, Min. 6 h.	112/176	63.6	540/889	60.7
Hara [26]	EEG	97/130	74.6	33/100	25.3
Mũnoz-Yunta et al. [35]	MEG EEG*	n/a	n/a	30/36 1/36*	83.0 3.0*
Oslejskova et al. [12]	EEG	15/71	21.0	28/71	39.0
Ekinci et al. [23]	EEG Awake and sleep	14/57	24.6	8/57	14.2
Hartley- McAndrew and Weinstock [17]	EEG Awake and sleep	5/15	33.3	5/6	83.3
Pameggiani et al. [25]	EEG Awake and sleep	157/345	45.5	86/345	24.9
Kanemura et al. [83]	EEG	5/21	23.8	11/21	52.4

that routine EEGs could provide significant data for those diagnosed with ASD, especially for children over 8 years old. An overnight EEG study ($n = 889$) of children without a diagnosis of epilepsy but with ASD finds a 60% prevalence rate of EDs [27] compared to a 5% prevalence rate of EDs in healthy children [28].

Ghacibeh and Fields [29] reviewed the presence of EEG abnormalities of individuals with ASD. Identified abnormalities included generalized and focal slowing, epileptiform activity and seizures. Epileptiform discharges (including generalized, multifocal and focal EDs) are more common than non-epileptiform abnormalities [16, 18, 27–32] with a variable frequency of discharges [33, 34]. EDs have a reported prevalence as high as 61% [27] and 86% [35] in ASD studies that have used longer recording times for EEG monitoring and magnetoencephalography, respectively [36]. There is growing evidence that EDs are not asymptomatic as had once been widely accepted [37, 38]. Children with ASD and no history of seizures are similar to children with epilepsy and ASD in that both have an increased risk for developmental regression, abnormal neurological examination and cerebral lesions [39].

There are few MEG studies investigating the electrophysiology of children with ASD [40]. Otsubo and Snead [41] used MEG to compare the rate of epileptiform activity between subjects with and without documented seizure disorders. Eighty-two percent of children with a history of seizures and 54% of patients with no clinical history of seizures had epileptiform abnormalities detected by MEG. Mũnoz-Yunta et al. [35] used MEG to investigate spontaneous neural activity in 36 children with ASD but no seizure history and found low amplitude monophasic and biphasic spikes in about 86% of subjects. Lewine et al. [42] compared 1-h EEG, 24-h EEG, and magnetoencephalogram (MEG) findings and found an increasing prevalence of abnormalities on 24-h EEGs compared with 1-h EEGs, and more abnormalities on MEG compared with 24-h EEG.

Detection of epileptiform discharges

During standard EEG, electrical activity is recorded from the standard sites on the scalp according to the international 10–20 system of electrode placement. Typically, 21 or more channels are displayed in a montage which forms the basis of EEG interpretation. With quantitative EEG (qEEG) technology, there is a virtually infinite ability to adjust the montages and other technical parameters to optimize interpretation and analysis of an individual recording. A standard EEG is 30–45 min in length; however, longer EEG monitoring increases the yield of the study [43].

Significant advances in computer technology have allowed not only for an increase in the number of electrodes from the standard 21 to as many as 256 [44], but also an ever-increasing level of sophisticated data analysis. Recent advances in qEEG signal processing provide the capabilities for mapping (demonstrating the topography of any detected change), source localization (identifying the deeper cerebral sources of identified abnormalities), and complexity analysis (specifying the linearity and non-linearity of the recorded signal). These advances are likely to be helpful in advancing our understanding of how EDs from various sources and of various strength and topographical distribution correlate with the behavioral aberration identified in individual patients.

It is suspected that the location of the EDs may contribute to clinical symptomatology. Focal discharges were reported in many different regions, with some studies suggesting temporal discharges to be more common [45]. Chez et al.'s [27] retrospective review of 24-h ambulatory digital EEG data collected from 889 patients with ASD with no known genetic conditions, brain malformations, prior medications, or clinical seizures shows that 60% of subjects had abnormal EEG epileptiform activity in sleep, with the most frequent sites of epileptiform abnormalities localized over the right temporal region.

Hashimoto et al. [46] suggest that the presence of both frontal and temporal abnormalities may be important for the emergence of ASD symptoms. This suggestion was further supported by Yasuhara [47] as reported that EDs were recorded from the frontal regions in 65% of all cases of ASD whether or not they had symptomatic epilepsy.

Correlates of epileptiform discharges to location of foci

Investigators have established that EDs manifest differently depending on where they originate in the brain. When EDs involve the right cerebral hemisphere, Opp et al. [48] demonstrated that impairments in visual-spatial and visual-motor tasks are more common. Bennie et al. [49] discovered that EDs in both the left and right hemispheres are associated with memory deficits. Sarco et al. [50] found that benign rolandic EDs are associated with depression and behavioral issues in children. Galliant and Hagerl [51] reveal that EDs in the limbic system are associated with anxiety and panic attacks. Episodic behavioral dyscontrol is described by Bach-Y-Rita et al. [52] in a majority of individuals with temporal lobe spikes. And finally, frontal lobe EEG abnormalities in a majority of 206 habitual aggressors are reported by Williams [53], while Howard [54] identifies a link between bilateral paroxysmal EEG features and violent acts committed against strangers.

Although the presenting symptoms may be specific to the location of EDs, it is likely that the paroxysmal nature of these events produces an atypical neurological presentation regardless of the foci of origin. Hughes [55] posits that

a single interictal discharge can produce neuronal, vascular, and metabolic changes throughout the brain. Although controversial, Trojaborg [56] asserts that there is an increased incidence of cognitive, behavioral and/or emotional issues associated with paroxysmal activity regardless of the location of the foci.

ASD and epilepsy shared etiology

The contribution of epilepsy to ASD in developmental neurosciences has grown as an established area of academic and clinical interest [57]. Epilepsy and ASD share several biological pathways that appear to be involved in the disease processes of both. Shared abnormalities are found in gene transcription regulation, cellular growth, synaptic channel function, and maintenance of synaptic structure [58]. Epilepsy and ASD also share common underlying brain structure abnormalities identified with functional MRI [59]. Specifically, prior to the onset of ASD and present in pediatric epilepsy is evidence of abnormal gray and white matter volumes. SPECT studies also find that both children with ASD as well as those with epilepsy have hyper- and hypo-perfusion in localized areas that likely correlates with reduced function in the prefrontal lobes, cingulate gyrus, superior temporal gyrus, and mesial temporal lobes [60].

The relationship between ASD and epilepsy is complex, and the exact origin of this association remains a matter of speculation. The literature supports two main hypotheses to explain the underlying pathophysiological mechanisms of co-occurring ASD and epilepsy [61]. First, both may reflect outcomes as a result of common processes, such as dysregulation in the balance of excitation and inhibition, due to defects in GABAergic fibers or γ-aminobutyric acid (GABA) receptor function [62], with several identified genetic syndromes and variants associated with ASD and epilepsy now known to cause such dysregulation [63]. Second, primary epilepsy may impact synaptic plasticity and cortical connectivity which may predispose the developing brain to cognitive and behavioral impairments manifested in ASD [64, 65].

It is hypothesized that multiple focal hyperexcitability loci in the brain function as the precursor for developing ASD, whether ASD occurs comorbid with epilepsy or in the absence of epilepsy. The dysfunction of specific neuronal networks, which accounts for the behavioral syndrome of ASD, is due to underlying cerebral neuro-excitability giving rise to EDs [66]. Accumulating evidence from the EEG literature supports the assumption that increased cortical excitability contributes to the significant overlap between ASD and epilepsy [8].

A single or specific type of epilepsy associated with ASD has not been identified. When the epileptic focus is located in the temporo-frontal region, autistic regression may demonstrate substantial improvement after pharmacologic or surgical treatment [67, 68]. A large meta-analysis [5] demonstrated a significant increase in the risk of epilepsy when ASD was associated with intellectual disability (ID). The pooled epilepsy prevalence was 21% in subjects with ASD and ID, versus 8% in subjects with ASD and without ID. Also, there was an inverse relationship between epilepsy rates and intelligence quotient (IQ). Several epileptic encephalopathies, including West Syndrome, were found to be associated with ID and ASD features [69].

Kayaalp et al. [70] examined a group of children with West Syndrome (infantile spasms with severe EEG abnormalities) and compared the rate of autistic features to the nature of EEG abnormalities in those with and without ASD. Hypsarrhythmic EEG, a very high-voltage, disorganized pattern of EEG abnormality, is a key finding in infantile spasms. The number of patients with at least one hypsarrhythmic EEG, at age one year or later, was significantly higher in the ASD group (86%) than in the non-ASD group (29%). Frontal predominance of the primary foci on EEGs was seen in 95% of the ASD group, but only 29% of the non-ASD group.

The special case of Acquired Epileptic Aphasia, often referred to as Landau–Kleffner syndrome (LKS), must be differentiated from ASD with language regression, especially when it is associated with isolated EEG abnormalities. LKS is often classified as part of the syndrome of electrical status epilepticus of sleep, also known as continuous spike and wave of slow-wave sleep [71].

Children with epilepsy and ASD are more likely to have a greater level of impairment in intellectual ability, social skills, and hyperactivity compared to children with ASD with no diagnosis of epilepsy [12]. Risk factors for seizure disorder in ASD include female gender [72], early onset ASD [73], family history of epilepsy, severity of cognitive impairment [74], motor impairment [75], history of autistic regression [76, 77], and age [39, 72, 75]. There appears to be 2 peaks of epilepsy onset in ASD: one in early childhood and a second in adolescence [39, 78]. Hormonal influences on neuronal excitability suggest that puberty may be a trigger for epilepsy [76–81]. Viscidi et al. [82] found in a large population study ($n=5815$) that the average prevalence of epilepsy in ASD is doubled by adolescence.

Epileptogenesis, puberty, and behavior

Epileptogenesis in the developing brain may directly impair cognitive and behavioral functioning by way of "transient cognitive impairment" mechanisms, as described by Binnie et al. [49]. Kanemura et al. [83] found that EEG paroxysmal abnormalities in childhood predict onset of epileptic seizures in adolescence. Epileptiform discharges may be an indication of underlying brain neurophysiological dysfunction, which may manifest in behavioral aberrations, even if not sufficient to result in observable seizures. This could be

due to a lack of properly functioning cortico-cortical fibers, which restricts the spread of epileptiform activity and prevents its evolution to a clinical seizure.

As puberty approaches, the increase of excitatory hormones becomes the trigger for many to develop seizures in adolescence [80, 81]. Gilmore et al. [84] suggested that the longer the EDs are present, the greater is the strength of the synapse. The longer children have EDs, the more likely they will become symptomatic as the ED focus spreads. Eventually, the encroaching spread manifests as behavioral aberrations. An animal model of isolated epileptiform discharges (rats with epileptic discharges in the absence of epilepsy) supports this hypothesis, in the demonstration of behavioral aberrations associated with EDs [85].

Clinical practice guidelines

The American Academy of Neurology (AAN) and Child Neurology Society (CNS) guidelines on screening and diagnosis for autism published almost two decades ago [86] stated that there was inadequate evidence at the time to recommend EEG screening in individuals with ASD. Specific indications for sleep-deprived EEG included clinical seizures (or suspicion of seizures) or history of regression (clinically significant loss of social and communicative function), especially in toddlers and preschool aged children.

The National Institute for Health and Clinical Excellence (NICE) Clinical guideline for Autism [87] specifies only to "consider…medical investigation (including)…encephalography if there is a suspicion of epilepsy", and the 2014 American Academy of Child and Adolescent Psychiatric Practice Parameter for Autism Spectrum Disorder [88] states "unusual features in the child (e.g., history of regression, dysmorphology, staring spells, family history) should prompt additional evaluations" and that "neurologic consultation, neuroimaging (and/or) EEG…should be obtained when relevant, based on examination or history" (p. 244).

Discussion

It should be emphasized that this review is addressing a population that has not been examined closely, specifically individuals with ASD and no history of seizure. One significant shortcoming of available literature is the lack of rigorous exclusion of epilepsy in studies involving children with ASD. Additionally, the large range of reported incidence of EDs in children with ASD without a history of seizures most likely reflects the variance in the populations studied as well as techniques used to detect EDs (e.g., duration of recording and sleep deprivation).

There are several considerations for future studies. There is a need to examine: (1) the neural pathway changes caused by EDs over time and their link to behavioral manifestations, (2) the relationship between risk factors and presence or absence of EDs in developing seizures and emotional or behavioral issues, and (3) the neurological, psychological and developmental differences of children with ASD who are epileptic versus those with only EDs.

Interictal EDs underlie epileptogenesis. Treating and preventing epileptogenesis may help to both avert seizures and prevent further cognitive impairment in children. A retrospective study involving 76 treatment refractory psychiatric patients (ages 5–52) with EDs and no history of seizures who were treated with anticonvulsants (most commonly lamotrigine and oxcarbazepine) was recently published [89], documenting 85% with significant clinical improvement in follow-up progress notes. Furthermore, Braun [90] suggests that early etiological diagnosis and strict control of EDs with anticonvulsants can prevent worsening of cognitive function.

In the last 10 years, we have treated hundreds of children, adolescents, and adults with ASD, but no history of seizures, with anticonvulsants and none to date have developed seizures. This is noteworthy because Hara [26] found that 25% of children with ASD who have epileptiform abnormalities go on to develop epilepsy. In addition, prescribing anticonvulsants for patients with EDs and no history of seizure has helped us to develop stratification biomarkers for the use of specific antiepileptic drugs as well as predicting cognitive outcomes in these patients. However, since anticonvulsant drugs were developed for the treatment of seizures and not EDs more research in this area is needed, particularly regarding risks versus benefits.

Retrospective clinical studies are subject to bias. However, to obtain an accurate assessment of the prevalence of epilepsy in ASD, and to determine the outcome of EDs in children with ASD without a history of seizures, we propose that data could be obtained from a prospective study in which EEGs are collected at the time that ASD is diagnosed. Long-term outcome studies could then be used to determine the predictive value of an abnormal EEG in the development of later epilepsy [91]. Regarding the use of antiepileptic drugs in children with ASD, Hirota [92] found that anticonvulsants were not superior to placebo in a randomized control trial (RTC). However, there have been no RCTs assessing the use of anticonvulsant drugs in children with ASD and EDs without a history of seizures. We are now collecting these data for a future pilot study.

For individuals with ASD who are receiving treatment for behavioral concerns, there is a high prevalence of psychotropic prescribing, most frequently including antipsychotics, stimulants and antidepressant drugs [93]. These medications, particularly the antipsychotics, tend to lower the seizure threshold, which creates the potential in turn to exacerbate psychiatric, cognitive, and behavioral issues. The evidence provided in this review suggests that EEG screening

is necessary for the selection of psychotropic medication for children with ASD.

Conclusion

EEG primarily measures neurophysiological changes related to postsynaptic activity in the neocortex [94] and has proven to be a powerful tool for studying healthy individuals as well as those with complex neurodevelopmental disorders. Standard EEG has been the primary measure used to capture and characterize epileptiform and abnormal paroxysmal activity through the detection of focal spikes (i.e., EDs), which occur with increased frequency in ASD [57, 95]. Technological advancements are allowing for increased levels of detection, as well as improved source localization of EDs.

The identification of EDs in children with ASD is vital. The literature suggests that using more prolonged EEG monitoring yields higher rates of EDs. However, these procedures are not well tolerated by hypersensitive children with ASD and, they cause considerable hardship for parents, making compliance a prohibitive issue. We find that routine EEG screening is much less invasive, less expensive, and generally well tolerated by children with ASD.

Given the significant incidence of epileptic seizures in individuals with ASD, clinicians should be alert for even subtle indications of epilepsy, and should routinely consider this possible comorbidity in the clinical assessment and bio-psycho-social evaluation of children with ASD. Making a diagnosis of seizures in ASD is particularly challenging because the behavioral features of complex partial or absence seizures including staring spells, non-responsiveness, and repetitive motor behaviors can all be manifestations of the ASD itself. In many circumstances, there is a complete lack of observable signs or symptoms to help predict which children with ASD will develop seizures.

In the past decade, there have been three primary and well-documented findings which provide evidence of the need for screening EEGs in children with ASD. First, that ASD and epilepsy are more connected than previously believed. Second, that EDs are highly prevalent in children with ASD and that these discharges are more common in patients with significant comorbid psychopathology. And third, those children with ASD and demonstrated evidence of EDs have an increased likelihood of developing epilepsy in adolescence.

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Authors' contributions AG developed the original draft and started constructing the table. RS, EM, AR, GK further developed the study with AR completing the table. RS, EM, AR, and GK expanded the scope of the study and developed the conclusions. RS, AG, EM, AR, and GK as a group approved the final manuscript.

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Compliance with ethical standards

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