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EEG abnormalities and clinical phenotypes in pre-school children with autism spectrum disorder

Marina Romero-González [a,b], Patricia Navas-Sánchez [a,b], Ester Marín-Gámez [a,b], Miguel Angel Barbancho-Fernández [b,*], Victoria Eugenia Fernández-Sánchez [a], José Pablo Lara-Muñoz [b], José Guzmán-Parra [a]

[a] Hospital Universitario Regional de Málaga, IBIMA, Avenida Carlos Haya, 84, 29010 Málaga, Spain
[b] Universidad de Málaga, Unidad de Salud Cerebral, Facultad de Medicina, Centro de Investigaciones Médico Sanitarias, C/Marqués de Beccaria, 3, 29010 Málaga, Spain

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ABSTRACT

Background: Abnormalities on electroencephalography (EEG) results have been reported in a high percentage of children with Autism Spectrum Disorder (ASD). The purpose of this study was to explore the prevalence of EEG abnormalities in a clinical population of pre-school children with Autism Spectrum Disorder and the differences in terms of the following phenotypic characteristics: adaptive behavior, executive functioning, severity of Autism Spectrum Disorder core symptoms, and comorbidity symptoms.
Methods: A cross-sectional analysis of 69 children who attended the Autism Spectrum Disorder early diagnosis program with electroencephalography and clinical diagnosis was performed. A battery of questionnaires was also made to parents to evaluate emotions, behavior, and functional skills for daily living.
Results: Out of 69 pre-school children with Autism Spectrum Disorder, twenty nine (42%) had abnormalities in electroencephalography results. The group with abnormal epileptiform electroencephalography exhibited more impairment in executive functioning and social-relationship coexisting symptoms.
Conclusions: The presence of an abnormal epileptiform electroencephalography in pre-school children with ASD already suggests a worse development in clinical features.

1. Introduction

Autism spectrum disorder (ASD) is a severe and lifelong developmental disability affecting about 1 in 59 children, according to the new data at The Center for Disease Control and Prevention (CDC) [1]. It is characterized by pervasive impairments in social communication and stereotyped and restricted interests [2]. In addition to these core symptoms of autism, 70–90% of children with ASD have significant additional psychiatric disorders that impair their everyday functioning and reduce quality of life for themselves and their families [3,4].

Also, different authors highlight the importance of carrying out a phenotypic characterization based not only on the specific core symptoms of ASD but also in their psychiatric and medical comorbidities and other factors that may influence the functionality of this complex spectrum of autism [5,6].

Comorbidity with other neurologic disorders, suggested widespread neuropathological changes, and an emerging literature of structural and functional neuroimaging differences in autism all herald an underlying central nervous system (CNS) abnormality. One of the best-known associations with CNS dysfunction is the high risk of epilepsy [7].

Across the literature, the reported prevalence of epilepsy in patients with ASD ranges from 2.4% [8] to 46% [9]. In the largest studies [10–15], the rates ranged between 2.4% and 26%. The prevalence of epilepsy among preschoolers with ASDs is estimated at 9% [16].

According to Roberto Tuchman, the concept of epileptiform disorder with cognitive symptoms include a subgroup of individuals with ASD who have epileptiform abnormalities on EEG results in the absence of clinical seizures; these epileptiform alterations are thought to be part of the language, cognitive, and behavioral dysfunctions seen in these children [17]. In addition, several studies have shown the impact of epileptiform abnormalities on the developing brain, also when seizures are absent [18,19]. Recently, there have been different studies that have reported high rates of epilep-

* Corresponding author at: C/Marqués de Beccaria, 3, 29010 Málaga, Spain.
E-mail address: mabarbancho@uma.es (M.A. Barbancho-Fernández).

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tiform electroencephalogram in children with autism without a history of seizures or epilepsy [20–22].

In an extensive study of 1014 children with autism showed that 86% of patients had epileptiform discharges; 43% had epilepsy and 57% had epileptiform EEGs, no epilepsy [21]. One of the other highest reported rates of abnormalities on EEG results was reported by Chez and colleagues on 889 patients with ASD without a history of seizures, which revealed epileptiform abnormalities at a rate of 60.7% [23]. Previous studies performed to date had reported that 15–20% of individuals with autism across a large age range exhibited epileptiform EEG abnormalities [24,25].

The diagnosis of seizure activity in ASD is much more complicated due to the behavioral problems associated with complex partial and/or absence seizures (*e.g.*, staring and non-responsiveness with or without repetitive motor behaviors) – all of which can be attributed to the autistic condition. The increased prevalence of epilepsy and/or epileptiform EEG abnormalities in individuals with ASD may be an important line of evidence to an underlying neurologic abnormality, at least for a subgroup of individuals. The rate of EEG abnormalities in individuals with ASD is more difficult to determine because of potential referral biases, various types of EEGs performed, and standards used to assess EEGs [26].

Lado et al, postulate an excellent theory related to the hypothesis that epileptiform discharges, with or without seizures, may have a negative impact on the brain development and may affect both cognition and behavior [19]. There are some lines of evidence in animals [18] that showed that persistent discharges on the early brain development inhibited the normal plasticity process, which is fundamental for cognitive functioning. Other authors also showed that epileptiform abnormalities in children with ASD are associated with a higher level of motor stereotypes and more symptoms of aggressive behavior [27]. Moreover, EEG abnormalities have been associated with language deficits, lower adaptative functioning, cognitive function, and other sociodemographic and clinical variables as age and diagnostic classification [20,25,28–31].

More research is needed to investigate whether abnormalities on EEG results are an epiphenomenon or play a more direct role in some of the features seen in ASD. Fundamental questions regarding the relationship among the occurrence of EEG abnormalities in early childhood, and the cognitive, language, and behavioral deficits seen in autism are still unanswered [29]. Studies in early childhood in children with diagnosis of ASD could help to elucidate the relationship between EEG abnormalities and cognitive and behavioral deficits.

Consequently, the primary objective of this study was to explore the prevalence and to characterize EEG abnormalities in a clinical population of pre-school children with early diagnosis of ASD and to analyze the association between EEG abnormalities (epileptiform and non-epileptiform) and the following phenotypic characteristics: 1) adaptive behavior, 2) executive functioning, 3) severity of ASD core symptoms, and 4) with other psychiatric symptoms.

2. Methods

2.1. Recruitment of participants

The current study was approved by the Research Ethics Committee on 23rd of February 2017.

All eligible families were invited to a face-to-face evaluation at our Child and Adolescent Mental Health. The target population for the study was children who attended the ASD early diagnosis program. The inclusion criteria were: clinical diagnosis of ASD with gold-standard tool confirmation (ADOS-2) and age between 2 and 6 years. The exclusion criteria were: any diagnosis of autism syndromic (X-Fragile, Sclerosis Tuberosis, Angelman Syndrome) or previous diagnosis of epilepsy. 149 pre-school children were referred to the unit between February 2017 and February 2019 for the clinical assessment of early diagnosis and 101 children were initially recruited into the study with a clinical diagnosis of ASD as 48 children did not meet the required criteria for the diagnosis of ASD. Finally, the current study focused on a cross-sectional analysis of 69 participants. We had 32 missing participants who refused participation or the EEG assessment was not completed or relevant information was missing during the assessment process.

2.2. Assessments

2.2.1. Child direct assessments

2.2.1.1. Electroencephalogram. All participants were invited to attend the Neurophysiology Unit of Materno Infantil Hospital to do an EEG. All EEGs were routine awake, performed in awake state using 32-channel XLTEK digital equipment. Surface electrodes located according to the international 10-20 system were used with bipolar and monopolar montages. The duration of the records was between 20 and 30 min. EEG results were obtained from the unit EEG report that was generated by experts.

An EEG result was considered abnormal if the report mentioned epileptiform abnormalities (spikes, sharp waves, polyspikes, spike–wave, or spike and slow wave complexes) or nonepileptiform abnormalities, which included background slowing, fast activity and/or focal slow activity (theta and delta activity).

0 = EEG Normal.
1 = EEG nonepileptiform abnormalities.
2 = EEG epileptiform abnormalities.

2.2.1.2 The final clinical diagnosis was made by the physician after reviewing the available assessments, including the ADOS, performing a medical history and physical exam, and directly observing the child, which is the current gold standard in diagnosing ASD. All patients met Diagnostic and Statistical Manual of Mental Disorder 5 criteria for ASD.

2.2.1.2. Autism diagnostic observation schedule – 2 (ADOS-2) [32]. It is a semi-structured, standardized assessment instrument that includes a number of play-based activities designed to obtain information in the areas of communication, reciprocal social interactions, and restricted and repetitive behaviors associated with a diagnosis of ASD. The ADOS-2 allows to accurately assess and diagnose autism spectrum disorders across age, developmental level, and language skills. It is one of the main "gold-standard" tools for the diagnosis of ASD [33].

2.2.2. Parent questionnaires

2.2.2.1. The Strengths & difficulties questionnaire parent (SDQ) [34]. It was used to assess the level of emotional and behavioral difficulties in children. The Strengths and Difficulties Questionnaire (SDQ) is a brief behavioral screening questionnaire for children aged between 2 and 16 years. The questionnaire has 25 items and is divided between 5 scales: 1) emotional symptoms; 2) conduct problems; 3) hyperactivity/inattention; 4) peer relationship problems; and 5) prosocial behavior. The internal consistency index of the Spanish version is adequate (Cronbach's Alpha = 0.77) [35].

2.2.2.2. Adaptive Behavior Assessment System-II (ABA-II) [36]. It is a multidimensional and standardized assessment tool used to evaluate functional skills necessary for daily living of individuals between 0 and 89 years of age. The ABAS-II assesses the following skill areas: Communication, Community, Functional academics,

School/home living, Health and safety, Leisure, Self-care, Self-direction, Social, and Motor. The internal consistency index (Cronbach's Alpha) ranges between 0.97 and 0.99 [37].

2.2.2.3. Behavior rating inventory of executive Function®–Preschool version (BRIEF-P) [38]. Is the first standardized rating scale designed to specifically measure executive function in preschool-aged children. It measures multiple aspects of executive functioning through different scales: Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize.

A single rating form allows parent providers to rate a child's executive functions within the context of his or her everyday environments—home and preschool. Three broad indexes (Inhibitory Self-Control, Flexibility, and Emergent Metacognition), one composite score, and two validity scales (Inconsistency and Negativity) are provided. The internal consistency index (Cronbach's Alpha) is 0.83 [39].

2.3. Statistical analysis

In the analysis for the categorical variables were used the chi-squared test and Fisher exact test if less than 80% of expected frequencies were higher than 5.

Linear regression models were used for the quantitative variables. To verify the assumptions of the linear regression models, we used the Breusch–Pagan homoscedasticity test, the Shapiro–Wilks normality test of the residuals, and a scatter plot to verify the linear relationship of the variables. If these assumptions were not fulfilled for the regression model, the Kruskal–Wallis non-parametric test and the Dunn post hoc test were used after correcting for Bonferroni p values; In this case, instead of Mean and Standard deviation were used Median and Interquartile Range (IQR). For all comparisons, a level of significance of 95% was used. The R program version 3.6.1 was used for the analysis.

3. Results

3.1. Children's characteristics

Analysis was performed on 69 participants with a diagnosis of ASD who had an EEG record and without any diagnosis of epilepsy around the time of their initial ASD diagnosis (Table 1). Male-to-female ratio was 4:1 overall and there were no statistical differences between group comparisons. The average age of participants was 48 ± 13.0 months at the time of assessments. Age of ASD diagnosis was lower in the group with abnormalities in EEG results than in the group with normal EEG results but without reaching significant differences (Table 1).

Twenty nine participants (42%) presented EEG abnormalities but only nine (13%) were considered epileptiform abnormalities (six participants had focal epileptiform abnormalities and three had generalized seizures). The most common location of focal epileptiform abnormalities was temporal-parietal (3 participants), right temporal (2 participants), and central-temporal (1 participant). Out of nine participants with epileptiform abnormalities, family history of epilepsy was only found in one participant with generalized seizures.

Six participants were taking neuroleptic treatment for severe behavior problems (8,8%) at the time of assessment: five of them (83%) presented abnormalities in the EEG results; two with no epileptiform abnormalities and 3 with epileptiform (one of them with possible history of seizures). Significant differences were found between groups with a $p < 0.001$.

Also, three participants (4,3%) had a possible history of seizures according to the parents' descriptions and all of them had an EEG with epileptiform abnormalities, one with generalized seizures and two with focal epileptiform abnormality (one with temporal-parietal and one with right temporal). All of them were referred to neurology department.

3.2. Group comparisons

Groups were then compared with each other in order to determine if differences in autism severity, adaptive behavior, executive functioning, and psychiatric coexisting symptoms were present.

When comparing the three groups, the group with epileptiform abnormal EEG exhibited higher scores (worst performance) on executive functioning, specifically in the area of inhibition control ($p < 0.05$); No significant differences were seen in Autism Severity (ADOS-2). Detailed information about executive function and Autism Severity is shown in Table 2.

There were also differences in coexisting psychiatric symptoms, specifically in the social area and in relationship area ($p < 0.05$), showing more impairments in both areas. In terms of co-existing psychiatric symptoms, no differences were found regarding emotional, behavior problems, or hyperactivity. There were no differences between groups regarding adaptative behavior. See Table 3 for detailed information.

4. Discussion

Our results show that a significant percentage (42%) of children with early diagnosis of ASD and without previous seizure have abnormalities on the EEG results [which included background slowing, fast activity and/or focal slow activity (theta and delta activity)], although only 13% had epileptiform EEG abnormalities (which include spikes, sharp waves, polyspikes, spike–wave, or

Table 1
Sociodemographic and clinical variables.

Variables	Total Media (Standard Deviation)	Non EEG abnormalities $n = 39$	EGG nonepileptiform abnormalities $n = 20$	EGG epileptiform abnormalities $n = 9$	*Statistic*	*p*
Age in months	48.0 (13.0)	50.2 (12.5)	45.4 (14.1)	44.1 (12.0)	$F = 1.374$	0.260
Gender					$X^2 = 0.548$	0.831
Male	53 (79.1)	31 (79.5)	15 (75)	7 (87.5)		
Female	14 (20.9)	8 (20.5)	5 (25)	1 (12.5)		
Educational level mother					$X^2 = 0.084$	1
University	23 (38.3)	13 (37.1)	7 (38.9)	3 (42.9)		
Other	37 (61.7)	22 (62.9)	11 (61.1)	4 (57.1)		
Educational level father					$X^2 = 2.944$	0.234
University	18 (30.5)	10 (29.4)	4 (22.2)	4 (57.1)		
Other	41 (69.5)	24 (70.6)	14 (77.8)	3 (42.9)		
Psychopharmacology prescription for behavioral problems	6 (8.8)	1 (2.6)	2 (10)	3 (42.9)	$X^2 = 10.539$	0.009*
Possible seizure history	3 (4.4)	0	0	3 (33.3)	$X^2 = 20.574$	0.002*

Table 2
Severity of autism and executive functions.

Variables	Total	Not EEG alterations $n = 39$	EGG nonepileptiform alterations $n = 20$	EGG epileptiform alterations $n = 9$	*Statistic*	*p*
ADOS Total Score (Median, IQR) Missing:1	14 (10.3)	15 (7)	14 (14)	13 (10.5)	1.181	0.554
Severity scale	4.9 (2.4)	4.6 (2.3)	5.2 (2.8)	5.8 (2.0)	0.859	0.428
Social scale	11.2 (5.5)	10.4 (5.3)	12.1 (6.3)	12.6 (4.3)	0.907	0.409
RRB	2.7 (1.6)	2.7 (1.6)	2.4 (1.6)	3.1 (1.7)	0.810	0.450
Executive functions Global Index Missing:10	122.8 (22.6)	123.9 (23.6)	116.1 (23.0)	134.9 (8.6)	1.896	0.160
Inhibitory self-control index Missing:6	52.3 (10.5)	53.3 (10.8)	47.9 (10.1)	59.1 (4.9)	3.559	0.034[1]
Flexibility index Missing:6	37.7 (9.9)	39.9 (10.2)	33.3 (9.4)	38.4 (5.9)	2.955	0.060
Metacognitive Index Missing:10	54.1 (10.1)	54.6 (9.7)	51.8 (11.9)	57.9 (5.6)	0.976	0.383

1. Differences epileptiform alterations and EGG non epileptiform alterations ($t = -2.514$, $p = 0.015$). $R^2 = 0.108$. Breusch Pagan Homoscedasticity test = 0.412. Shapiro Wilks test of residuals = 0.595.

Table 3
Psychopathology and adaptive behavior.

Variables	Total	Not EEG alterations $n = 39$	EGG nonepileptiform alterations $n = 20$	EGG epileptiform alterations $n = 9$	*Statistic*	*p*
Psychopathology (SDQ) Total Missing:8	18.0 (5.4)	18.2 (4.9)	16.4 (6.2)	20.4 (5.6)	1.556	0.220
Emotional (SDQ) (Median, IQR)	2.0 (3.0)	2.0 (2.8)	3.0 (4.0)	1.5 (2.8)	0.444	0.801
Behavior (SDQ)	3.4 (2.0)	3.4 (1.9)	3.1 (2.1)	4.1 (2.5)	0.768	0.469
Relationships (SDQ)	4.8 (1.9)	4.8 (1.6)	4.2 (2.2)	6.3 (1.8)	3.314	0.043[1]
Hyperactivity (SDQ)	7.2 (2.1)	7.4 (2.1)	6.6 (2.4)	7.8 (0.8)	1.587	0.452
Social (SDQ)	3.5 (2.3)	3.4 (2.1)	4.4 (2.7)	1.75 (1.6)	4.123	0.021[2]
Adaptive Behavior Global Index (Median, IQR) Missing:6	56.0 (14.3)	56.0 (14.2)	58.0 (11.0)	53.0 (6.0)	1.350	0.509
Conceptual (Median, IQR)	60.0 (16)	58 (17)	62 (15.5)	60 (7.5)	0.481	0.786
Social (Median, IQR)	64 (20)	63 (26)	64 (10.8)	64 (16)	0.817	0.665
Practical (Median, IQR)	62 (16)	62 (18)	63 (15)	56 (0)	3.658	0.161

1. Differences between EEG epileptiform alterations and EGG non epileptiform alterations ($t = -2.572$, $p = 0.013$). $R^2 = 0.104$. Breusch Pagan Homoscedasticity test = 0.393. Shapiro Wilks test of residuals = 0.175.
2. Differences between EEG epileptiform alterations and EGG non epileptiform alterations ($t = 2.850$, $p = 0.006$). $R^2 = 0.126$. Breusch Pagan Homoscedasticity test = 0.104. Shapiro Wilks test of residuals = 0.176.

spike and slow wave complexes). Young children with epileptiform abnormalities on EEG results exhibit more affectation, particularly in the areas of prosocial behavior and social relationship. Furthermore, children with epileptiform abnormalities performed worse on executive functioning assessments and exhibited higher scores in inhibition self-control compared with patients with nonepileptiform abnormalities. In addition, patients with epileptiform abnormal EEG results in the setting of ASD tended to exhibit lower adaptive functioning, higher scores on global executive functioning, severity of ASD, and total scores of co-existing psychiatric problems but did not quite reach statistical significance. To the best of our knowledge, this is the first study that describes the association between epileptiform abnormalities on EEG and cognitive, clinical, and behavioral variables in pre-school children with ASD.

The large range and lack of precise frequency of abnormalities on EEG results in previous studies highlight the significant variability in methodology, including difference in ages, clinical features, and EEG recording methods. This study only reports data of preschool participants (<6 years old) because we hypothesized from a theoretical point of view, that the earlier the abnormalities appear, the higher the brain development can be affected. So, prevalence is expected to be lower than older population. For example, the prevalence of epilepsy in samples of children with ASD varies according to the age group studied; seizures in the majority of children with autism began after 10 years of age [40].

For example, one of the highest reported rates of abnormalities on EEG results was by Chez and colleagues in which 24-hour EEG recordings performed a rate of 60.7% [23]. Most of these abnormalities occurred only during sleep and were most frequently seen in the right temporal region followed by bilateral central temporal regions. However, the researchers did not further characterize these abnormalities with regard to specific features of ASD. The present study does not report 24-hour EEG recording, consequently it is less likely to detect EEG abnormalities. In accordance with Chez et al. [23], the group of participants with generalized seizures tended to have a family history of generalized seizures while the triphasic or biphasic spikes in central temporal regions or temporal regions did not. We also found, in our limited sample, one participant with generalized seizure with a family history of epilepsy; however, no family history was found in the group of participants with focal seizure.

Mulligan and Trauner identified 101 children between 1 and 18 years with ASD who had undergone prolonged EEG monitoring and found an incidence of 23% of epilepsy in individuals with autism and the majority of patients in the study (59.4%) had epileptiform abnormalities [27]. Recently, Capal et al., showed that approximately 30% of patients had abnormalities during sleep only with an additional 15% exhibiting epileptiform discharges during sleep on a sample of 433 children with ASD. However, although our sample size is small, the majority of these studies are based on retrospective EEG database with a clinical diagnosis of ASD, including adolescents and youth adults [20,27]. The fact that only routine EEG was carried out and the lower age of the sample could have influenced the low rate of epileptiform abnormalities in our study.

The presence of intellectual disability has been reported as an independent risk factor in the development of epilepsy in the set-

ting of ASD [8,41]. Capal et al., also showed that patients with epilepsy exhibited lower cognitive and adaptive functioning scores compared to the other groups, particularly in expressive and receptive language subdomains and the group with abnormal EEG results also exhibited more impaired adaptive functioning compared with the group with normal EEG results [20]. When comparing the three groups in the present study, no significant differences were seen in adaptive functioning although the scores showed more impairment but without reaching significance.

On the other hand, our study shows significant differences in prosocial behavior and relationship in terms of psychiatric co-existing symptoms. Capal et al., did not show differences as measured by the CBCL [20]. Nevertheless, our results are supported by other studies that differ on the relationship between seizures, abnormal EEG results, and ASD co-existing psychiatric symptoms. For example, Mulligan and Trauner found an association between abnormalities on EEG results and behavior [27]. They performed a retrospective chart review and found a higher incidence of epileptiform abnormalities in children with aggressive behavior and stereotypies.

The present study exhibits more impairment in executive functioning (control inhibition) in the group of participants with epileptiform abnormalities. Other studies also showed an association between executive functioning and epilepsy in pediatric population [42–45].

Other studies also indicated that there exists an association between executive functioning and social communication impairment in children with ASD [46,47]. One more co-existing symptomatology well established with ASD and epilepsy is Attention Deficit and Hyperactivity disorder (ADHD). ADHD has a strong association with executive functioning alteration overall for deficits in control inhibition, working memory, and regulation of motivation [48]. Moreover, children with new-onset epilepsy are more likely to have ADHD than healthy controls without epilepsy [49]. Also, parents of children with newly diagnosed epilepsy report higher behavioral problem scores (Child Behavior Checklist CBCL) [50]. However, our study did not report any association with hyperactivity although it showed higher impairment in executive functioning (control inhibition) in the group of patients with epileptiform abnormalities.

According to our results, we suggest that early epileptiform discharges may have a negative impact on the brain development and may affect cognition, behavior, and other phenotype characteristics, overall in social, relationship, executive functioning (inhibition control), and behavior problems. Early detection of abnormalities in EEG signals may be an early biomarker for developmental cognitive or co-existing disorders. However, we should be careful at the time of drawing strong conclusions because this is just a cross-sectional study with a medium size of participants and the literature shows a lack of homogeneity and substantial variability in methodology.

5. Strength and limitations

Strengths of this study include its careful sampling method and the large proportion of pre-school children with early diagnosis of ASD. To our knowledge, this is the first study in providing results about the relationship between EEG abnormalities and ASD features focusing on pre-school children with early ASD diagnosis. Moreover, we also used an objective tool for the assessment of ASD, using the *"gold-standard"* tool of ADOS-2 and not retrospective information. Moreover, the EEG were recorded prospectively so that we avoid information bias from database of retrospective EEG results.

There are also some additional limitations:

First, the data in the current study were collected at a single time-point; therefore, we cannot determine the long-term consequences of EEG abnormalities on the brain development of children with ASD. We would need longitudinal studies in order to establish the temporal sequences and the long-term effect.

Second, this study relied on single informant, parent-reported data for the assessment of executive functioning, adaptive behavior, and co-existing symptoms which could rather result in a response set. Also, we should consider the possibility of information bias in terms of parental reliability.

Additionally, this study is limited by the lack of 24-hour EEG recording and we just provide the results of a normal awake EEG that limited the probability to find epileptiform abnormalities. However, in our clinical practice, longer EEG recording or with sleep deprivation is performed in children in whom epileptic seizures are suspected and there is no evidence of epileptiform abnormalities on the awake EEG.

We also focused on a clinical recruitment, so that we cannot extrapolate the results to the general population with ASD to determine the real prevalence in general population of EEG abnormalities in pre-school children with ASD. Also, the small sample size limited the generalizability of the results obtained.

In accordance with the literature, speech receptive processing seen in ASD is correlated with temporal central parietal spikes, and bitemporal and left temporal abnormalities are also consistent with sites of potential language dysfunction [39]. Receptive and expressive speech was not tested in our study. However, the ABAS-II includes a subscale of communication (conceptual) and no correlation was found.

Finally, our results have important implications into directions of future clinical and longitudinal research targeted at understanding the impact of epileptiform discharge on the brain development in children with ASD and the potential use of EEG monitoring as part of standard evaluation in order to identify at-risk individuals. If we are better able to understand this, we could then develop clinical treatment trials using antiepileptic drugs (AEDs) in participants with EEG epileptiform abnormalities only, and we may be in a better position to see if there is any improvement in behavior, cognition, and other clinical features as a result of AED treatment in this population. Also, future research may then give us a cleaner population with a higher risk to target with early interventions focused on the cognitive and behavioral symptoms.

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Declarations of interest

The authors have no conflicts of interest to declare.

References

[1] Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2014. MMWR Surveillance Summaries 2018;67(6):1. https://doi.org/10.15585/mmwr.ss6706a1.

[2] American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub.

[3] Hofvander B, Delorme R, Chaste P, Nydén A, Wentz E, Ståhlberg O, et al. Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. BMC Psychiatry 2009;9(1). https://doi.org/10.1186/1471-244X-9-35.

[4] Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. J Am

Acad Child Adolesc Psychiatry 2008;47(8):921–9. https://doi.org/10.1097/CHI.0b013e318179964f.
[5] Grzadzinski R, Huerta M, Lord C. DSM-5 and autism spectrum disorders (ASDs): an opportunity for identifying ASD subtypes. Mol Autism 2013;4(1):12. https://doi.org/10.1186/2040-2392-4-12.
[6] Romero M, Aguilar JM, Del-Rey-Mejías Á, Mayoral F, Rapado M, Peciña M, et al. Psychiatric comorbidities in autism spectrum disorder: a comparative study between DSM-IV-TR and DSM-5 diagnosis. Int J Clin Health Psychol 2016;16(3):266–75. https://doi.org/10.1016/j.ijchp.2016.03.001.
[7] Spence SJ, Schneider MT. The role of epilepsy and epileptiform EEGs in autism spectrum disorders. Pediatr Res 2009;65(6):599–606. https://doi.org/10.1203/PDR.0b013e31819e7168.
[8] Amiet C, Gourfinkel-An I, Bouzamondo A, Tordjman S, Baulac M, Lechat P, et al. Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. Biol Psychiatry 2008;64(7):577–82. https://doi.org/10.1016/j.biopsych.2008.04.030.
[9] Hughes JR, Melyn M. EEG and seizures in autistic children and adolescents: further findings with therapeutic implications. Clin EEG Neurosci 2005;36(1):15–20. https://doi.org/10.1177/155005940503600105.
[10] Amiet C, Gourfinkel-An I, Laurent C, Carayol J, Génin B, Leguern E, et al. Epilepsy in simplex autism pedigrees is much lower than the rate in multiplex autism pedigrees. Biol Psychiatry 2013;74(3):e3–4. https://doi.org/10.1016/j.biopsych.2013.01.037.
[11] Jokiranta E, Sourander A, Suominen A, Timonen-Soivio L, Brown AS, Sillanpää M. Epilepsy among children and adolescents with autism spectrum disorders: a population-based study. J Autism Dev Disord 2014;44(10):2547–57. https://doi.org/10.1007/s10803-014-2126-6.
[12] Kohane IS, McMurry A, Weber G, MacFadden D, Rappaport L, Kunkel L, et al. The co-morbidity burden of children and young adults with autism spectrum disorders. PLoS ONE 2012;7(4):e33224. https://doi.org/10.1371/journal.pone.0033224.
[13] Viscidi EW, Triche EW, Pescosolido MF, McLean RL, Joseph RM, Spence SJ, et al. Clinical characteristics of children with autism spectrum disorder and co-occurring epilepsy. PLoS ONE 2013;8(7):e67797. https://doi.org/10.1371/journal.pone.0067797.
[14] Surén P, Bakken IJ, Aase H, Chin R, Gunnes N, Lie KK, et al. Autism spectrum disorder, ADHD, epilepsy, and cerebral palsy in Norwegian children. Pediatrics 2012;130(1):e152–8. https://doi.org/10.1542/peds.2011-3217.
[15] Mouridsen SE, Rich B, Isager T. Epilepsy and other central nervous system diseases in atypical autism: a case control study. J Neural Transm 2011;118(4):621–7. https://doi.org/10.1007/s00702-010-0566-5.
[16] Höglund Carlsson L, Norrelgen F, Kjellmer L, Westerlund J, Gillberg C, Fernell E. Coexisting disorders and problems in preschool children with autism spectrum disorders. Sci World J 2013;2013:1–6. https://doi.org/10.1155/2013/213979.
[17] Tuchman R. Treatment of seizure disorders and EEG abnormalities in children with autism spectrum disorders. J Autism Dev Disord 2000;30(5):485–9. https://doi.org/10.1023/a:1005572128200.
[18] Hernan AE, Alexander A, Jenks KR, Barry J, Lenck-Santini P-P, Isaeva E, et al. Focal epileptiform activity in the prefrontal cortex is associated with long-term attention and sociability deficits. Neurobiol Dis 2014;63:25–34. https://doi.org/10.1016/j.nbd.2013.11.012.
[19] Lado FA, Rubboli G, Capovilla P, Avanzini G, Moshé SL. Pathophysiology of epileptic encephalopathies. Epilepsia 2013;54:6–13.
[20] Capal JK, Carosella C, Corbin E, Horn PS, Caine R, Manning-Courtney P. EEG endophenotypes in autism spectrum disorder. Epilepsy Behav 2018;88:341–8. https://doi.org/10.1016/j.yebeh.2018.09.036.
[21] Yasuhara A. Correlation between EEG abnormalities and symptoms of autism spectrum disorder (ASD). Brain Develop 2010;32(10):791–8. https://doi.org/10.1016/j.braindev.2010.08.010.
[22] Kim HL, Donnelly JH, Tournay AE, Book TM, Filipek P. Absence of seizures despite high prevalence of epileptiform EEG abnormalities in children with autism monitored in a tertiary care center. Epilepsia 2006;47(2):394–8. https://doi.org/10.1111/j.1528-1167.2006.00434.x.
[23] Chez MG, Chang M, Krasne V, Coughlan C, Kominsky M, Schwartz A. Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005. Epilepsy Behav 2006;8(1):267–71. https://doi.org/10.1016/j.yebeh.2005.11.001.
[24] Giovanardi Rossi P, Posar A, Parmeggiani A. Epilepsy in adolescents and young adults with autistic disorder. Brain Develop 2000;22(2):102–6. https://doi.org/10.1016/S0387-7604(99)00124-2.
[25] Tuchman R, Rapin I. Regression in pervasive developmental disorders: seizures and epileptiform electroencephalogram correlates. Pediatrics 1997;99(4):560–6. https://doi.org/10.1542/peds.99.4.560.
[26] Spence S, Scheneider M. The role of epilepsy and epileptiform EEGs in autism spectrum disorders. Pediatrics Res 2009;65(6):599–606. https://doi.org/10.1203/PDR.0b013e31819e7168.
[27] Mulligan CK, Trauner DA. Incidence and behavioral correlates of epileptiform abnormalities in autism spectrum disorders. J Autism Dev Disord 2014;44(2):452–8. https://doi.org/10.1007/s10803-013-1888-6.
[28] Swatzyna RJ, Tarnow JD, Turner RP, Roark AJ, MacInerney EK, Kozlowski GP. Integration of EEG into psychiatric practice: a step toward precision medicine for autism spectrum disorder. J Clin Neurophysiol 2017;34(3):230–5. https://doi.org/10.1097/WNP.0000000000000365.
[29] Ballaban-Gil K, Tuchman R. Epilepsy and epileptiform EEG: Association with autism and language disorders. Mental Retardation Develop Disabilities Res 2000;6(4):300–8. https://doi.org/10.1002/1098-2779(2000)6:4<300.
[30] Trauner DA. Behavioral correlates of epileptiform abnormalities in autism. Epilepsy Behav 2015;47:163–6. https://doi.org/10.1016/j.yebeh.2014.10.020.
[31] Tuchman R. Epilepsy, language, and behavior: clinical models in childhood. J Child Neurol 1994;9(1):95–102. https://doi.org/10.1177/088307389400900124.
[32] Lord C, Rutter M, DiLavore PC, Risi S, Gotham K, Bishop SL. Autism diagnostic observation schedule, (ADOS-2) modules 1–4. Los Angeles, California: Western Psychological Services; 2012.
[33] Kamp-Becker I, Albertowski K, Becker J, Ghahreman M, Langmann A, Mingebach T, et al. Diagnostic accuracy of the ADOS and ADOS-2 in clinical practice. Eur Child Adolesc Psychiatry 2018;27(9):1193–207. https://doi.org/10.1007/s00787-018-1143-y.
[34] Goodman R. The strengths and difficulties questionnaire: a research note. J Child Psychol Psychiatry 1997;38(5):581–6. https://doi.org/10.1111/j.1469-7610.1997.tb01545.x.
[35] Rodríguez-Hernández PJ, Betancort M, Ramírez-Santana GM, García R, Sanz-Álvarez EJ, De las Cuevas-Castresana C. Psychometric properties of the parent and teacher versions of the Strength and Difficulties Questionnaire (SDQ) in a Spanish sample. Int J Clin Health Psychol 2012;12(2):265–79.
[36] Harrison PL. Oakland T: adaptive behavior assessment system ed 2 San Antonio. TX Psychological Corporation; 2003.
[37] Rust JO, Wallace MA. Book review: Adaptive behavior assessment system. J Psychoedu Assess 2004;22(4):367–73. https://doi.org/10.1177/073428290402200407.
[38] Gioia GA, Andrwes K, Isquith PK. Behavior rating inventory of executive function-preschool version (BRIEF-P). Odessa, FL: Psychological Assessment Resources; 1996.
[39] Bausela Herreras, E. (2019). BRIEF-P: Validation study in children in early childhood with neurodevelopmental disorders. SAGE Open, 9(3), 2158244019879166.
[40] Bolton PF, Carcani-Rathwell I, Hutton J, Goode S, Howlin P, Rutter M. Epilepsy in autism: features and correlates. Br J Psych 2011;198(4):289–94. https://doi.org/10.1192/bjp.bp.109.076877.
[41] Tuchman R, Cuccaro M, Alessandri M. Autism and epilepsy: historical perspective. Brain Develop 2010;32(9):709–18. https://doi.org/10.1016/j.braindev.2010.04.008.
[42] Parrish J, Geary E, Jones J, Seth R, Hermann B, Seidenberg M. Executive functioning in childhood epilepsy: parent-report and cognitive assessment. Dev Med Child Neurol 2007;49(6):412–6. https://doi.org/10.1111/j.1469-8749.2007.00412.x.
[43] Hernandez MT, Sauerwein HC, Jambaqué I, De Guise E, Lussier F, Lortie A, et al. Deficits in executive functions and motor coordination in children with frontal lobe epilepsy. Neuropsychologia 2002;40(4):384–400. https://doi.org/10.1016/s0028-3932(01)00130-0.
[44] Hommet C, Sauerwein HC, De Toffol B, Lassonde M. Idiopathic epileptic syndromes and cognition. Neurosci Biobehav Rev 2006;30(1):85–96. https://doi.org/10.1016/j.neubiorev.2005.06.004.
[45] Høie B, Sommerfelt K, Waaler PE, Alsaker FD, Skeidsvoll H, Mykletun A. Psychosocial problems and seizure-related factors in children with epilepsy. Dev Med Child Neurol 2006;48(3):213–9. https://doi.org/10.1017/S0012162206000454.
[46] Dichter GS, Lam KSL, Turner-Brown LM, Holtzclaw TN, Bodfish JW. Generativity abilities predict communication deficits but not repetitive behaviors in autism spectrum disorders. J Autism Dev Disord 2009;39(9):1298–304. https://doi.org/10.1007/s10803-009-0742-3.
[47] McEvoy RE, Rogers SJ, Pennington BF. Executive function and social communication deficits in young autistic children. J Child Psychol Psychiatry 1993;34(4):563–78. https://doi.org/10.1111/j.1469-7610.1993.tb01036.x.
[48] Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 1997;121(1):65. https://doi.org/10.1037/0033-2909.121.1.65.
[49] Hesdorffer DC, Ludvigsson P, Olafsson E, Gudmundsson G, Kjartansson O, Hauser WA. ADhd as a risk factor for incident unprovoked seizures and epilepsyin children. Arch Gen Psychiatry 2004;61(7):731–6. https://doi.org/10.1001/archpsyc.61.7.731.
[50] Austin JK, Dunn DW, Caffrey HM, Perkins SM, Harezlak J, Rose DF. Recurrent seizures and behavior problems in children with first recognized seizures: a prospective study. Epilepsia 2002;43(12):1564–73. https://doi.org/10.1046/j.1528-1157.2002.26002.x.