Published in final edited form as:
Autism. 2014 November ; 18(8): 996–1006. doi:10.1177/1362361313508027.

The association between epilepsy and autism symptoms and maladaptive behaviors in children with Autism Spectrum Disorder

Emma W Viscidi[1], **Ashley L Johnson**[2,3], **Sarah J Spence**[4], **Stephen L Buka**[1], **Eric M Morrow**[1,2,3], and **Elizabeth W Triche**[1]

[1]Brown University School of Public Health, USA

[2]Emma Pendleton Bradley Hospital, USA

[3]Brown University Medical School, USA

[4]Harvard Medical School, USA

Abstract

Background—Epilepsy is common in children with Autism Spectrum Disorder (ASD) but little is known about how seizures impact the autism phenotype.

Objectives—To examine the association between epilepsy and autism symptoms and associated maladaptive behaviors in children with ASD.

Methods—Cross-sectional study of 2,645 children with ASD, of whom 139 had epilepsy, from the Simons Simplex Collection. The relationship between epilepsy and parent-reported autism symptoms and maladaptive behaviors was examined using Poisson regression.

Results—Children with ASD and epilepsy had significantly more autism symptoms and maladaptive behaviors than children without epilepsy. However, only hyperactivity symptoms remained significantly increased (13% higher) after adjusting for IQ. Among children with ASD without intellectual disability, children with epilepsy had significantly more irritability (20% higher) and hyperactivity (24% higher) symptoms.

Conclusions—This is the largest study to date comparing the autism phenotype in children with ASD with and without epilepsy. Children with ASD and epilepsy showed greater impairment than children without epilepsy, which was mostly explained by the lower IQ of the epilepsy group. However, children with ASD and epilepsy had significantly more hyperactivity symptoms even after accounting for differences in IQ. These findings have important clinical implications for patients with ASD.

Keywords

autism spectrum disorder; epilepsy; intellectual disability; autism symptoms; hyperactivity

Eric M Morrow, Department of Molecular Biology, Cell Biology and Biochemistry, and Institute for Brain Science, Laboratories for Molecular Medicine, Brown University, 70 Ship Street, Providence, RI 02912, USA. eric_morrow@brown.edu.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction and communication and the presence of restricted and repetitive behavior, which affects an estimated 1 in 88 children (Baio 2012). Epilepsy is a condition defined by unprovoked, recurrent seizures. The co-occurrence of ASD and epilepsy is well established (Tuchman 2002; Canitano 2007; Spence 2009). Epilepsy prevalence estimates in persons with ASD have ranged from 5% to 46% (Spence 2009) and studies that have followed children with ASD into adolescence/early adulthood have reported rates between 22% and 38% (Danielsson 2005; Hara 2007; Bolton 2011).

Much of the prior research on epilepsy and ASD has focused on clinical features of seizures, as well as IQ and gender differences. Lower cognitive ability in persons with ASD and epilepsy as compared to persons with ASD only has been consistently shown. Intellectual disability (ID) is known to co-occur with both ASD and epilepsy, and many studies have found higher rates of epilepsy among children with ASD and comorbid ID than in children with ASD without ID (Volkmar 1990; Volkmar and Nelson 1990; Tuchman 1991; Rossi, Parmeggiani et al. 1995; Hrdlicka 2004; Danielsson 2005; Hara 2007; Amiet 2008; Bolton 2011). Prior studies have also reported higher rates of epilepsy in females than males with ASD (Danielsson 2005; Amiet 2008; Turk 2009; Bolton 2011). In addition, there is evidence that individuals with ASD and epilepsy have worse behavioral and social outcomes than those with ASD only (Hara 2007; Turk 2009)

The core symptoms of ASD include impaired social interaction, communication and imaginative play, and restrictive and repetitive activities and interests. Maladaptive behaviors frequently associated with ASD include hyperactivity/inattention, aggression, and motor stereotypies. At present, little is known about differences in the autism phenotype between children with and without epilepsy. The occurrence of seizures may lead to changes in brain function that impact core autism symptoms and associated maladaptive behaviors in children with comorbid ASD and epilepsy. A better understanding of the effect of seizures on autism symptoms and behaviors in persons with ASD can help guide clinical care for patients. This research can also aid in our understanding of the co-occurrence of ASD and epilepsy and in the identification, assessment, and treatment of patients. Furthermore, increasing our knowledge of the behavioral features of the ASD-epilepsy phenotype may shed light on the biological underpinnings of these co-occurring disorders. For example, evidence of specific symptoms or behaviors that are more frequent in individuals with epilepsy and ASD may indicate particular areas of the brain that are impacted by seizures.

In a sample of 60 children with ASD and epilepsy and 60 children with ASD only, Turk and colleagues (Turk 2009) found that children with epilepsy had more motor difficulties, impaired daily living skills, and challenging behaviors than children with ASD alone. But no differences were observed in social functioning. Cuccaro and colleagues (Cuccaro, Tuchman et al. 2011) examined 577 children with ASD, of whom 64 had epilepsy. Using latent class cluster analysis, they found that the cluster with the highest rate of epilepsy was also characterized by repetitive object use and unusual sensory interests.

These studies provide initial evidence to suggest that individuals with comorbid ASD and epilepsy may demonstrate higher levels of certain autism symptoms and associated impairment. However, further research is needed. A large study is required with reliable, quantitative measures of autism symptoms and maladaptive behaviors in order to better investigate the association between epilepsy and autism symptoms. Furthermore, it is important to account for IQ as a confounder because IQ is associated with both autism symptoms (Poustka and Lisch 1993; Matson and Shoemaker 2009) and epilepsy (Ellenberg, Hirtz et al. 1984; Amiet 2008; Berg, Langfitt et al. 2008) and some investigators believe that the association between ASD and epilepsy is primarily driven by the presence of ID (Berg and Plioplys 2012).

In the present study we examined autism symptomatology and associated maladaptive behaviors in children with ASD from the Simons Simplex Collection (SSC), a large, well-phenotyped sample of simplex families with ASD (those with only one affected child). The aim of the study was to determine whether autism symptomology and maladaptive behaviors varied by epilepsy status. We hypothesized that children with ASD and epilepsy would have more autism symptoms and maladaptive behaviors than children without epilepsy. We examined the association between epilepsy and parent-reported autism symptoms and behaviors on the Social Responsiveness Scale (SRS), Repetitive Behavior Scale-Revised (RBS-R), and Aberrant Behavior Checklist (ABC).

Methods

Participants

2,645 children with ASD from the Simons Simplex Collection (SSC), a collection of phenotypic and genetic information on simplex families recruited from 12 university-based sites across the United States. Families were recruited from clinics serving children with ASD and were included in the study if the family had only one child aged 4 to 18 years who met criteria for ASD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition Revised* (DSM-IV-TR) (APA 2000) and had a nonverbal mental age of at least 18 months. The majority of the families (75%) had at least one unaffected sibling. Probands with Fragile X Syndrome and Down Syndrome (Trisomy 21) were excluded; other genetic diagnoses were not excluded. Probands with prematurity (fewer than 36 weeks gestation and less than 2000 grams at birth) and extensive pregnancy or birth complications were also excluded. Further information on inclusion and exclusion criteria for probands and other family members can be found in the SFARI Base/SSC Researcher Welcome Packet (Simons 2010) and additional information on the study methodology has been previously described (Fischbach 2010). Parents gave informed consent and the study was approved by Institutional Review Boards at each university involved in the study. The SSC sample used in the present study includes the 2,648 probands from version 13 (released 8/10/2011) (of these participants, 3 subjects were not used in our analyses because they were missing data on epilepsy).

Measures

Autism Spectrum Disorder (ASD)—Study subjects were required to have a clinical "Best Estimate Diagnosis" of Autistic Disorder, Asperger's Disorder, or PDD-NOS, according to the DSM-IV-TR. The Best Estimate Diagnosis was made by a psychologist or physician with appropriate training and experience requisite for making diagnoses. Diagnosis was based on observation, chart review, and Autism Diagnostic Interview–Revised (ADI-R) (Lord 1994) and Autism Diagnostic Observation Schedule (ADOS) (Lord, Risi et al. 2000) findings. Both the ADOS and the ADI-R have excellent established reliability and validity for diagnosis of ASD.

Epilepsy—Epilepsy was assessed through use of the medical section of the ADI-R and a medical history interview administered by SSC clinical staff to parents. On the ADI-R, the parent was asked if their child "has ever fainted or had a fit or seizure or convulsion?" Responses were classified as "no attacks," "history of attacks that might be epileptic, but diagnosis not established," "definite diagnosis of epilepsy," and "febrile convulsions only, with no continuing daily medication outside the period of fever." During the medical history interview the parent was asked if the child had ever had non-febrile seizures. A composite variable was created by SSC researchers that combined information from the ADI-R and medical history interview. Children were classified as having: a diagnosis of epilepsy (code 3); likely presence of non-febrile seizures (code 2); possible presence of non-febrile seizures or caregiver report that they were "not sure" if the child had experienced non-febrile seizures (code 1); or no evidence for presence of non-febrile seizures (code 0). The variable was coded conservatively so that if there was inconsistency, a lower score was assigned. In the present study, children with epilepsy were defined as children who were classified as having a diagnosis of epilepsy (code 3) or the likely presence of non-febrile seizures (code 2). Children without epilepsy were those who were reported as possible presence of non-febrile seizures (code 1) or no evidence for presence of non-febrile seizures (code 0).

Cognitive ability—Cognitive ability was measured via standardized intelligence tests administered based on the child's age, each of which provided an intelligence quotient (IQ) or equivalent score. The majority of participants completed the *Differential Ability Scales, Second edition* (DAS-II) (Elliott 2007a) (administered to participants ages 4–17 years 11 months). A minority of participants completed the *Wechsler Intelligence Scale for Children, Fourth edition* (WISC-IV) (Wechsler 2003a) (administered to participants ages 9–17 years), the *Wechsler Abbreviated Scale of Intelligence* (WASI) (Wechsler 1999) (administered to participants ages 9– 17 years), or the *Mullen Scales of Early Learning* (Mullen and American Guidance Service. 1995) (administered to participants ages 4–5 years). An IQ score was derived from each of the cognitive assessments using either deviation IQs (derived from standard scores) or ratio IQs (derived by dividing the child's averaged mental age by chronological age for individuals who were not able to obtain a full-scale deviation IQ due to the type of test administered). Intellectual Disability (ID) was defined as full scale IQ score less than or equal to 70.

Autism symptoms and associated behaviors—The following assessments were used to measure core autism symptoms and associated maladaptive behaviors. These

measures have been used to assess a range of behavioral symptoms in persons with ASD (Constantino, Davis et al. 2003; Constantino, Gruber et al. 2004; Brinkley, Nations et al. 2007) and have demonstrated associations with functional outcomes among children with ASD (Belsito, Law et al. 2001; Aman, Novotny et al. 2004; Arnold, Aman et al. 2006).

Social Responsiveness Scale (SRS)—The SRS is a reliable and validated psychometric, quantitative measure of autistic behaviors in 4 to 18 year olds (Constantino 2002). The SRS is commonly used as a screening tool for identifying children with ASD. The scale is completed by caregivers or companions and contains 65 items spanning five domains: (1) social awareness; (2) social cognition, including information processing and interpretation; (3) social and reciprocal communication; (4) social motivation, including questions on social anxiety and avoidance; and (5) autistic preoccupations and mannerisms such as stereotyped behavior. In the present study we used raw scores, which have been recommended for research use (Constantino 2002). Higher scores on the SRS indicate greater severity of social impairment. In the present study, we used SRS scores based on the parent-completed questionnaire. The SRS has strong reliability and acceptable internal consistency (Constantino, Davis et al. 2003).

Repetitive Behavior Scales-Revised (RBS-R)—The RBS-R is an empirically derived clinical rating scale for measuring the presence and severity of repetitive behaviors, which are a key feature of ASD (Bodfish 1999; Bodfish, Symons et al. 2000). The items have been conceptually grouped into six subscales: stereotyped behavior; self-injurious behavior; compulsive behavior; ritualistic behavior; sameness behavior; and restricted behavior. Higher scores indicate more symptoms. The RBS-R is frequently used in ASD research and has been shown to have high inter-rater reliability (Lam and Aman 2007).

Aberrant Behavior Checklist (ABC)—The ABC (Aman, Singh et al. 1985) is a 58-item checklist that assesses maladaptive behaviors in individuals with developmental disabilities using a four-point rating scale (0–3, with higher scores reflecting more problems). The ABC is made up of five subscales; Irritability, agitation, crying; Lethargy, social withdrawal; Stereotypy; Hyperactivity, non-compliance; and Inappropriate speech. Higher scores indicate more symptoms. The ABC has good reliability, as evidenced by very good internal consistency, acceptable inter-rater reliability and very good test–retest reliability (Aman, Singh et al. 1985).

Statistical Analyses

Statistical analyses were conducted using SAS software, version 9.3. Statistical significance was evaluated using 2-sided tests at a 0.05 alpha-level. The association between epilepsy and autism symptoms and maladaptive behaviors (as measured by symptom counts on the SRS, RBS-R, and ABC) was estimated with Poisson regression models using the log link function for generalized linear models (GLM). Rate ratios (RR) and 95% confidence intervals (CI) were computed using the GENMOD procedure in SAS. Over-dispersion was addressed by using the p-scale option for all of the Poisson models, which provides a scale parameter estimated by the square root of Pearson's Chi-Square/degrees of freedom. Cases with missing values were excluded.

We constructed separate models for total score and subdomain score for each of the three assessments. In the first set of models, unadjusted RRs were estimated. In the second set of models, RRs were adjusted for age; in the third, for age and gender, and in the final, RRs were adjusted for age, gender, and full-scale IQ score. We stratified the sample by intellectual disability and examined the association between epilepsy and autism symptoms and maladaptive behaviors using Poisson regression models adjusted for age and gender.

Results

Based on the special criteria established by the SSC, out of 2,645 children with ASD, 59 had a confirmed diagnosis of epilepsy (2.2%) (code 3) and 80 were classified as likely to have had non-febrile seizures (3.0%) (code 2). For the purposes of our study, we combined these two groups, which resulted in 139 participants (5.2%) who we refer to as the epilepsy group. The mean age of the entire sample was 9 years (standard deviation (SD) 3.6 years) and the mean age of the epilepsy group was 10.1 years (SD 3.8 years).

A comparison of the demographic characteristics of children with and without epilepsy is presented in Table 1. There were no differences in the prevalence of epilepsy by gender, race, or ethnicity. Older children were more likely to have epilepsy; 10% of 13 to 15 year olds and 7.8% of 16 to 18 year olds had epilepsy, as compared to 3.9% of 4 to 6 year olds ($p < 0.01$). Epilepsy was more prevalent in children with ID; 9.6% of children with ID had epilepsy, as compared to 3.4% of children without ID ($p < 0.01$). Among children with epilepsy, 55.4% (n = 77) had ID, while 44.6% (n = 62) did not have ID. The mean IQ of children with epilepsy was 60.8 (SD 28.7), as compared to mean IQ of 82.3 (SD 27.4) in children without epilepsy ($p < 0.01$) (data not shown).

Table 2 presents the association between autism symptoms and maladaptive behaviors and potential confounders (gender, ID, and age) among all subjects. All of these characteristics were significantly related to autism symptoms and behaviors in children with ASD. There were no gender differences on the SRS, but females had significantly more self-injurious behavior and less restricted behavior on the RBS-R. Females also had significantly more irritability and lethargy symptoms, but fewer hyperactivity symptoms, on the ABC. Children with ID had significantly more symptoms in the majority of domains on the SRS, RBS-R, and ABC. Age was also highly associated with symptoms; children over age 10 had significantly more symptoms on the SRS, but in general fewer symptoms on the RBS-R and ABC.

The unadjusted and adjusted associations between epilepsy and autism symptoms and maladaptive behaviors in children with ASD are presented in Table 3. In the unadjusted models, children with epilepsy had significantly higher scores on the SRS, RBS-R, and ABC. Children with epilepsy had 9% more total SRS symptoms ($p < 0.01$), 15% more total RBS-R symptoms ($p = 0.01$), and 12% more total ABC score symptoms ($p = 0.02$), as compared to children without epilepsy. Significantly higher scores were also seen on all sub-domains of the SRS and most subdomains of the RBS-R and ABC. Adjusting for age (model 1) had little effect on the estimates; and further adjusting for gender (model 2) also did not change the results. However, additionally adjusting for full scale IQ score attenuated the

effect estimates. In the fully adjusted models, there were no significant differences in SRS or RBS-R scores between children with and without epilepsy. The only score that remained significant was the ABC hyperactivity score; children with epilepsy had 13% more hyperactivity symptoms ($p = 0.01$) than children without epilepsy.

Because of the large effect of IQ overall on the association between autism symptoms and behaviors and epilepsy, we wanted to determine if there was an effect of epilepsy on the autism phenotype even in the absence of intellectual disability (ID). Table 4 shows the association between epilepsy and autism symptoms and maladaptive behaviors stratified by ID and adjusted for age and gender. Among children with ASD without ID, there were still no differences in core autism symptoms as measured by the SRS and RBS-R, but children with epilepsy had significantly more irritability (20% higher, $p = 0.05$) and hyperactivity (24% higher, $p < 0.01$) symptoms. Among children with ASD with ID, children with epilepsy had significantly more autistic mannerisms (8% higher, $p = 0.05$).

Discussion

Among children with ASD from simplex families, we found significant differences in autism symptoms and associated maladaptive behaviors between children with and without epilepsy. Children with epilepsy had more symptoms and maladaptive behaviors, indicating greater impairment. Adjusting for age and gender did not change the results, but adjusting for IQ had a large effect on symptom rates. After adjusting for IQ, there were no significant differences between the groups, with the exception of hyperactivity symptoms, which were higher in children with epilepsy. When stratified by ID, hyperactivity and irritability symptoms were significantly higher among children with ASD and comorbid epilepsy who did not have ID.

Our findings indicate that epilepsy is not *independently* associated with more severe autism symptoms and maladaptive behaviors, as we failed to find an association after controlling for IQ. Instead, the evidence suggests that children with ASD and epilepsy are at risk for elevated autism symptoms and behaviors due to the increased likelihood of these children having low IQ. In our sample, ID was associated with epilepsy (Table 1) and with increased autism symptoms and maladaptive behaviors (Table 2). Prior studies have also shown that ID is a strong predictor of greater severity in ASD (Matson and Shoemaker 2009) and is associated with various maladaptive behaviors (Emerson, Kiernan et al. 2001). Based on our statistical models, much of the association between epilepsy and autism symptoms and maladaptive behaviors in children with ASD is explained by the association between epilepsy and low IQ/ID. However, we did find higher rates of hyperactivity behavior in the epilepsy group even after adjusting for IQ.

Our finding that epilepsy is associated with increased hyperactivity is consistent with prior epidemiologic studies that have reported more inattention, hyperactivity, and impulsivity in children with epilepsy, compared with controls (Carlton-Ford, Miller et al. 1995). It is possible that seizures impact specific parts of the brain that regulate behavior control, but further research is needed. While hyperactivity is not one of the core symptoms of ASD, hyperactivity, short attention span, and impulsivity are common associated features of ASD.

Studies show that a large proportion of children with ASD meet diagnostic criteria for attention ADHD (Leyfer, Folstein et al. 2006) or have been diagnosed with both disorders (Kogan, Blumberg et al. 2009). Hyperactivity is therefore an important behavioral feature in ASD, which has been linked to problems with executive function, autistic traits, adaptive function, and externalizing behaviors (Yerys, Wallace et al. 2009). In the present study, hyperactivity symptoms were 13% higher in the epilepsy group. The mean hyperactivity score in children with epilepsy was 19, as compared to a mean of 16 in children without epilepsy. This is an average difference of 3 points, which may be clinically meaningful.

Intellectual disability in persons with ASD has clinical relevance and patients with comorbid ID may represent a distinct subgroup of ASD patients. In addition, it has been proposed that the association between ASD and epilepsy is driven by comorbid ID (Berg and Plioplys 2012). Therefore, we wanted to determine if there was an effect of epilepsy on the autism phenotype in the absence of ID. We found differences in the association between epilepsy and autism symptoms and maladaptive behaviors by intellectual disability. Specifically, among children with ASD without ID, the epilepsy group had significantly higher irritability (20% higher) and hyperactivity (24% higher) symptoms. In contrast, among children with ID, no differences emerged except for a moderately increased rate of autistic mannerisms (8% higher) in the epilepsy group. These findings suggest that there are differences in the association of epilepsy with the autism phenotype in patients with and without comorbid ID, but further research is needed.

The present study somewhat contrasts the findings by Turk and colleagues (Turk 2009) comparing 60 children with ASD and epilepsy matched on verbal IQ to 60 children with ASD alone. Using the Diagnostic Interview for Social and Communication Disorders (DISCO), they found significant differences between children with ASD with and without epilepsy, even after matching on cognitive level. In their study, children with ASD and epilepsy were significantly more likely to have abnormal fascination with objects and inappropriate eye contact, but there were no significant differences in social interaction. The study by Turk and colleagues had several limitations. In addition to a small sample size, the participants were very low functioning with over half of the children having IQ in the severe ID range. Thus, the study findings may not be applicable to all children with ASD. In contrast, our study is larger and includes many participants with high-functioning ASD.

Children with epilepsy in our study had lower cognitive functioning, which is in line with prior studies in the general population (Steffenburg, Hagberg et al. 1995; van Blarikom, Tan et al. 2006) and in ASD populations. In a meta-analysis of studies of ASD and epilepsy, Amiet and colleagues (Amiet 2008) reported a pooled prevalence of epilepsy of 21% in subjects with ASD and ID, as compared to 8% in subjects with ASD without ID. Evidence suggests that the occurrence of seizures do not cause lower IQ or cognitive decline, instead, lower IQ is more frequent in children with epilepsy due to neurological abnormalities present before seizures develop (Ellenberg, Hirtz et al. 1986). This implies a shared underlying pathology increasing risk of both epilepsy and ID. The relationship between autistic traits, epilepsy, and cognitive functioning is complex. In a recent study, van Eeghen and colleagues (van Eeghen, Pulsifer et al. 2013) found a strong inverse association between

autistic traits and IQ in persons with epilepsy. They concluded that autistic features appear to be part of the neurocognitive construct of disorders like epilepsy.

Evidence also suggests that there may be underlying etiologies and pathologies responsible for both seizures and the deficits and behaviors that define ASD (Tuchman, Moshe et al. 2009; Bernard, Castano et al. 2013). There may be shared susceptibility factors, such as genetic mutations or environmental insults that concurrently lead to both epilepsy and ASD. There is biological evidence that a common cause of both disorders is disruptions in neural networks (Spencer 2002; Minshew and Williams 2007). Another area of research is abnormalities in synaptic structure and function (Sutcliffe 2008). One hypothesis currently being pursued is that abnormalities in synaptic plasticity early in development, either as the result of early seizures or genetic variants, may be a common cause of ASD and epilepsy (Tuchman and Cuccaro 2011). Finally, there is overlap in copy number variants (CNVs) associated with ASD, epilepsy, and ID (Morrow 2010; Tuchman and Cuccaro 2011; Owen 2012) suggesting a shared genetic etiology to all three of these disorders.

In the present study, 44% of children with ASD and comorbid epilepsy did not have ID, which may simply reflect the ascertainment strategies of the SSC and an intrinsic bias towards recruitment of children with higher-functioning ASD. Alternatively, this high proportion of epilepsy in ASD participants without ID may reflect the simplex pedigree structure. Further study will be necessary to explore this aspect further; however, the SSC represents an opportunity to study the association between epilepsy and ASD in a relatively high functioning sample. Prior studies on epilepsy and the autism phenotype have been limited to participants with comorbid ASD and epilepsy of low IQ (Hara 2007; Turk 2009). We believe that the identification and characterization of a large group of high-functioning patients makes our study fairly unique, as this population of higher-functioning ASD requires state-of-art methods to phenotypically characterize and is often missed in ASD/epilepsy studies.

The prevalence of epilepsy in our sample was 5.2%. This is somewhat lower than would be expected in a representative sample of children with ASD, which is closer to 15% (Tuchman, Moshe et al. 2009; Levy 2010; Suren, Bakken et al. 2012). The low prevalence of epilepsy in our study is likely explained by the specific inclusion and exclusion criteria of the SSC study. In particular, the SSC recruited more children with high-functioning ASD and required a minimum nonverbal mental age for inclusion in the study. Among all SSC participants in the current study, 30% had ID, which is lower than current estimates in representative ASD samples of approximately 40% (Baio 2012). Higher IQ is associated with lower rates of epilepsy in children with ASD (Amiet 2008; Viscidi 2013), which could explain the relatively low prevalence of epilepsy in the SSC sample. In addition, the age of the sample was young; 35% of children were 4–6 years while only 5% were 16–18 years. The prevalence of epilepsy in ASD increases with age (Hara 2007; Tuchman and Cuccaro 2011; Viscidi 2013) and as such, lower prevalence rates are expected in younger samples. In studies that include preadolescent children the reported rate of epilepsy is less than 10% (Tuchman, Moshe et al. 2009).

The present study is the largest to date examining the autism phenotype in children with ASD with and without epilepsy. The large sample size allowed us to use multivariate modeling to control for confounders, most importantly IQ, and to stratify our sample by ID. Another strength of the study is the SSC sample, which is a cohort of well-characterized children with ASD. It includes carefully confirmed cases of ASD who were administered detailed and standardized assessments using modern, reliable measures. Our autism symptom and behavior assessments are valid and reliable quantitative measures of autism symptomology.

Despite these strengths, a few limitations should be considered in interpreting the results of the study. Epilepsy diagnosis was based on parent report, which is subject to misclassification. However, two different parent report assessments (the ADI-R and medical history interview) were used to improve reliability. The composite measure developed by SSC staff is conservative and takes into account both assessments. The epilepsy group includes both children with an epilepsy diagnosis and those considered likely to have a history of non-febrile seizures. We combined these groups because the number of participants with a strict epilepsy diagnosis (n = 59) was small and likely an overly conservative cut-off for epilepsy. In a sensitivity analysis we included only the 59 children with a confirmed epilepsy diagnosis. The effect estimates were in the same direction but not statistically significant (data available upon request). This suggests that the results would be similar if we restricted our sample to only children with an SSC category 3 epilepsy diagnosis but we would not have had sufficient power to detect statistically significant differences. We also conducted a sensitivity analysis excluding children classified as having ‘possible seizures’ or ‘the parent was unsure of whether the child had seizures’ (code 1) from the non-epilepsy group and this did not change the results (data available upon request). Together these findings suggest that our results were not greatly affected by our classification of epilepsy.

Another limitation is that the SSC sample may not be representative of all children with ASD because participants were recruited from families with only one child with ASD, and other specific inclusion/exclusion criteria were applied. The SSC recruited a large number of high-functioning children with ASD. Approximately 30% of children in the sample have ID, which is somewhat lower than the 40% expected in a representative ASD sample (Baio 2012). However, the IQ distribution of the SSC sample is also a strength of the present study because we were able to examine the autism phenotype in a large number of children with epilepsy without ID.

A final limitation is that the sample included a large number of young participants, and as such, we cannot be certain that some of the participants without epilepsy will not develop epilepsy at a later time, as there is evidence that epilepsy onset in ASD often occurs after 10 years of age (Bolton 2011). However, this misclassification is unlikely to have biased the study findings given the overall low prevalence of epilepsy in the sample. In sub-analyses we compared all children with epilepsy to children without epilepsy aged 13 years and older (n=399). The effect estimates were larger, which indicates that the inclusion of younger children in our study somewhat attenuated the results (data available upon request). Future research might address this issue by designing a longitudinal study of children with ASD

that follows participants through young adulthood to ensure sufficient time for epilepsy to develop.

Finally, we conducted several statistical tests to examine the association between autism symptoms and behaviors and epilepsy. We ran 19 separate models for each symptom/behavior scale. It is therefore important to consider the issue of multiple comparisons. When conducting multiple statistical tests there is a greater probability of declaring a significant result when in fact there is not one. If we use a Bonferonni adjustment and consider only p-values less than or equal to 0.002 as statistically significant, then none of the effect estimates in the models adjusted for IQ are statistically significant. It is therefore possible that our results are due to chance or that our sample size is insufficient to address the study question. Our methods should be replicated in a sample with a larger number of participants with epilepsy to confirm the findings.

Conclusions

Children with ASD and epilepsy had more autism symptoms and associated maladaptive behaviors than children without epilepsy, but this difference was largely explained by the lower IQ of children with epilepsy. However, even after adjusting for IQ, children with epilepsy had significantly more hyperactivity symptoms. When stratified by ID, hyperactivity and irritability symptoms were elevated among children with comorbid ASD and epilepsy without ID. These findings have important clinical implications for patients with ASD and highlight the important role of cognitive ability in the relationship between epilepsy and the autism phenotype. Further research on the biological mechanisms explaining these associations is needed and the results should be replicated in other ASD populations, including predominantly multiplex samples.

Acknowledgments

Senior authorship is shared by Eric M Morrow and Elizabeth W Triche.

Funding:

Dr Morrow received funding from a Career Award for Medical Scientists from the Burroughs Wellcome Fund; NIH P20 GM103645-01; and the Brown University Salomon Award. Dr Viscidi received funding from Brown University Institute for Brain Science.

References

Aman MG, Novotny S, et al. Outcome measures for clinical drug trials in autism. CNS Spectr. 2004; 9(1):36–47. [PubMed: 14999174]

Aman MG, Singh NN, et al. The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. Am J Ment Defic. 1985; 89(5):485–491. [PubMed: 3993694]

Aman MG, Singh NN, et al. Psychometric characteristics of the aberrant behavior checklist. Am J Ment Defic. 1985; 89(5):492–502. [PubMed: 3158201]

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; 64:577–582. [PubMed: 18565495]

APA. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000.

Arnold LE, Aman MG, et al. Atomoxetine for hyperactivity in autism spectrum disorders: placebo-controlled crossover pilot trial. J Am Acad Child Adolesc Psychiatry. 2006; 45(10):1196–1205. [PubMed: 17003665]

Baio J. Prevalence of autism spectrum disorders - autism and developmental disabilities monitoring network, 14 sites, United States, 2008. MMWR Surveill Summ. 2012; 61(3):1–19.

Belsito KM, Law PA, et al. Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial. J Autism Dev Disord. 2001; 31(2):175–181. [PubMed: 11450816]

Berg AT, Langfitt JT, et al. Global cognitive function in children with epilepsy: a community-based study. Epilepsia. 2008; 49(4):608–614. [PubMed: 18070088]

Berg AT, Plioplys S. Epilepsy and autism: is there a special relationship? Epilepsy Behav. 2012; 23(3): 193–198. [PubMed: 22381386]

Bernard PB, Castano AM, et al. Phosphorylation of FMRP and alterations of FMRP complex underlie enhanced mLTD in adult rats triggered by early life seizures. Neurobiol Dis. 2013; 59C:1–17. [PubMed: 23831253]

Bodfish, J.; Symons, F.; Lewis, M. The Repetitive Behavior Scales: A test manual. Morganton, NC: Western Carolina Center Research Reports; 1999.

Bodfish JW, Symons FJ, et al. Varieties of repetitive behavior in autism: comparisons to mental retardation. J Autism Dev Disord. 2000; 30(3):237–243. [PubMed: 11055459]

Bolton PF, Carcani-Rathwell I, Hutton J, Goode S, Howlin P, Rutter M. Epilepsy in autism: features and correlates. The British Journal of Psychiatry. 2011; 198:289–294. [PubMed: 21972278]

Brinkley J, Nations L, et al. Factor analysis of the aberrant behavior checklist in individuals with autism spectrum disorders. J Autism Dev Disord. 2007; 37(10):1949–1959. [PubMed: 17186368]

Canitano R. Epilepsy in Autism Spectrum Disorders. Eur Child Adolesc Psychiatry. 2007; 16:61–66. [PubMed: 16932856]

Carlton-Ford S, Miller R, et al. Epilepsy and children's social and psychological adjustment. J Health Soc Behav. 1995; 36(3):285–301. [PubMed: 7594360]

Constantino, JN. Social Responsiveness Scale. Los Angeles: Western Psychological Services; 2002.

Constantino JN, Davis SA, et al. Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. J Autism Dev Disord. 2003; 33(4):427–433. [PubMed: 12959421]

Constantino JN, Gruber CP, et al. The factor structure of autistic traits. J Child Psychol Psychiatry. 2004; 45(4):719–726. [PubMed: 15056304]

Cuccaro ML, Tuchman RF, et al. Exploring the Relationship Between Autism Spectrum Disorder and Epilepsy Using Latent Class Cluster Analysis. J Autism Dev Disord. 2011

Danielsson S, Gillberg IC, Billstedt E, Gillberg C, Olsson I. Epilepsy in young adults with autism: A prospective population-based follow-up study of 120 individuals diagnosed in childhood. Epilepsia. 2005; 46(6):918–923. [PubMed: 15946331]

Ellenberg JH, Hirtz DG, et al. Age at onset of seizures in young children. Ann Neurol. 1984; 15(2): 127–134. [PubMed: 6703653]

Ellenberg JH, Hirtz DG, et al. Do seizures in children cause intellectual deterioration? N Engl J Med. 1986; 314(17):1085–1088. [PubMed: 3960080]

Elliott, CD. Differential Ability Scales. 2. San Antonio, TX: Harcourt; 2007a. (DAS-II)

Emerson E, Kiernan C, et al. The prevalence of challenging behaviors: a total population study. Research in Developmental Disabilities. 2001; 22(1):77–93. [PubMed: 11263632]

Fischbach GD, Lord C. The Simons Simplex Collection: A Resource for Identification of Autism Genetic Risk Factors. Neuron. 2010; 68(2):192–195. [PubMed: 20955926]

Hara H. Autism and epilepsy: a retrospective follow-up study. Brain Dev. 2007; 29:486–490. [PubMed: 17321709]

Hrdlicka M, Komarek V, Propper L, Kulisek R, et al. Not EEG abnormalities but epilepsy is associated with autistic regression and mental functioning in childhood autism. Eur Child Adolesc Psychiatry. 2004; 13:209–213. [PubMed: 15365890]

Kogan MD, Blumberg SJ, et al. Prevalence of Parent-Reported Diagnosis of Autism Spectrum Disorder Among Children in the US, 2007. Pediatrics. 2009; 124(5):1395–1403. [PubMed: 19805460]

Lam KS, Aman MG. The Repetitive Behavior Scale-Revised: independent validation in individuals with autism spectrum disorders. J Autism Dev Disord. 2007; 37(5):855–866. [PubMed: 17048092]

Levy SE, Giarelli E, Lee LC, Schieve LA, Kirby RS, Cunniff C, Nicholas J, Reaven J, Rice CE. Autism spectrum disorder and co-occurring developmental, psychiatric, and medical conditions among children in multiple populations of the United States. J Dev Behav Pediatr. 2010; 31(4): 267–275. [PubMed: 20431403]

Leyfer OT, Folstein SE, et al. Comorbid psychiatric disorders in children with autism: interview development and rates of disorders. J Autism Dev Disord. 2006; 36(7):849–861. [PubMed: 16845581]

Lord C. Autism Diagnostic Interview--Revised: A Revised Version of a Diagnostic Interview for Caregivers of Individuals with Possible Pervasive Developmental Disorders. Journal of Autism and Developmental Disorders. 1994; 24(5):659–686. [PubMed: 7814313]

Lord C, Risi S, et al. The Autism Diagnostic Observation Schedule-Generic: A Standard Measure of Social and Communication Deficits Associated with the Spectrum of Autism. Journal of Autism and Developmental Disorders. 2000; 30(3):205–223. [PubMed: 11055457]

Matson JL, Shoemaker M. Intellectual disability and its relationship to autism spectrum disorders. Research in Developmental Disabilities. 2009; 30(6):1107–1114. [PubMed: 19604668]

Minshew NJ, Williams DL. The new neurobiology of autism: cortex, connectivity, and neuronal organization. Arch Neurol. 2007; 64(7):945–950. [PubMed: 17620483]

Morrow EM. Genomic copy number variation in disorders of cognitive development. J Am Acad Child Adolesc Psychiatry. 2010; 49(11):1091–1104. [PubMed: 20970697]

Mullen, EM. American Guidance Service. Mullen Scales of Early Learning. Circle Pines, MN: AGS; 1995.

Owen MJ. Intellectual disability and major psychiatric disorders: a continuum of neurodevelopmental causality. Br J Psychiatry. 2012; 200(4):268–269. [PubMed: 22474230]

Poustka F, Lisch S. Autistic behaviour domains and their relation to self-injurious behaviour. Acta Paedopsychiatr. 1993; 56(2):69–73. [PubMed: 8135114]

Rossi PG, Parmeggiani A, et al. EEG features and epilepsy in patients with autism. Brain Dev. 1995; 17(3):169–174. [PubMed: 7573755]

Simons. SFARI Base/SSC Researcher Welcome Packet. 2010 Apr 19. 2010Retrieved July 26, 2012, from http://simonsfoundation.s3.amazonaws.com/share/SFARI_Researcher_Welcome.pdf

Spence SJ, Schneider MT. The role of epilepsy and epileptiform EEGs in autism spectrum disorders. Pediatric Research. 2009; 65(6):599–606. [PubMed: 19454962]

Spencer SS. Neural networks in human epilepsy: evidence of and implications for treatment. Epilepsia. 2002; 43(3):219–227. [PubMed: 11906505]

Steffenburg U, Hagberg G, et al. Active epilepsy in mentally retarded children. I. Prevalence and additional neuro-impairments. Acta Paediatr. 1995; 84(10):1147–1152. [PubMed: 8563227]

Suren P I, Bakken J, et al. Autism spectrum disorder, ADHD, epilepsy, and cerebral palsy in Norwegian children. Pediatrics. 2012; 130(1):e152–158. [PubMed: 22711729]

Sutcliffe JS. Genetics. Insights into the pathogenesis of autism. Science. 2008; 321(5886):208–209. [PubMed: 18621658]

Tuchman R, Cuccaro M. Epilepsy and autism: neurodevelopmental perspective. Curr Neurol Neurosci Rep. 2011; 11(4):428–434. [PubMed: 21424677]

Tuchman R, Moshe SL, et al. Convulsing toward the pathophysiology of autism. Brain Dev. 2009; 31(2):95–103. [PubMed: 19006654]

Tuchman R, Rapin I. Epilepsy in autism. Lancet Neurology. 2002; 1:352–358. [PubMed: 12849396]

Tuchman R, Rapin I, Shinnar S. Autistic and Dysphasic Children. II: Epilepsy. Pediatrics. 1991; 6:1219–1225. [PubMed: 1956740]

Turk J. Autism spectrum disorder in children with and without epilepsy: impact on social functioning and communication. Acta Pædiatrica. 2009; 98:675–681.

van Blarikom W I, Tan Y, et al. Epilepsy, intellectual disability, and living environment: a critical review. Epilepsy Behav. 2006; 9(1):14–18. [PubMed: 16714148]

van Eeghen AM, Pulsifer MB, et al. Understanding relationships between autism, intelligence, and epilepsy: a cross-disorder approach. Dev Med Child Neurol. 2013; 55(2):146–153. [PubMed: 23205844]

Viscidi EW, Triche EW, Pescosolido MF, McLean RL, Joseph RM, Spence SJ, Morrow EM. Clinical Characteristics of Children with Autism Spectrum Disorder and Co-Occurring Epilepsy. PLoS ONE. 2013; 8(7)

Volkmar FR, Nelson DS. Seizure disorders in autism. J Am Acad Child Adolesc Psychiatry. 1990; 29(1):127–129. [PubMed: 2295565]

Volkmar FR, Nelson DS. Seizure disorders in autism. J Am Acad Child Adolesc Psychiatry. 1990; 29(1):127–129. [PubMed: 2295565]

Wechsler, D. Wechsler abbreviated scale of intelligence: WASI. San Antonio: Psychological Corporation Harcourt Brace; 1999.

Wechsler, D. Wechsler Intelligence Scale for Children. 4. San Antonio, TX: The Psychological Corporation; 2003a.

Yerys BE, Wallace GL, et al. Attention deficit/hyperactivity disorder symptoms moderate cognition and behavior in children with autism spectrum disorders. Autism Res. 2009; 2(6):322–333. [PubMed: 19998356]

Autism. Author manuscript; available in PMC 2015 May 01.

Table 1

Demographic Characteristics by Epilepsy among Children with Autism Spectrum Disorder

	No Epilepsy (n=2,506) N (%)	Epilepsy (n=139) N (%)	p value
Gender			0.15
Male	2181 (95.0)	115 (5.0)	
Female	325 (93.1)	24 (6.9)	
Age			<.01*
4–6 years	886 (96.1)	36 (3.9)	
7–9 years	754 (95.7)	34 (4.3)	
10–12 years	467 (94.3)	28 (5.7)	
13–15 years	269 (90.0)	30 (10.0)	
16–18 years	130 (92.2)	11 (7.8)	
Race			0.57
White	1962 (94.6)	113 (5.5)	
African-American	95 (93.1)	7 (6.9)	
Asian	109 (98.2)	2 (1.8)	
More than one Race	200 (95.7)	9 (4.3)	
Other	120 (93.3)	8 (6.7)	
Ethnicity			0.48
Hispanic	282 (95.6)	13 (4.4)	
Non-Hispanic	2220 (94.6)	126 (5.4)	
Intellectual Disability			<.01*
No	1776 (96.6)	62 (3.4)	
Yes	725 (90.4)	77 (9.6)	

* $p \leq 0.05$.

Intellectual disability defined as full scale IQ score of less than or equal to 70.

Table 2

Unadjusted Relative Risks for the Association between Gender, Intellectual Disability, and Age and Autism Symptoms/Maladaptive Behaviors in Children with Autism Spectrum Disorder

	Gender[a]			Intellectual Disability[b]			Age[c]		
	RR	(95% CI)	p value	RR	95% CI	p value	RR	95% CI	p value
SRS									
Total	1.02	(0.99 – 1.06)	0.14	1.14	(1.11 – 1.16)	<.01*	1.05	(1.03 – 1.07)	<.01*
Autistic Mannerisms	1.00	(0.96 – 1.05)	0.89	1.14	(1.11 – 1.17)	<.01*	1.07	(1.04 – 1.11)	<.01*
Social Awareness	1.02	(0.99 – 1.05)	0.29	1.12	(1.09 – 1.14)	<.01*	0.98	(0.96 – 1.00)	0.07
Social Cognition	1.03	(1.00 – 1.07)	0.07	1.15	(1.13 – 1.18)	<.01*	1.03	(1.00 – 1.05)	0.03*
Social Communication	1.03	(1.00 – 1.06)	0.09	1.14	(1.11 – 1.17)	<.01*	1.05	(1.03 – 1.07)	<.01*
Social Motivation	1.03	(0.99 – 1.08)	0.18	1.12	(1.08 – 1.15)	<.01*	1.10	(1.07 – 1.13)	<.01*
RBS-R									
Total	0.99	(0.92 – 1.07)	0.83	1.19	(1.13 – 1.25)	<.01*	0.94	(0.89 – 0.99)	0.01*
Stereotyped behavior	0.94	(0.86 – 1.02)	0.15	1.55	(1.46 – 1.64)	<.01*	0.80	(0.75 – 0.85)	<.01*
Self-injurious behavior	1.17	(1.01 – 1.36)	0.03*	1.50	(1.35 – 1.66)	<.01*	1.11	(1.00 – 1.24)	0.05*
Compulsive behavior	1.03	(0.92 – 1.14)	0.62	1.32	(1.23 – 1.43)	<.01*	0.96	(0.89 – 1.04)	0.29
Ritualistic behavior	1.02	(0.93 – 1.11)	0.74	0.97	(0.91 – 1.04)	0.44	0.92	(0.86 – 0.98)	0.01*
Sameness behavior	1.03	(0.95 – 1.12)	0.49	1.04	(0.98 – 1.11)	0.23	1.03	(0.97 – 1.09)	0.41
Restricted Behavior	0.82	(0.74 – 0.90)	<.01*	1.12	(1.06 – 1.20)	<.01*	0.84	(0.79 – 0.89)	<.01*
ABC									
Total	1.03	(0.97 – 1.10)	0.29	1.21	(1.15 – 1.26)	<.01*	0.88	(0.84 – 0.92)	<.01*
Irritability	1.14	(1.05 – 1.24)	<.01*	1.13	(1.06 – 1.20)	<.01*	0.84	(0.78 – 0.89)	<.01*
Lethargy	1.13	(1.04 – 1.22)	<.01*	1.22	(1.15 – 1.30)	<.01*	1.16	(1.09 – 1.23)	<.01*
Stereotypy	1.00	(0.91 – 1.10)	1.00	1.64	(1.53 – 1.75)	<.01*	0.96	(0.90 – 1.03)	0.29
Hyperactivity	0.92	(0.86 – 0.99)	0.03*	1.15	(1.09 – 1.21)	<.01*	0.74	(0.70 – 0.78)	<.01*
Inappropriate Speech	1.01	(0.92 – 1.11)	0.78	1.16	(1.08 – 1.23)	<.01*	0.97	(0.91 – 1.04)	0.39

Abbreviations: SRS, Social Responsiveness Scale; RBS-R, Repetitive Behavior Scale Revised; ABC, Aberrant Behavior Checklist.

[a] Unadjusted model of the RR of autism symptoms in females vs. males (referent group).

[b] Unadjusted model of the RR of autism symptoms in children with intellectual disability vs. children without intellectual disability (referent group)

[c] Unadjusted model of the RR of autism symptoms in children aged 10 years or older vs. aged 4 to 9 years (referent group).

* $p \leq 0.05$

Table 3

Relative Risks for the Association between Epilepsy and Autism Symptoms/ Maladaptive Behaviors in Children with Autism Spectrum Disorder

	Unadjusted			Model 1: Adjusted for Age			Model 2: Adjusted for Age and Gender			Model 3: Adjusted for Age, Gender, and IQ		
	RR	**95% CI**	**p value**	**RR**	**95% CI**	**p value**	**RR**	**95% CI**	**p value**	**RR**	**95% CI**	**p value**
SRS												
Total	1.09	(1.04 – 1.14)	<.01*	1.08	(1.04 – 1.13)	<.01*	1.08	(1.03 – 1.13)	<.01*	1.03	(0.98 – 1.08)	0.21
Autistic Mannerisms	1.12	(1.06 – 1.19)	<.01*	1.11	(1.04 – 1.17)	<.01*	1.11	(1.04 – 1.17)	<.01*	1.05	(0.99 – 1.12)	0.09
Social Awareness	1.06	(1.02 – 1.12)	0.01*	1.07	(1.02 – 1.12)	0.01*	1.07	(1.02 – 1.12)	0.01*	1.02	(0.98 – 1.07)	0.34
Social Cognition	1.10	(1.05 – 1.15)	<.01*	1.09	(1.04 – 1.15)	<.01*	1.09	(1.04 – 1.15)	<.01*	1.03	(0.99 – 1.07)	0.19
Social Communication	1.09	(1.04 – 1.15)	<.01*	1.08	(1.03 – 1.14)	<.01*	1.08	(1.03 – 1.14)	<.01*	1.03	(0.98 – 1.08)	0.23
Social Motivation	1.07	(1.00 – 1.14)	0.04*	1.05	(0.99 – 1.12)	0.12	1.05	(0.99 – 1.12)	0.12	1.01	(0.94 – 1.07)	0.86
RBS-R												
Total	1.15	(1.04 – 1.27)	0.01*	1.16	(1.05 – 1.28)	<.01*	1.16	(1.05 – 1.28)	<.01*	1.08	(0.97 – 1.19)	0.17
Stereotyped behavior	1.12	(0.99 – 1.27)	0.07	1.16	(1.03 – 1.31)	0.02*	1.16	(1.03 – 1.31)	0.01*	0.97	(0.86 – 1.09)	0.60
Self-injurious behavior	1.37	(1.12 – 1.68)	<.01*	1.35	(1.10 – 1.66)	<.01*	1.34	(1.10 – 1.65)	<.01*	1.14	(0.93 – 1.40)	0.21
Compulsive behavior	1.26	(1.08 – 1.46)	<.01*	1.27	(1.09 – 1.47)	<.01*	1.26	(1.09 – 1.46)	<.01*	1.12	(0.97 – 1.30)	0.13
Ritualistic behavior	1.05	(0.92 – 1.19)	0.51	1.05	(0.92 – 1.20)	0.43	1.05	(0.92 – 1.20)	0.44	1.07	(0.93 – 1.22)	0.35
Sameness behavior	1.15	(1.02 – 1.30)	0.02*	1.14	(1.01 – 1.29)	0.04*	1.14	(1.01 – 1.29)	0.04*	1.11	(0.98– 1.26)	0.10
Restricted Behavior	1.09	(0.96 – 1.24)	0.19	1.11	(0.98 – 1.26)	0.10	1.12	(0.99 – 1.27)	0.08	1.05	(0.93 – 1.20)	0.42
ABC												
Total	1.12	(1.02 – 1.22)	0.02*	1.14	(1.04 – 1.24)	0.01*	1.13	(1.04 – 1.24)	0.01*	1.04	(0.95 – 1.14)	0.38
Irritability	1.11	(0.98 – 1.26)	0.10	1.14	(1.01 – 1.29)	0.04*	1.13	(1.00 – 1.28)	0.05*	1.07	(0.94 – 1.21)	0.32
Lethargy	1.06	(0.94 – 1.20)	0.33	1.03	(0.92 – 1.17)	0.59	1.03	(0.91 – 1.16)	0.66	0.95	(0.84 – 1.07)	0.38
Stereotypy	1.19	(1.04 – 1.37)	0.01*	1.20	(1.05 – 1.38)	0.01*	1.20	(1.05 – 1.38)	0.01*	0.97	(0.85 – 1.11)	0.63
Hyperactivity	1.15	(1.04 – 1.27)	0.01*	1.21	(1.10 – 1.34)	<.01*	1.21	(1.10 – 1.34)	<.01*	1.13	(1.02 – 1.25)	0.01*
Inappropriate Speech	1.00	(0.87 – 1.15)	0.98	1.00	(0.87 – 1.15)	0.97	1.00	(0.87 – 1.15)	0.98	0.94	(0.81 – 1.08)	0.35

Abbreviations: SRS, Social Responsiveness Scale; RBS-R, Repetitive Behavior Scale Revised; ABC, Aberrant Behavior Checklist. Relative Risk (RR) comparing children with epilepsy to children without epilepsy (referent group).

* $p \leq 0.05$

Table 4

Relative Risks for the Association between Epilepsy and Autism Symptoms/Maladaptive Behaviors in Children with Autism Spectrum Disorder, By Intellectual Disability

	Adjusted for Age and Gender					
	Children without ID			Children with ID		
	RR	95% CI	p value	RR	95% CI	p value
SRS						
Total	1.05	(0.98 – 1.13)	0.16	1.05	(0.99 – 1.11)	0.08
Autistic Mannerisms	1.06	(0.97 – 1.16)	0.22	1.08	(1.00 – 1.16)	0.05*
Social Awareness	1.04	(0.96 – 1.12)	0.33	1.04	(0.98 – 1.11)	0.22
Social Cognition	1.08	(1.00 – 1.17)	0.06	1.03	(0.98 – 1.09)	0.26
Social Communication	1.06	(0.98 – 1.14)	0.13	1.05	(0.99 – 1.11)	0.14
Social Motivation	1.00	(0.91 – 1.11)	1.00	1.05	(0.97 – 1.14)	0.22
RBS-R						
Total	1.09	(0.92 – 1.28)	0.31	1.11	(0.98 – 1.26)	0.11
Stereotyped behavior	1.00	(0.82 – 1.23)	0.99	1.04	(0.91 – 1.20)	0.54
Self-injurious behavior	1.16	(0.82 – 1.64)	0.39	1.25	(0.97 – 1.62)	0.08
Compulsive behavior	1.16	(0.92 – 1.48)	0.21	1.16	(0.97 – 1.40)	0.11
Ritualistic behavior	1.04	(0.86 – 1.26)	0.69	1.04	(0.87 – 1.26)	0.66
Sameness behavior	1.12	(0.93 – 1.35)	0.24	1.12	(0.95 – 1.33)	0.17
Restricted Behavior	1.07	(0.89 – 1.30)	0.47	1.08	(0.91 – 1.28)	0.36
ABC						
Total	1.14	(0.99 – 1.30)	0.06	1.04	(0.92 – 1.17)	0.52
Irritability	1.20	(1.00 – 1.44)	0.05*	1.02	(0.86 – 1.21)	0.84
Lethargy	0.98	(0.81 – 1.18)	0.83	1.00	(0.86 – 1.17)	0.98
Stereotypy	1.06	(0.84 – 1.34)	0.64	1.05	(0.90 – 1.24)	0.53
Hyperactivity	1.24	(1.07 – 1.44)	<.01*	1.11	(0.97 – 1.26)	0.12
Inappropriate Speech	1.02	(0.83 – 1.26)	0.85	0.89	(0.74 – 1.07)	0.21

Abbreviations: ID, intellectual disability; SRS, Social Responsiveness Scale; RBS-R, Repetitive Behavior Scale Revised; ABC, Aberrant Behavior Checklist.

Relative Risk (RR) comparing children with epilepsy to children without epilepsy (referent group).

Intellectual disability defined as full scale IQ score of less than or equal to 70.

Children without ID: Comparison of 62 children with epilepsy to 1,776 children without epilepsy.

Children with ID: Comparison of 77 children with epilepsy to 725 children without epilepsy.

* $p \leq 0.05$