Autism Spectrum Disorder (ASD) remains difficult to treat and medications can only help with related symptoms such as attention, anxiety, depression, and severe behavioral problems. However, these medications often fail to alleviate symptoms and produce unacceptable side-effects. One reason for medication failure could be the presence of Isolated Epileptiform Discharges (IED). The purpose of this study was to determine the prevalence of IED in children, adolescents, and young adults diagnosed with ASD and to provide psychiatrists with data possibly improving medication selection. This study identified IED in 36% of those with ASD. Overall, these results suggest EEG screening may be most beneficial for children, adolescents, and young adults with autism, especially those who have failed multiple medication attempts.
The Prevalence of Epileptiform Discharges in a Psychiatric Practice: A Study of Children, Adolescents, and Young Adults with Autism

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Abstract

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Key Words
Autism Spectrum Disorder, Isolated Epileptiform Discharges, Electroencephalograms, Research Domain Criteria Project, Low Resolution Electromagnetic Tomography

Abbreviations

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Abstract

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The Prevalence of Epileptiform Discharges in a Psychiatric Practice: A Study of Children, Adolescents, and Young Adults with Autism

Autism Spectrum Disorder (ASD) remains difficult to treat and medications can only help with related symptoms such as attention, anxiety, depression, and severe behavioral problems. However, medications for these issues often fail to alleviate symptoms and at times produce unacceptable side-effects. A study of medication failure identified isolated epileptiform discharges (IED) as one of four neurobiological measures that account for medication failure in those asymptomatic for epilepsy (Swatzyna et al. 2014; Swatzyna, Kozlowski, and Tarnow 2015). It is well accepted that there is a high rate of epilepsy in those with ASD (Spence and Schneider 2009). In a comprehensive review of literature, seizures are common to 20-30% of children with ASD (Kagan-Kushnir, Roberts, and Snead 2005). The prevalence of IED in Autism without epilepsy needs further investigation.

The population of ASD has a high prevalence of EEG abnormalities compared to other psychiatric disorders (Bhaskara, Trimble, and Boutros 2008). When Mulligan and Trauner (2014) compared forms of Autism, they found that those with more aggressive behavior had higher incidence of IED compared to those with less severe forms of Autism. Boutros (2013) stated, “IED in pediatric neurobehavioral disorders may represent an epiphenomenon of cerebral dysfunction or underlying cortical morphofunctional abnormalities, and/or reflect a brain neurophysiological disorder which is not sufficient to be expressed as epilepsy.” Although those with IED may never have a seizure, the disruption to cognitive functioning can be extensive, especially in cases where they are more multifocal and paroxysmal in nature (Kayaalp et al. 2007). In prepubescent individuals, whose brains are forming rapidly, the cerebral dysrhythmia
from IED may also contribute to maturation issues by way of transient cognitive impairment (Aarts et al. 1984; Binnie et al. 1987; Marston, Besag, and Binnie 1993).

As previously stated, medications prescribed to those with ASD commonly target attention, anxiety, depression, and severe behavioral problems. These symptoms are commonly treated with stimulants, Selective Serotonin Reuptake Inhibitors (SSRI), and antipsychotics. What they all have in common is that they lower seizure threshold and can exacerbate IED. This may explain some of the difficulty encountered when medicating those with ASD. Despite the prevalence of research regarding IED in ASD populations, the clinical significance is far from being well studied.

The prevalence of IED in the general population without epilepsy has been established. In three large studies of neurologically healthy children from 1955 to 1993 the average prevalence of IED was 5% (n=4,854) (Cavazzuti Cappella, and Naliin1980; Corbin and Bickford 1955; Okubo et al. 1994). Examining EEGs from 11 studies (total n=3,099), an average of 41% nonepileptic children with ASD had IED (Canitano, Luchetti, and Zappella 2005; Chez et al. 2006; Ekinci et al. 2010; Giannotti 2008; Hashimoto 2011; Hrdlicka 2004; Hughes and Melyn 2005; Parmeggiani et al. 2010; Reinhold, Molloy, and Manning-Courtney 2005; Rossi et al. 1995; Yasuhara 2010). Research in this area commonly takes place in university or hospital settings. It is rare to find psychiatric clinics studying the prevalence rate of IED in those with ASD, either due to their lack of funding or data. The purpose of this study was to determine the prevalence of IED in children, adolescents, and young adults diagnosed with ASD, and to assess whether EEG analysis can provide psychiatrists with data that would help improve medication selection.

Methods
The dataset was obtained from a multidisciplinary practice that treats a wide variety of neuroatypical children and adolescent refractory cases. Diagnoses were made by board certified psychiatrists and psychologists according to the DSM-IV-TR criteria. The data were collected over a five-year period for those whom were referred for an EEG/qEEG assessment. The database was submitted to a university committee for the protection of human subjects and was granted a waiver of approval meeting the exemption categories set forth by the federal regulation 45 CFR 46.101 (b) (2) and (4).

It should be noted that a number of electroencephalographers consider IED within the normal range of variation. According to Asokan, Pareja, and Niedermeyer (1987) “Modern views in clinical electroencephalopathy tend to minimize or even ignore such minor deviations. Such trends can be detrimental to EEG by depriving the electroencephalographers of important clinical-electrical correlations and withholding valuable information from the referring clinician.” This study’s electroencephalographer did report all IED, however, those with no clear correlation to symptomology were excluded, as well as those taking anticonvulsants, diagnosed with epilepsy.

The 140 patients diagnosed with ASD, ages 4 to 25, were drawn from 466 aged matched clinical cases. Age and gender were explored to assess statistical differences. In an attempt to reflect consistency with pediatric terminology offered through the National Institute of Child Health and Human Development, age ranges were set at 4 to 12 for children (early to middle childhood), 13 to 18 for adolescents (early adolescence), and 19 to 25 (late adolescence to young adulthood) for young adults. Of the 140 patients, 108 (77%) were male and 32 (23%) were female. The majority of those identified were Caucasian, however specifics about other racial groups who received services were not recorded at the time of data collection.
Each patient’s EEG were recorded using the Deymed TruScan 32 equipment, with impedance maintained below 10 k Ohm. The patients were seated in a slightly reclining chair in a silent and low light environment. An Electrocap™ was used to collect the data according to the International 10–20 System with linked ears (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). A minimum of 20 minutes total data was recorded in both eyes open (10 minutes) and eyes closed (10 minutes) resting conditions (order of these could vary among subjects).

The EEG background activity was analyzed by Low Resolution Electromagnetic Tomography (LORETA) (Pascual-Marqui, Michel, and Lehmann 1994; Saletu, Anderer, and Saletu-Zyhlarz 2006). Voxel-based, normalized broad-band (delta, theta, alpha, and beta) and very narrow band (VNB, 1Hz bandwidth, from 1 to 25Hz) LORETA activity (=current source density, A/m(2)) were computed for each person. Group comparison included subtraction (average patient data minus average control data) and group statistics (multiple t-tests, where Bonferroni-corrected p<0.05 values were accepted as statistically significant) (Puskás, Bessenyei, Fekete, Hollódy, Clemens 2010).

All data were manually artifacted, processed and analyzed by the same team, using both the Human Brain Indices and the Neuroguide databases as appropriate for the age of the client. Each of the raw EEG scores were read by the same board certified electroencephalographer. In addition to visual detection, automatic spike detection software was employed as a component of the qEEG data analysis and the impact over time was assessed by comparison to the two normative databases by the same qEEG evaluator for each case.

Descriptive statistics were used to identify the children with nonconvulsive seizure activity. Cross-tabulations were used to present the frequency distributions and clarify the
relationships between the variables. Chi-square analysis was used to determine if there were significant differences between genders among the three age groups with IED.

Results

Table 1 shows the number of patients diagnosed with ASD, those with IED, and the overall percent, each by age and gender grouping. Of the 140 patients, the EEG and qEEG identified 51 (36%) with IED, most of whom (82%) were male (n=42). When gender and age were assessed, the young adults have higher rates of IED compared to children; from 17% to 75% for females and 33% to 50% for males. The Chi-square analysis found no significant difference between genders among the three age groups with IED.

Discussion

Typically, patients referred for an EEG in this study were those who had failed multiple trials with medications. It should be noted that this is a well-established practice that only accepts private pay patients, therefore, the findings reflect only families who have the financial means to pay for testing. Variables such as socioeconomic status, race, and gender should be more fully examined in future studies of this nature.

Findings indicate a high prevalence of IED among those with ASD (36%). Although there was no control group used in this study, prior studies identify an average IED prevalence rate of 5% in neurotypical children (Cavazzuti Cappella, and Nallin1980; Corbin and Bickford 1955; Okubo et al. 1994). There was no significant difference between age or gender suggesting that IED may be nonspecific for these two parameters in the ASD population. These findings suggest: 1) in a psychiatric practice, the prevalence rate of IED is much higher in children, adolescents and young adults with ASD, 2) that there may be a relationship between IED and
ASD, thus representing a subgrouping of ASD that is yet to be identified; and, 3) that IED could explain why prior medication attempts failed.

Many medications lower seizure threshold and would likely make IED worse, particularly medicines commonly prescribed to those with ASD. Selective Serotonin Reuptake Inhibitors (SSRI) are commonly prescribed in children with obsessive-compulsive disorder (OCD). A recent study (n = 238,632) found that the risk of epilepsy/seizures is significantly increased for all classes of antidepressant medication in adults ages 20 to 64 (Hill et al. 2015). It is likely that those with pre-existing IED are at a higher risk of developing seizures than those with no IED. This may explain the negative side-effects encountered when stimulants, antipsychotics, and antidepressants are prescribed to this population. In order for the medication to work effectively, IED need to be stabilized. Millichap, Millichap, and Stack (2011) recommended stabilizing IED with anticonvulsants prior to the consideration of stimulants. When IED are identified in the EEG, it has been our experience that removing medications that lower seizure threshold and adding an anticonvulsant has resulted in positive outcomes. Additional outcome studies are needed in this area for validation. We intend to conduct an outcome study to assess medication changes based on EEG findings.

The use of EEG to assess neurological abnormalities linked to symptoms complies with the National Institute for Mental Health (NIMH) request for research. In 2013, the NIMH launched The Research Domain Criteria project (RDoC) with the goal to explicate fundamental bio-behavioral dimensions that cut across heterogeneous disorder categories in psychiatry. One major research domain is defined by the arousal and regulatory systems. Instead of completely relying on the DSM’s categorization approach, a biological based classification may show potential. The (RDoC) highlights the importance of psychiatry exploring the potential use of
EEG analysis and this study highlights the importance for children and adolescents diagnosed with ASD. Other researchers agree that the EEG has great potential and believe it can improve psychiatric diagnosis, which could lead to greater accuracy in medication selection (Chez et al. 2006; Pressler, Robinson, Wilson, and Binnie 2015). Overall, there is significant evidence that EEG screening will benefit those diagnosed with ASD, psychiatrists, and future research in general.

**Conclusion**

This study contributes to the ASD and IED literature and offers suggestions for future research of this nature. Providing prevalence rates from a psychiatric practice is an advantageous contribution for the research community. Our results find that compared to the healthy population, a large number of children with ASD have IED despite never having a seizure. This abnormal neuronal activity, if accompanied by symptoms, may create serious issues in the maturing brain. Our findings support the use of EEG in children, adolescents, and young adults with IED, regardless of gender or age. This is particularly true for those who exhibit aggressive behaviors or those who have failed prior medications attempts with stimulants, antidepressants, and/or antipsychotics.
References


Table 1 - Frequency of Autism Spectrum Disorder (ASD) and Isolated Epileptiform Discharges (IED) Discussion (Female plus Male)

<table>
<thead>
<tr>
<th>Age</th>
<th>Patients with ASD</th>
<th>Patients with ASD and IED</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 - 12</td>
<td>73 (16f + 57m)</td>
<td>23 (4f + 19m)</td>
<td>32%</td>
</tr>
<tr>
<td>12 - 18</td>
<td>51 (12f + 39m)</td>
<td>19 (2f + 17m)</td>
<td>37%</td>
</tr>
<tr>
<td>19 - 25</td>
<td>16 (4f + 12m)</td>
<td>9 (3f + 6m)</td>
<td>56%</td>
</tr>
<tr>
<td>Total</td>
<td>140 (32f + 108m)</td>
<td>51 (9f + 42m)</td>
<td>36%</td>
</tr>
</tbody>
</table>

Table Abbreviations: ASD – Autism Spectrum Disorder, IED – Isolated Epileptiform Discharges, (f + m) - (female plus male)
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Jacob Mardick has now returned to Millsaps College.

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RS conceived of the study and lead the design, drafting of manuscript, and interpretation of data; JT made contributions to the coordination and interpretation of the data; SM performed the statistical analysis and participated in revisions; AR participated in the design, drafting of the manuscript, and interpretation of data; JM participated in the design and drafting of the manuscript; GK participated in interpretation, editing and revising it critically for important intellectual content. All authors read and approved the final manuscript.

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