ORIGINAL RESEARCH

Integration of EEG Into Psychiatric Practice: A Step Toward Precision Medicine for Autism Spectrum Disorder

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Introduction: Data from an EEG is not commonly used by psychiatrists to plan treatment and medication. However, EEG abnormalities such as isolated epileptiform discharges are found to be more prevalent in psychiatric patients, particularly those diagnosed with autism spectrum disorder (ASD). Most medications prescribed for ASD lower seizure threshold and increase side effects. Therefore, it may be prudent to order an EEG for ASD cases, especially those categorized as refractory.

Methods: The data set was obtained from a multidisciplinary practice that treats a wide variety of neuroatypical children and adolescent refractory patients. This study investigated 140 nonepileptic subjects diagnosed with ASD, aged 4 to 25 years. Visual inspection of the EEG was performed to search for paroxysmal, focal, or lateralizing patterns.

Results: Of the 140 subjects, the EEG data identified 36% with isolated epileptiform discharges. The χ^2 analysis found no significant difference between genders among the three age groups. Findings indicated a high prevalence of isolated epileptiform discharges among individuals with ASD.

Conclusions: Our results find that compared with the healthy population, a large number of patients with ASD have isolated epileptiform discharges despite never having a seizure. Our findings support the use of EEG in children, adolescents, and young adults with ASD, regardless of gender or age. This is particularly true for those who exhibit aggressive behaviors or those who have failed previous medication attempts with stimulants, antidepressants, and/or antipsychotics.

Key Words: Autism spectrum disorder, EEG, Isolated epileptiform discharges, Research domain criteria project, Precision medicine.

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The National Institute of Mental Health (NIMH) has started the movement toward evidence-based intervention with the Research Domain Criteria (RDoC) project. Currently, psychiatry is based on symptoms analysis and phenomenology. Medication recommendations are made on a trial and error basis. One of the areas of interest for psychiatry is the Arousal and Regulatory Systems domain. Physiology is one unit of analysis in this domain, and EEG is a suggested technology. The EEG has primarily been a tool for the field of neurology despite the fact that its inventor Hans Berger was a psychiatrist. Since its invention in 1924, Satterfield (1973–74) published a series of articles about the application of EEG analysis in child psychiatry.[1]

In neurology, there is a prevailing concept of not treating a patient with EEG abnormalities with anticonvulsants in the absence of seizures. Boutros et al.[2] stated that this has lead to further deemphasizing nonspecific findings that may be connected to psychiatric symptomatology. More than 50 investigations have found momentary cognitive deficits during isolated epileptiform discharges (IEDs).[3] According to Asokan, Pareja, and Niedermeyer, "Modern views in clinical electroencephalopathy tend to minimize or even ignore such minor deviations. Such trends can be detrimental to EEG by depriving the electroencephalographer of important clinical–electrical correlations and withholding valuable information from the referring clinician."[4(p209)] Transitory cognitive change during IEDs fulfills the criteria of an epileptic seizure by current definition.[5] Therefore, there is justification to treat the EEG when IEDs are manifested with transient aberrant presentation.

In an extensive literature review of PubMed/MEDLINE, there have been an increased number of papers in brain wave abnormalities, particularly IEDs. "Isolated epileptic discharges are EDs that are detected in nonepileptic individuals."[2(p21)] It is important to note that IEDs can only be detected with an EEG. Isolated epileptiform discharges are known to occur, albeit rarely, in the general population, though an exact prevalence is unknown. In three large studies of neurologically healthy children from 1955 to 1993, the average prevalence of IEDs was 5% ($n = 4{,}854$).[6–8] This is further supported by the large number of electroencephalographers who consider IEDs to be within the normal range of variation in nonepileptic individuals.

Compared with the general population, IEDs are more prevalent in those with psychiatric issues[9] and even more so with those diagnosed with autism spectrum disorder (ASD).[10] Therefore, IEDs should not be considered within the normal range of variation as would be in the general population. Isolated epileptiform discharges seen in nonepileptic patients are usually "focal in nature and tend to be recorded from the more behaviorally salient brain regions like the temporal and frontal areas."[2,11(p21)]

It is accepted that multiple foci discharges across hemispheres are those that have greater potential to develop into

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epilepsy. Therefore, Zimmerman and Konopka hypothesized that increased spatial distribution of EDs would be associated with greater severity of symptoms.[9] Unexpectedly, this hypothesis was found to be not true, and single foci IEDs were more psychiatrically symptomatic and least likely to become an epileptic seizure compared with multiple foci EDs. They found that EDs in only one brain area had a significantly greater number of emotional dysregulation symptoms than those who had EDs in multiple locations. In addition, they found that IEDs increase with age compared with those with multiple foci discharges. Boutros stated, "IEDs 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."[10(p55)] Isolated epileptiform discharges could represent an RDoC biomarker for a subgroup that would remain undiscovered without an EEG.

In certain subpopulations of patients, there are increased numbers of IEDs that justify doing an EEG. The literature suggests that IEDs tend to be more prevalent in specific conditions including habitual violence/aggression and panic attacks.[12] In prepubescent individuals whose brains are changing rapidly, the cerebral dysrhythmia from IEDs may also contribute to maturation issues by way of transient cognitive impairment.[13–15] Isolated epileptiform discharges also have a higher prevalence among childhood psychiatric disorders as compared with healthy children, specifically ASD, attention-deficit/hyperactivity disorders, and Tourette syndrome.[12]

The population of ASD has a high prevalence of EEG abnormalities compared with other psychiatric disorders.[16] When Mulligan and Trauner compared forms of ASD, they found that those patients with more aggressive behavior had higher incidence of IEDs compared with those with less severe forms of Autism.[17] Specifically, when the findings from 11 studies were combined (total $n = 3{,}099$), an average of 41% of nonepileptic children with ASD had IEDs.[18–28]

Autism spectrum disorder often presents a treatment challenge because of the variety of symptoms that make each case unique. Medication prescribed to manage ASD-associated symptoms such as attention issues, anxiety, depression, poor reality testing, and behavioral problems often fail to alleviate symptoms and can produce undesirable side effects. Medication selection is primarily guided by patient history and clinical presentation. The three most commonly prescribed medications for ASD symptoms: stimulants, selective serotonin reuptake inhibitors, and antipsychotics.[29] The stimulants are prescribed for the attention-deficit/hyperactivity disorder symptoms, the selective serotonin reuptake inhibitors for the anxiety and obsessive compulsive disorder symptoms, and the antipsychotics for behavioral issues, mood stability, and poor reality testing.

Our recent studies of refractory cases identifies that IEDs were one of four neurobiomarkers accounting for medication failure in those asymptomatic for epilepsy.[30,31] In these cases, one of the exclusionary criteria was none of the patients were neither diagnosed with a seizure disorder nor were prescribed anticonvulsants. Without anticonvulsants, the side effects from most other medications are unmasked.

EEG research commonly takes place in university or hospital settings. Despite its potential value, it is rare to find a psychiatric clinic that integrates EEG into its practice and takes this data into account when selecting medications. The purpose of this study was to use an RDoC approach by integrating the EEG into a psychiatric practice. The majority of patients referred to our clinic are children, adolescents, and young adults who commonly respond atypically to medication. The group we chose to study was an ASD population due to their high prevalence of IEDs in the literature. We hypothesized that the integration of EEG technology into our practice would identify a biological basis to explain symptoms and produce evidence to assist in medication selection. In doing this, we hope to find results that will bring us closer to the principles of precision medicine.

METHODS

Data

The data set 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 5-year period for those referred for an EEG/quantitative EEG assessment. The majority of those referred were refractory cases failing multiple attempts with different medications. The database and the informed consent form was submitted to Texas Southern University, Houston, Texas, the 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).

Subjects

Special school educators in the community referred the children, adolescents, and young adults with ASD to this clinic. These are high functioning individuals with no other special needs or intellectual disabilities. The majority of these individuals were white; however, specifics about other racial groups who received services were not recorded at the time of data collection. In addition, subjects referred to this private pay only clinic are of higher-to-middle socioeconomic standing and able to afford services.

To obtain subjects for this study, the data archive consisting of 581 cases was narrowed down to 466 based on the inclusive age range of 4 to 25 years. Ages 26 to 72 years were excluded because they did not fit within the children, adolescent, or young adult categories. Of the 466 cases, subjects with a history of seizures ($n = 23$) or reported as taking anticonvulsants ($n = 6$) were excluded from the study. The remaining 437 cases were reviewed and 297 were eliminated based on a lack of ASD diagnosis. The study is based on the EEG and clinical data of the remaining 140 nonepileptic subjects diagnosed with ASD, ages 4 to 25 years. In an attempt to reflect consistency with pediatric terminology offered through the National Institute of Child Health and Human Development, years of 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 for young adults (late adolescence to young adulthood). Of the 140 nonepileptic subjects, 108 (77%) were male and 32 (23%) were female.

EEG Data Acquisition

EEG acquisition was done using Mitsar-EEG-10/70-201 equipment, with impedance maintained below 10 kΩ. The subjects were seated in a slightly reclining chair in a silent and low light environment. Electro-cap was used to collect the data according to the International 10 to 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 were recorded in both eyes open (10 minutes) and eyes closed (10 minutes). The order of these could vary among subjects.

EEG Analysis

Data artifacts were determined using independent component analysis, 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. All EEG data were evaluated and interpreted by the same neurophysiologist, a member of the American Board of Electroencephalography and Neurophysiology and the American Board of Clinical Neurophysiology. The neurophysiologist was blinded to the subject's diagnoses and medications. Visual inspection of the EEG was performed to search for paroxysms that are either focal or lateralizing. Spikes have a base period from 20 to 80 milliseconds, with paroxysms seen as sudden onset and cessation with greater than 50% increase from the background.[32] The following are samples of atypical/abnormal findings taken from the EEGs of individuals with no history of seizures or paroxysmal clinical events: Figure 1 demonstrates bilaterally independent focal EDs. Figure 2 demonstrates an abnormal paroxysmal discharge with intermixed EDs, not attributable to movement artifact or drowsiness. Figure 3 demonstrates both isolated and brief bursts of a primarily generalized spike–wave discharge.

IEDs Symptoms Presentation

Linking symptoms to neurologic abnormalities is a priority of the National Institute of Mental Health RDoC project.[33] Criteria for inclusion in this study required the location of the IEDs to correspond with the symptom presentation. To accomplish this, a generic 296-item screening questionnaire (CNC1020; EEG Professionals, Vestdijk, the Netherlands) was used to assess various psychological aspects correlated with locations in the brain. This resulted in standardized data across various DSM disorders and enabled to link physiology with behavior to the IED location, independent of DSM diagnosis, and in line with the RDoC approach. The Comprehensive Diagnostic Checklist 10/20 was reported to have high reliability (Cronbach alpha = 0.982) (*http://www.eegprofessionals.nl/cnc1020_isnr_2011.pdf*). When the location of the IEDs was not accompanied by the expected clinical issues, the cases were excluded.

Statistics

Descriptive statistics were used to identify the subjects with nonconvulsive seizure activity. Cross-tabulations were used to present the frequency distributions and clarify the relationships between the variables. Chi-square analysis and a Fisher exact test were performed to determine the association between gender and the likelihood of IEDs. In addition, a χ^2 analysis and a Fisher exact test were also performed to determine the association between age dichotomized into two groups (a. children and the rest, and b. adolescents and the rest) to test their association.

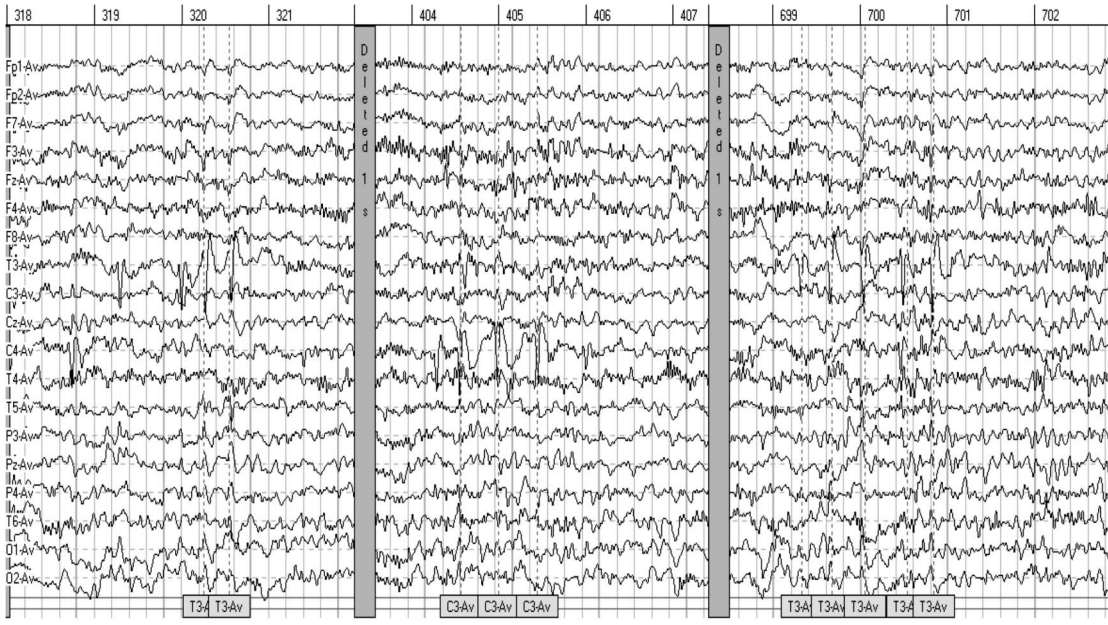

FIG. 1. Bilaterally independent focal epileptiform discharges, maximal over left temporal regions and over right central regions.

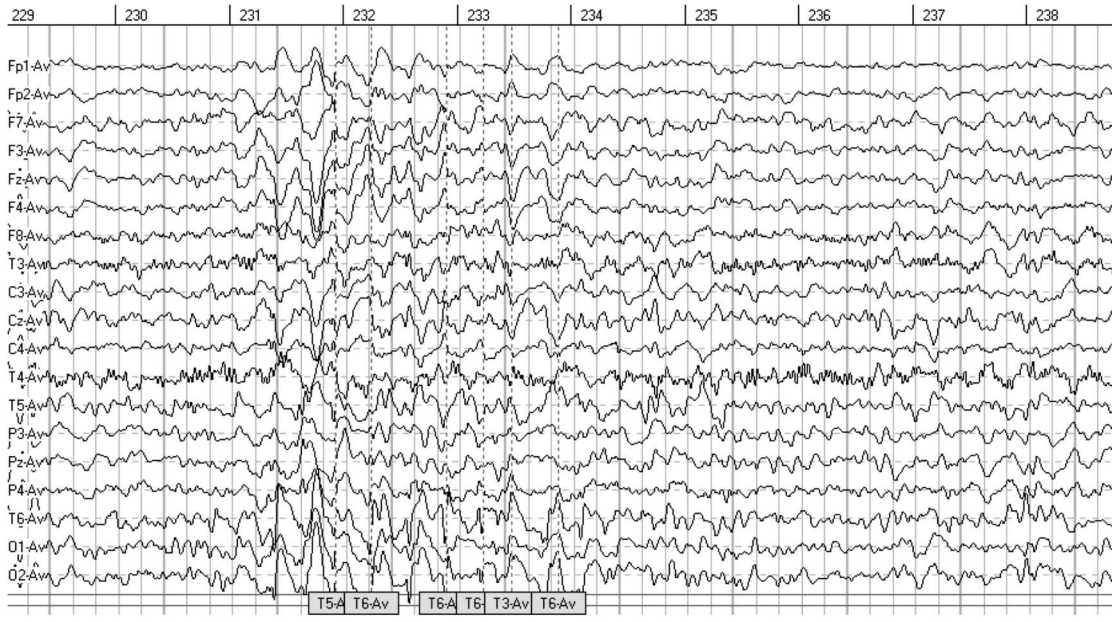

FIG. 2. Abnormal primarily generalized paroxysmal discharge, with intermixed epileptiform discharges over the right posterior (parietal/occipital) regions.

RESULTS

In keeping within the objectives of this article, our results identify the breakdown of subjects with IEDs and according to gender and age. Table 1 shows the number of subjects diagnosed with ASD, those with IEDs, and the overall percentage of each by age and gender grouping. Of the 140 subjects, the EEG data identified 51 (36%) with IEDs, most of whom (82%) were male ($n = 42$, 30%). When gender and age were assessed, the young adults have higher rates of IEDs compared with children; from 17% to 75% for females and 33% to 50% for males.

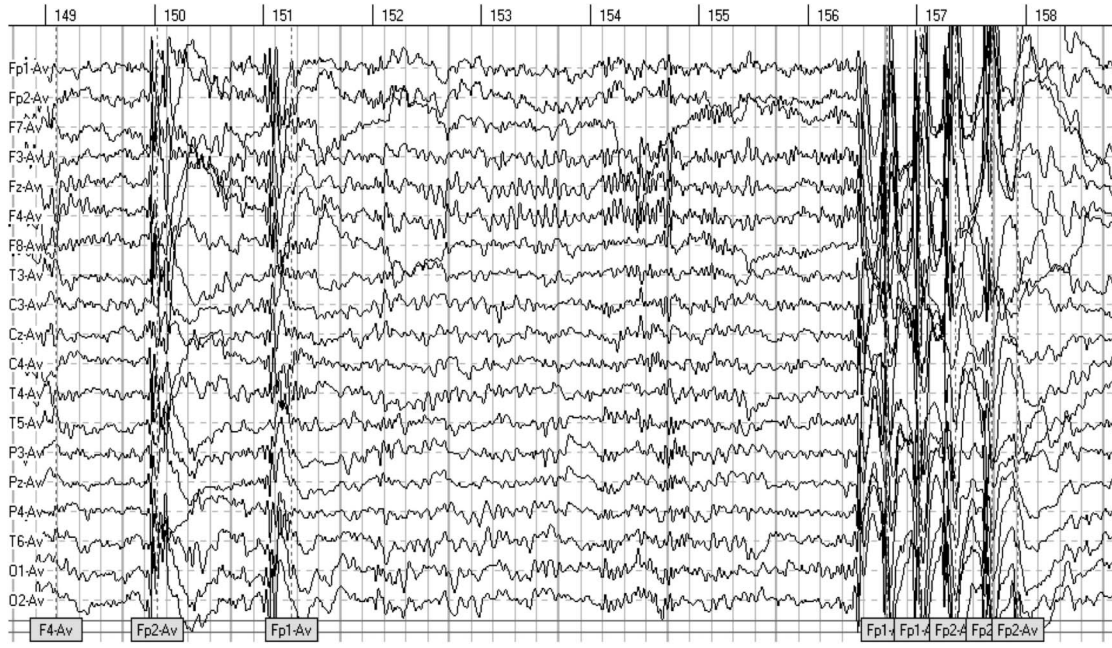

FIG. 3. Two isolated generalized spike/polyspike epileptiform discharges, followed 5 seconds later by a ~1,500 milliseconds burst of a 3 to 4 Hz, primarily generalized spike/polyspike epileptiform discharge.

TABLE 1. Frequency of Autism Spectrum Disorder and Isolated Epileptiform Discharges

	Patients With ASD			Patients With ASD and IEDs			
Age Groups	**Total**	**Female**	**Male**	**Total**	**Female**	**Male**	**% of ASD and IEDs**
4–12	73	16	57	23	4	19	32
13–18	51	12	39	19	2	17	37
19–25	16	4	12	9	3	6	56
Total	140	32	108	51	9	42	36

ASD, autism spectrum disorder; IED, isolated epileptiform discharge.

Chi-square analysis and a Fisher exact test found no evidence of a significant association at the 0.05 level (Pearson $\chi^2 = 1.235$, Fisher exact test [two tail] P value $= 0.032$, Ln [Odds] $= -0.486$, 95% confidence interval, -1.349 to 0.376). When testing the association between the dichotomized into two groups, children and the rest, and the likelihood of IEDs, there was no evidence of a significant association at the 0.05 level (Pearson $\chi^2 = 1.596$, Fisher exact test (two tail) P value $= 0.223$, Ln(Odds) $= -0.445$, 95% confidence interval, -1.138 to 0.247). When testing the association between the dichotomized into two groups, adolescents and the rest, and the likelihood of IEDs, there was no evidence of a significant association at the 0.05 level (Pearson $\chi^2 = 0.024$, Fisher exact test (two tail) P value $= 1.00$, Ln(Odds) $= 0.056$, 95% confidence interval, -0.658 to 0.770). Findings indicate a high prevalence of IEDs among individuals with ASD (36%) regardless of age or gender.

DISCUSSION

A precision medicine approach in psychiatry will not come from a single data source. Linking symptoms to their underlying neurologic/biological cause may take input from many sources including symptoms, genotype, physiology, cognitive assessment, family dynamics, environmental exposures, and cultural background.[34] Mental dysfunction needs to be perceived as disorders of brain structure and function that involve the domains of cognition, emotion, and behavior. When we speak of brain structure, this is outside the range of integration for psychiatry. Imaging equipment and interpretation is more in the realm of neurology and radiology. However, EEG is a good measure of brain electrical function and well within the realm of psychiatry. EEG equipment is already being increasingly used in many mental health practices for quantitative EEG brain mapping and neurofeedback therapy.

The history of pharmacologic development has yet to find an all inclusive medication for those with ASD. We suggest that the existence of IEDs may truly represent a homogeneous subset that would confound the findings in medication trials. For instance, Hirota et al. did a systematic review and meta-analysis on the application of antiepileptic medication for ASD; they found that antiepileptic medications did not seem to have a large effect size to treat behavioral symptoms. However, no EEG screening was performed in any of these studies and if less than 40% had the potential to respond to antiepileptic medications, than it would account for his negative results.[35]

In this study, the subjects referred for an EEG 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 subjects; therefore, the findings represent 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. An additional limitation to this study is the use of only one board-certified electroencephalographer because of it being conducted in a clinical setting. Future studies could consider having the EEGs visually rated by more than one electroencephalographer to verify findings.

Although there was no control group used in this study, previous studies identified an average IED prevalence rate of 5% in neurotypical children.[6–8] There was no significant difference between age and gender, suggesting that IEDs may be nonspecific for these two parameters in the ASD population. These findings suggest (1) in a psychiatric practice, the prevalence rate of IEDs is much higher in children, adolescents, and young adults with ASD; (2) that there may be a relationship between IEDs and ASD, thus representing a subgrouping of ASD that is yet to be identified; and (3) that IEDs could explain why previous medication attempts failed.

Many medications commonly prescribed to those with ASD lower seizure threshold. This could lead to an increase in the prevalence of IEDs and subsequent worsening of symptoms. Selective serotonin reuptake inhibitors are often prescribed in children with obsessive compulsive disorder. A recent study ($n =$ 238,632) found that the risk of developing epilepsy/seizures is significantly increased for all classes of antidepressant medication in adults aged 20 to 64.[36] It is likely that adults with preexisting IEDs are at a higher risk of developing seizures than those with no IEDs. 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, IEDs need to be stabilized. Swatzyna, et al. and Millichap, Millichap, and Stack recommended stabilizing IEDs with anticonvulsants before the administration of stimulants.[33,37] When IEDs are identified in the EEG, it has been our experience that removing medications that lower the seizure threshold and adding an anticonvulsant has resulted in positive outcomes. In addition, the EEG is used for dose titration until the IEDs are controlled. We have been collecting and analyzing this data for the past 5 years and recently initiated an outcome study to assess medication changes based on EEG findings. Additional outcome studies will be needed in this area for validation.

The integration of EEG into psychiatric practice fits well into the National Institute of Mental Health RDoC initiative. In regard to the treatment of children, adolescents, and young adults with ASD, EEG prescreening for refractory cases is suggested. This study contributes to the ASD and IEDs 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 and demonstrates the need for EEG screening for ASD. Our results supports previous findings that compared with the healthy population, a large number of children with ASD have IEDs despite never having a seizure.[6–8] This abnormal neuronal activity may create serious developmental issues in the maturing brain particularly for those prescribed medication that lower seizure threshold. Our findings support the use of EEG in children, adolescents, and young adults with ASD, regardless of gender or age. This is particularly true for those who exhibit aggressive behaviors or those who have failed previous medication attempts with stimulants, antidepressants, and/or antipsychotics.

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