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Review

Behavioral correlates of epileptiform abnormalities in autism

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ABSTRACT

There is a high incidence of epileptiform abnormalities in children with autism even in the absence of clinical seizures. These findings are most prominent during sleep recordings. The significance of these abnormalities is unclear. Although studies do not all agree, there may be some association between cognitive function, behavior, and the presence or absence of epileptiform discharges. Small studies of anticonvulsant treatment mostly suggest an improvement in certain aspects of cognitive or behavioral functioning in these children, but larger and more comprehensive studies are needed to determine the potential relationship between epileptiform discharges on EEG, cognitive and behavioral functioning, and treatment effects in the population with autism.

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1. Introduction

Despite many years of study, there is still limited information regarding the underlying neurobiological substrates associated with autism. One of the potential reasons for this may be the heterogeneous nature of the condition. Autism may be a number of different conditions manifesting as a common clinical phenotype. The core features of impairment in social communication and social interaction; restricted range of interests; and repetitive, stereotyped behaviors define the clinical disorder. Abnormal (either hypo- or hyper-) sensitivity to sensory stimuli is included within the stereotyped behaviors and can include behaviors such as excessive smelling or touching of objects and avoidance of certain textures, sounds, or smells. There are additional commonly associated, although not core, features, such as disturbances in sleep, gastrointestinal problems, and behavioral issues including hyperactivity, attention problems, and aggressive and impulsive behaviors. Seizures are one common associated complication of autism, occurring at a much higher rate than that in the general population, with estimates of 6–46% of individuals with autism having clinical seizures at some time during their lives [1–5]. Moreover, even in individuals with autism without a history of clinical seizures, there is a very high incidence of epileptiform abnormalities on electroencephalographic (EEG) recordings [6–12]. This observation raises several questions. Are the epileptiform discharges reflecting cortical dysfunction in autism, or are they coincidental findings unrelated to the neurobiology? Are the epileptiform discharges associated with underlying behavioral or cognitive problems commonly found in autism? Could treatment of the epileptiform discharges alter the clinical symptoms?

2. Incidence and type of epileptiform abnormalities

There have been a number of reports of the presence of epileptiform abnormalities on EEG in children with autism spectrum disorder (ASD) or pervasive developmental disorder (PDD) [6–12] (see Table 1 for a summary of relevant studies). Most have looked at a possible association between the presence of epileptiform activity and autistic regression, an occurrence in approximately 20–30% of children with autism. In regressive autism, the children appear to be developing normally and then lose eye contact, stereotypies and repetitive behaviors appear, and communication and social behaviors regress. Tuchman and Rapin [1] reported on 585 young children with PDD, 30% of whom had a history of regression in early development. Eleven percent of their population had a history of epilepsy. Of the 392 children in their study who had EEGs performed, 59% of the children with epilepsy had epileptiform abnormalities on EEG, but only 8% of the children without epilepsy had abnormal EEG findings. There was a slightly higher incidence (14% vs. 6%) of autistic regression in the group with epileptiform abnormalities than in the group without epileptiform discharges. Rossi et al. [6] found an 18.9% incidence of paroxysmal discharges on EEG in children and adults with autism who did not have epilepsy. These authors also did not find EEG abnormalities or epilepsy to be associated with autistic regression.

In a large retrospective study, 889 patients with autism (mean age: 5.8 years) with no prior history of epilepsy received 24-hour ambulatory EEGs over a 10-year period [12]. The incidence of epileptiform EEG

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Table 1
Studies of epileptiform abnormalities in autism.

	Number of subjects	Sample characteristics	Type of recording	Clinical seizures	EEG findings	Other related findings
Rossi et al. (1995)	106	Age range: 3–31 years	Wake and sleep	23.6%	ED in 18.9% of patients without clinical seizures	Higher incidence of severe intellectual disability in patients with ED and ED + epilepsy
Tuchman and Rapin (1997)	585 (392 with EEG)	Age not reported	Sleep	11%	ED in 59% of patients with epilepsy; 8% of those without epilepsy	Autistic regression more common in children with epilepsy or ED on EEG
Chez et al. (2006)	889	Average age: 5.3 years	Overnight	None (excluded from study)	60.7% abnormal	No association between ED and regressive autism
Hartley-McAndrew and Weinstock (2010)	123	Age range: 7–23 years	Routine EEG	28.6%	31% abnormal	In a small subset (n = 21), no association between abnormal EEG and behavior
Mulligan and Trauner (2014)	101	Age range: 1.7–18.3 years	Overnight	23.1%	59.4% ED	Aggression and stereotypies more frequent with ED

ED - Epileptiform discharges

abnormalities in their population was 60.7%. As in previous studies, the authors found no difference between children with a history of autistic regression and those without such a history. Interestingly, all of their patients had EEG abnormalities in sleep only. There was not a consistent location found for EEG abnormalities in their population. The most common site for abnormal electrical discharges was the right temporal lobe or the bilateral temporal and central regions, but frontal, occipital, and parasagittal spikes were seen in some patients, and generalized spike–wave discharges were found in 16% of the recordings.

More recently, Mulligan and Trauner [12] identified 101 children with autism (mean age: 7.1 years) who had undergone 24-hour EEGs. We found that 59.4% of children with ASD had epileptiform discharges on EEG and that 21.8% had nonepileptiform abnormalities, primarily slowing of the background activity. When only children without a history of epilepsy were included, 50% had epileptiform abnormalities, whereas 95% of children with a history of seizures had interictal epileptiform discharges. Sixty percent had abnormalities during sleep only, again highlighting the fact that a sleep EEG is essential to detect such abnormalities. Only 3.6% had epileptiform activity in waking only. The presence of epileptiform activity was associated with lower functional levels (intellectual and behavioral) in the children with autism, whereas those with high-functioning autism (HFA; Asperger's) had only a 20% incidence of such abnormalities. The reciprocal association between intellectual functioning and the presence of epileptiform discharges is also of interest with relation to the question of causality, i.e., do the epileptiform discharges cause the symptoms of autism, do they co-occur as a result of a common underlying brain disorder that causes both, or are they coincidental to each other? This reciprocal association has been demonstrated between autism and clinical epilepsy as well [13–15].

The presence of epileptiform abnormalities in the Mulligan and Trauner [12] study was also associated with a higher incidence of motor stereotypies (61% vs. 36% without epileptiform abnormalities). As was found in earlier studies, there was no association between epileptiform abnormalities and autistic regression. There was a markedly higher association of aggressive behaviors with the presence of epileptiform abnormalities, but the numbers were too small to allow for meaningful statistical analysis. However, this study raises the question of whether interictal epileptiform abnormalities may play a role in some of the behavioral difficulties observed in many children with autism.

The studies of Chez et al. [8] and Mulligan and Trauner [12] both found a very high percentage of children with autism with epileptiform abnormalities in the absence of clinical seizures. Most often, the abnormalities were detected during sleep only. These studies highlight the importance of a sleep EEG in this population and, ideally, a prolonged (overnight) EEG in order to capture all stages of the sleep cycle.

Magnetoencephalography (MEG) is a noninvasive technique that utilizes neurophysiological and magnetic resonance imaging paradigms to identify areas of abnormal activity in the brain. Magnetoencephalography studies of children with autism have identified areas of persistent epileptiform discharges primarily in the perisylvian regions [16,17]. Magnetoencephalography may be more sensitive than routine EEG and possibly better able to detect abnormalities than 24-hour EEGs [16].

3. Are the epileptiform discharges reflecting cortical dysfunction in autism, or are they coincidental findings unrelated to the neurobiology?

The above studies raise the crucial question of whether the epileptiform abnormalities found in many children with autism reflect underlying cortical dysfunction and create or add to the clinical symptomatology or whether they are merely coincidental findings that are not in themselves responsible for any of the clinical manifestations. There are a number of studies demonstrating a higher risk of autism with certain types of epilepsy (e.g., infantile spasms, Lennox Gastaut syndrome) [18–20]. There is also a higher risk of autism in children who have seizure onset under two years of age [21]. However, these observations do not prove causation. More relevant to the current topic is that there is very little information published with regard to the presence of epileptiform EEG abnormalities having a causal role in autism. Several studies have demonstrated transient subtle cognitive impairments in individuals without autism with epilepsy during the time that epileptiform discharges are occurring [22–25]. The possibility that recurrent epileptiform abnormalities may cause permanent cognitive, social, or behavioral impairments is much more difficult to demonstrate. Animal studies [26] have documented that persistent interictal epileptiform discharges in the prefrontal cortex that were initiated during early brain development led to deficits in social behavior in adult rats, even though the epileptiform discharges were no longer present. Such work indicates that early persistent epileptiform discharges can have long-lasting effects on synaptic plasticity and lead to deficits reminiscent of what might be found in individuals with autism.

A relevant study of patients with tuberous sclerosis complex (TSC), a condition associated with a high incidence of autistic spectrum disorders, showed an association between frequency of epileptiform discharges in the left temporal lobe and the presence of autism [27]. The authors conclude that persistent epileptiform activity in specific brain regions, particularly the temporal lobe, early in brain development may lead to long-term social and communication deficits.

Of interest with regard to the above studies is that although epileptiform discharges may be seen in any area of the brain in children with

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